Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study

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The Hisayama Study

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BACKGROUND: Several observational studies have reported that higher visit-to-visit blood pressure variability is a risk factor for cognitive impairment and dementia. However, no studies have investigated the association of day-to-day blood pressure variability assessed by home blood pressure measurement with the development of dementia.

METHODS: A total of 1674 community-dwelling Japanese elderly without dementia, ≥60 years of age, were followed up for 5 years (2007–2012). Home blood pressure was measured 3 times every morning for a median of 28 days. Day-to-day systolic (SBP) and diastolic blood pressure variabilities, calculated as coefficients of variation (CoV) of home SBP and diastolic blood pressure, were categorized into quartiles. The hazard ratios and their 95% confidence intervals of the CoV levels of home blood pressure on the development of all-cause dementia, vascular dementia (VaD), and Alzheimer disease (AD) were computed with a Cox proportional hazards model.

RESULTS: During the follow-up, 194 subjects developed all-cause dementia; of these, 47 had VaD and 134 had AD. The age- and sex-adjusted incidences of all-cause dementia, VaD, and AD increased significantly with increasing CoV levels of home SBP (all *P* for trend <0.05). These associations remained unchanged after adjustment for potential confounding factors, including home SBP. Compared with subjects in the first quartile of CoV levels of home SBP, the risks of the development of all-cause dementia, VaD, and AD were significantly higher in those in the fourth quartile (hazard ratio=2.27, 95% confidence interval=1.45–3.55, *P*<0.001 for all-cause dementia; hazard ratio=2.79, 95% confidence interval=1.04–7.51, *P*=0.03 for VaD; hazard ratio=2.22, 95% confidence interval=1.31–3.75, *P*<0.001 for AD). Similar associations were observed for CoV levels of home diastolic blood pressure. Meanwhile, home SBP levels were significantly associated with the risk of VaD but not with the risks of all-cause dementia and AD. There was no interaction between home SBP levels and CoV levels of home SBP on the risk of each subtype of dementia.

CONCLUSIONS: Our findings suggest that increased day-to-day blood pressure variability is, independently of average home blood pressure, a significant risk factor for the development of all-cause dementia, VaD, and AD in the general elderly Japanese population.

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Clinical Perspective

What Is New?

- This prospective cohort study of a general Japanese population demonstrated a significant independent association between increased day-to-day blood pressure variability measured with home blood pressure monitoring and risk for the development of all-cause dementia, vascular dementia, and Alzheimer disease.
- Both higher day-to-day blood pressure variability and hypertension were independently associated with the risk of vascular dementia, whereas the risk of Alzheimer disease was increased significantly in subjects with higher blood pressure variability regardless of absolute blood pressure values.

What Are the Clinical Implications?

- The findings of this study indicate that the measurement of day-to-day blood pressure variability with home blood pressure monitoring may be useful to assess future risk of dementia, regardless of its subtype.
- Further studies are needed to clarify whether day-to-day blood pressure variability is an indicator of future dementia or an interventional target for the prevention of dementia.

Blood pressure is well known to have short-term (over a period of 24 hours), midterm (over a period of days), and long-term fluctuations within more prolonged periods of change measured in weeks, months, seasons, and even years. Such fluctuation of blood pressure, or so-called blood pressure variability (BPV), is increasingly recognized to play clinically important roles in the progression of target-organ damage and cardiovascular events independently of absolute blood pressure values.[1–3]

Dementia is a worldwide priority in terms of both public health and social care as a result of the mounting burdens it is placing on communities.[4] Recently, the influence of BPV on cognitive function has attracted attention. One cross-sectional study[5] and several longitudinal studies[6–9] have reported that increased BPV is significantly associated with higher risks of cognitive impairment[5–8] and dementia.[9] However, most of these studies were based on visit-to-visit BPV assessed by office blood pressure over months or years. In contrast, only 1 longitudinal study has shown a significant association between day-to-day BPV assessed by home blood pressure measurements and risk of cognitive impairment,[10] and no studies have examined the association of day-to-day BPV with the development of dementia and its subtypes.

Compared with the measurement of visit-to-visit BPV on the basis of office blood pressure measurements, measurement of day-to-day BPV with home blood pressure monitoring is more reproducible and has no white coat effect,[11,12] which enables us to collect more reliable information and to optimize the blood pressure management earlier.[13] In addition, several factors such as arterial compliance, use of antihypertensive agents (dosing, adherence, etc), and daily physical activities have been shown to contribute to day-to-day BPV, whereas little is known about the factors responsible for BPV observed over months or years among office visits. The significance of BPV based on office blood pressure measurements at different times of visits is particularly unclear.[13,14] On the other hand, 24-hour ambulatory blood pressure monitoring is widely used in clinical practice. Short-term BPV within a 24-hour period assessed by ambulatory blood pressure monitoring mainly reflects the influences of central and reflex autonomic modulation. Previous studies using ambulatory blood pressure monitoring have highlighted that circadian variation and short-term BPV can predict cardiovascular events.[13] However, short-term BPV (over a period of 24 hours) and long-term BPV are independently associated with the development of vascular events[13] and cognitive decline.[15] In addition, measures of day-to-day BPV can be obtained with ambulatory blood pressure monitoring performed over a 48-hour period (consecutive days).[13] However, this strategy is not always well accepted by patients. As an alternative, home blood pressure monitoring can be performed under fairly standardized conditions and used to monitor blood pressure change over several days. Thus, it would be clinically valuable to evaluate the influence of day-to-day BPV as determined with home blood pressure monitoring on the incidence of dementia. The aim of the present study was thus to clarify the association between day-to-day BPV on a home blood pressure basis and the risk for the development of dementia and its subtypes in a prospective study of an elderly Japanese population.

