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Original Article

Coffee Consumption and Incidence of Subarachnoid Hemorrhage: The Jichi Medical School Cohort Study

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ABSTRACT

Background: Previous studies on the association between coffee consumption and subarachnoid hemorrhage (SAH) have provided inconsistent results. We examine the risk of SAH from coffee consumption in a Japanese population.

Methods: Our analyses were based on the Jichi Medical School Cohort Study, a large-scale population-based prospective cohort study. A total of 9941 participants (3868 men and 6073 women; mean age 55 years) with no history of cardiovascular disease or carcinoma were examined. Participants were asked to choose one of five options to indicate their daily coffee consumption: none, less than 1 cup a day, 1–2 cups a day, 3–4 cups a day, or 5 or more cups a day. The incidence of SAH was assessed independently by a diagnostic committee. Cox proportional hazards models were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CI) after adjustment for age and sex (HR1) and for additional potential confounders (HR2).

Results: During 10.7 years of follow-up, SAH occurred in 47 participants. When compared with the participants who consumed less than 1 cup of coffee a day, the HR of SAH was significantly higher in the group who consumed 5 or more cups a day in both models (HR1 4.49; 95% CI, 1.44–14.00; HR2 3.79; 95% CI, 1.19–12.05).

Conclusions: The present community-based cohort study showed that heavy coffee consumption was associated with an increased incidence of SAH after adjusting for age, sex, and multiple potential cardiovascular confounders.

Key words: coffee consumption; subarachnoid hemorrhage; community-based cohort study

PROOF

INTRODUCTION

Coffee is one of the most widely consumed beverages in the world,[1] although its effects on health are controversial.[2] As caffeine in coffee elevates blood pressure, coffee drinking has been thought to be a risk factor for incidence of cardiovascular diseases (CVD).[2] However, some epidemiological studies have reported that coffee intake decreases the risk of cardiovascular[3,4] and cerebrovascular diseases.[5–7]

Subarachnoid hemorrhage (SAH) is a type of severe intracranial bleeding that has a fatality rate of almost 50%.[8,9] About 10% of patients die in the prehospital period, and survivors often suffer long-term neurological or cognitive impairments.[8–10] Thus, clarifying the risk factors for SAH remains crucial. To date, high blood pressure,[11–13] smoking,[11–15] and alcohol drinking[15] have been shown to increase the risk of SAH, while a high body mass index (BMI) decreases the risk.[13,15]

Given the cerebrovascular effects of coffee,[5–7,16] studies on incident SAH in relation to coffee consumption are important. However, little information on the association between coffee consumption and SAH is available, and results are mixed.[5,6,11,12] Japan has a nontraditional culture of coffee consumption, with few high-volume consumers of this beverage.[17] Only one Japanese study has assessed the association of coffee consumption with incident SAH, and the study reported no association.[16] With the coffee culture in Japan growing and given the mixed results of previous studies, further Japanese research on this topic would be valuable. The purpose of this study was to evaluate the association of coffee consumption in a Japanese population with the incidence of SAH using data from the Jichi Medical

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School Cohort Study, a large-scale population-based prospective cohort study.[18]

METHODS

Subjects

This study used the data of the Jichi Medical School Cohort Study, which enrolled 12 490 participants (4911 men and 7579 women) from 12 communities in Japan.[18] The Japanese government has conducted mass screening for CVD since 1982 according to a system established by the Health and Medical Service Law for the Aged. The baseline data of the study were obtained during mass screening examinations. The baseline examinations occurred from April 1992 through July 1995, and the examinations included physical examinations, blood tests, and a self-administered questionnaire about socio-demographic status, history of medication use, and diet, including coffee consumption.

Of all participants, 95 declined to participate in follow-up and seven could not be contacted after the baseline examinations. In total, 4869 men and 7519 women were followed up as a complete cohort population. Subjects with a history of CVD or malignant neoplasms and those with missing data on coffee intake were excluded. Ultimately, the data from 9941 participants (3868 men and 6073 women) were used for this study. Further details of the baseline examinations and follow-up methods have been published elsewhere.[18]

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Baseline examination

Dietary habits

Dietary habits were assessed using a food frequency questionnaire (FFQ) with 30 items, including an item regarding coffee consumption. Subjects chose one of five options indicating their daily coffee consumption: none, less than 1 cup a day, 1–2 cups a day, 3–4 cups a day, or 5 or more cups a day. The FFQ was already used in the Japan Collaborative Cohort Study, conforming the validity and reproducibility of the frequency assessment.[19] In order to test the reproducibility, the FFQs were distributed twice, at one-year intervals, and validity was assessed using a weighted dietary record.[15]

Lifestyle exposures

The other lifestyle- and health-related exposures were self-reported in semi-structured interviews.[18] Smoking status was classified as never smoker, ex-smoker, or current smoker. Alcohol consumption was categorized as never drinker, ex-drinker, or current drinker.

Physical and blood examinations

Body height was measured without shoes, and weight measured while fully clothed was determined by subtracting 0.5 kg (in the summer) and 1 kg (in other seasons) from the recorded weight values. BMI was calculated as weight in kilograms divided by squared body height in meters. Systolic blood pressure (SBP) was measured using an automated sphygmomanometer on the right arm of the participants after sitting for 5 minutes. Serum concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) cholesterol were measured using an enzymatic method.

Follow-up

The health status of the participants was followed up each year after the baseline examination. Participants were asked whether they had a diagnosis of CVD and, if so, which hospital they had visited and when they received the diagnosis. Additionally, if the participants did not attend the screening examination each year, they were contacted by mail, telephone, or via a public health nurse's home visit to obtain information on their health status. Death certificates of the participants were collected from public health centers with permission from the Agency of General Affairs and the Ministry of Health, Labour and Welfare. The follow-up of participants who died before the end of the study was stopped at that time. Information on participants who moved out of the study communities during the follow-up period was obtained annually from the relevant municipal governments; these participants ($n = 340$) were no longer followed up from the day they left the study communities. Follow-up of all other participants was continued until the end of 2005.

