METHODS

Study population

This investigation is a part of a longitudinal observational study of HBP measurements among Ohasama residents since 1987. The socioeconomic and demographic characteristics of this region and complete details of the project are described elsewhere.[14–16] The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. Between 2000 and 2006, we contacted all 4809 individuals aged 35 years or older in four districts of Ohasama town. Those who were not at home during the normal working hours of the study nurses (n=1298) and those hospitalized (n=192) or incapacitated (n=120) were not eligible. Of the remaining 3199 residents, 2181 (68%) provided written, informed consent to participate in the HBP measurement program. We excluded 68 individuals from this analysis as their morning HBP values were the averages of <3 readings (3 days). Of the remaining 2113 individuals, 397 (19%) voluntarily participated in the screening program for diabetes mellitus, including an oral glucose-tolerance test and measurement of WC. Those treated with antidiabetic agents (n=2) were excluded from this analysis. Thus, the total number of participants statistically analyzed was 395. The 395 individuals who participated in the diabetes-screening program were significantly older, had lower systolic HBP levels and comprised a lower proportion of men than those who did not participate (n=1786).

Diabetes screening program

In the screening program for diabetes mellitus, the oral glucose-tolerance test was carried out with a 75-g glucose-equivalent carbohydrate load (Trelan G; Ajinomoto Pharma Co., Ltd, Tokyo, Japan) after the fasting blood samples had been taken. WC was measured at the umbilical level by trained public-health nurses. Individuals were asked to breathe out gently at the time of the measurement, and the tape was held firmly in a horizontal position. Hip circumference was measured over the widest part of the gluteal region. WHR was calculated as WC in centimeters divided by hip circumference in centimeters.

Blood pressure measurements

HBP was measured using the semi-automatic HEM-747IC-N (Omron Healthcare Co., Ltd, Kyoto, Japan), a device based on the cuff-oscillometric method that generates a digital display of both systolic and diastolic BP values.[17] Physicians and public health nurses instructed the participants on how to use the device and record HBP results. The participants then measured their own BP once in the morning, in the sitting position within 1 h after awaking, and after ⩾2 min of rest and recorded such measurements for 4 weeks. Those on antihypertensive drugs measured their BP before taking medication. Although many participants measured their HBP twice or more per occasion, we used the first value from each measurement in our analysis to exclude individual selection bias.[18] HBP was defined as the mean of all measurements.

The CBP measurements were taken twice consecutively using an automatic device (HEM-907, Omron Healthcare Co. Ltd.) in the morning before the oral glucose-tolerance test after at least 2 min of rest. The average of two consecutive readings from each individual was used as CBP.

The HBP and CBP measuring devices used in this study have been validated[17,19] and meet the criteria established by the Association for the Advancement of Medical Instrumentation.[20]

Categorization of participants according to blood pressure

Participants were classified into four groups on the basis of their HBP and CBP values: sustained normotension (CBP: systolic BP<140 mm Hg and diastolic BP<90 mm Hg; HBP: systolic BP<135 mm Hg and diastolic BP<85 mm Hg); white-coat hypertension (CBP: systolic BP⩾140 mm Hg and/or diastolic BP⩾90 mm Hg; HBP: systolic BP<135 mm Hg and diastolic BP<85 mm Hg); masked hypertension (CBP: systolic BP<140 mm Hg and diastolic BP<90 mm Hg; HBP: systolic BP⩾135 mm Hg and/or diastolic BP⩾85 mm Hg); and sustained hypertension (CBP: systolic BP⩾140 mm Hg and/or diastolic BP⩾90 mm Hg; HBP: systolic BP⩾135 mm Hg and/or diastolic BP⩾85 mm Hg). The cut-off values were derived from several guidelines.[21–23] In this analysis, those with sustained normotension included untreated individuals with sustained normotension and treated individuals with controlled sustained normotension. The white-coat hypertension group included treated individuals with uncontrolled BP only when this was measured in the medical setting. Similarly, the masked hypertension group included those with 'masked uncontrolled hypertension,' which would represent uncontrolled BP 'masked' by the use of CBP measurement alone. These concepts are consistent with those used in earlier studies[7,8] and are based on earlier reports showing that an insufficient duration of action for antihypertensive drugs represents an important factor in causing higher HBP or ambulatory BP values compared with CBP.[24] As reported earlier, the prevalence of masked hypertension was significantly higher among men than among women (25% in men, 12% in women, P<0.01), whereas that of white coat hypertension was significantly higher among women than among men (11 and 19% in men and women, respectively, P=0.04).[14]

Statistical analysis

The homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated using the following formula: HOMA-IR=fasting plasma-glucose (mg per 100 ml)×fasting plasma-insulin (μg per 100 ml)/405. Metabolic risk factors, obesity-related anthropometric indices and other characteristics among the four groups were compared using analysis of variance or Fisher's exact test. Analysis of covariance was used to adjust for between-group differences in obesity-related anthropometric indices. The odds ratios (ORs) for masked hypertension were examined using the logistic regression model. The following anthropometric criteria were used for the analysis: WC, criteria of the Japanese metabolic syndrome,[25] International Diabetes Federation metabolic syndrome[26] or Ohasama;[14] BMI, criteria of the Japan Society for the Study of Obesity;[27] and WHR, criteria of the World Health Organization.[28]

All data are expressed as mean ± s.d. unless otherwise stated. Statistical significance was established at P<0.05 (two-tailed). All statistical calculations were carried out using the SAS system (version 9.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

The characteristics of participants classified under the four groups are shown in Table 1. Those with sustained hypertension were significantly older than those with sustained normotension. The mean HOMA-IR was significantly higher in individuals with sustained hypertension (1.92 ± 2.67) than in those with sustained normotension (1.21 ± 0.78).

Table 2 shows the means of obesity-related anthropometric indices among the four hypertensive subgroups. The mean WC, BMI and WHR were significantly higher in individuals with masked hypertension and sustained hypertension than in those with sustained normotension. The mean WC in men was significantly higher in individuals with masked hypertension (87.3 ± 9.9) than in those with sustained normotension (81.0 ± 7.9) and those with white-coat hypertension (79.3 ± 6.2), whereas the mean WC in women was significantly higher in individuals with sustained hypertension (79.5 ± 8.5) than in those with sustained normotension (75.0 ± 8.5). The mean BMI in men was significantly higher in individuals with masked hypertension (25.5 ± 3.2) than in those with sustained normotension (23.1 ± 3.0) and those with white-coat hypertension (21.8 ± 1.9), whereas the mean BMI in women was significantly higher in individuals with sustained hypertension (24.7 ± 3.3) and those with white-coat hypertension (24.3 ± 3.0) than in those with sustained normotension (22.7 ± 2.9). The mean WHR in each sex did not differ significantly among the four groups. Similar results were obtained after adjustment of these anthropometric indices by confounding factors (data not shown).

Table 3 shows the adjusted ORs per certain-value increase in obesity-related anthropometric indices for the presence of masked hypertension. Higher WC, BMI and WHR were significantly

Table 1 Characteristics of the study subjects

	SNBP (n=188, 48%)	*WCHT (n=67, 17%)*	*MHT (n=61, 15%)*	*SHT (n=79, 20%)*	P
Men (%)	21.3	19.4	47.5	45.6	<0.001
Age (years)	61.7±9.3	63.7±6.6	64.0±8.6	67.2±8.9*	<0.001
Height (cm)	153.8±7.9	152.4±7.8	155.6±10.1	154.1±9.3	0.2
Weight (cm)	54.1±9.2	55.3±8.2	59.9±13.2*	58.8±11.0*	<0.001
Hip circumference (cm)	91.7±6.1	92.8±6.4	94.1±5.8*	94.2±6.0*	0.005
Triglyceride (mg per 100 ml)	87.7±45.9	112.9±79.8*	101.4±51.3	112.1±72.9*	0.003
Uric acid (mg per 100 ml)	4.7±1.2	4.8±1.3	5.3±1.6*	5.1±1.5	0.01
Fasting plasma glucose (mg per 100 ml)	92.1±9.4	95.7±10.5	94.1±9.4	99.1±13.6*,‡	<0.001
Fasting plasma insulin (μU per 100 ml)	5.3±3.4	6.0±3.6	5.6±4.3	7.6±10.0*	0.02
HOMA-IR	1.21±0.78	1.43±0.94	1.34±1.11	1.92±2.67*	0.004
Smoking habit (%)	9.6	6.0	23.0	12.8	0.01
Drinking habit (%)	37.8	25.4	50.8	49.4	0.007
Antihypertensive drugs (%)	11.2	29.9	37.7	51.9	<0.001
Antihyperlipidemic drugs (%)	3.7	4.5	8.2	3.8	0.5
Systolic CBP (mm Hg)	121±12	152±11*	127±10*,†	153±13*,‡	<0.001
Diastolic CBP (mm Hg)	72±9	87±10*	74±10†	86±12*,‡	<0.001
Systolic HBP (mm Hg)	117±12	123±8*	142±8*,†	147±10*,†,‡	<0.001
Diastolic HBP (mm Hg)	70±7	74±6*	83±8*,†	83±9*,†	<0.001

Abbreviations: CBP, casual-screening blood pressure; HBP, home blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance index; MHT, masked hypertension; SNBP, sustained normal blood pressure; SHT, sustained hypertension; WCHT, white coat hypertension.
$P<0.05$ compared with *SNBP, †WCHT and ‡MHT.
Values are expressed as mean±s.d. unless otherwise stated.

