Blood Pressure Variability and the Risk of Dementia
A Nationwide Cohort Study

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Abstract—To investigate the association between visit-to-visit variability in blood pressure and the incidence of dementia and its subtypes in a general population, we conducted a population-based retrospective cohort study using the Korean National Health Insurance System database. We identified 7 844 814 subjects without a history of any dementia who underwent ≥3 health examinations from 2005 to 2012 in the Korean National Health Insurance System cohort. Blood pressure variability (BPV) was measured using the variability independent of the mean, coefficient of variation, and SD. During the median follow-up of 6.2 years, there were 200 574 cases of all-cause dementia (2.8%), 165 112 cases of Alzheimer's disease (2.1%), and 27 443 cases of vascular dementia (0.3%). There was a linear association between higher BPV and outcome measures. In the multivariable adjusted model, the hazard ratios and 95% CIs of all-cause dementia were 1.06 (1.04–1.07) for the highest quartile of variability independent of the mean of diastolic blood pressure only, 1.09 (1.08–1.11) for that of systolic blood pressure only, and 1.18 (1.16–1.19) for that of both systolic and diastolic blood pressure compared with subjects having no highest quartile for BPV. Consistent results were noted for Alzheimer's disease and vascular dementia using other indices of variability and in various sensitivity and subgroup analyses. BPV is an independent predictor for developing dementia and its subtypes. A dose-response relationship was noted between higher BPV and dementia incidence. Reducing BPV may be a target for preventing dementia in the general population. **(*Hypertension*. 2020;75:982-990. DOI: 10.1161/HYPERTENSIONAHA.119.14033.)**
● **Online Data Supplement**

Key Words: Blood pressure ■ Variability ■ Dementia ■ Alzheimer's disease ■ Vascular dementia

Worldwide, nearly 35 million people live with dementia and this number is expected to double by 2030 and more than triple by 2050, representing a public health priority.[1] Due to the lack of effective treatments to prevent or reverse the cognitive decline, the search for putative preventive measures to lower its prevalence rate or slow down its progression may represent a reasonable clinical strategy and have important practical implications.[2] In this respect, vascular risk factors are placed among those considered of greatest interest. Managing these factors offers a feasible method for managing cerebrovascular impairment.[2]

Along with the traditionally assessed conditions, such as arterial hypertension, diabetes mellitus, dyslipidemia, or arterial fibrillation, visit-to-visit variability in blood pressure (BP) is related to cerebrovascular damage and independent of mean blood pressure.[3] In addition, regardless mean blood pressure, higher blood pressure variability (BPV) is associated with increased white matter hyper-intensity lesions on brain MRI,[4] increased carotid artery intima media thickness,[5] and early atherosclerosis progression.[6]

Recently, raised BPV has emerged as a novel risk factor for the development and progression of Alzheimer's dementia, whose hallmarks include brain parenchymal and vascular deposits of amyloid-β peptide (Aβ), neurofibrillary tangles of hyperphosphorylated tau protein, gliosis, and neuronal loss.[7] Previous studies have suggested that BPV is a risk factor for cognitive decline. Some findings have examined the association of BPV with structural brain damage[4,8,9] and progression of cognitive decline.[2,10,11] These studies assessed BPV using either systolic BP (SBP) or diastolic BP (DBP)[2,4,8–13] and did not investigate combined effects of SBPV and DBPV.[2,4,8–13] However, the association of BPV with incidence of dementia[12,13] and its subtypes[13] is not well established. These studies were are also limited by having relatively small study populations (N<6506[12]) or by having difficulties in generalizing findings. The latter was due to the specific populations

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studied, such as an elderly cohort,[9,12,13] thus there were difficulties generalizing the findings to mid-life hypertension.

Therefore, in the present study, we aimed to evaluate the association between visit-to-visit BPV and the incidence of dementia and its subtypes for a nationally representative sample of adults aged 40 or older. We also investigated the additive effect of having both higher systolic and diastolic BPV on dementia.

Methods

Because of the confidentiality of the data used for this study and a strict privacy policy from the data holder that the data must be kept among designated research personnel only, the data cannot be provided to others, whether or not the data are made anonymous.

Data Source

The Korean National Health Insurance Service (KNHIS) is the single insurer and manages all the administrative processes for the enrollees of national health insurance (≈97% of the population) and medical aid program (3% of the population in the lowest income bracket). The KNHIS also provides free biennial cardiovascular health screening to the entire population aged 40 and above and all employees regardless of age. These services are also available annually for workers in physical labor jobs.

Therefore, the National Health Information database comprises a complete set of health information pertaining to 50 million Koreans, which includes an eligibility database (eg, age, sex, place of residence, and income level), a medical treatment database (based on the medical bills that were claimed by medical service providers for their medical expense claims), a health examination database (results of general health examinations), and a medical care institution database.[14,15]

Study Population

Among 23 503 802 subjects who underwent health examinations between January 1, 2009 and December 31, 2012 (baseline and index date), we identified 11 305 147 subjects who underwent ≥3 health examinations from January 1, 2005 to December 31, 2012. Subjects who were younger than 40 years old at baseline (n=3 427 494) and who had a history of all-cause dementia (*International Classification of Disease, 10th Revision [ICD-10]* codes: F00, F01, F02, F03, G23.1, G30, G31) before the index date were also excluded (n=32 849). Ultimately, the study population consisted of 7 844 814 subjects (Figure 1; Table S1 in the online-only Data Supplement). This study was approved by the Institutional Review Board of Samsung Medical Center (IRB File No. SMC 2018-08-071). The review board waived requirement for written informed consent because of anonymous and de-identified information used for analysis and retrospective features.