Diagnostic criteria of CVD, including SAH

In this study, CVD was defined as stroke, myocardial infarction, and sudden cardiac death, whichever occurred first. In participants with an event suspected to be related to CVD, computed tomography (CT) scans or magnetic resonance images in cases of stroke or electrocardiograms in cases of myocardial infarction was duplicated. A set of the image copy was sent to the diagnostic committee. CVD events were diagnosed independently by a diagnosis committee, which was composed of a neurologist, a radiologist, and two cardiologists. Stroke was diagnosed according to the diagnostic criteria of the National Institute of Neurological Disorders and Stroke (ie, in cases with a sudden onset of a focal, non-convulsive, and neurological deficit persisting longer than 24 hours).[20] SAH was diagnosed with a cranial CT scan performed to confirm the hyperdense appearance of extravasated blood in the subarachnoid space and/or basal cisterns. Myocardial infarction was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of the Trends and Determinants in Cardiovascular Disease (MONICA) Project.[21]

Statistical analysis

The Statistical Package for Social Science (SPSS) for Windows, version 21.0 (IBM SPSS Japan Inc., Tokyo, Japan) was used for all analyses. General characteristics of participants were analyzed by frequency of coffee consumption and reported as proportions and means

Table 1. Baseline characteristics of participants by frequency of coffee intake

	Frequency of coffee intake						
	None	Less than 1 cup a day	1–2 cups a day	3–4 cups a day	5 or more cups a day	Total	*P*-value[a]
Number of subjects	2631	3198	2924	883	305	9941	
Female, %	65.1	60.6	60.9	56.9	44.6	61.1	<0.001
Age, years	59.8 (9.8)	56.1 (10.8)	51.2 (11.9)	48.1 (12.2)	52.3 (12.5)	54.8 (11.7)	<0.001
Body mass index, kg/m^2	23.1 (3.2)	23.1 (3.0)	23.0 (3.0)	22.8 (3.0)	22.8 (3.1)	23.0 (3.1)	0.011
Systolic blood pressure, mm Hg	132.2 (20.9)	129.9 (20.7)	126.3 (20.6)	123.6 (19.8)	126.1 (21.7)	128.8 (20.9)	<0.001
Serum cholesterol concentration							
Total cholesterol, mg/dL	192.5 (34.5)	191.7 (34.8)	191.1 (35.4)	189.5 (35.3)	188.1 (32.4)	191.5 (34.9)	0.078
HDL cholesterol, mg/dL	51.0 (12.9)	50.9 (12.7)	51.3 (12.8)	51.1 (12.9)	49.4 (13.6)	51.0 (12.8)	0.150
Triglycerides, mg/dL	122.0 (77.2)	118.1 (74.1)	110.0 (71.7)	109.3 (77.1)	117.4 (74.4)	115.9 (74.7)	<0.001
Current smoker, %	16.4	20.2	26.2	38.5	50.5	23.5	<0.001
Current alcohol drinker, %	36.4	44.0	48.2	54.8	54.2	44.5	<0.001

HDL, high-density lipoprotein.
[a]Values were calculated using one-way analysis of variance for continuous variables or the chi-square test for categorical variables and are reported as mean (standard deviation) unless otherwise noted.

PROOF

(standard deviations). The associations between the frequency of coffee consumption and the confounders were analyzed by one-way analysis of variance and the chi-square test. A Cox proportional hazards model was used for calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) of the incidence of SAH in relation to categories of coffee consumption, with adjustment for age and sex (HR1) or adjustment for age, sex, BMI, SBP, TC, smoking status, and alcohol consumption (HR2). Age, BMI, SBP, and TC were entered in the model as continuous variables; sex, smoking (current, ex-, or never smoker), and alcohol drinking (current, ex-, or never drinker) were entered as categorical variables.

Ethical considerations

This study was approved by the Institutional Review Board of Jichi Medical School (Epidemiology 03-01) and the Ethics Committee of Saitama Prefectural University (524716). Written informed consent was obtained from each participant.

RESULTS

The baseline characteristics by frequency of coffee intake are shown in Table 1. High-frequency drinkers were more likely to be young, smokers, and alcohol drinkers and less likely to be female and obese. The group who drank 3–4 cups of coffee a day had lower SBP and TG.

During an average follow-up of 10.7 years, we documented 488 CVD events (270 in men and 218 in women): 360 strokes (187 in men and 173 in women) including 47 SAHs (13 in men and 34 in women), 84 hemorrhagic strokes (42 in men and 42 in women), and 228 cerebral infarctions (132 in men and 96 in women). The incidence of SAH was 4.4 per 10 000 person-years.

Adjusted HRs and 95% CIs by frequency of coffee intake are shown in Table 2. HRs of SAH incidence were significantly higher among those who drank 5 or more cups a day than in those who drank less than 1 cup a day (HR1 4.49; 95% CI, 1.44–14.00 and HR2 3.79; 95% CI, 1.19–12.05).

DISCUSSION

The present study found that subjects who consumed 5 or more cups of coffee a day had a significantly higher risk of SAH incidence, while no significant risk increase was observed among those who drank less than 5 cups a day. To our knowledge, this is the first report of a significant increase of SAH incidence among heavy coffee drinkers in Japan. Given the mixed epidemiological research results on the cerebrovascular effects of coffee,[5–7,11,12,16] this finding is valuable.

Among our subjects, those who consumed 5 or more cups of coffee a day can be regarded as extremely high consumers. Such individuals might have other unhealthy nutrition-taking behaviors, meaning that the magnitude of the risk could be exaggerated. Further nutritional study is needed.

The Miyagi cohort study in Japan reported that frequent coffee intake was not significantly correlated with SAH mortality.[16] The Miyagi study categorized the frequency of coffee intake into three groups (never, occasionally, and one or more cups a day) while our analysis used five groups. This different categorization of coffee consumption could explain the different results.

Table 2. Hazard ratios and 95% confidence intervals for the incidence of subarachnoid hemorrhage by frequency of coffee intake adjusted for potential cardiovascular confounders

	Frequency of coffee intake				
	None	Less than 1 cup a day	1–2 cups a day	3–4 cups a day	5 or more cups a day
Person-years	27 719	34 682	31 629	9442	3200
Number of cases					
Total	15	12	13	3	4
Men	5	1	4	2	1
Women	10	11	9	1	3
Incidence rate, per 10 000 person-years	5.4	3.5	4.1	3.2	12.5
HR1 (95% CI)	1.29 (0.60–2.77)	1.00	1.44 (0.65–3.17)	1.28 (0.36–4.60)	4.49 (1.44–14.00)
HR2 (95% CI)	1.31 (0.61–2.82)	1.00	1.28 (0.57–2.87)	1.16 (0.32–4.23)	3.79 (1.19–12.05)

CI, confidence interval; HR1, Hazard ratio adjusted for age and sex; HR2: Hazard ratio adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol concentration, smoking status, and alcohol consumption.