Table 2 Obesity-related anthropometric indices among four hypertensive subgroups

	SNBP	*WCHT*	*MHT*	*SHT*	P
Waist circumference (cm)					
All participants	76.3±8.7	78.0±8.5	82.7±10.6*,†	81.7±8.9*	<0.001
Men	81.0±7.9	79.3±6.2	87.3±9.9*,†	84.5±8.8	0.007
Women	75.0±8.5	77.7±9.0	78.5±9.6	79.5±8.5*	0.008
Body mass index ($kg\,m^{-2}$)					
All participants	22.8±2.9	23.8±3.0	24.5±3.2*	24.6±3.1*	<0.001
Men	23.1±3.0	21.8±1.9	25.5±3.2*,†	24.5±2.7†	<0.001
Women	22.7±2.9	24.3±3.0*	23.5±2.9	24.7±3.3*	<0.001
Waist-to-hip ratio					
All participants	0.83±0.07	0.84±0.07	0.88±0.08*,†	0.87±0.07*	<0.001
Men	0.88±0.06	0.89±0.06	0.91±0.06	0.89±0.07	0.2
Women	0.82±0.07	0.83±0.07	0.85±0.09	0.84±0.06	0.06

Abbreviations: MHT, masked hypertension; SNBP, sustained normal blood pressure; SHT, sustained hypertension; WCHT, white coat hypertension.
$P<0.05$ compared with *SNBP and †WCHT.
Values are expressed as mean±s.d. unless otherwise stated.

associated with masked hypertension, especially in individuals with normal CBP. An analysis of these findings classified by sex indicated that the association was stronger in men than in women. The interactions between sex and anthropometric indices were significant in BMI ($P=0.02$ for model 1, and $P=0.004$ for model 2), whereas no significant interaction was observed in WC and in WHR (all $P>0.05$).

The ORs for the presence of masked hypertension related to criteria reported earlier for metabolic syndrome or obesity are shown in Table 4. Out of five anthropometric criteria examined (that is, criteria from five groups), the prevalence of masked hypertension was most likely to be present in individuals who met the Japanese Metabolic Syndrome criteria (that is, men with a WC≥85 cm and women with a WC≥90 cm). Further analyses classified by sex indicated that the ORs related to each criterion in men were substantially larger than those in women, although with wider 95% confidence intervals (data not shown).

DISCUSSION

We found that individuals with masked hypertension or sustained hypertension had significantly higher WC than individuals with sustained normotension. Increases in obesity-related anthropometric indices such as WC, BMI or WHR were associated with masked hypertension. The ORs of Japanese metabolic syndrome criteria for WC and the International Diabetes Federation metabolic syndrome criteria for WC for the presence of masked hypertension were higher than those of the other criteria.

There were sex-specific associations of WC and BMI with masked hypertension. Mean WC and BMI in men were significantly higher in individuals with masked hypertension compared with those with sustained normotension, suggesting that men with high WC or BMI should measure their HBP to diagnose masked hypertension. The higher prevalence of masked hypertension in men than in women also supports the importance of HBP measurement in detection of masked hypertension in men. Meanwhile, high WC and high BMI in women were not significantly associated with masked hypertension; high BMI in women was significantly associated with white-coat hypertension and sustained hypertension. Women with high BMI should also measure their own HBP, as Ugajin *et al.*[12] reported that white-coat hypertension was a transitional condition to sustained hypertension and suggested that white-coat hypertension carries a poor cardiovascular prognosis. However, the number of participants in this study was relatively small which resulted in wider 95% confidence intervals classified by sex. The generally lesser values of ORs in women than those in men suggest that an impact of WC or other anthropometric indices for masked hypertension might vary between sexes; further studies with larger number of participants should be needed.

Table 3 Odds ratios for the presence of masked hypertension per one standard unit increase in obesity-related anthropometric indices

	All (n=395)		*Normal CBP (n=249)*	
	Odds ratio (95% CI)	*P for interaction**	*Odds ratio (95% CI)*	*P for interaction**
Waist circumference (per 10 cm increase)				
Model 1				
All participants	1.54 (1.13–2.11)		1.80 (1.28–2.58)	
Men	1.93 (1.15–3.39)		2.33 (1.28–4.70)	
Women	1.26 (0.83–1.88)	0.2	1.52 (0.98–2.37)	0.2
Model 2				
All participants	1.67 (1.17–2.40)		1.72 (1.17–2.58)	
Men	2.71 (1.29–6.51)		2.95 (1.26–8.48)	
Women	1.34 (0.84–2.13)	0.06	1.68 (1.01–2.83)	0.4
Body mass index (per 5 kg m^{-2} increase)				
Model 1				
All participants	1.67 (1.06–2.63)		2.33 (1.40–4.00)	
Men	2.96 (1.40–6.77)		3.66 (1.55–10.1)	
Women	1.07 (0.59–1.94)	0.02	1.68 (0.86–3.33)	0.1
Model 2				
All participants	1.90 (1.11–3.27)		2.02 (1.12–3.75)	
Men	4.79 (1.70–15.6)		3.72 (1.25–13.2)	
Women	1.01 (0.50–2.01)	0.004	1.53 (0.70–3.43)	0.1
Waist-to-hip ratio (per 0.1 increase)				
Model 1				
All participants	1.63 (1.09–2.43)		1.80 (1.18–2.79)	
Men	1.84 (0.91–3.90)		2.49 (1.07–6.46)	
Women	1.40 (0.84–2.32)	0.5	1.54 (0.93–2.58)	0.3
Model 2				
All participants	1.73 (1.12–2.69)		1.80 (1.11–2.93)	
Men	2.15 (0.86–5.79)		3.22 (1.00–12.7)	
Women	1.60 (0.91–2.83)	0.4	2.11 (1.13–4.09)	0.8

Abbreviations: CBP: casual-screening blood pressure; CI: confidence interval, HOMA-IR: homeostasis model assessment-insulin resistance index.
**P* for interaction between sex and anthropometric indices on the odds ratios for the presence of masked hypertension.
Model 1: adjusted by age and sex (only in all subjects).
Model 2: adjusted by age, sex (only in all subjects), triglyceride, uric acid, HOMA-IR, drinking habit, smoking habit, antihypertensive drugs and antihyperlipidemic drugs.

Table 4 Odds ratios for the presence of masked hypertension related to metabolic syndrome or obesity criteria

	All (n=395)	*Normal CBP (n=249)*
	Odds ratio (95% CI)	*Odds ratio (95% CI)*
Waist circumference ≥85 cm in men, ≥90 cm in women (Japanese MS criteria)		
Prevalence of masked hypertension	12.0%/31.9%	18.7%/55.0%
Model 1	3.45 (1.88–6.33)	5.32 (2.59–10.9)
Model 2	3.71 (1.73–7.95)	4.46 (1.80–11.0)
Waist circumference ≥90 cm in men, ≥80 cm in women (IDF MS criteria)		
Prevalence of masked hypertension	12.7%/21.1%	19.8%/35.1%
Model 1	1.83 (1.05–3.20)	2.26 (1.23–4.15)
Model 2	2.09 (1.12–3.92)	1.92 (0.96–3.86)
Waist circumference ≥87 cm in men, ≥80 cm in women (Ohasama criteria)		
Prevalence of masked hypertension	13.0%/19.7%	19.8%/34.2%
Model 1	1.64 (0.94–2.85)	2.14 (1.17–3.89)
Model 2	1.76 (0.94–3.32)	1.70 (0.85–3.39)
Body mass index ≥25 kg m^{-2} (Japanese obesity criterion)		
Prevalence of masked hypertension	12.9%/20.5%	19.4%/36.5%
Model 1	1.68 (0.96–2.96)	2.16 (1.15–4.05)
Model 2	1.80 (0.95–3.41)	1.87 (0.91–3.83)
Waist-to-hip rario ≥0.9 in men, ≥0.85 in women (WHO MS criteria)		
Prevalence of masked hypertension	13.0%/19.7%	20.3%/32.6%
Model 1	1.63 (0.94–2.83)	1.85 (1.02–3.36)
Model 2	1.63 (0.90–2.95)	1.66 (0.84–3.25)

Abbreviations: CBP: casual-screening blood pressure; CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance index; IDF: International Diabetes Federation; MS: metabolic syndrome; WHO: World Health Organization.
Model 1: adjusted by age and sex (only body mass index criterion).
Model 2: adjusted by age, sex (only body mass index criterion), triglyceride, uric acid, HOMA-IR, drinking habit, smoking habit, antihypertensive drugs and antihyperlipidemic drugs.
Prevalence of masked hypertension represents the percentage of subjects without/with fulfilling each of five anthropometric criteria.

Smoking habit was approximately threefold higher in masked hypertension as compared with sustained normotension or white-coat hypertension. Smoking was an independent predictor of the magnitude of the difference between CBP and HBP in our earlier study.[29] The lower BP observed in smokers is suggested to be only a transient decline in the BP as a result of abstinence from a short-time 'off smoking' before the measurement of BP.[30] Accordingly, the smoker might show a comparably high BP in the daily measurement at home. Mikkelsen *et al.*[31] also showed that smoking seems to diminish the screening daytime difference. Physicians might need to pay special attention to smoking habits in individuals to avoid their masked hypertension, as well as to reduce their CVD risks directly.

