Association of environmental tobacco smoke exposure with elevated home blood pressure in Japanese women: the Ohasama study

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Objective **Only a few of numerous epidemiological studies have demonstrated a positive association between environmental tobacco smoke (ETS) exposure and blood pressure (BP), despite experimental studies showing such a positive association. The association between home blood pressure (HBP) and ETS exposure was investigated in the general population.**

Methods **Five hundred and seventy-nine nonsmoking Japanese women were enrolled. The participants were classified into four categories according to their responses to a self-administered questionnaire: unexposed women (non-ETS), women exposed at home [ETS(home)], at the workplace/other places [ETS(work/other)] and at home and at the workplace/other places [ETS(both)]. Variables were compared using analysis of covariance adjusted for age, marital status, body mass index, diabetes mellitus, stroke, heart disease, hyperlipidemia, alcohol intake, salt intake and activity levels.**

Results **In participants without antihypertensive medication, systolic morning HBP in ETS(both) was 4 mmHg higher than that in non-ETS (116.8 ± 1.01 vs. 113.1 ± 1.08 mmHg, $P = 0.02$) and systolic morning HBP in ETS(home) and systolic evening HBP in ETS(both) were 3 mmHg higher than those in non-ETS (116.2 ± 1.07 vs. 113.1 ± 1.08 mmHg, $P = 0.04$; and 115.3 ± 1.02 vs. 111.9 ± 1.09 mmHg, $P = 0.03$, respectively). In participants with antihypertensive medication, ETS exposure status was not significantly associated with increased HBP levels.**

Conclusions **A positive association between HBP levels and ETS exposure was confirmed. HBP measurement is recommended in population-based studies investigating the effects of ETS exposure. ETS exposure may increase BP, thereby synergistically contributing to unfavorable cardiovascular outcomes along with other deleterious effects of ETS.** *J Hypertens* **28:1814–1820 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2010, 28:1814–1820

Keywords: blood pressure, blood pressure monitoring ambulatory, cardiovascular diseases, home blood pressure monitoring, particulate matter, passive smoking

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; CBP, casual clinic blood pressure; ETS, environmental tobacco smoke; ETS(both), participants exposed to ETS both at home and at the workplace and/or other places; ETS(everyday), participants exposed to ETS everyday; ETS(home), participants exposed to ETS at home; ETS(occasionally), participants exposed to ETS less frequently than everyday; ETS(work/other), participants exposed to ETS at the workplace and/or other places; HBP, home blood pressure; non-ETS, participants not exposed to ETS

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Received 27 July 2009 Revised 2 March 2010
Accepted 22 March 2010

See editorial comment on page 1806

Introduction

Exposure to environmental tobacco smoke (ETS) is a well known risk factor for morbidity and mortality from cardiovascular diseases such as coronary heart disease [1] and stroke [2–9]. Numerous studies have investigated the pathophysiological changes caused by ETS exposure, and one of the findings of these studies is that ETS causes endothelial dysfunction, such as impaired endothelium-dependent vasodilatation [10–14] and decreased nitric oxide production [15]. Some experimental studies have also shown that blood pressure (BP) is elevated for a short time period [16] or for 24 h after brief ETS exposure [15].

These pathophysiological and hemodynamic findings imply that ETS exposure increases BP in the general population. To the best of our knowledge, however, only a few of the numerous epidemiological studies investigating this relationship have shown a positive association between chronic ETS exposure and BP [17,18]. One possible reason for these inconsistent findings is that

DOI:10.1097/HJH.0b013e32833a3911

most results are based on measurement of casual clinic blood pressure (CBP), which is less sensitive in detecting true changes in BP compared to home blood pressure (HBP) measurement [19,20]. HBP is measured by individuals themselves at home with a validated device over a long observation period, providing more reproducible and reliable values with less random error, without observer bias and without the white-coat effect [19,20]. Because of these advantages, HBP values have better predictive power for morbidity and mortality from cardiovascular diseases than CBP values [19–22], and HBP monitoring is now widely recommended in guidelines [19,21] and in a scientific statement [20].

To test the hypothesis that HBP measurements detect differences in BP between individuals exposed and those not exposed to ETS in the general population, the association between HBP values and ETS exposure was examined in a population-based, cross-sectional study.

Methods

Study population

The study was conducted as a part of the Ohasama study, a Japanese community-based, BP measurement project [23,24]. The total population of Ohasama was 7202 in 1998. Of this total population, 4964 were 35 years old or older. Of those, 1410 working outside of the town were considered ineligible and excluded from the study because they were not in the town during normal working hours. Of the remaining 3554 individuals, 213 were also excluded from the study because they were hospitalized, mentally ill, or bedridden. A total of 3341 participants were thus eligible for the study. A questionnaire was sent to each participant, and 1895 of the eligible participants gave their informed consent and responded to the questionnaire. Of those, 585 were excluded from the analysis because they were ex-smokers or current active smokers. Thus, the number of lifelong nonsmokers was 1310. Another 505 individuals with incomplete answers to the questions regarding demographic factors including ETS exposure were also excluded. Of the remaining 805 individuals, 754 who measured their HBP in the morning on at least three occasions (3 days) during the 4-week study period were included. This criterion was based on our previous observation that the average BP on the first three occasions was not significantly different from the mean for the entire study period [23]. Men ($n = 175$) were also excluded from the analysis because their number was small. Therefore, the study included 579 women [54.9% of the total number of lifelong nonsmoking women ($n = 1054$)].

Table 1 compares the characteristics of the included study participants with lifelong nonsmoking women who participated in the study but were ultimately excluded from the analysis due to incomplete data on ETS exposure (nonparticipants). The participants were characterized by a lower mean age, by lower percentages of participants taking antihypertensive medication and having a history of stroke and by higher percentages of participants being married and current drinkers.

Table 1 Characteristics of participants and nonparticipants in lifelong nonsmoking women ($n = 998$)

	Participants	Nonparticipants[a]	*P* value
N	579	419	
Mean age (years)	59.2 ± 13.1	64.1 ± 11.2	<0.0001
Marital status (married %)	71.0	61.3	0.0014
BMI (kg/m^2)	23.7 ± 3.3	23.7 ± 3.4	NS
Antihypertensive medication (%)	18.1	25.1	0.0081
History			
Diabetes mellitus (%)	8.6	9.3	NS
Stroke (%)	1.0	2.9	0.0323
Heart disease (%)	6.0	5.0	NS
Hyperlipidemia (%)	12.1	14.8	NS
Alcohol intake (current drinker %)	24.5	15.0	0.0003
Salt intake (≥12.28 g/day %)	50.1	43.9	NS
Time spent walking (≥1 h/day %)	79.8	81.1	NS

BMI, body mass index; ETS, environmental tobacco smoke. Student's *t*-test for continuous variables and χ^2-test for categorical variables. Continuous variables are expressed as mean ± SD. NS = $P > 0.05$. [a]Lifelong nonsmoking female participants who participated in the study but were ultimately excluded from the analysis due to incomplete data on ETS exposure.

Blood pressure and pulse rate measurement

The procedures used for HBP, pulse rate and CBP measurements, as well as the measuring devices, have been described elsewhere [23,25,26]. Briefly, physicians and public health nurses conducted health education classes to inform the participants about the HBP and pulse rate recording method, to teach them how to measure their own HBP and pulse rate, and to validate their ability to perform these tasks consistently. The women were then asked to measure their HBP and pulse rate every morning and evening and to record the results for 4 weeks. Measurements of morning HBP and pulse rate were made within 1 h of waking, before breakfast or taking any drugs, with the women seated and having rested for at least 2 min [27]. Measurements of evening HBP and pulse rate were obtained in a homologous way just before going to bed. The HBP and pulse rate of an individual were defined as the mean of all measurements obtained from that person. The mean ± SD numbers of morning HBP, morning pulse rate, evening HBP and evening pulse rate measurements were 22.6 ± 6.5 ($n = 579$), 22.4 ± 6.6 ($n = 567$), 22.8 ± 6.5 ($n = 577$) and 22.7 ± 6.6 ($n = 566$), respectively.

Two consecutive measurements of CBP were taken by a nurse or technician after the participant had been seated at rest for at least 2 min [23]. CBP was defined as the average of the two readings.

Blood pressure and pulse rate measuring device

HBP and pulse rate were measured with the HEM 701C (Omron Healthcare Co. Ltd, Kyoto, Japan), an automatic device based on the cuff-oscillometric method that

generates a digital display of systolic BP, diastolic BP and pulse rate. CBP was measured with a USM-700F (UEDA Electronic Works Co. Ltd, Tokyo, Japan), a fully automatic device based on the Korotkoff sound technique (a microphone method). The circumference of the arm was less than 34 cm in most cases, so a standard arm cuff was used for both BP measurements. All devices used in this study had been validated [25,26] and satisfied the criteria of the Association for the Advancement of Medical Instrumentation [28].

Definition of environmental tobacco smoke exposure

Environmental tobacco smoke exposure status was evaluated by the following two questions: 'How often are you exposed to smoke from cigarette smoking by other family members or guests at home?' and 'How often are you exposed to smoke from cigarette smoking by other persons at the workplace and/or other places?'. The women who responded 'hardly exposed' to both questions were categorized as those not exposed to ETS (non-ETS), whereas those who responded 'everyday', '3 or 4 days a week', '1 or 2 days a week' or 'occasionally' were categorized as those exposed to ETS. The exposed women were further classified into three categories according to their location of ETS exposure: those exposed to ETS at home [ETS(home)], those exposed to ETS at the workplace and/or other places [ETS(work/other)] and those exposed to ETS both at home and at the workplace and/or other places [ETS(both)]. For an additional analysis based on frequency of ETS exposure, the women who responded 'everyday' to either question were categorized as those exposed to ETS everyday [ETS(everyday)], whereas the remaining women who responded '3 or 4 days a week', '1 or 2 days a week' and 'occasionally' to either question were categorized as those exposed to ETS less frequently than everyday [ETS(occasionally)].