METHODS

Study Population

The Hisayama study, a population-based prospective cohort study of cerebro-cardiovascular diseases, has been underway in the town of Hisayama, which is located in a suburb of Fukuoka City on Kyushu Island in Japan. According to the national census and nutrition survey, the age and occupational distributions of the Hisayama population have been similar to those in Japan as a whole since the 1960s.[16] Full community surveys of the health status and neurological condition of residents ≥40 years of age have been repeated every 1 to 2 years since 1961.[16] In addition, comprehensive surveys of cognitive impairment in the elderly, including neuropsychological tests such as the Mini-Mental State Examination (MMSE),[17] the Hasegawa's Dementia Scale,[18] and the Hasegawa's Dementia

Scale revised version,[18] were also conducted in 1985, 1992, 1998, 2005 to 2006, and 2012 to 2013, and we have also performed a follow-up survey of dementia in our community since 1985.[19]

In 2007 and 2008, a screening survey for the present study was performed in the town. A total of 1996 residents ≥60 years of age (86.3% of the total population of this age group) consented to participate in the examination and underwent the home blood pressure measurement. Among these, 1740 residents measured their home blood pressure for ≥3 days. We identified and excluded 66 subjects who had already developed dementia at baseline by using the data from the 2005 to 2006 prevalence survey and a follow-up survey from 2005 to 2007. After exclusion of these cases with dementia, a total of 1674 subjects (738 men and 936 women) were enrolled in the present study. This study was approved by the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from all participants.

Home Blood Pressure Measurements and Day-To-Day Variability Assessment

Physicians or public health nurses instructed the subjects on the appropriate way to measure home blood pressure. The subjects were instructed to measure their home blood pressure 3 times after >5 minutes of rest in the sitting position every morning, within 1 hour after getting up, and before breakfast and taking medication for 28 days with a validated digital electronic device (HEM-7080IC; Omron Healthcare, Kyoto, Japan) based on the cuff oscillometric method. The HEM-7080IC features memory storage for up to 350 blood pressure measurements and can extract these data for analysis. The mean of the 3 measurements was used as the value on each day, and all available daily averages were used in the present analysis. Home blood pressure was measured for a median of 28 days (range, 3–28 days), and mean home blood pressure and its SD were calculated from all the obtained measurements. Day-to-day systolic (SBP) and diastolic blood pressure variabilities were defined using the coefficient of variation (CoV) of home SBP and diastolic blood pressure. The CoV values (percent) were calculated with the formula (SD/mean blood pressure×100) and were categorized into quartiles as follows: SBP: quartile 1, ≤5.07%; quartile 2, 5.08% to 6.21%; quartile 3, 6.22% to 7.59%; and quartile 4, ≥7.60%; and diastolic blood pressure: quartile 1, ≤4.83%; quartile 2, 4.84% to 5.99%; quartile 3, 6.00% to 7.60%; and quartile 4, ≥7.61%. We considered other methods of variability, namely the SD, the maximum and minimum difference, the average real variability (ARV), and the variability independent of the mean (VIM). The ARV is computed as the average of absolute differences between consecutive day blood pressure measurements, and the VIM is calculated as the SD divided by the mean to the power x, which is obtained by fitting a curve through a plot of SD against mean blood pressure level.

Other Risk Factors

At the baseline examination, each subject was asked to complete a self-administered questionnaire covering educational status, medical history, treatments of hypertension and diabetes mellitus, smoking habits, alcohol intake, and physical activity. A low education level was defined as ≤9 years of formal education. History of cardiovascular disease was defined as any preexisting event of stroke or coronary heart disease, including myocardial infarction and coronary intervention. All cardiovascular events were adjudicated on the basis of physical examinations and a review of all available clinical information, including medical records and imaging. Plasma glucose levels were measured by the glucose oxidase method. Diabetes mellitus was determined by medical history, plasma glucose levels (fasting glucose level ≥7.0 mmol/L or postprandial glucose level ≥11.1 mmol/L), or a 75-g oral glucose tolerance test using the 1998 World Health Organization criteria and/or by the use of oral hypoglycemic agents or insulin. Serum total cholesterol levels were measured enzymatically. Body height and weight were measured in light clothing without shoes, and body mass index was calculated (kilograms per meter squared). ECG abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, 3), or atrial fibrillation (8-3). Smoking habits and alcohol intake were classified as either current use or not. Subjects engaging in sports at least 3 times a week during their leisure time were defined as the regular exercise group.

Follow-Up Survey

The subjects were followed up prospectively from June 2007 to November 2012 (median, 5.3 years). Details of the follow-up survey on dementia were published previously.[20,21] In brief, information about new events, including stroke and dementia, was collected through a daily monitoring system established by the study team, local physicians, and members of the town's Health and Welfare Office. In this system, the physicians in the study team visited clinics, hospitals, and the town's office regularly to collect information on events of stroke and dementia, including suspected cases. Regular health examinations, including physical and neurological examinations, were also repeated every year to obtain information on new events of stroke and dementia missed by the monitoring system. Health information was checked annually by letter or telephone for any subjects who did not undergo regular examination or who had moved away from town. In addition, comprehensive assessment of cognitive function, including neuropsychological tests such as the MMSE[17] and the Hasegawa's Dementia Scale revised version[18] were conducted in 2005 to 2006 and 2012 to 2013 to precisely detect dementia cases to the greatest extent possible. When a subject was suspected of having new neurological symptoms, including cognitive impairment, he/she was carefully evaluated by the study team. This team, which consisted of stroke physicians and psychiatrists, conducted various investigations, including physical and neurological examinations, interviews of the family and attending physician, and a review of the clinical records. In addition, when a subject died, we reviewed all the available clinical information, interviewed the attending physician and the family of the deceased, and tried to obtain permission for autopsy from the family. During the follow-up period, 128 subjects died, of whom 74 underwent brain examination at autopsy. Except for the deceased individuals, no subject was lost to follow-up through November 2012.

Diagnosis of Dementia

The guidelines of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* were used to define the diagnosis of dementia.[22] The criteria of the National Institute of Neurological Disorders and Stroke–Association International pour la Recherche et l'Enseignement en Neurosciences were used to make a diagnosis of vascular dementia (VaD),[23] and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were used to define subjects with Alzheimer disease (AD).[24] Every dementia case was adjudicated by expert stroke physicians and psychiatrists. The diagnosis of possible or probable dementia subtypes was based on clinical information and morphological examination from neuroimagings. Definite dementia subtypes were also decided on the basis of clinical and neuropathological information in subjects with dementia who underwent autopsy. The diagnostic procedure for autopsy cases was reported previously.[25]

Statistical Analysis

The trends in mean values or frequencies of risk factors for the CoV quartiles of home blood pressure were tested with linear or logistic regression analysis, respectively. The cumulative incidences of dementia and its subtypes were estimated with the Kaplan-Meier method, and the differences among the CoV levels were tested with a Cox proportional hazards model. The annual incidences of dementia and its subtypes were calculated by a person-year method. The hazard ratios (HRs) with their 95% confidence intervals (CIs) of the BPV for the development of dementia were estimated with the Cox proportional hazards model. The proportional hazards assumption was checked graphically with the log cumulative hazard plot for outcomes according to the levels of BPV. The trends in risk of dementia and its subtypes across BPV levels of a categorical variable assigned ordered natural numbers (ie, 1, 2, 3, and 4) were tested with the Cox proportional hazards model. The heterogeneity in the association between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. Sensitivity analyses were examined with other methods of variability such as the SD, maximum and minimum difference, ARV, and VIM. We also conducted another sensitivity analysis among the subjects with available MMSE data in 2005 to 2006. A 2-sided value of $P<0.05$ was considered to be statistically significant in all analyses. All statistical analyses were performed with the SAS statistical software program, version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

The baseline characteristics of the study population according to the CoV levels of home SBP are summarized in Table 1. The mean age and home SBP and the frequencies of women, low education, and use of antihypertensive agents increased significantly with higher CoV levels of home SBP, whereas the frequency of regular exercise decreased significantly with higher CoV levels of home SBP.

