Table 1. Baseline characteristics of men, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	308	304	304	308	
Waist-to-height ratio	0.374–0.475	0.476–0.508	0.509–0.536	0.537–0.761	
Waist, cm	74.0 ± 4.3	81.2 ± 2.9	85.7 ± 3.1	92.8 ± 5.5	<0.01
Height, cm	165.0 ± 5.3	164.9 ± 5.6	164.4 ± 5.4	163.7 ± 5.3	0.01
Age, years	59.0 ± 5.3	59.1 ± 5.2	59.1 ± 5.5	59.4 ± 5.3	0.77
Body mass index, kg/m^2	20.1 ± 1.7	22.1 ± 1.5	23.7 ± 1.5	25.9 ± 2.3	<0.01
Hypertension, %	31	35	45	51	<0.01
Diabetes, %	6	7	9	11	0.045
Hypercholesterolemia, %	23	28	40	35	<0.01
Smoking status (current/quit/never), %	58/25/17	50/31/19	46/35/19	44/38/19	0.01
Drinking status (current/quit/never), %	79/2/19	74/4/22	79/4/17	76/4/21	0.58
Age ≥70 years					
No. of subjects	120	120	124	119	
Waist-to-height ratio	0.352–0.472	0.473–0.508	0.509–0.543	0.544–0.688	
Waist, cm	70.6 ± 5.0	79.8 ± 3.4	84.9 ± 3.3	92.2 ± 5.6	<0.01
Height, cm	162.5 ± 6.0	162.2 ± 5.7	161.3 ± 5.3	159.3 ± 6.0	<0.01
Age, years	74.0 ± 3.0	73.5 ± 2.7	74.1 ± 2.7	73.7 ± 2.9	0.40
Body mass index, kg/m^2	18.5 ± 1.7	21.3 ± 1.7	22.7 ± 1.4	25.6 ± 2.0	<0.01
Hypertension, %	42	44	51	57	0.07
Diabetes, %	4	7	7	8	0.70
Hypercholesterolemia, %	23	29	26	31	0.46
Smoking status (current/quit/never), %	37/48/16	42/41/18	38/47/15	30/50/19	0.66
Drinking status (current/quit/never), %	58/8/33	62/11/28	62/6/32	65/8/28	0.73

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

increase was observed in the HRs for CVD (P for trend = 0.04). However, after further adjustment for hypertension, diabetes, and hypercholesterolemia, these associations were no longer significant among men or women.

The χ^2 values for the likelihood ratio test were 6.49 ($P = 0.01$) for WHtR and 3.63 ($P = 0.06$) for WC among men aged 50 to 69 years, and 4.45 ($P = 0.03$) for WHtR and 4.54 ($P = 0.03$) for WC among women aged 50 to 69 years.

DISCUSSION

Our main findings were that WHtR was significantly positively associated with CVD and CHD risk among men aged 50 to 69 years and with stroke risk among women aged 50 to 69 years. Among men, there was a significant interaction between age and WHtR for CVD incidence. Among women aged 50 to 69 years, there was a borderline association between a WHtR in the highest quartile and increased CVD risk. In addition, among women aged 70 years or older, a WHtR in the upper level of the highest quartile was associated with significantly elevated CVD risk. These findings suggest that the association between WHtR and CVD incidence differs according to age and sex.

Two previous studies, in the United States and China, reported that the association between WHtR and CVD risk was stronger among younger adults as compared with elderly adults.[12,13] We too observed a significantly stronger association between WHtR and CVD risk among relatively young adults (age 50–69 years) as compared with elderly adults (age ≥70 years), which supports the results of previous studies. Consequently, these findings suggest that age stratification is important in estimating the association between WHtR and CVD risk.

In this population, physical frame, eg, WC and height, differed by age group. It has been reported that WC and the ratio of abdominal fat to whole-body fat differ by age.[9,10] In addition, the National Health and Nutrition Examination Survey in Japan noted that height clearly differed by generation.[11] This generational difference in physical frame, as well as aging, could lead to age differences in the association between WHtR and CVD risk.