Data analysis

Information on smoking status, ETS exposure status, marital status, history of diabetes mellitus, history of stroke, history of heart disease, history of hyperlipidemia, alcohol intake, salt intake and activity levels (time spent walking per day) was obtained from the questionnaire. A standardized methodology was used to calculate dietary salt (NaCl) intake from a Japanese version of the food-frequency questionnaire. The reproducibility and validity of this version were previously reported in detail [29,30]. Information on age and use of antihypertensive medication was obtained from another questionnaire sent to each household at the time of the HBP measurements. Body mass index (BMI) information was obtained from medical records kept at Ohasama Hospital and from annual health check-up records.

The participants were stratified according to use of antihypertensive medication to avoid possible mitigation of pressor effect of ETS, because relatively small differences in BP between the participants exposed and those not exposed to ETS were expected to be detected from previous findings [17,18]. Variables were compared using the *t*-test, analysis of variance (ANOVA), χ^2-test, a logistic regression analysis adjusted for age (years) or analysis of covariance (ANCOVA) adjusted for age (years), marital status (married or single/divorced/widowed), BMI (kg/m^2), history of diabetes mellitus, history of stroke, history of heart disease, history of hyperlipidemia, alcohol intake (current drinker or not current drinker), salt intake (less than the median of 12.28 g/day or greater than or equal to the median) and time spent walking (less than 1 h/day or greater than or equal to 1 h/day), as appropriate. The level of statistical significance was set at $P < 0.05$. Data are presented as percentages or means ± SD (for the *t*-test and ANOVA) or means ± SE (for ANCOVA). All analyses were performed with SAS software version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Home blood pressure and pulse rate of the participants without antihypertensive medication

The characteristics of the study participants are presented in Table 2. Mean age, marital status and percentages of current drinkers were significantly different among the categories of ETS exposure status. This might have been due to the marked differences in age, because working women are usually younger than retirement age and their spouses may be comparatively younger and healthier. Younger women may also have more social opportunities to consume alcohol. A logistic regression analysis was performed to determine whether these factors are significantly different among the categories of ETS exposure status after adjusting for age. The results showed that marital status was not significantly different ($P = 0.40$), whereas percentages of current drinkers remained significantly different among the categories of ETS exposure status ($P = 0.01$).

Table 3 shows HBP and pulse rate levels by location of ETS exposure. The systolic morning HBP value in ETS(both) was approximately 4 mmHg higher than that in non-ETS ($P = 0.02$), and the systolic morning HBP value in ETS(home) and the systolic evening HBP value in ETS(both) were approximately 3 mmHg higher than those in non-ETS ($P = 0.04$ and $P = 0.03$, respectively). There was also a tendency for systolic morning HBP and systolic evening HBP values of all categories exposed to ETS to be higher than those in non-ETS. Systolic morning HBP and systolic evening HBP levels were not significantly different among the categories exposed to ETS, and diastolic HBP and pulse rate levels were not significantly associated with any ETS exposure status. There were no significant interactions between age and ETS exposure status on any HBP and pulse rate levels (all P for interaction >0.2).

Table 2 Characteristics of the participants without antihypertensive medication by ETS location ($n = 474$)

	non-ETS	ETS(work/other)	ETS(home)	ETS(both)	*P* value
N	143	47	129	155	
Mean age (years)	64.0 ± 10.7	47.7 ± 9.4	58.3 ± 12.8	52.3 ± 10.7	<0.0001
Marital status (married %)	64.3	85.1	72.9	83.2	0.0007
BMI (kg/m^2)	23.2 ± 3.2	23.4 ± 2.4	23.6 ± 3.5	23.5 ± 3.2	NS
History					
Diabetes mellitus (%)	6.3	8.5	8.5	7.1	NS
Stroke (%)	0.7	0.0	0.8	0.0	NS
Heart disease (%)	6.3	4.3	4.7	2.6	NS
Hyperlipidemia (%)	14.0	4.3	12.4	6.5	NS
Alcohol intake (current drinker %)	12.6	36.2	24.0	40.0	<0.0001
Salt intake (≥12.28 g/day%)	50.3	44.7	47.3	55.5	NS
Time spent walking (≥1 h/day %)	81.1	70.2	82.9	83.2	NS

BMI, body mass index; ETS, exposure to environmental tobacco smoke. Analysis of variance for continuous variables and χ^2-test for categorical variables. Continuous variables are expressed as mean ± SD. NS = $P > 0.05$.

Because percentages of current drinkers were significantly different among the categories of ETS exposure status after adjusting for age, subgroup analysis was performed in noncurrent drinkers. The results showed a similar tendency presented in Table 3 (data not presented).

Table 4 presents the results of the additional analysis based on frequency of ETS exposure. There was a similar tendency for systolic morning HBP and systolic evening HBP values of all categories exposed to ETS, including the values in ETS(occasionally), to be higher than those in non-ETS, as presented in Table 3. The results showed significant differences between the systolic morning HBP value in ETS(everyday) and that in non-ETS and between the systolic evening HBP value in ETS(everyday) and that in non-ETS ($P = 0.02$ and $P = 0.03$, respectively).

Home blood pressure and pulse rate of the participants with antihypertensive medication

Home blood pressure and pulse rate levels by location and frequency of ETS exposure ($n = 105$) showed no significant differences in systolic HBP values between any ETS exposure group and the non-ETS group ($P > 0.2$ and $P > 0.5$, respectively). No other HBP and pulse rate levels were significantly associated with any ETS exposure status (data not presented).

Casual clinic blood pressure and pulse rate of the participants without antihypertensive medication

Table 5 shows mean CBP levels by location of ETS exposure. CBP values were available from 296 (62.4%) study participants without antihypertensive medication. The systolic and diastolic CBP values in ETS(home) were significantly higher than those in non-ETS ($P = 0.02$ and $P = 0.04$, respectively). No other significant differences in CBP values were seen between any ETS exposure group and the non-ETS group ($P > 0.6$).

Discussion

The present results confirm that there is a relationship between increased HBP levels and ETS exposure in Japanese women without antihypertensive medication. HBP measurements detect approximately a 3–4 mmHg difference in BP between the ETS(home) and the ETS-(both) groups and the non-ETS group, whereas CBP measurements detect significant differences only between the ETS(home) group and the non-ETS group. Thus, HBP measurement is a more sensitive measurement for detecting small BP changes.

In the present study, systolic morning HBP values in ETS(home) and in ETS(both) and systolic evening HBP value in ETS(both) were significantly higher than those in non-ETS, whereas diastolic HBP and pulse rate levels were not significantly associated with any ETS exposure status. These findings are consistent with those of Heiss *et al.* [15] and Mahmud and Feely [16], who investigated the relationship between ETS exposure and BP levels in experimental studies. Makris *et al.* [17] investigated the association between ambulatory BP values and ETS exposure in 254 clinically normotensive nonsmokers who were self-referred to their outpatient

Table 3 HBP and PR of the participants without antihypertensive medication by ETS location

	non-ETS	ETS(work/other)	ETS(home)	ETS(both)
Systolic morning HBP (mmHg)	113.1 ± 1.08	114.7 ± 1.85	116.2 ± 1.07[a]	116.8 ± 1.01[a]
Diastolic morning HBP (mmHg)	71.0 ± 0.73	71.4 ± 1.24	71.6 ± 0.72	72.0 ± 0.68
Morning PR (beats/min)	66.2 ± 0.62	66.9 ± 1.06	66.9 ± 0.63	66.9 ± 0.59
Systolic evening HBP (mmHg)	111.9 ± 1.09	114.2 ± 1.86	114.3 ± 1.08	115.3 ± 1.02[a]
Diastolic evening HBP (mmHg)	69.0 ± 0.74	70.3 ± 1.26	69.4 ± 0.73	70.6 ± 0.69
Evening PR (beats/min)	68.7 ± 0.60	68.4 ± 1.02	68.7 ± 0.60	69.4 ± 0.57

BMI, body mass index; ETS, exposure to environmental tobacco smoke; HBP, home blood pressure; PR, pulse rate. Analysis of covariance. Data were adjusted for age, marital status (married or single/divorced/widowed), BMI, history of diabetes mellitus, history of stroke, history of heart disease, history of hyperlipidemia, alcohol intake (current drinker or not current drinker), salt intake (≥12.28 g/day or <12.28 g/day) and time spent walking (≥1 h/day or <1 h/day). Data are expressed as mean ± SE.
[a] $P < 0.05$ compared to non-ETS.

Table 4 HBP and PR of the participants without antihypertensive medication by ETS frequency

	Non-ETS	ETS(occasionally)	ETS(everyday)
N	143	155	176
Systolic morning HBP (mmHg)	113.0 ± 1.08	115.9 ± 0.98	116.7 ± 0.95[a]
Diastolic morning HBP (mmHg)	71.1 ± 0.72	72.0 ± 0.66	71.5 ± 0.64
Morning PR (beats/min)	66.2 ± 0.62	66.5 ± 0.57	67.2 ± 0.55
Systolic evening HBP (mmHg)	111.9 ± 1.08	114.2 ± 0.99	115.2 ± 0.96[a]
Diastolic evening HBP (mmHg)	69.1 ± 0.74	70.2 ± 0.67	69.9 ± 0.65
Evening PR (beats/min)	68.7 ± 0.60	68.6 ± 0.55	69.3 ± 0.53

BMI, body mass index; ETS, exposure to environmental tobacco smoke; HBP, home blood pressure; PR, pulse rate. Analysis of covariance. Data were adjusted for age, marital status (married or single/divorced/widowed), BMI, history of diabetes mellitus, history of stroke, history of heart disease, history of hyperlipidemia, alcohol intake (current drinker or not current drinker), salt intake (≥12.28 g/day or <12.28 g/day) and time spent walking (≥1 h/day or <1 h/day). Data are expressed as mean ± SE. [a] $P < 0.05$ compared to non-ETS.

hypertension clinic. Their results show that 24-h and daytime systolic BP, heart rate and daytime diastolic BP values are significantly higher in those with at least 1 h daily ETS exposure, compared with those with less exposure and those without ETS exposure. Although the study population and categories of ETS exposure status are different, the present results are consistent with their findings in that out-of-clinic BP measurements detect a difference in BP between individuals exposed and those not exposed to ETS.