During the 5-year follow-up period, 194 subjects (72 men and 122 women) developed all-cause dementia: 183 underwent evaluation with brain imaging, 21 received a brain autopsy, and in 20 cases both were performed. Thus, 184 subjects in all (94.8%) had some kind of morphological examination. Among dementia cases, 7 cases were a mixed type of VaD and AD and

Table 1. Baseline Characteristics of Subjects According to Coefficient of Variation Levels of Home Systolic Blood Pressure: The Hisayama Study, 2007

Variable	All (n=1674)	Quartile of Coefficient of Variation Levels (%)				*P* for Trend
		Q1 (≤5.07) (n=418)	Q2 (5.08–6.21) (n=419)	Q3 (6.22–7.59) (n=419)	Q4 (≥7.60) (n=418)	
Age, mean (SD), y	71 (7)	69 (7)	70 (7)	72 (7)	73 (8)	<0.001
Women, %	55.9	46.4	56.3	59.7	61.2	<0.001
Education ≤9 y, %	43.5	37.7	42.0	44.6	49.8	<0.001
Systolic blood pressure, mean (SD), mm Hg	138 (18)	135 (18)	138 (18)	139 (18)	139 (18)	0.002
Diastolic blood pressure, mean (SD), mm Hg	77 (9)	78 (9)	78 (9)	77 (9)	77 (10)	0.10
Use of antihypertensive agents, %	43.3	38.8	43.2	42.7	48.6	0.008
ECG abnormalities, %	19.9	18.7	21.5	19.8	19.6	0.89
Diabetes mellitus, %	21.4	20.1	21.5	21.7	22.3	0.45
Serum total cholesterol, mean (SD), mmol/L	5.37 (0.91)	5.39 (0.87)	5.42 (0.91)	5.37 (0.90)	5.33 (0.95)	0.25
Body mass index, mean (SD), kg/m^2	23.1 (3.4)	23.2 (3.2)	23.1 (3.4)	23.1 (3.3)	22.8 (3.6)	0.13
History of cardiovascular disease, %	8.0	7.2	7.6	6.7	10.5	0.13
Smoking habits, %	13.0	15.6	11.2	12.7	12.7	0.33
Alcohol intake, %	42.4	46.7	40.1	41.5	41.3	0.17
Regular exercise ≥3 times/wk, %	14.2	17.7	14.8	12.4	11.7	0.008

ECG abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3.

counted as events in the analysis for each subtype. Taking these results together, 47 subjects experienced VaD and 134 experienced AD. Figure 1 demonstrates the unadjusted cumulative incidences of all-cause dementia and its subtypes according to quartiles of CoV levels of home SBP. The incidences of all-cause dementia, VaD, and AD were significantly higher among the subjects in the fourth quartile of CoV levels of home SBP compared with the first quartile.

Table 2 shows unadjusted incidences and the estimated HRs and 95% CIs for the development of dementia and its subtypes according to CoV levels of home SBP. The age- and sex-adjusted HRs of dementia and its subtypes increased significantly with increasing CoV levels of home SBP (*P* for trend <0.001 for all-cause dementia; *P*=0.01 for VaD; and *P*<0.001 for AD). After adjustment for age, sex, low education, use of antihypertensive agents, ECG abnormalities, diabetes mellitus, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habits, alcohol intake, and regular exercise, the risk of all-cause dementia, VaD, and AD increased significantly with increasing CoV levels of home SBP. These associations were unchanged even after adjustment for the mean values of home SBP for 4 weeks in addition to the above-mentioned confounding factors: compared with those in the first quartile of CoV levels of home SBP, the multivariable-adjusted HRs of all-cause dementia, VaD, and AD were significantly higher in subjects in the fourth quartile (HR=2.27, 95% CI=1.45–3.55, *P*<0.001 for all-cause dementia; HR=2.79, 95% CI=1.04–7.51, *P*=0.03 for VaD; and HR=2.22, 95% CI=1.31–3.75, *P*<0.001 for AD). When we conducted analyses using the CoV levels of home diastolic blood pressure, the significant associations with the risks of all-cause dementia, VaD, and AD were even stronger than those using the CoV levels of home SBP (Table I in the online-only Data Supplement). Moreover, we considered other methods of variability, namely SD, maximum and minimum difference, ARV, and VIM. Similarly significant associations were observed in these analyses, except for the association between BPV defined by ARV and VIM with risk of VaD (Table II in the online-only Data Supplement). On the other hand, when we used the mean SBP levels (Table III in the online-only Data Supplement), the risk of VaD increased significantly with increasing levels of mean SBP (*P* for trend=0.03), whereas no clear associations were observed for all-cause dementia and AD (Table IV in the online-only Data Supplement).

