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

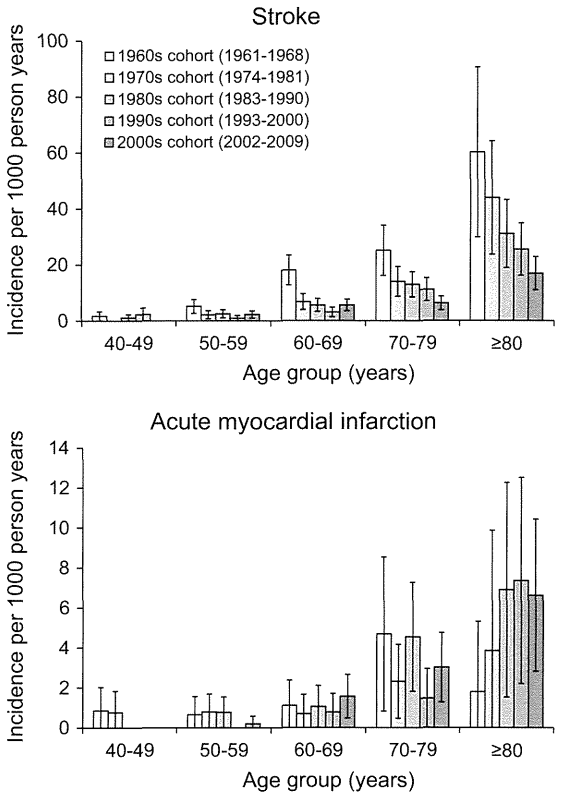


**Figure 1.** Age-specific incidence of stroke (**top**) and acute myocardial infarction (**bottom**) with adjustment for sex, among 5 cohorts of the Hisayama Study. Bars indicate 95% confidence intervals.

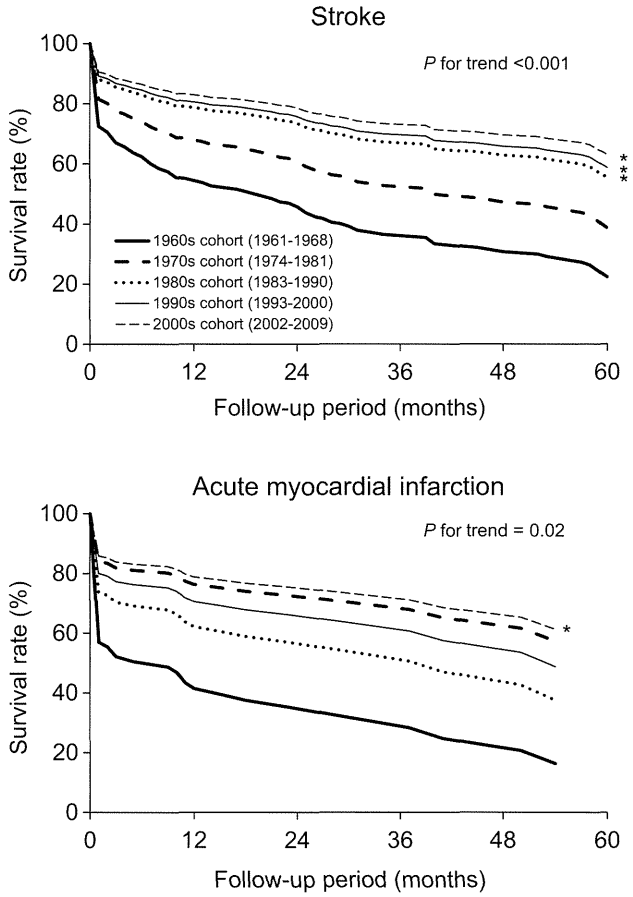


**Figure 2.** Age- and sex-adjusted 5-year survival curves after the onset of stroke (**top**) and acute myocardial infarction (**bottom**) among 5 cohorts of the Hisayama Study. *$P$<0.05 compared with 1960s cohort (after Bonferroni correction for multiple comparisons).

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.

**SUPPLEMENTAL MATERIALS**

# Secular Trends in Cardiovascular Disease and Its Risk Factors in Japanese

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

**Authors:** Jun Hata, MD, PhD; Toshiharu Ninomiya, MD, PhD; Yoichiro Hirakawa, MD, PhD; Masaharu Nagata, MD, PhD; Naoko Mukai, MD, PhD; Seiji Gotoh, MD, PhD; Masayo Fukuhara, MD, PhD; Fumie Ikeda, MD, PhD; Kentaro Shikata, MD, PhD; Daigo Yoshida, PhD; Koji Yonemoto, PhD; Masahiro Kamouchi, MD, PhD; Takanari Kitazono, MD, PhD; Yutaka Kiyohara MD, PhD

## Supplemental Methods

### Definition of glucose intolerance in 1961

For participants with glycosuria at the baseline examination, researchers additionally performed either a full stomach test (with ≥2 bowls of rice plus a bar of sweet bean jelly) or 100-g oral glucose tolerance test (OGTT) at Kyushu University Hospital. For participants who underwent the full stomach test, glucose intolerance was defined as 2-hour or 3-hour postload blood glucose ≥7.8 mmol/L (140 mg/dL). For participants who underwent the 100-g OGTT, glucose intolerance was defined as 1-hour postload blood glucose ≥11.1 mmol/L (200 mg/dL) and 2-hour postload blood glucose ≥8.3 mmol/L (150 mg/dL).

### Definition of glucose intolerance in 1974 and 1983

A single measurement of plasma glucose was performed at the baseline examination. Glucose intolerance was defined as either of the following criteria: (1) fasting plasma glucose ≥6.4 mmol/L (115 mg/dL), (2) 2-hour postprandial plasma glucose ≥7.8 mmol/L (140 mg/dL), (3) casual plasma glucose ≥11.1 mmol/L (200 mg/dL), or (4) known glucose intolerance in the earlier health examination or a medical history of diabetes.