Not only were the systolic HBP values of the ETS(home), the ETS(both) and the ETS(everyday) groups significantly higher than those in non-ETS, but systolic morning HBP and systolic evening HBP values of all categories exposed to ETS, including the ETS(work/other) and the ETS(occasionally) groups, tended to be higher than those in non-ETS in the present study. These findings indicate that ETS exposure may elevate systolic HBP regardless of location and frequency of exposure, which is consistent with the previous findings that even a small amount of ETS exposure causes detrimental effects at the clinical level [31,32]. Since systolic HBP is a strong predictive factor for morbidity and mortality from cardiovascular diseases [33,34], the present results may also reflect that a pressor effect, as well as other deleterious effects, of ETS exposure contribute to increased morbidity and mortality from cardiovascular diseases [1–9] in the general population.

Considering the fact that the pathophysiological and hemodynamic effects of ETS exposure last for 24 h after 30 min of ETS exposure at the experimental level [15], that the systolic HBP values of all categories exposed to ETS were consistently higher than those of the non-ETS group, and that the present results were obtained from multiple HBP measurements for a mean of 3 weeks, the present results may reflect a nonlinear persistent pressor effect caused by ETS exposure in the general population. Although there is a possibility that the present results may reflect a much shorter duration of pressor effects of ETS just after exposure, especially in the morning when many smokers tend to smoke just after waking, the present results are important from a prognostic hemodynamic standpoint. Since HBP measurement detects small BP changes, it may reflect persistent effects of ETS exposure and is more feasible to monitor a large population regularly, a further study using HBP measurement is necessary to clarify the chronic deleterious hemodynamic effects of ETS exposure at the population level, with more detailed data on ETS exposure status. HBP measurement may also be useful for future studies investigating the hemodynamic effects of other air pollutants, such as ambient particulate matter [35].

Differences in HBP between women exposed and those not exposed to ETS were not observed in women with antihypertensive medication. This might be because the relatively small pressor effect of ETS exposure was mitigated by the large BP-lowering effects of antihypertensive drugs. It is necessary to consider a pressor effect of ETS exposure at least when interpreting HBP data from normotensive or prehypertensive patients in clinical practice. The present results obviously raise concerns over public health. Achievement of smoke-free environments is thus also important from a hemodynamic standpoint.

Several limitations of the present study need to be discussed. First, as more detailed data on time, duration

Table 5 CBP of the participants without antihypertensive medication by ETS location ($n = 296$)

	non-ETS	ETS(work/other)	ETS(home)	ETS(both)
N	102	21	96	77
Systolic CBP (mmHg)	126.6 ± 1.46	125.4 ± 3.24	131.5 ± 1.46[a]	126.5 ± 1.68
Diastolic CBP (mmHg)	71.6 ± 0.89	70.8 ± 1.98	74.2 ± 0.89[a]	72.4 ± 1.03

BMI, body mass index; CBP, casual clinic blood pressure; ETS, exposure to environmental tobacco smoke. Analysis of covariance. Data were adjusted for age, marital status (married or single/divorced/widowed), BMI, history of diabetes mellitus, history of stroke, history of heart disease, history of hyperlipidemia, alcohol intake (current drinker or not current drinker), salt intake (≥12.28 g/day or <12.28 g/day) and time spent walking (≥1 h/day or <1 h/day). Data are expressed as mean ± SE. [a] $P < 0.05$ compared to non-ETS.

and quantity of ETS exposure were unavailable in our study population, the dose–response relationship between HBP levels and ETS exposure is unknown. A further study using HBP measurement is necessary with more detailed data on ETS exposure status. Second, although age distribution of the categories of ETS exposure status was uneven, age did not significantly interact with ETS exposure status on the present results. Third, as the study was cross-sectional, the results do not show a causal relationship between ETS exposure and BP elevation or development of hypertension. A longitudinal study is necessary to investigate this causal relationship in the Ohasama study, as well as in other populations. Fourth, the study excluded men due to the small number of lifelong nonsmoking men. It remains to be investigated whether a positive association between ETS exposure and BP is present in men. Lastly, since a biological marker of ETS exposure, such as cotinine concentration, was not measured, there may be misclassification of ETS exposure status. However, ETS exposure status in a self-administered questionnaire is shown to be generally accurate in a large-scale cohort study in a Japanese population, with a slightly higher rate of passive smokers falsely reporting themselves to be nonpassive smokers compared to Western studies [36]. Therefore, we believe that the present results are acceptable, but they may underestimate the true magnitude of the hemodynamic effects of ETS exposure due to these misclassifications.

In conclusion, this is the first population-based study demonstrating a significant association between increased HBP and ETS exposure. HBP measurement is recommended to investigate the effects of ETS exposure in the general population. ETS exposure may increase BP levels, which may synergistically contribute to unfavorable cardiovascular outcomes, along with the other deleterious effects of ETS.

Acknowledgements

We are grateful to the residents in Ohasama Town, all related investigators and study staff, and staff members of the Ohasama Town Government, Ohasama Hospital and Iwate Prefectural Stroke Registry for their valuable support on this project.

Funding sources of support: This study was supported in part by Grants for Scientific Research (15790293, 16590433, 17790381, 18390192, 18590587, 19590929 and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; Grants-in-Aid [H17-Kenkou-007, H18-Junkankitou (Seishuu)-Ippan-012, and H20-Junkankitou (Seishuu)-Ippan-009, 013] from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Grants-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477 and 20.54043); Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; Uehara Memorial Foundation; Takeda Medical Research Foundation; National Cardiovascular Research Grants: and Biomedical Innovation Grants.

Information about previous presentations of the whole or part of the work: Material in this manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language.

There are no conflicts of interest.

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Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study

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BACKGROUND

Several observational studies have shown that treated hypertensives are characterized as having worse prognosis than nonhypertensives. However, there is little evidence based on home blood pressure (home BP) measurement. We compare the risk of stroke between untreated individuals and those taking antihypertensive medication based on home BP and casual-screening BP (casual BP) in the general population.

METHODS

The study included 1,690 untreated and 700 treated subjects aged ≥35 years. We measured home BP and casual BP at the beginning of the study. The risk of first stroke was examined by using the Cox proportional hazards model.

RESULTS

During 11.9 years of follow-up, we observed 242 first-time stroke cases. Treated subjects had significantly higher risk for stroke than untreated subjects based on home BP (relative hazard (RH) = 1.48) as well as on casual BP (RH = 1.78), adjusted for systolic BP values and characteristics. When subjects were classified into six categories based on BP (optimal, normal, high normal, and grade 1–3 hypertension), RHs in treated hypertensives linearly increased (trend $P < 0.01$) based on home BP. However, there was no consistent association for casual BP (trend *P: not significant*) in treated subjects. Stroke risk was linearly increased regardless of the BP information source in untreated subjects (home BP: trend $P < 0.01$, casual BP: trend $P < 0.01$).

CONCLUSION

The results suggest a strong association between elevated home BP and increased risk of stroke. Home BP is a better tool to assess stroke risk, especially in treated hypertensives.

Keywords: *antihypertensive agents; blood pressure; home blood pressure monitoring; hypertension; population; prognosis; stroke*

Am J Hypertens 2010; **23**:508-514 © 2010 American Journal of Hypertension, Ltd.

Hypertension is a major risk factor for stroke; therefore, accurate diagnosis and treatment of hypertension are necessary for better stroke prevention. We have reported that self-measurement of blood pressure (BP) at home (home BP) was more likely to reflect an individual's "true" BP and thus had a stronger predictive power for cardiovascular disease compared with casual-screening BP (casual BP).[1–4] Home BP is useful in distinguishing "white-coat hypertension," also known as "office hypertension",[5,6] and "masked hypertension".[7]

Many interventional trials have demonstrated that treatments that lower BP can significantly reduce the risk of cardiovascular events.[8–11] Although individuals treated with antihypertensive medication were characterized as having a worse prognosis than those without treatment in several observational studies conducted in the general population,[12–17] these outcomes were based on casual BP. Little is known about the long-term implications of using antihypertensive medications based on home BP readings.

The objective of this study was to investigate the prognostic value of home BP as well as casual BP in treated individuals, and to evaluate both as management tools to achieve the therapeutic target.

METHODS

Design and study population. This study was a part of a longitudinal observational study of subjects who had been participating since 1987 in a home BP measurement program in Ohasama, a rural community in Japan. The socioeconomic and demographic characteristics of this region[18] and the details of the selection of the study subjects have been

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Received 23 November 2009; first decision 19 December 2009; accepted 17 January 2010; advance online publication 25 February 2010. doi:10.1038/ajh.2010.15

previously described.[19] From 1988 to 1995, we contacted all 4,969 subjects, aged ≥35 years, who lived in four districts of Ohasama Town. Subjects who were not at home during the normal working hours of the data collection nurses (n = 1,057) and those hospitalized (n = 166) or incapacitated (n = 94) were ineligible. Home BP data were obtained from 2,760 subjects who collected their own data more than three times during the 4-week study period. This criterion was based on our previous observation that the average BP value obtained during the first 3 days was not significantly different from the values obtained for the entire study period. Casual BPs were not obtained for 256 subjects who did not participate in annual health check-ups. In order to examine the risk of the first onset of stroke, 114 individuals who had a previous history of stroke were further excluded from the present analysis. Therefore, the study population consisted of 2,390 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 subject.