Measurements

The KNHIS screening examination includes anthropometric measurements (BP, height, weight, waist circumference), laboratory tests (eg, blood glucose, lipid profile, and creatinine), and questionnaires on health behaviors.[16] Hospitals wherein these health examinations were performed were certified by the KNHIS and subjected to regular quality control from the Korean Association of Laboratory Quality Control.

According to the KNHIS health screening protocol, brachial BP was measured by a trained clinician. The average of the 2 brachial BP measurements were taken after the participant had been seated for 5 minutes with an arm in the appropriate position. Body mass index was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters, and body mass index was categorized by Asian criteria.[17] Information on smoking and alcohol consumption was dichotomized (current versus none). Regular exercise was defined as >30 minutes of moderate physical activity ≥5× per week or as >20 minutes of strenuous physical activity ≥3× per week. Blood samples for the measurement of serum fasting glucose and total cholesterol levels were drawn after an overnight fast.

The presence of diabetes mellitus was defined according to the following criteria: (1) at least one claim per year under *ICD-10* codes E11–14 and at least one claim per year for the prescription of antidiabetic medication or (2) fasting glucose level ≥126 mg/dL. The presence of hypertension was defined according to (1) the presence of at least one claim per year under *ICD-10* codes I10-13 or I15 and at least one claim per year for the prescription of antihypertensive agents or (2) SBP/DBP ≥140/90 mmHg. The presence of dyslipidemia was defined according to (1) the presence of at least one claim per year under *ICD-10* code E78 and at least one claim per year for the prescription of a lipid-lowering agent or (2) total cholesterol ≥240 mg/dL. The presence of chronic kidney disease was defined glomerular filtration rate <60 mL/minute per 1.73 m^2 as estimated by the Modification of Diet in Renal Disease equation. The history of ischemic heart disease or stroke was obtained by self-administered questionnaire.

Definition of BPV

BPV was defined as the variability in BP values measured on health examinations. Three indices of variability were used: (1) variability independent of the mean (VIM), (2) coefficient of variation (CV), and (3) SD.[18,19] The VIM was calculated as $100\times SD/mean^{\beta}$, where β is the regression coefficient based on the natural logarithm of SD over the natural logarithm of the mean.[18] CV is defined as SD/mean. VIM was used for the primary analysis, and CV and SD were used for secondary analyses. The number of BP measurements per subject ranged from 3 to 5 (median 4); 3 measurements (n=2 021 033, 25.8%), 4 measurements (n=3 364 196, 42.9%), and 5 measurements (n=2 459 585, 31.3%).

For the subsequent analyses, BPV was categorized in several ways: (1) by quartiles of SBP and DBP variability separately (SBPV and DBPV Q1-Q4), (2) by deciles of SBP and DBPs separately (SBPV and DBPV D1-D10), (3) by dichotomizing quartiles (SBPV and DBPV highest quartile versus others, ie, Q4 versus Q1–Q3) for SBP and DBP, (4) by combination of the dichotomized SBPV and DBPV (SBPV and DBPV Q4, SBPV Q4 only, DBPV Q4 only, and others).

Study Outcomes and Follow-Up

The end points of the study were newly diagnosed dementia, which was defined if antidementia drugs were prescribed at least 2× and the codes with Alzheimer's disease (AD, ICD-10 F00, or G30), vascular dementia (VaD, ICD-10 F01), or other dementia (ICD-10 F02, F03, G23.1, or G31). To file expense claims for the prescription of acetylcholinesterase inhibitors (donepezil hydrochloride, rivastigmine, galantamine) or NMDA receptor antagonist (memantine) for dementia treatment, physicians need to document evidence of cognitive dysfunction according to National Health Insurance Reimbursement criteria: a Mini-Mental State Examination ≤26 and either a Clinical Dementia Rating ≥1 or a Global Deterioration Scale ≥3.[20,21] The cohort was followed from baseline (last BP measurement date) to the date of incident dementia or until the end of the study period (December 31, 2016), whichever came first (Figure S1).

Statistical Analysis

Continuous variables were presented as the mean±SD, and categorical variables were presented as numbers and percentages. A Cox proportional hazards model was used to estimate the hazard ratios and 95% CIs for each group of BPV. Multivariate analyses accounted for (1) age and sex (Model 1); (2) Model 1+body mass index, smoking, alcohol consumption, regular exercise and income status (Model 2); (3) Model 2+the presence of diabetes mellitus and dyslipidemia, mean SBP, or DBP level at baseline, and use of antihypertensive drugs (Model 3); (4) Model 3+the presence of ischemic heart disease and stroke (Model 4). The potential effect modification via age, sex, obesity, diabetes mellitus, hypertension, stroke, heart disease, use of BP-lowering agents, BP control status, and absolute BP change was evaluated through a stratified analysis and interaction testing using a likelihood ratio test. In subgroup analyses, hazard ratio (95% CI) of the highest quartile (Q4) group was compared with the lower 3 quartiles (Q1–Q3) as a reference group. Sensitivity analyses were also performed with (1) other methods of variability such as CV and SD; (2) excluded subjects with