Last, we estimated the combined influences of home SBP levels and CoV levels of home SBP on the risk of VaD and AD because different blood pressure–related pathological processes might be involved in the development of VaD and AD (Figure 2). We divided the subjects into 4 groups according to the status of hypertension based on home SBP values (SBP ≥135 mm Hg and/or the use of antihypertensive agents versus others) and the CoV values of home SBP (the fourth quartile [≥7.60%] versus others [<7.60%]). When subjects with home SBP levels <135 mm Hg and a CoV of home SBP <7.60% were used as a reference group, the risk of VaD increased significantly in subjects with home SBP ≥135 mm Hg or the use of antihypertensive agents and a CoV of home SBP ≥7.60% (HR, 3.44; 95% CI, 1.10–10.74; *P*<0.05), whereas the risk of AD more than doubled in subjects with a CoV of home SBP ≥7.60% regardless of the home SBP values. There was no interaction between home SBP levels and CoV levels of home SBP on the risk of each sub-

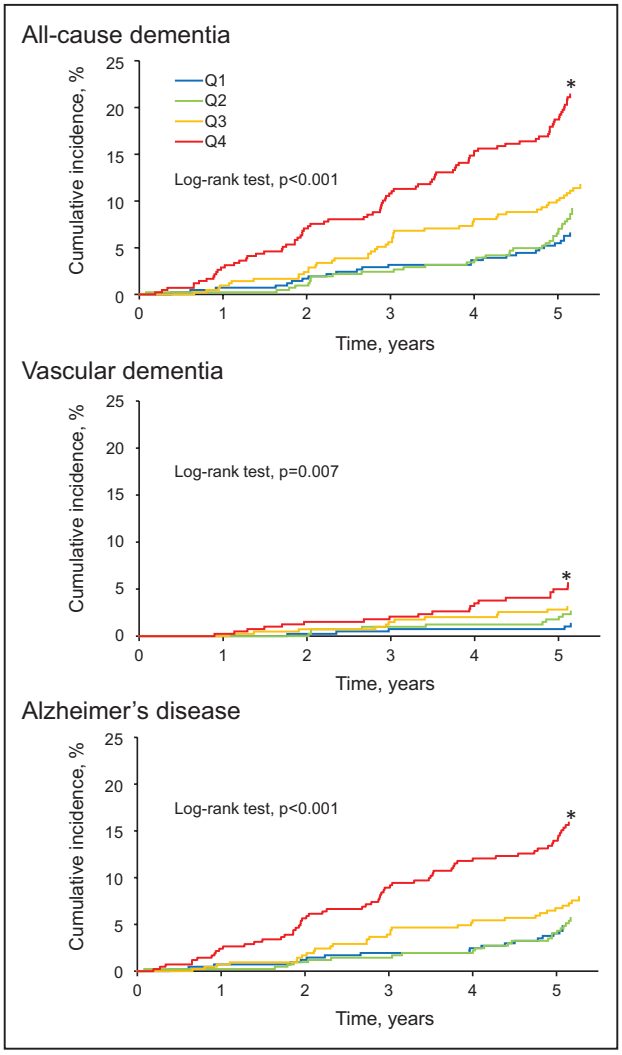

Figure 1. The cumulative incidences of all-cause dementia, vascular dementia, and Alzheimer disease according to quartiles of coefficient of variation (CoV) levels of home systolic blood pressure (SBP).
Q1 through Q4 indicate ascending quartiles of CoV levels of home SBP (Q1, ≤5.07%; Q2, 5.08%–6.21%; Q3, 6.22%–7.59%; and Q4, ≥7.60%). **P*<0.01 vs the first quartile of CoV levels of home SBP. The values are unadjusted.

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Table 2. Association Between Coefficient of Variation Levels of Home Systolic Blood Pressure and the Development of All-Cause Dementia and Its Subtypes, 2007 to 2012

Coefficient of Variation Levels (%)	Person-Years at Risk	Events, n	Incidence Rates (Per 10^3 Person-y)*	Hazard Ratio (95% Confidence Interval)		
				Age and Sex Adjusted	Model 1	Model 2
All-cause dementia						
Q1 (≤5.07)	2095	26	12.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2 (5.08–6.21)	2102	36	17.1	1.27 (0.77–2.11)	1.27 (0.76–2.10)	1.27 (0.76–2.10)
Q3 (6.22–7.59)	2066	47	22.7	1.29 (0.80–2.09)	1.29 (0.79–2.09)	1.29 (0.79–2.09)
Q4 (≥7.60)	1934	85	44.0	2.38 (1.52–3.71)	2.27 (1.45–3.55)	2.27 (1.45–3.55)
P for trend				<0.001	<0.001	<0.001
Vascular dementia						
Q1 (≤5.07)	2095	5	2.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2 (5.08–6.21)	2102	10	4.8	1.92 (0.66–5.62)	1.82 (0.62–5.37)	1.71 (0.58–5.05)
Q3 (6.22–7.59)	2066	12	5.8	1.95 (0.68–5.57)	1.91 (0.67–5.48)	1.86 (0.65–5.34)
Q4 (≥7.60)	1934	20	10.3	3.34 (1.24–9.00)	2.86 (1.06–7.71)	2.79 (1.04–7.51)
P for trend				0.01	0.04	0.03
Alzheimer disease						
Q1 (≤5.07)	2095	19	9.1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2 (5.08–6.21)	2102	22	10.5	1.04 (0.56–1.93)	1.06 (0.57–1.97)	1.07 (0.58–1.98)
Q3 (6.22–7.59)	2066	31	15.0	1.10 (0.62–1.95)	1.09 (0.61–1.95)	1.11 (0.62–1.98)
Q4 (≥7.60)	1934	62	32.1	2.22 (1.32–3.74)	2.22 (1.31–3.75)	2.22 (1.31–3.75)
P for trend				<0.001	<0.001	<0.001

Model 1 was adjusted for age, sex, education level, use of antihypertensive agents, ECG abnormalities, diabetes mellitus, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, and regular exercise. Model 2 was adjusted for the covariates included in model 1 plus the mean values of home systolic blood pressure for 4 weeks.

*The values are unadjusted.

type of dementia (AD: *P* for heterogeneity=0.62; VaD: *P* for heterogeneity=0.90). In the sensitivity analysis, we used the median values of home SBP (137 mm Hg or not) and CoV levels of home SBP (6.20% or not) as cutoff values and found no significant interaction between mean home SBP and CoV category on the risk of all-cause dementia and VaD (*P* for interaction=0.15 and 0.51, respectively) but a marginally significant interaction on the risk of AD (*P* for interaction=0.06). In the subgroup analysis of the status of antihypertensive agent use, there was no significant interaction in subjects not taking antihypertensive agents (*P* for interaction=0.23), whereas a significant interaction was observed in those taking antihypertensive agents (*P* for interaction=0.048). In the latter, subjects with both reduced home SBP and higher CoV were likely to have greater risk of incident AD.

There was no evidence of heterogeneity in these associations of day-to-day BPV with the risk of dementia among the subgroups of subjects with various potential risk factors such as sex, diabetes mellitus, use of antihypertensive agents, and smoking habits (all *P* for heterogeneity >0.10; Table V in the online-only Data Supplement).

