cardiovascular disease than controls, while a similar but weaker trend was observed in women. The prevalence of diabetes was higher in women with coronary heart disease and total cardiovascular disease than controls and a similar but non-significant trend was observed in men. Mean values of total cholesterol was lower in women with total and hemorrhagic strokes while that of HDL-cholesterol was lower in men with ischemic stroke and in women with coronary heart disease and total cardiovascular disease than controls. The proportion of walking ≥0.5 h/day was lower in men with total stroke and total cardiovascular disease than controls. Mean values of body mass index, alcohol intake, n-3-polyunsaturated fat intake and the proportion of sports ≥3 h/week did not differ significantly between cases and controls for either sex. Median values of hs-CRP levels were higher in men with coronary heart disease than controls, and similar but weaker trend was observed in women.

Table 2 shows sex-specific age- and community-matched, as well as multivariable odds ratios (95% CIs) for mortality from cardiovascular disease according to quartiles of and 1-SD increment in log hs-CRP levels. For men, there was a dose–response relationship between hs-CRP and mortality from total stroke, coronary heart disease, and total cardiovascular disease. The adjustment for cardiovascular risk factors did not cause any material change in these associations. The multivariable odds ratios for the highest vs. lowest quartiles of hs-CRP levels in men were 1.60 (0.90–2.85)

for total stroke, 3.68 (1.02–13.3) for coronary heart disease, and 2.31 (1.49–3.59) for total cardiovascular disease. For women, there were similar but weaker associations with hs-CRP levels, showing corresponding multivariable odds ratios of 1.07 (0.58–1.97), 3.74 (0.91–15.3), and 1.69 (1.06–2.68). The findings did not change materially when men and women combined adjusting for sex. The respective multivariable odds ratios were 1.21 (0.82–1.78), 3.01 (1.38–6.57), and 1.84 (1.36–2.50).

Table 3 presents the multivariable odd ratios of total cardiovascular disease according to quartiles of and 1-SD increment in log hs-CRP levels stratified by sex, age, smoking status and median body mass index. The associations between hs-CRP levels and mortality from total cardiovascular disease did not vary significantly between men and women (p for interaction = 0.19), between the 40–64 and 65–79-year age groups (p = 0.25), between never-smokers and ever-smokers (p = 0.45) or, between for persons with body mass index <22.6 kg/m² and those with the higher body mass index (p for interaction = 0.53).

4. Discussion

Our nested case-control study performed as part of a large prospective study showed dose–response relationships between hs-CRP levels with risks of mortality from total stroke, coronary heart disease and total cardiovascular disease. These associa-

Table 3
Odds ratios of mortality from cardiovascular disease according to quartiles of serum hs-CRP levels, stratified by sex, age, smoking status and body mass index (BMI).

	Quartiles of serum hs-CRP (mg/L)				p for trend	OR for 1-SD increment of log hs-CRP	p for interaction
	1 (low)	2	3	4 (high)			
Serum hs-CRP							
Median (mg/L)	0.16	0.28	0.56	1.73			
Range (mg/L)	0.04–0.18	0.19–0.39	0.40–0.90	0.91–3.75			
Men							
No. of cases	86	94	118	186			
No. of controls	120	121	122	121			
Multivariable OR[a]	1.00	1.13 (0.72–1.75)	1.26 (0.79–1.99)	2.31 (1.49–3.59)	<0.001	1.36 (1.17–1.58)	
Women							
No. of cases	99	112	113	131			
No. of controls	114	114	112	115			
Multivariable OR[a]	1.00	1.63 (1.07–2.51)	1.42 (0.91–2.23)	1.69 (1.06–2.68)	0.17	1.17 (1.00–1.36)	0.19
Ages 40–64							
No. of cases	69	77	86	99			
No. of controls	88	82	80	85			
Multivariable OR[a]	1.00	1.10 (0.65–1.86)	1.28 (0.73–2.25)	1.38 (0.79–2.45)	0.31	1.09 (0.90–1.31)	
Ages 65–79							
No. of cases	116	129	145	218			
No. of controls	146	153	154	151			
Multivariate OR[a]	1.00	1.36 (0.93–1.99)	1.34 (0.90–1.99)	2.10 (1.43–3.10)	<0.001	1.30 (1.14–1.48)	0.25
Never-smokers							
No. of cases	113	135	144	178			
No. of controls	167	176	152	153			
Multivariable OR[a]	1.00	1.19 (0.79–1.79)	1.30 (0.82–2.06)	1.66 (1.06–2.60)	0.04	1.19 (1.02–1.40)	
Ex- and current smokers							
No. of cases	48	56	75	114			
No. of controls	52	47	66	64			
Multivariate OR[a]	1.00	0.62 (0.17–2.18)	1.31 (0.37–4.65)	1.37 (0.40–4.65)	0.40	1.42 (0.91–2.21)	0.45
BMI <22.6 kg/m²							
No. of cases	101	95	103	149			
No. of controls	141	120	102	84			
Multivariable OR[a]	1.00	1.62 (0.80–3.29)	1.60 (0.76–3.40)	3.52 (1.72–7.21)	<0.001	1.40 (1.11–1.77)	
BMI ≥22.6 kg/m²							
No. of cases	62	96	112	151			
No. of controls	82	105	120	139			
Multivariable OR[a]	1.00	1.15 (0.58–2.26)	0.95 (0.45–2.03)	1.53 (0.77–3.03)	0.17	1.33 (1.05–1.69)	0.53

[a] Adjusted for the same variables, except for stratified variables, as shown in the footnote of Table 2.

tions were primarily observed for men, and the association with mortality from total cardiovascular disease was also statistically significant for women.

Median hs-CRP levels in Japanese populations are reportedly low compared to those in Western countries [10–14]. Our study found that median hs-CRP values for control subjects were 0.38 mg/L for men and 0.41 mg/L for women, which were much lower than reported median values of 2.0–3.0 mg/L for Caucasians, Blacks and Hispanics [21,22]. Median CRP levels in the top quartile in our study (1.5–1.8 mg/L) were close to those in the bottom tertile in previous studies conducted in western countries (approximately 1.0 mg/L) [1,2]. In western populations, individuals with hs-CRP >3.0 mg/L were regarded as a high-risk group for cardiovascular disease since the risk for this group twice as high as for control [23]. A recent clinical trial has demonstrated that rosuvastatin treatment reduced hs-CRP levels by 37% and reduced the incidence of major cardiovascular disease events by 44% for non-hyperlipidemic men and women with hs-CRP ≥2.0 mg/L [24]. In our study, however, the proportion of subjects with hs-CRP >3.0 mg/L was only 10% for men and 9% for women. The respective proportion of hs-CRP 2.0 mg/L was 16 and 13%. Thus, the clinical cut-off point is racially contingent. Our study observed the 1.7- to 2.3-fold higher risk of mortality from total cardiovascular disease for men and women with hs-CRP ≥0.9 mg/L than for those with hs-CRP <0.2 mg/L. Our finding thus supports the notion of CRP-cardiovascular disease association in populations with low levels of CRP.

In spite of the low CRP levels, the magnitudes of the associations were similar to or even greater than those determined by previous meta-analyses of prospective studies in western countries, which reported a summary odds ratio (95% CI) for ischemic stroke in top-vs.-bottom quartiles of CRP levels of 1.7 (1.4–2.0) [2] and for coronary heart disease in top-vs.-bottom tertiles of 1.5 (1.3–1.7) [1].

We found that the association of hs-CRP levels with mortality from total cardiovascular disease did not vary according to sex, age, smoking status, or body mass index. Our study implies that CRP is a predictor for mortality from cardiovascular disease even when persons are lean.

The strengths of the present study were its prospective design and the comprehensive nature of the cardiovascular surveys, which allowed us to make adjustments for important potential confounding variables such as body mass index, serum lipids, smoking, ethanol intake, history of hypertension and diabetes as well as matching for age and community for examination of CRP-disease associations. The hs-CRP was measured with a standardized method with satisfactory reliability and precision, which appears to be make our findings comparable with those of other studies [19]. Furthermore, the large sample size of men and women enabled us to examine the sex-specific impact of hs-CRP on cardiovascular disease that was not achieved by previous Japanese cohort studies [9–11].

However, our study also has several potential limitations. First, approximately 35% of the total participants in population-based health examination with high participant rates had provided blood samples. There were, however, no apparent differences in age-adjusted mean values or proportions of major cardiovascular risk factors between the subjects who had and had not provided blood samples [25]. Thus, the selection bias may be small for evaluation of CRP-cardiovascular disease associations. Second, we used frozen serum to estimate hs-CRP concentrations and did not examine long-term changes in the stored serum samples. However, a previous study confirmed that serum hs-CRP levels remained stable in serum samples stored for up to 7 years at −70 °C [26]. Third, we did not have the information on administered CRP-lowering drugs such as statins [24] as well as on actual blood pressure values and glucosylated hemoglobin levels. The use of stains, however, was uncommon in 1988–1990 at the baseline surveys. Fourth, we used the mortality data, not incidence data as endpoints, which may lead to misclassification in the diagnosis of stroke and coronary heart disease. As for stroke, however, the widespread use of computed tomography scans, even in Japanese local hospitals, since the 1980s has probably made the death certificate diagnosis of stroke and its subtypes sufficiently accurate [27]. Death certificate diagnosis of coronary heart disease may be more problematic since one-fourth of the coronary heart disease deaths appearing on the death certificates were contaminated [28,29]. The associations between hs-CRP and mortality from total cardiovascular disease for both sexes were robust.

