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Original Article

ORIGINAL ARTICLE

Association between visit-to-visit blood pressure variability and risks of dementia in CKD patients: a nationwide observational cohort study

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ABSTRACT

Background. The association between visit-to-visit blood pressure (BP) variability and dementia risk in chronic kidney disease (CKD) patients has rarely been studied.

Methods. In this retrospective observational study, individuals who received three or more general health screenings were identified in the nationwide database of Korea. Those with persistent non-dialysis-dependent CKD [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+] were included. The study exposure was systolic or diastolic BP variability, calculated as the variation independent of the mean and categorized into quartiles (Q4: the highest quartile; Q1: the lowest quartile). The risks of all-cause dementia, including Alzheimer's disease and vascular dementia, were analyzed by Cox regression adjusted for various clinical characteristics, including baseline BP and eGFR values.

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Results. We included 103 139 CKD patients and identified 7574 (7%) dementia events, including 5911 (6%) Alzheimer's disease cases, 886 (1%) vascular dementia events and 777 (1%) cases categorized as other types of dementia. Higher systolic BP variability was significantly associated with higher risks of all-cause dementia {[Q4 versus Q1], hazard ratio [HR] 1.173 [95% confidence interval (CI) 1.102–1.249], *P* for trend < .001}. The results were also significant for the risk of Alzheimer's disease [HR 1.162 (95% CI 1.083–1.248), *P* < .001] and vascular dementia [HR 1.282 (95% CI 1.064–1.545), *P* = .039]. The results were similar when diastolic BP variability was the exposure, as high diastolic BP variability was significantly associated with higher risks of all-cause dementia [HR 1.191 (95% CI 1.117,1.270), *P* < .001].
Conclusions. Higher visit-to-visit BP variability is significantly associated with a higher risk of dementia in CKD patients.

Keywords: blood pressure, chronic kidney disease, epidemiology, hypertension

INTRODUCTION

The risk of dementia, a state of cognitive decline, is increased in chronic kidney disease (CKD) patients [1, 2]. The prevalence of dementia is reported to be higher in those with a lower glomerular filtration rate, and CKD patients with dementia experience severe impairments in quality of life [2]. Considering the global aging trend and increasing prevalence of CKD in the elderly population, the importance of dementia in CKD patients is considered to further increase.

Metabolic disorders have been reported to be closely linked to dementia risks in CKD patients, as in the general population [3, 4]. Among such disorders, hypertension, one of the most common comorbidities found in CKD patients, has been reported to be associated with the risk of dementia [3, 5]. A previous clinical trial showed that extensive blood pressure (BP) control reduced the risk of dementia regardless of kidney function, suggesting that thorough management of hypertension may also be beneficial for dementia risk in CKD patients [6]. Furthermore, a previous study showed that visit-to-visit BP variability was significantly associated with the risk of dementia in the general population [7], suggesting that reducing high BP variability may be helpful to ameliorate the risk of dementia. However, a large-scale study investigating the clinical significance of visit-to-visit BP variability in regards to dementia risk and focusing on CKD patients has yet to be performed. Such evidence would be helpful for guiding BP control strategies in CKD patients, particularly as BP variability is increased in individuals with kidney function impairment [8, 9].

In this study, we aimed to investigate the association between visit-to-visit BP variability and the incident risk of dementia in non-dialysis-dependent CKD patients identified from a nationwide health screening cohort in Korea. We hypothesized that CKD patients with high BP variability would have a high risk of dementia.

MATERIALS AND METHODS

Ethics considerations

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital (E-2012-006-1177). The investigation of the Korea National Health Insurance Service (NHIS) database was approved by the relevant government organization (NHIS-2021-1-366). The need to obtain informed consent was waived by the above organizations, as the study was observational and investigated anonymous public databases.

Study setting

This study was a retrospective observational cohort study including individuals who underwent nationwide general health screenings in Korea, which has been previously described [10, 11]. Korea is one of the nations that provides general health insurance services for all people with Korean citizenship, and the NHIS is the single insurer. In Korea, the NHIS provides free-of-charge health screenings for the general population, including clinicodemographic assessments, lifestyle evaluations and laboratory measurements. Health screenings, provided on an annual or biennial basis, are performed by registered health screening centers in Korea. Because the health screening data are linked to the claims database, which includes information related to nationwide insured medical services, studies assessing various health outcomes and comorbidities have been performed based on these data.

In the current study, following our previous study [12], we first identified non-dialysis-dependent CKD patients based on estimated glomerular filtration rate (eGFR) and dipstick urine albumin results measured in consecutive health screenings. After determining the visit-to-visit BP variability of the study population, the association between BP variability and the risk of dementia, identified from the claims database, was investigated.

