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ORIGINAL ARTICLE

Impaired kidney function, cerebral small vessel disease and cognitive disorders: the Framingham Heart Study

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ABSTRACT

Background and hypothesis. It remains unclear whether the relation of chronic kidney disease (CKD) with cognitive dysfunction is independent of blood pressure (BP). We evaluated kidney function in relation to premorbid BP measurements, cerebral small vessel disease (CSVD), and incident mild cognitive impairment (MCI) and dementia in Framingham Offspring Cohort participants.

Methods. We included Framingham Offspring participants free of dementia, attending an examination during midlife (exam cycle 6, baseline) for ascertainment of kidney function status, with brain magnetic resonance imaging late in life (exam cycles 7–9), cognitive outcome data, and available interim hypertension and BP assessments. We related CKD (estimated glomerular filtration rate $<$60 ml/min/1.73 m^2) and albuminuria (urine albumin-to-creatinine ratio $\geq$30 mg/g) to CSVD markers and cognitive outcomes using multivariable regression analyses.

Results. Among 2604 participants (mean age 67.4 $\pm$ 9.2, 64% women, 7% had CKD, and 9% albuminuria), albuminuria was independently associated with covert infarcts [adjusted OR, 1.55 (1.00–2.38); $P = 0.049$] and incident MCI and dementia [adjusted hazard ratio (HR), 1.68 (1.18–2.41); $P = 0.005$ and 1.71, (1.11–2.64); $P = 0.015$, respectively]. CKD was not associated with CSVD markers but was associated with a higher risk of incident dementia [HR, 1.53 (1.02–2.29); $P = 0.041$]. While albuminuria was predictive of the Alzheimer's disease subtype [adjusted HR = 1.68, (1.03–2.74); $P = 0.04$), CKD was predictive of vascular dementia [adjusted HR, 2.78 (1.16–6.68); $P = 0.023$].

Conclusions. Kidney disease was associated with CSVD and cognitive disorders in asymptomatic community dwelling participants. The relation was independent of premorbid BP, suggesting that the link between kidney and brain disease may involve additional mechanisms beyond BP-related injury.

Keywords: albuminuria, cerebral small vessel disease, CKD, cognitive impairment, dementia, hypertension

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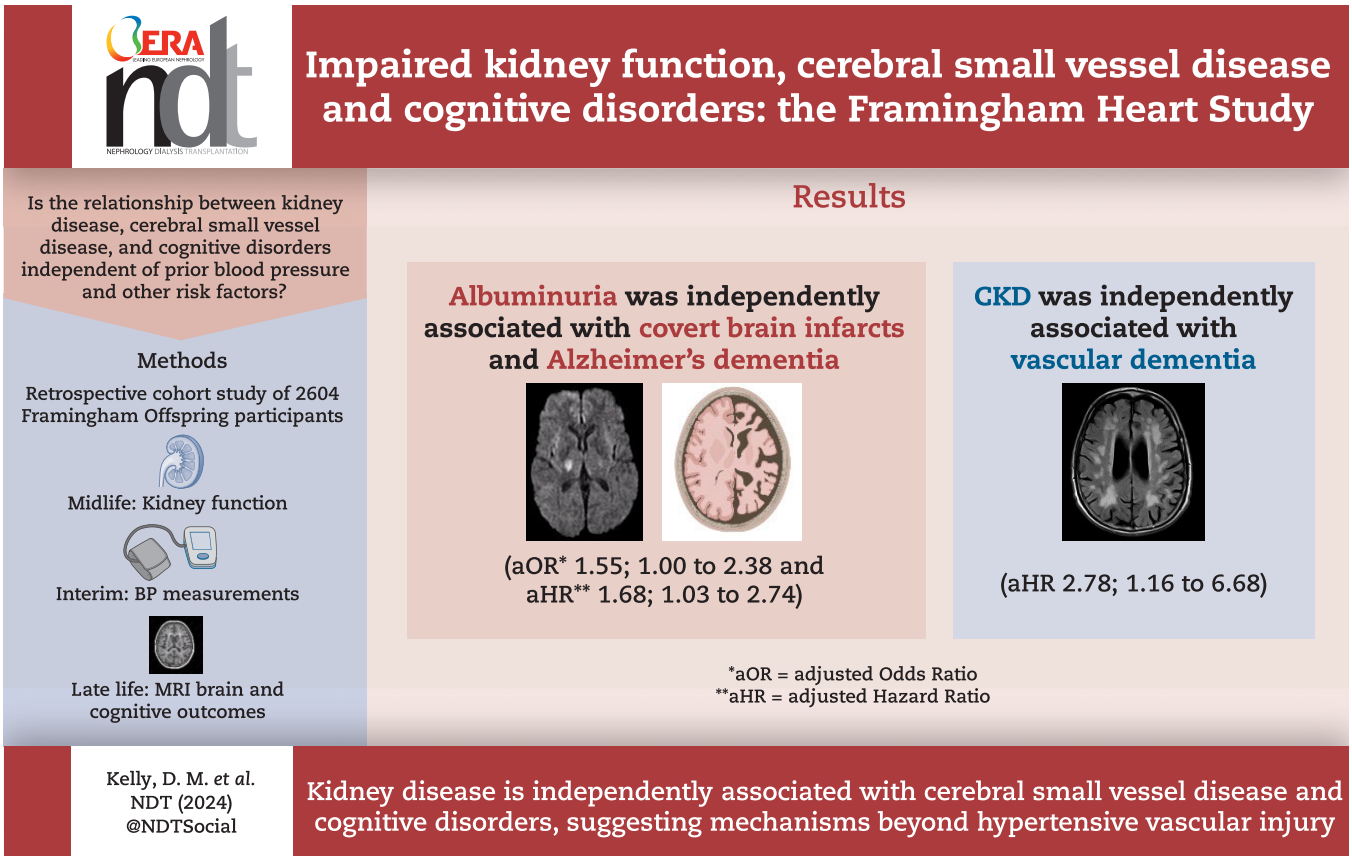
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Chronic kidney disease (CKD) affects over 10% of the global population and is associated with a higher risk of cognitive disorders, including dementia. Furthermore, over half of CKD patients exhibit covert brain infarctions, which are associated with vascular cognitive impairment. The extent to which the burden of cognitive dysfunction and cerebral small vessel disease in patients with CKD is driven by hypertensive vascular injury has not previously been explored.