Most previous studies of the association between coffee intake and SAH were conducted in Western countries; two of these were incidence studies. Swedish women with high coffee intake showed significantly lower SAH incidence,[6] but coffee intake was not significantly associated with SAH incidence among Finnish male smokers.[5] Subjects in the Swedish study were about 60 years old and were participants in a mammography program. Their measured coffee intake was similar to that of our subjects, but they were older than our subjects by about 5 years on average and had a lower incidence of SAH (2.2 per 10 000 person-years). Compared with the subjects in our study, they may represent a healthier population. Age and incidence of SAH (5.4 per 10 000 person-years) of the Finnish men were similar to those of our subjects, but they were smokers and heavier coffee drinkers, and 21% reported consuming 8 or more cups of coffee a day. These differences in characteristics between the Scandinavian subjects and our own may help explain the differences in the findings.

A Colombian case-control study found no significant association between coffee intake and SAH.[12] Our results appear to be consistent with those of a Norwegian study[11] that showed significantly increased SAH mortality among subjects who drank more than 6 cups of coffee a day.

Findings from the present epidemiological study cannot fully explain the underlying mechanisms of the relation between coffee consumption and incidence of SAH. Many experimental and clinical studies have reported both protective and harmful effects of coffee. Excess intake of caffeine, the most investigated component in coffee, may elevate blood pressure by increasing systemic vascular resistance.[16] Hydroxyhydroquinone generated by roasting coffee beans could interfere with the vasodilatory effect of chlorogenic acids,[2] which have antioxidant functions[17] that benefit vascular health.[22,23] Another possibility is that the addition of sugar, milk, and cream to coffee leads to high energy intake that may induce oxidative stress and insulin resistance. However, when our study results were adjusted to account for factors related to oxidative stress and insulin resistance, including smoking, BMI, and blood pressure, the adjustments did not attenuate the statistical significance of the findings.

The strengths of this study are the large size, use of a community-based cohort study design with incident disease outcomes, and careful case review by an independent diagnostic committee. However, our study has several limitations. First, the group with a significantly increased risk of SAH included only four cases. While the results were statistically significant after adjusting for sex, age, and five major CVD risk factors, the robustness of the observed association is probably limited, and the finding could be a chance observation. No statistically significant trend in risk was observed among those who drank less than 5 cups a day. Statistical power may be low due to the small number of SAH cases ($n = 47$) in the cohort population, while the incidence of SAH in this study is almost three times as high as the mortality of SAH (1.46 per 10 000 person-years) reported in a previous Japanese study.[16] Second, a high prehospital mortality rate could make SAH diagnosis difficult. During follow-up, we documented 41 cases of sudden death defined as death within 24 hours after the onset of symptoms. All cases of sudden death were reviewed carefully by the diagnostic committee to rule out SAH. However, considering difficulty in identifying cause of out of hospital death, it is possible that some SAH cases could not be diagnosed. Finally, the FFQ was self-administered and implemented only once at baseline, so the evaluation of dietary habits might not be accurate. We did not clarify whether dietary habits changed during the follow-up period, although the validity and reliability of the FFQ are known to be acceptable.[19] Types of coffee and its additives were not assessed by the FFQ.

In conclusion, the present study from the Jichi Medical School Cohort Study showed that, compared with subjects who consumed less than 1 cup a day, those who consumed 5 or more cups of coffee a day had a significantly higher risk of incident SAH, while no significant increase in risk was observed among those who drank less than 5 cups a day. This suggests that heavy coffee consumption is a risk factor for incident SAH.

PROOF

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Conflicts of interest: None declared.

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PROOF

ORIGINAL PAPER

Sleep Blood Pressure Self-Measured at Home as a Novel Determinant of Organ Damage: Japan Morning Surge Home Blood Pressure (J-HOP) Study

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To study whether sleep blood pressure (BP) self-measured at home is associated with organ damage, the authors analyzed the data of 2562 participants in the J-HOP study who self-measured sleep BP using a home BP monitoring (HBPM) device, three times during sleep (2 AM, 3 AM, 4 AM), as well as the home morning and evening BPs. The mean sleep home systolic BPs (SBPs) were all correlated with urinary albumin/creatinine ratio (UACR), left ventricular mass index (LVMI), brachial-ankle pulse wave velocity (baPWV), maximum carotid intima-media thickness, and plasma N-terminal pro-hormone pro brain-type natriuretic peptide (NTproBNP) (all $P<.001$). After controlling for clinic SBP and home morning and evening SBPs, associations of home sleep SBP with UACR, LVMI, and baPWV remained significant (all $P<.008$). Even in patients with home morning BP <135/85 mm Hg, 27% exhibited masked nocturnal hypertension with home sleep SBP ≥120 mm Hg and had higher UACR and NTproBNP. Masked nocturnal hypertension, which is associated with advanced organ damage, remains unrecognized by conventional HBPM. *J Clin Hypertens (Greenwich)*. 2015; 17:340–348. © 2015 Wiley Periodicals, Inc.