In conclusion, our study established that high hs-CRP levels were associated with increased risk of mortality from cardiovascular disease for Japanese men and women whose CRP levels are much lower than those seen in western populations.

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Association of Sleep Duration with Mortality from Cardiovascular Disease and Other Causes for Japanese Men and Women: the JACC Study

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Study Objectives: To examine sex-specific associations between sleep duration and mortality from cardiovascular disease and other causes.

Design: Cohort study.

Setting: Community-based study.

Participants: A total of 98,634 subjects (41,489 men and 57,145 women) aged 40 to 79 years from 1988 to 1990 and were followed until 2003.

Interventions: N/A.

Measurements and Results: During a median follow-up of 14.3 years, there were 1964 deaths (men and women: 1038 and 926) from stroke, 881 (508 and 373) from coronary heart disease, 4287 (2297 and 1990) from cardiovascular disease, 5465 (3432 and 2033) from cancer, and 14,540 (8548 and 5992) from all causes. Compared with a sleep duration of 7 hours, sleep duration of 4 hours or less was associated with increased mortality from coronary heart disease for women and noncardiovascular disease/noncancer and all causes in both sexes. The respective multivariable hazard ratios were 2.32 (1.19-4.50) for coronary heart disease in women, 1.49 (1.02-2.18) and 1.47 (1.01-2.15) for noncardiovascular

disease/noncancer, and 1.29 (1.02-1.64) and 1.28 (1.03-1.60) for all causes in men and women, respectively. Long sleep duration of 10 hours or longer was associated with 1.5- to 2-fold increased mortality from total and ischemic stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for men and women, compared with 7 hours of sleep in both sexes. There was no association between sleep duration and cancer mortality in either sex.

Conclusions: Both short and long sleep duration were associated with increased mortality from cardiovascular disease, noncardiovascular disease/noncancer, and all causes for both sexes, yielding a U-shaped relationship with total mortality with a nadir at 7 hours of sleep.

Keywords: Sleep duration, coronary heart disease, mortality, prospective study

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PREVIOUS COHORT STUDIES HAVE DEMONSTRATED THAT SHORT OR LONG SLEEP DURATION IS ASSOCIATED WITH THE INCIDENCE OF OR MORTALITY FROM cardiovascular disease,[1-4] as well as total mortality.[1,3-6] The National Health and Nutrition Examination Survey I showed a 1.5-fold increase in the risk of stroke for persons with more than 8 hours of sleep, compared with those with 6 to 8 hours of sleep.[1] The Nurse's Health Study also reported that, compared with 8 hours of sleep, short or long sleep duration of 5 or more hours or 9 or more hours was associated with an increased incidence of coronary heart disease for women aged 40 to 65 years,[2] and, compared with 7 hours of sleep, long sleep duration of 9 or more hours was associated with mortality from cardiovascular disease, noncardiovascular disease/noncancer, and all causes, whereas short sleep duration of 5 hours or less was associated with mortality from all causes and noncardiovascular disease for women aged 40 to 65 years.[3] The Whitehall II cohort study found a U-shaped association between sleep duration and

mortality from cardiovascular disease and noncardiovascular disease and between sleep duration and all causes for men and women aged 35 to 55 years.[4] An earlier report of our Japanese cohort study[5] also showed a U-shaped relationship between sleep duration and total mortality, but cause-specific analyses were not carried out. Thus, the association between short or long sleep duration and mortality from cardiovascular disease and other causes for Japanese men and women has remained unclear.

To examine the sex-specific associations of sleep duration and mortality from stroke, coronary heart disease, and other causes, as well as total mortality, we analyzed the extended follow-up data from a large-scale prospective study of approximately 98,000 Japanese men and women.

METHODS

Study Population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho (JACC study) was conducted from 1988 to 1990, when 110,792 subjects (46,465 men and 64,327 women) aged 40 to 79 years and living in 45 communities across Japan participated in municipal health-screening examinations and completed self-administered questionnaires, including lifestyle data and medical histories of previous cardio-

vascular disease and cancer at baseline. The details of the study procedure have been described previously.[7] In most communities, informed consent was obtained individually and directly from members of the cohort, whereas, in several communities, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders and mayors. Of the 110,792 cohort participants, data from 6782 (2613 men and 4169 women) were excluded because of missing information on sleep duration, as were data from 5376 subjects (2363 men and 3013 women) who reported a history of cancer, stroke, or coronary heart disease. Finally, a total of 41,489 men and 57,145 women were included in the study.

Mortality Surveillance

For mortality surveillance in each of the communities, investigators conducted a systematic review of death certificates, all of which had been forwarded to the public health center in the area of residency. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the *International Classification of Diseases*, 10th revision (ICD-10). Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as withdrawals from observation when they moved out. Cause-specific mortality was determined separately in terms of cancer (C00-C97), total cardiovascular disease (I01-I99), coronary heart disease (I20-I25), and total stroke (I60-I69); noncardiovascular disease/noncancer was listed as the cause of death when cardiovascular disease and cancer were excluded. Stroke deaths were further subdivided into intraparenchymal hemorrhage (I61), subarachnoid hemorrhage (I60), and ischemic stroke (I63 and I693). The follow-up is believed to be complete and accurate as a result of systematic examination of death certificates and residency status. By December 31, 2003, except for 4 communities in which follow-up was terminated at the end of 1999, 14,540 subjects were treated as withdrawals from observation when they died, and 4188 subjects were treated as withdrawals from observation when they moved out of the study community. The median follow-up period for the participants was 14.3 years. This study was approved by the ethics committees of the Nagoya University School of Medicine and the University of Tsukuba.

Baseline Survey

The baseline data were collected by means of a self-administered questionnaire, which included sleep duration; demographic characteristics; and histories of hypertension, diabetes mellitus, and other chronic diseases, as well as habits related to smoking, alcohol consumption, diet, and exercise. We obtained information about the average sleep duration on weekdays during the preceding year. The average sleep duration per day was classified into 7 categories: less than 4.5 hours (≤ 4 hours); 5, 6, 7, 8, and 9 hours; and equal to or longer than 9.5 hours (≥ 10 hours). Fractions hours were rounded off (eg, 7 hours represented responses from 6.5 to 7.4 hours). Depressive symptom

was assessed by using 4 psychological or behavior items[5]: (1) Do you think that your life is meaningful? (2) Do you think that you make decisions quickly? (3) Are you enjoying your life? (4) Do you feel that others rely very much on you? These 4 items were then combined into an overall index of depressive symptoms. Questions with positive/neutral or negative responses were scored as 0 or 1, respectively. Thus, the overall index of depressive symptoms had a possible range from 0 to 4 (Cronbach α coefficient of 0.52), and subjects were grouped according to whether they had no symptoms, 1 symptom, or 2 or more symptoms. The reproducibility and validity for dietary intake have been reported elsewhere.[8]

Statistical Analysis

Statistical analyses were based on sex-specific mortality rates of disease outcomes and all cause during the follow-up period from 1988-1990 to 2003 (to 1999 for 4 communities). The person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving out of the community, or the end of follow-up, whichever came first. Sex-specific age-adjusted mean values and prevalence of cardiovascular risk factors were calculated. The sex-specific hazard ratios with 95% confidence interval (CI) of mortality from disease outcomes and all causes were calculated with reference to the risk for 7 hours of sleep. These estimates were adjusted for age and other potential confounding factors by means of the Cox proportional hazards model. The other potential confounding factors were history of hypertension, history of diabetes, body mass index (sex-specific quintiles), smoking status (never, exsmoker, current smoker of 1-19, and current smoker of ≥ 20 cigarettes per day), alcohol consumption (nondrinker, exdrinker, current drinker of 0.1-22.9, 23.0-45.9, 46.0-68.9, and ≥ 69.0 g ethanol per day), hours of exercise (almost never and 1-2, 3-4, and ≥ 5 hours per week), hours of walking (almost never and 0.5, 0.6-0.9, and ≥ 1 hours per day), perceived mental stress (low, moderate, and high), depressive symptoms (0, 1, and ≥ 2 symptoms), education level (< 13, 13-15, 16-18, and ≥ 19 years), regular employment or not, fresh fish intake (almost never, 1 to 2 days a month, 1 to 2 days a week, 3 to 4 days a week, and almost every day). SAS (SAS, Inc., Cary, NC)(version 9.13) was used for all statistical analyses.

RESULTS

After a follow-up of 1,270,585 person-years, the deaths of 1964 (men and women: 1038 and 926) from stroke, 881 (508 and 373) from coronary heart disease, 4287 (2297 and 1990) from total cardiovascular disease, 5465 (3432 and 2033) from cancer, and 14,540 (8548 and 5992) from all causes had been documented.

Table 1 shows sex-specific age-adjusted mean values or prevalence of risk characteristics at baseline by sleep-duration category. The respective percentages of ≤ 4, 5, 6, 7, 8, 9, and ≥ 10 hours of sleep were 1%, 3%, 13%, 32%, 39%, 8%, and 4%, respectively, for men and 1%, 5%, 20%, 38%, 29%, 5%, and 2%, respectively, for women. Compared with 7 hours of sleep, short or long sleep duration tended to be associated with older age and more depressive symptoms for both men and women.