This study adds:

- Impaired kidney function, specifically assessed by albuminuria, is independently associated with covert brain infarctions (CBI), but not with other markers of cerebral small vessel disease (CSVD), after accounting for potential confounders including premorbid blood pressure. Both CKD and albuminuria are independently associated with an increased risk of dementia, with albuminuria showing a stronger association, which does not seem to be mediated by premorbid blood pressure. This study underscores the potential existence of a generalized small vessel vasculopathy beyond hypertensive vascular damage, with albuminuria emerging as a key risk factor for cerebrovascular and cognitive conditions.

Potential impact:

- The observed associations between kidney disease and cognitive disorders suggest a possible synergy between cerebrovascular disease and Alzheimer's pathology, indicating the need for further investigations and clinical trials targeting albuminuria to potentially modify cerebrovascular and cognitive risks.

BACKGROUND

Chronic kidney disease (CKD) is a growing global health burden that affects >10% of the general population worldwide [1]. Prevalence rates increase to nearly 40% in people aged 60+ years [2]. Multiple epidemiological studies suggest that individuals at all stages of CKD are at increased risk of developing cognitive disorders and dementia, and thus represent a vulnerable population [3, 4]. In a recent, large population-based study, it was shown that as many as 10% of dementia cases may be attributable to CKD [5].

The pathobiology of cognitive disorders in individuals with CKD is poorly understood with multiple purported mechanisms based on both vascular and neurodegenerative hypotheses [6, 7]. Premorbid midlife to late-life BP is strongly associated with cognitive decline in the general population [8] but its role in dementia pathogenesis in CKD is unknown. A recent systematic review and

meta-analysis of stroke risk in CKD suggested that most of the risk in this setting may be attributable to long-term BP burden [9]. Premorbid BP may therefore also play a similarly central role in the etiology of cognitive dysfunction in CKD.

There are also strong associations between cerebral small vessel disease (CSVD) and CKD [10]. For example, covert brain infarctions (CBI) are present in over half of patients with CKD [11], and have been associated with vascular cognitive impairment [12]. Several mechanisms for the association of CSVD and CKD have been proposed including their shared anatomical and physiological susceptibility to hypertensive vascular injury [13], but this hypothesis has not been previously examined.

The Framingham Heart Study (FHS) is a prospective population-based longitudinal cohort study with detailed cognitive phenotyping and neuroimaging. Using this study, we aimed to investigate whether the associations of CKD with CSVD, and with mild cognitive impairment (MCI) and dementia were truly independent of premorbid BP as well as other relevant cardiovascular and cognitive risk factors.

MATERIALS AND METHODS

Sample

The FHS is a community-based, prospective cohort study that was initiated in 1948 with the Original cohort and now comprises three generations of participants. This present study includes participants from the Framingham Offspring Cohort (children of the Original cohort and their spouses), consisting of 5124 persons examined approximately once every 4 years since enrollment (1971). Each examination visit includes a detailed medical history, physical examination including BP measurements, anthropometry, and laboratory assessment of risk factors.

Participants with prior history of stroke, dementia, or other neurological conditions were excluded. We included 2604 Offspring participants who attended a clinical examination during midlife (exam cycle 6, baseline, ages 40–64 years) and later life (exam 8, ≥65 years) for ascertainment of kidney function status, with available brain magnetic resonance imaging (MRI) acquisition late in life (exam cycles 7–9), cognitive outcome data, and interim hypertension and BP assessments.

Exposures

Kidney function

Serum creatinine was measured at each examination cycle using the modified Jaffé method. We applied serum creatinine distribution of the National Health and Nutrition Examination Survey III (NHANES III) as reference panel for calibrated serum creatinine adjusted for age and sex [14, 15]. Estimated glomerular filtration rate (eGFR) was generated using the CKD-EPI equation [16]. CKD at baseline was defined as an eGFR <60 ml/min/1.73 m^2 as per 2012 Kidney Disease: Improving Global Outcomes guidelines [17].

A single-void urine sample at the baseline examination was used to measure urine albumin: creatinine ratio (UACR) (mg/g). The cut-off level for albuminuria was ≥30 mg/g Cr (moderately increased albuminuria was defined as UACR = 30–299 mg/g Cr, and severely increased albuminuria was defined as UACR ≥300 mg/g Cr).

Brain MRI

A 1.5-tesla MR machine (Siemens Magnetom) was used to obtain the following sequences: coronal T2-weighted 2470/20 to 80 (TR/TE), echo train length 8, field of view 22 cm, acquisition matrix 192 × 256 interpolated to 256 × 256 with one excitation, 4-mm slice thickness from nasion to occiput, sagittal T1-weighted 11.4/4.4, 3D FLASH, 192 mm slab, 128 slices of 1.5-mm thickness, 12° flip angle and axial T2* gradient echo 656/26 (TR/TE), field of view 22 cm, acquisition matrix 144 × 256, 30° flip angle, 19 slices of 5-mm thickness, and 2 mm gap.

MRI data were analyzed using a custom-designed image analysis package written for the Linux operating system. All analyses were done blind to the participant's demographic and clinical characteristics, and outcome ascertainment.