The anthropometric indices that would be most applicable to the detection of masked hypertension remain uncertain. In a meta-regression analysis of prospective studies, de Koning *et al.*[32] reported that WHR and WC were significantly associated with the risk of CVD events, although they could not determine which indices had a stronger predictive power. Vazquez *et al.*[5] also reported that BMI, WC and WHR had consistently strong associations with the incidence of diabetes, but did not determine the priority of these indices. Further research is needed to clarify which anthropometric index would be the most applicable to diagnose masked hypertension.

In 2005, eight Japanese scientific associations collaborated to define metabolic syndrome for the Japanese population;[25] however, many arguments remain, particularly in terms of the higher cutoff value of WC for women than for men.[33–38] In this study, WC cutoff values of the Japanese metabolic syndrome criteria (≥85 cm in men, ≥90 cm in women) had the highest detective power for masked hypertension among five anthropometric indices used. We had earlier proposed optimal cutoff values of WC (≥87 cm in men, ≥80 cm in women; Ohasama criteria for WC) for a diagnosis of metabolic syndrome by receiver operating characteristic analysis.[14] In the earlier report, we used a lower HBP cutoff point (systolic ≥125 mm Hg or diastolic ≥80 mm Hg) compared with this study that represents hypertension on the basis of HBP (systolic ≥135 mm Hg or diastolic ≥85 mm Hg). Furthermore, the number of selected individuals using the Japanese metabolic syndrome criteria (n=19) was lower than that using the Ohasama criteria (n=61); accordingly, comparably high-risk individuals were selected using the Japanese metabolic syndrome criteria, resulting in a discrepancy between the two studies. Although masked hypertension and metabolic syndrome are different disease states, further prospective studies are needed to investigate the appropriate criteria of WC to identify high-risk patients.

This study showed a close association of masked hypertension with high WC as well as high BMI, which are important risk factors for metabolic syndrome. We had earlier reported that elevated HBP levels were significantly associated with a clustering of metabolic risk factors.[14] HBP has a stronger predictive power for CVD mortality and morbidity than CBP.[16,39,40] HBP values improve the accuracy of screening for hypertension and for assessing BP control during treatment, and encourage drug compliance.[40] Although CBP-based metabolic syndrome is useful for detecting CVD risk,[3–5] it is reasonable to assume that risk assessment on the basis of HBP might be a more effective tool than that based on CBP.

The study cohort was significantly older, had lower systolic HBP levels and comprised a lower proportion of men than non-participants. Those with sufficient time and health concerns might have been more likely to voluntarily participate. Moreover, diabetes is screened on weekdays, which might lead to a lower proportion of men participating. We included age and gender in the logistic regression models as major confounding factors. However, the possibility of selection bias needs to be considered when generalizing the present findings.

In conclusion, men with high WC or BMI should measure their HBP to detect masked hypertension and women with high BMI should also measure their HBP to predict future sustained hypertension. Furthermore, early-stage, non-pharmacologic intervention, such as lifestyle modification, might be useful for these individuals. HBP measurements should be taken in abdominally obese people because of their high probability of masked or sustained hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Detection of silent cerebrovascular lesions in individuals with 'masked' and 'white-coat' hypertension by home blood pressure measurement: the Ohasama study

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Objective To investigate the risk of silent cerebrovascular lesions in individuals with masked hypertension (MHT) and white-coat hypertension.

Methods Self-measured home blood pressure (HBP) and casual blood pressure (CBP) measurements were recorded in 1060 individuals at least 55 years of age (mean age, 66.3 years) in a general population of Ohasama, Japan. The relationships between silent cerebrovascular lesions (white matter hyperintensity and lacunar infarct) detected on MRI and four blood pressure groups [sustained normal blood pressure (SNBP), HBP <135/85 mmHg, CBP <140/90 mmHg; white-coat hypertension, HBP <135/85 mmHg, CBP ≥140/90 mmHg; MHT, HBP ≥135/85 mmHg, CBP <140/90 mmHg; sustained hypertension, HBP ≥135/85 mmHg, CBP ≥140/90 mmHg] were examined using multivariate analysis adjusted for possible confounding factors.

Results The odds ratios of sustained hypertension (1.74, 95% confidence interval 1.18–2.57) and MHT (2.31, 95% confidence interval 1.32–4.04) for the presence of silent cerebrovascular lesions were significantly higher than the odds ratio of SNBP, whereas there was no significant difference between white-coat hypertension and SNBP (1.03, 95% confidence interval 0.75–1.41). The odds ratios for the presence of either lacunar infarct or white matter hyperintensity in the four groups were similar to those for silent cerebrovascular lesions.

Conclusion The present study is the first to demonstrate that the risk of silent cerebrovascular lesions is higher with MHT than with SNBP and similar to that of sustained hypertension. *J Hypertens* 27:1049–1055 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: general population, home blood pressure, masked hypertension, silent cerebrovascular lesions, white-coat hypertension

Abbreviations: ABP, ambulatory blood pressure; BP, blood pressure; CBP, casual blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HBP, home blood pressure; MHT, masked hypertension; OR, odds ratio; SBP, systolic blood pressure; SCLs, silent cerebrovascular lesions; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; WMH, white matter hyperintensity

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Introduction

The measurement of blood pressure (BP) outside medical settings has identified a subgroup of individuals with white-coat hypertension (WCHT) [1], who have persistently elevated casual blood pressure (CBP) but normal home blood pressure (HBP) or ambulatory blood pressure (ABP), and a subgroup of individuals with masked hypertension (MHT) [2], who have normal CBP but elevated HBP or ABP. Several studies have confirmed the existence of WCHT, but controversy remains as to whether WCHT is a benign condition [3–6] or is linked to an increased risk of target organ damage and a worse prognosis [7–11]. With respect to MHT, some data support the hypothesis that individuals with MHT may have a worse prognosis [5,6,12,13].

Silent cerebrovascular lesions (SCLs), seen as white matter hyperintensity (WMH) and lacunar infarcts, are frequently observed on MRI scans of elderly individuals. SCLs constitute an independent predictor of the risk of

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symptomatic stroke [14,15] and are associated with cognitive impairment or dementia [16]. Hypertension is a major risk factor for SCLs [17,18].

However, there have been no data on the risk of SCLs in patients with MHT. With respect to WCHT, only two studies have reported that the risk of SCLs in the WCHT group as determined by ABP was not significantly different from that in the sustained normal blood pressure (SNBP) group, but it was significantly less than that in the sustained hypertension (SHT) group [4,19,20]. However, no studies have investigated the risk of SCLs in individuals with WCHT as determined by HBP. ABP monitoring is expensive and usually impractical for most patients. Therefore, it could be worthwhile to examine whether the risk of SCLs in WCHT determined by HBP is similar to that determined by ABP. The objective of this study was to compare the risk of SCLs in individuals from the general Japanese population with WCHT, MHT, SNBP, and SHT using HBP.

Methods

Design

This study was a part of the Ohasama study, an HBP measurement project. The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere [21].

Study population

The details of the selection of study participants have been described previously [22]. In 1998, the total population of Ohasama was 7202. Of these inhabitants, 3077 were 55 years of age or above. Individuals who were hospitalized, mentally ill, or bedridden were excluded from the study ($n = 185$). Individuals who worked outside the town were also excluded ($n = 492$), as our project included ABP measurements, and public health nurses needed to visit the participants to attach a device for ABP monitoring on workdays. Of the remaining 2400 eligible individuals, 1060 (44.2%, mean age 66.3 ± 5.9 years, 67.5% women) gave their informed consent, measured their HBP, completed MRI examinations, and provided details of their medical histories and cardiovascular risk factors.

Silent cerebrovascular lesions

The evaluation of SCLs using MRI has been reported elsewhere [22]. SCLs were defined as WMH of grade 1 or more, presence of lacunar infarcts, or any combination of these findings.

Blood pressure measurements

HBP was measured with the HEM701C (Omron Healthcare Co. Ltd., Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric method [23], which generates a digital display of both systolic blood pressure (SBP) and diastolic blood pressure (DBP). The standard arm cuff was used for HBP measurement; almost all participants had an arm circumference between 22 and 34 cm [21].

Physicians or public health nurses or both instructed participants about how to take HBP measurements. Participants were asked to measure their BP every morning within 1 h of waking, in the sitting position, after more than a 2-min interval of rest, and to record the results over a 4-week period. Participants on antihypertensive drugs measured their BP before taking their medication. During a 4-week period, participants were also asked to measure their BPs once in the evening just before going to bed. Participants were allowed to measure their own BP two or more times and were asked to record all measurements on the worksheet on each occasion, although only the first measurement value on each occasion was used for averaging and evaluation of HBP, in order to exclude selection bias by the participants [24]. The mean (± SD) number of total HBP measurements was 48.9 ± 11.4 (morning, 24.7 ± 5.7; evening, 24.2 ± 6.3).

At the time of MRI examination, a physician measured the CBP twice consecutively with the participant sitting after a minimum 2-min rest interval using a mercury sphygmomanometer or an automatic device (HEM907, Omron Healthcare Co. Ltd., Kyoto, Japan). CBP measurements were taken during the daytime from 10:00 to 13:00 or from 14:00 to 16:00 h. The average of the two readings was defined as the CBP.