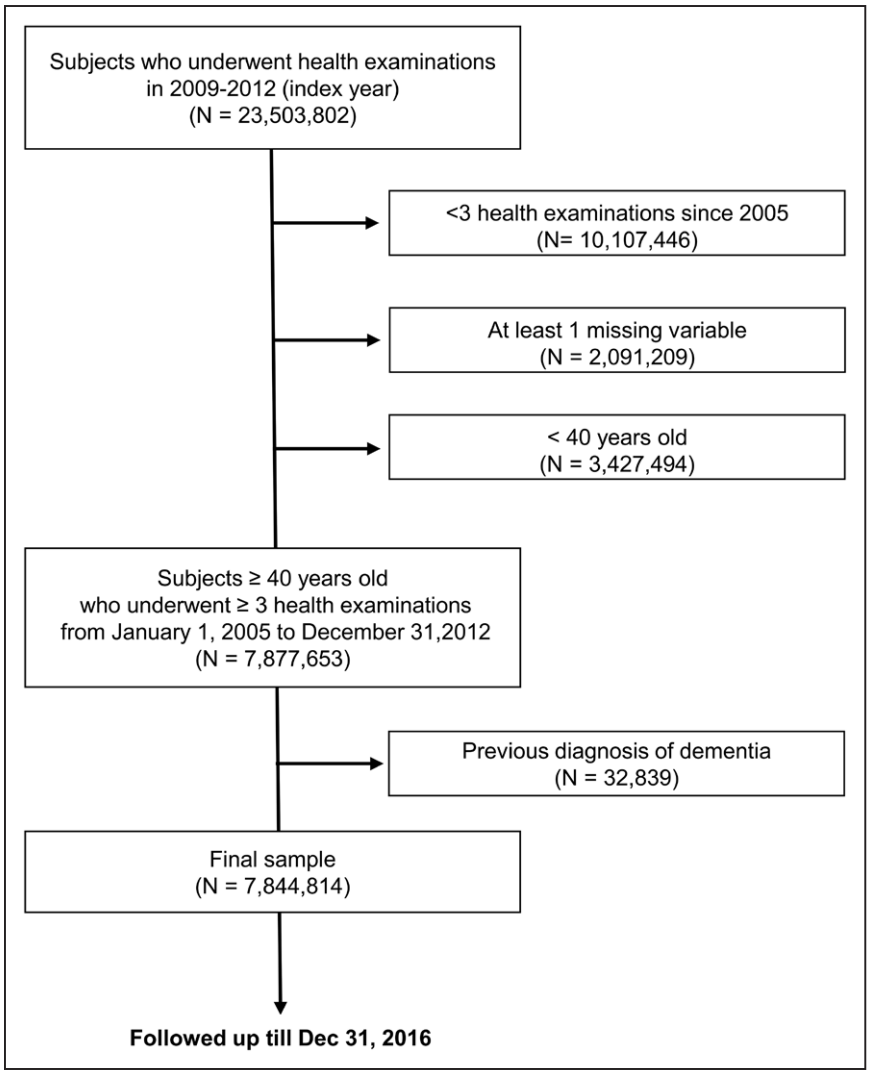

Figure 1. Flow chart of the study population.

dementia occurring within 2 years of follow-up to account for the possibility of reverse causation. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC), and a P value <0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics of the Study Population

In the study population, VIM was normally distributed, and median VIM of SBP and DBP was 8.71 (range, 0.29–58.74) and 6.04 (range, 0.33–38.70), respectively (Figure S2). The cutoff points of VIM for the definition of the quartiles were 5.70, 8.71, 12.43 for SBPV, and 4.32, 6.04, and 8.91 for DBPV. Characteristics of participants by quartiles of VIM for BP are described in Table 1. Subjects in higher quartiles of BPV were older, more likely to be female, and had a higher prevalence of comorbid conditions. The mean SBP and DBP levels were ≈126 and 78 mm Hg in all 4 groups, respectively. Median number of BP measurement was same as 4 according to the incident dementia. Baseline coefficient of variation, SD, and VIM of BP were significantly higher in subjects with incident dementia than in those without dementia, although the baseline and mean SBP and DBP levels were higher according to the occurrence of dementia (Table S2). The P value was <0.0001 for all variables owing to the large study population.

Incidence of Dementia According to BP Variability

During the median follow-up of 6.22 years (range, 0–8 years), there were 200 574 new cases of all-cause dementia (2.8%), 165 112 cases of AD (2.1%), and 27 443 cases of VaD (0.3%). Hypertension increases the risk of all-cause dementia, AD, and VaD (Table S3). An incrementally higher risk of all those outcomes was observed with higher SBPV (Q4 versus Q1: aHR, 1.16 [95% CI, 1.14–1.17]) or DBPV (Q4 versus Q1: aHR, 1.12 [95% CI, 1.11–1.14]) quartiles compared with lowest quartile group in all models (Table 2). Subjects in the only DBPV Q4 group had an ≈6% higher risk of all-cause dementia (aHR, 1.06 [95% CI, 1.04–1.07]), and those in the only SBPV Q4 group had an ≈9% higher risk of all-cause dementia (aHR, 1.09 [95% CI, 1.08–1.11]) compared with the subjects who were in the lowest 3 quartiles for both SBPV and DBPV. Moreover, subjects in the both SBPV and DBPV Q4 group had an ≈18% higher risk of all-cause dementia (aHR, 1.18 [95% CI, 1.16–1.19]). Similar patterns were also observed in both AD and VaD (Table 2). As the number of BP measurement time increasing, there was a higher association between BPV and the risk of dementia. (Table S4). Analysis according to decile groups revealed that the risk of dementia significantly increased from the sixth