BP measurement. Subjects were seated at rest for ≥2 min, and then casual BP was measured by well-trained nurses or technicians. In Ohasama, BPs were measured twice consecutively during the health check-up, using a semiautomatic BP measuring device (USM700F; Ueda Electronic Work, Tokyo, Japan) based on the microphone method.

We used the following procedure to ascertain the accuracy of home BP. Briefly, health education classes were conducted by physicians and well-trained public health nurses to inform the population of the significance of home BP recording and to teach them how to measure their own BP. Approximately 80% of household members living in Ohasama Town attended the classes; public health nurses visited all of the remaining households to provide instruction on home BP measurement. After their ability to measure home BP was verified, subjects were asked to measure their own home BP in a sitting position every morning within 1 h after waking and after ≥2 min of rest, and to record the measurements for 4 weeks. If individuals were taking antihypertensive drugs, home BP was measured before medication was taken. These procedures were described in detail in our previous report.[20] Home BP was measured with a semiautomatic BP measuring device (HEM401C; Omron Healthcare, Kyoto, Japan) based on the cuff-oscillometric principle, which generates a digital display of systolic and diastolic BP.

The devices for measurement of casual BP and home BP were calibrated before the start of the study.[20] All devices met the criteria set by the Association for the Advancement of Medical Instrumentation.[21]

Classification of groups. Subjects were classified into 12 groups based on their treatment status of antihypertensive medication, and their home BP levels or casual BP levels, respectively: optimal (home BP <115/75 mm Hg, casual BP <120/80 mm Hg), normal (home BP <125/80 mm Hg, casual BP <130/85 mm Hg), high normal (home BP <135/85 mm Hg, casual BP <140/90 mm Hg), grade 1 hypertension (home BP <150/95 mm Hg, casual BP <160/100 mm Hg), grade 2 hypertension (home BP <165/105 mm Hg, casual BP <180/110 mm Hg), and grade 3 hypertension (home BP ≥165/105 mm Hg, casual BP ≥180/110 mm Hg). The cutoff values for home BP and casual BP were based on several guidelines[22–24] and our previous studies.[19,25] The untreated group was defined as subjects who did not take any antihypertensive medication regardless of their BP levels, while the treated group was defined as subjects who took antihypertensive medications regardless of their BP levels. We used data that were collected at the beginning of the study for classification.

Status of use of antihypertensive medication. Subjects' characteristics, including age, sex, body mass index, smoking status, drinking status, use of antihypertensive medication, history of cardiovascular disease, diabetes mellitus, and hypercholesterolemia, were obtained from the initial questionnaire survey and regular check-up results. We reviewed the medical records of Ohasama Hospital to confirm the treatment status of antihypertensive medication.

Follow-up and risk ascertainment. In this study, we accumulated follow-up data until 31 December 2004. The incidence and past history of stroke were investigated by use of the Stroke Registration System of Iwate Prefecture, death certificates, receipt of National Health Insurance, and questionnaires sent to each household at the time of home BP measurement. This was then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital in the town. Computed tomography scan and magnetic resonance imaging of the brain were available, and >90% of the subjects had their regular check-ups at this facility. We defined stroke as a clinical disorder with focal brain dysfunction. The diagnostic criteria of stroke and their subtypes were based on the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.[26] We used computed tomography scan and magnetic resonance imaging to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis in this study included only the first event for those who had multiple nonfatal events. Cardiovascular disease risks were obtained from the questionnaires and medical records at Ohasama Hospital.

Data analysis. Casual BP of each subject was the average of two consecutive casual BP readings. Home BP values were the average of all home measurements per subject. The risk of first stroke was examined by using the Cox proportional hazards model. The dependent variable was the number of days from the measurement of the initial BP to the event or censoring for survivors until 31 December 2004. The independent variables were age, sex, obesity, smoking status, drinking status, history of diabetes mellitus, hypercholesterolemia, past history of cardiovascular disease, and subgroups of home BP or casual BP classifications. The estimated relative hazard (RH) and 95% confidence intervals of variables

were derived from the coefficient and s.e.m. determined by the Cox model. The RH was expressed relative to untreated individuals with optimal BP (RH = 1) except for diastolic casual BP (those with normal BP). All data were expressed as mean (s.d.) unless otherwise stated. $P < 0.05$ (two-sided test) was considered statistically significant. The SAS system (version 9.13; SAS Institute, Cary, NC) was used for all statistical calculations.

RESULTS

The subjects were followed up for median of 11.9 (interquartile 9.8–15.2) years, to a maximum of 16.9 years. The characteristics of subjects are shown in **Table 1**. The mean number of measurements for home BP of all subjects was 22.8 (7.4).

Table 1 | Clinical characteristics among subjects

		AHM		
Variables	All subjects	Untreated	Treated	*P* values
Number of subjects	2,390	1,690	700	
Age (years)	59.3 ± 12.2	56.5 ± 12.0	66.2 ± 9.6	<0.01
Male (%)	38.6	39.0	37.6	NS
Body mass index (kg/m^2)	23.5 ± 3.1	23.2 ± 2.9	24.1 ± 3.4	<0.01
Past history of CVD (%)	0.7	0.4	1.3	0.030
Diabetes mellitus (%)	9.6	8.0	13.3	<0.01
Hypercholesterolemia (%)	27.7	23.0	38.9	<0.01
Current smoking (%)	19.5	21.1	15.9	<0.01
Current drinking (%)	26.6	27.0	25.6	NS
Use of AHM (%)	29.3	N/A		
Systolic HBP (mm Hg)	124.3 ± 15.1	120.0 ± 13.4	134.7 ± 13.8	<0.01
Diastolic HBP (mm Hg)	74.6 ± 10.0	72.6 ± 9.2	79.3 ± 10.0	<0.01
Systolic CBP (mm Hg)	131.0 ± 17.9	127.8 ± 17.0	138.6 ± 17.8	<0.01
Diastolic CBP (mm Hg)	74.5 ± 11.3	73.2 ± 10.8	77.5 ± 11.8	<0.01

Values are expressed as mean ± s.d. *P* values were calculated using Student's *t*-test (continuous variables) or Fisher's exact test (categorical variables).
AHM, antihypertensive medication; CBP, casual-screening BP; CVD, cardiovascular disease; HBP, self-measurement of home BP; NS: not significant.

We observed 242 incident cases of first stroke among the 2,390 individuals: 173 (71%) cerebral infarction, 53 (22%) intracerebral hemorrhage, and 16 (7%) subarachnoid hemorrhage. Among untreated subjects, there were 116 (6.9%) stroke cases, whereas there were 126 (18.0%) cases among subjects taking antihypertensive medication.

Table 2 indicates the RH of stroke and the subtypes among treated subjects in reference to the risk for untreated subjects. Treated subjects had significantly higher risk for stroke than untreated subjects based on home BP (RH =1.48), as well as on casual BP (RH = 1.78) adjusted for systolic BP values and characteristics. Treated subjects had similarly higher risk for cerebral infarction than untreated subjects. For the risk of intracerebral hemorrhage and subarachnoid hemorrhage, there was no significant risk difference between treated and untreated subjects because of the insufficient number of events. The results were essentially similar when diastolic BP, instead of systolic BP, was used as a covariable adjusted factor in the Cox model.

Figure 1 indicates the risk of first stroke among 12 categories based on casual BP levels and usage of antihypertensive medication. The RH increased linearly with an increase in the grade of BP category among untreated subjects (trend $P < 0.01$). However, no stepwise increase in risk was observed among treated subjects (trend *P*: not significant). The interaction analysis indicated that casual BP category did not significantly interact with antihypertensive medication.

The risk of first stroke for the 12 categories based on home BP is shown in **Figure 2**. In contrast to **Figure 1** based on casual BP, the RH increased linearly with an increase in the grade of BP category among treated (trend $P < 0.01$) as well as untreated subjects (trend $P < 0.01$). When compared to untreated individuals with optimal BP, untreated subjects with normal BP tended to have a higher risk for stroke (RH 1.68, 95% confidence intervals 0.92–3.09), and those with high-normal BP had significantly higher risk (RH 2.55, 95% confidence intervals 1.40–4.64). There was no significant interaction between antihypertensive medication and home BP category. Similar results were observed when continuous BP information was used (**Table 3**); among 700 treated subjects, the RHs for stroke risk based on home BP increased linearly with the elevation of BP values, whereas no significant risk increase was observed when based on casual BP values.

Table 2 | Risk of stroke in treated subjects after adjustment for covariables with and without BP values

	Without BP			With casual BP			With home BP		
	RH	95% CI	*P* values	RH	95% CI	*P* values	RH	95% CI	*P* values
Total stroke	1.91	1.45–2.51	<0.01	1.78	1.35–2.35	<0.01	1.48	1.11–1.97	<0.01
Infarction	2.23	1.61–3.09	<0.01	2.09	1.50–2.91	<0.01	1.76	1.26–2.48	<0.01
Hemorrhage	1.43	0.78–2.59	NS	1.30	0.72–2.37	NS	1.09	0.59–2.03	NS
SAH	0.93	0.30–2.91	NS	0.85	0.27–2.72	NS	0.60	0.19–1.96	NS

RHs of first stroke and subtypes in treated subjects compared with untreated ones in the Cox model are indicated. Untreated subjects are defined as reference for each analysis. All models were adjusted for age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. "Without BP" model was not adjusted for any BP values. "With casual BP" model was adjusted for casual systolic BP values. "With home BP" model was adjusted for home systolic BP values.
CI, confidence intervals; hemorrhage, intracranial hemorrhage; infarction, cerebral infarction; RH, relative hazard; SAH, subarachnoid hemorrhage; NS, not significant.