Both the HBP measuring device and the CBP measuring device used in the present study were validated previously [23,25] and met the criteria of the Association for the Advancement of Medical Instrumentation [26].

Participant categorization based on blood pressure levels

Participants were classified into four groups on the basis of their HBP and CBP levels: SNBP, with systolic CBP of less than 140 mmHg and diastolic CBP of less than 90 mmHg, and systolic HBP of less than 135 mmHg and diastolic HBP of less than 85 mmHg; WCHT, with systolic CBP of at least 140 mmHg or diastolic CBP of at least 90 mmHg or both, and systolic HBP of less than 135 mmHg and diastolic HBP of less than 85 mmHg; MHT, with systolic CBP of less than 140 mmHg and diastolic CBP of less than 90 mmHg, and systolic HBP of at least 135 mmHg or diastolic HBP of at least 85 mmHg or both; and SHT, with systolic CBP of at least 140 mmHg or diastolic CBP of at least 90 mmHg or both, and systolic HBP of at least 135 mmHg or diastolic HBP of at least 85 mmHg or both. Cut-off values were derived from several guidelines [27–30]. The average of all HBP values measured in the morning and the evening was first used for the classification. Then, the average of the HBP

values measured in the morning and the evening, respectively, was used in the additional analysis. In the present analysis, the SNBP group included untreated individuals with 'SNBP' and treated individuals with 'controlled SNBP'. The WCHT group included untreated individuals with 'WCHT' and treated individuals with uncontrolled BP status only in medical settings. Similarly, the MHT group included untreated individuals without previous evidence of high BP in the medical setting and treated patients with 'masked uncontrolled hypertension', which would represent uncontrolled BP status 'masked' by the use of CBP measurement alone. The SHT group included untreated individuals with 'SHT' and treated individuals with uncontrolled BP status in both home and medical settings. These concepts are consistent with those used in previous studies [12,13,31] and are based on previous reports showing that an insufficient duration of action of antihypertensive drugs represents an important factor in causing higher HBP or ABP compared with CBP [32].

Biochemical examinations

A nonfasting blood sample was drawn to measure serum levels of total cholesterol (TC), glucose, and glycosylated hemoglobin (HbA_{1c}). Participants were asked whether they smoked, drank, used medication for hypertension, hypercholesterolemia, or diabetes mellitus, and had a history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus. Hypercholesterolemia was defined as a TC of at least 220 mg/dl, the use of medication for hypercholesterolemia, a history of hypercholesterolemia, or all three. Diabetes mellitus was defined as a fasting glucose level of at least 126 mg/dl, a nonfasting glucose level of at least 200 mg/dl, an HbA_{1c} level of at least 6.5%, the use of medication for diabetes, a history of diabetes mellitus, or all five.

Data analysis

The SCL indices, WMH and lacunar infarcts, were compared among the four groups using the χ^2 test. A logistic regression model was used to adjust for between-group differences in cardiovascular risk factors. Furthermore, a multiple logistic regression model was used to investigate factors associated with MHT among participants whose CBP was lower than 140/90 mmHg. Associations between SCL indices and cardiovascular risk factors were examined using logistic regression analysis, in which cardiovascular risk factors were introduced as independent variables. SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina, USA) was used for all statistical analyses, and a two-tailed P value of less than 0.05 was considered statistically significant.

Results

Silent cerebrovascular lesions in the four groups

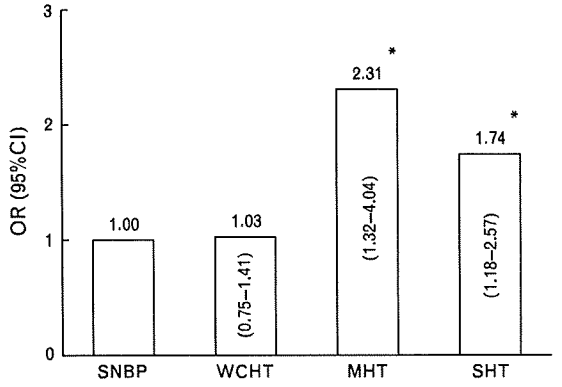
With respect to the proportion of risk factors that were present, individuals with MHT were similar to those with SHT, whereas individuals with WCHT had characteristics similar to those with SNBP (Table 1). When the average of two HBP values measured once in the morning and in the evening on the first day was used for classification (the same number of measurements as CBP), the

Table 1 Population characteristics classified by threshold of blood pressure normality by measurement method

	SNBP	WCHT	MHT	SHT	*P*
Number of individuals, *n* (%)	456 (53)	312 (29)	90 (9)	202 (19)	
Men, %	26	31	52	41	<0.0001
Age, year	66 ± 6	66 ± 6	70 ± 6	67 ± 7	<0.0001
BMI, kg/m^2	23 ± 3	24 ± 3	24 ± 3	25 ± 3	<0.0001
Blood pressure, mmHg					
Home					
All					
Systolic	116 ± 10	122 ± 8	140 ± 7	143 ± 9	<0.0001
Diastolic	70 ± 7	73 ± 7	83 ± 8	83 ± 7	<0.0001
Morning					
Systolic	118 ± 11	125 ± 10	142 ± 9	146 ± 10	<0.0001
Diastolic	71 ± 7	75 ± 7	85 ± 8	85 ± 8	<0.0001
Evening					
Systolic	115 ± 10	120 ± 10	137 ± 8	141 ± 10	<0.0001
Diastolic	69 ± 7	71 ± 7	82 ± 8	81 ± 7	<0.0001
Casual					
Systolic	124 ± 10	154 ± 13	130 ± 9	161 ± 18	<0.0001
Diastolic	72 ± 8	82 ± 10	75 ± 9	86 ± 12	<0.0001
Smoker, %	14	18	35	26	<0.0001
Drinker, %	25	27	26	36	0.045
Antihypertensive medication, %	23	39	71	63	<0.0001
Hypercholesterolemia, %	34	39	27	42	0.051
Diabetes, %	14	14	23	16	0.13
Atrial fibrillation, %	3	2	3	3	0.77
Cardiovascular disease, %	9	14	14	18	0.009
Silent cerebral lesions, %	42	46	74	62	<0.0001
WMH, %	36	40	63	57	<0.0001
Lacunar infarcts, %	20	22	53	38	<0.0001

BMI, body mass index; MHT, masked hypertension; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; WMH, white matter hyperintensity.

Fig. 1



Odds ratios and 95% confidence intervals for the presence of silent cerebrovascular lesions in the four groups classified by blood pressure threshold. Adjusted for age, sex, BMI, smoking status, drinking status, antihypertensive medication, and history of cardiovascular disease, atrial fibrillation, hypercholesterolemia, or diabetes. CI, confidence interval; MHT, masked hypertension; OR, odds ratio; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension. *$P < 0.05$ vs. SNBP.

proportion of treated patients in the MHT group decreased from 71.1 to 56.4%, whereas the proportions of treated patients in the SNBP, WCHT, and SHT groups were similar (21.2, 38.4, and 57.2%, respectively).

The adjusted odds ratios (ORs) for the presence of SCLs were significantly higher for SHT (Fig. 1). In all four groups, the adjusted ORs for either WMH or lacunar infarcts were similar to those observed for SCLs (Fig. 2).

Use of antihypertensive medication did not significantly interact with any of the above results (all P for interaction >0.2) [SCLs of untreated participants: WCHT vs. SNBP, OR 1.09, 95% confidence interval (CI) 0.74–1.62; MHT vs. SNBP, OR 1.89, 95% CI 0.78–4.57; SHT vs. SNBP, OR 2.08, 95% CI 1.18–3.67; SCLs of treated participants: WCHT vs. SNBP, OR 0.87, 95% CI 0.50–1.51; MHT vs. SNBP, OR 2.12, 95% CI 0.97–4.63; SHT vs. SNBP, OR 1.39, 95% CI 0.78–2.45].

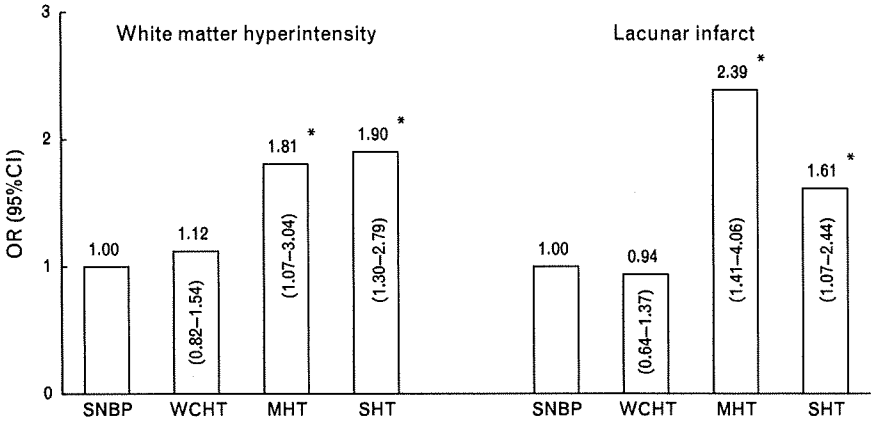
Similar trends were observed when the four groups were classified on the basis of the average of HBP values measured either in the morning or in the evening (data not shown). When the average of two HBP values measured once in the morning and once in the evening on the first day was used, a lesser trend was observed for the difference in the risk of SCLs among the four groups (data not shown).