Study population

We first screened individuals who had received baseline health screenings from 2013 to 2014. As three or more health screenings were necessary to determine visit-to-visit BP variability, those who had two or more health screenings before the baseline visits were included [12]. After excluding those with missing information for any collected variable, the target CKD population included those with persistent eGFR <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+ during the exposure assessment period. We excluded those with an eGFR <15 mL/min/1.73 m^2. As we aimed to assess incident dementia risks, those with prevalent dementia before the baseline visits were excluded.

Ascertainment of BP exposures

Considering its clinical significance in elderly people among whom CKD is prevalent [13], systolic BP variability was the main exposure of this study. Variability in diastolic BP value was also calculated as another exposure variable. BP measurements were performed by each health screening center via automated or manual reading. We calculated variability independent of the mean (VIM), which was the main exposure in previous studies regarding variabilities in metabolic parameters [12, 14]. VIM has the advantage of being independent of mean levels, which is distinct from the standard deviation or coefficient of variation. Calculation of VIM transforms standard deviation into a value uncorrelated with the mean value by dividing with mean levels and multiplying by the regression coefficient from a linear regression model [15]. The collected exposures were divided into

quartiles (Q1: the lowest quartile; Q4: the highest quartile). We also assessed the baseline BP values as another supplemental exposure.

Ascertainment of study outcomes

Dementia events were identified according to multiple prescription histories of antidementia drugs and relevant International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes in the claims database. The diagnostic codes included Alzheimer's disease (F00 or G30), vascular dementia (F01) and other types of dementia (F02, F03 and G31) [7]. Along with all-cause dementia, Alzheimer's disease and vascular dementia were separately analyzed as secondary outcomes. When an individual had both diagnoses, we followed the principal diagnosis or the event was categorized as another type of dementia if the principal diagnosis was also mixed. The outcome definition was considered to have certain validity, as prescription for dementia treatment medications (acetylcholinesterase inhibitors or N-methyl-D-aspartate receptor antagonists) requires documented evidence of cognitive dysfunction following the criteria suggested by the National Health Insurance System: a Mini-Mental State Examination score ≤26 and either a Clinical Dementia Rating ≥1 or a Global Deterioration Scale score ≥3 [16]. Follow-up was initiated after the exposure assessment was completed, the day after the baseline visits, and was censored on the last date of data availability or the date of death.

Ascertainment of covariates

We collected information on age and sex at baseline. At baseline health screenings, the following anthropometric measures and lifestyle factors were assessed: body mass index (BMI), waist circumference, current smoking history, alcohol intake (>0 g of alcohol intake/day) and regular physical activity (moderate-intensity physical activity ≥5 days or vigorous-intensity physical activity ≥3 days/week). Claims information was used to collect information on economic status and medical comorbidities such as low income, diabetes mellitus (ICD-10 codes E11–14 with relevant antidiabetic medication history), hypertension (ICD-10 codes I10–13 or I15 with relevant antihypertensive medication history), dyslipidemia (ICD-10 code E78 with relevant dyslipidemia medication history), chronic lung disease (ICD-10 codes J41–44) and cancer (specific insurance code for malignancies in the NHIS data). Baseline laboratory data were collected from the health screening results, including baseline eGFR, presence of dipstick albuminuria (≥1+), fasting glucose, high-density lipoprotein and low-density lipoprotein. The variability in eGFR during the exposure assessment period was also collected as a covariate, as kidney function variability may determine BP variability itself [12, 17]. The variability of eGFR was also determined as VIM by including three or more eGFR values for each individual. In addition, the number of examinations was identified as a variable that could reflect the health-seeking behavior of a subject and reflect measurement errors that may occur when health screening examinees attend different health exam centers [12].

Statistical analysis

The risk of dementia was assessed according to BP exposure, in ordinal categories, by Cox regression analysis with a univariable model, an age- and sex-adjusted model and multivariable model, including age, sex, smoking status, alcohol usage, regular physical activity, low-income status, BMI, diabetes mellitus, dyslipidemia, antihypertensive medication usage, baseline systolic BP, diastolic BP, pulse pressure, eGFR values at baseline, eGFR variability and number of health exams. Kaplan–Meier survival curves were used to plot the cumulative risk of dementia according to BP variability. We performed subgroup analysis dividing the study population according to sex and the presence of decreased eGFR (<60 mL/min/1.73 m^2) at baseline. We calculated interaction term *P*-values in the multivariable model to assess whether there was a significant interaction with the variable used to divide the subgroups. Two-sided *P*-values <0.05 for trend according to the ordinal exposure were considered statistically significant in the survival analysis and interaction term *P*-values <0.1 were considered to indicate a possible presence of an interaction. All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC, USA).