### Definition of glucose intolerance in 1993 and 2002

We performed 75-g OGTT for almost all participants aged 40-79 years, or a fasting blood glucose measurement for others. Glucose intolerance was defined as either impaired fasting glycemia, impaired glucose tolerance, diabetes mellitus (according to the 1998 WHO criteria), or use of oral hypoglycemic agents or insulin.

## Legends to Supplementary Figures

**Figure I: Comparison of age distributions in the town of Hisayama and in the country of Japan as a whole in 1960 and 2010 (National Census)**

Proportions among the total population of Hisayama or Japan are shown.

**Figure II: Comparison of occupational distribution in the town of Hisayama and in Japan as a whole in 1960 and 2010 (National Census)**

Occupational distributions among the employed population aged ≥15 years, classified by the sectors of industry, are shown. Each sector was defined on the basis of the Japan Standard Industrial Classification (JSCI) by the Statistics Bureau, Ministry of Internal Affairs and Communications of Japan (http://www.stat.go.jp/english/index/seido/sangyo/san07-3.htm).

The primary sector includes (Division A) agriculture and forestry; and (B) fisheries. The secondary sector includes (C) mining and quarrying of stone and gravel; (D) construction; and (E) manufacturing. The tertiary sector includes (F) electricity, gas, heat supply and water; (G) information and communications; (H) transport and postal activities; (I) wholesale and retail trade; (J) finance and insurance; (K) real estate and goods rental and leasing; (L) scientific research, professional and technical services; (M) accommodations, eating and drinking services; (N) living-related and personal services and amusement services; (O) education learning support; (P) medical, health care and welfare; (Q) compound services; (R) services, not elsewhere classified; (S) government, except elsewhere classified; and (T) industries that could not be classified.

**Figure III. Flow chart of cohorts for the present study**

Participants in health examinations in 1961, 1974, 1983, 1993, and 2002 (all aged ≥40 years) were used to establish 5 cohorts in different decades (the 1960s, the 1970s, the 1980s, the 1990s, and the 2000s cohorts, respectively). Participants with a history of stroke or coronary heart disease (CHD) were excluded from each cohort. Participants who died during the examination period (except for the 2000s cohort), who moved out of the town during the examination period (for the 1960s and the 1990s cohorts), or who refused follow-up assessments (for the 2000s cohort) were also excluded. Consequently, the numbers of

participants were 1618 for the 1960s cohort, 2038 for the 1970s cohort, 2459 for the 1980s cohort, 1983 for the 1990s cohort, and 3108 for the 2000s cohort. Each cohort was followed up for 7 years (i.e., 1961-1968, 1974-1981, 1983-1990, 1993-2000, and 2002-2009, respectively).