Recent population-based and clinical studies using ambulatory blood pressure (BP) monitoring (ABPM) demonstrate that sleep BP is a better predictor of cardiovascular disease than awake BP.[1–3] Nocturnal hypertension with higher sleep BP, and a nondipper/riser pattern with higher sleep BP than awake BP (even they are normotensive), are reported to constitute risks for hypertensive target organ damage and subsequent cardiovascular events.[4–8]

ABPM has historically been the gold standard for measuring sleep BP. Recently, however, self-measured home BP monitoring (HBPM) was introduced to measure sleep BP at home.[9] In the first-ever study of sleep BP using HBPM, BP was measured once at 2 AM automatically.[10] We recently developed an HBPM device that automatically measures sleep home BP (HBP) 20 times with data memory (Medinote; Omron Healthcare Inc., Kyoto, Japan). We showed that the sleep HBP level measured using the Medinote device was almost identical to the sleep BP level measured by ABPM, and both sleep BPs measured by HBPM and ABPM were similarly correlated with hypertensive target organ damage.[11] Another study also demonstrated that HBPM was well accepted for the assessment of nocturnal BP and the detection of nondipping status.[12]

To verify the hypothesis that sleep HBP is worth monitoring in addition to conventional HBPM in the morning (morning HBP) and in the evening (evening HBP), we studied the associations of sleep HBP and target organ damage. For this purpose, we obtained data for 2562 participants of the Japan Morning Surge Home Blood Pressure (J-HOP) study. The J-HOP study is the largest nationwide HBP cohort and employs the same HBP monitoring device and method as used in the present study: self-measurement of sleep HBP using the Medinote three times during sleep (2 AM, 3 AM, 4 AM), as well as three times in the morning and three times in the evening for 14 days.

METHODS

The recruitment of the study patients of the J-HOP study was consecutively conducted from January 2005 to May 2012 by 75 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and four specialized university hospitals) throughout Japan. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. The study protocol was registered on a clinical trials registration site (University Hospital Medical Information Network

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Clinical Trials Registry: #UMIN000000894). Written informed consent was obtained from all patients who enrolled in the study.

Study Subjects

Between January 2005 and May 2012, we enrolled 4310 ambulatory outpatients with one or more of the following cardiovascular risks: hypertension, hyperlipidemia, diabetes (fasting blood sugar ≥126 mg/dL, receiving an antidiabetic drug), glucose intolerance, metabolic syndrome, chronic kidney disease (estimated glomerular filtration rate <60 mL), history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, congestive heart failure), atrial fibrillation, current smoking, chronic obstructive pulmonary disease, and sleep apnea syndrome. We excluded patients who had malignancy or chronic inflammatory disease. The time interval of HBPM and the assessment of organ damage was <3 months.

BP Measurements

HBP measurement was performed using a validated cuff oscillometric device (HEM-5001; Medinote; Omron Healthcare Co., Ltd)[11] according to hypertension guidelines for the management of hypertension.[13–15] This self-measured HBPM automatically makes three measurements at 15-second intervals on each occasion. The device can be set at bedtime to measure BP during sleep, and all recorded BP parameters are stored in its memory. This new computerized HBPM device automatically stores BP data separately measured in the morning, the evening, and during sleep.

We asked study patients to measure their morning HBP (measured after awakening and before breakfast and taking antihypertensive medication) and evening HBP (measured before taking antihypertensive medication and going to bed) in a sitting position for a 2-week period. All HBP data of the HBPM device were downloaded into a computer and sent to the study control center (Jichi Medical University, Tochigi, Japan). After exclusion of the data from the first day, the averages of all HBPs measured three times in the morning (morning HBP) and three times in the evening (evening HBP) for 13 days (78 readings in total) were separately calculated by the study coordinator, who was blinded to the clinical characteristics of the study participants.

In addition, those participants who agreed to do so (n=2562, or 59% of the total sample) also measured their sleep HBP on at least 1 day within the 2 weeks. Sleep HBP measurements were made only once at each of three preset times (2 AM, 3 AM, and 4 AM), and sleep HBPs were defined as the average of all sleep BPs measured.

Clinic BP was measured at local medical centers using the same HBP device and cuff used for HBP measurement after the patients had been seated for 2 minutes and was calculated as the mean of three consecutive measurements. We generally used cuffs with rubber bags 13 cm wide and 22- to 32-cm long, or 32- to 42-cm long in the case of patients with a large upper arm; this choice was left to the physicians who measured the clinic BP.

Echocardiographic and Ultrasonographic Measurements of the Carotid Artery and Pulse Wave Velocity

Echocardiography was performed at each participating institute. Two-dimensional M-mode or B-mode images were obtained using an ultrasound machine according to the guidelines of the American Society of Echocardiology. Left ventricular (LV) mass (LVM) was obtained using the formula validated by the American Society of Echocardiology: LVM=0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3−[LVIDD]^3))+0.6 g, where IVSTD is the diastolic interventricular septal diameter, LVIDD is the diastolic LV dimension, and PWTD is the diastolic posterior wall diameter. The LVM index (LVMI) was calculated as LVM/body surface area, where IVSd is the interventricular septum thickness at the end of diastole, PWd is the posterior wall thickness at the end of diastole, and LVDd is the LV internal dimension at the end of diastole. Carotid intima-media thickness (IMT) was assessed for the right and left common carotid artery using a B-mode ultrasound scanner at each participating institute. Carotid IMT was measured at three points proximal to the bilateral carotid bulbus (far wall) in 10-mm segments at end-diastole and always in plaque-free segments. If plaque existed at the IMT measuring point, an appropriate adjacent portion was chosen. The mean of the right and left maximum carotid IMT (six points in total) was used in the analysis (MaxIMT). The brachial-ankle PWV (baPWV) was measured by using the volume plethysmographic method with previously validated equipment (form PWV/ABI; Omron Healthcare Co., Ltd). We used the mean of right and left baPWV values for the analysis.

Biomarker Assays

Blood and spot urine samples were collected in the morning in a fasting state at enrollment and at the end of the study. The blood samples were centrifuged at 3000 ×*g* for 15 minutes at room temperature. Plasma/serum samples after separation and urine samples were stored at 4°C in refrigerated containers and sent to a commercial laboratory (SRL Inc., Tokyo, Japan) within 24 hours. Serum samples after separation were also stored at −80°C in a refrigerator. All assays were performed within 24 hours of sample collection at this single laboratory center.

The urinary albumin level was measured using a turbidimetric immunoassay (SRL Inc.) and expressed as UACR (mg/gCr). Both serum and urine creatinine were measured by enzymatic assay. Using the stored serum samples, N-terminal pro–brain-type natriuretic peptide (NTproBNP) was measured as previously described, and high-sensitivity cardiac troponin T (hs-cTnT) levels were measured using a highly sensitive assay on an automated platform (Elecsys-2010 Troponin T hs

STAT; Roche Diagnostics, Mannheim, Germany K.K.), with a lower detection limit of 0.003 ng/mL and a reported 99th percentile value in apparently healthy individuals of 0.014 ng/mL.