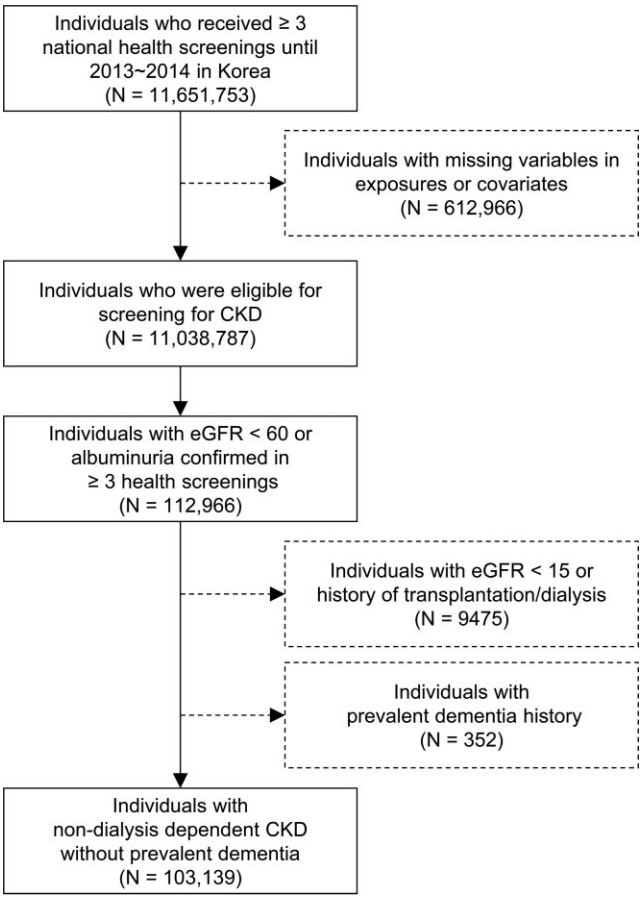

FIGURE 1: Study population.

RESULTS

Study population

There were 11 651 753 individuals who underwent three or more health screenings during the exposure assessment period (Figure 1). Among them, 112 966 individuals had a persistent eGFR <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+. After excluding those with prevalent end-stage kidney disease or dementia histories, 103 139 non-dialysis-dependent CKD patients with identifiable BP variability were included in the final study population.

Baseline characteristics

The study population had a mean age of 68.4 ± 10.0 years and was 49% male (Table 1). The baseline mean systolic BP and diastolic BP values were 29.7 ± 15.7 and 77.3 ± 10.1 mmHg,

Table 1. Clinical characteristics of the study population according to systolic BP variability