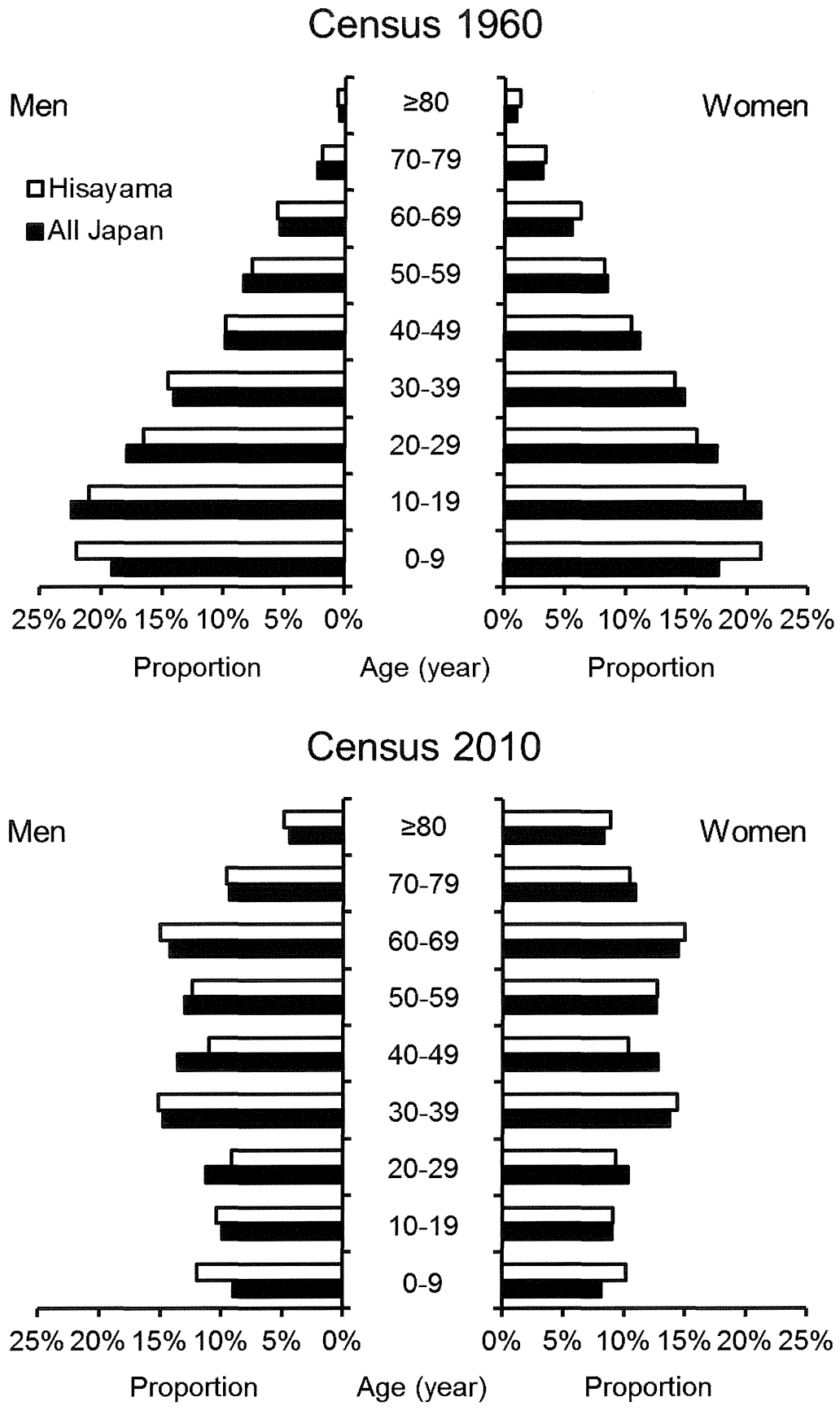

Census 1960
Men
Women
Hisayama
All Japan
≥80
70-79
60-69
50-59
40-49
30-39
20-29
10-19
0-9
25% 20% 15% 10% 5% 0%
0% 5% 10% 15% 20% 25%
Proportion
Age (year)
Proportion
Census 2010
Men
Women
≥80
70-79
60-69
50-59
40-49
30-39
20-29
10-19
0-9
25% 20% 15% 10% 5% 0%
0% 5% 10% 15% 20% 25%
Proportion
Age (year)
Proportion

**Figure I**

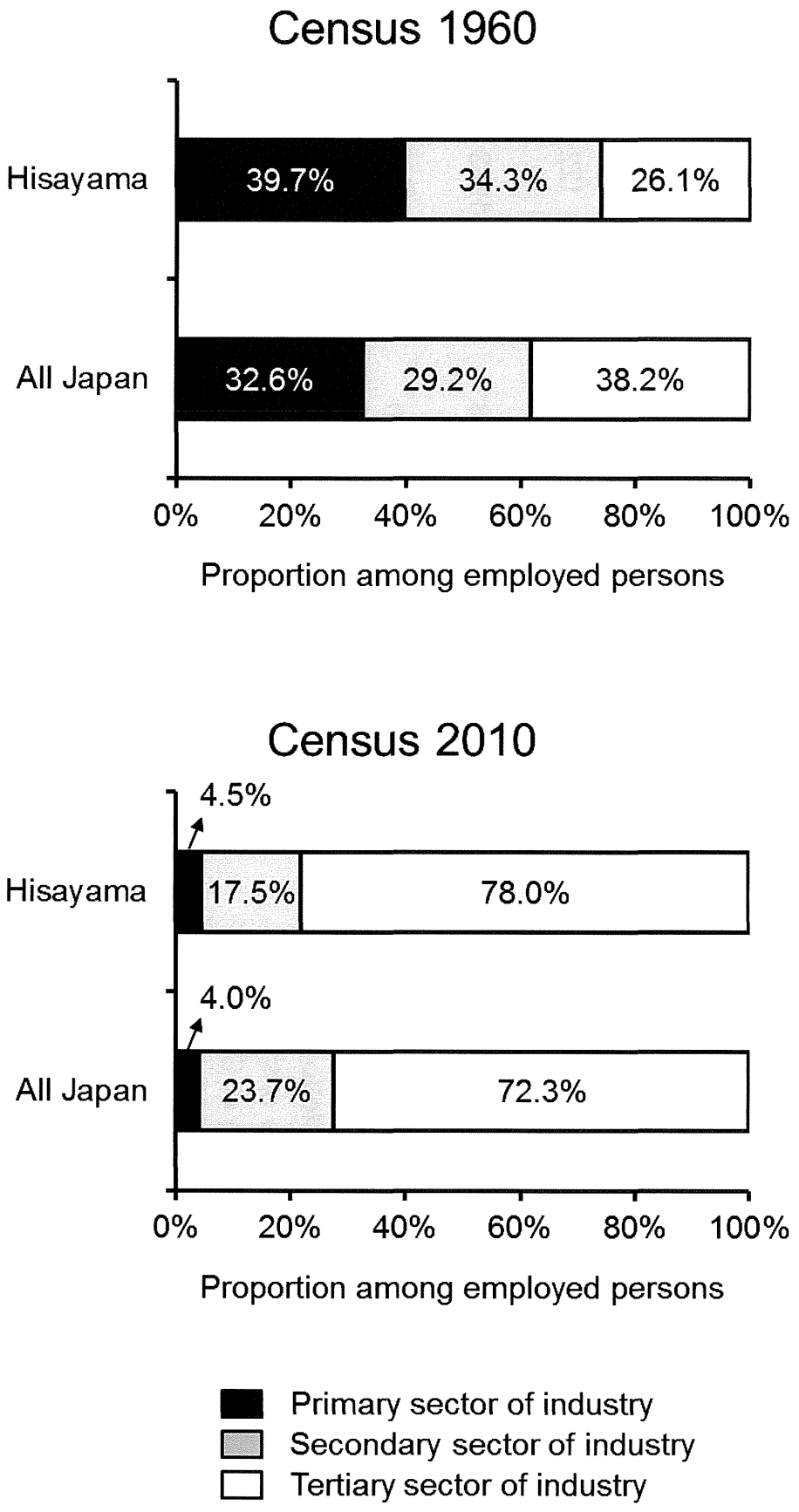
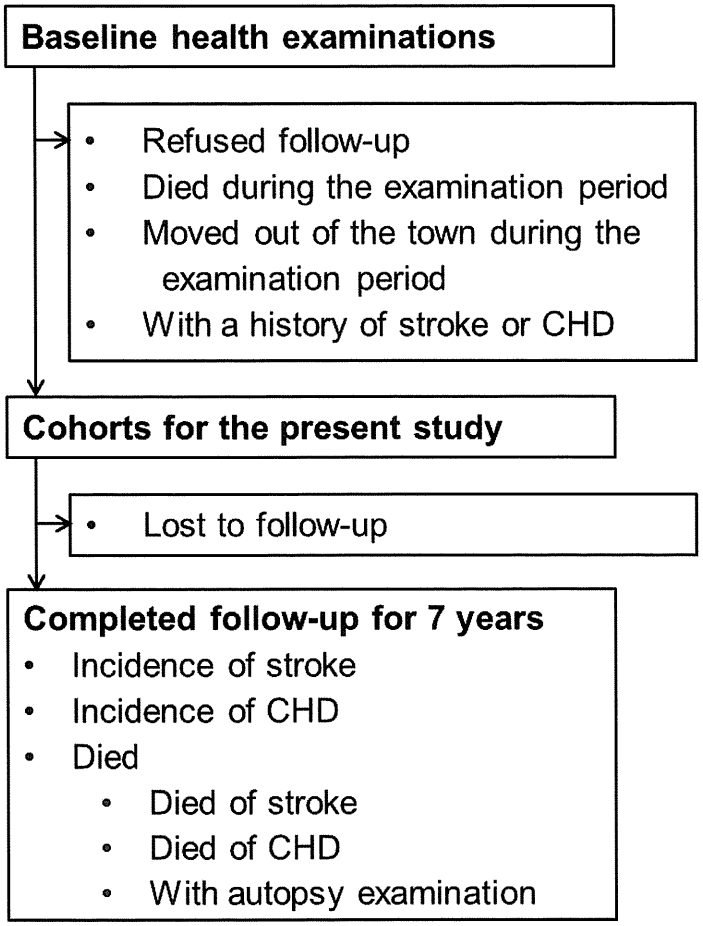