A recent meta-analysis reported an optimal cut-off point of 0.50 for WHtR in both sexes.[7] However, the present findings suggest that, regardless of age or sex, a cut-off of 0.50 is somewhat low for identifying individuals at higher risk for CVD. The association with CVD risk was of at least

Table 2. Baseline characteristics of women, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	337	340	335	339	
Waist-to-height ratio	0.348–0.472	0.473–0.520	0.521–0.568	0.569–0.838	
Waist, cm	67.3 ± 4.1	75.4 ± 3.3	82.7 ± 3.4	92.1 ± 6.6	<0.01
Height, cm	153.0 ± 4.7	151.8 ± 4.9	152.1 ± 5.1	150.3 ± 5.2	<0.01
Age, years	57.6 ± 5.3	58.5 ± 5.3	59.5 ± 5.2	60.5 ± 5.4	<0.01
Body mass index, kg/m^2	19.8 ± 2.0	21.7 ± 2.0	23.1 ± 2.3	25.9 ± 3.3	<0.01
Hypertension, %	21	32	36	52	<0.01
Diabetes, %	2	3	5	9	<0.01
Hypercholesterolemia, %	49	57	57	62	0.01
Smoking status (current/quit/never), %	11/2/86	11/3/86	9/3/88	12/5/84	0.43
Drinking status (current/quit/never), %	26/2/73	29/2/69	28/2/71	31/1/68	0.75
Postmenopausal, %	90	94	95	94	0.06
Age ≥70 years					
No. of subjects	103	103	103	103	
Waist-to-height ratio	0.379–0.496	0.497–0.554	0.556–0.602	0.603–0.812	
Waist, cm	68.1 ± 4.4	77.3 ± 4.1	85.6 ± 3.6	95.2 ± 6.4	<0.01
Height, cm	148.4 ± 5.5	147.7 ± 6.1	148.1 ± 5.1	145.8 ± 5.1	<0.01
Age, years	73.8 ± 2.9	73.4 ± 2.7	73.8 ± 2.7	74.0 ± 2.6	0.56
Body mass index, kg/m^2	19.1 ± 2.1	21.3 ± 2.3	23.1 ± 2.1	26.2 ± 2.9	<0.01
Hypertension, %	53	44	50	64	0.03
Diabetes, %	2	5	6	4	0.54
Hypercholesterolemia, %	42	51	53	52	0.32
Smoking status (current/quit/never), %	12/6/83	9/4/87	6/5/89	7/5/88	0.78
Drinking status (current/quit/never), %	22/5/73	18/2/81	19/1/80	19/4/77	0.62
Postmenopausal, %	100	100	100	100	1.00

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

borderline significance for a WHtR in the fourth quartile, except among men aged 70 years or older. Additional analyses showed that the risks markedly increased, particularly in the upper level of the fourth WHtR quartile, among men aged 50 to 69 years and women aged 70 years and older. These results suggest the presence of a threshold rather than a dose-response relation for WHtR, although the present sample was too small to confirm this hypothesis. Additionally, we think that cut-offs should be set in relation to age and sex. On the basis of our results, we propose the following cut-offs (which do not include men aged 70 years or older): 0.560 for men aged 50 to 69 years, 0.569 for women aged 50 to 69 years, and 0.647 for women aged 70 years or older.

The risk of CVD among men aged 50 to 69 years, and women aged 70 years, in the upper level of the highest quartile was significantly elevated even after adjustment for hypertension, hyperlipidemia, and diabetes. We believe that there are 2 possible explanations for this finding. First, an extremely high WHtR might actually be an independent risk factor ie, separate from classical cardiometabolic risks. It has been reported that abdominal obesity is related to increased levels of plasminogen activator inhibitor-1, which can lead to blood coagulation.[20] Such background mechanisms might be important. Second, our findings could be due to insufficient adjustment for confounders in the Cox regression model. Irrespective of the reason, men aged 50 to 69 years, and women aged 70 years or older, with extremely high WHtRs have a considerably higher risk for CVD and should be closely monitored.