Table 1. Baseline characteristics of subjects according to the blood pressure variability (variability independent of the mean)

Variable	Total (n = 7844814)	Blood pressure variability group			
		Q1-Q3 (n = 4895999)	SBPV Q4 only (n = 979293)	DBPV Q4 only (n = 986205)	SBPV & DBPV Q4 (n = 983317)
Age, mean (SD), years	55.5 (10.2)	54.0 (10.0)	55.8 (10.5)	56.5 (10.5)	56.9 (10.6)
Male, No. (%)	4118325 (52.5)	2679677 (54.7)	515168 (52.6)	458589 (46.5)	464891 (47.3)
Body mass index, mean (SD), kg/m^2	24.2 (3.0)	24.2 (3.0)	24.2 (3.0)	23.9 (3.0)	24.0 (3.1)
Systolic BP, mean (SD), mm Hg	126.3 (15.2)	126.3 (13.5)	126.5 (14.6)	125.8 (18.4)	126.6 (19.6)
Diastolic BP, mean (SD), mm Hg	78.7 (10.0)	78.8 (8.8)	79.1 (12.2)	77.2 (9.4)	79.0 (12.9)
Fasting glucose, mean (SD), mg/dL	102.3(25.4)	102.3 (25.2)	102.3 (25.2)	102.1 (25.7)	102.4 (26.2)
Total cholesterol, mean (SD), mg/dL	203.8 (37.1)	204.0 (36.9)	203.7 (37.2)	203.6 (37.3)	203.5 (37.9)
SBP variability, mean (SD)					
SD	9.7 (5.7)	7.1 (3.5)	15.5 (4.5)	8.6 (3.6)	17.8 (5.8)
CV	7.8 (4.3)	5.7 (2.6)	12.6 (2.7)	6.8 (2.5)	14.3 (3.8)
VIM	9.4 (5.2)	6.9 (3.0)	15.4 (2.6)	8.2 (2.9)	17.4 (4.2)
DBP variability, mean (SD)					
SD	6.8 (3.9)	5.0 (2.4)	5.9 (2.3)	11.2 (2.6)	12.4 (3.4)
CV	8.8 (4.9)	6.4 (3.0)	7.7 (2.8)	14.5 (2.7)	16.1 (3.7)
VIM	6.7 (3.7)	5.0 (2.3)	5.9 (2.1)	11.1 (2.1)	12.3 (2.8)
Current smoker, No. (%)	1532756 (19.5)	982032 (20.1)	191071 (19.5)	175924 (17.8)	183729 (18.7)
Alcohol consumption, No. (%)	3275365 (41.8)	2126864 (43.4)	406459 (41.5)	368714 (37.4)	373328 (38.0)
Regular exercise, No. (%)	1698128 (21.7)	1085171 (22.2)	210312 (21.5)	204467 (20.7)	1981778 (20.2)
Income (lower 20%), No. (%)	1590775 (20.3)	9633448 (19.7)	202217 (20.7)	209211 (21.2)	215999 (22.0)
Hypertension, No. (%)	2575400 (32.8)	1537622 (31.4)	339601 (34.7)	320455 (32.5)	377722 (38.4)
Diabetes mellitus, No. (%)	978614 (12.5)	599455 (12.2)	124293 (12.7)	125436 (12.7)	129430 (13.2)
Dyslipidemia, No. (%)	1278692 (16.3)	790239 (16.1)	160325 (16.4)	164519 (16.7)	163609 (16.6)
Chronic kidney disease, No. (%)	572409 (7.3)	343907 (7.0)	72577 (7.4)	75861 (7.7)	80064 (8.2)

BP indicates blood pressure; CV, coefficient of variation; DBPV, diastolic blood pressure variability; Q, quartile group; Q1-Q3, both systolic and diastolic blood pressure lower quartile group; SBPV, systolic blood pressure variability; SD, mean; and VIM, variability independent of the mean.

decile (D6) of the SBPV group, and the risk of dementia significantly increased in the DBPV D8 group (*P* value for trend <0.0001) (Figure 2).

Subgroup Analysis

Stratified analyses by age, sex, smoking status, obesity status, diabetes mellitus, hypertension, stroke, and heart disease were conducted. The BPV Q4 group remained predictive of higher incidence of dementia in all subgroups compared with the Q1–3 group. Slightly higher adjusted hazard ratios of dementia were observed among the subgroups of younger age, male, absence of hypertension, and current smoking (Figure 3; Tables S5 and S6). The associations between BPV and dementia were consistent even after stratification for antihypertensive agent use, BP control status, and absolute BP change (Table S7; Figures S3, S4, and S5).

Sensitivity Analysis

The results were consistent when BPV was determined using other parameters of variability, that is, CV and SD (Tables S8 and S9). Furthermore, similar to the original analysis, the results of a 2-year lag time showed a higher risk of dementia with higher BPV (Table S10).