Cerebral small vessel disease (CSVD)

Extensive white matter hyperintensities (WMH) were defined as log WMH areas >1 standard deviation (SD) above the age-specific mean, assessed using fluid-attenuated inversion recovery sequences and expressed as a percentage of total intracranial volume [18]. The presence of CBI was determined based on the size (≥3 mm), location, and imaging characteristics of the lesion (cerebrospinal fluid signal intensity on subtraction images (proton density-T2) and hyperintense on T2-weighted images) and using previously described methods [19].

MRI characteristics of enlarged perivascular spaces (ePVS) were based on consensus criteria by the Standards for Reporting Vascular Changes on Neuroimaging Criteria (STRIVE Consortium) [20, 21]. The ePVS met the following criteria: diameter <3 mm, signal intensity similar to cerebrospinal fluid on all sequences, adherence to the course of penetrating vessels, and linear (parallel to the penetrating vessel) or round/ovoid (perpendicular to the penetrating vessel). The ePVS rating methodology has been previously described [22] but briefly, ratings were performed on T2-weighted axial MRI sequences using a validated method that groups ePVS by brain topography into centrum semiovale (CSO) and basal ganglia (BG) [23]. The CSO area includes MRI slices above the roof of the lateral ventricles up through the subcortical white matter in cerebral hemispheres. The BG region involves the deep structures, including the caudate nucleus, internal capsule, thalamus, lentiform nucleus, external capsule, and insular cortex. The burden of ePVS in each region was categorized into grades based on ePVS counts: I (1–10), II (11–20), III (20–40), and IV (>40). We also defined high burden ePVS as grade III–IV in the respective region. This definition was then used to create a mixed region variable to reflect the number of regions with high ePVS burden (0 = neither region, 1 = either the CSO, or BG, 2 = both regions).

We did not include cerebral microbleeds as a CSVD parameter for this paper due to small sample of participants with available ratings. All CSVD MRI ratings were blinded to the participants' demographic and clinical information, other imaging sequences, and to each other.

Assessment of incident MCI and dementia

The primary outcome was a composite of incident MCI and dementia, whichever occurred first. Methods for surveillance of incident MCI and dementia in the FHS have been previously published [24, 25]. Briefly, ongoing surveillance for dementia is carried through FHS clinic evaluations, biennial questionnaires, annual telephone health history updates, and/or report by participants, their relatives, or care providers. A concern of cognitive symptoms can be raised by the participant, family member, FHS staff, or physician by a drop in mini-mental status exam of >3 points in sequential visits, >5 points across all visits or a score below an education specific cut point. Such concerns trigger further detailed evaluation including review of all records, comprehensive

neurological assessment and neuropsychological evaluation including a comprehensive battery of cognitive testing, interview of family members, and in some cases review of autopsy data when available. Potential incident MCI and dementia cases are then adjudicated by a panel including at least one neurologist and one neuropsychologist.

A diagnosis of MCI was made in accordance with the conventional Petersen–Winblad criteria [26]. Dementia was defined using the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM IV) criteria [27]. The diagnosis of Alzheimer's disease is based on criteria for possible, probable, or definite Alzheimer's disease from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [28, 29]. The diagnosis of vascular dementia is based on criteria for possible or probable vascular dementia from the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences [30]. The diagnostic algorithm allows participants to have more than one subtype of dementia.

For the composite MCI and dementia endpoint, participants (including those who died during follow-up) were censored at the earliest date known to be dementia and MCI free.

Covariates

We adjusted for demographics and baseline covariates associated with a greater risk of dementia, including age, sex, education, diabetes mellitus, prior cardiovascular disease (CVD), and mean premorbid systolic blood pressure (SBP) from exams 6–8. CVD included peripheral vascular disease (including intermittent claudication), coronary artery disease (including coronary insufficiency, angina pectoris, and myocardial infarction), cerebrovascular disease (including stroke), and congestive heart failure. Systolic and diastolic BP (DBP) were each taken as the average of the Framingham clinic physician's two measurements. Hypertension was defined by the JNC-7 classification (SBP ≥140 mmHg and/or DBP ≥90 mmHg or use of antihypertensive medications). Premorbid hypertension was defined as the presence of hypertension prior to the development of CSVD or incident MCI/dementia. Premorbid BP measurements were presented as long-term average SBP (mean SBP taking into account all measurements in participants with at least one premorbid BP measurement) between exams 6–8. Diabetes was defined as fasting glucose ≥126 mg/dl (≥7 mmol/L) for the Offspring cohort or use of insulin or oral hypoglycemic medications.

We then examined APOE-ε4 carrier status as effect modifier of the relationship between kidney function and cognitive outcomes. APOE genotyping in the FHS has been described elsewhere [31].

Statistical analysis

Baseline characteristics of study participants were evaluated overall and stratified by CKD and albuminuria status. We examined the relationship between CKD (GFR <60) and albuminuria (UACR ≥30) separately with CSVD markers (ePVS, CBI, extensive WMH) and MCI/dementia.

Specifically, logistic regression was used to relate CKD and albuminuria to high burden PVS (grade III–IV) in the CSO and BG regions, CBI, and extensive WMH. Ordinal logistic regression was used for the mixed CSO-BG high burden score describing the number of regions with high burden ePVS (0, 1, or 2); proportionality of the odds was assessed via the score test. Models for these CSVD markers adjusted (i) for age at exam 8, sex, and time interval between MRI date and exam 8 (model 1); (ii) additionally adjusted for diabetes mellitus and prior CVD (model 2); and (iii) with further adjustment for mean premorbid SBP (exams 6–8) (model 3). In a sensitivity analysis, we repeated these analyses considering eGFR and albuminuria (as log-transformed UACR) as continuous variables.