Characteristics	Total	Q1	Q2	Q3	Q4
Sample size, *n*	103 139	25 783	25 786	25 788	25 782
Age (years), mean ± SE	68.4 ± 10.0	68.1 ± 10.0	67.8 ± 10.2	68.2 ± 10.0	69.3 ± 9.7
Male sex, *n*(%)	50 402 (49)	12 895 (50)	12 886 (50)	12 684 (49)	11 937 (46)
BMI (kg/m^2), mean ± SE	24.79 ± 3.23	24.91 ± 3.18	24.87 ± 3.18	24.76 ± 3.23	24.6 ± 3.3
Waist circumference (cm), mean ± SE	84.87 ± 8.83	85.13 ± 8.7	85.01 ± 8.74	84.81 ± 8.89	84.53 ± 8.97
BP variability (variation independent of mean, unit), mean ± SE	10.02 ± 5.7	3.72 ± 1.58	7.46 ± 1.02	11.08 ± 1.16	17.81 ± 4.12
Systolic BP (mmHg), mean ± SE	129.7 ± 15.7	130.45 ± 11.4	129.9 ± 13.7	129.4 ± 15.8	129.0 ± 20.5
Diastolic BP (mmHg), mean ± SE	77.3 ± 10.1	77.8 ± 8.9	77.5 ± 9.5	77.1 ± 10.1	76.7 ± 11.7
Health screenings, *n*(%)					
3	92 789 (90)	23 838 (92)	22 647 (88)	22 663 (88)	23 641 (92)
4	5968 (6)	1187 (5)	1682 (7)	1722 (7)	1377 (5)
5	4382 (4)	758 (3)	1457 (6)	1403 (5)	764 (3)
Social factors, *n*(%)					
Urban residence	57 125 (55)	13 940 (54)	13 855 (54)	14 214 (55)	15 116 (58)
Low income (<25th percentile)	19 143 (19)	4506 (17)	4727 (18)	4947 (19)	4963 (19)
Lifestyle factors, *n*(%)					
Current smoker	10 989 (11)	2615 (10)	2762 (11)	2802 (11)	2810(11)
Alcohol intake (>0 g/day)	24 659 (24)	6361 (25)	6435 (25)	6183 (24)	5680 (22)
Regular physical activity	23 158 (22)	6136 (24)	5935 (23)	5845 (23)	5242 (20)
Comorbidities, *n*(%)					
Diabetes mellitus	37 094 (36)	8997 (35)	8961 (35)	9269 (36)	9867 (38)
Hypertension	80 362 (78)	19 219 (75)	19 524 (76)	20 128 (78)	21 491 (83)
Cancer	4626 (4)	1171 (5)	1083 (4)	1157 (4)	1215 (5)
Chronic lung disease	13 319 (13)	3244 (13)	3101 (12)	3382 (13)	3592 (14)
Dyslipidemia	55 265 (54)	13 733 (53)	13 666 (53)	13 763 (53)	14 103 (55)
Chronic heart failure	7196 (7)	1572 (6)	1621 (6)	1803 (7)	2200 (9)
Atrial fibrillation	3908 (4)	880 (3)	891 (3)	972 (4)	1165 (5)
Medication history, *n*(%)					
ACEI or ARB	64 152 (62)	15 271 (59)	15 565 (60)	16 089 (62)	17 227 (67)
Calcium channel blocker	46 732 (45)	11 258 (44)	11 211 (43)	11 615 (45)	12 648 (49)
Beta-blocker	23 566 (23)	5359 (21)	5665 (22)	5878 (23)	6664 (26)
Insulin	8475 (8)	1889 (7)	1965 (8)	2151 (8)	2470 (10)
Statin	45 719 (44)	11 241 (44)	11 279 (44)	11 338 (44)	11 861 (46)

There are no missing data in the table. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; SE: standard error.

Table 2. Laboratory characteristics of the study population according to systolic BP variability

Characteristics	Total	Q1	Q2	Q3	Q4
Sample size, *n*	103 139	25 783	25 786	25 788	25 782
Fasting glucose (mg/dL), mean ± SE	110.65 ± 33.53	110.57 ± 32.92	110.32 ± 33.4	110.57 ± 33.42	111.14 ± 34.38
Total cholesterol (mg/dL), mean ± SE	187.04 ± 41.46	188.35 ± 41.29	187.58 ± 41.12	186.93 ± 41.4	185.31 ± 41.96
HDL (mg/dL), mean ± SE	49.63 ± 13.58	49.87 ± 13.76	49.69 ± 13.78	49.51 ± 13.29	49.46 ± 13.48
LDL (mg/dL), mean ± SE	107.82 ± 37.73	108.78 ± 37.31	108.4 ± 37.34	107.87 ± 38.52	106.21 ± 37.68
Hemoglobin (g/dL), mean ± SE	13.07 ± 1.79	13.2 ± 1.79	13.17 ± 1.79	13.07 ± 1.78	12.86 ± 1.79
Urine albuminuria (≥1+), *n*(%)	29 099 (28)	7383 (28.64)	7281 (28)	7341 (28)	7094 (28)
Serum creatinine (mg/dL), mean ± SE	1.38 ± 0.46	1.36 ± 0.44	1.38 ± 0.46	1.39 ± 0.46	1.42 ± 0.49
eGFR (mL/min/1.73 m^2), *n*(%)					
≥60	12 131 (12)	3395 (13)	3208 (12)	2994 (12)	2534 (10)
≥30–<60	84 185 (82)	20 972 (81)	20 962 (81)	21 042 (82)	21 209 (82)
≥15–<30	6823 (7)	1416 (5)	1616 (6)	1752 (7)	2039 (8)
eGFR variability (variation independent of mean, unit), mean ± SE	7.56 ± 10.47	7.2 ± 10.76	7.43 ± 10.67	7.6 ± 10.54	8.02 ± 9.88

There are no missing data in the table. HDL: high-density lipoprotein; LDL: low-density lipoprotein; SE: standaard error.

respectively. Most (90%) of the study population received three health screenings. The mean BMI was 24.79 ± 3.23 kg/m^2, with a mean waist circumference of 84.87 ± 8.83 cm. In the study population, 11% were smokers, 24% were alcohol users and 22% engaged in regular physical activity. The prevalence of hypertension and diabetes mellitus was 78% and 36%, respectively. Among the study population, 12% had a baseline eGFR ≥60 mL/min/1.73 m^2 but persistent albuminuria, while others had a baseline eGFR <60 mL/min/1.73 m^2 (Table 2).