We previously investigated the association between WC and CVD risk without age stratification[21] and found a significant association between WC and the risks of CVD and stroke among women but no significant association among men. However, the present age-stratified analysis of WC suggests that our previous results were substantially influenced by age. Therefore, we compared WHtR and WC in relation to CVD in analysis stratified by age group and found that the HRs associated with the highest quartile of WHtR were higher than those associated with WC among middle-aged men and that the predictive value of WHtR was greater than that of WC. Several previous studies reported similar results[12,22–24]; therefore our findings are consistent with those

Table 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4070	3069	3879	3842	
CVD, no. of cases	28	31	32	47	
HRs	1	1.14 (0.68–1.90)	1.23 (0.74–2.05)	1.82 (1.13–2.92)	0.01
CHD, no. of cases	10	16	16	23	
HRs	1	1.57 (0.71–3.47)	1.72 (0.77–3.80)	2.42 (1.15–5.12)	0.02
Stroke, no. of cases	18	15	16	24	
HRs	1	0.91 (0.46–1.81)	0.95 (0.48–1.87)	1.56 (0.84–2.89)	0.16
Ischemic stroke, no. of cases	10	9	15	18	
HRs	1	0.99 (0.40–2.43)	1.59 (0.71–3.56)	2.06 (0.94–4.49)	0.04
Age ≥70 years					
Person-years	1055	1128	1193	1155	
CVD, no. of cases	21	29	27	30	
HRs	1	1.36 (0.77–2.39)	1.09 (0.62–1.93)	1.36 (0.78–2.38)	0.45
CHD, no. of cases	13	11	10	15	
HRs	1	0.87 (0.39–1.97)	0.63 (0.28–1.45)	1.09 (0.52–2.30)	0.99
Stroke, no. of cases	8	18	17	15	
HRs	1	2.09 (0.90–4.81)	1.79 (0.77–4.15)	1.84 (0.78–4.35)	0.29
Ischemic stroke, no. of cases	4	12	10	11	
HRs	1	2.84 (0.91–8.83)	2.22 (0.69–7.07)	2.71 (0.86–8.53)	0.18
Women					
Age 50–69 years					
Person-years	4811	4863	4477	4470	
CVD, no. of cases	16	18	21	33	
HRs	1	1.09 (0.56–2.14)	1.32 (0.69–2.54)	1.80 (0.98–3.32)	0.04
CHD, no. of cases	9	4	4	13	
HRs	1	0.47 (0.14–1.51)	0.47 (0.14–1.54)	1.35 (0.56–3.22)	0.43
Stroke, no. of cases	7	14	17	20	
HRs	1	1.85 (0.75–4.60)	2.35 (0.97–5.70)	2.43 (1.01–5.85)	0.04
Ischemic stroke, no. of cases	3	7	9	10	
HRs	1	2.09 (0.54–8.10)	2.78 (0.75–10.33)	2.35 (0.63–8.77)	0.22
Age ≥70 years					
Person-years	1095	1259	1164	1094	
CVD, no. of cases	15	15	13	24	
HRs	1	1.00 (0.48–2.08)	0.91 (0.43–1.93)	1.83 (0.95–3.53)	0.08
CHD, no. of cases	6	7	5	9	
HRs	1	1.23 (0.40–3.77)	0.98 (0.29–3.32)	1.78 (0.62–5.14)	0.34
Stroke, no. of cases	9	8	8	15	
HRs	1	0.85 (0.32–2.23)	0.88 (0.34–2.29)	1.92 (0.83–4.45)	0.11
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.83 (0.22–3.16)	0.77 (0.21–2.91)	1.99 (0.66–6.04)	0.21

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WHtR, waist-to-height ratio; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

of previous studies. In contrast, WHtR and WC had similar predictive values for CVD among women in the present study. Many previous studies found that WHtR was similar to WC in predicting CVD risk among women.[12,22,24–26] The effect of dividing WC by height might be limited because the correlation of WC with height is weaker among women than among men. Consequently, we believe that WHtR is a better predictor than WC, particularly among middle-aged men.

The superiority of WHtR might be explained by the fact that WHtR, as measured by computed tomography, was more closely correlated than WC with intra-abdominal fat,[27] and a previous study reported that intra-abdominal fat was positively associated with number of cardiometabolic risk factors.[28] In addition, shorter adults tend to have more cardiometabolic risk factors than do taller individuals with a similar WC.[29] This suggests that WHtR, ie, dividing WC by height, is more strongly related than WC to cardiometabolic risk factors. Thus, we believe that WHtR better reflects the accumulation of cardiometabolic risks and leads to superior prediction of CVD.