Compared with the SNBP group, the MHT group was characterized by male gender ($P < 0.0001$) and obesity ($P = 0.003$), habitual smoking ($P < 0.0001$), higher HBP and CBP ($P \leq 0.0001$), presence of renal dysfunction ($P = 0.0507$), and the use of antihypertensive drugs ($P < 0.0001$). In the logistic regression analysis that was further adjusted for these factors, the OR for the risk of SCLs with MHT compared with SNBP was 2.31 (95% CI 1.32–4.04).

Risk factors associated with silent cerebrovascular lesions

Independent associations between cardiovascular risk factors and the presence of SCLs are presented in Table 2. Overall, the significant determinants for the

Fig. 2



Odds ratios and 95% confidence intervals for the presence of white matter hyperintensities and lacunar infarcts in the four groups classified by blood pressure threshold. Adjusted for age, sex, BMI, smoking status, drinking status, antihypertensive medication, and history of cardiovascular disease, atrial fibrillation, hypercholesterolemia, or diabetes. CI, confidence interval; MHT, masked hypertension; OR, odds ratio; SHT, sustained hypertension; SNBP, sustained normal blood pressure; WCHT, white-coat hypertension. *$P < 0.05$ vs. SNBP.

Table 2 Odds ratios and 95% confidence intervals for silent cerebral lesions associated with cardiovascular risk factors ($n=1060$)

	OR	95% CI	*P*
Sex (male : female)	1.08	0.71–1.64	0.73
Age (per 10-year increase)	2.71	2.11–3.49	<0.0001
BMI (≥25 kg/m^2 : <25 kg/m^2)	0.76	0.56–1.02	0.066
Home SBP (per 10 mmHg increase)	1.18	1.05–1.34	0.0057
Casual SBP (per 10 mmHg increase)	0.98	0.91–1.05	0.56
Smoker (smokers : nonsmokers)	0.99	0.64–1.54	0.97
Drinker (drinkers : nondrinkers)	1.08	0.74–1.58	0.69
Antihypertensive medication (treated : untreated)	2.02	1.51–2.72	<0.0001
Hypercholesterolemia (present : absent)	1.05	0.79–1.40	0.72
Diabetes (present : absent)	1.06	0.73–1.52	0.78
Atrial fibrillation (present : absent)	1.04	0.41–2.63	0.93
CVD (present : absent)	1.31	0.84–2.04	0.24

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; SBP, systolic blood pressure.

presence of SCLs were older age, higher home SBP values, and the use of antihypertensive medication. Casual SBP was not a significant determinant for the presence of SCLs when home SBP was simultaneously included in the same regression model (Table 2). When home and casual DBP were entered into this model instead of SBP, home DBP was also a significant determinant of the presence of SCLs [OR per 10 mmHg increase in DBP: home DBP, 1.51 (95% CI 1.24–1.84), $P<0.0001$; casual DBP, 0.94 (95% CI 0.81–1.08), $P=0.38$].

Associations between cardiovascular risk factors and the presence of WMH or lacunar infarcts, respectively, were similar to the associations between cardiovascular risk factors and the presence of SCLs (Tables 3 and 4). Results were similar to those described above when HBP was defined on the basis of the averages of either the morning or evening values (data not shown). Furthermore, the average of two HBP values measured once in the morning and once in the evening on the first day, which includes the same number of measurements as CBP, had a stronger relationship with SCLs than CBP

Table 3 Odds ratios and 95% confidence intervals for white matter hyperintensity associated with cardiovascular risk factors ($n=1060$)

	OR	95% CI	*P*
Sex (male : female)	0.95	0.62–1.44	0.80
Age (per 10-year increase)	2.63	2.04–3.37	<0.0001
BMI (≥25 kg/m^2 : <25 kg/m^2)	0.85	0.64–1.14	0.29
Home SBP (per 10 mmHg increase)	1.18	1.05–1.33	0.0055
Casual SBP (per 10 mmHg increase)	1.00	0.93–1.08	0.96
Smoker (smokers : nonsmokers)	1.09	0.70–1.70	0.69
Drinker (drinkers : nondrinkers)	0.91	0.63–1.34	0.65
Antihypertensive medication (treated : untreated)	1.78	1.33–2.37	0.0001
Hypercholesterolemia (present : absent)	0.97	0.73–1.29	0.83
Diabetes (present : absent)	1.10	0.77–1.58	0.61
Atrial fibrillation (present : absent)	1.02	0.42–2.47	0.96
CVD (present : absent)	1.14	0.74–1.76	0.55

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; SBP, systolic blood pressure.

Table 4 Odds ratios and 95% confidence intervals for lacunar infarcts associated with cardiovascular risk factors ($n=1060$)

	OR	95% CI	*P*
Sex (male : female)	1.52	0.97–2.38	0.069
Age (per 10-year increase)	2.74	2.07–3.61	<0.0001
BMI (≥25 kg/m^2 : <25 kg/m^2)	0.84	0.60–1.17	0.31
Home SBP (per 10 mmHg increase)	1.20	1.05–1.37	0.0063
Casual SBP (per 10 mmHg increase)	0.96	0.88–1.04	0.32
Smoker (smokers : nonsmokers)	0.84	0.53–1.35	0.47
Drinker (drinkers : nondrinkers)	1.24	0.81–1.89	0.32
Antihypertensive medication (treated : untreated)	2.08	1.51–2.87	<0.0001
Hypercholesterolemia (present : absent)	1.02	0.73–1.41	0.93
Diabetes (present : absent)	1.02	0.69–1.52	0.93
Atrial fibrillation (present : absent)	1.43	0.59–3.46	0.43
CVD (present : absent)	1.46	0.93–2.29	0.097

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; SBP, systolic blood pressure.

values, although the OR per 10 mmHg increase in HBP value decreased (data not shown).

Discussion

Using HBP measurement, a specific group of individuals with MHT was identified in the current population of relatively older Japanese individuals. In previous studies, the degree of hypertensive target organ damage was significantly higher in individuals with MHT than in those with SNBP and similar to that in individuals with SHT [31,33–37]. SCLs, such as WMH and lacunar infarcts, are also evidence of hypertensive target organ damage. The present study is the first to demonstrate that the risk of SCLs was higher with MHT than with SNBP and similar to that with SHT.

In the present study, the MHT group included both treated patients with good clinic BP control but poor BP control outside the clinic and untreated individuals without previous evidence of high BP in the medical setting. These two conditions (treated MHT and untreated MHT) might have different pathophysiologies. Untreated MHT has been reported to be associated with older age and smoking [38]. On the contrary, in the present study, a large proportion of treated MHT patients was included. The explanation for this is attributable to when the BPs were measured and when antihypertensive drugs were taken [38]. Early morning, before taking antihypertensive drugs, is the time that the effect of antihypertensive medication is minimum, whereas later in the morning is the time that the effect of this medication would be maximum. Thus, HBP measurement in the morning would provide a higher value than the CBP. Another possibility is that individuals who are being treated medically might be accustomed to medical settings and exhibit a lower BP increase in a medical setting than those who are not undergoing treatment. It is clinically very important that treated MHT patients constitute a large proportion of MHT patients. Such patients have masked uncontrolled hypertension, in that

their poor BP control could continue to be masked without HBP measurement.

It is well known that hypertensive patients with uncontrolled BP have a higher cardiovascular risk and greater organ damage as well as more white matter lesions [39–41]. However, in the present study, there was no difference between treated and untreated participants in terms of the principal study result. However, the higher risk was greater for treated patients, although the heterogeneity was not significant ($P > 0.2$). These results suggest that independent of antihypertensive treatment, high HBP, even with normal CBP, is associated with a risk of SCLs.

In the present study, the risk for SCLs was lower in WCHT patients than in SHT and MHT ones and equal to that in SNBP individuals. Similar results with respect to the risk for SCLs with WCHT as determined by ABP were obtained in the three previous studies [4,19,20]. However, some long-term studies have shown that WCHT is not a benign condition [8–11]. Thus, the risk for SCLs in WCHT patients might increase over the long term. Therefore, WCHT remains a condition that warrants careful follow-up.

The difference in the number of BP measurements might be associated with the risk of the four groups. Therefore, a sensitivity analysis according to the number of HBP measurements was performed. In the present study, CBP was defined as the average of two measurements; thus, the average of the first two HBP values was used. The results showed a less marked tendency in the difference in the risk of SCLs among the four groups. These results were consistent with our previous results that showed that the number of BP measurements was also important [42]. It is possible that office BP measured many times may have a predictive value equivalent to that of HBP [43], although it is generally difficult to obtain multiple office BP measurements under usual clinical settings.

The possibility of selection bias needs to be considered when generalizing the present findings, as the participation rate of the study participants was only 44.2%. In addition, marked differences exist in the epidemiology of cardiovascular disease between Japan and the United States or European countries. Thus, further research on other ethnic and cultural populations is needed to confirm the generalizability of the present study's findings.

CBP measurements alone may not identify individuals with MHT and WCHT, but HBP measurements can be used to identify such individuals. Further prospective studies dealing with the associations between SCLs and MHT or WCHT are necessary. Given the present study's findings, HBP measurement has the potential to become a valuable tool for predicting SCLs.