Crude incidence rates (per 100 000 person-years), stratified by CKD status and albuminuria, were calculated for each type of cognitive event (MCI, all-cause dementia, AD type, vascular dementia, and composite MCI/dementia) by dividing the total number of events by the total person follow-up time. We used multivariable Cox proportional hazards regression analyses to obtain hazard ratios (HR) and 95% confidence intervals (95% CI) for each cognitive event and examine CKD as well as albuminuria as exposures. Regression analyses were adjusted (i) for age at exam 8, sex, and educational level (model 1); (ii) additionally adjusted for diabetes mellitus; and (iii) prior CVD with further adjustment for mean premorbid SBP (exams 6–8) (model 3).

In exploratory analyses, we stratified our analyses by APOE-ε4 allele presence to investigate whether APOE-ε4 carrier status modifies the association between impaired kidney function and MCI/dementia risk. Thereafter, we used causal mediation analysis to further investigate to what extent the association between albuminuria and cognitive outcomes is mediated by premorbid SBP. We used the publicly available SAS macro %mediate to calculate the proportion of the effect of CKD and albuminuria on each outcome that is explained by mean premorbid SBP [32, 33].

All statistical analyses were performed using SAS version 9.4 (Cary, NC). A P value < 0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

The Institutional Review Board of Boston University Medical Center approved the study protocol and written informed consent was obtained from all subjects.

RESULTS

Demographics and baseline kidney function

The study cohort included 2604 participants (Fig. 1). Table 1 shows the baseline demographic and clinical characteristics for all characteristics and according to CKD and albuminuria status. The mean age of participants was 57.7 years (SD: 9.2) and 1677 were women (64%). 175 individuals (7%) had CKD and 237 (11%) had albuminuria. All but 53 participants (2%) had three BP measurements between clinic exams 6–8. UACR data was missing for 348 individuals ($N = 2256$ for these analyses). A total of 1138 participants (44%) had an eGFR≥90 ml/min/1.73 m^2, 1291 (50%) 60–89 ml/min/1.73 m^2, 173 (7%) 30–59 ml/min/1.73 m^2, and two (0.1%) <30 ml/min/1.73 m^2. The median eGFR and UACR were 87.2 (75.3, 98.9) and 6.0 (2.8, 14.0), respectively. Notably, compared to those with normal renal function, the CKD and albuminuria groups were older and had a higher burden of vascular risk factors and co-morbidities including hypertension, diabetes mellitus, prevalent CVD, and atrial fibrillation.

Associations of kidney function with CSVD markers

The prevalence of CSVD markers according to baseline kidney function status are shown in Fig. 2 and Supplementary Table SI. Both CKD and albuminuria were associated with CBI in the crude

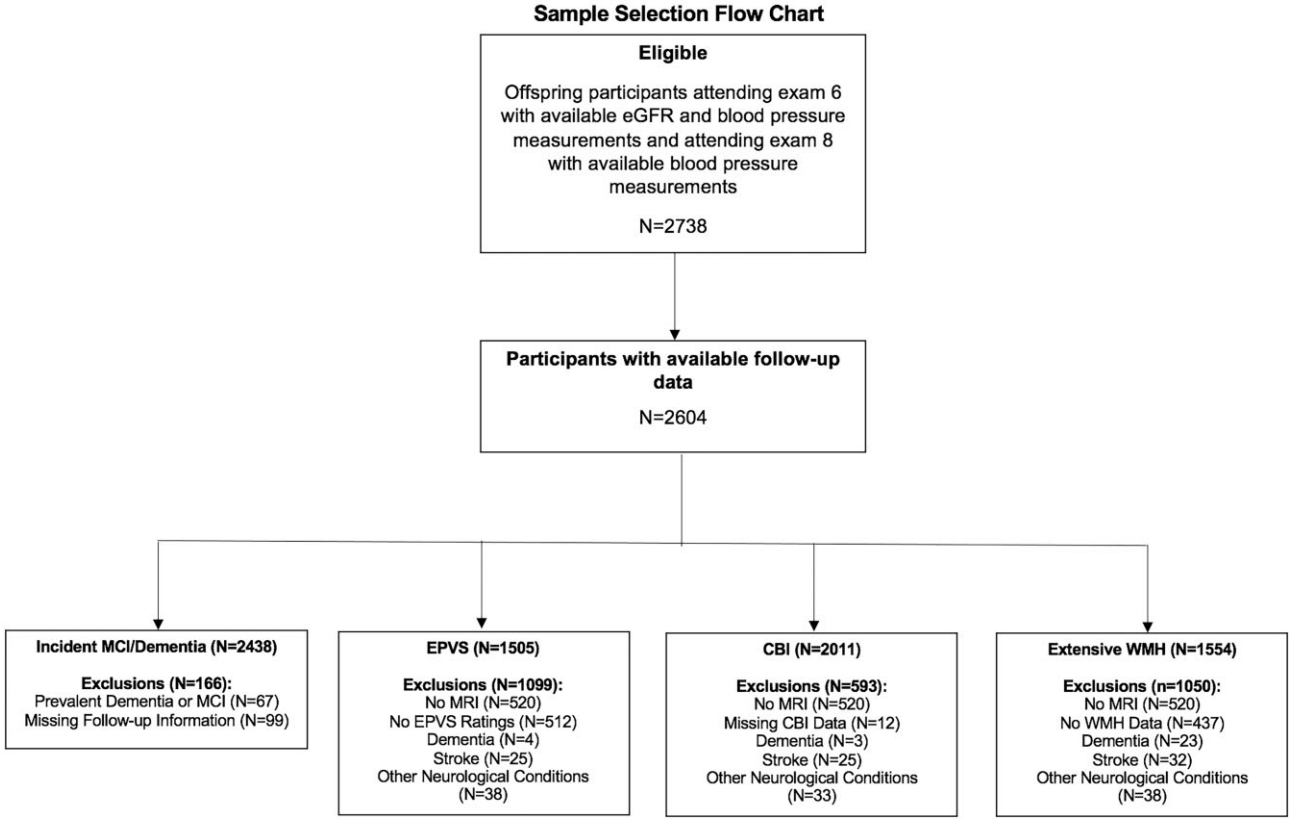


Figure 1: Flow of cohort participants.

analysis (OR = 2.18, 95% CI: 1.39–3.40; $P = 0.001$ and OR = 2.10, 1.40–3.13; $P = 0.0003$, respectively) (Table 2). However, with multivariable adjustment for age, sex, time interval and known vascular risk factors including premorbid SBP, only albuminuria remained independently associated with CBI in the fully adjusted model (adjusted OR = 1.55, 1.00–2.38; $P = 0.049$). Neither CKD nor albuminuria were associated with extensive WMH in either univariable or multivariable analyses (Table 2).