BMI, along with indices of central obesity, has been an important obesity index in predicting CVD incidence,[30] although a meta-analysis reported that the predictive power of WHtR for CVD was higher than that of BMI.[7] Another report found a significant association between BMI and CVD after adjustment for WHtR[12] and suggested that WHtR and BMI are independently associated with CVD risk. Therefore, it might be better to use both BMI and WHtR to assess obesity.

Table 4. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WC: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4078	4004	3872	3806	
CVD, no. of cases	32	33	29	44	
HRs	1	1.07 (0.66–1.75)	0.97 (0.58–1.61)	1.63 (1.03–2.59)	0.06
CHD, no. of cases	13	17	12	23	
HRs	1	1.28 (0.62–2.63)	0.96 (0.44–2.12)	2.02 (1.02–4.02)	0.07
Stroke, no. of cases	19	16	17	21	
HRs	1	0.97 (0.50–1.88)	0.96 (0.49–1.86)	1.43 (0.76–2.67)	0.31
Ischemic stroke, no. of cases	13	9	13	17	
HRs	1	0.80 (0.34–1.87)	1.07 (0.49–2.31)	1.64 (0.79–3.41)	0.15
Age ≥70 years					
Person-years	999	1208	1200	1124	
CVD, no. of cases	25	28	27	27	
HRs	1	0.94 (0.55–1.62)	0.91 (0.53–1.58)	1.06 (0.61–1.84)	0.87
CHD, no. of cases	14	11	12	12	
HRs	1	0.67 (0.30–1.47)	0.65 (0.30–1.43)	0.82 (0.38–1.78)	0.60
Stroke, no. of cases	11	17	15	15	
HRs	1	1.29 (0.60–2.77)	1.21 (0.55–2.66)	1.36 (0.62–2.99)	0.52
Ischemic stroke, no. of cases	5	10	10	12	
HRs	1	1.70 (0.58–4.98)	1.82 (0.62–5.37)	2.26 (0.79–6.47)	0.14
Women					
Age 50–69 years					
Person-years	4669	4685	5046	4221	
CVD, no. of cases	15	18	25	30	
HRs	1	1.19 (0.60–2.36)	1.43 (0.75–2.71)	1.87 (1.00–3.51)	0.04
CHD, no. of cases	7	5	5	13	
HRs	1	0.74 (0.24–2.34)	0.65 (0.21–2.08)	1.86 (0.73–4.72)	0.18
Stroke, no. of cases	8	13	20	17	
HRs	1	1.56 (0.65–3.77)	2.06 (0.90–4.70)	1.93 (0.82–4.54)	0.11
Ischemic stroke, no. of cases	4	6	9	10	
HRs	1	1.44 (0.41–5.10)	1.70 (0.52–5.54)	2.00 (0.62–6.52)	0.23
Age ≥70 years					
Person-years	1175	1234	1046	1157	
CVD, no. of cases	16	16	15	20	
HRs	1	1.05 (0.52–2.11)	1.11 (0.54–2.25)	1.45 (0.74–2.83)	0.28
CHD, no. of cases	8	6	7	6	
HRs	1	0.85 (0.29–2.49)	1.21 (0.43–3.43)	0.88 (0.30–2.59)	0.98
Stroke, no. of cases	8	10	8	14	
HRs	1	1.24 (0.49–3.14)	1.10 (0.41–2.93)	2.00 (0.83–4.87)	0.15
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.85 (0.23–3.21)	0.93 (0.25–3.47)	1.86 (0.61–5.61)	0.24

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WC, waist circumference; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

Our study has several limitations. First, the number of cases of CVD among participants aged 30 to 49 years was insufficient for statistical analysis. Further study is required to confirm an association between WHtR and CVD risk among younger adults. Second, the effect of visceral fat could not be estimated because we did not use computed tomography to measure abdominal fat distribution. Third, changes in WHtR during the follow-up period were not considered in the present study. Finally, because WC was measured once, the estimated risks might have been underestimated because of regression dilution bias.[31]

In conclusion, the present findings suggest that WHtR is useful in identifying middle-aged Japanese at higher risk of CVD and is more predictable than WC in determining CVD risk, especially among men. In addition, the data indicate that WHtR cut-off points should be set according to sex and age. This study enrolled a limited Japanese population, and further studies with larger and more ethnically diverse samples are required to confirm our findings.