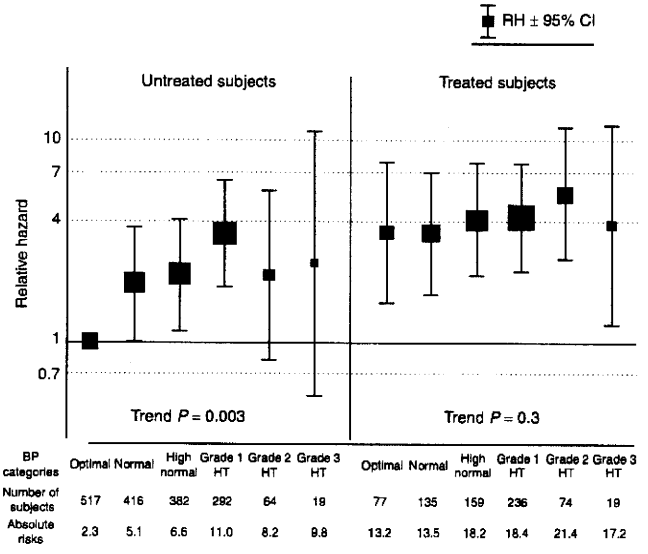

Figure 1 | Risk of first stroke among 12 categories based on casual blood pressure (BP) levels and usage of antihypertensive medication. Relative hazard (RH) and 95% confidence intervals (CIs) for classifications based on BP levels are displayed. Optimal (<120/80 mm Hg); normal (120/80–129/84 mm Hg); high normal (130/85–139/89 mm Hg); grade 1 hypertension (HT) (140/90–159/99 mm Hg); grade 2 HT (160/100–179/109 mm Hg); and grade 3 HT (≥180/110 mm Hg). Optimal BP category was treated as the reference category. Closed squares indicate the RH point and are sized in proportion to the number of events observed. Trend *P* value expresses the linearity among groups. The covariables were adjusted for age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. Absolute risks display incidence per 1,000 person-years.

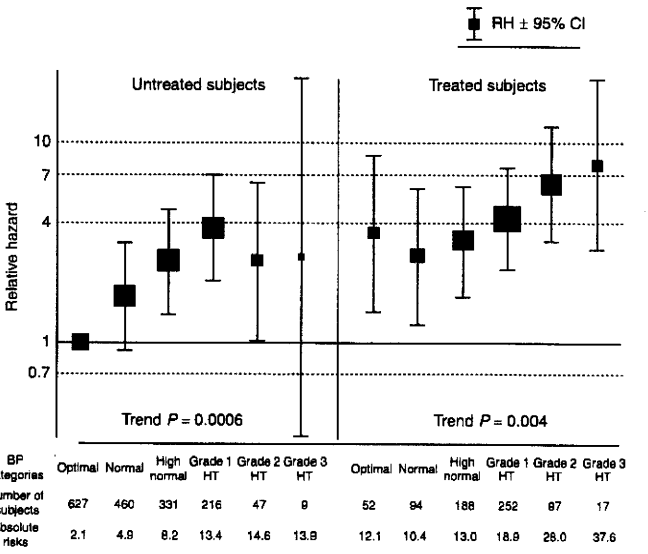

Figure 2 | Risk of first stroke among 12 categories based on home blood pressure (BP) levels and usage of antihypertensive medication. Relative hazard (RH) and 95% confidence intervals (CIs) for classifications based on BP levels are displayed. Optimal (<115/75 mm Hg); normal (115/75–124/79 mm Hg); high normal (125/80–134/84 mm Hg); grade 1 hypertension (HT) (135/85–149/94 mm Hg); grade 2 HT (150/95–165/105 mm Hg); and grade 3 HT (≥165/105 mm Hg). Optimal BP category was treated as the reference category. Closed squares indicate the RH point and are sized in proportion to the number of events observed. Trend *P* value expresses the linearity among groups. The covariables were adjusted for age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. Absolute risks display incidence per 1,000 person-years.

Table 3 | Risk of stroke according to BP value as the continuous variable

	Untreated			Treated		
	RH	95% CI	*P* values	RH	95% CI	*P* values
Systolic CBP	1.26	1.06–1.50	<0.01	1.08	0.91–1.28	NS
Diastolic CBP	1.22	1.01–1.47	0.038	1.10	0.92–1.32	NS
Systolic HBP	1.38	1.16–1.65	<0.01	1.40	1.17–1.68	<0.01
Diastolic HBP	1.35	1.12–1.63	<0.01	1.23	1.02–1.50	0.035

RHs indicated the relative hazards of first stroke associated with a 1 s.d. increase for BP variables in the Cox model. All models were adjusted for age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease.
BP, blood pressure; CBP, casual-screening BP; CI, confidence intervals; HBP, self-measurement of home BP; NS, not significant; RH, relative hazard.

When home BP and casual BP were simultaneously included into the Cox model as categorical variables, casual BP did not predict stroke incidence independent of home BP among untreated (home BP: $P = 0.023$, casual BP: not significant) or treated subjects (home BP: $P < 0.01$, casual BP: not significant). Similar results were observed when continuous BP information was used (untreated; home BP: $P = 0.010$, casual BP: not significant. Treated; home BP: $P < 0.01$, casual BP: not significant).

DISCUSSION

This is the first study to compare the prognostic values of home BP and casual BP in relation to the use of antihypertensive medications in a general population. The risk of first stroke in individuals using antihypertensive medications was significantly higher than that in untreated individuals for a given level of baseline BP when based on home BP as well as casual BP. Moreover, home BP–based classification showed a linear increase in stroke risk among treated individuals, whereas a linear association was not observed when based on casual BP.

Although many large-scale randomized trials have proved the beneficial effects of lowering BP in preventing cardiovascular diseases,[8–11] individuals treated with antihypertensive medication were characterized as having a worse prognosis than those without treatment in several observational studies conducted among the general population.[12–17] We demonstrated that individuals using antihypertensive medications had a higher stroke risk compared to those without treatment after adjustment for major confounding factors and BP values based on home BP as well as casual BP. These results were also consistent with those obtained in previous studies that used casual BP values.[12–16] The results did not indicate that antihypertensive therapy increases the risk of stroke, as we have discussed in detail in our previous study.[17] One possibility for the higher stroke risk in treated subjects compared to untreated subjects was that treatment *per se* was a sort of marker, not

only for greater severity of hypertension, but also for other cardiovascular risk factors such as diabetes mellitus or hypercholesterolemia, which led to a greater rate of events.

Hypertensive patients are exposed to atherosclerotic risk and target organ damage for long periods of time both before and during therapy; early introduction of antihypertensive medication has beneficial long-term effects for vascular events.[27] As there are several kinds of undetectable residual confounding factors in addition to the classical risk factors,[28] stroke incidence even adjusted by classical risk factors including age would be high among treated individuals.[15]

Previously, the association of stroke and usage of antihypertensive medications based on home BP had not been investigated. This study indicated that home BP has a linear relationship to stroke incidence ($P < 0.01$), whereas there is no significant relationship between casual BP levels and stroke incidence among treated subjects. Casual BP values in this study were defined as the average of only two measurements; this might account for the weaker predictive power of casual BP for stroke risk when compared with home BP. However, in our previous study, even one measurement value of home BP on the first occasion was superior to the average of two casual BP values in terms of stroke prediction.[2] These results suggest that, in addition to the number of measurements, other factors may be associated with the superior predictive power of home BP.

We have repeatedly reported on the high reproducibility, reliability, and predictive power of home BP.[1,18,20,25,29–33] One of the possible reasons is that home BP might be more related with the condition of night-time BP. Night-time BP based on ambulatory BP has great prognostic accuracy.[34] Moreover, masked hypertension and white coat hypertension were observed in ~20% of treated Japanese individuals.[35] White coat hypertension is known as an essentially benign condition; however, individuals who have masked hypertension (casual BP within normal limits) have a worse prognosis than sustained normotensives.[36–39] A certain proportion of treated individuals with masked hypertension may be assigned to optimal or normal BP groups based on casual BP in this study, and this could have contributed to high stroke incidence in those groups. It seems reasonable to suppose that home BP rather than casual BP should be used as the management tool to achieve individual treatment goals. In this study, we used a standardized procedure to measure home BP. There are many advantages of home BP, partly related to the multiple measurements over a long period of time in the same setting. Therefore, practitioners should encourage their patients to measure home BP on a regular basis in a familiar setting to increase the accuracy of the BP data that they report back to the physician.

The number of untreated hypertensive subjects in this study was relatively small, which would result in an extension of 95% confidence intervals. It should be emphasized that hypertensive subjects are usually advised to consult a doctor after the annual health check-up, and antihypertensive medication is usually prescribed. However, the number of treated subjects with grade 1 hypertension was much greater than the number in the optimal, normal, and high-normal BP groups, indicating that BP was not adequately controlled among treated individuals. Poor control of hypertension is still a serious clinical issue even in Japan.[17] Health-care providers should monitor for residual cardiovascular risks among treated patients, and be alert for untreated hypertensive subjects regardless of BP information.

In 1992, 70% of hypertensive subjects of this Ohasama population were treated with the sustained-release tablet form of nifedipine, nicardipine, or diltiazem.[40] At that time, β-blockers, diuretics, and angiotensin-converting enzyme inhibitors were prescribed for 30, 25, and 10% of hypertensive subjects, respectively.[40] Because the duration of action of most antihypertensive drugs used in 1992 was <12 h for a twice-a-day prescription and <24 h for a once-a-day prescription,[33] it is likely that home BP in the morning was mediated at least in part by insufficient duration of action of the antihypertensive drugs. Caution is necessary when comparing or applying the results of this study to patients in other countries since diuretics and β-blockers have been used more extensively in European countries and the United States than in Japan. However, it must be noted that, although new long-acting calcium-channel blockers and new angiotensin II receptor blockers have been marketed, the control of home BP is reported to be far from ideal even at the present time.[41]

This study should be interpreted within the context of potential limitations. First, although possible confounding factors were adjusted in the Cox model, several characteristics of treated and untreated subjects were different—e.g., treated subjects were ~10 years older than untreated subjects. It is noteworthy that these variables might not be fully adjusted in the model. Second, BP data and treatment status information were obtained at the beginning of the follow-up period, as the objective of the study was to examine the stroke risk as defined according to initial baseline BP and treatment status. Third, the stroke mortality rates in Eastern Europe, China, the "Stroke Belt" in the southeastern United States, and Japan are ~2–6 times higher than those in other European countries, the United States outside of the "Stroke Belt", and Canada.[42] Such differences may be explained by differential environmental and genetic risk factors; therefore, other populations might have different results. Additional population-based randomized trials in other countries and studies using different prognostic parameters including cardiovascular attacks and total mortality are needed to clarify the clinical significance and reference values of home BP in treated individuals.