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See REVIEWER COMMENTARY page 1134

Influence of Alcohol Intake on Circadian Blood Pressure Variation in Japanese Men: The Ohasama Study

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BACKGROUND

Both a large habitual alcohol intake and a pattern of circadian blood pressure (BP) variation characterized by a high morning/daytime BP have been reported to be risk factors for cerebral hemorrhage. Therefore, the association between these two factors was examined.

METHODS

A total of 194 men in the general population of Ohasama underwent ambulatory BP measurement, completed a lifestyle questionnaire, and were classified into three categories according to current alcohol consumption: nondrinkers, light drinkers, and heavy drinkers. Two-hour moving averages of BP (2h-BP) were used to compare BP variation during a 24-h period among the drinking categories. 2h-BP Dif (defined as 2h-BP 2 h after waking minus 2h-BP 2 h before waking) and the percentage decline in nocturnal BP were also assessed as indicators of circadian BP variation. Multivariate analysis was conducted after adjustment for possible confounding factors including daily salt intake.

RESULTS

Analysis of 2h-BP revealed that BP variation in drinkers had specific characteristics: a rapid BP increase before waking and higher morning BP levels ($P = 0.0001$). 2h-BP Dif was significantly higher in heavy drinkers than in nondrinkers ($P = 0.04$), while there was no significant association between drinking status and the magnitude of the nocturnal BP decline.

CONCLUSION

Habitual alcohol intake was associated with a higher 2h-BP Dif.

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Several prospective studies have reported that heavy alcohol intake increases the risk of stroke, especially hemorrhagic stroke.[1–4] Moreover, we previously demonstrated that a high morning/daytime blood pressure (BP) was associated with an increased risk of cerebral hemorrhage.[5,6] Therefore, circadian BP variation may be associated with alcohol intake.

A previous experimental study demonstrated that repeated alcohol intake causes biphasic changes in BP, decreasing BP for several hours after alcohol intake and increasing it from 6 h after the last drink.[7] Another experimental study reported that restriction of alcohol intake reduced daytime BP but not nighttime BP.[8] However, as these studies were conducted in hospitalized hypertensive patients, the generalizability of these findings to subjects in the general population has not been established.

Recently, Ohira *et al.*[9] reported that habitual alcohol intake was positively associated with higher daytime BP and a large morning BP surge among middle-aged Japanese men in four communities with heterogeneous characteristics. However, as these studies were conducted in hospitalized hypertensive patients, the generalizability of their findings to populations including treated hypertensive patients was also unclear. Furthermore, although alcohol intake is known to be associated with dietary factors related to BP, such as salt intake, they did not adjust for any dietary factors.

Therefore, in this study, the relationship between habitual alcohol intake and circadian BP variation was investigated in a general male Japanese population that included treated patients, after adjustment for dietary salt intake.

METHODS

Design. This cross-sectional investigation was part of the Ohasama study, a community-based project to measure ambulatory BP. The socioeconomic and demographic characteristics of this region and the full details of the project have been described

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elsewhere.[5,6,10,11] The institutional review board of Tohoku University School of Medicine and the Department of Health of the Ohasama Town Government approved the study protocol.

Data collection. Individual information about habitual alcohol intake, smoking consumption, antihypertensive medication, and history of stroke, heart disease, diabetes mellitus, and hypercholesterolemia was obtained from a standardized, self-administered questionnaire. These data were confirmed by participant interviews with trained public health nurses at a health check-up, as well as by the medical records kept at the Ohasama Hospital.

The question on habitual alcohol intake was worded, "Do you drink alcoholic beverages?," and the subjects were asked to themselves choose one of three options to describe their drinking status: current drinker, former drinker, or life-long abstainer (nondrinker).

Current drinkers reported their frequency of consumption as one of four categories: almost daily, 3–4 days/week, 1–2 days/week, and <1 day/week. Furthermore, they were asked about beverage type usually consumed (sake, spirits, beer, whiskey, wine, or others) and amount per occasion; this information was recorded as "5 go or more," "4 go," "3 go," "2 go," "1 go," or "less than 1 go" (a go is a traditional Japanese unit containing 22.8 g of ethanol). One go is equal to ~180 ml of sake, and it corresponds to two measures of spirits (50 ml), one bottle (633 ml) of beer, two single shots (75 ml) of whiskey, or two glasses of wine (200 ml). The amount of ethanol per day was calculated as follows: the amount consumed per occasion multiplied by the frequency of alcohol consumption per week divided by seven. This self-reporting of alcohol consumption has been previously validated, as evidenced by a high correlation with objective data from liver function tests.[12]

For the assessment of smoking status, the questionnaire first asked whether subjects were current, ex-, or never smokers; the subjects themselves chose the answers. Current smokers were further asked about the average number of cigarettes smoked per day. The subjects were then classified into four categories: "heavy smokers (≥20 cigarettes per day)," "moderate smokers (<20 cigarettes per day)," "exsmokers," and "never smokers."

Hypertension was defined as a 24-h average ambulatory BP ≥130 mm Hg systolic or 80 mm Hg diastolic or the use of antihypertensive drugs.[13,14]

Hypercholesterolemia was defined as total cholesterol ≥5.68 mmol/l (220 mg/dl), use of medication for hypercholesterolemia, based on the Japan Atherosclerosis Society guidelines,[15] and/or a history of hypercholesterolemia. Diabetes mellitus was defined as a random blood glucose level ≥11.11 mmol/l (200 mg/dl), HbA_{1c} level ≥6.5%, use of medication for diabetes, according to the criteria of the Japan Diabetes Society,[16] and/or a history of diabetes mellitus.

A standardized methodology was used to calculate dietary salt intake (NaCl) from data obtained in a Japanese version of a food-frequency questionnaire. The reproducibility and validity of this questionnaire were previously reported in detail.[17,18]

Study population. In 1998, the total population of Ohasama was 7,202, of which 3,077 were ≥55 years of age. Individuals (n = 492) who were not at home during the normal working hours of the study nurses, and those who were hospitalized, mentally ill, or bedridden (n = 185) were not eligible for inclusion. Of the remaining 2,400 eligible individuals, 705 (29%) provided written informed consent to participate in the ambulatory BP monitoring study. In total, 26 subjects whose ambulatory BP was not adequately measured were excluded. In this study, women (n = 450) were excluded because of the small number of drinkers in this group. Individuals who did not respond to the questionnaire about lifestyle and health (n = 19), as well as former drinkers, because their health was likely to be poor (n = 16), were also excluded. Therefore, the study population consisted of 194 men. These subjects were then classified into three categories according to calculated daily alcohol consumption: nondrinkers, light drinkers (consuming <22.8 g/day of alcohol), and heavy drinkers (consuming ≥22.8 g/day of alcohol) (ref. 19).

Ambulatory BP monitoring and devices. Ambulatory BP monitoring was performed using the ABPM-630 (Nippon Colin, Komaki, Japan), a fully automatic device that utilizes the cuff-oscillometric method to measure BP and heart rate (HR). This was preset to measure BP and HR every 30 min. The device was attached by well-trained public health nurses who visited the participants' homes on a weekday morning and detached the device the next morning. Participants were asked to report their daily activities, including the time they went to bed and the time they got up. Artifactual measurements during recordings were defined according to previously described criteria[20] and were omitted from the analysis.

The averages of four systolic BP (SBP) readings obtained every 30 min during each consecutive 2-h period (moving averages) were defined as the "2h-SBPs."[6] When any readings were omitted due to artifactual measurements, the remaining readings (minimum of one) obtained during the 2 h were used for the calculations. The 2-h diastolic moving averages (2h-DBPs) and 2-h HR moving averages (2h-HRs) were defined in the same manner as the 2h-SBPs.

Calculation of the 2h-BP difference and the nocturnal decline in BP. The amplitude of the 2h-BP difference (2h-BP Dif) in SBP was calculated as follows:

$$\text{2h-BP Dif in SBP} = (\text{2h-SBP 2h after waking}) - (\text{2h-SBP 2h before waking})$$

The percentage decline in nocturnal SBP was calculated as follows:[21]

$$\text{Nocturnal decline in SBP} = (\text{daytime SBP} - \text{night-time SBP}) \times 100/\text{daytime SBP}$$

The 2h-BP difference in DBP and the percentage decline in nocturnal DBP were calculated in the same manner.

Statistical analysis. Analysis of variance and the χ^2-test were used for comparisons among the three groups. The associations between habitual alcohol intake and adjusted mean values of ambulatory BP, 2h-BP, 2h-BP Dif, and nocturnal decline were estimated using analysis of covariance and adjusted for age, smoking, obesity (body mass index ≥25 kg/m^2) (ref. 22), use of antihypertensive drugs, a history of diabetes mellitus, hypercholesterolemia, heart disease, stroke, and dietary salt intake. Tukey's multiple comparison test was carried out on continuous variables in the analysis of variance or analysis of covariance. 2h-BP Dif and nocturnal decline were further adjusted for 24-h average ambulatory SBP. Two-hour moving averages were examined by a mixed linear model with confounding factors as the fixed effect and subject as the random effect.