ONLINE ONLY MATERIALS

eTable 1. Baseline characteristics and CVD incidence among men and women aged 30–49 years according to quartile of waist-to-height ratio: the Suita Study, Japan.

eTable 2. Multivariable-adjusted hazard ratios for cardiovascular disease in the upper and lower fourth quartile of WHtR according to sex and age group: the Suita Study, Japan.

eTable 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: the Suita Study, Japan.
Abstract in Japanese.

ACKNOWLEDGMENTS

The present study was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-5), a grant-in-aid from the Ministry of Health, Labour and Welfare (H23-Seishu-005), and a grant-in-aid for scientific research (C) from the Japan Society for the Promotion of Science (no. 24590837). We are sincerely grateful to the members of the Suita Medical Foundation and the Suita City Health Center. We also thank all researchers and co-medical staff at the Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, for their excellent medical examinations and follow-up surveys. Finally, we thank the Satsuki-Junyukai, the society members of the Suita Study.

Conflicts of interest: None declared.

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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

Received November 6, 2012; accepted July 22, 2013.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.002424/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.002424**

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

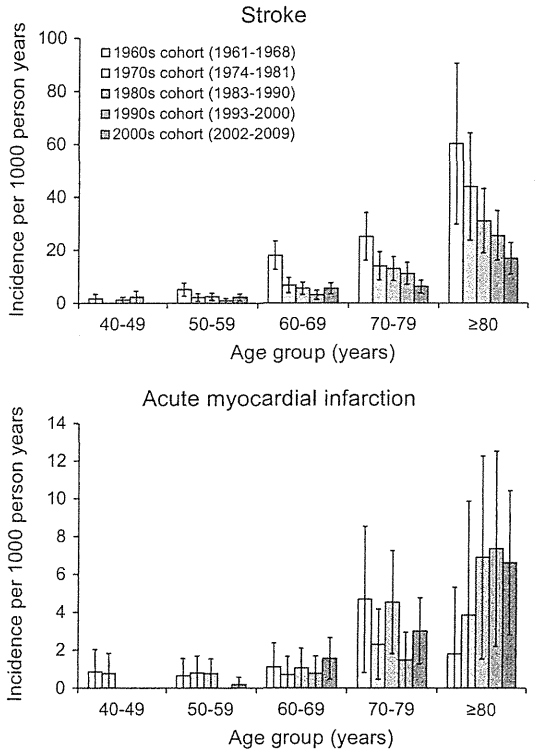

Figure 1. Age-specific incidence of stroke (**top**) and acute myocardial infarction (**bottom**) with adjustment for sex, among 5 cohorts of the Hisayama Study. Bars indicate 95% confidence intervals.

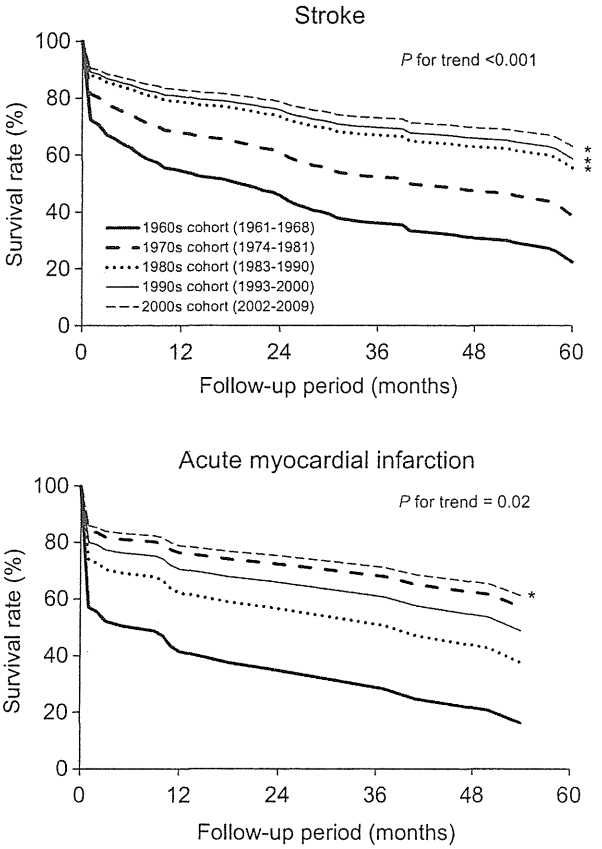

Figure 2. Age- and sex-adjusted 5-year survival curves after the onset of stroke (**top**) and acute myocardial infarction (**bottom**) among 5 cohorts of the Hisayama Study. *P<0.05 compared with 1960s cohort (after Bonferroni correction for multiple comparisons).