Discussion

In this large-scale and long-term follow-up study, we confirmed that higher visit-to-visit BPV is associated with the incidence of all-cause dementia, AD and VaD. In addition, in a novel result, we found that having both higher SBPV and DBPV additively increased the risk of dementia and its subtypes in a general population. Derived from subgroup analysis, these associations were independent of various factors, including use of antihypertensive drugs, BP control status, or absolute BP change during follow-up, providing further support for the association of BPV and dementia incidence.

Consistent with our findings, recent studies showed that increased day-to-day[13] or visit-to-visit[12] BPV, assessed by CV index, was associated with the development of dementia. In addition, to the best of our knowledge, the present study provides the first evidence that having both higher SBPV and DBPV had a greater impact on the development of dementia, compared with having only one of them.

Table 2. Hazard ratios and 95% confidence intervals of dementia by quartiles of blood pressure variability (variability independent of the mean)

Variable		Subjects (N)	Events (n)	Person-years (PYs)	Incidence rate (per 1000 PYs)	Model 1	Model 2	Model 3	Model 4
All-cause dementia									
SBPV	Q1	1961461	48059	12115349	4.0	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1956627	46622	12239096	3.8	**1.03 (1.02-1.04)**	**1.03 (1.02-1.04)**	**1.02 (1.01-1.04)**	**1.02 (1.01-1.04)**
	Q3	1957204	52832	12287963	4.3	**1.07 (1.06-1.09)**	**1.07 (1.05-1.08)**	**1.07 (1.05-1.08)**	**1.07 (1.05-1.08)**
	Q4	1969522	73061	12151163	6.0	**1.17 (1.16-1.18)**	**1.15 (1.14-1.17)**	**1.16 (1.15-1.18)**	**1.16 (1.14-1.17)**
DBPV	Q1	1961231	47531	12119464	3.9	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1959454	53743	12292681	4.4	**1.04 (1.03-1.05)**	**1.04 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.02-1.05)**
	Q3	1961519	49866	12271449	4.1	**1.04 (1.02-1.05)**	**1.03 (1.02-1.04)**	**1.03 (1.02-1.04)**	**1.03 (1.02-1.04)**
	Q4	1962610	69434	12109979	5.7	**1.13 (1.12-1.15)**	**1.12 (1.11-1.14)**	**1.13 (1.12-1.14)**	**1.12 (1.11-1.14)**
Combination group	Q1-Q3	4895999	117040	30588424	3.8	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	DBPV Q4 only	979293	30473	6053985	5.0	**1.06 (1.05-1.10)**	**1.06 (1.04-1.07)**	**1.06 (1.05-1.07)**	**1.06 (1.04-1.07)**
	SBPV Q4 only	986205	34100	6095169	5.6	**1.10 (1.08-1.11)**	**1.09 (1.07-1.10)**	**1.10 (1.08-1.11)**	**1.09 (1.08-1.11)**
Alzheimer's dementia	SBPV&DBPV Q4	983317	38961	6055994	6.4	**1.19 (1.18-1.20)**	**1.17 (1.16-1.19)**	**1.19 (1.17-1.20)**	**1.18 (1.16-1.19)**
SBPV	Q1	1961461	35871	12115349	3.0	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1956627	34819	12239097	2.8	**1.03 (1.02-1.05)**	**1.03 (1.01-1.04)**	**1.03 (1.01-1.04)**	**1.02 (1.01-1.04)**
	Q3	1957204	39434	12287963	3.2	**1.07 (1.06-1.09)**	**1.07 (1.05-1.08)**	**1.06 (1.05-1.08)**	**1.06 (1.05- 1.08)**
	Q4	1969522	54988	12151163	4.5	**1.17 (1.15-1.18)**	**1.15 (1.14-1.17)**	**1.16 (1.14-1.17)**	**1.15 (1.14-1.17)**
DBPV	Q1	1961231	35448	12119464	2.9	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1959454	40208	12292681	3.3	**1.04 (1.03-1.05)**	**1.04 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.02-1.05)**
	Q3	1961519	37323	12271449	3.0	**1.04 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.02-1.05)**	**1.03 (1.01-1.04)**
	Q4	1962610	52133	12109979	4.3	**1.13 (1.12-1.15)**	**1.12 (1.10-1.13)**	**1.12 (1.11-1.14)**	**1.12 (1.10-1.13)**
Combination group	Q1-Q3	4895999	87254	30588424	2.9	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	DBPV Q4 only	979293	22870	6053985	3.8	**1.06 (1.04-1.07)**	**1.05 (1.04-1.07)**	**1.06 (1.04-1.07)**	**1.05 (1.04-1.07)**
	SBPV Q4 only	986205	25725	6095169	4.2	**1.10 (1.08-1.11)**	**1.09 (1.07-1.10)**	**1.09 (1.08-1.11)**	**1.09 (1.08-1.11)**
	SBPV&DBPV Q4	983317	29263	6055994	4.8	**1.18 (1.17-1.20)**	**1.17 (1.15-1.18)**	**1.18 (1.16-1.19)**	**1.17 (1.15-1.19)**
Vascular dementia									
SBPV	Q1	1961461	6026	12115349	0.5	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1956627	5874	12239097	0.5	1.03 (0.99-1.06)	1.02 (0.99-1.06)	1.03 (0.99-1.06)	1.03 (0.99-1.06)
	Q3	1957204	6711	12287963	0.5	**1.09 (1.05-1.13)**	**1.09 (1.05-1.13)**	**1.09 (1.05-1.13)**	**1.09 (1.05-1.13)**
	Q4	1969522	8832	12151163	0.7	**1.18 (1.14-1.22)**	**1.17 (1.13-1.21)**	**1.20 (1.16-1.22)**	**1.19 (1.15-1.23)**
DBPV	Q1	1961231	5936	12119464	0.5	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	Q2	1959454	6694	12292681	0.5	**1.05 (1.02-1.09)**	**1.05 (1.01-1.09)**	**1.05 (1.01-1.08)**	**1.04 (1.01-1.08)**
	Q3	1961519	6241	12271449	0.5	**1.04 (1.01-1.08)**	**1.04 (1.00-1.08)**	**1.05 (1.00-1.09)**	**1.04 (1.01-1.07)**
	Q4	1962610	8572	12109979	0.7	**1.17 (1.13-1.21)**	**1.16 (1.13-1.20)**	**1.18 (1.15-1.22)**	**1.17 (1.14-1.21)**
Combination group	Q1-Q3	4895999	14821	30588424	0.5	1(ref.)	1(ref.)	1(ref.)	1(ref.)
	DBPV Q4 only	979293	3790	6053985	0.6	**1.08 (1.04-1.12)**	**1.08 (1.04-1.12)**	**1.10 (1.06-1.14)**	**1.09 (1.06-1.13)**
	SBPV Q4 only	986205	4050	6095169	0.7	**1.08 (1.04-1.12)**	**1.07 (1.04-1.11)**	**1.10 (1.07-1.14)**	**1.10 (1.06-1.14)**
	SBPV&DBPV Q4	983317	4782	6055994	0.8	**1.22 (1.18-1.26)**	**1.21 (1.17-1.25)**	**1.24 (1.20-1.28)**	**1.22 (1.18-1.26)**