Table 1—Sex-Specific, Age-Adjusted Mean Values or Prevalence of Cardiovascular Risk Factors at Baseline by Sleep Duration

	Sleep duration, h/day						
	≤ 4	5	6	7	8	9	≥ 10
Men							
No. at risk	215	1142	5513	13423	16042	3491	1663
Age, y	60.1	58.6	56.1	55.1	57.3	60.2	64.4
BMI, kg/m²	22.3	22.7	22.9	22.6	22.6	22.4	22.5
Overweight	18.9	21.9	22.0	17.8	17.5	17.2	18.6
History of hypertension	27.0	24.8	20.4	19.4	19.9	21.5	22.9
History of diabetes	13.4	7.8	7.5	6.5	6.3	6.1	7.1
Ethanol intake, g/day	41.9	36.7	33.4	32.1	34.9	37.4	40.1
Current smoker	47.3	45.8	50.3	53.5	55.5	56.8	58.7
College or higher education	12.1	17.5	20.1	19.8	16.2	12.4	11.1
High perceived mental stress	37.9	37.7	31.4	23.6	19.3	20.3	20.8
2 or more depressive symptoms	14.5	9.2	6.1	4.5	5.2	7.3	10.0
Exercise ≥ 5 h/wk	9.5	7.5	6.8	6.7	7.2	8.8	7.8
Walking ≥ 1 h/day	42.4	45.8	46.5	49.3	51.3	53.0	51.3
Regular employment	60.7	73.1	76.7	77.8	76.6	72.9	68.8
Fresh fish intake, no./wk	6.4	6.8	6.7	6.8	7.1	7.1	7.4
Women							
No. at risk	430	2699	11668	21501	16643	2935	1269
Age, y	62.8	58.5	55.6	55.4	59.0	63.0	67.5
BMI, kg/m²	22.8	22.8	22.9	22.8	23.0	23.1	23.2
Overweight	21.0	23.1	22.4	21.5	23.6	25.2	26.7
History of hypertension	22.9	23.6	22.1	22.2	22.8	22.0	23.9
History of diabetes	2.8	5.0	3.9	3.5	3.9	4.0	4.4
Ethanol intake, g/day	12.9	13.0	10.1	9.5	11.1	12.2	13.4
Current smoker	7.8	8.5	5.7	4.7	5.3	4.9	7.9
College or higher education	9.7	11.4	11.5	10.4	9.0	7.0	7.1
High perceived mental stress	36.8	30.7	24.6	19.2	16.7	16.6	19.4
2 or more depressive symptoms	17.1	10.1	7.4	7.0	7.8	10.6	19.1
Exercise ≥ 5 h/wk	4.3	5.2	4.4	4.3	5.1	4.4	4.3
Walking ≥ 1 h/day	50.4	49.7	51.7	51.9	52.0	53.0	44.6
Regular employment	32.5	33.7	34.8	34.1	31.6	29.4	31.1
Fresh fish intake, no./wk	6.0	6.7	6.9	7.1	7.3	7.2	7.2

Data are presented as percentage, except age, body mass index (BMI), ethanol intake, and fresh fish intake, which are presented as mean.

Men and women with short sleep duration were more likely to have high perceived mental stress, whereas those with long sleep duration were less educated.

Tables 2 show sex-specific, age-adjusted, and multivariable hazard ratios of total stroke, stroke subtypes, coronary heart disease, total cardiovascular disease, cancer, noncardiovascular disease/noncancer, and all causes by sleep duration. Increased risks of age-adjusted mortality from total and ischemic strokes and total cardiovascular disease, cancer, noncardiovascular disease/noncancer, and all causes were observed among men and women with 10 or more hours of sleep, compared with those with 7 hours of sleep. These associations, except for mortality from cancer, were slightly weaker but remained statistically significant after adjustment for cardiovascular risk factors and depressive symptoms. The respective multivariable hazard ratios (95% CI) of mortality from total and ischemic strokes, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for long sleepers were 1.66 (1.31-2.08), 1.58 (1.19-2.12), 1.56 (1.33-1.83), 1.66 (1.44-1.91), and 1.41 (1.29-1.54), respectively, for men, and 1.69 (1.29-2.20), 2.37 (1.70-3.32), 1.54 (1.28-1.86), 1.99 (1.65-2.39), and 1.56 (1.40-1.75), respectively, for women.

There was an increased risk of mortality from coronary heart disease for women with 4 or fewer hours and 5 hours of sleep, compared with those with 7 hours of sleep. The respective multivariable hazard ratios (95% CI) for those with 4 or fewer hours and 5 hours of sleep were 2.32 (1.19-4.50) and 1.64 (1.07-2.53). Short sleep of 4 or fewer hours for men tended to be associated with an increased risk of mortality from hemorrhagic stroke, although this association did not reach statistical significance (hazard ratio = 2.15, 95% CI: 0.78-5.89, P = 0.14). When stratified by alcohol-consumption status, the multivariable hazard ratios of mortality from hemorrhagic stroke for male short sleepers (≤ 4 and 5 hours of sleep) were 2.03 (1.01-4.08) for current drinkers and 1.33 (0.38-4.66) for exdrinkers or never drinkers. After further adjustment for individual quantity of alcohol consumption as a continuous variable, the multivariable hazard ratio for male short sleepers was 1.92 (95% CI: 0.96-3.86, P = 0.07). Also, short sleep duration or 4 or fewer hours was associated with increased risk of mortality from noncardiovascular disease/noncancer for both men and women; the multivariable hazard ratios were 1.49 (1.02-2.18) for men and 1.47 (1.01-2.15) for women.

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Table 2—Sex-Specific Hazard Ratios and 95% Confidence Intervals for Mortality from Cardiovascular Disease and Other Causes by Sleep Duration