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.

Sources of Funding

This study was supported in part by Grants-in-Aid for Scientific Research on Innovative Areas (22116010) and for Scientific Research (A, 25253048 and 22240073; B, 25293428; and C, 23590797, 23590798, 23500842, 24590797, 24590796, and 25460758) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by Health and Labor Sciences Research Grants of the Ministry of Health, Labor and Welfare of Japan (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H22-Junkankitou [Seishuu]-Ippan-005, H23-Junkankitou [Seishuu]-Ippan-005, H25-Junkankitou [Seishuu]-Ippan-005, H25-Junkankitou [Seishuu]-Ippan-009, and H25-Junkankitou [Seishuu]-Sitei-022; and Comprehensive Research on Dementia: H25-Ninchisho-Ippan-004).

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 mmHg 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.

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.

Received January 7, 2013; final revision received February 28, 2013; accepted March 19, 2013.

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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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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.000704**

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

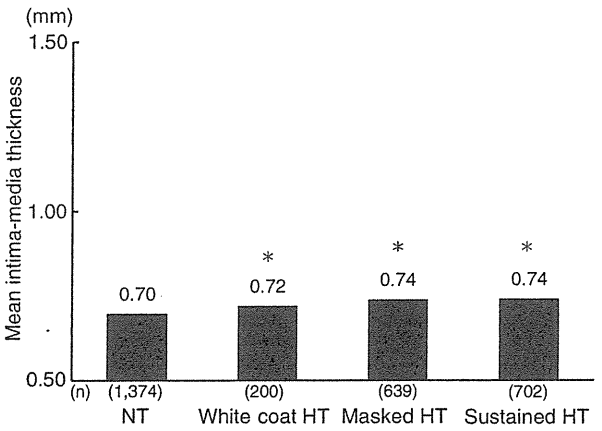

Figure 1. Multivariable-adjusted geometric average of mean intima-media thickness, according to blood pressure category. HT indicates hypertension; and NT, normotension. *P<0.001 vs normotension. Results were adjusted for age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol,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

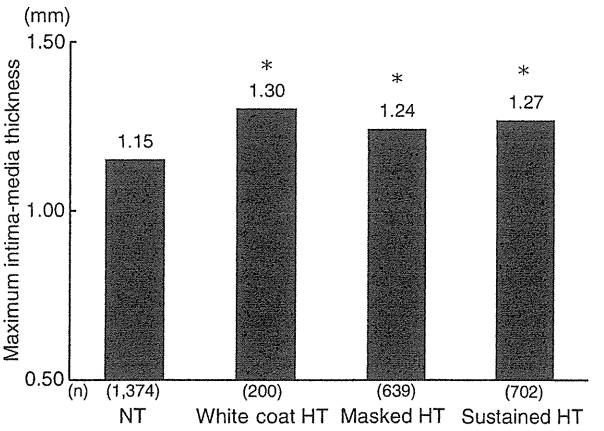

Figure 2. Multivariable-adjusted geometric average of maximum intima-media thickness, according to blood pressure category. HT indicates hypertension; and NT, normotension. *P<0.001 vs normotension. Results were adjusted for age, sex, diabetes mellitus, total cholesterol, high-density lipoprotein–cholesterol, 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]

Sources of Funding

This study was supported in part by grants-in-aid for Scientific Research on Innovative Areas (22116010) and for Scientific Research (C; 22590892, 23590797, 23590798, 23500842, 24590797, and 24590796) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and by Health and Labor Sciences Research Grants of the Ministry of Health, Labor and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004; Comprehensive Research on LifeStyle-Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H22-Junkankitou [Seishuu]-Ippan-005, H22-Junkankitou [Seishuu]-Ippan-017, H23-Junkankitou [Seishuu]-Ippan-002, and H23-Junkankitou [Seishuu]-Ippan-005; and Comprehensive Research on Dementia: H23-Ninchisho-Ippan-004).

Disclosures

None.

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