DISCUSSION

The present study clearly demonstrated that increased day-to-day BPV by self-home measurements was significantly associated with the development of all-cause dementia, VaD, and AD even after adjustment for blood pressure values and other potential dementia risk factors. In addition, the risk of VaD increased significantly in subjects with both higher day-to-day BPV and home systolic hypertension compared with those with lower BPV and normotension, whereas the risk of AD increased significantly in subjects with higher BPV regardless of the home SBP values. These findings demonstrate that BPV is an important indicator for the development of dementia or a possible interventional target against dementia.

Several observational studies have demonstrated the association between BPV levels and cognitive impairment or dementia. However, the findings in most studies are based on visit-to-visit BPV measured by office blood pressures. Some studies have shown that higher visit-to-visit BPV assessed by office blood pressure was significantly associated with cognitive impairment.[5–8] In addition, the Three-City Study examined the as-

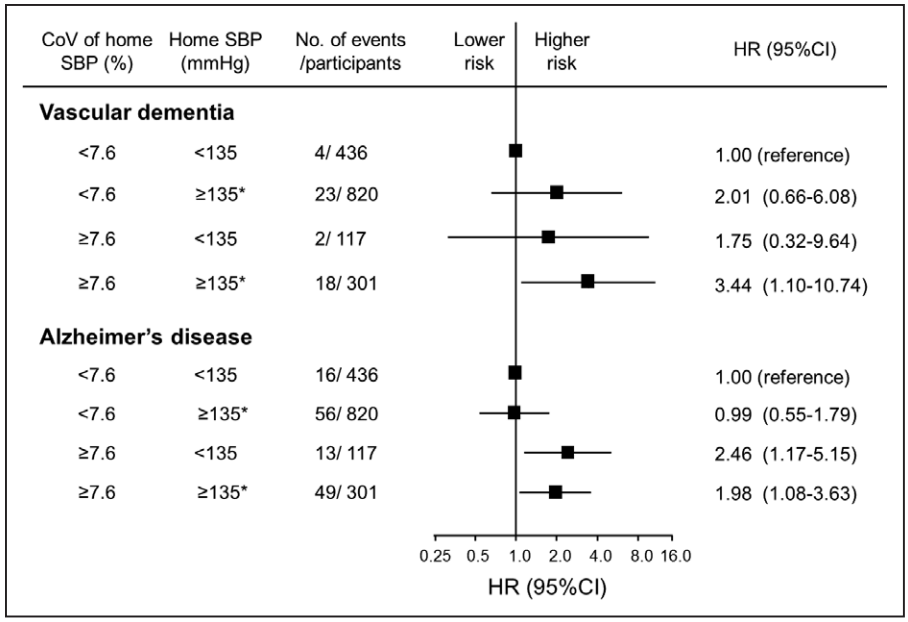

Figure 2. Multivariable-adjusted hazard ratios (HRs) for the development of dementia subtypes according to home systolic blood pressure (SBP) levels and coefficient of variation (CoV) levels of home SBP, 2007 to 2012.
HRs were adjusted for age, sex, education level, ECG abnormalities, diabetes mellitus, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habits, alcohol intake, and regular exercise. *Home SBP ≥135 mm Hg or use of antihypertensive agents.

sociation between BPV and the risk of dementia and reported that increased visit-to-visit systolic BPV evaluated by office blood pressure was a significant risk factor for the development of all-cause dementia and AD but not VaD, probably because of the small number of VaD cases.[9] Only 1 study, the Ohasama Study, has investigated the influence of day-to-day BPV measured on a home blood pressure basis on cognitive impairment; in that report, subjects with an increased day-to-day systolic BPV exhibited an increased risk of cognitive impairment.[10] To the best of our knowledge, the present study provides the first prospective evidence that an increased day-to-day BPV assessed by home blood pressure measurement is associated with the development of dementia and its subtypes in an elderly general population.

The present study demonstrated that both higher day-to-day BPV and SBP values were significantly associated with VaD. Elevated SBP is widely known to be a risk factor for small vessel disease, stroke, and VaD.[20,26,27] Some observational studies have also reported that elevated visit-to-visit BPV was a significant risk factor for the development of stroke, white matter hyperintensities,[28,29] cerebral microbleeds,[30] and cortical microinfarcts.[6] Hemodynamic instability via elevated BPV may increase shear stress, which could directly lead to small vessel disease and cerebral hypoperfusion[28] and subsequent neuronal cell injury.[6,27,29] In addition, increased BPV may be a marker of arterial stiffness, which is associated with increased risk of VaD, because arterial stiffness can magnify random blood pressure changes.[30]

On the other hand, the risk of AD was increased significantly with higher BPV in this study, regardless of absolute blood pressure values, which were not associated with the development of AD.[20] This finding may reflect autonomic dysfunction caused by changes in the central nervous system structure in individuals with prodromal AD, rather than direct shear stress on the cerebral arteries. Because the structure of the central nervous system has been shown to play a role in regulating the autonomic nervous system, it has been hypothesized that the central cholinergic dysfunction observed in AD could lead to autonomic dysfunction.[31,32] Meanwhile, high BPV without hypertension might increase the risk of hypoperfusion, which may be associated with increasing risk of cognitive decline and dementia via deteriorating neuronal damage.[33,34] From the above, BPV may be a causative factor of the alterations in brain structure and function, which in turn might lead to the development of dementia, especially VaD. On the other hand, BPV may be a marker of neurodegeneration, which has specific findings in AD, but the exact mechanisms responsible for these associations are unclear. Any clinical trial in which BPV was modified (eg, a trial using long-lasting antihypertensive agents) could help to clarify these mechanisms.[35] Evidence is accumulating that diuretics and calcium channel blockers are associated with lower levels of BPV compared with other antihypertensive classes.[36,37] However, the magnitude of the difference in BPV between classes was relatively low in these reports, and few clinical trials have addressed the class effects of antihypertensive agents on cardiovascular disease and cognitive function. Further studies are needed to elucidate the pathogenesis of increased BPV in the development of dementia and its subtypes.