Albuminuria was significantly associated with high burden of ePVS in the BG after adjusting for age, sex, time interval, and vascular risk factors (OR: 1.70, 1.01–2.87; $P = 0.048$). The score test for the number of regions of high burden ePVS was not significant and assumed proportionality of the odds. In the mixed CSO-BG regions, albuminuria was also significantly associated with higher burden of ePVS (OR: 1.53, 1.02–2.31; $P = 0.039$). However, the associations in the BG and mixed regions were attenuated when we further adjusted for premorbid SBP (OR: 1.60, 0.94–2.72; $P = 0.084$; and OR 1.48, 0.99–2.24; $P = 0.059$; respectively) (Table 3). Neither albuminuria nor CKD were associated with a high burden of ePVS in the CSO after models were adjusted for age. Findings were similar in the sensitivity analyses when we repeated the analyses using eGFR and log-UACR (Supplementary Tables SII and SIII).

Associations of kidney function with MCI and dementia

During a median follow-up period of 7.5 (Q1: 5.7, Q3: 11.9) years, 326 (13%) participants were diagnosed with MCI or dementia. The incidence rate was 15.27 (11.57, 20.15) and 11.33 (8.72, 14.73) per 100 000 person-years for patients with CKD and albuminuria, respectively (Figs 2 and 3 and Supplementary Table SIV). In total, 127 (5%) were diagnosed with AD and 34 (1%) were diagnosed with vascular dementia. Again, albuminuria but not CKD, was associated with risk of incident MCI in the univariable analysis (Crude HR = 2.38, 1.70–3.33; $P < 0.0001$) and this association remained significant even after complete adjustment for age, sex, education, vascular risk factors, and premorbid SBP (adjusted HR = 1.68, 1.18–2.41; $P = 0.005$) (Table 4). However, both CKD and albuminuria were associated with risk of incident all-cause dementia in the most fully adjusted model (adjusted HR = 1.53, 1.02–2.29; $P = 0.041$ and 1.71, 1.11–2.64; $P = 0.015$, respectively). While albuminuria was predictive of the AD subtype (adjusted HR = 1.68, 1.03–2.74; $P = 0.04$), CKD was predictive of VaD (adjusted HR = 2.78, 1.16–6.68; $P = 0.023$) (Table 4). When analyses were stratified by APOE-ε4 allele presence, APOE-ε4 carrier status modified the association between CKD and combined MCI/dementia risk (adjusted HR = 2.07, 1.16–3.70; $P = 0.014$ if APOE-ε4 allele was present vs 1.01, 0.67–1.53; $P = 0.950$ if not; Supplementary Table SV).

Mediation analysis

We then performed an exploratory mediation analysis to determine what proportion of the total effect of albuminuria on dementia risk is potentially mediated by premorbid SBP (Fig. 4). Using the covariates from model 2, the total and direct effects of albuminuria on risk of dementia were HR = 1.75, 95% CI: 1.14–2.70, and 1.71, 95% CI: 1.11–2.64, respectively, with only 4.2% (0.5–28.3%) of the total effect mediated by premorbid SBP ($P = 0.16$).

Table 1: Baseline demographic and clinical characteristics of patients included in analyses stratified by CKD and albuminuria status.

Baseline characteristics[a]	All (*N* = 2604)	CKD present (*N* = 2604)		Albuminuria present (*N* = 2256)	
		No (eGFR ≥ 60) (*n* = 2429)	Yes (eGFR < 60) (*n* = 175)	No (UACR < 30) (*n* = 2019)	Yes (UACR ≥ 30) (*n* = 237)
Age Exam 6, mean (SD), years	57.7 (9.2)	57.0 (8.9)	67.2 (7.9)	57.2 (9)	61.8 (9.6)
Age Exam 8, mean (SD), years	67.2 (9.2)	66.6 (8.9)	76.2 (8.1)	66.6 (9)	71.1 (9.6)
Women, *n* (%)	1677 (64)	1554 (64)	123 (70)	1283 (64)	171 (72)
Education, *n* (%) *N* = 2546					
Less than high school	96 (4)	83 (3)	13 (8)	68 (3)	14 (6)
High school	732 (29)	672 (28)	60 (35)	569 (29)	78 (34)
Some college	760 (30)	714 (30)	46 (27)	572 (29)	74 (32)
College or more	958 (38)	904 (38)	54 (31)	762 (39)	65 (28)
Hypertension, *n* (%)	973 (37)	865 (36)	108 (62)	691 (34)	145 (61)
Diabetes mellitus, *n* (%); *N* = 2575	216 (8)	191 (8)	25 (14)	130 (7)	61 (26)
Smoker, *n* (%)	364 (14)	351 (14)	13 (7)	270 (13)	47 (20)
History of atrial fibrillation, *n* (%)	53 (2)	46 (2)	7 (4)	33 (2)	14 (6)
History of CVD, *n* (%)	214 (8)	187 (8)	27 (15)	153 (8)	33 (14)
Antihypertensive therapy, *n* (%)	648 (25)	561 (23)	87 (50)	451 (22)	104 (44)
Premorbid SBP, mean (SD), mmHg	126.8 (18.2)	126.2 (17.9)	135.4 (20.8)	126.0 (17.9)	134.6 (21.3)
Premorbid DBP, mean (SD), mmHg	75.5 (9.4)	75.5 (9.4)	74.3 (10)	75.5 (9.4)	76.5 (9.6)
BMI, mean (SD), kg/m^2	27.8 (5.1)	27.8 (5.1)	28.4 (5.1)	27.7 (5)	28.5 (6.2)
LDL cholesterol, mean (SD), mg/dl	127.4 (33)	127.5 (32.9)	126.4 (35)	126.9 (33)	128.0 (33)
HDL cholesterol, mean (SD), mg/dl	51.8 (16.1)	51.7 (16)	52.4 (16.8)	51.9 (16.1)	50.2 (16.8)
Total cholesterol, mean (SD), mg/dl	205.8 (36.9)	205.8 (36.8)	206.2 (39.5)	205.1 (36.4)	208.8 (41.1)
eGFR, mean (SD), ml/min/1.73 m^2	86.6 (17.5)	89.0 (15.2)	52.3 (7.1)	87.0 (17.1)	80.7 (19.2)
UACR, median (Q1, Q3), mg/g; *N* = 2256	6.0 (2.8, 14.0)	5.8 (2.6, 13.2)	10.9 (4.1, 32.3)	5.2 (2.4, 10.4)	50.0 (39.0, 99.6)
APOE E4 allele, *n* (%), *N* = 2042	458 (22)	420 (22)	38 (25)	358 (23)	43 (24)