	≤ 4	5	6	7	8	9	≥ 10
Men							
Person-years	2501	14176	69125	173026	204761	43152	18724
Total stroke							
No.	10	28	105	244	413	126	112
Age-adjusted HR (95%CI)	1.62 (0.86-3.06)	0.95 (0.64-1.40)	0.96 (0.76-1.21)	1.00	1.15 (0.98-1.35)	1.25 (1.00-1.55)	1.90 (1.51-2.38)
Multivariable HR (95%CI)	1.56 (0.82-2.94)	0.85 (0.58-1.26)	0.95 (0.76-1.20)	1.00	1.11 (0.95-1.30)	1.14 (0.92-1.42)	1.66 (1.31-2.08)
Hemorrhagic stroke							
No.	4	11	40	82	145	31	26
Age-adjusted HR (95%CI)	2.45 (0.90-6.70)	1.29 (0.69-2.43)	1.14 (0.78-1.67)	1.00	1.30 (0.99-1.71)	1.10 (0.73-1.67)	1.73 (1.10-2.70)
Multivariable HR (95%CI)	2.15 (0.78-5.89)	1.20 (0.64-2.26)	1.13 (0.77-1.65)	1.00	1.27 (0.97-1.66)	1.01 (0.66-1.53)	1.56 (0.99-2.45)
Ischemic stroke							
No.	5	15	50	143	235	85	74
Age-adjusted HR (95%CI)	1.18 (0.48-2.87)	0.78 (0.46-1.34)	0.75 (0.55-1.04)	1.00	1.07 (0.87-1.31)	1.29 (0.98-1.69)	1.84 (1.39-2.45)
Multivariable HR (95%CI)	1.28 (0.52-3.15)	0.70 (0.41-1.20)	0.76 (0.55-1.04)	1.00	1.02 (0.83-1.26)	1.18 (0.90-1.55)	1.58 (1.19-2.12)
Coronary heart disease							
No.	1	17	53	140	206	54	37
Age-adjusted HR (95%CI)	0.31 (0.04-2.18)	1.05 (0.64-1.75)	0.86 (0.63-1.18)	1.00	1.02 (0.83-1.27)	0.99 (0.72-1.35)	1.19 (0.82-1.72)
Multivariable HR (95%CI)	0.29 (0.04-2.05)	1.02 (0.62-1.70)	0.86 (0.63-1.19)	1.00	1.02 (0.82-1.27)	0.96 (0.70-1.31)	1.12 (0.77-1.63)
Total cardiovascular disease							
No.	16	70	248	548	913	274	228
Age-adjusted HR (95%CI)	1.17 (0.71-1.92)	1.06 (0.83-1.36)	1.01 (0.87-1.18)	1.00	1.14 (1.02-1.26)	1.22 (1.05-1.41)	1.74 (1.48-2.03)
Multivariable HR (95%CI)	1.11 (0.67-1.83)	0.99 (0.77-1.27)	1.01 (0.87-1.18)	1.00	1.11 (1.00-1.24)	1.14 (0.99-1.32)	1.56 (1.33-1.83)
Cancer							
No.	26	91	413	940	1361	385	216
Age-adjusted HR (95%CI)	1.31 (0.89-1.94)	0.90 (0.72-1.12)	1.02 (0.91-1.14)	1.00	1.04 (0.96-1.13)	1.13 (1.01-1.28)	1.17 (1.00-1.35)
Multivariable HR (95%CI)	1.24 (0.84-1.83)	0.90 (0.72-1.12)	1.03 (0.92-1.16)	1.00	1.02 (0.94-1.11)	1.07 (0.95-1.21)	1.10 (0.94-1.27)
Noncardiovascular/noncancer							
No.	28	104	359	660	1040	342	286
Age-adjusted HR (95%CI)	1.76 (1.20-2.57)	1.34 (1.09-1.65)	1.23 (1.08-1.39)	1.00	1.09 (0.99-1.20)	1.30 (1.14-1.48)	1.89 (1.64-2.17)
Multivariable HR (95%CI)	1.49 (1.02-2.18)	1.20 (0.97-1.48)	1.20 (1.06-1.37)	1.00	1.06 (0.96-1.17)	1.20 (1.05-1.37)	1.66 (1.44-1.91)
All causes							
No.	70	265	1020	2148	3314	1001	730
Age-adjusted HR (95%CI)	1.42 (1.12-1.80)	1.08 (0.95-1.23)	1.08 (1.00-1.16)	1.00	1.08 (1.02-1.14)	1.21 (1.12-1.30)	1.56 (1.43-1.69)
Multivariable HR (95%CI)	1.29 (1.02-1.64)	1.02 (0.90-1.16)	1.08 (1.00-1.16)	1.00	1.06 (1.00-1.12)	1.13 (1.05-1.22)	1.41 (1.29-1.54)
Women							
Person-years	5183	34039	151458	284289	217774	37576	14801
Total stroke							
No.	12	46	125	228	339	96	80
Age-adjusted HR (95%CI)	1.15 (0.64-2.05)	1.05 (0.77-1.45)	0.95 (0.76-1.18)	1.00	1.28 (1.08-1.51)	1.35 (1.06-1.71)	1.87 (1.44-2.43)
Multivariable HR (95%CI)	1.07 (0.59-1.91)	0.99 (0.72-1.37)	0.93 (0.75-1.16)	1.00	1.24 (1.05-1.47)	1.29 (1.01-1.64)	1.69 (1.29-2.20)
Hemorrhagic stroke							
No.	3	19	54	115	142	33	13
Age-adjusted HR (95%CI)	0.74 (0.24-2.35)	1.01 (0.62-1.64)	0.84 (0.61-1.17)	1.00	1.19 (0.93-1.52)	1.16 (0.78-1.71)	0.84 (0.47-1.50)
Multivariable HR (95%CI)	0.68 (0.22-2.15)	0.93 (0.57-1.52)	0.82 (0.60-1.14)	1.00	1.17 (0.91-1.51)	1.16 (0.78-1.72)	0.78 (0.43-1.40)
Ischemic stroke							
No.	9	27	62	94	159	52	61
Age-adjusted HR (95%CI)	1.67 (0.84-3.32)	1.31 (0.86-2.02)	1.10 (0.80-1.51)	1.00	1.33 (1.03-1.72)	1.48 (1.05-2.09)	2.68 (1.92-3.73)
Multivariable HR (95%CI)	1.57 (0.79-3.13)	1.26 (0.82-1.94)	1.10 (0.79-1.51)	1.00	1.29 (1.00-1.67)	1.38 (0.98-1.95)	2.37 (1.70-3.32)
Coronary heart disease							
No.	10	28	60	83	127	45	20
Age-adjusted HR (95%CI)	2.40 (1.24-4.64)	1.68 (1.09-2.58)	1.24 (0.89-1.72)	1.00	1.27 (0.96-1.67)	1.61 (1.11-2.32)	1.16 (0.70-1.90)
Multivariable HR (95%CI)	2.32 (1.19-4.50)	1.64 (1.07-2.53)	1.23 (0.88-1.72)	1.00	1.24 (0.94-1.64)	1.52 (1.05-2.19)	1.04 (0.63-1.72)
Total cardiovascular disease							
No.	30	117	275	470	725	217	156
Age-adjusted HR (95%CI)	1.34 (0.93-1.95)	1.28 (1.04-1.56)	1.01 (0.87-1.17)	1.00	1.31 (1.16-1.47)	1.43 (1.22-1.69)	1.70 (1.41-2.04)
Multivariable HR (95%CI)	1.28 (0.88-1.86)	1.22 (1.00-1.50)	1.00 (0.86-1.16)	1.00	1.28 (1.14-1.44)	1.37 (1.17-1.62)	1.54 (1.28-1.86)
Cancer							
No.	24	113	333	672	638	156	97
Age-adjusted HR (95%CI)	1.16 (0.77-1.75)	1.10 (0.90-1.34)	0.90 (0.79-1.03)	1.00	0.97 (0.87-1.08)	1.05 (0.88-1.25)	1.28 (1.03-1.59)
Multivariable HR (95%CI)	1.14 (0.76-1.72)	1.07 (0.87-1.31)	0.90 (0.79-1.03)	1.00	0.95 (0.85-1.06)	1.01 (0.85-1.21)	1.20 (0.97-1.50)
Noncardiovascular/noncancer							
No.	29	92	314	446	676	224	161
Age-adjusted HR (95%CI)	1.56 (1.07-2.28)	1.15 (0.91-1.43)	1.35 (1.17-1.56)	1.00	1.35 (1.20-1.52)	1.72 (1.46-2.02)	2.16 (1.79-2.60)
Multivariable HR (95%CI)	1.47 (1.01-2.15)	1.07 (0.85-1.34)	1.34 (1.16-1.54)	1.00	1.33 (1.18-1.50)	1.65 (1.40-1.94)	1.99 (1.65-2.39)
All causes							
No.	83	322	949	1588	2039	597	414
Age-adjusted HR (95%CI)	1.34 (1.08-1.67)	1.17 (1.03-1.32)	1.06 (0.98-1.15)	1.00	1.18 (1.10-1.26)	1.37 (1.25-1.51)	1.70 (1.52-1.90)
Multivariable HR (95%CI)	1.28 (1.03-1.60)	1.11 (0.98-1.25)	1.05 (0.97-1.14)	1.00	1.16 (1.08-1.24)	1.32 (1.20-1.45)	1.56 (1.40-1.75)

Multivariable adjustment: age, body mass index (quintiles), history of hypertension, history of diabetes, alcohol consumption, smoking, education level, hours of exercise, hours of walking, regular employment, perceived mental stress, depressive symptoms and frequency of fresh fish intake. HR refers to hazard ratio; CI, confidence interval.

As for total cardiovascular disease for women and noncardiovascular disease and all causes for men and women, there was a U-shaped relationship between sleep duration and mortality, with a nadir at 7 hours of sleep. These associations were essentially unchanged when we excluded subjects whose events occurred within 5 years after baseline. Compared with women

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who slept for 7 hours, the multivariable hazard ratios (95% CI) of mortality from total cardiovascular disease were 1.41 (0.94-2.12) for 4 hours or less, 1.24 (0.99-1.57) for 5 hours, 1.04 (0.88-1.23) for 6 hours, 1.29 (1.13-1.47) for 8 hours, 1.35 (1.12-1.62) for 9 hours, and 1.51 (1.21-1.87) for 10 hours or longer. The respective multivariable hazard ratios of mortality from noncardiovascular disease/noncancer were 1.65 (1.08-2.52), 1.32 (1.05-1.66), 1.26 (1.09-1.45), 1.08 (0.97-1.21), 1.19 (1.03-1.39) and 1.66 (1.40-1.95), respectively, for men, and 1.43 (0.94-2.18), 1.03 (0.80-1.33), 1.35 (1.16-1.58), 1.34 (1.18-1.53), 1.58 (1.32-1.90), and 1.83 (1.48-2.26), respectively, for women. Furthermore, the respective hazard ratios of mortality from all causes were 1.27 (0.96-1.68), 1.06 0.91-1.22), 1.07 (0.98-1.17), 1.04 (0.98-1.11), 1.11 (1.01-1.21) and 1.37 (1.24-1.52) for men, and 1.26 (0.98-1.62), 1.08 (0.95-1.24), 1.04 (0.95-1.14), 1.13 (1.05-1.22), 1.27 (1.14-1.42), and 1.46 (1.29-1.67) for women.

DISCUSSION

In this large-scale prospective study of Japanese men and women aged 40 to 79 years, we confirmed that, compared with 7 hours of sleep, short sleep duration of 4 hours or less was associated with a 2-fold increase in mortality from coronary heart disease for women and a 1.5-fold increase in mortality from noncardiovascular disease/noncancer and a 1.3-fold increase in total mortality for both men and women, whereas long sleep duration (≥ 10 hours) was associated with a 1.5- to 2-fold increase in mortality from total stroke, ischemic stroke, total cardiovascular disease, noncardiovascular disease/noncancer and all causes for both men and women. There was a robust U-shaped relationship between sleep duration and mortality from all causes, with a nadir at 7 hours of sleep in both sexes, which extended the evidence of the earlier report,[5] based on the approximately 30% larger number of deaths.

To the best of our knowledge, ours is the first study to provide evidence of the association of short sleep duration with an increase in mortality from coronary heart disease for Asian women. Previous studies of Americans or Europeans support our findings. The Nurses' Health Study of 71,617 women aged 40 to 65 years reported that, compared with 8 hours of sleep, short sleep duration of 5 hours or less was associated with a 1.4-fold increase in risk of coronary heart disease.[2] The MONICA/KORA Augsburg Cohort Study of 3508 men and 3388 women aged 45 to 74 years showed that the risk of myocardial infarction was approximately 3 times higher for women with 5 or fewer hours of sleep, compared with 8 hours of sleep, but such an increase in risk was not observed for men.[9] We observed an increased mortality from coronary heart disease associated with short sleep only for women, and the mortality among female short sleepers did not differ significantly from that among male short sleepers. The hazard ratio (95% CI) of coronary heart disease for short sleepers in women versus those in men was 4.60 (0.58-36.2). This finding contrasts with the result that risk of mortality from cardiovascular disease, other causes, and all causes were approximately half among women than among men. The age-adjusted hazard ratios for women versus men were 0.56 (0.51-0.61) for total stroke, 0.46 (0.40-0.53) for coronary heart disease, 0.55 (0.51-0.58) for total cardiovascular disease, 0.39 (0.37-0.41) for cancer, 0.44

(0.42-0.47) for noncardiovascular disease/noncancer, and 0.45 (0.44-0.47) for all causes.