DBPV indicates diastolic blood pressure variability; SBPV, systolic blood pressure variability; Q, quartile; Q1-Q3, both systolic and diastolic blood pressure lower quartile group.

Model 1: adjusted for age and sex

Model 2: adjusted for model 1 plus alcohol consumption, smoking, regular exercise, income and body mass index

Model 3: adjusted for model 2 plus diabetes mellitus, dyslipidemia, mean blood pressure (systolic BP for SBPV, diastolic BP for DBPV, both systolic BP and diastolic BP for combination group, respectively) and use of anti-hypertensive drug

Mode 4: adjusted for model 3 plus ischemic heart disease and stroke

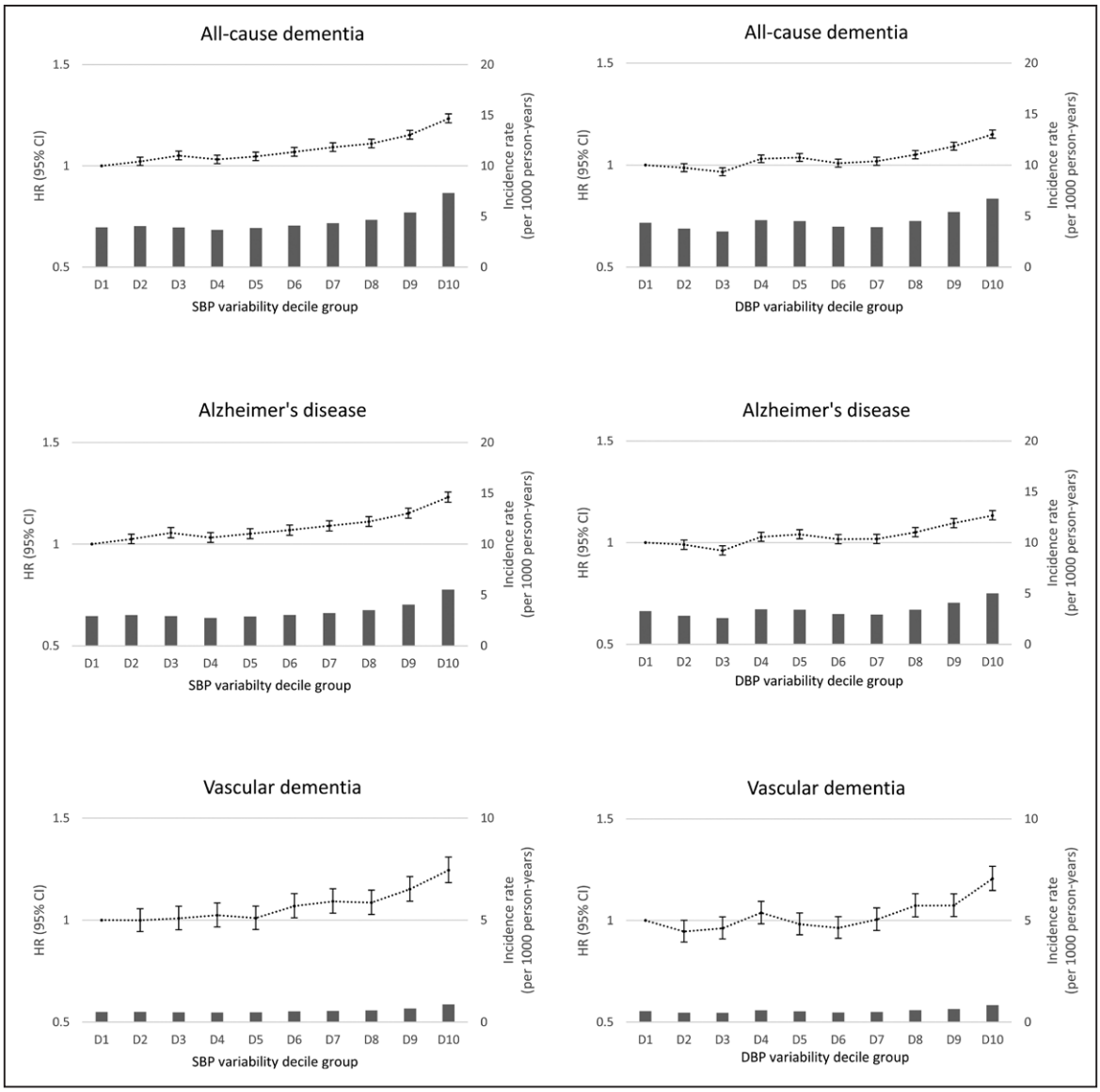

Figure 2. Incidence rates and hazard ratio (HR) of dementia by deciles of blood pressure (BP) variability D1-D10: deciles of blood pressure. Adjusted for age, sex, body mass index, alcohol consumption, smoking, regular exercise, income, diabetes mellitus, dyslipidemia, ischemic heart disease, stroke, mean blood pressure (systolic BP for SBPV, diastolic BP for DBPV, both systolic BP and diastolic BP for combination group, respectively) and use of anti-hypertensive drugs. DBPV indicates diastolic blood pressure variability; and SBPV, systolic blood pressure variability.

Vascular and degenerative pathways critically interact and contribute to AD pathology.[22] While the exact mechanism remains unclear, possible explanations have been suggested.[23] First, marked fluctuations in BP and inconsistent perfusion result in repeated episodes of tissue hypoxia-ischemia. This oligemia can lead to brain amyloidogenesis by enhancing expression and processing of Aβ precursor protein, activating microglia, impairing neuronal protein synthesis, and causing neuronal damage and cellular death. In particular, these changes occur in the most vulnerable areas such as the hippocampi,[24,25] which are among the