The intracoefficients/intercoefficients of variation were 1.93%/3.13% for NTproBNP, 2.02%/3.02% for hs-cTnT, and 1.30%/1.85% for urinary albumin assay.

Statistical Analysis

All analyses were performed in the 2562 patients. We included patients with atrial fibrillation, and data were expressed as means (±standard deviation [SD]) or percentages. When we excluded patients with atrial fibrillation (4.1%), all the results were essentially the same. Because the distributions of UACR, hs-cTnT, and NTproBNP were highly skewed, they were log-transformed before statistical analysis and expressed as the geometric mean (±SD). Values of hs-cTnT <0.003 ng/mL (detection limit) were assigned as 0.0015 ng/mL. The chi-square test was used to evaluate differences in prevalence rates. Unpaired *t* tests were used for comparison of the mean values between two groups. Correlations among variables were analyzed using Pearson's correlation coefficient. To investigate whether lowest or highest sleep BP provides a better index of organ damages, linear regression analysis was performed, and the correlation coefficients were compared after Fisher's *z* transformation. Multiple regression analysis of biomarkers (dependent variables) was performed using BP parameters as independent variables after controlling for age, sex, body mass index, antihypertensive drug use, evening or bedtime dosing of antihypertensive drug, sleep duration, and clinic, morning, evening home SBPs. Variance inflation factors were calculated to examine the possible existence of substantial multicollinearity among the BP measurements, and values >3.0 were considered to indicate collinearity. Associations/differences with a *P* value <.05 (two-tailed) were considered to be statistically significant. All statistical analyses were performed with SPSS version 11 software (IBM, Armonk, NY).

RESULTS

Patient Characteristics

The age, BP level, and degree of target organ damage were only slightly lower in the sleep BP analysis group (n=2562) than in the group of all J-HOP study patients (n=4310) (Table I). The average number of BP readings was 73±15 for morning and evening HBP and 18±13 for sleep HBP. The average of the number of home sleep BP readings was the same (6.14±4.50 for 2 AM, 6.11±4.50 for 3 AM, and 6.03±4.50 for 4 AM; not significant). In the sleep BP analysis group, the mean clinic SBP, morning home SBP, and home sleep SBP levels were 140 mm Hg, 136 mm Hg, and 121 mm Hg, respectively. These are near the threshold of each SBP for defining uncontrolled hypertension (140 mm Hg, 135 mm Hg, and 120 mm Hg), suggesting that almost

TABLE I. Baseline Characteristics of Study Patients

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
Age, y	64.8±10.9	63.3±10.3[a]
Male, %	47.0	49.1[a]
Body mass index, kg/m^2	24.3±3.5	24.4±3.5
Waist/hip ratio	0.90±0.07	0.89±0.07
Alcohol, %	28.0	28.5[b]
Smoking, %	12.0	11.8
Dyslipidemia, %	40.7	43.2[a]
Diabetes, %	23.5	24.1
History, %		
Angina	7.2	7.3
Myocardial infarction	3.9	4.4[b]
Aortic dissection	0.7	0.8
Stroke	4.1	3.9
Congestive heart failure	1.7	1.8
Peripheral artery disease	1.0	0.8
Atrial fibrillation	3.7	4.1
Sleep apnea syndrome	3.3	4.2
Sleep duration, h	7.1±1.2	7.0±1.1[a]
eGFR<60 mL/min/1.73 m^2, %	20.4	20.6
Antihypertensive drug, %	79.1	82.5[a]
Calcium antagonist	50.8	51.3
ACE inhibitor	6.6	6.4
ARBs	51.8	51.9
β-Blocker	13.7	15.4
α-Blocker	5.0	5.1
Diuretics	26.1	28.7[a]
Aldosterone blocker	2.2	2.4
Evening or bedtime dosing of antihypertensive drug, %	27.7	29.0[b]
Statin, %	23.6	23.7
Aspirin, %	15.1	17.4[a]
Clinic SBP, mm Hg	141.3±16.5	140.0±15.3[a]
Clinic DBP, mm Hg	81.2±10.6	81.8±10.2[a]
Home morning SBP, mm Hg	138.4±15.9	136.4±14.7[a]
Home morning DBP, mm Hg	79.1±10.0	79.3±9.6
Home evening SBP, mm Hg	130.1±15.0	128.9±14.3[a]
Home evening DBP, mm Hg	72.7±9.7	72.9±9.3
UACR, mg/gCr	13.2 (7.2, 30.8)	12.1 (6.9, 27.5)[a]
LVMI, g/m^2	100±27.9	97.8±26.3[a]
baPWV, cm/s	1675±352	1630±320[a]

TABLE I. Baseline Characteristics of Study Patients (Continued)

	All J-HOP Study Patients (n=4310)	Sleep BP Analysis Group (n=2562)
MaxIMT, mm	1.05±0.45	1.08±0.48[a]
NTproBNP, pg/mL	50.6 (25.6, 97.8)	45.9 (22.9, 88.2)[a]
hs-cTnT, ng/mL	0.003 (0.003, 0.007)	0.003 (0.003, 0.006)[a]

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; baPWV, brachial-ankle pulse wave velocity (n=1489); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T (n=2289); LVMI, left ventricular mass index (n=1092); MaxIMT, maximum carotid intima-media thickness (n=828); NTproBNP, N-terminal pro–brain-type natriuretic peptide (number of patients included in the sleep blood prssure analysis: n=2292); SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio (n=2554). Data are presented as mean±standard deviation, median (25%, 75%), or percentage. [a]$P<.001$ vs the patients excluded from the sleep blood pressure analysis. [b]$P<.05$.

half of the study patients were uncontrolled above these thresholds.

Clinic BP and HBP Levels

There was no difference between the sleep home SBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg ($P<.001$) (Figure 1). Sleep diastolic BP (DBP) was also slightly increased by 1.6 mm Hg between the 2 AM and 4 AM measurements.

Distributions of Sleep HBPs

Figure 2A and 2B show the distribution of sleep HSBP (average of the sleep SBPs at 2 AM, 3 AM, and 4 AM) of the sleep BP analysis group. Among these patients, 49% and 47% exhibited uncontrolled hypertension above the threshold for sleep home SBP and DBP (120/70 mm Hg), respectively.