[a]Numbers are *n* (%) unless otherwise stated. Sample sizes were based on eGFR and albuminuria data availability.
Baseline demographic and clinical characteristics were defined at examination 6 except for education and APOE4.
BMI indicates body mass index; HDL, high-density lipoprotein; interquartile range; LDL, low-density lipoprotein; SD, standard deviation.

DISCUSSION

In a large, prospective, population-based cohort study, we found that impaired kidney function, as assessed by albuminuria, but not CKD, was independently associated with CBI but not with other markers of CSVD after adjustment for potential confounders. Albuminuria was related to BG ePVS after adjustment for vascular risk factors but the relation was not independent of premorbid BP. Both CKD and albuminuria were independently predictive of incident dementia risk with stronger associations in the case of the latter that did not appear to be mediated by premorbid BP. Our results highlight the importance of albuminuria as a cerebrovascular and cognitive risk factor and indicate that there may be additional shared pathobiology in the kidney and the brain beyond premorbid BP.

Consistent with earlier studies of patients with more advanced CKD [11, 34], we found a higher prevalence of CBI in patients with CKD. Although previous work did not demonstrate an independent association after adjustment for age, sex, and hypertension in a population-based study of 3178 patients with acute stroke [35], we show an independent relationship between albuminuria and CBI in this study even after similar adjustments. However, there was not an independent association between CKD and CBI. Stronger associations between CKD and CBI have been observed in younger age groups suggesting the possibility of shared genetic susceptibility and an age-dependent association [36]. However, a recent, large GWAS study did not show causal relationships between impaired kidney function and the small vessel stroke phenotype [37]. These discrepancies may relate to phenotypic variability of small vessel stroke, which means that it has the lowest heritability of the subtypes. Regardless of the mechanism, the presence of CBI in CKD has important implications as it has been shown to independently predict cerebrovascular and all-type vascular events, vascular cognitive impairment or executive dysfunction, and kidney disease progression in this setting [11, 12, 38].

Similarly, albuminuria was initially associated with a high burden of ePVS, particularly in the BG but not after further adjustment for premorbid SBP. However, the absence of strong associations between kidney disease and ePVS in this study may be a consequence of the underlying predominantly White study population as recent evidence suggests that CKD may relate differently to CSVD markers such as ePVS according to race [39]. Among patients with CKD, Black patients had 2-fold higher odds of severe ePVS in the BG and CSO compared to White and other racial groups. It is unclear whether there is racial variation in the relationship between albuminuria and ePVS. An earlier systematic review and meta-analysis found stronger associations between albuminuria and ePVS in the CSO compared to those in the BG, although these pooled results were based on few studies [40]. Our growing insights into the heterogeneity that exists within specific CSVD subtypes [41] may underlie some of the variable associations between markers of kidney disease and CSVD demonstrated in this study, but overall, the independent relationship between specifically albuminuria and CSVD markers such as CBI highlights the possibility of a generalized small vessel vasculopathy beyond hypertensive vascular damage that is yet to be fully elucidated.