Census 1960
Hisayama
39.7%
34.3%
26.1%
All Japan
32.6%
29.2%
38.2%
0%
20%
40%
60%
80%
100%
Proportion among employed persons
Census 2010
4.5%
Hisayama
17.5%
78.0%
4.0%
All Japan
23.7%
72.3%
0%
20%
40%
60%
80%
100%
Proportion among employed persons
Primary sector of industry
Secondary sector of industry
Tertiary sector of industry

**Figure II**




| | Number of participants | | | | |
|---|---|---|---|---|---|
| | 1960s | 1970s | 1980s | 1990s | 2000s |
| **Baseline health examinations** | **1658** | **2135** | **2551** | **2111** | **3328** |
| • Refused follow-up | - | - | - | - | 30 |
| • Died during the examination period | 4 | 28 | 3 | 5 | - |
| • Moved out of the town during the examination period | 8 | - | - | 1 | - |
| • With a history of stroke or CHD | 28 | 69 | 89 | 122 | 190 |
| **Cohorts for the present study** | **1618** | **2038** | **2459** | **1983** | **3108** |
| • Lost to follow-up | 0 | 0 | 0 | 24 | 0 |
| **Completed follow-up for 7 years** | **1618** | **2038** | **2459** | **1959** | **3108** |
| • Incidence of stroke | 117 | 84 | 100 | 83 | 103 |
| • Incidence of CHD | 27 | 31 | 44 | 41 | 65 |
| • Died | 232 | 196 | 221 | 190 | 267 |
| • Died of stroke | 57 | 27 | 24 | 16 | 20 |
| • Died of CHD | 10 | 12 | 14 | 10 | 15 |
| • With autopsy examination | 181 | 165 | 185 | 156 | 170 |

**Figure III**

**Table I. Estimated survival rate at 5 years and hazard ratio for death after the onset of stroke or acute myocardial infarction among 5 cohorts of the Hisayama Study**

| | Number of events* | Number of deaths† | Estimated survival rate at 5 years (%)‡ | Hazard ratio for death (95% confidence interval) ‡ | Unadjusted *P* value |
|---|---|---|---|---|---|
| Stroke | | | | | |
| 1960s cohort (1961-1968) | 117 | 71 | 22.2 | 1.00 (reference) | |
| 1970s cohort (1974-1981) | 84 | 41 | 38.5 | 0.64 (0.43-0.94) | 0.02 |
| 1980s cohort (1983-1990) | 100 | 35 | 55.3 | 0.39 (0.26-0.59) | <0.001§ |
| 1990s cohort (1993-2000) | 83 | 30 | 58.7 | 0.36 (0.23-0.55) | <0.001§ |
| 2000s cohort (2002-2009) | 103 | 36 | 63.0 | 0.31 (0.20-0.47) | <0.001§ |
| *P* for trend | | | | <0.001 | |
| Acute myocardial infarction | | | | | |
| 1960s cohort (1961-1968) | 14 | 8 | 16.3 | 1.00 (reference) | |
| 1970s cohort (1974-1981) | 15 | 4 | 57.3 | 0.31 (0.09-1.05) | 0.06 |
| 1980s cohort (1983-1990) | 26 | 15 | 37.5 | 0.54 (0.22-1.34) | 0.18 |
| 1990s cohort (1993-2000) | 16 | 10 | 48.7 | 0.40 (0.14-1.11) | 0.08 |
| 2000s cohort (2002-2009) | 34 | 12 | 61.2 | 0.27 (0.10-0.70) | 0.007§ |
| *P* for trend | | | | 0.02 | |

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 for each cohort).

* Number of stroke or acute myocardial infarction during 7 years.

† Number of death within 5 years after stroke or acute myocardial infarction.

‡ Age- and sex-adjusted.

§ $P<0.05$ after Bonferroni's correction for multiple comparisons.