sites to be affected earlier stage in AD. Second, the damage to endothelial cells and the blood-brain barrier induced by the BP fluctuations and perfusion imbalance can increase the secretion of proinflammatory cytokines and reactive oxygen species and induce microglia overactivation.[26] The upregulation of the neuroinflammatory cascade and the reactive gliosis are key moderators of critical events involved in AD pathogenesis, such as misfolding, aggregation, and propagation of Aβ and tau protein.[27] Third, visit-to-visit BPV is an upstream determinant of arterial remodeling. Cerebral arterial remodeling can also contribute to the disruption of vascular dynamics involved in perivascular flow and clearance of Aβ.[28,29] Notably, amyloid angiopathy is commonly observed in pathological analysis of AD-affected brains.[30]

On the contrary, BPV was also associated with the incidence of VaD, which is caused by an altered supply of blood to the brain, typically by a series of strokes. This is not surprising since VaD is generally considered as a manifestation of cardiovascular disease. High fluctuations of BP levels have been independently associated with arterial stiffness.[31] Increased large artery stiffness provides direct harmful effects on the structure

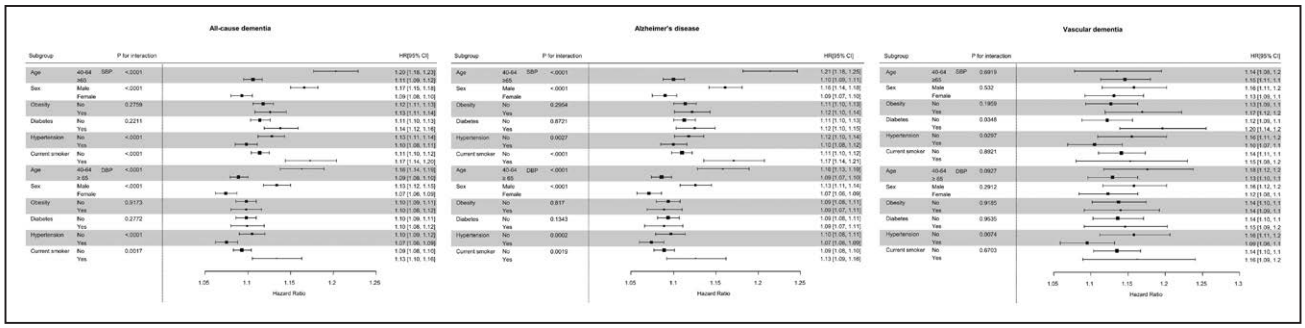

Figure 3. Subgroup analysis of association between blood pressure variability and dementia incidence: the highest quartile vs. lower three quartiles of blood pressure variability. Adjusted for age, sex, body mass index, alcohol consumption, smoking, regular exercise, income, diabetes mellitus, dyslipidemia, ischemic heart disease, stroke, mean blood pressure (systolic BP [SBP] for SBPV, diastolic BP [DBP] for DBPV, respectively) and use of anti-hypertensive drugs.
DBPV indicates diastolic blood pressure variability; and SBPV, systolic blood pressure variability.