Association with Covariates

Home sleep SBP was positively correlated with age, use of diuretics, and clinic and home morning and evening SBPs even in the subgroup with well-controlled morning BP (all, $P<.001$) (Table S1).

Association with Target Organ Damage

The average (Figure 3), the highest, and the lowest sleep home SBPs were significantly correlated with all six measures of target organ damage (UACR, LVMI, baPWV, MaxIMT, plasma NTproBNP, hs-cTnT), while sleep home DBP was correlated only with UACR (Table II). There was no significant difference between lowest and highest sleep SBP in a comparison of the correlation coefficients from these relationship.

We subclassified the study participants into three groups (few reading, moderate reading, frequent reading) according to the number of home sleep BP readings. The correlation coefficients of home sleep SBP with measures of organ damage were higher the higher tertile than the lower tertile (Table S2).

After controlling for clinic SBP and morning and evening home SBPs, the associations of sleep home SBP with UACR, LVMI, baPWV, NTproBNP, and hs-cTnT remained significant (Table III).

Masked Home Nocturnal Hypertension

In the subanalysis of hypertensive patients with well-controlled morning HBP <135/85 mm Hg (n=1179), 27% exhibited masked home nocturnal hypertension, defined by sleep home SBP ≥120 mm Hg, and 31%

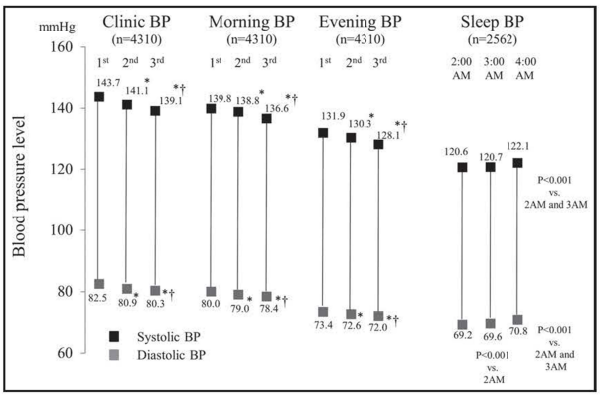

FIGURE 1. Clinic and home blood pressure (BP) level (mean) in the Japan Morning Surge Home Blood Pressure study patients. *$P<.001$ vs first measurement. †$P<.001$ vs second measurement by paired t test. Home BPs were self-measured three times during sleep, three times in the morning, and three times in the evening, and the average for each time point is shown.

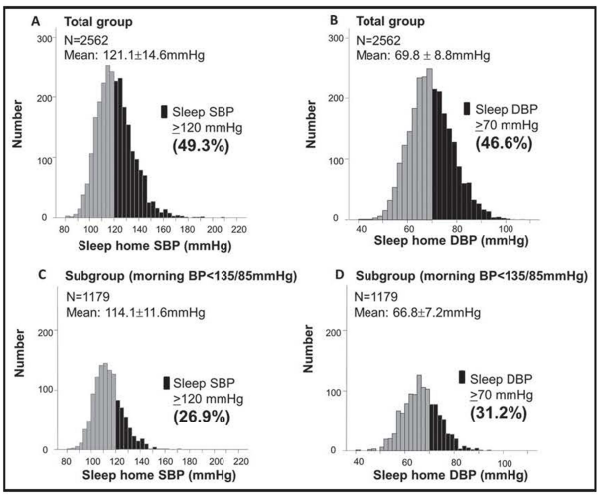

FIGURE 2. Distribution of sleep home blood pressure (BP). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

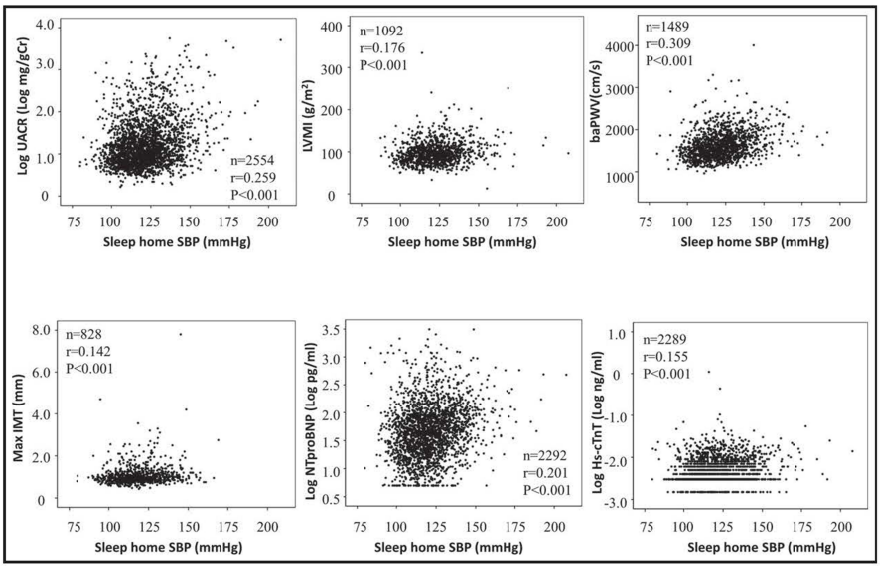

FIGURE 3. Associations of sleep home systolic blood pressure (SBP) with measures of target organ damage. UACR indicates urinary albumin/creatinine ratio; LVMI, left ventricular mass index; baPWV, brachial-ankle pulse wave velocity; MaxIMT, maximum carotid intima-media thickness; NT-proBNP, N-terminal pro-brain-type natriuretic peptide level; hs-cTnT, high-sensitivity cardiac troponin T. Sleep home SBP is calculated as the average of three sleep home blood pressures measured at 2 AM, 3 AM, and 4 AM.