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# White-Coat and Masked Hypertension Are Associated With Carotid Atherosclerosis in a General Population: The Hisayama Study

Masayo Fukuhara, Hisatomi Arima, Toshiharu Ninomiya, Jun Hata, Yoichiro Hirakawa, Yasufumi Doi, Koji Yonemoto, Naoko Mukai, Masaharu Nagata, Fumie Ikeda, Kiyoshi Matsumura, Takanari Kitazono and Yutaka Kiyohara

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# White-Coat and Masked Hypertension Are Associated With Carotid Atherosclerosis in a General Population

## The Hisayama Study

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***Background and Purpose***—On the basis of combined measurements of clinic blood pressure (CBP) and home blood pressure (HBP), blood pressure status can be divided into normotension, white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT). Despite the clear impact of MHT and SHT on clinical and subclinical arterial disease, uncertainty about the influence of WCHT remains. The objective of this study was to investigate the associations of WCHT, MHT, and SHT with carotid atherosclerosis in a general population.

***Methods***—This is a cross-sectional survey of 2915 community-dwelling Japanese aged ≥40 years. Normotension was defined as CBP<140/90 and HBP<135/85 mm Hg; WCHT, CBP≥140/90 and HBP<135/85 mm Hg; MHT, CBP<140/90 and HBP≥135/85 mm Hg; and SHT, CBP≥140/90 and HBP≥135/85 mm Hg. Mean intima-media thickness of carotid arteries was measured using a computer-automated system, and carotid stenosis was defined as diameter stenosis ≥30%.

***Results***—There were 1374 subjects (47.1%) with normotension, 200 (6.9%) with WCHT, 639 (21.9%) with MHT, and 702 (24.1%) with SHT. The geometric average of mean intima-media thickness was significantly higher among subjects with WCHT (0.73 mm), MHT (0.77 mm), and SHT (0.77 mm) than those with normotension (0.67 mm; all $P<0.001$ versus normotension). Compared with normotension, all types of hypertension were also associated with increased likelihood of carotid stenosis (age- and sex-adjusted odds ratio, 2.36 [95% confidence interval, 1.27–4.37] for WCHT, 1.95 [1.25–3.03] for MHT, and 3.02 [2.01–4.54] for SHT). These associations remained significant even after adjustment for other cardiovascular risk factors.

***Conclusions***—WCHT, as well as MHT, and SHT were associated with carotid atherosclerosis in a general Japanese population. (***Stroke*. 2013;44:1512-1517.)**

**Key Words:** atherosclerosis ■ clinic blood pressure ■ home blood pressure ■ intima-media thickness ■ masked hypertension ■ white-coat hypertension

On the basis of combined measurements of clinic blood pressure (CBP) and out-of-office blood pressure (BP), such as home blood pressure (HBP) and ambulatory BP, BP status can be divided into 4 categories: normotension (NT), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT).[1,2] Although several authors have reported clear associations of MHT and SHT with cardiovascular disease,[3–7] there is still uncertainty about the influence of WCHT on subclinical organ damage, such as carotid atherosclerosis,[4,5,7–9] as well as on cardiovascular or renal disease.[3,6,10–13]

Present guidelines for the management of hypertension recommend assessment of subclinical arterial disease as an intermediate stage in the continuum of vascular disease among subjects at high risk of cardiovascular disease.[1,14] Among several noninvasive screening tests of subclinical arterial disease, ultrasound examination of the carotid arteries with assessment of intima-media thickness (IMT) and atherosclerotic plaques has been clearly shown to be useful in predicting the future risks of coronary heart disease and stroke.[15–17]

In the present cross-sectional study, we evaluated the associations of WCHT, MHT, and SHT defined using CBP and HBP with carotid atherosclerosis evaluated using ultrasound examination in a general Japanese population.

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**The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.000704/-/DC1.**

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# Methods

## Study Population

The Hisayama study is a population-based prospective cohort study of cardiovascular disease established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan.[18–20] On the basis of data from the national census, the age and occupational distributions in Hisayama have been almost identical to those in Japan since the 1960s.[18,21] The present cross-sectional study was based on a screening survey conducted in 2007 and 2008. A total of 3376 residents aged ≥40 years (78.0% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment, including HBP measurement and carotid ultrasonography. After the exclusion of 211 subjects without HBP measurements for >3 days, 75 subjects without information on carotid ultrasonography, and 175 subjects lacking both types of information, a total of 2915 subjects (1267 men and 1648 women) were enrolled in the present study.

## CBP Measurements

CBP was measured 3 times using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare Co, Ltd, Kyoto, Japan) based on the cuff oscillometric method with an appropriately sized cuff on the right arm in the sitting position after rest for ≥5 minutes. The mean of the 3 measurements was used for the analysis.

## HBP Measurements

Before starting the HBP measurements, physicians and public health nurses taught the subjects how to measure their HBP accurately. The subjects were advised to measure their HBP 3 times: every morning before breakfast, within 1 hour of waking, and after >5 minutes of rest in the sitting position for 4 weeks. Participants on BP-lowering medication were advised to measure their HBP before taking medication. The subjects were also instructed to place appropriately sized cuffs directly around their nondominant arms and to maintain the position of the cuffs at the level of the heart. HBP measurements were performed using an automatic device (HEM-7080IC; Omron Healthcare Co, Ltd) based on the cuff oscillometric method. HEM-7080IC uses the identical components and BP determining algorithm as another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol.[22] The device has a memory, which allows recording of 350 measurements, and a data output port, which enables data extraction for the analysis. The mean value of all available daily averages was used in the present analysis.