Short sleep of 4 or fewer hours was found to be associated with increased risk of mortality from hemorrhagic stroke for men, although this association was not statistically significant. However, when stratified by alcohol consumption habits, an increased risk of mortality from hemorrhagic stroke was observed among male drinkers with 4 or fewer hours and 5 hours of sleep. A cross-national study on sleep habits of approximately 35,000 men and women of 10 countries, including Japan,[10] showed that the prevalence of the use of alcohol as a sleep aid was the highest in Japan (30.3%). A recent cross-sectional survey conducted in Japan[11] also reported that the prevalence of alcohol consumption as a sleep aid at least once a week was 48% for men aged 20 years or older. It is possible that the habit of using alcohol as a sleep aid enhances the risk of mortality from hemorrhagic stroke associated with short sleep duration.

There is some evidence that may explain why short sleep duration is associated with an increase in mortality from coronary heart disease and total cardiovascular disease. Previous studies showed that short-term sleep deprivation leads to increased sympathetic nervous system activity,[12,13] elevated blood pressure,[12,14] elevated cortisol levels,[13] impaired glucose tolerance,[13] and increased inflammatory markers,[15] which may reflect and increase the risk of cardiovascular disease. Furthermore, recent epidemiologic studies have demonstrated that short sleep duration is associated with higher levels of hemoglobin A (1c),[16] total cholesterol,[17] and triglycerides,[17] higher blood pressure,[17] and increased incidence of hypertension.[18] Short sleep was also associated with increased mortality from noncardiovascular disease/noncancer for both men and women. This finding suggests other mechanisms for increasing nonspecific mortality, which need to be explored in further studies.

The association of long sleep duration with higher risks of mortality from total stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes observed in our study was consistent with the results of previous cohort studies.[1-3] A 10-year follow-up of the National Health and Nutrition Examination Survey I cohort comprising 7844 men and women aged 32 years and older showed a 1.5-fold increase in risk of stroke for persons with more than 8 hours of sleep, compared with those with 6 to 8 hours of sleep.[1] The Nurses' Health Study of 82,969 women aged 40 to 65 years showed that, compared with 7 hours of sleep, long sleep of 9 or more hours was associated with a 1.6-fold increase in mortality from cardiovascular disease, a 1.5-fold for noncardiovascular disease/noncancer, and a 1.4-fold for all causes.[3] Another report from the Nurses' Health Study of 71,617 women aged 40 to 65 years showed that, compared with 8 hours of sleep, long sleep of 9 or more hours was associated with 1.4-fold increased risk of coronary heart disease.[2] Although the mechanisms for the association between long sleep duration and increased mortality from cardiovascular disease and other causes were not clear, long sleep duration may be an early symptom of disease and may precede clinical diagnoses. However, the association of long sleep duration with excess mortality from total cardiovascular disease, noncardiovascular disease/noncancer, and all causes did not change substantially after exclusion of the subjects whose events occurred within 5 years from baseline.

The following limitations of our study need to be addressed. First, we could not obtain information about the quality of sleep, such as the presence or absence of sleep apnea, which is associated with increased risk of cardiovascular disease.[19] A previous cohort study of 1024 volunteers showed that short sleep duration was associated with an increased body mass index along with a reduction in leptin and elevated levels of ghrelin.[20] Since being overweight is a strong risk factor for sleep apnea, this disorder can be a confounder for the association between short sleep duration and increased risk of mortality from cardiovascular disease. However, men and women with short sleep duration enrolled in our study did not have a higher mean body mass index, and we did not have a higher percentage of overweight subjects among short sleepers than long sleepers, so that the potential confounding effect of sleep apnea may be minor. Second, data on sleep duration were obtained by self-administrated questionnaire and, thus, may include misclassification. However, self-assessed sleep duration was shown in a previous study to yield valid results in comparison with quantitative sleep assessment with actigraphy.[21] Another study has suggested, however, that depressed mood is associated with both underextimation and overestimation of habitual sleep duration.[22] We therefore conducted a statistical analysis including these psychological factors as covariates, which showed that the association between sleep duration and coronary heart disease remained substantially unchanged. Finally, we used the mortality data, rather than incidence data, as endpoints, which may lead to misclassification in the diagnosis of discuss outcomes, especially stroke, stroke subtypes, and coronary heart disease. However, the widespread use of computed tomography in local hospitals since the 1980s has probably made the diagnosis of stroke and its subtypes reported on the death certificates sufficiently accurate.[23, 24] For coronary heart disease, approximately one fourth to one third of deaths attributed to ischemic heart disease on the death certificate were misdiagnosed, according to the validation studies.[25,26] Therefore, the contamination of other cardiovascular diseases in the diagnosis of coronary heart disease would probably underestimate the excess mortality from coronary heart disease for female short sleepers, and the real association may be stronger.

The strengths of our study are its prospective design and high statistical power to detect sex-specific associations of short and long sleep duration with cause-specific mortality, as well as with total mortality.

In conclusion, short sleep duration was associated with increased mortality from coronary heart disease for women and from noncardiovascular disease/noncancer and all causes for both sexes, whereas long sleep duration was associated with increased mortality from stroke, total cardiovascular disease, noncardiovascular disease/noncancer, and all causes for both sexes, yielding a U-shaped relationship with total mortality, with a nadir at 7 hours of sleep.

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Study Investigators

DISCLOSURE STATEMENT

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Stroke Risk of Blood Pressure Indices Determined by Home Blood Pressure Measurement

The Ohasama Study

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Background and Purpose—The purpose of this prospective cohort study was to investigate associations between stroke and blood pressure (BP) indices (systolic BP [SBP], diastolic BP [DBP], mean BP, and pulse pressure [PP]) determined by home BP measurement.

Methods—Associations between stroke and BP indices were examined in a rural Japanese population. Home BP data of 2369 subjects (40% men) $\geq$35 years of age (mean, 59 years) without a history of stroke were obtained. Associations between stroke and each index were determined using Cox proportional hazards regression and the likelihood ratio (LR) test.

Results—During follow-up (mean, 11.7 years), 238 strokes occurred. The LR test showed that SBP and mean BP were significantly more strongly associated with total and ischemic stroke than DBP and PP (LR $\chi^2 \geq$9.3, $P<$0.01 for SBP/mean BP, LR $\chi^2 \leq$3.8, $P\geq$0.05 for DBP/PP). SBP tended to be more strongly associated with total/ischemic stroke than mean BP (LR $\chi^2=$3.8, $P=$0.05 for SBP, LR $\chi^2 \leq$0.2, $P>$0.6 for mean BP). PP tended to be slightly more strongly associated with ischemic stroke than DBP (LR $\chi^2=$7.5, $P<$0.01 for DBP, LR $\chi^2=$9.3, $P<$0.01 for PP), whereas DBP was significantly more strongly associated with hemorrhagic stroke than PP (LR $\chi^2=$9.2, $P<$0.01 for DBP, LR $\chi^2=$2.5, $P=$0.01 for PP).

Conclusion—PP obtained from home BP measurements was weakly associated with stroke, whereas SBP showed the strongest association. Additionally, DBP and PP may be associated with different stroke types. (*Stroke.* 2009;40:2859-2861.)

Key Words: diastolic blood pressure ■ home blood pressure measurement ■ mean blood pressure
■ pulse pressure ■ stroke ■ systolic blood pressure

R ecently, pulse pressure (PP) was reported to be associated with coronary heart disease.[1,2] However, several studies showed that PP is not strongly associated with stroke when compared with other blood pressure (BP) indices.[3,4] These studies were based on casual-screening BP (CBP). Thus, the present study evaluated associations between stroke and systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), and PP obtained from home BP (HBP) measurement, which has been demonstrated to predict cardiovascular diseases more accurately than CBP.[5]

Methods

The present study is part of a longitudinal observational cohort study of subjects who have been participating in our HBP measurement project in Ohasama, Japan. The socioeconomic and demographic characteristics of Ohasama, the selection procedure of the study populations, the HBP and CBP measurement procedures, and the data collection procedures have been described previously.[5-7] The present study population consisted of 2369 individuals (40% men), $\geq$35 years of age (mean, 59.2 years), without a history of stroke and with $\geq$3 days of morning HBP and a CBP.[6]

The subjects were followed from the dates of HBP measurement (approximately 1992) until December 31, 2004. The procedures for diagnosing stroke were described previously.[7,8] Cerebral infarction (International Classification of Diseases, 10th Revision code I63) was defined as ischemic stroke, and intracerebral hemorrhage (I61) and subarachnoid hemorrhage (I60) were defined as hemorrhagic stroke.