TABLE II. Simple Correlations of Home Sleep Blood Pressure Parameters With Measures of Target Organ Damage

mean±SD, mm Hg		Log UACR *R*	LVMI *R*	baPWV *R*	MaxIMT *R*	Log NTproBNP *R*	Log hs-cTnT *R*
Sleep SBP							
Average	121.1±14.6	0.26[a]	0.18[a]	0.31[a]	0.14[a]	0.20[a]	0.16[a]
2 AM	120.6±15.4	0.25[a]	0.17[a]	0.28[a]	0.13[a]	0.18[a]	0.14[a]
3 AM	120.7±15.5	0.24[a]	0.17[a]	0.29[a]	0.13[a]	0.19[a]	0.13[a]
4 AM	122.1±15.7	0.24[a]	0.16[a]	0.32[a]	0.14[a]	0.20[a]	0.15[a]
Highest	126.2±15.6	0.26[a]	0.20[a]	0.32[a]	0.12[a]	0.19[a]	0.15[a]
Lowest	116.2±14.6	0.24[a]	0.15[a]	0.27[a]	0.16[a]	0.20[a]	0.15[a]
Sleep DBP							
Average	69.8±8.8	0.12[a]	0.02	−0.01	−0.02	−0.03	−0.04[b]
2 AM	69.2±9.5	0.11[a]	0.03	−0.007	0.003	−0.04[b]	−0.05[b]
3 AM	69.6±9.3	0.10[a]	0.02	−0.02	−0.02	−0.04	−0.05[b]
4 AM	70.9±9.7	0.10[a]	0.002	0.01	−0.03	−0.03	−0.02
Highest	73.4±9.5	0.12[a]	0.04	0.01	−0.05	−0.04[b]	−0.03
Lowest	66.3±9.1	0.10[a]	−0.01	−0.03	0.01	−0.02	−0.04[b]

Abbreviations: baPWV, brachial-ankle pulse wave velocity; DBP, diastolic blood pressure; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness; NTproBNP, N-terminal pro-brain-type natriuretic peptide; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin/creatinine ratio. Values are presented as Pearson's correlation coefficients (*R*). [a]$P<.001$. [b]$P<.05$.

exhibited masked home nocturnal hypertension defined by sleep home DBP ≥70 mm Hg (Figure 2C and 2D). The masked home nocturnal hypertension group (n=318) with sleep systolic HBP ≥120 mm Hg had higher UACR (11.5 [7.0–23.1 vs 8.9 [5.9–17.4] mg/gCr, $P<.001$]) and NTproBNP (49.1 [23.7–88.8] vs 36.3 [18.5–70.0] pg/mL, $P=.003$) than those with sleep systolic HBP <120 mm Hg (n=861).

Even in those with both well-controlled clinic BP <140/90 mm Hg and well-controlled morning HBP <135/85 mm Hg (n=787; average clinic, morning, and sleep HBP: 126.8±8.8/76.7±7.5 mm Hg, 123.6±7.7/74.0±6.6 mm Hg, 112.6±11.1/66.2±6.7 mm Hg, respectively), 22% exhibited masked home nocturnal hypertension defined by sleep home SBP >120 mm Hg, and 27% exhibited masked home nocturnal hypertension defined by sleep home DBP >70 mm Hg (Figure S1). The masked nocturnal hypertension group (n=173) with sleep systolic HBP >120 mm Hg had higher UACR (11.4 [7.1–21.2 vs 8.3 [5.6–16.2] mg/gCr, $P=.002$]) and NTproBNP (49.2 [26.1–88.4] vs 35.1 [17.6–69.5] pg/mL, $P=.002$) than those with sleep systolic HBP <120 mm Hg (n=614).

DISCUSSION

This study was the first to demonstrate that sleep BP measured by HBPM was associated with almost all the measures of hypertensive target organ damage independently of clinic BP and HBPs measured in the morning and in the evening, and that the prevalence of masked nocturnal hypertension with sleep SBP ≥120 mm Hg was 27% among those with well-controlled morning HBP <135/85 mm Hg in the baseline data of the largest of the nationwide HBPM cohorts that used a single high-quality automatic HBPM device with data memory and three automatic measurements of BP during the sleep period.

Sleep BP Parameters and Target Organ Damage

There was no difference between the three sleep HBP levels at 2 AM and 3 AM, while that at 4 AM was slightly higher by 1.5 mm Hg systolic and 1.6 mm Hg diastolic. However, these differences were not clinically significant. In addition, the sleep BP of ABPM was calculated as the average of the BPs during the sleep period; we also used the average of three sleep HBPs.

The average of all the sleep systolic HBPs and also the individual sleep systolic HBPs at 2 AM, 3 AM, and 4 AM were significantly correlated with all the measures of hypertensive target organ damage, such as UACR, LVMI, baPWV, MaxIMT, and the plasma levels of cardiac biomarkers (NTproBNP and hs-cTnT), while the association of sleep diastolic HBP was only found with UACR. These measures of target organ damage are the surrogate markers for predicting cardiovascular events.[16–20] Thus, a higher sleep BP level would constitute a risk for cardiovascular events independently of morning and evening BPs measured by conventional HBP measurement.

TABLE III. Multiple Linear Regression Analysis Between Sleep SBP and Target Organ Damage Additionally Adjusted for Another Blood Pressure Parameter

	Log UACR, Log mg/gCr		LVMI, g/m^2	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.007 (0.006–0.009)	<.001	0.215 (0.096–0.335)	<.001
+Morning SBP	0.005 (0.004–0.007)	<.001	0.143 (0.007–0.280)	.040
+Evening SBP	0.006 (0.004–0.008)	<.001	0.172 (0.034–0.310)	.034
+Clinic SBP, morning and evening SBP	0.005 (0.003–0.007)	<.001	0.137 (−0.006 to 0.280)	.061
	baPWV, cm/s		MaxIMT, mm	
	Sleep SBP, mm Hg			
Additional Adjusted Factor	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	3.006 (2.026–3.985)	<.001	0.003 (0.001–0.006)	.011
+Morning SBP	2.394 (1.249–3.540)	<.001	0.002 (−0.001 to 0.005)	.167
+Evening SBP	1.954 (0.810–3.098)	.001	0.002 (0.000–0.005)	.105
+Clinic SBP, morning and evening SBP	1.905 (0.713–3.097)	.002	0.002 (−0.001 to 0.004)	.240
	Log NTproBNP, Log pg/mL		Log Hs-cTnT, Log ng/mL	
	Sleep SBP, mm Hg			
	B (95% CI)	*P* Value	B (95% CI)	*P* Value
+Clinic SBP	0.005 (0.003–0.006)	<.001	0.002 (0.001–0.003)	<.001
+Morning SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.017
+Evening SBP	0.004 (0.003–0.006)	<.001	0.002 (0.001–0.002)	.001
+Clinic SBP, morning and evening SBP	0.004 (0.002–0.005)	<.001	0.001 (0.000–0.002)	.022

Abbreviations: baPWV, brachial-ankle pulse wave velocity; hs-cTnT, high-sensitivity cardiac troponin T; LVMI, left ventricular mass index; MaxIMT, maximum carotid intima-media thickness of carotid artery; NTproBNP, N-terminal pro–brain-type natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio. Each blood pressure parameter was added separately to the baseline regression models, which included age, sex, body mass index, use of antihypertensive drug, evening or bedtime dosing of antihypertensive drug, and sleep duration.