## BP Classification

On the basis of the combined measurements of CBP and HBP, irrespective of the use of antihypertensive medication, the subjects were divided into 4 groups: NT (CBP <140/90 mm Hg and HBP <135/85 mm Hg), WCHT (CBP ≥140/90 mm Hg and HBP <135/85 mm Hg), MHT (CBP <140/90 mm Hg and HBP ≥135/85 mm Hg), and SHT (CBP ≥140/90 mm Hg and HBP ≥135/85 mm Hg).[1,2,14]

## Carotid Ultrasonography

Carotid ultrasound was performed using a real-time, B-mode ultrasound imaging unit (Toshiba Sonolayer SSA-250A; Toshiba, Tokyo, Japan) with a 7.5-MHz annular array probe. The ultrasound examination was performed in a supine position by specially trained laboratory technicians using a standardized technique. The technicians were blinded to the medical history, BP values, and laboratory data of each participant. Mean IMT was measured using the long-axis view of each common carotid artery. An image was obtained in the region 20 mm proximal to the origin of the bulb at the far wall of each common carotid artery, and the average IMT as a mean value of IMT measurements at 250 computer-based points in the region was automatically calculated on each side using a computer-assisted measurement system (Intimascope; Media Cross Co, Ltd, Tokyo, Japan).[23] Mean IMT was defined as the mean of the left and right sides of the average IMT. Maximum IMT in the possible areas of observation of the left and right common carotid arteries, bulbs, and internal carotid arteries was measured manually using the short-axis view, and carotid wall thickening was defined as a maximum IMT of >1.0 mm. Percent diameter stenosis was measured on the short-axis view using the European Carotid Surgery Trial method,[24] and carotid stenosis was defined as a percent diameter stenosis of ≥30%.

## Other Risk Factor Measurements

Details about other risk factor measurements are in the online-only Data Supplement.

## Statistical Analysis

The differences in the mean values or frequencies of risk factors across BP categories were tested using an ANOVA or a logistic regression model. IMT was log-transformed to remove skewness, and geometric means were reported by back transformation. The effects of BP categories on the adjusted average of the mean and maximum IMT were assessed using an ANCOVA. The age- and sex-adjusted prevalence rate of carotid wall thickening and carotid stenosis were calculated using the direct method. The age- and sex-adjusted or multivariable-adjusted odds ratio and its 95% confidence interval (CI) for the presence of carotid wall thickening or carotid stenosis were assessed using a multivariable logistic regression model. The heterogeneity in the effects of BP categories on outcomes between subgroups was estimated by adding interaction terms to the relevant statistical model. All statistical analyses were performed using the SAS program package version 9.3 (SAS Institute, Inc, Cary, NC). *P* values of <0.05 were considered statistically significant.

## Ethical Considerations

The study protocol was approved by Kyushu University Institutional Review Board for Clinical Research, and the procedures followed were in accordance with national guidelines. All participants provided written informed consent.

# Results

Baseline characteristics of included (n=2915) and excluded participants (n=461) in the study are shown in Table I in the online-only Data Supplement. Compared with the included subjects, those excluded were significantly older and had higher levels of CBP. Use of antihypertensive medication and history of cardiovascular disease were more prevalent in excluded participants.

Among the 2915 subjects included, there were 1374 (47.1%) with NT, 200 (6.9%) with WCHT, 639 (21.9%) with MHT, and 702 (24.1%) with SHT. The mean values or frequencies of cardiovascular risk factors are listed, according to BP categories in Table 1. Compared with the NT group, subjects with WCHT, MHT, and SHT were significantly older and had higher CBP and HBP levels. The subjects with WCHT, MHT, and SHT were more likely to have diabetes mellitus and to receive antihypertensive and lipid-lowering medication compared with the NT subjects.

Among the total subjects, the geometric average of mean IMT was 0.72 mm (95% CI, 0.71–0.72). The crude geometric average of the mean IMT was significantly higher in the WCHT (0.73 mm; 95% CI, 0.71–0.75), MHT (0.77 mm; 0.76–0.78), and SHT (0.77 mm; 0.76–0.78) groups than the NT group (0.67 mm; 0.66–0.68; all $P<0.001$ versus NT). These associations remained significant even after adjustment for other cardiovascular risk factors, such as age, sex, diabetes

**Table 1. Baseline Characteristics of Participants, According to Blood Pressure Category**

| Variables | Normotension (n=1374) | White-Coat HT (n=200) | Masked HT (n=639) | Sustained HT (n=702) |
|---|---|---|---|---|
| Age, y | 58.7±11.3 | 64.0±10.1† | 67.2±11.1† | 66.1±11.4† |
| Men, % | 36.9 | 39.0 | 49.6† | 52.0† |
| Clinic systolic blood pressure, mm Hg | 118.4±11.7 | 150.0±9.0† | 128.4±8.8† | 154.2±11.9† |
| Clinic diastolic blood pressure, mm Hg | 73.1±7.7 | 88.6±7.2† | 77.7±7.2† | 90.3±8.5† |
| Home systolic blood pressure, mm Hg | 117.6±10.1 | 126.3±6.5† | 144.9±11.0† | 151.0±13.1† |
| Home diastolic blood pressure, mm Hg | 71.6±6.9 | 74.8±6.7† | 83.0±8.3† | 85.2±9.7† |
| Days of home blood measurement | 25.0±6.2 | 26.2±5.0* | 25.5±6.0 | 24.7±6.8 |
| Antihypertensive medication, % | 13.5 | 34.0† | 49.9† | 48.3† |
| Diabetes mellitus, % | 9.2 | 26.0† | 22.2† | 24.5† |
| Total cholesterol, mmol/L | 5.45±0.93 | 5.60±0.98 | 5.29±0.91† | 5.46±0.85 |
| HDL-cholesterol, mmol/L | 1.80±0.46 | 1.72±0.47 | 1.68±0.43† | 1.66±0.46† |
| Lipid-lowering medication, % | 10.4 | 21.0† | 19.4† | 20.7† |
| Body mass index, kg/m$^2$ | 22.2±3.0 | 24.1±4.1† | 23.5±3.2† | 24.3±3.7† |
| Current drinking, % | 47.3 | 40.0 | 52.3* | 52.6* |
| Current smoking, % | 19.4 | 8.0† | 20.5 | 20.2 |
| Regular exercise, % | 11.4 | 11.0 | 12.7 | 14.8* |
| History of cardiovascular disease, % | 3.2 | 5.0 | 8.0† | 6.7† |