A two-tailed *P* value <0.05 was taken to indicate statistical significance. A two-tailed *P* value <0.002 (0.05 divided by 24) was also taken to indicate statistical significance when the Bonferroni correction was applied, because each 2h-BP and each 2h-HR was calculated 24 times. Statistical analysis was performed using the SAS package (version 9.1; SAS Institute, Cary, NC).

RESULTS

Characteristics

Table 1 shows the subjects' characteristics. As alcohol intake increased, mean age decreased, while the proportion of obese subjects increased. None of the study subjects were exsmokers. Daytime SBP, 24-h and daytime DBP, and 24-h and night-time HR levels rose with increasing alcohol intake. After adjustment for possible confounding factors, only night-time HR was significantly associated with alcohol intake (**Table 2**).

Table 1 | Population characteristics classified by alcohol consumption status

	Nondrinkers	Light drinkers	Heavy drinkers	*P*[a]
Number of subjects	43	86	65	
Age, years	69±7	67±6	66±5*	0.02
BMI ≥25 kg/m^2, %	26	26	42	0.08
Ambulatory BP				
24-h				
Systolic, mm Hg	126±14	128±12	131±11	0.13
Diastolic, mm Hg	73±7	75±7	77±6*	0.01
Heart rate, bpm	65±7	66±7	68±8	0.05
Daytime				
Systolic, mm Hg	130±14	133±13	136±12*	0.04
Diastolic, mm Hg	77±8	79±7	81±7*	0.01
Heart rate, bpm	70±8	71±8	73±9	0.15
Night time				
Systolic, mm Hg	118±14	119±14	120±12	0.78
Diastolic, mm Hg	67±8	69±8	69±7	0.20
Heart rate, bpm	57±7	58±7*	61±8*	0.01
Smoking[b]				0.21
Never smoker, %	44	44	26	
Moderate smoker, %	27	25	34	
Heavy smoker, %	29	30	40	
Antihypertensive treatment, %	42	49	63	0.07
History of				
Hypertension, %	56	72	82	0.01
Hypercholesterolemia, %	21	24	20	0.79
Diabetes, %	28	21	22	0.65
Stroke, %	16	15	11	0.66
Heart diseases, %	19	19	12	0.54
Salt intake, g/day	11±8	15±11	15±9	0.07

Data are presented as means ± s.d.
BMI, body mass index; BP, blood pressure; bpm, beats per minute.
[a]Overall comparisons made by analysis of variance for continuous variables and χ^2 for categorical variables. [b]There was no exsmoker among the study subjects. *$P < 0.05$ vs. nondrinkers by Tukey's multiple comparison test in the analysis of variance.

Table 2 | Adjusted mean ambulatory blood pressures

	Non-drinkers	Light Drinkers	Heavy Drinkers	P^a
24-h				
Systolic, mm Hg	127 ± 2	128 ± 1	129 ± 1	0.52
Diastolic, mm Hg	74 ± 1	75 ± 1	76 ± 1	0.37
Heart Rate, bpm	66 ± 1	66 ± 1	68 ± 1	0.21
Daytime				
Systolic, mm Hg	131 ± 2	133 ± 1	135 ± 2	0.33
Diastolic, mm Hg	78 ± 1	79 ± 1	80 ± 1	0.30
Heart Rate, bpm	70 ± 1	71 ± 1	72 ± 1	0.55
Night time				
Systolic, mm Hg	118 ± 2	120 ± 1	119 ± 2	0.85
Diastolic, mm Hg	67 ± 1	69 ± 1	69 ± 1	0.67
Heart Rate, bpm	57 ± 1	58 ± 1	61 ± 1*	0.01

Data are presented as means ± s.e. (adjusted for age, smoking, obesity, use of antihypertensive drugs, as well as for history of diabetes mellitus, hypercholesterolemia, heart disease, stroke, and salt intake.)
[a]*P*: Overall comparisons made by analysis of covariance for continuous variables and χ^2 for categorical variables.
*$P < 0.05$ vs. nondrinkers by Tukey's multiple comparison test in the analysis of covariance.

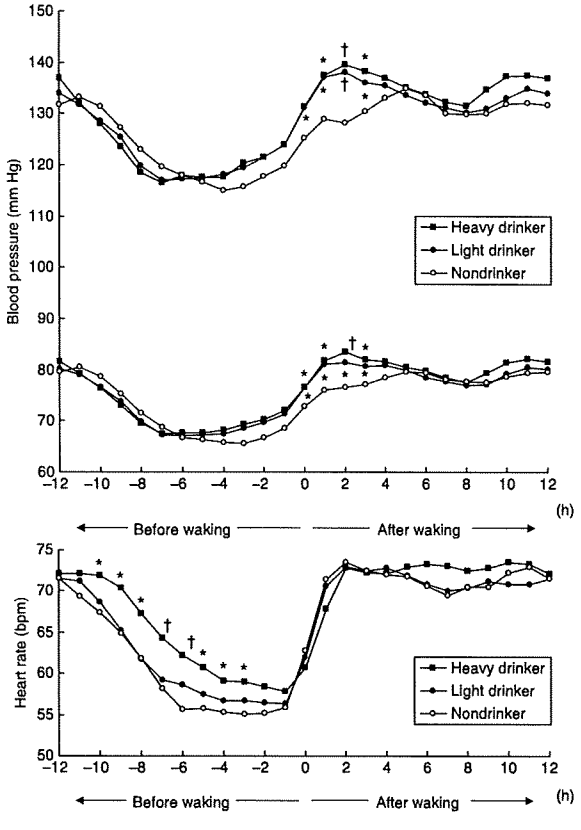

Figure 1 | Moving averages of blood pressure (BP) and heart rate (HR) by drinking status. Moving averages of BP (systolic/diastolic) and HR were adjusted for age, smoking, obesity, use of antihypertensive drugs, and history of diabetes mellitus, hypercholesterolemia, heart disease, stroke, and dietary salt intake. *$P < 0.05$ vs. nondrinkers, †$P < 0.002$ vs. nondrinkers (Bonferroni adjustment). There was a significant trend in the 2-h moving average across the categories of drinking consumption by a mixed linear model with confounding factors as the fixed effect and subject as the random effect ($P < 0.0001$).

Circadian BP variation by drinking category

As shown in **Figure 1**, morning 2h-SBP and 2h-DBP were significantly higher in light and heavy drinkers than in nondrinkers. Even after the Bonferroni adjustment for multiple assessments, 2h-SBP 2 h after waking remained significantly higher in heavy drinkers than in nondrinkers. Thus, "2h-BP Dif" was defined as (2h-BP 2 h after waking – 2h-BP 2 h before waking). The 2h-HR 6–7 h before waking, the period approximately corresponding to the time just before and after going to bed, was significantly higher in heavy drinkers than in nondrinkers after the Bonferroni adjustment, whereas this trend was not observed in light drinkers. There was a significant trend in the 2-h moving average across the categories of drinking consumption ($P < 0.0001$).

2h-BP Dif and nocturnal decline in BP

Figure 2 shows the 2h-BP Dif for SBP and DBP. The 2h-BP Dif for SBP was significantly higher in heavy drinkers than in nondrinkers (P = 0.044/0.24 for SBP/DBP). Similar trends were also observed when smokers were excluded (nondrinkers, 5.5 ± 4.1/5.2 ± 2.7 mm Hg; light drinkers, 15.9 ± 2.8/9.2 ± 1.8 mm Hg; heavy drinkers, 22.2 ± 4.5/19.0 ± 3.0 mm Hg; P for overall comparison = 0.03/0.01). The nocturnal declines in both SBP and DBP did not differ significantly among the drinking categories (nondrinkers, 9.7%; light drinkers, 10.2%; heavy drinkers, 11.7%; both P for overall comparison >0.1). The exclusion of those with a history of stroke produced similar results (data not shown).

DISCUSSION

The results of this study demonstrate that habitual alcohol intake was associated with a higher 2h-BP Dif among men in a general population, adjusting for possible confounding factors including dietary salt intake.

We previously reported that elevated morning BP levels were most closely associated with the risk of hemorrhagic

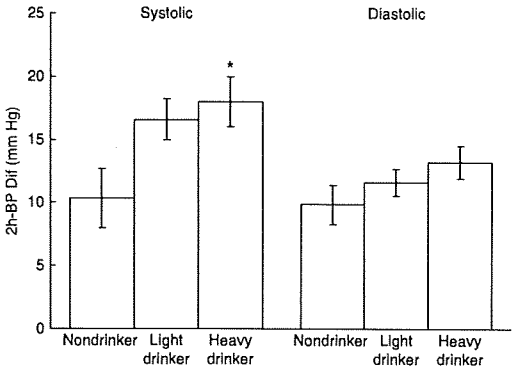

Figure 2 | Two-hour blood pressure (2h-BP) difference (Dif) by drinking status. 2h-BP Dif (systolic/diastolic) was adjusted for age, smoking, obesity, use of antihypertensive drugs, history of diabetes mellitus, hypercholesterolemia, heart disease, stroke, and dietary salt intake and 24-h average ambulatory blood pressure (mean ± s.e.). *$P < 0.05$ vs. nondrinkers by Tukey's multiple comparison test in the analysis of covariance.

stroke.[5,6] Because heavy alcohol intake is known to increase the risk of stroke, especially hemorrhagic stroke,[1–4] it is possible that a higher risk of hemorrhagic stroke in heavy drinkers is, in part, mediated by the effects of alcohol on circadian BP variation, although the present results could not show any direct evidence of this. Further prospective studies are necessary to elucidate the associations among alcohol intake, circadian BP variation, and the future risk of hemorrhagic stroke.