In addition, we also used the highest and lowest sleep HBP among the three sleep HBPs at 2 AM, 3 AM, and 4 AM as another sleep HBP parameter. The lowest sleep SBP, under the condition of the lowest sympathetic tone, may be a closer index of basal sleep BP, which is predominantly determined by the circulating volume or the structural remodeling of small resistance arteries.[9] The highest sleep BP may be a closer index of increased sympathetic tone–related sleep BP, which may be prominent in those with sleep apnea syndrome.[9,21,22] In this study, there were no significant differences in the impact of the average, the highest, and the lowest sleep BPs on target organ damage. A future study on hypertensive patients under various conditions could clarify the different impact of these sleep HBP parameters.

Association Independently of Morning BP

The association of sleep systolic HBP with measures of target organ damage (except MaxIMT) remained significant, independently not only of clinic SBP, but also of morning systolic HBP and evening systolic HBP, although morning HBP measured within 1 hour after awakening may partly be influenced by the preceding sleep BP.[23] Considering that approximately 25% of hypertensives with well-controlled morning HBP <135/85 mm Hg exhibit masked nocturnal hypertension with sleep systolic HBP >120 mm Hg, and significantly higher UACR and NTproBNP, sleep BP is worth monitoring in order to identify hypertensive patients with remaining risk during sleep, even if they are normotensive with respect to both clinic BP and morning HBP.

Recommendation of Sleep HBP-Guided Antihypertensive Medication

Sleep BP is more important in medicated than in nonmedicated hypertensive patients. The international ABPM database demonstrated that sleep BP was independently and more closely associated with cardiovascular events than awake BP in medicated hypertensives.[3] In our recent study of HBP-guided antihypertensive treatment in hypertensive patients,[24] sleep BP measured by ABPM was more closely associated with the plasma BNP level than was awake BP.[25] Even in those patients with well-controlled HBP <135/85 mm Hg, those whose sleep BP by ABPM was uncontrolled exhibited markedly higher UACR and higher plasma BNP levels.[26] These results suggest that sleep BP is a "blind spot" in current antihypertensive medication. To reduce cardiovascular events more effectively, strict 24-hour

BP, including sleep BP, is important in the management of hypertension. As a first step, recent guidelines have recommended using HBPM widely in clinical practice.[13–15] These guidelines generally recommend that HBP be measured on two occasions (in the morning and in the evening).[13–15] The measurement of sleep BP by HBPM is referred to in the guidelines, but is not conventionally recommended.[15] In this study, home sleep BP was significantly correlated with morning and evening BPs; however, home sleep BP is worth measuring, particularly in patients with diabetes mellitus, chronic kidney disease, sleep apnea syndrome, or target organ damage (those who are likely to have masked nocturnal hypertension). In this study, HBP was positively associated with age and diabetes, and "masked home nocturnal hypertension" was associated with higher UACR and NTproBNP levels. Although ABPM is the gold standard for assessing sleep BP, ABPM is inconvenient for frequent use in clinical practice. In the future, after the available data on HBPM-measured sleep BP has been expanded, HBPM could be used as an alternative device for sleep BP–guided antihypertensive medication.

Study Limitations

Various types of cardiovascular disease were included in the J-HOP study. The cause and effect relationship between sleep BP and cardiovascular disease may have varied by the nature of cardiovascular disease. Thus, by the association study using baseline data of the prospective J-HOP study, we could not refer to the cause and effect relationship between sleep HBP and measures of organ damage. Finally, the causal implication of self-measured sleep HBP will be clarified in the prospective follow-up results of the J-HOP study after adjustment for baseline cardiovascular profiles.

In addition, sleep duration and quality may modulate the association between sleep BP and organ damage. We collected the baseline data of duration and quality of sleep (presence or absence of insomnia and frequency of awakening and nocturia in each of the 14 days) in the J-HOP study, and the association between this sleep information and BPs will be studied more extensively in the future.

Finally, we should note that we did not specify the timing of the clinic BP measurement, leaving this decision to the discretion of the individual medical centers. Therefore, it might be possible that the clinic BP was underestimated because of the peak effect of the drug treatment.

CONCLUSIONS

This study first demonstrated that self-measurement of sleep HBP is feasible in a large cohort, and sleep HBP is significantly correlated with target organ damage independently of clinic BP and morning and evening HBPs. Masked nocturnal hypertension, one fourth of well-controlled morning hypertensives, remains unrecognized by conventional HBPM without sleep BP monitoring, and it was associated with advanced organ damage. Thus, sleep HBP in addition to morning HBP is worth monitoring, particularly in high-risk hypertensive patients with target organ damage. However, there are no prospective studies demonstrating that a strategy of lowering nighttime BP reduces the risk of target organ injury from hypertension. In the future, it needs to be emphasized that clinical significance of self-measured sleep BP at home should prospectively be demonstrated in the J-HOP study.

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Contributors: Kazuomi Kario is the principle investigator of the J-HOP study, supervised its conduct and data analysis, and had primary responsibility for the writing of this paper. Satoshi Hoshide, the secretary in general of the J-HOP, conducted all statistical analyses.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of sleep home blood pressure (BP) at subgroup (morning BP <135/85 mm Hg and clinic BP <140/90 mm Hg). SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Sleep home BP is calculated as the average of three sleep home BPs measured at 2 AM, 3 AM, and 4 AM.

Table S1. Simple correlations of home sleep blood pressure with covariates in the total sleep blood pressure analysis group and in subgroup well-controlled in home morning blood pressure <135/85 mm Hg.

Table S2. Simple correlations of home sleep blood pressure with measures of target organ damage in tertile of number of sleep blood pressure readings.

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