The strengths of our study include its longitudinal community-based design, high participation rate in the baseline examination, perfect follow-up of sub-

jects, and accuracy of diagnosis of dementia. However, some limitations of our study should be discussed. First, we could not obtain information on change of blood pressure control and other risk factors resulting from modifications in lifestyle or medication during the follow-up. The lack of this information may have reduced the accuracy of our findings to some extent. Second, the number of events was insufficient for a more detailed analysis. Third, there could be residual confounding caused by unmeasured factors such as poor adherence to an antihypertensive regimen, inadequate blood pressure control, mental/physical stress, and sleep deprivation.[38,39] Poor adherence to hypertension treatment and poor blood pressure control might have played particularly prominent roles in the elevated day-to-day BPV. The present study revealed that subjects who had both reduced home SBP and higher CoV were likely to have greater risk of incident AD among those taking antihypertensive agents. This finding may reflect the influence of hypotension and subsequent hypoperfusion on the cognitive dysfunction among subjects with intensive blood pressure lowering and greater CoV. Fourth, data on neuropsychological tests were not available for all participants at baseline. Among the 1674 subjects, 1030 underwent the MMSE in 2005 to 2006. However, when the analysis was restricted to subjects with available MMSE data at baseline (Table VI in the online-only Data Supplement), the associations between the CoV of SBP/mean SBP and risk of dementia and its subtypes remained significant even after adjustment for MMSE in addition to the potential confounding covariates (Tables IV and VII in the online-only Data Supplement). In addition, sensitivity analyses after the exclusion of subjects who developed dementia during the initial 2 years of follow-up did not make any material difference in the findings (*P* for trend=0.006 for all-cause dementia; *P*=0.18 for VaD; *P*=0.01 for AD). These data suggest that the possibility of prodromal dementia cases at baseline was relatively low, and this limitation might not have exerted a meaningful influence on the results of our study. Fifth, the influence of psychoactive medications on the findings could not be assessed sufficiently. However, only 1.3% of subjects (n=22) took any antidepressants in this study, and the significant associations between BPV and the risk of dementia were substantially unchanged after additional adjustment for the use of antidepressants (data not shown). Last, the present study could not clearly distinguish the influence of BPV from that of high excursion on the risk of dementia. Nevertheless, there were significant associations of VIM, which is an indicator of BPV independently of BP level, with the risk of dementia. These findings may suggest that higher BPV itself is associated with greater risk of dementia, regardless of the presence or absence of high or low BP levels, such as high excursion.

CONCLUSIONS

The present study demonstrated that an increased day-to-day BPV on a home blood pressure basis was significantly associated with the development of all-cause dementia, VaD, and AD, regardless of average home blood pressure. Moreover, both higher day-to-day BPV and hypertension were significantly associated with the risk of VaD, whereas the risk of AD increased significantly in subjects with higher BPV regardless of absolute blood pressure values. These findings raise the possibility that the measurement of day-to-day BPV on a home blood pressure basis would be useful for assessing future risk of dementia and elucidating blood pressure–related pathological processes in each dementia subtype. However, further investigations are required to clarify whether day-to-day BPV is an indicator of future dementia or an interventional target for the prevention of dementia.

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DISCLOSURES

None.

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FOOTNOTES

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Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Hazard ratios for the development of all-cause dementia and its subtypes according to CoV levels of home diastolic blood pressure, 2007-2012

CoV levels (%)	No. of events	No. of participants	HR (95% CI)		
			Age- and sex-adjusted	Model 1	Model 2
All-cause dementia					
Q1 (≤4.83)	21	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	37	419	1.65 (0.97-2.83)	1.62 (0.94-2.78)	1.65 (0.96-2.83)
Q3 (6.00-7.60)	56	419	2.08 (1.26-3.45)	2.09 (1.26-3.48)	2.13 (1.28-3.54)
Q4 (≥7.61)	80	418	2.75 (1.69-4.46)	2.72 (1.67-4.43)	2.73 (1.68-4.44)
P for trend			<0.001	<0.001	<0.001
Vascular dementia					
Q1 (≤4.83)	14	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	25	419	2.39 (0.75-7.62)	2.58(0.80-8.32)	2.95 (0.91-9.57)
Q3 (6.00-7.60)	39	419	2.95 (0.96-8.99)	3.12 (1.01-9.59)	3.51 (1.13-10.91)
Q4 (≥7.61)	56	418	3.67 (1.24-10.88)	3.39 (1.14-10.07)	3.57 (1.19-10.68)
P for trend			0.02	0.03	0.03
Alzheimer's disease					
Q1 (≤4.83)	4	418	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (4.84-5.99)	10	419	1.66 (0.87-3.20)	1.60 (0.82-3.09)	1.60 (0.82-3.10)
Q3 (6.00-7.60)	14	419	2.09 (1.13-3.87)	2.05 (1.11-3.81)	2.05 (1.10-3.81)
Q4 (≥7.61)	19	418	2.79 (1.54-5.03)	2.87 (1.59-5.19)	2.87 (1.59-5.19)
P for trend			<0.001	<0.001	<0.001

CoV indicates the coefficient of variation; HR, hazard ratio; and CI, confidence interval.
Model 1 was adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, and regular exercise.
Model 2 was adjusted for the covariates included in model 1 plus the mean values of home diastolic blood pressure for 4 weeks.

Supplemental Table 2. Hazard ratios for the development of all-cause dementia and its subtypes according to SD, MMD, ARV, and VIM levels of home systolic blood pressure, 2007-2012