When the characteristics were stratified according to BP variability, the group with higher visit-to-visit systolic BP variability had a lower male proportion and a lower BMI. The group with

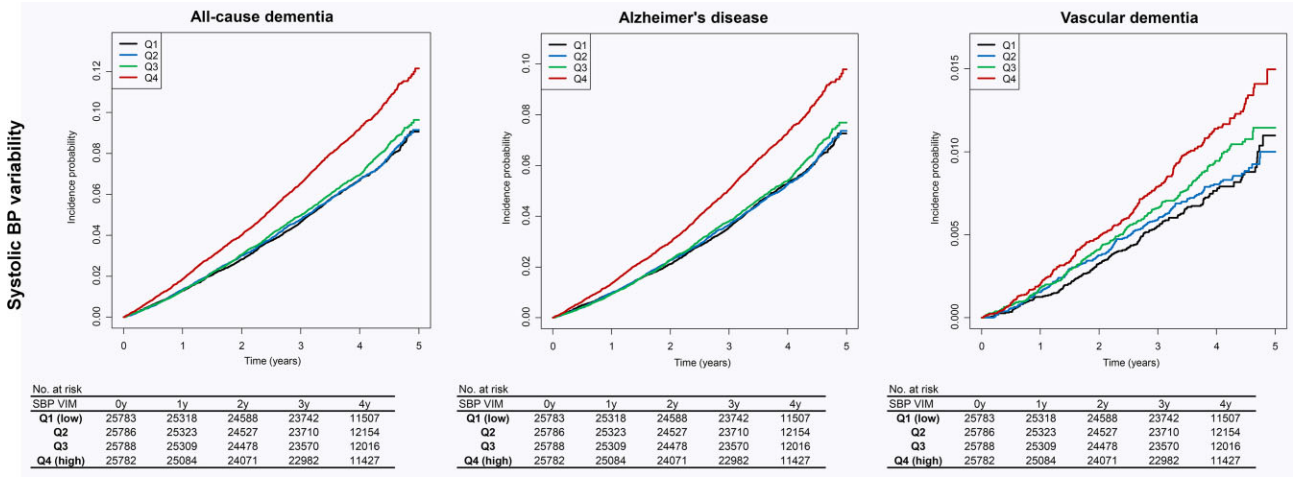

FIGURE 2: Kaplan–Meier survival curves show the cumulative risks for dementia according to systolic BP variabilities. The y-axes indicate the cumulative adjusted incidence probability and the x-axes indicate the time (years). The survival curves are stratified by BP variability quartiles [black: Q1 (low variability), blue: Q2, green: Q3 and red: Q4 (high variability)]. The survival tables are presented below the survival curves.