As shown in **Figure 1**, 2h-BPs 6–8 h before waking, the period approximately corresponding to the time just before and after going to bed, were lower in drinkers than in nondrinkers, whereas the 2h-BPs before waking were higher in drinkers. This may be a possible explanation for the fact that habitual alcohol intake was not associated with the degree of nocturnal BP decline in this study.

The prevalence of heavy smoking was 30% higher in heavy drinkers than in nondrinkers. However, when smokers were excluded, similar results were obtained. Therefore, we believe that we observed the effects of alcohol, not smoking.

The mechanisms of the pressor and depressor effects of alcohol have not been clarified. The depressor mechanism of alcohol intake is considered to be direct vasodilation, because total peripheral resistance decreases with BP reduction.[7] There are several possible explanations for the BP elevation caused by alcohol, including increased sympathetic activity and activation of the renin–angiotensin system.[23]

This study must be interpreted within the context of its potential limitations. First, as the information regarding alcohol intake on the exact day of ambulatory BP monitoring was not available, it is possible that the association between drinking status and circadian BP variation found in this study might be underestimated. Second, the influence of the type of alcoholic beverage on BP was not assessed. However, a previous study reported that the type of alcohol beverage consumed did not influence the BP increase.[24] Third, we could not estimate alcohol consumption resulting from binge drinking because the questionnaire did not ask about this. However, 92% of the drinkers who were consuming ≥45.6 g of ethanol per occasion in this study reported consuming alcohol beverages almost every day. Fourth, in **Table 2**, we show that daily BP was not associated with alcohol consumption. It is possible that the lack of difference in adjusted BP across alcohol categories might be related to the relatively small sample of this study, as several previous studies have found such an association; the difference of 4 mm Hg across drinking groups might be significant in a larger sample.[13] Fifth, this study excluded women because of the small number of drinkers among women. It remains to be investigated whether this association is present in women. Sixth, because we did not have actigraphy data, the effect of sleeping patterns could not be determined.

In conclusion, this study shows that habitual alcohol intake was associated with a higher 2h-BP Dif. Further prospective studies are necessary to elucidate the associations among alcohol intake, circadian BP variation, and the future risk of hemorrhagic stroke.

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Depressed serum selenoprotein P: possible new predicator of increased risk for cerebrovascular events

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Abstract

Selenium protection against cellular damage by oxygen radicals is accomplished through selenoproteins. Thus, selenium protection during the development of stroke, an oxidative stress–related disease, may not be appropriately reflected in the total serum selenium concentration. Therefore, we hypothesized that serum selenoproteins should also be measured to understand the relationship between selenium status and oxidative stress. To establish whether stroke is associated with changes in serum selenoprotein levels, a population-based, nested case-control study was performed. The subjects were recruited from 1632 residents older than 40 years who had completed health examinations in 1992. Blood samples collected from 30 controls and 30 initial stroke victims between 1992 and 1994 were analyzed for total serum selenium and selenium-containing protein distribution. Selenium-containing proteins were separated using 2 high-performance liquid chromatography columns in tandem and detected by inductively coupled plasma–mass spectrometry. The mean serum selenium concentration was lower in the patients who had a stroke than in the controls (105.2 vs 116.5 μg/L). Selenium contents in glutathione peroxidase and albumin did not show any significant difference; however, selenoprotein P was significantly lower in the stroke cases than in the controls (54.5 vs 63.0 μg/L, $P = .006$). Results from multivariate logistic regression analysis showed that reduced serum level of selenoprotein P was associated with a higher risk of stroke (odds ratio = 0.28; 95% confidence interval, 0.10-0.85).

Keywords: Selenoprotein P; High-performance liquid chromatography; Inductively coupled plasma–mass spectrometry; Selenium; Stroke; Cohort; Human

Abbreviations: %HDL-C, ratio of high-density lipoprotein cholesterol to total cholesterol; CI, confidence interval; GPx, glutathione peroxidase; HDL-C, high-density lipoprotein cholesterol; UGA, uracil-guanine-adenine.

1. Introduction

The role of oxidative stress in stroke has been well established [1-3]. Selenium, which is an essential component of several antioxidant enzymes, has drawn particular interest for its potential role in the prevention of oxidative stress–related diseases, including stroke [4-6]. Epidemiologic studies on the association of serum selenium concentration and the development of stroke have reported conflicting results [7,8]. It should be noted that selenium status should be monitored not only by measuring total

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selenium concentration in serum or plasma, but also by the measurement of selenoproteins [9].

There are at least 3 selenium-containing proteins in serum [10]: albumin, extracellular glutathione peroxidase (GPx), and selenoprotein P. Among these, GPx and selenoprotein P are classified as selenoproteins [11], which contain selenocysteine encoded by the uracil-guanine-adenine (UGA) triplet and involve transfer ribonucleic acid$^{[Ser]Sec}$ [12]. In albumin, selenium occurs as selenomethionine, which is biologically indistinguishable from methionine in animals and nonspecifically incorporated into proteins in place of methionine [13]. Selenium protection of cellular components from damage by oxygen radicals was reported to occur through these selenoproteins [14,15]. Therefore, to accurately investigate selenium protection in the development of stroke, we hypothesize that it is necessary to quantify levels of serum selenoproteins as well as serum selenium.

To test this hypothesis, we have developed a method for isolating selenium from serum samples [16]. The method achieves the rapid and direct chromatographic determination of serum selenium among GPx, albumin, and selenoprotein P. In the present study, we conducted a population-based, nested case-control study to establish whether the development of stroke is associated with changes in the levels of serum selenoproteins. We compared serum selenoproteins levels in patients who had a stroke with those of matched healthy controls.

2. Methods and materials

2.1. Survey site and study population

The present study was conducted in conjunction with the Ohasama study, a longitudinal cohort study that has been conducted in the town of Ohasama, Iwate Prefecture, Japan, since 1987. Ohasama is a rural community that had 8040 inhabitants in 1991. The socioeconomic and geographic characteristics of Ohasama have been described by Imai and coworkers [17] in a previous report. The most frequent cause of death among the residents was cerebrovascular disease. The rate of cerebrovascular death was 142.9 per 100 000 in 1992, and the standardized mortality ratio was 1.31 compared with the overall mortality in Japan.

From 2716 residents older than 40 years, 1632 had completed a health examination in 1992. Subjects who were taking antihypertensive medication, those who had a history of stroke, and those who had atrial fibrillation were excluded to avoid the effects of these risk factors. Subjects were also excluded if their blood pressure and high-density lipoprotein cholesterol (HDL-C) were out of the reference range. The cases and the controls in the present study were derived from the population of 1256 remaining after exclusion criteria were implemented.

All blood samples were obtained in 1992. From 1992 to December 31, 1994, 39 initial strokes (26 men and 13 women) were identified [18]. Information on cerebrovascular events was mainly obtained from the stroke registry and verified by a questionnaire distributed to each household every year and by inspection of death certificates.

The Ohasama study was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama town government. The Ethics Committee of Tohoku University School of Medicine approved the measurement of trace elements in community-based serum samples. Signed informed consent was obtained from all subjects.

2.2. Health examination

The blood pressure was measured using a USM700F sound-based blood pressure monitor (Ueda Electronic Works Co, Ltd, Tokyo, Japan), a fully automatic device that has been previously validated [19] and meets the criteria of the Association for the Advancement of Medical Instrumentation.

Each individual's body height and weight were measured, and the body mass index was calculated as the weight (in kilograms) divided by the square of the height (in meters). A supine resting electrocardiogram was taken, a blood sample was obtained using Venoject tubes (VP-P, Terumo, Tokyo, Japan), and the serum was separated by centrifugation. The total cholesterol and HDL-C were measured using an enzymatic and colorimetric method, and the ratio of HDL-C to total cholesterol (%HDL-C) was then calculated. The remaining serum was frozen at −80°C until the selenium measurements were performed.

A survey of health status was also conducted by means of interviews. The questions related to patient stroke history and medication intake associated with stroke, hypertension, coronary heart disease, and smoking and alcohol intake habits.

2.3. Definition of stroke cases and matched controls

The diagnosis of stroke was based on the occurrence of clinical signs of focal or global disturbances in cerebral function that lasted more than 24 hours or resulted in death. Computed tomographic scans or magnetic resonance images of the brain were referred to for the classification of stroke, when available (76.9%). The stroke cases were classified into 23 cases of cerebral infarction, 9 cases of cerebral hemorrhage, 6 cases of subarachnoid hemorrhage, and 1 case of undetermined type. From these 39 cases, blood samples of 9 cases were not available because they had been previously used for other purposes. The remaining 30 stroke cases (17 cases of cerebral infarction, 8 cases of cerebral hemorrhage, 4 cases of subarachnoid hemorrhage, 1 case of undetermined type) were used for data analysis. Control samples were chosen to match the sex, age (within 1 year), level of total cholesterol (within 5%), and the year of blood sampling of the stroke cases. All of the controls were alive as of December 31, 1994. The relationship between selenium status and stroke type was not examined because of the limited number of available blood samples.