The relative hazard and 95% CI were estimated for a 1-SD difference for each index using Cox proportional hazards regression, adjusted for age, sex, smoking status, use of antihypertensive medica-

Table 1. **Baseline BP Values and Age for All Subjects, for Those Who Developed Stroke, and for Those Who Did Not Develop Stroke**

Variables	Overall	Stroke		Type of Stroke	
		Did Not Develop	Developed	Ischemic	Hemorrhagic
N	2369	2131	238	169	69
Age	59.2±12.1	58.4±12.1	66.2±9.7*	67.0±9.4	64.3±10.3
Home BP					
SBP	124.2±15.1	123.0±14.6	134.4±15.6*	134.9±14.9	133.0±17.5
DBP	74.5±9.9	74.1±9.8	78.9±10.4*	78.8±10.6	79.1±9.9
MBP	91.1±10.9	90.4±10.7	97.4±11.3*	97.5±11.2	97.1±11.7
PP	49.6±9.9	49.0±9.6	55.5±10.8*	56.1±10.3	53.9±12.0
CBP					
SBP	130.9±18.0	130.1±17.9	138.3±17.2*	138.6±17.1	137.5±17.7
DBP	74.4±11.3	74.1±11.3	77.1±10.5*	77.0±10.4	77.3±10.9
MBP	93.3±12.3	92.8±12.3	97.5±11.3*	97.5±11.1	97.4±11.9
PP	56.5±13.4	56.0±13.2	61.2±14.3*	61.6±14.6	60.2±13.8

Note: Data are presented as mean±SD. Hemorrhagic stroke included intracerebral hemorrhage and subarachnoid hemorrhage.
*$P<0.001$.

tion, and history of heart disease, diabetes mellitus, or hypercholesterolemia. The likelihood ratio (LR) χ^2 value was used as a measure of the improvement of goodness of fit[9] between the model containing a single BP index (and confounding factors) and the model containing 2 indices. A significant LR χ^2 indicates that the index represents a significantly stronger association with stroke.[9]

Results

During follow-up (mean, 11.7 years), 238 strokes occurred (169 ischemic, 69 hemorrhagic).

All baseline BP indices were significantly higher in subjects who developed stroke than in those who did not (Table 1).

Figure A shows relative hazards for total stroke. Of the HBP indices, SBP and MBP were strongly associated with total stroke followed by DBP. The association between total stroke and PP was relatively weak. Associations between stroke and the CBP indices were generally weak. Table 2 shows the LR χ^2 values when 2 HBP indices were analyzed simultaneously. For total stroke, the LR χ^2 values of SBP and MBP (LR χ^2 ≥11.8, $P<0.01$) were significantly higher than those of DBP and PP (LR χ^2 ≤3.8, $P≥0.05$). The LR χ^2 value of SBP tended to be larger than that of MBP, although the difference was not significant. The LR χ^2 values of DBP and PP were not significantly different when DBP and PP were compared.

Figure B shows the relative hazards for ischemic stroke. The association between ischemic stroke and SBP was the strongest followed by MBP. Associations between ischemic stroke and DBP and PP were relatively weak. As shown in Table 2, the LR χ^2 of SBP tended to be larger than that of MBP when SBP was compared with MBP, but there were no significant differences. The LR χ^2 values of SBP and MBP were significantly stronger than those of DBP and PP when SBP and MBP were compared with DBP and PP. The LR χ^2 values of DBP and PP were not significantly different when DBP and PP were compared, although that of PP tended to be larger than that of DBP.

Figure C shows the relative hazards for hemorrhagic stroke. SBP, DBP, and MBP were similarly associated with

hemorrhagic stroke, and PP was not significantly associated. No significant differences were observed when the LR χ^2 values of SBP, DBP, and MBP were compared; these values were also significantly larger than that of PP (Table 2). These
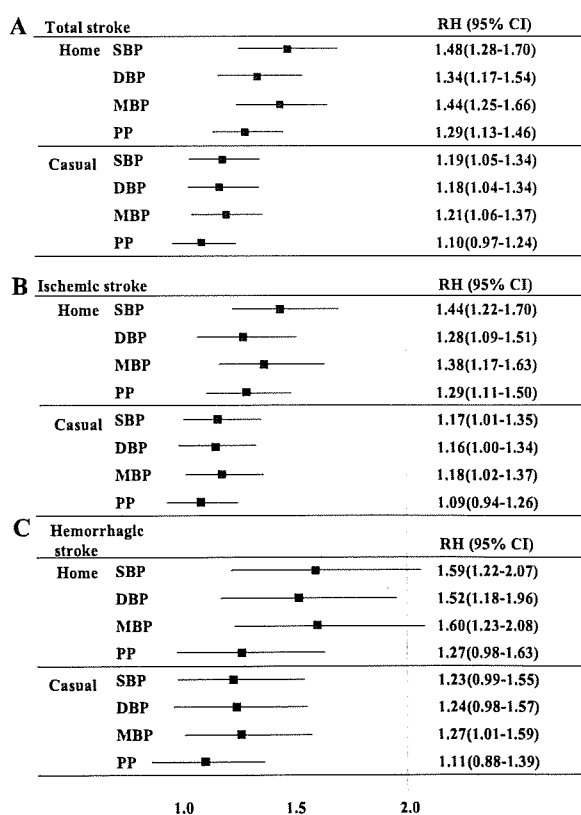
Figure. Relative hazards (RHs) and 95% CIs of BP indices for stroke risk. Boxes represent RHs. Horizontal lines represent 95% CIs. (A), Total stroke; (B) ischemic stroke; (C) hemorrhagic stroke.

Table 2.   Increases in Goodness of Fit Adding HBP Indices

Comparison		Total Stroke		Ischemic Stroke		Hemorrhagic Stroke	
		LR χ^2	P	LR χ^2	P	LR χ^2	P
MBP versus PP	MBP	15.3	<0.01	7.5	<0.01	9.2	<0.01
	PP	3.8	0.05	3.8	0.05	0.3	0.59
SBP versus PP	SBP	15.3	<0.01	7.5	<0.01	9.2	<0.01
	PP	0.2	0.67	0.009	0.92	1.0	0.32
DBP versus PP	DBP	15.3	<0.01	7.5	<0.01	9.2	<0.01
	PP	11.8	<0.01	9.3	<0.01	2.5	0.11
SBP versus DBP	SBP	11.8	<0.01	9.3	<0.01	2.5	0.11
	DBP	0.2	0.67	0.009	0.92	1.0	0.32
SBP versus MBP	SBP	3.8	0.05	3.8	0.05	0.3	0.59
	MBP	0.2	0.67	0.009	0.92	1.0	0.32
MBP versus DBP	MBP	11.8	<0.01	9.3	<0.01	2.5	0.11
	DBP	3.8	0.05	3.8	0.05	0.3	0.59

Note: This table shows increases in goodness of fit from adding one BP index to a model including another index and vice versa. The degrees of freedom for LR χ^2 are all 1. The P values are for LR χ^2 values; an LR χ^2 of 3.8 corresponds to a P value of 0.05, 6.6 to 0.01, and 10.8 to 0.001.

results did not change for the analysis of intracerebral hemorrhage alone.

Discussion

Recent studies using CBP[3,4] and ambulatory BP,[8] which investigated associations between stroke and BP indices, showed that PP was not very strongly associated with stroke. In the present study using HBP, like in these previous studies, PP was not strongly associated with stroke. LR tests showed that SBP and MBP were significantly more strongly associated with total or ischemic stroke than DBP and PP. SBP, MBP, and DBP were all significantly more strongly associated with hemorrhagic stroke than PP. Thus, PP may not be important for predicting stroke. However, PP tended to be slightly more strongly associated with ischemic stroke than DBP, suggesting that different BP indices are specifically associated with different stroke types.

SBP tended to be more strongly associated with total and ischemic stroke than MBP, although the differences were not significant. Considering that MBP has to be calculated from the formula as an approximation, SBP may be the most useful index to follow in daily medical practice.

In conclusion, PP obtained from HBP measurements was not strongly associated with stroke. SBP showed a strong association with stroke and appears to be a useful index. DBP and PP may be associated with different stroke types.

Sources of Funding

Disclosures

None.

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Repeated evening home blood pressure measurement improves prognostic significance for stroke: a 12-year follow-up of the Ohasama study

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Objective To compare the predictive power of home blood pressure (HBP) measured in the evening (E-HBP) and that of casual screening BP (CBP) for stroke risk in relation to the number of E-HBP measurements.

Methods We obtained E-HBP (measured once in the evening just before going to bed for 4 weeks) and CBP (measured twice during the health checkup) from 2234 Japanese participants aged $\geq$ 35 years who had no history of a previous stroke. The participants were followed-up for a median duration of 11.9 years. The multivariate adjusted relative hazard (RH) and 95% confidence intervals (CI) for each 10 mmHg (systolic) or 5 mmHg (diastolic) increase in BP was determined by Cox regression model.

Results There were 226 incidences of stroke. Even the initial E-HBP values significantly predicted future stroke events (systolic RH = 1.19, 95% CI = 1.11–1.28; diastolic RH = 1.12, 95% CI = 1.06–1.19), and the predictive power of E-HBP increased progressively with the increased number of measurements. When initial systolic E-HBP and systolic CBP values were simultaneously included into the Cox model, only initial E-HBP was significantly related with stroke risk (E-HBP RH = 1.17, 95% CI = 1.08–1.26; CBP RH = 1.07, 95% CI = 0.99–1.15).