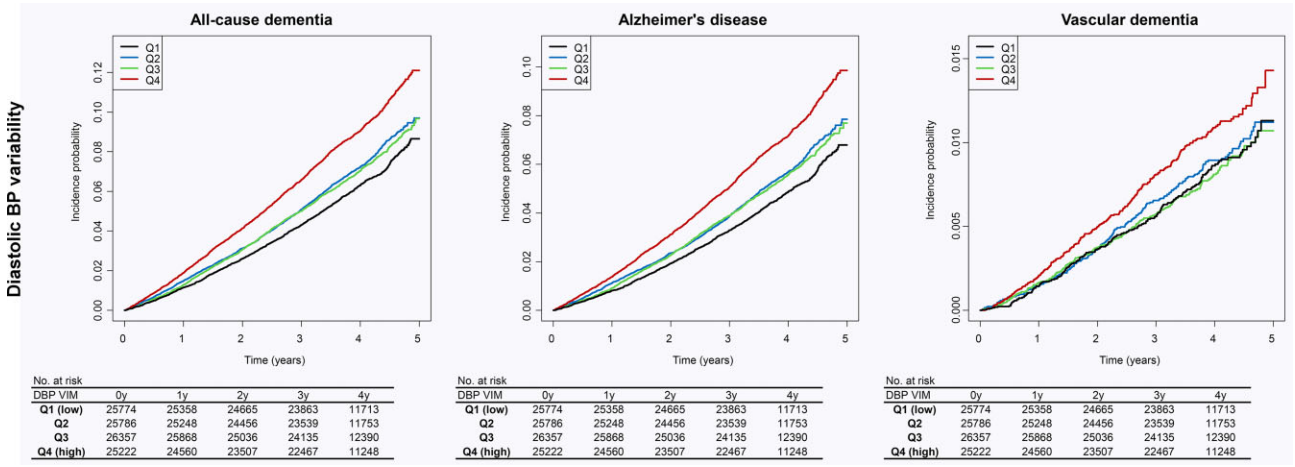

FIGURE 3: Kaplan–Meier survival curves show the cumulative risks for dementia according to diastolic BP variabilities. The y-axes indicate the cumulative adjusted incidence probability and the x-axes indicate the time (years). The survival curves are stratified by BP variability quartiles [black: Q1 (low variability), blue: Q2, green: Q3 and red: Q4 (high variability)]. The survival tables are presented below the survival curves.

higher BP variability tended to have a higher proportion of current smokers and a lower proportion of individuals engaging in regular physical activity. The prevalence of diabetes mellitus, hypertension and eGFR <60 mL/min/1.73 m^2 was also higher in those with higher BP variabilities. The number of exams did not show a notable relationship with the ordinal systolic BP variability variable.

Risk of dementia according to BP exposure

During a median 3.9 years (interquartile range: 3.3–4.5), we identified 7574 (7%) dementia events, including 5911 (6%) Alzheimer's disease cases, 886 (1%) vascular dementia cases and 777 (1%) cases of other types of dementia.

The incidence rate of dementia was higher in the higher quartiles of systolic BP variability (Q1: 17.4, Q2: 17.6, Q3: 18.6 and Q4: 24.3/1000 person-years) (Fig. 2). In the regression analyses (Table 2), even in the stringently adjusted multivariable model, the risk of dementia was significantly higher in the groups with higher systolic BP variabilityw (Table 3). The results were similar when Alzheimer's disease and vascular dementia were separately analyzed as the outcome. Regarding the hazard ratios (HRs) for vascular dementia and Alzheimer's disease according to the systolic BP variability exposure, the high systolic BP variability (Q4) group showed 27% higher adjusted HRs for vascular dementia and 16% higher adjusted HRs for Alzheimer's disease.

When diastolic BP variability was assessed as the exposure (Table 3 and Fig. 3), similar results were identified for all-cause dementia, as higher visit-to-visit diastolic BP variability was significantly associated with higher risks of dementia. Such a significant association was also identified between diastolic BP variability and Alzheimer's disease risks. However, for vascular dementia risks, the association, which was significant only in the univariable model, was attenuated in multivariable models.

In the analysis with baseline BP values (Supplemental data, Table S1), the associations were attenuated or inconsistent