All values are given as the means±SD or as a percentage. HDL indicates high-density lipoprotein; and HT, hypertension.
*$P$<0.05.
†$P$<0.001 vs normotension.

mellitus, total cholesterol, high-density lipoprotein–cholesterol, body mass index, smoking, drinking, exercise, antihypertensive medication, and lipid-lowering medication (NT 0.70 mm [95% CI, 0.69–0.70], WCHT 0.72 mm [0.70–0.73], MHT 0.74 mm [0.73–0.75], and SHT 0.74 mm [0.73–0.75]; all $P$<0.001 versus NT; Figure 1). The difference between WCHT and SHT reached statistical significance ($P$=0.03), whereas there were no significant differences between WCHT and MHT ($P$=0.055) or MHT and SHT ($P$=0.98). Similar results were obtained from multivariable analysis with a past history of cardiovascular disease (data not shown).

Among the total subjects, the geometric average of the maximum IMT was 1.21 mm (95% CI, 1.19–1.23). Compared with the NT group (1.07 mm; 95% CI, 1.04–1.09), the WCHT (1.31 mm; 1.24–1.38), MHT (1.36 mm; 1.32–1.40), and SHT (1.36 mm; 1.33–1.41) groups had clearly higher values of the maximum IMT (all $P$<0.001 versus NT). These associations remained significant even after adjusting for other cardiovascular risk factors (NT 1.15 mm [95% CI, 1.13–1.17], WCHT 1.30 mm [1.24–1.37], MHT 1.24 mm [1.21–1.28], and SHT 1.27 mm [1.24–1.31]; all $P$<0.001 versus NT; Figure 2). There were no clear differences in maximum IMT

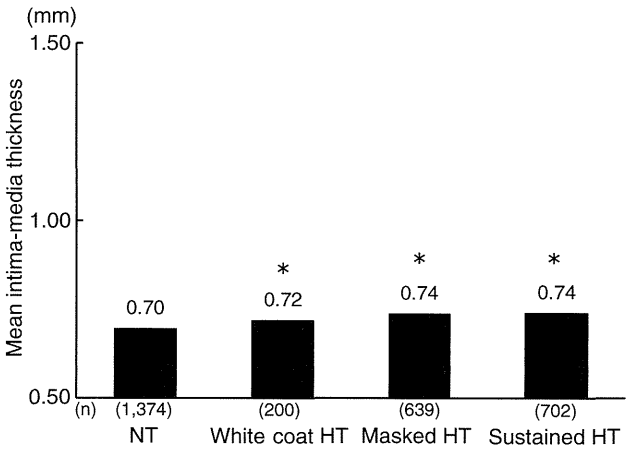


**Figure 1.** Multivariable-adjusted geometric average of mean intima-media thickness, according to blood pressure category. HT indicates hypertension; and NT, normotension. *$P$<0.001 vs normotension. Results were adjusted for age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol, body mass index, smoking, drinking, exercise, antihypertensive medication, and lipid-lowering medication.

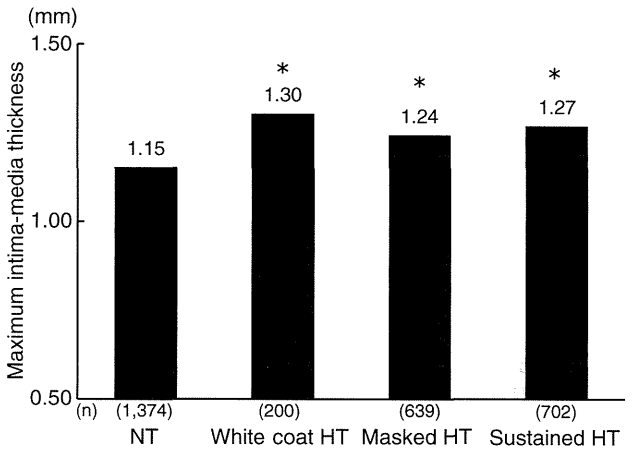


**Figure 2.** Multivariable-adjusted geometric average of maximum intima-media thickness, according to blood pressure category. HT indicates hypertension; and NT, normotension. *$P$<0.001 vs normotension. Results were adjusted for age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol, body mass index, smoking, drinking, exercise, antihypertensive medication, and lipid-lowering medication.

across the 3 hypertension subtypes ($P$=0.23 for WCHT versus MHT, $P$=0.65 for WCHT versus SHT, $P$=0.57 for MHT versus SHT). Compared with NT, all types of hypertension, including WCHT, were also associated with increased likelihood of carotid wall thickening (maximum IMT >1.0 mm) and carotid stenosis (Table 2).

There were similar associations of WCHT, MHT, and SHT with mean IMT ($P$ heterogeneity=0.14), maximum IMT ($P$ heterogeneity=0.59), carotid wall thickening ($P$ heterogeneity=0.33), and carotid stenosis ($P$ heterogeneity=0.92) between the participant subgroups defined by the use of antihypertensive medication, although the effects of WCHT did not reach statistical significance among subjects with antihypertensive medication, probably because of the limited number of subjects (Tables II and III in the online-only Data Supplement).

## Discussion

The findings from the present population-based cross-sectional study provided good evidence of clear associations of all types of hypertension, including WCHT, defined using CBP and HBP with increased risks of carotid wall thickening and carotid stenosis. These associations remained significant even after adjustment for potential confounding factors, such as age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol, body mass index, smoking, drinking, exercise, antihypertensive medication, and lipid-lowering medication.