Conclusion E-HBP has a stronger predictive power than CBP regardless of the number of measurements. Our findings emphasize the important clinical significance of E-HBP over CBP, even though the measurement conditions of E-HBP are generally less strict than that of morning HBP measurements. *Blood Press Monit* 14:93–98 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Self-measurement of blood pressure (BP) at home (HBP) is acknowledged worldwide as a useful clinical tool [1–6], primarily because it is highly reproducible and reliable. We have previously reported on the strong predictive power of morning HBP (M-HBP) for cardiovascular disease mortality and stroke incidence [7–9]. Because of circadian BP variation and other latent confounding factors, the characteristics of M-HBP and evening HBP (E-HBP) are different [10,11]. M-HBP was superior to the average of two casual screening BP (CBP) values in terms of stroke prediction, and the predictive value

increased progressively with the number of M-HBP measurements [12]. However, the predictive power of E-HBP, based on an increased number of measurements, has never been examined.

The aim of this study was to compare the predictive power of E-HBP with that of CBP for stroke risk in relation to the number of E-HBP measurements.

Methods
Study population

This study is a part of the longitudinal observational study of participants who have participated in our HBP measurement project in Ohasama, a rural community in

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the northern part of Japan, since 1987. The socioeconomic and demographic characteristics of the Ohasama study have been described previously [7–9,13–16]. From 1988 to 1995, we contacted all 4969 participants, 35 years or over, who lived in four districts of Ohasama town. Participants who were not at home during the normal working hours of the study nurses ($n = 1057$) and those who were hospitalized ($n = 166$) or incapacitated ($n = 94$) were ineligible. Of the remaining 3652 residents, 2764 (76%) participated in baseline examinations with CBP measurement and follow-up. As E-HBP measurements were based on the average of 14 times (14 days) or more; we excluded 426 participants who measured E-HBP less than 14 times. To examine the risk of the first onset of stroke, 104 individuals who had a previous history of stroke were further excluded from this analysis. Therefore, the study population consisted of 2234 individuals. 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. Informed consent was obtained from each participant.

Blood pressure measurements

At annual health checkups, participants were seated at rest for at least 2 min, and then CBP was measured twice consecutively by well-trained nurses or technicians. We used a semiautomatic CBP measuring device (USM700F; Elquest Corporation, Chiba, Japan) based on the microphone method.

Physicians and well-trained public health nurses conducted health education classes to inform the participants on how to perform HBP. After their ability to measure HBP was verified, participants measured their own BPs once in the evening in the sitting position after 2 mins or more of rest just before going to bed. They were instructed to record the measurements for 4 weeks. We allowed participants to measure their own BP two or more times on each occasion; however, the first measurement value from each occasion was used for analysis to exclude participants' selection biases. All participants were instructed to hold their cuff-covered arm at heart level during HBP measurements. These procedures were described in detail in our previous report [15], and followed the Japanese guidelines for self-monitoring of BP at home [3]. HBP was measured using the HEM 401C (Omron Healthcare, Kyoto, Japan), a semiautomatic device based on the cuff-oscillometric principle, which generates a digital display of both systolic and diastolic BP [17]. The devices for measurement of CBP and HBP were calibrated before the start of the study [17]. The devices met the criteria set by the Association for the Advancement of Medical Instrumentation [18]. We used a standard arm cuff for HBP measurements, as none of the participants had an arm circumference of 34 cm or more.

Follow-up and risk assessment

We accumulated follow-up data from 1987 until 31 December 2004. The participants' residence status in Ohasama was confirmed by registration cards. These cards are accurate and reliable because they are used for pensions and social security benefits in Japan.

The incidence and past history of stroke were investigated through the Stroke Registration System of Iwate Prefecture, death certificates, receipt of National Health Insurance, and questionnaires sent to each household at the time of HBP measurement. The information was then confirmed by checking the medical records of Ohasama hospital, where more than 90% of the participants had their regular health checkups. We used computed tomography scans and magnetic resonance imaging reports to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis included only the first event in those who had multiple nonfatal events. The diagnostic criteria of stroke and their subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke [19].

Other information for individuals such as height, weight, smoking status, drinking habits, use of antihypertensive medication at baseline, history of heart disease, hypercholesterolemia, or diabetes mellitus, was obtained from questionnaires sent to each household at the time of HBP measurements, from records of annual health checkups, and from medical records at Ohasama Hospital. Participants using lipid-lowering drugs or those with serum cholesterol levels of ≥ 5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolemia. Participants with a fasting glucose level of ≥ 7.0 mmol/l (126 mg/dl) or nonfasting glucose level of ≥ 11.1 mmol/l (200 mg/dl), or those using insulin or oral antihyperglycemic drugs, were defined as having diabetes mellitus. A past history of cardiovascular disease included a history of myocardial infarction, angina pectoris, atrial fibrillation, and cardiac failure.

Data analysis

HBP values were averaged separately in individuals; for example, the HBP value in an individual who measured his/her BP for 20 days was the average of these 20 measurements. CBP of each participant was the average of two consecutive CBP readings taken at the beginning of the study.

The Cox proportional hazard model was used for examining the risk of the first stroke. The dependent variable was the number of days from the measurement of the first HBP to event or censoring for survivors until 31 December 2004. The independent variables were

age, sex, body mass index, smoking status, use of anti-hypertensive medication at baseline, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. The estimated relative hazard (RH) and the 95% confidence intervals of variables were derived from the coefficient and SEM determined by the Cox model. The RH is expressed as the RH for each 10 mmHg (systolic) or 5 mmHg (diastolic) increase in BP. All the data are shown as mean (SD) unless otherwise stated. Student *t*-test, Fisher's exact test, and analysis of variance were used for appropriate analysis. *P* value less than 0.05 (2-sided test) was accepted as indicative of statistical significance. The SAS system (version 9.13, SAS Institute Inc., Cary, North Carolina, USA) was used for all statistical analyses.

Results

The characteristics of participants are shown in Table 1. They were followed-up for a median of 11.9 (interquartile 9.8–15.4) years, to a maximum of 16.9 years. We obtained 226 incident cases of first stroke among the 2234 individuals: 157 (69.5%) cerebral infarction, 50 (22.1%) intracerebral hemorrhage, 17 (7.5%) subarachnoid hemorrhage, and 2 (0.9%) unknown cases.

The averaged systolic E-HBP values were significantly lower than the averaged systolic CBP even for the initial days (*P* < 0.001). Although the averaged diastolic BP values were not significantly different between initial E-HBP and CBP (*P* = 0.4), the discrepancy increased with an increased number of E-HBP measurements (Table 2). All BP values for those participants who had a stroke before the follow-up period were significantly higher than those who did not have a stroke (all *P* values < 0.001).

Figure 1 shows the risk of first onset of stroke as a continuous model. A 10 mmHg elevation of systolic CBP (*P* = 0.002) and systolic E-HBP (all *P* values < 0.001) were significantly associated with the risk of stroke. The predictive value of E-HBP increased progressively with

Table 1 Clinical characteristics of study participants

Variables	All participants	Stroke occurrence Yes	No	*P**
Number of participants	2234	226	2008	
Age (years)	59.2±11.9	66.1±9.2	58.4±11.9	<0.0001
Men (%)	37.0	50.4	35.5	<0.0001
Body mass index (kg/m²)	23.5±3.1	23.4±3.1	23.5±3.1	<0.0001
Past history of CVD (%)	0.6	1.3	0.5	0.2
Diabetes (%)	9.9	14.2	9.4	0.03
Smoking (%)	18.3	24.3	17.6	0.02
Hypercholesterolemia (%)	28.1	27.0	28.2	0.8
Use of antihypertensive medication	29.2	51.8	26.6	<0.0001

Values are expressed as mean ± SD.
CVD, cardiovascular disease.
*P values for comparison between stroke developed and non-developed participants.

Table 2 Blood pressure values of study participants

Variables	All participants	Stroke occurrence Yes	No
Systolic BP			
CBP	130.8±18.1	138.6±17.3	129.9±17.9
E-HBP 1 day	124.3±18.1	134.6±19.2	123.2±17.6
2 days	123.6±16.6	133.9±17.3	122.4±16.1
1 week	122.6±15.2	133.2±15.7	121.4±14.6
2 weeks	122.2±14.9	132.9±15.3	121.0±14.3
Multiple	121.7±14.5	132.3±14.9	120.6±14.0
Diastolic BP			
CBP	74.3±11.3	77.4±10.6	73.9±11.3
E-HBP 1 day	74.0±12.2	78.7±12.2	73.5±14.0
2 days	73.6±10.9	78.6±10.9	73.0±12.1
1 week	73.0±9.9	78.0±9.7	72.4±10.8
2 weeks	72.7±9.6	77.8±9.7	72.1±9.8
Multiple	72.4±9.4	77.4±9.4	71.9±9.5

CBP, casual screening blood pressure; E-HBP, self-measurement of BP measured at home in the evening.
t-test, all *P* values <0.001 between stroke developed and non-developed.