Levels of variability	All-cause dementia		Vascular dementia		Alzheimer's disease	
	No. of events/ No. of participants	HR(95%CI)	No. of events/ No. of participants	HR(95%CI)	No. of events/ No. of participants	HR(95%CI)
SD (mmHg)						
Q1 (≤6)	23/418	1.00 (reference)	3/418	1.00 (reference)	17/418	1.00 (reference)
Q2 (7-8)	35/419	1.21 (0.71-2.05)	9/419	2.37 (0.64-8.85)	23/419	1.07 (0.57-2.02)
Q3 (9-10)	49/419	1.52 (0.91-2.53)	11/419	2.52 (0.68-9.28)	34/419	1.39 (0.76-2.53)
Q4 (≥11)	87/418	2.22 (1.35-3.65)	24/418	3.95 (1.12-13.86)	60/418	2.17 (1.20-3.91)
P for trend		<0.001		0.02		0.003
MMD (mmHg)						
Q1 (≤26.99)	24/410	1.00(reference)	4/410	1.00 (reference)	17/410	1.00 (reference)
Q2 (27.00-34.50)	36/426	1.07(0.63-1.80)	7/426	1.27 (0.37-4.40)	27/426	1.12 (0.61-2.07)
Q3 (34.67-42.66)	45/413	1.38(0.83-2.29)	13/413	2.26 (0.71-7.15)	28/413	1.23 (0.66-2.27)
Q4 (≥42.67)	89/425	1.89(1.16-3.08)	23/425	2.65 (0.86-8.12)	62/425	1.87 (1.04-3.35)
P for trend		0.002		0.03		0.02
ARV (mmHg)						
Q1 (≤6.41)	26/417	1.00 (reference)	4/417	1.00 (reference)	18/417	1.00 (reference)
Q2 (6.42-8.09)	34/420	1.03 (0.61-1.72)	10/420	1.52 (0.47-4.92)	24/420	1.19 (0.67-2.13)
Q3 (8.10-10.17)	51/419	1.44 (0.88-2.34)	15/419	2.15 (0.69-6.73)	32/419	1.19 (0.67-2.09)
Q4 (≥10.18)	83/418	1.75 (1.08-2.84)	18/418	1.66 (0.52-5.31)	60/418	2.08 (1.23-3.51)
P for trend		0.005		0.44		0.004
VIM (units)						
Q1 (≤6.67)	30/418	1.00(reference)	8/418	1.00 (reference)	20/418	1.00 (reference)
Q2 (6.68-8.11)	39/419	1.21(0.75-1.96)	9/419	1.31 (0.50-3.44)	27/419	1.19 (0.67-2.13)
Q3 (8.12-9.90)	50/419	1.37(0.87-2.16)	14/419	1.70 (0.71-4.12)	31/419	1.19 (0.67-2.09)
Q4 (≥9.91)	75/418	1.97(1.27-3.05)	16/418	1.93 (0.81-4.60)	56/418	2.08 (1.23-3.51)

P for trend	0.001	0.11	0.004

SD indicates standard deviation; MMD, maximum and minimum differences; ARV, average real variability; VIM, variability independent of the mean; HR, hazard ratio; and CI, confidence interval.

Adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise, and mean values of home systolic blood pressure for 4 weeks.

Supplemental Table 3. Baseline characteristics of subjects according to mean values of home systolic blood pressure levels, the Hisayama Study, 2007

Variables	Quartile of mean systolic blood pressure levels (mmHg)				*P* for trend
	Q1 (≤125) n=418	Q2 (126-136) n=419	Q3 (137-150) n=419	Q4 (≥151) n=418	
Age, mean (SD), y	69 (7)	70 (7)	72 (7)	74 (8)	<0.001
Women, %	62.2	55.1	52.7	53.6	0.009
Education ≤ 9 years, %	37.4	40.4	47.8	48.3	<0.001
Systolic blood pressure, mean (SD), mmHg	116 (7)	131 (3)	143 (4)	161 (10)	<0.001
Diastolic blood pressure, mean (SD), mmHg	70 (6)	76 (7)	80 (8)	84 (9)	<0.001
Use of antihypertensive agents, %	17.0	41.1	53.5	61.7	<0.001
Electrocardiogram abnormalities, %	11.0	14.8	22.7	31.1	<0.001
Diabetes mellitus, %	13.4	20.3	23.9	28.0	<0.001
Serum total cholesterol, mean (SD), mmol/L	5.49 (0.89)	5.44 (0.97)	5.25 (0.89)	5.33 (0.87)	<0.001
Body mass index, mean (SD), kg/m^2	21.8 (3.0)	23.2 (3.3)	23.6 (3.3)	23.6 (3.5)	<0.001
History of cardiovascular disease, %	5.3	6.9	9.1	10.8	0.002
Smoking habits, %	12.2	10.0	14.6	15.3	0.06
Alcohol intake, %	36.6	40.8	45.1	47.0	0.001
Regular exercise ≥ 3 times/w, %	14.1	15.3	15.8	11.5	0.34
MMSE score, mean (SD)	27.5 (2.4)	27.5 (2.1)	27.5 (2.2)	27.4 (2.2)	0.50

SD indicates standard deviation; and MMSE, Mini-Mental State Examination.

Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3. MMSE was examined in 2005-2006 in 1,030 participants.

Supplemental Table 4. Association between mean values of home systolic blood pressure levels and the development of all-cause dementia and its subtypes, 2007-2012

Mean systolic blood pressure levels (mmHg)	Person-years at risk	No. of events	Incidence rates (per 10^3 person-years)*	HR (95% CI)		
				Age- and sex-adjusted	Model 1	Model 2
All-cause dementia						
Q1 (≤125)	1916	32	16.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	35	16.2	0.92 (0.57-1.48)	0.88 (0.54-1.44)	0.78 (0.46-1.30)
Q3 (137-150)	1800	55	30.6	1.14 (0.73-1.77)	1.02 (0.64-1.64)	0.91 (0.56-1.48)
Q4 (≥151)	2321	72	31.0	1.08 (0.70-1.67)	0.98 (0.61-1.56)	0.81 (0.50-1.32)
P for trend				0.52	0.88	0.58
Vascular dementia						
Q1 (≤125)	1916	5	2.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	6	2.8	1.00 (0.30-3.27)	1.08 (0.32-3.64)	1.22 (0.35-4.27)
Q3 (137-150)	1800	15	8.3	2.05 (0.74-5.70)	2.29 (0.78-6.70)	2.08 (0.67-6.45)
Q4 (≥151)	2321	21	9.0	2.29 (0.84-6.28)	2.55 (0.88-7.42)	2.26 (0.72-7.10)
P for trend				0.04	0.03	0.10
Alzheimer's disease						
Q1 (≤125)	1916	25	13.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (126-136)	2161	26	12.0	0.88 (0.51-1.53)	0.83 (0.47-1.45)	0.70 (0.39-1.25)
Q3 (137-150)	1800	34	18.9	0.89 (0.53-1.51)	0.79 (0.45-1.37)	0.68 (0.38-1.20)
Q4 (≥151)	2321	49	21.1	0.90 (0.54-1.49)	0.78 (0.45-1.33)	0.62 (0.35-1.08)
P for trend				0.75	0.41	0.14

HR indicates hazard ratio; and CI, confidence interval.

Model 1 was adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, and regular exercise.

Model 2 was adjusted for the covariates included in model 1 plus the Mini-Mental State Examination score in 2005-2006 (n=1030).

*The values are unadjusted.