Table 3. Risk of dementia according to BP variability (VIM) in CKD patients

Exposure	Outcome	Exposure quartile	Sample size, *n*	Event, *n*	Follow-up duration (person-years)	Incidence rate (per 1000 person-years)	Univariable model, HR (95% CI)	*P*-value (for trend)	Age- and sex-adjusted model, HR (95% CI)	*P*-value (for trend)	Multivariable model, HR (95% CI)	*P*-value
Systolic BP variability	Any dementia	Q1	25 783	1695	97 273	17.4	Reference	<.001	Reference	< 0.001	Reference	<.001
		Q2	25 786	1727	97 970	17.6	1.009 (0.944–1.079)		1.016 (0.951–1.087)		1.016 (0.950–1.086)	
		Q3	25 788	1815	97 695	18.6	1.064 (0.996–1.137)		1.038 (0.972–1.109)		1.024 (0.958–1.094)	
		Q4	25 782	2337	96 214	24.3	1.393 (1.309–1.483)		1.22 (1.146–1.299)		1.166 (1.095–1.242)	
	Alzheimer's disease	Q1	25 783	1328	97 273	13.7	Reference	<.001	Reference	< 0.001	Reference	<.001
		Q2	25 786	1345	97 970	13.7	1.003 (0.929–1.082)		1.009 (0.935–1.088)		1.008 (0.934–1.087)	
		Q3	25 788	1408	97 695	14.4	1.053 (0.977–1.135)		1.025 (0.951–1.104)		1.010 (0.937–1.089)	
		Q4	25 782	1830	96 214	19.0	1.392 (1.297–1.494)		1.208 (1.126–1.297)		1.156 (1.076–1.241)	
	Vascular dementia	Q1	25 783	188	97 273	1.9	Reference	<.001	Reference	0.007	Reference	.039
		Q2	25 786	197	97 970	2.0	1.039 (0.851–1.269)		1.050 (0.859–1.282)		1.049 (0.859–1.281)	
		Q3	25 788	228	97 695	2.3	1.207 (0.995–1.464)		1.191 (0.982–1.445)		1.169 (0.963–1.418)	
		Q4	25 782	273	96 214	2.8	1.468 (1.219–1.768)		1.344 (1.116–1.618)		1.271 (1.054–1.532)	
Diastolic BP variability	Any dementia	Q1	25 774	1598	97 763	16.3	Reference	<.001	Reference	< 0.001	Reference	<.001
		Q2	25 786	1858	97 530	19.1	1.164 (1.089–1.245)		1.076 (1.006–1.150)		1.059 (0.990–1.132)	
		Q3	26 357	1845	99 965	18.5	1.128 (1.055–1.206)		1.079 (1.009–1.153)		1.063 (0.994–1.137)	
		Q4	25 222	2273	93 894	24.2	1.483 (1.391–1.58)		1.246 (1.169–1.329)		1.183 (1.109–1.262)	
	Alzheimer's disease	Q1	25 774	1228	97 763	12.6	Reference	<.001	Reference	< 0.001	Reference	<.001
		Q2	25 786	1449	97 530	14.9	1.181 (1.095–1.275)		1.087 (1.007–1.173)		1.071 (0.993–1.156)	
		Q3	26 357	1446	99 965	14.5	1.15 (1.066–1.241)		1.096 (1.016–1.183)		1.082 (1.002–1.167)	
		Q4	25 222	1788	93 894	19.0	1.518 (1.412–1.632)		1.264 (1.175–1.359)		1.203 (1.118–1.294)	
	Vascular dementia	Q1	25 774	206	97 763	2.1	Reference	.008	Reference	0.207	Reference	.594
		Q2	25 786	218	97 530	2.2	1.060 (0.876–1.283)		1.001 (0.827–1.211)		0.979 (0.809–1.185)	
		Q3	26 357	206	99 965	2.1	0.978 (0.806–1.186)		0.949 (0.782–1.151)		0.930 (0.766–1.128)	
		Q4	25 222	256	93 894	2.7	1.296 (1.078–1.556)		1.144 (0.952–1.375)		1.064 (0.885–1.28)	

The multivariable model was adjusted for age, sex, smoking status, alcohol usage, regular physical activity, low-income status, BMI, diabetes mellitus, dyslipidemia, history of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker usage, calcium channel blocker usage, beta-blocker usage, baseline systolic BP, diastolic BP, pulse pressure, eGFR values at baseline, eGFR variability and number of health exams.

in the multivariable models, although the regression analyses identified a significant association between higher systolic BP or lower diastolic BP and dementia risks in the univariable model. The adjusted HRs were nonlinear according to systolic BP quartiles, as Q2 and Q3 showed the lowest hazards, while Q1 (low baseline systolic BP) and Q4 (high baseline systolic BP) showed higher adjusted HRs for dementia. Diastolic BP showed a similar association with dementia risks, as the Q2 group showed the lowest adjusted HRs for dementia, while those with higher baseline diastolic BP showed higher risks.

Subgroup analysis of BP variability

When the population was stratified into male and female subgroups, most results indicated the absence of a sex interaction with BP variability exposure regarding dementia risks (Supplemental data, Table S2). A suspected interaction by sex was identified only for the association between diastolic BP variability and the risk of Alzheimer's disease; however, a significant association was identified in both males and females (Supplemental data, Table S3), suggesting that higher BP variability was significantly associated with dementia risks regardless of sex.

When the study population was stratified according to baseline eGFR <60 mL/min/1.73 m^2, the incidence rates for dementia in CKD patients with baseline eGFR <60 mL/min/1.73 m^2 were ∼2- to 3-fold higher than those among individuals without such reduced baseline eGFR. The interaction term *P*-values indicated that there was no significant interaction of eGFR <60 mL/min/1.73 m^2 with BP variability exposure (Supplemental data, Table S2). On the other hand, related to the small number of samples and events of those with baseline eGFR ≥60 mL/min/1.73 m^2, the analysis within the subgroup without reduced baseline eGFR was considered underpowered, as large confidence intervals (CIs) were observed (Supplemental data, Table S4).

DISCUSSION

In this nationwide observational study, including non-dialysis-dependent CKD patients, we demonstrated that higher visit-to-visit BP variability was significantly associated with higher risks of dementia, including risks of Alzheimer's disease and vascular dementia. The association was significant regardless of sex or reduced baseline eGFR, further suggesting that the results may be applied to the general CKD population. Our study encourages clinicians to pay attention to visit-to-visit BP variability and its association with cognitive function impairment in the population with kidney function impairment.