Although several studies have reported positive associations between WCHT and carotid atherosclerosis,[8,9,25] present evidence is mainly derived from hospital-based case-control or case-series studies. Furthermore, most previous studies defined WCHT using ambulatory BP, but HBP measurement is more widely available and better accepted. A population-based study of 812 individuals from a general Japanese population investigated the association of WCHT defined based on HBP with carotid atherosclerosis, but it failed to demonstrate a clear influence of WCHT on carotid wall thickening.[4] In the present large-scale population-based study, however, WCHT as well as MHT and SHT defined using HBP were clearly associated with carotid wall thickening and carotid stenosis. With regard to clinical cardiovascular events, most of the previous prospective studies failed to demonstrate clear influence of WCHT on cardiovascular disease, probably because of the relative small number of subjects with WCHT. However, a meta-analysis of prospective cohort studies demonstrated a nonsignificant trend toward increased risk of stroke incidence among subjects with WCHT.[12] On the basis of the totality of the present evidence, there seems to be a link between WCHT and clinical/subclinical cardiovascular disease, but larger studies with longer periods of follow-up are necessary to clarify this issue. Meanwhile, as recommended by the present guidelines for management of hypertension,[1,14] routine use of antihypertensive medication for subjects with WCHT should be avoided, particularly for those without organ damage or cardiovascular disease.

The mechanisms underlying the association between WCHT and carotid atherosclerosis have not been completely resolved. One possible mechanism is that increased sympathetic tone, which is commonly observed in subjects with WCHT,[26] may promote the development and progression of arterial damage. Another possible mechanism involves insulin resistance, which is associated with WCHT as well as a risk of atherosclerosis.[26] It is also possible that a decrease in baroreflex sensitivity associated with carotid atherosclerosis[27,28] increases BP variability, which is frequently observed in WCHT.

In the present analysis, MHT and SHT were also clearly associated with increased risks of carotid wall thickening and carotid stenosis. These findings are directly in line with the results of previous observational studies that identified close associations of MHT and SHT with carotid atherosclerosis,[4,5,7] other forms of subclinical arterial disease,[5] and cardiovascular disease.[3,6]

Several cross-sectional studies have reported that carotid IMT was significantly thinner in WCHT than in MHT or

**Table 2. Age- and Sex-Adjusted Prevalence and Adjusted OR of Carotid Wall Thickening and Carotid Stenosis, According to Blood Pressure Category**

| Outcomes | Normotension (n=1374) | White-Coat HT (n=200) | Masked HT (n=639) | Sustained HT (n=702) |
|---|---|---|---|---|
| *Carotid wall thickening** | | | | |
| No. of cases | 603 | 134 | 438 | 476 |
| Age- and sex-adjusted prevalence, % | 51.3 | 65.6 | 60.8 | 60.8 |
| Age- and sex-adjusted OR (95% CI) | 1.00 (reference) | 2.00 (1.43–2.81) | 1.58 (1.27–1.97) | 1.60 (1.30–1.98) |
| Multivariable-adjusted OR (95% CI)† | 1.00 (reference) | 1.86 (1.32–2.64) | 1.49 (1.18–1.88) | 1.48 (1.18–1.85) |
| Carotid stenosis‡ | | | | |
| No. of cases | 38 | 16 | 55 | 84 |
| Age- and sex-adjusted prevalence, % | 3.8 | 7.4 | 6.8 | 10.1 |
| Age- and sex-adjusted OR (95% CI) | 1.00 (reference) | 2.36 (1.27–4.37) | 1.95 (1.25–3.03) | 3.02 (2.01–4.54) |
| Multivariable-adjusted OR (95% CI)† | 1.00 (reference) | 2.45 (1.30–4.62) | 1.95 (1.23–3.08) | 3.03 (1.97–4.67) |

CI indicates confidence interval; HT, hypertension; and OR, odds ratio.

*Maximum intima-media thickness >1.0 mm.

†Adjusted for age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol, body mass index, smoking, drinking, exercise, antihypertensive medication and lipid-lowering medication.

‡Percent diameter stenosis ≥30%.

SHT,[4,5,7] whereas other studies showed no significant differences.[8,9,25] In the present study, mean IMT was significantly lower among subjects with WCHT than among those with SHT, although there were no significant differences in maximum IMT across the 3 types of hypertension. Future large studies will be needed to clarify whether the risk of carotid atherosclerosis is modest in WCHT compared with that in MHT and SHT.

To our knowledge, this is the largest population-based study to demonstrate the close association between WCHT and carotid atherosclerosis, although corresponding definitive evidence about the influence of WCHT in each subgroup defined by the use of antihypertensive medication was not provided in the present analysis. The present study has several limitations. First, because of the cross-sectional nature of this study, we were unable to determine whether there is a causal relationship between WCHT and carotid atherosclerosis. Second, several laboratory technicians measured maximum IMT and carotid stenosis manually without assessment of inter-rater reliability, although they were specially trained to use a standardized technique. This limitation, however, is not likely to invalidate the findings observed in the present analysis because similar results were obtained for mean IMT, which was estimated automatically using a computer-assisted measurement system. Third, compared with the subjects included in the study, those excluded were older and had higher levels of CBP and more frequent history of cardiovascular disease. Therefore, our findings may not be applicable to old or high-risk populations. Fourth, inclusion of participants on antihypertensive medication may have resulted in misclassification of BP categories. However, stratified analysis demonstrated comparable influence of each type of hypertension on carotid atherosclerosis between participants with and without antihypertensive medication. Fifth, CBP was classified based on just 3 measurements on a single day in the present study. However, this source of variability could not account for the relation observed in the present study because a random misclassification of this nature would tend to cause an underestimation of the study findings. Sixth, possible confounding of unknown risk factors may not be fully adjusted for, although we included all the traditional risk factors for cardiovascular disease in statistical models.

## Conclusions

WCHT as well as MHT and SHT were associated with carotid atherosclerosis in a general Japanese population. Because WCHT is not likely to be totally benign, subjects with WCHT seem to require lifestyle changes and a close follow-up as recommended by present guidelines for the management of hypertension.[1,14]

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## Disclosures

None.

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