Supplemental Table 5. Multivariable-adjusted hazard ratios of dementia per 1-SD increment in CoV of home systolic blood pressure in various subgroups of the study population, 2007-2012

Subgroups of variables	No. of events	No. of participants	HR (95% CI) per 1-SD increment in CoV of home systolic blood pressure (1 SD=3.11%)	*P* for interaction
All-cause dementia				
Sex				
Men	72	738	1.31 (1.10-1.56)	
Women	122	936	1.24 (1.06-1.45)	0.46
Age (years)				
60-74	58	1145	1.23 (1.00-1.51)	
≥75	136	529	1.31 (1.14-1.50)	0.93
Diabetes mellitus				
No	149	1315	1.31 (1.15-1.49)	
Yes	44	358	1.22 (0.96-1.55)	0.27
Use of antihypertensive agents				
No	90	949	1.24 (1.04-1.48)	
Yes	104	725	1.27 (1.08-1.48)	0.69
Smoking habits				
No	172	1456	1.27 (1.13-1.44)	
Yes	22	218	1.19 (0.80-1.79)	0.79
Vascular dementia				
Sex				
Men	24	738	1.14 (0.83-1.58)	
Women	23	936	1.09 (0.74-1.62)	0.88
Age (years)				
60-74	17	1145	1.21 (0.83-1.76)	
≥75	30	529	0.99 (0.72-1.37)	0.35
Diabetes mellitus				
No	34	1315	1.08 (0.81-1.45)	
Yes	13	358	1.18 (0.75-1.83)	0.92

Use of antihypertensive agents				
No	21	949	0.88 (0.57-1.35)	
Yes	26	725	1.20 (0.87-1.65)	0.78
Smoking habits				
No	39	1456	1.11 (0.84-1.47)	
Yes	8	218	1.93 (0.34-10.96)	0.72
Alzheimer's disease				
Sex				
Men	41	738	1.40 (1.11-1.76)	
Women	93	936	1.30 (1.08-1.55)	0.43
Age (years)				
60-74	37	1145	1.18 (0.90-1.55)	
≥75	97	529	1.44 (1.23-1.69)	0.37
Diabetes mellitus				
No	106	1315	1.36 (1.16-1.58)	
Yes	28	358	1.32 (0.98-1.77)	0.52
Use of antihypertensive agents				
No	64	949	1.34 (1.09-1.64)	
Yes	70	725	1.32 (1.10-1.59)	0.79
Smoking habits				
No	121	1456	1.36 (1.18-1.57)	
Yes	13	218	1.00 (0.59-1.70)	0.36

SD indicates standard deviation; CoV, coefficient of variation; HR, hazard ratio; and CI, confidence interval.
The HRs were adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise and mean values of home systolic blood pressure for 4 weeks. The variable relevant to the subgroup was excluded from each model.

Supplemental Table 6. Baseline characteristics of subjects according to CoV levels of home systolic blood pressure, the Hisayama Study, 2007 (n=1030)

Variables	All	Quartile of CoV levels (%)				*P* for trend
	n=1030	Q1 (≤5.32) n=257	Q2 (5.33-6.41) n=258	Q3 (6.42-7.79) n=258	Q4 (≥7.80) n=257	
Age, mean (SD), y	75 (6)	74 (6)	75 (5)	76 (6)	76 (6)	<0.001
Women, %	57.4	46.7	58.5	62.0	62.3	<0.001
Education ≤ 9 years, %	51.6	50.2	50.8	50.8	54.7	0.34
Systolic blood pressure, mean (SD), mmHg	141 (18)	140 (18)	141 (18)	143 (18)	141 (17)	0.35
Diastolic blood pressure, mean (SD), mmHg	77 (9)	77 (9)	77 (10)	77 (9)	76 (9)	0.16
Use of antihypertensive agents, %	50.7	51.0	50.8	46.1	54.9	0.62
Electrocardiogram abnormalities, %	21.8	22.2	23.6	18.2	23.4	0.87
Diabetes mellitus, %	22.8	21.4	24.8	23.3	21.9	0.99
Serum total cholesterol, mean (SD), mmol/L	5.26 (0.87)	5.23 (0.82)	5.26 (0.83)	5.28 (0.92)	5.26 (0.91)	0.74
Body mass index, mean (SD), kg/m^2	22.9 (3.4)	22.9 (3.3)	23.2 (3.4)	22.9 (3.4)	22.6 (3.3)	0.19
History of cardiovascular disease, %	9.2	7.4	7.8	9.3	12.5	0.04
Smoking habits, %	10.8	14.4	7.4	9.7	11.7	0.50
Alcohol intake, %	37.4	41.3	34.1	37.2	37.1	0.49
Regular exercise ≥ 3 times/w, %	13.7	16.3	15.5	11.6	11.3	0.05
MMSE score, mean (SD)	27.3 (2.3)	27.7 (2.2)	27.7 (2.0)	27.3 (2.3)	27.2 (2.2)	0.005

CoV indicates the coefficient of variation; SD, standard deviation; and MMSE, Mini-Mental State Examination.

Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3.

MMSE was examined in 2005-2006.

Supplemental Table 7. Association between CoV levels of home systolic blood pressure and the development of all-cause dementia and its subtypes after including pre-baseline cognitive assessment in the analyses (n=1030), 2007-2012

CoV levels (%)	Population at risk	No. of events	HR (95% CI)
			Multivariable-adjusted*
All-cause dementia			
Q1 (≤5.07)	223	23	1.00 (reference)
Q2 (5.08-6.21)	249	31	1.18 (0.69-2.04)
Q3 (6.22-7.59)	271	46	1.34 (0.81-2.23)
Q4 (≥7.60)	287	80	2.27 (1.42-3.65)
P for trend			<0.001
Vascular dementia			
Q1 (≤5.07)	223	4	1.00 (reference)
Q2 (5.08-6.21)	249	8	2.01 (0.59-6.89)
Q3 (6.22-7.59)	271	11	2.34 (0.72-7.64)
Q4 (≥7.60)	287	20	3.74 (1.23-11.38)
P for trend			0.01
Alzheimer's disease			
Q1 (≤5.07)	223	17	1.00 (reference)
Q2 (5.08-6.21)	249	21	1.08 (0.56-2.05)
Q3 (6.22-7.59)	271	30	1.09 (0.60-2.00)
Q4 (≥7.60)	287	57	2.16 (1.24-3.75)
P for trend			0.002

CoV indicates the coefficient of variation; HR, hazard ratio; and CI, confidence interval.

*Adjusted for age, sex, education level, use of antihypertensive agents, electrocardiogram abnormalities, diabetes, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise, and Mini-Mental State Examination score in 2005-2006.