The prognostic importance of visit-to-visit or day-to-day BP variability has been emphasized in previous studies, as high BP variability has been associated with adverse cardiovascular or kidney outcomes [9, 12, 14]. In addition, a recent study suggested that the visit-to-visit BP variability is significantly associated with dementia risks in the general population [7]. Considering that kidney function impairment is one of the conditions associated with a substantial increase in BP variability [8, 18], further investigation focusing on the clinical significance of BP variability in regard to the dementia risks of CKD patients is warranted. Herein we performed a large-scale observational study investigating the association between visit-to-visit BP variability and dementia risks and identified that high BP variability is a significant risk factor for dementia risks in CKD patients. The main strengths of this study are a large sample size of CKD patients with available multiple measurements for BP parameters, nationwide dementia events identified through the claims database and wide ranges of adjusted covariates covering multiple aspects that may confound the associations between BP variability and dementia risks.

In our results, unlike the null or inconsistent results observed for baseline BP exposures, high BP variability showed a consistent and prominently significant association with dementia risk even after adjusting for baseline BP values. This encourages clinicians to pay attention not only to BP values at a single time point, but also to BP trends or visit-to-visit BP variability and their association with dementia risks in CKD patients. Furthermore, a future trial may test whether minimizing such BP variability would have a beneficial effect on the cognitive function of individuals with kidney function impairment.

The high risk of cognitive function impairment in CKD patients or in those with kidney function decline has been noted previously, particularly in those with chronic hypertension and cardiovascular risk factors [3, 6]. The vascular hypothesis explaining the mechanism of cognitive function impairment development supports stringent control of cardiovascular risk factors to prevent cognitive function impairment, as endothelial dysfunction or vascular injury would cause subclinical ischemic injuries or microbleeds, resulting in an accelerated cognitive function decline [1, 19]. Considering that high visit-to-visit BP variability may lead to repetitive brain ischemic–reperfusion injury that results in neuronal damage or impaired neuronal protein synthesis, the state of high BP variability may be considered another vascular risk factor related to the risk of Alzheimer's disease [20]. Additionally, high BP variability, which is directly associated with arterial stiffness, may cause cerebral small vessel diseases, contributing to the risk of vascular dementia [21]. As CKD is a state where high BP variability and cardiovascular risk factors are common [3], the clinical importance of visit-to-visit BP variability related to dementia risks may be accentuated in the population with kidney function impairment.

There are several limitations of this study. First, the study sample is affected by healthy volunteer bias considering the low prevalence of CKD in the health screening data, although the prevalence of CKD has been reported to be 8.2% in the general population in Korea [22]. Second, survivorship bias is another source of selection bias in this study, as multiple health screening exams over 3–5 years were required to determine BP exposures. Third, the measurements of BP values were not standardized among the health screening centers, although the centers were quality controlled by the NHIS of Korea. Different measurement devices or methods might have caused measurement bias and affected the BP exposures, particularly as the variability exposures were determined from few BP measurements. In addition, information on quantified proteinuria was unavailable, and dipstick albuminuria results were used to determine urine abnormalities, which would be a source of measurement bias. Last, this observational study cannot determine the efficacy of an intervention reducing BP variability for reducing dementia risks in CKD patients. A future trial is necessary to assess the benefits of controlling hypertension along with achieving stable BP without fluctuation for the risk of dementia in individuals with kidney function impairment.

In conclusion, high BP variability is associated with a higher risk of dementia in CKD patients. Recent trends of visit-to-visit BP variability may be evaluated when assessing cognitive dysfunction risks in individuals with kidney function impairment. Current study findings may be considered when designing optimal BP control strategies for CKD patients with high risks of cognitive function impairment.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

The corresponding author attests that all of the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. S.P., H.L., K.W.J., K.H. and D.K.K. contributed to the conception and design of the study. S.P., S.L., Y.K., H.H., S.C., K.H., J.P.L., K.W.J., C.S.L., Y.S.K. and D.K.K. advised on statistical aspects and interpreted the data. S.P. and K.H. performed the main statistical analysis, assisted by S.L., H.L., J.P.L., K.W.J. and C.S.L., and Y.S.K. and D.K.K. offered advice regarding the data interpretation. D.K.K. obtained funding and supervised the overall project. All of the authors participated in drafting the manuscript. All of the authors reviewed the manuscript and approved the final version to be published.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data for this study are available from the NHIS of Korea under accession number NHIS-2021-1-366.

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