In conclusion, the results of this study suggest a strong association between elevated home BP and increased risk of stroke among untreated and treated individuals. Home BP would be a better tool to assess stroke risk associated with BP levels, especially in treated hypertensives.

Acknowledgments: We are grateful to the residents in Ohasama Town, all related investigators and study staff, and staff members of the Ohasama Town Government, Ohasama Hospital and Iwate Prefectural Stroke Registry for their valuable support on this project. This study was supported in part by Grants for Scientific Research (15790293, 16590433, 17790381, 18390192,

18590587, 19590929, and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; Grant-in-Aid (H17-Kenkou-007, H18-Junkankitou [Seishuu]-Ippan-012, and H20-Junkankitou [Seishuu]-Ippan-009, 013) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477, and 20.54043); Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; Uehara Memorial Foundation; Takeda Medical Research Foundation; National Cardiovascular Research Grants; and Biomedical Innovation Grants. The study sponsors had no direct role in the study design, data analysis, data interpretation, or writing of this article.

Disclosure: The authors declared no conflict of interest.

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Factors Associated With Day-By-Day Variability of Self-Measured Blood Pressure at Home: The Ohasama Study

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BACKGROUND

We previously reported that high day-by-day blood pressure (BP) variability derived from self-measured BP at home (home BP) predicted cardiovascular mortality over and beyond other risk factors. The objective of this study is to clarify the determinants of the day-by-day home-BP variability.

METHODS

We conducted a cross-sectional community survey in 1,215 inhabitants (female gender 59%, mean age 62 years) of Ohasama, Japan. The subjects measured their BP and heart rate once every morning and once every evening for 4 weeks. The day-by-day BP variability and heart rate variability were defined as within individual standard deviation of all home BP and heart rate, respectively. We also considered coefficient of variation (CV). These parameters in the morning and those in the evening were calculated separately.

RESULTS

The level and standard deviation of home systolic/diastolic BP (SBP/DBP) in the morning were 123.4 ± 15.1/75.7 ± 9.0 mm Hg and 8.6 ± 3.1/5.8 ± 2.0 mm Hg. Multivariate linear regression analysis demonstrated that older age, female gender, elevated home BP, low home heart rate, and elevated home heart rate variability were significant determinants of elevated home-BP variability. In addition to these factors, alcohol intake and sedentary lifestyle were also determinants of elevated home-BP variability in the evening.

CONCLUSIONS

Day-by-day home-BP variability was associated with home BP, alcohol intake or sedentary lifestyle. Whether modifying these factors would reduce BP variability and whether such reduction would lead to better outcomes needs further study.

Keywords: *blood pressure; blood pressure measurement/monitoring; epidemiology; hypertension; population science; risk factors*

Am J Hypertens 2010; **23**:980-986 © 2010 American Journal of Hypertension, Ltd.

Hypertension is usually diagnosed based on blood pressure (BP) values determined by physicians at clinics, i.e., casual-clinic BP. However, values obtained at clinics do not necessarily represent BP outside the medical setting, because of the "white-coat" effect, circadian variation, short-term and random variation in BP, and the paucity of measurements.[1] In contrast, self-measurement of BP at home (home BP) allows multiple values to be obtained over a long period in familiar, nonthreatening surroundings, thus avoiding the so-called white-coat effect.[2,3] Results indicate that the predictive power of home BP is more accurate than casual BP values obtained by medical practitioners.[4–6] Home measurement of BP also allows the patient to be more actively involved in their treatment, thereby improving compliance.[7,8] Therefore, home-BP measurement is widely practiced in developed countries.

The clinical significance of home BP is mainly due to being able to obtain several measurements,[6] which can also indicate long-term daily variability. Our recent study[9] showed that high daily-BP variability derived from home BP indicated a risk of total, cardiovascular, and stroke mortality, independently of BP value and other cardiovascular risk factors.[9] Thus, the factors that affect daily home-BP variability should be defined to improve cardiovascular mortality rates. The determinants of daily home-BP variability have not been investigated. Short-term heart rate variability is closely associated with BP variability.[10,11] We therefore hypothesized that long-term heart rate variability also has a role in long-term BP control. With

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Received 19 January 2010; first decision 21 February 2010; accepted 2 April 2010; advance online publication 6 May 2010. doi:10.1038/ajh.2010.94

this in mind, we examined lifestyle-related factors and heart rate variability that might affect daily home-BP variability in the general Japanese population.

METHODS

Study population. This investigation comprised part of the Ohasama study, a community-based BP measurement project established in 1987. The socioeconomic and demographic characteristics of this region and details of the project have been described.[12,13] The institutional review board of Tohoku University School of Medicine, Sendai, Japan and the Department of Health of the Ohasama Town Government approved the study. Details of participant selection have been described.[14,15] In February 1998, the total population of three of the four regions of Ohasama numbered 4,208. Of these, 2,769 were ≥40 years of age. Among this subgroup, 621 worked outside the town and were considered ineligible for the study. This exclusion was necessary because the study participants had to wear ambulatory BP-monitoring devices, which required them to be in town during working days. Of the remaining 2,148 residents, those who were hospitalized (n = 124), mentally ill or bedridden (n = 40) were not invited to participate. Thus, from a total of 1,984 eligible residents, 1,662 provided written informed consent to participate in the BP-measurement program. We excluded 281 individuals from the present analysis because they obtained <10 home-BP recordings in the morning or evenings during the 4-week study period. This exclusion criterion was based on our recent observation that the standard deviation of BP and heart rate for the first 10 measurements did not significantly differ from the mean for a 1-month measurement period.[9] We also excluded individuals who did not respond to the questionnaire about lifestyle and health (n = 166). Therefore, the study population comprised 1,215 individuals.

Measurement of home BP and heart rate. The procedures and the measuring device used for home-BP measurements have been described in detail elsewhere.[12,16] Briefly, physicians and public health nurses conducted health education classes to inform the participants about home-BP recording and to teach them how to measure their BP. The participants then measured their BP once every morning and once every evening, and recorded the results for 4 weeks. Morning measurements were taken while seated within 1 h after awakening, before breakfast or taking any drugs and having rested for at least 2 min.[17] Evening measurements were taken while seated just before going to bed, and after resting for at least 2 min.[17] Home BP and heart rate were measured using an HEM701C automatic device (Omron Healthcare, Kyoto, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic/diastolic BP (SBP/DBP) and heart rate. Home BP and heart rate of an individual were defined as the mean of all measurements obtained for each individual and separately for SBP and DBP. The daily variability of home BP was defined as the standard deviation of home BP for each individual.[9,12] We also considered the coefficient of variation (CV), defined as the within individual standard deviation divided by the mean BP value. The daily variability of home heart rate was defined in the same manner. These parameters obtained in the morning and in the evening were separately calculated. The device used for the home-BP measurements has been validated[18] and satisfies the criteria of the Association for the Advancement of Medical Instrumentation.[19]

Data collection. Trained public health nurses measured anthropomorphic characteristics at the time of annual health check. Individual information about age, smoking[20] or alcohol consumption,[20] antihypertensive medication, history of stroke, heart diseases, diabetes mellitus, or hypercholesterolemia, coffee or green tea consumption, activity levels (time spent walking per day), and sleep status (hours of sleep per day) was obtained from a questionnaire sent to each participant at the time of starting the home-BP and heart rate measurement. With regard to previous medical history, subjects were categorized according to their answer to the question, "Have you ever had the following diseases? Stroke (yes or no), heart diseases (yes or no), diabetes mellitus (yes or no), or hypercholesterolemia (yes or no)." Furthermore, the subjects were asked about the average frequency of consumption of coffee; this information was recorded as "no consumption," "1–2 cup/week," "3–4 cup/week," "5–6 cup/week," "1 cup/day," "2–3 cup/day," "4–6 cup/day," "7–9 cup/day," or "≥10 cup/day." These subjects were then classified into two categories according to frequency of consumption of coffee: ≥1 cup/day or <1 cup/day. Similarly, green tea consumption was defined as ≥1 cup/day or <1 cup/day. With regard to activity levels (time spent walking per day), subjects were categorized according to their answer to the question, "How many times do you normally walk per day?" This information was recorded as "≤1 hours/day," "1–3 hours/day," "3–5 hours/day," or "≥5 hours/day." The responses were divided into two groups according to the frequency of walk: ≥1 h/day or <1 h/day. The question on sleep status (hours of sleep per day) was worded, "How many times do you normally sleep?" The duration of sleep were dichotomized into ≥8 h/day and <8 h/day. Information about antihypertensive medication was confirmed from medical records stored at Ohasama Hospital.