Fig. 1
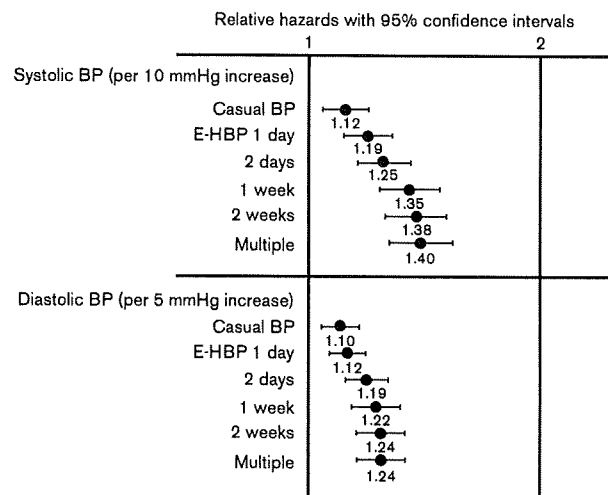
Predictive values of self-measurement of BP at home in the evening (E-HBP) and casual screening blood pressure (CBP). Relative hazard (RH) and 95% confidence intervals (CI) of E-HBP at initial 1 day, 2 days, 1 week, 2 weeks, and multiple times are shown. CBP is also shown. RH is represented by solid circles and expressed as an increase in stroke risk per 10-mmHg elevation of systolic BP (upper portion of figure) and per 5-mmHg elevation of diastolic BP (lower portion of figure). Horizontal lines represent 95% CI. Adjusted factors included age, sex, body mass index, smoking status, drinking habits, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease.

an increase in the number of measurements, showing the highest predictive value when E-HBP was measured multiple times. Similar associations were observed based on diastolic BP. The results were similar when men and women were analyzed separately; E-HBP had stronger predictive power for stroke than CBP, and the power increased as the measurement number increased (data not shown).

Table 3 Adjusted RH of E-HBP and CBP levels for stroke incidence with a BP increase of 10 (systolic) and 5 mmHg (diastolic)

	E-HBP			CBP		
	RH	95% CI	χ^2	RH	95% CI	χ^2
Systolic BP						
1 day	1.17	1.08–1.26	15.5	1.07	0.99–1.15	3.0
2 days	1.23	1.13–1.34	22.1	1.06	0.98–1.14	2.2
1 week	1.33	1.21–1.47	33.5	1.03	0.96–1.11	0.7
2 weeks	1.36	1.23–1.50	36.0	1.03	0.95–1.11	0.5
Multiple	1.38	1.25–1.54	38.0	1.02	0.95–1.10	0.3
Diastolic BP						
1 day	1.10	1.04–1.17	11.2	1.07	1.00–1.13	4.4
2 days	1.17	1.09–1.25	19.6	1.05	0.99–1.11	2.3
1 week	1.20	1.11–1.30	22.0	1.04	0.98–1.10	1.4
2 weeks	1.22	1.13–1.32	24.5	1.03	0.97–1.10	0.9
Multiple	1.22	1.13–1.33	24.4	1.03	0.97–1.09	0.8

CBP and each E-HBP were simultaneously included into the Cox model. χ^2, Wald χ^2 tests; CBP, casual screening blood pressure; CI, confidence intervals; E-HBP self-measurement of BP at home in the evening; RH, relative hazard.

When initial E-HBP and CBP values were simultaneously included in the Cox model, initial E-HBP was more closely related with stroke risk than CBP (Table 3). Similarly, at 2 days, 1 week, 2 weeks, and multiple times E-HBP values showed a significantly greater relation with the risk of stroke than the CBP values (E-HBP: all P values < 0.001, CBP: all P values < 0.1). Furthermore, log likelihood tests indicated the same results; for example, even the model, including both 1 day systolic E-HBP and systolic CBP, lost goodness of fit when 1 day systolic E-HBP was removed ($P < 0.05$), whereas no significant changes occurred when systolic CBP was removed ($P = 0.2$). A sensitivity analysis after exclusion of participants under antihypertensive drugs produced similar results (data not shown).

Discussion

In the current prospective cohort study, we have demonstrated that E-HBP has a stronger predictive power than CBP, regardless of the number of measurements. This suggests the clinical significance of E-HBP over CBP, even though the conditions of E-HBP measurement are generally less strict compared with M-HBP measurements.

In our previous study, initial M-HBP was superior to the average of two CBP values as a stroke predictor [12]. This study adds evidence that HBP *per se* has a superior predictive power that is irrelevant to the number of measurements. It is possible that CBP measured many times may have a predictive value equivalent to that of HBP. However, the advantage of HBP measurements is that individuals are able to measure their own BP repeatedly at home, making it easy to obtain many HBP measurements. In several studies, HBP was defined as

the average of M-HBP and E-HBP [20–22], whereas in other surveys including ours [7,23], HBP was calculated using only M-HBP measurements. Although we have indicated that M-HBP and E-HBP would have a different prognostic power for stroke incidence [24], the accurate evaluation of these two separate measurements in relation to cardiovascular morbidity and mortality remains to be investigated.

It is emphasized that while E-HBP has a good predictive power for stroke incidence, E-HBP was taken under relatively uncontrolled measurement conditions compared with conditions for M-HBP. For E-HBP, typical evening activities, such as taking a bath, drinking alcohol, eating supper or taking drugs at the time of E-HBP measurement were not taken into account in this study. Approximately one third of adults in Ohasama drink alcohol in the evening [25]; this could cause a transient fall in BP in the late evening. It is likely that the prognostic significance of E-HBP would be improved when E-HBP is measured under controlled conditions. Furthermore, the time of E-HBP measurement varies; E-HBP was measured in the early evening in European studies [26,27], whereas in Japanese studies, based on the Japanese guidelines for HBP measurement [3], measurements were taken in the late evening just before bedtime [10,11,28]. There is room for further investigation of whether E-HBP would have the same predictive power for people from other countries.

HBP offers the opportunity to assess the duration of action of antihypertensive medications. This can be done by measuring BP at the time of trough drug effect (before the morning dose) and peak drug effect (at midday or in the evening) [29]. Based on these measurements, it is possible to calculate the morning: evening ratio, which may provide similar information with the trough: peak ratio, an index widely used to reflect the duration of action of antihypertensive medications [29,30]. The morning: evening ratio is a useful index for evaluating the duration of action of a drug administered once daily in the morning [31]. It is a reasonable assumption that only initial E-HBP, as well as initial M-HBP, would be useful in assessing the morning: evening ratio. However, as our present findings show, an increasing number of HBP measurements, regardless of time of measurement, would improve the data quality.

Cuff-oscillometric devices were used for HBP measurement. There is no universally accepted method of BP measurement in patients with arrhythmias, and BP devices vary greatly in their ability to measure BP accurately [5]. Although arrhythmia might cause inter-observer and intra-observer error, as indicated by the American Heart Association recommendation for BP measurement devices [32], automated devices are widely accepted in

clinical practice, and we would like to investigate stroke risk in relation to E-HBP measurement using an epidemiological approach. In this analysis, we used an adjusting factor – past history of cardiovascular disease – to consider participants with arrhythmia or atrial fibrillations. Further analysis, excluding individuals with past histories of cardiovascular disease, showed the same results (data not shown). Although further testing is required, devices with an arrhythmia detection function might be useful.

In conclustion, E-HBP has a stronger predictive power than CBP, regardless of the number of measurements. E-HBP, as well as M-HBP, is a useful tool to predict future incidence of cardiovascular disease such as stroke. Therefore, daily measurements of both M-HBP and E-HBP are recommended. To improve the prognostic significance of E-HBP, measurement conditions should be reconsidered in future studies.

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ORIGINAL ARTICLE

The association between masked hypertension and waist circumference as an obesity-related anthropometric index for metabolic syndrome: the Ohasama study

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Masked hypertension has been proven to be associated with an increased risk for cardiovascular diseases. The purpose of this study was to examine the direct associations of obesity-related anthropometric indices, including waist circumference, with masked hypertension. Participants in this population-based survey included 395 residents (≥35 years) of Ohasama, a rural Japanese community. They measured blood pressure at home (HBP) and underwent an oral glucose-tolerance test. Participants were classified into four groups on the basis of their HBP and casual-screening blood pressure (CBP) values: sustained normotension, white-coat hypertension, masked hypertension or sustained hypertension. The relationships between the obesity-related anthropometric indices and the four blood pressure groups were examined using multivariate analysis adjusted for confounding factors. The mean waist circumference in men was significantly higher in individuals with masked hypertension (87.3 cm) than in those with sustained normotension (81.0 cm) and white-coat hypertension (79.3 cm), whereas the mean waist circumference in women was significantly higher in individuals with sustained hypertension (79.5 cm) than in those with sustained normotension (75.0 cm). In the multivariate analysis, waist circumference, body mass index (BMI) and waist-to-hip ratio were significantly associated with masked hypertension, particularly in individuals with normal CBP. Our results suggest that HBP measurements might be particularly important in abdominally obese people for the early detection of masked hypertension.
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INTRODUCTION
Metabolic syndrome is the concurrence of multiple metabolic abnormalities associated with cardiovascular disease (CVD).[1,2] Metabolic syndrome has been reported to be an important risk factor for CVD and mortality,[3,4] and is useful in predicting diabetes mellitus.[5]

Blood pressure (BP) measurements outside of medical settings, such as self-measured BP at home (HBP), have identified two subgroups of individuals: those with white-coat hypertension,[6] who have persistently increased BP levels in a medical setting (referred to as casual-screening BP or CBP) but normal HBP, and individuals with

masked hypertension,[7,8] who have normal CBP but increased HBP. Whether white-coat hypertension is a benign condition[9,10] or is linked with an increased risk for target organ damage and a worse prognosis[11–13] is still controversial, but there is a general agreement that individuals with masked hypertension have an increased risk of CVD.[7,8] However, there have been few reports regarding the association between masked hypertension and waist circumference (WC) or metabolic syndrome.

The aim of this study is to investigate whether or not obesity-related anthropometric indices, including WC, BMI and waist-to-hip ratio (WHR), are associated with masked hypertension.

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