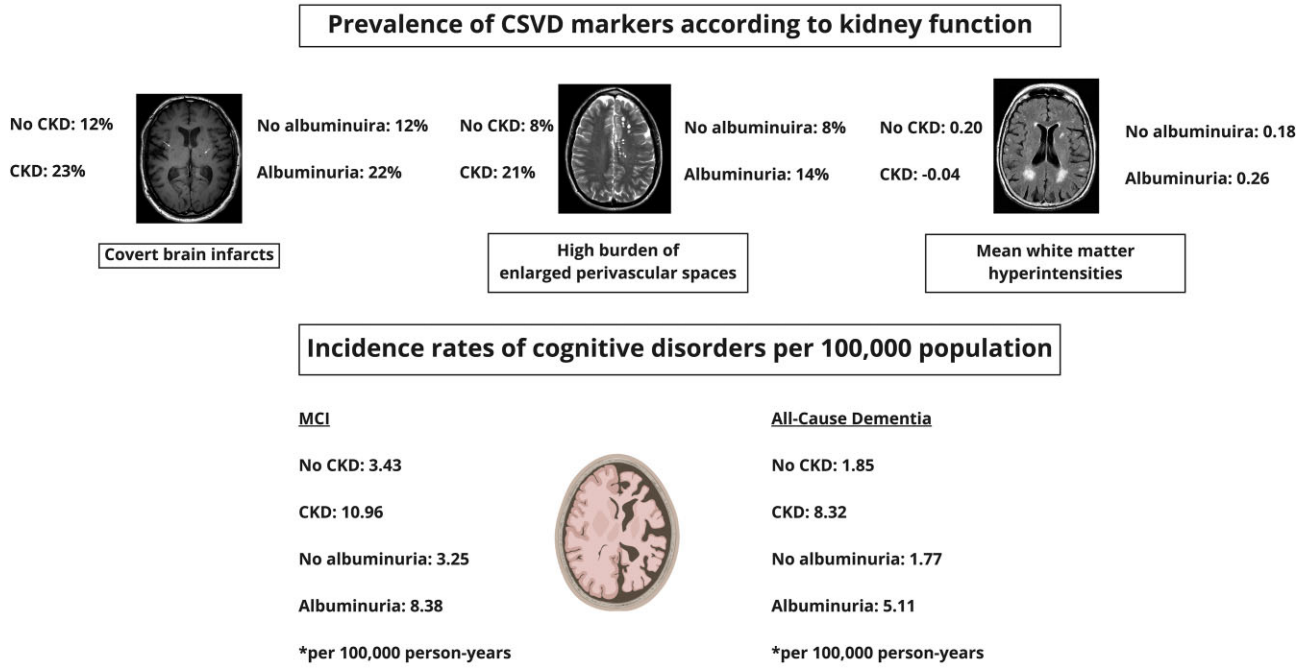


Figure 2: Prevalence of CSVD markers and incidence rates of cognitive disorders according to baseline kidney function status.

Table 2: Associations of CKD and albuminuria with CBI and extensive WMH.

	Unadjusted		Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
CBI								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	2.18(1.39–3.40)	.001	1.38(0.86–2.21)	.178	1.35(0.84–2.16)	.217	1.34(0.83–2.14)	.227
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.10(1.40–3.13)	.0003	1.70(1.12–2.57)	.013	1.57(1.02–2.42)	.041	1.55(1.00–2.38)	.049
Extensive WMH								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	0.69(0.34–1.41)	.309	0.93(0.45–1.93)	.847	0.93(0.45–1.93)	.850	0.92(0.44–1.91)	.825
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	1.21(0.72–2.04)	.467	1.32(0.78–2.23)	.309	1.23(0.72–2.11)	.453	1.19(0.69–2.04)	.538

CI, confidence interval; OR, odds ratio.
CKD is defined as eGFR <60 ml/min per 1.73 m^2. Albuminuria is defined as a UACR ≥30 mg/g Cr.
[a]Model I: adjusted for age at exam 8, sex, and time interval.
[b]Model II: adjusted for Model 1 + CVD and Diabetes (Exam 6).
[c]Model III: adjusted for Model 2 + mean SBP.

Extending the findings of previous work [3, 42], we have shown that both CKD and albuminuria are independently associated with dementia, even after complete adjustment for typical cognitive risk factors and mean premorbid BP. Furthermore, premorbid BP did not appear to mediate a significant proportion of the relationship between albuminuria and cognitive dysfunction when formally tested in mediation analysis. In keeping with earlier studies, we found that albuminuria appears to be more strongly associated with cognitive decline than low eGFR for reasons that are not entirely clear [43, 44]. This finding is, however, consistent with recently published meta-analyses data on the relationship between low eGFR, proteinuria, and stroke risk [9, 45]. These differential associations may be explained by the Steno hypothesis that proposes that urinary protein excretion not only reflects localized subclinical renal disease but also a more generalized vascular endothelial dysfunction [46]. In this study and others [42], we have shown a specific association between albuminuria and the AD dementia subtype. Impaired amyloid β clearance at the blood–brain barrier via endothelial dysfunction may play a role in this relationship [47].

It is now understood that the co-occurrence of mixed neurodegenerative and vascular pathologies is the rule rather than the exception in most dementia pathobiology [48]. In late onset AD, CSVD is almost invariably co-existent and is known to worsen

Table 3: Associations of CKD and albuminuria with high burden of ePVS by brain region.

	Unadjusted		Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Centrum aemiovale (CSO)								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	2.50 (1.65, 3.80)	<.0001	1.25 (0.79, 1.96)	.342	1.25 (0.80, 1.98)	.330	1.25 (0.79, 1.96)	.346
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	1.76 (1.18, 2.62)	.006	1.34 (0.87, 2.06)	.183	1.27 (0.81, 1.97)	.298	1.25 (0.80, 1.95)	.325
BG								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	2.59 (1.62, 4.12)	<.0001	1.24 (0.75, 2.07)	.402	1.23 (0.73, 2.06)	.433	1.18 (0.70, 1.99)	.534
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.07 (1.31, 3.26)	.0019	1.59 (0.96, 2.64)	.071	1.70 (1.01, 2.87)	.048	1.60 (0.94, 2.72)	.084
Mixed region CSO-BG score[a]								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	2.73 (1.84, 4.04)	<.0001	1.30 (0.85, 1.98)	.229	1.29 (0.84, 1.98)	.240	1.27 (0.83, 1.94)	.280
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.02 (1.40, 2.92)	.0002	1.56 (1.05, 2.33)	.027	1.53 (1.02, 2.31)	.039	1.48 (0.99, 2.24)	.059

CI, confidence interval; OR, odds ratio;
CKD is defined as eGFR <60 ml/min per 1.73 m^2. Albuminuria is defined as a UACR ≥30 mg/g Cr. High burden of ePVS is defined as grades III or IV in the respective region (i.e. counts >20).
[a]Model I: adjusted for age at exam 8, sex, and time interval.
[b]Model II: adjusted for Model 1 + CVD and Diabetes (Exam 6).
[c]Model III: adjusted for Model 2 + Mean SBP
[a]Mixed region score: 0 = no high burden 1 = high burden in either the CSO or BG 2 = high burden in both the CSO and BG