Personality assessment. We analyzed the association between home-BP variability and the personality of a subset of 828 individuals as measured by the Japanese version of the short-form Eysenck personality questionnaire.[15,21,22] The short-form Eysenck personality questionnaire consists of 48 items, yielding the following four scores: personality psychoticism (P score), which is an index of deviation tendencies and cooperation; personality extroversion (E score), which is an index of sociability and cheerfulness; personality neuroticism (N score), which is an index of anxiety and emotional instability; and social desirability (L score). Because a standard value for the L score has not been established, we used the first three scores (P, E, N) for the analysis. Personality has been estimated according to a quartile based on the P, E and N scores[15] and the validity and

reliability of the Japanese version of the short-form Eysenck personality questionnaire has been confirmed.[21]

Statistical analysis. Data are expressed as means ± s.d. Variables were compared using Pearson's correlation coefficient, the *t*-test, analysis of variance or multivariate linear regression analysis as appropriate. For subjects with unknown history of heart diseases (17%), coffee consumption (11%), and duration of sleep (3%), we set design variables coded 1 or 0 if the data was missing or present, respectively. In the multiple regression analyses, the design variables were included as independent variables. The threshold level for statistical significance was established at $P < 0.05$ (two-sided test). All data were statistically analyzed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study participants

Of the 1,215 participants with a mean age of 62.6 ± 11.6 years 61.7% (n = 750) were female, 30% were obese (body mass index ≥25 kg/m^2)[23], 16.6% were current smokers, and 38.1% currently consumed alcohol. A history of stroke, heart diseases, diabetes mellitus, and hypercholesterolemia were identified in 3.9, 8.6, 12.9, and 15.4%, respectively, of the participants. The mean numbers of morning and evening home-BP measurements were comparable (24.3 ± 4.4 vs. 24.3 ± 4.7; P = 0.9). The morning home SBP/DBP level was 123.4 ± 15.1/75.7 ± 9.0 mm Hg, which was significantly higher than that in the evening (121.0 ± 14.6/73.5 ± 8.9 mm Hg, $P <$ 0.0001). On the other hand, the standard deviation of home SBP/DBP (mm Hg) was significantly lower in morning than in the evening (8.6 ± 3.1/5.8 ± 2.0 vs. 8.8 ± 3.1/6.2 ± 2.1 mm Hg; $P < 0.005$). Of the 1,215 participants, 380 (29%) were medicated with antihypertensive drugs as follows: calcium antagonists, 245 (64%); angiotensin-converting enzyme inhibitors, 71 (17%); β-blockers, 60 (16%); α-blockers, 33 (9%); diuretics 25 (7%); and others, 6 (2%).

Bivariate analysis of factors associated with standard deviation of home BP

Table 1 and **Figure 1** summarize the results for the standard deviation of home BP. Variables such as gender, body mass index (9% with missing data), green tea consumption (18% with missing data), past history of stroke (23% with missing data), diabetes mellitus (19% with missing data), and hypercholesterolemia (22% with missing data) were not associated with the standard deviation of home BP.

Multivariate linear regression analysis of factors associated with standard deviation of home BP

We performed a multivariate linear regression analysis including variables shown in **Table 1**. The results showed that the morning standard deviation of home SBP was associated positively with female gender, age, home SBP, and standard deviation of home heart rate, and negatively with home heart rate (**Table 2**). The evening standard deviation of home SBP

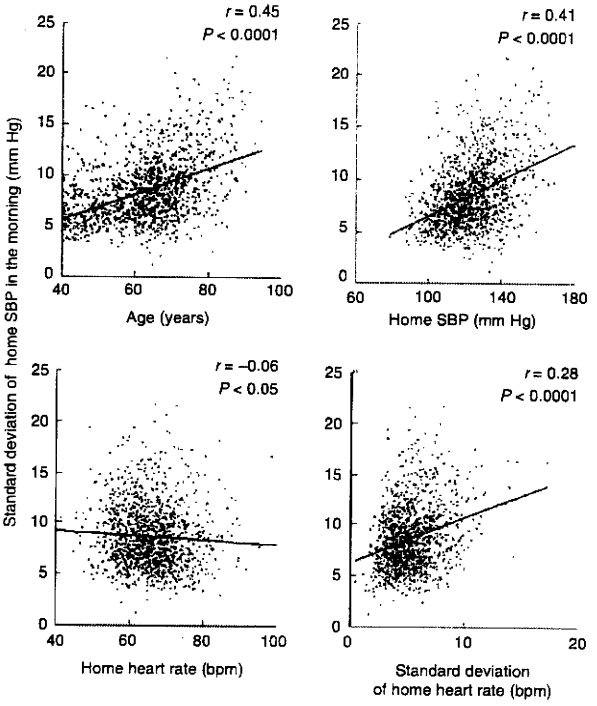

Figure 1 | Correlation of morning home-SBP variability with age, home SBP, home heart rate, and heart rate variability. Variables were tested by Pearson's correlation analysis. bpm, beats per minute; SBP, systolic blood pressure.

was similarly associated with these variables. The standard deviation of evening home SBP was also associated positively with current alcohol consumption, and negatively with time spent walking. The results of the factors associated with the standard deviation of home DBP were similar. The results of our sensitivity analysis of home-SBP variability in the morning in which we separately considered males and females, and being medicated or not with antihypertensive drugs were confirmatory (**Table 3**).

Multivariate linear regression analysis of factors associated with CV of home BP

We also analyzed the CV of home BP using a method similar to that with which the standard deviation of home BP was examined. We did not include home BP and heart rate in the model, because the CV values of BP and of heart rate were defined as the within individual standard deviation divided by the mean BP and heart rate. The results were consistent with those of the standard deviation of home BP, except for no significant association between standard deviation of evening home DBP and time spent walking (regression coefficient, −0.26, P = 0.15).

Effects of antihypertensive medication on daily home-BP variability

The standard deviation of morning home SBP was significantly increased in patients taking calcium antagonists (with vs. without: 9.9 vs. 8.2 mm Hg; $P < 0.0001$), angiotensin-converting enzyme inhibitors (with vs. without: 10.0 vs. 8.5 mm Hg; P = 0.0001) and α-blockers (with vs. without: 10.9 vs. 8.5 mm Hg; $P < 0.0001$). The other antihypertensive drugs were not

Table 1 | Bivariate analysis of factors associated with standard deviation of home BP

		Systolic		Diastolic	
		Morning	Evening	Morning	Evening
Continuous variables (correlation coefficients with standard deviation of home BP)					
Age		0.45**	0.41**	0.20**	0.12**
Home BP		0.41**	0.40**	0.15**	0.20**
Home heart rate		−0.06*	0.02	0.01	0.05
Standard deviation of home heart rate		0.28**	0.28**	0.38**	0.41**
Categorical variables (mean ± s.d. (mm Hg))					
Males		8.7 ± 3.0	8.7 ± 2.9	5.7 ± 2.0	6.4 ± 2.1
Females		8.4 ± 3.2	8.9 ± 3.2	5.9 ± 2.1	6.1 ± 2.0
Current smoker		8.3 ± 3.0	8.5 ± 2.9	5.7 ± 1.9	6.6 ± 2.2
Formerly or never smoked		8.7 ± 3.2	8.8 ± 3.1	5.8 ± 2.1	6.1 ± 2.0
Current alcohol consumption		8.3 ± 3.0	8.8 ± 3.0	5.8 ± 2.0	6.6 ± 2.2
Former or never consumed alcohol		8.7 ± 3.2	8.7 ± 3.1	5.8 ± 2.0	6.0 ± 1.9
Treated		9.8 ± 3.5	9.9 ± 3.5	6.1 ± 2.1	6.4 ± 2.1
Untreated		8.0 ± 2.8	8.3 ± 2.8	5.7 ± 2.0	6.1 ± 2.1
History of heart diseases (n = 1,005)	Present	9.7 ± 3.6	9.3 ± 3.3	6.4 ± 2.4	6.6 ± 2.2
	Absent	8.4 ± 3.0	8.7 ± 3.0	5.7 ± 2.0	6.2 ± 2.1
Coffee consumption (n =1,077)	≥1 cup/day	8.1 ± 2.9	8.4 ± 3.1	5.7 ± 2.0	6.2 ± 2.3
	<1 cup/day	8.7 ± 3.2	8.9 ± 3.0	5.8 ± 2.0	6.2 ± 2.0
Time spent walking	≥1 h/day	8.3 ± 2.9**	8.5 ± 2.9**	5.7 ± 2.0**	6.1 ± 2.0**
	<1 h/day	9.5 ± 3.7**	9.8 ± 3.4**	6.2 ± 2.2**	6.7 ± 2.3**
Duration of sleep (n = 1,184)	≥8 h/day	9.0 ± 3.3**	9.4 ± 3.3**	5.9 ± 2.1**	6.3 ± 2.2**
	<8 h/day	8.0 ± 2.7**	8.5 ± 2.7**	5.6 ± 1.9**	6.1 ± 1.9**

BP, blood pressure.
Continuous variables were tested by Pearson's correlation analysis. Categorical variables were tested by t-test. Gender, body mass index (9% with missing data), green tea consumption (18% with missing data), past history of stroke (23% with missing data), diabetes mellitus (19% with missing data), and hypercholesterolemia (22% with missing data) were not associated with the standard deviation of home BP.
*$P < 0.05$, **$P < 0.01$.

associated with the standard deviation of morning home SBP. However, multiple linear regression analysis adjusted for gender, age, and home BP revealed no significant association between medication with each antihypertensive drug and daily home-BP variability (all $P > 0.2$).

Association between personality and daily home-BP variability

We found using analysis of variance that personality was not significantly associated with daily home-BP variability in a subset of 828 individuals (all $P > 0.1$; **Table 4**). Personality is presumably associated with other factors associated with daily home-BP variability, so we adjusted for gender, age, and home BP, after which no significant associations were identified (all P for trend >0.2).

DISCUSSION

We defined factors that affect the standard deviation of home BP in a general population. In multivariable analyses, home-BP variability was associated positively with female gender, age, home-BP value, home heart rate variability, and current alcohol consumption, and negatively with home heart rate and time spent walking. Among the factors influencing daily home-BP variability, home BP, alcohol consumption and time spent walking were modifiable. Our recent study showed that a 3.2-mm Hg increase in the standard deviation of home SBP is associated with an increased hazard ratio for total (hazard ratio = 1.13), cardiovascular (hazard ratio = 1.26), and stroke mortality (hazard ratio = 1.29).[9] The joint effects of modification of these factors (10-mm Hg reduction in home BP, alcohol restriction and walking ≥1 h per day) correspond to an approximate 1-mm Hg decrease in the standard deviation of home SBP, suggesting that these modifications will decrease cardiovascular mortality risk by $(1.26^{1/3.2} - 1) = 7.4\%$.