and function of cerebral penetrating arteries.[32,33] BPV could cause a tsunami effect in the cerebral parenchyma leading to cerebral small vessel diseases, including silent infarcts and microbleeds.[34] These subclinical vascular damages caused by higher BPV may play a role in developing dementia. Indeed, a meta-analysis of 13 prospective studies suggested that BPV is a predictor of cardiovascular and all-cause mortality and stroke.[35] In line with our study, visit-to-visit BPV has been shown to be associated with stroke incidence.[3,36,37]

In the present study, excessive fluctuations in BP consistently increased risk of dementia even after various stratifications. This finding may highlight the causal relationship between BPV and development of dementia. Subgroup analyses also demonstrated that high BPV was related to increased risk of dementia in the groups of subjects younger than 65 years, male, without hypertension, and current smokers. Although statistically significant associations between DBPV and the risk of dementia were found, clinically significance of this finding is unclear due to the presence of only small differences.

The clinical implication of our study lies in the fact that amelioration of BPV could be considered a potentially important target in hypertension. Available data suggest that calcium-channel blockers (CCBs) are superior to other therapeutic classes in attenuating long-term BPV.[38] For instance, in the Systolic Hypertension Europe (Syst-Eur) trial, CCBs were found to reduce the incidence of dementia more than other antihypertensive drugs,[39] and separate studies have shown CCBs to be most effective for reducing BPV among all antihypertensive drug classes.[38] These findings suggest that BP-lowering therapy initiated with a CCBs may offer benefits in reducing dementia risk in high-risk groups for dementia. In accordance with current major guidelines for hypertension, CCBs are preferred for the elderly as first-line hypertension treatment.[40]

One strength of our study is the use of visit-to-visit variability and VIM as our primary methods of BPV measurement. Although a number of methods have been proposed for quantifying BPV, visit-to-visit BPV is a useful and easily measurable marker of cardiovascular disease. Also, visit-to-visit BPV assessment is known to be more suitable in assessing long-term BPV than day-to-day measuremetns.[41] Second, VIM is theoretically better than other indices, such as CV and SD, as VIM is not correlated with the mean level of BP. High BP itself is associated with dementia as evidenced by our own data (Table S1) and that of others,[42–44] so the assessment of the impact of BPV should be independent of BP level itself. However, CV was found to be correlated with mean levels in most cohorts.[3,45,46] To determine the prognostic value of variability, VIM may be useful to derive a measure of variability that is uncorrelated with mean levels. Thus, our study has a particular strength in that we used VIM index to describe visit-to-visit BPV, and this enabled us to further support higher BPV as a predictor of dementia development. In addition, the use of CV and SD in our sensitivity analyses revealed similar results, providing further evidence of the robustness of our finding.

There are several limitations of our study. First, while KNHI provided the protocol for BP measurement, it is possible that such a protocol was not accurately followed in the real-world setting. However, such measurement bias will lead to a decreased association, and the actual association between BPV and dementia would be higher if measurements were optimally taken. In addition, different BP devices were used in each center, and this could be a source of extra variability. However, most people received their examinations in the same hospital near their residence, and hospitals wherein health examinations were performed were certified by the KNHIS and subjected to regular quality control including calibration of equipment on a regular basis. Second, discrepancies between the diagnosis of individuals in medical practice and that recorded in claim data may have led to inaccurate analysis. However, under the KNHIS, the specificity of the data is usually high because this degree of specificity is required to fulfill strict insurance criteria. High sensitivity of the data should also be true because dementia can be detected with only clinically meaningful symptoms owing to accessibility to healthcare system. Third, because this study was based on data that were not originally designed for studying dementia, such as the mini mental state examination, we were not able to assess subject baseline cognitive function. This may be partially overcome by conducting subgroup analysis for dementia development to minimize the risk of influence from those other relevant characteristics. Fourth, there is no information on the ECG abnormalities which might have a substantial impact on the development of dementia. Fifth, this was a retrospective study, and the findings should be interpreted accordingly. To

minimize the possible effects of reverse causality, subjects with preexisting dementia were excluded. Sensitivity analysis excluding subjects with outcomes occurring in the first 2 years of follow-up also revealed similar results. Last, selection of study subjects based on repeated participation in health examinations might be a source of bias as healthier people with better health behavior and healthcare access are more likely to participate in regular health checkups.

Perspectives

In this nationwide population-based cohort study, we demonstrated that BPV is an independent predictor for developing dementia and its subtypes. A dose-response relationship was noted between higher BPV and dementia incidence. The data were largely consistent in various subgroups. These findings suggest that BPV is an important risk factor, not only in patients with dementia, but also in general populations. Further research is warranted to examine whether reducing variability of blood pressure parameters decreases adverse outcomes.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Blood pressure variability (BPV) is an independent predictor for developing dementia and its subtype in general population. Furthermore, a dose-response relationship was noted between higher BPV and dementia incidence.

What Is Relevant?

- Amelioration of BPV could be considered as potentially important target in hypertension. BP-lowering therapy initiated with a calcium channel blockers, which are superior to other therapeutic classes in attenuating long-term BPV, may offer benefits in reducing dementia risk in high-risk groups for dementia.

Summary

BPV is an important risk factor, not only in patients with dementia, but also in general populations. Future studies are needed to confirm that reducing variability of blood pressure parameters decreases adverse outcomes