BP might fluctuate more over several days, weeks, or months.[16] Long-term fluctuations in arterial BP can be quantified and interpreted only by observing a large number of measurements for a long period. Casual-clinic measurements do not necessarily provide a representative estimate of an individual's BP outside the medical setting, because of the "white-coat" effect, circadian variation, short-term and random variations in BP, and the paucity of measurements.[1] Home-BP

Table 2 | Multivariate regression coefficients for factors associated with standard deviation of home BP

	Standard deviation of home SBP (per mm Hg)		Standard deviation of home DBP (per mm Hg)	
Variables	**Morning**	**Evening**	**Morning**	**Evening**
Gender (female = 1, male = 0)	0.92**	0.89**	0.73**	0.46**
Age (per 10 years)	0.85**	0.79**	0.31**	0.20**
Home BP (per 10 mm Hg)	0.55**	0.55**	0.37**	0.34**
Home heart rate (per 5 bpm)	−0.21**	−0.11*	−0.14**	−0.18**
Standard deviation of home heart rate (per bpm)	0.48**	0.40**	0.41**	0.40**
Smoking (current = 1)	0.15	−0.05	0.11	0.33
Alcohol consumption (current = 1)	0.20	0.56**	0.21	0.49**
Antihypertensive medication (present = 1)	0.11	0.24	−0.16	−0.05
Heart diseases (present = 1)	0.05	−0.45	0.32	0.13
Coffee consumption (≥1 cup/day = 1)	0.22	0.25	0.11	0.08
Time spent walking (≥1 h/day = 1)	−0.26	−0.50**	−0.01	−0.26*
Duration of sleep (≥8 h/day = 1)	0.21	0.06**	0.12	0.06

BP, blood pressure; bpm, beats per minute; DBP, diastolic BP; NA, not analyzed; SBP, systolic BP.
*$P < 0.05$, **$P < 0.01$.

Table 3 | Multivariate regression coefficients for factors associated with standard deviation of morning home SBP in sensitivity analysis

	Stratification			
Variables	**Males ($n = 465$)**	**Females ($n = 750$)**	**Untreated ($n = 835$)**	**Treated ($n = 380$)**
Gender (female = 1, male = 0)	NA	NA	0.96**	0.58
Age (per 10 years)	0.76**	0.92**	0.85**	0.94**
Home SBP (per 10 mm Hg)	0.62**	0.52**	0.51**	0.66**
Home heart rate (per 5 bpm)	−0.25**	−0.19**	−0.13*	−0.31**
Standard deviation of home heart rate (per bpm)	0.56**	0.42**	0.49**	0.42**
Smoking (current = 1)	0.02	1.37	0.42	−0.65
Alcohol consumption (current = 1)	0.18	0.22	0.31	−0.20
Antihypertensive medication (present = 1)	−0.14	0.24	NA	NA
Heart diseases (present = 1)	0.71	−0.45	−0.05	0.02
Coffee consumption (≥1 cup/day = 1)	0.22	0.21	0.30	−0.13
Time spent walking (≥1 h/day = 1)	−0.20	−0.29	−0.20	−0.36
Duration of sleep (≥8 h/day = 1)	0.37	0.16	0.24	0.13

bpm, Beats per minute; NA, not analyzed because of stratification of gender and antihypertensive medication; SBP, systolic blood pressure.
*$P < 0.05$, **$P < 0.01$.

measurement presently offers the most valuable means of obtaining reliable data about long-term variability in BP.

Few studies have examined long-term variability in BP. We previously found that the standard deviation of individual home-SBP values gradually increases with age, indicating a wider distribution of BP values among the elderly than in younger groups of both males and females.[12] The standard deviation of home DBP also gradually increases with age among elderly men.[12] In this study, more advanced age was one determinant of an elevated standard deviation of home SBP and of DBP variability, which is consistent with our previous findings.[12] Wang *et al.* examined BP variability derived from casual-clinic BP measurements in hypertensive patients[24] and found that BP variability was greater among females than males. This study identified female gender as a determinant of an elevated standard deviation of home SBP and of DBP variability, which was consistent with their findings. However, they estimated BP variability from only four readings,[24] which might be insufficient for an accurate assessment. Hata *et al.* reported long-term monthly variability in BP derived from casual-clinic BP measurements in hypertensive patients.[25,26] They found that the CV of casual-clinic BP is associated with age, body mass index, DBP, pulse pressure, heart rate, and serum total protein concentration. In addition, higher long-term BP variability was also associated with a history of angina pectoris and renal insufficiency. This study

Table 4 | Standard deviation of home BP in participants grouped according to quartiles of personality based on scores of psychoticism, extroversion, and neuroticism

Personality trait and BP variability	Trait score				P
Psychoticism	0–1 (n = 130)	2 (n = 179)	3–4 (n = 362)	5–10 (n = 157)	
Standard deviation of SBP (mm Hg)	8.0 ± 3.1	8.2 ± 2.7	8.4 ± 3.0	8.8 ± 3.5	0.13
Standard deviation of DBP (mm Hg)	5.7 ± 2.2	5.6 ± 2.0	5.6 ± 1.8	5.9 ± 2.4	0.49
Extroversion	0–3 (n = 225)	4–5 (n = 192)	6–8 (n = 231)	9–12 (n = 180)	
Standard deviation of SBP (mm Hg)	8.4 ± 3.1	8.2 ± 3.0	8.3 ± 3.2	8.7 ± 3.1	0.48
Standard deviation of DBP (mm Hg)	5.9 ± 1.9	5.7 ± 2.2	5.6 ± 1.9	5.7 ± 2.1	0.58
Neuroticism	0–3 (n = 181)	4–6 (n = 260)	7–8 (n = 177)	9–12 (n = 210)	
Standard deviation of SBP (mm Hg)	8.6 ± 3.1	8.3 ± 2.9	8.4 ± 3.2	8.4 ± 3.2	0.81
Standard deviation of DBP (mm Hg)	5.7 ± 2.0	5.7 ± 1.8	5.8 ± 2.2	5.7 ± 2.1	0.82

Variables were tested by analysis of variance.
BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.

examined a general population, and daily-BP variability was determined from home-BP measurements. Differences in the environment where BP measurements were taken (casual vs. home) and in the population (hypertensive vs. general) might have influenced the variation in results between the two studies. We previously observed that morning surge was significantly higher in heavy drinkers than in nondrinkers.[27] Our findings of this study extend the association between alcohol intake and BP variability from circadian variability to day-by-day variability.

We could not directly determine which mechanisms elevate daily-BP variability. However, our results might be explained as follows. The increase in BP variability might be partly due to the diminished baroreflex function associated with increased stiffness and decreased compliance of the large elastic arteries.[10,11] Daily-BP variability might be influenced by clinical conditions such as atherosclerosis and arteriosclerosis and lifestyle. Vaitkevicius *et al.* reported that age is associated with arterial stiffening[28] and Hara *et al.* reported that elevated home BP is closely associated with carotid atherosclerosis.[29] Kurihara *et al.* reported that alcohol consumption increases the risk of arterial stiffening[30] and Boreham *et al.* reported that physical activity is inversely associated with pulse-wave velocity.[31] Decreased compliance of large elastic arteries might eventually disturb baroreceptor reflex function, which would relate to an exaggerated pressor response to mental and physical stimuli and mediate orthostatic hypotension, postprandial hypotension, and other conditions, resulting in increased BP variability. These mechanisms may explain chronic effects of alcohol intake and sedentary lifestyle. The increased home-BP variability can be also explained by an acute effect of alcohol intake, i.e. an acute depressor effect due vasodilation.[20] Poor patient compliance with antihypertensive drug therapy might also have played a role in increasing BP variability via inadequate BP control in medical practice. However, the results were similar after patients medicated with antihypertensive drugs were excluded (**Table 3**). Therefore, poorer compliance with therapy alone might not fully explain the larger variability in BP.

Beat-to-beat heart rate variability correlates with baroreflex sensitivity.[10] An inverse relationship between BP and heart rate variability also reflects baroreflex function,[11] as heart rate variability is reflexively mediated by BP variability, which it also buffers. High home-BP variability is assumed to be mediated at least in part by a disturbed cardiac baroreflex function. However, we found a positive relationship between daily home-BP variability and daily home heart rate variability. BP was measured under controlled conditions with less psychological stress in this study, thus the relationship between short-term BP variability and heart rate variability might differ from that between long-term values. In addition, sympathetic activity might simply affect BP variability and heart rate variability toward the same direction.

This study has some limitations. Our data might not be applicable to other regional or racial groups. Individual information was obtained mainly from a self-reported questionnaire, which might be less precise than medical records. However, the information about antihypertensive medication was confirmed from medical records stored at Ohasama Hospital. The quality of the measurement procedure could have affected BP variability, although long-term reproducibility of day-by-day variability was moderate.[9] We emphasize that multivariate linear regression analysis can only suggest associations between dependent and independent variables and cannot prove a cause-and-effect relationship. We can only speculate about the mechanisms that elevate daily-BP variability. Further studies are required to detect and measure other factors that could affect daily home-BP variability, such as obstructive sleep apnea syndrome. We did not survey obstructive sleep apnea syndrome, which is a highly prevalent condition and associated with hypertension,[32] as well as cardiovascular disease.[33]

In conclusion, we identified several factors associated with daily home-BP variability in a general population. Among them, home BP, alcohol consumption, and time spent walking were modifiable. Our observational study was unable to resolve the issue of whether modifying these factors would reduce BP variability and whether such reduction would lead to better outcomes. The answers to such questions