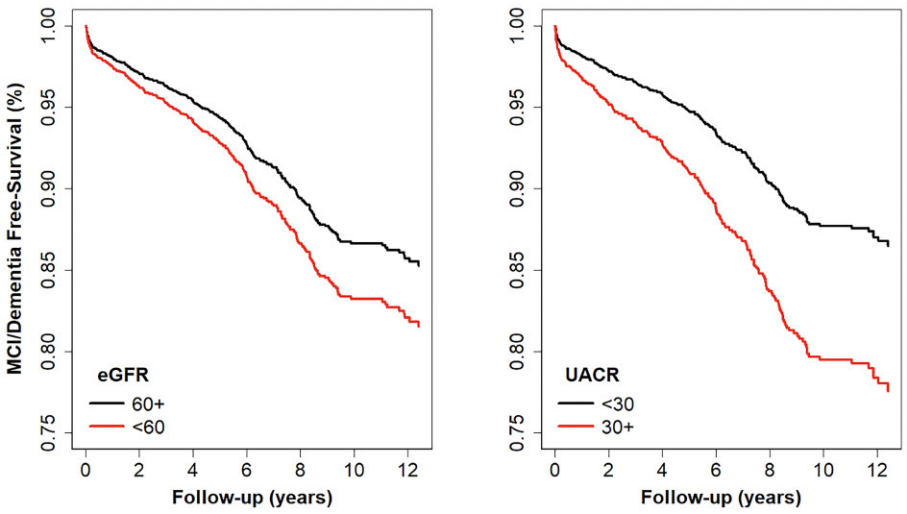


Figure 3: Adjusted dementia/cognitive impairment survival curves by CKD and albuminuria status.
Adjusted for age at exam 8, sex, education, CVD, diabetes, and mean SBP from exams 6–8.

cognitive deterioration. Chronic cerebral inflammation due to vascular risk factors exposure and genetic modulators (including APOE ε4) may lead to increase Aβ production while chronic CSVD (arteriosclerosis, lipohyalinosis, cerebral amyloid angiopathy) and vascular inflammation may drive inefficient perivascular and cell-mediated Aβ clearance [49]. Given the high burden of CSVD in patients with CKD and albuminuria, it follows then that kidney disease may augment potential neurodegenerative mechanisms through the interplay of cerebrovascular disease and Alzheimer's pathology [50]. Furthermore, in our analysis, the presence of APOE ε4 was shown to modify the association between CKD and MCI/dementia leading to stronger disease associations, which further underscores the intricate relationship between neurodegenerative and vascular diseases. CKD may further exacerbate Aβ deposition through its impact on clearance mechanisms and blood–brain barrier integrity [51]. This dual effect could

Table 4: Risk of incident MCI, dementia, and dementia subtypes according to kidney function status.

	Unadjusted		Model 1[a]		Model 2[b]		Model 3[c]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MCI								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	3.06(2.14–4.37)	<.0001	1.13(0.77–1.64)	.535	1.14(0.78–1.66)	.494	1.13(0.78–1.65)	.517
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.38(1.70–3.33)	<.0001	1.65(1.17–2.35)	.005	1.68(11.17–2.40)	.005	1.68(1.18–2.41)	.005
All-cause dementia								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	4.58(3.13–6.70)	<.0001	1.56(1.04–2.35)	.031	1.57(1.05–2.35)	.029	1.53(1.02–2.29)	.041
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.64(1.77–3.94)	<.0001	1.74(1.14–2.66)	.010	1.75(1.14–2.70)	.011	1.71(1.11–2.64)	.015
Combined MCI and dementia								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	3.55(2.62–4.80)	<.0001	1.27(0.93–1.75)	.138	1.30(0.94–1.78)	.111	1.28(0.93–1.76)	.127
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.68(2.01–3.58)	<.0001	1.77(1.31–2.39)	.0002	1.76(1.29–2.39)	.0003	1.75(1.28–2.38)	.0004
Alzheimer's dementia								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	4.44(2.85–6.93)	<.0001	1.42(0.89–2.28)	.144	1.47(0.91–2.35)	.112	1.45(0.90–2.32)	.125
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.84(1.80–4.45)	<.0001	1.75(1.09–2.83)	.022	1.70(1.04–2.76)	.034	1.68(1.03–2.74)	.038
Vascular dementia								
CKD status								
No CKD	1.00		1.00		1.00		1.00	
CKD present	5.94(2.68–13.14)	<.0001	2.44(1.03–5.76)	.042	2.87(1.19–6.90)	.019	2.78(1.16–6.68)	.023
Albuminuria								
No albuminuria	1.00		1.00		1.00		1.00	
Albuminuria present	2.23(0.86–5.75)	.099	1.56(0.52–4.71)	.428	1.68(0.55–5.17)	.364	1.65(0.54–5.06)	.385

AD indicates Alzheimer's dementia; CI, confidence interval; HR, hazard ratio; VaD, vascular dementia.
CKD is defined as eGFR<60 ml/min per 1.73 m^2. Albuminuria is defined as a UACR ≥30 mg/g Cr.
[a]Model I: adjusted for age at exam 8, sex, and education.
[b]Model II: adjusted for Model 1 + CVD and diabetes (Exam 6).
[c]Model III: adjusted for Model 2 + mean SBP.

lead to a higher risk of dementia in individuals with APOE $\varepsilon 4$ and CKD.

Our study has several strengths, which include a large community-based sample with long-term prospective follow-up, the availability of multiple, accurate BP readings that allowed us to adjust associations for long-term premorbid mean BP, and the high reproducibility of the brain MRI measurements. Interpretation of brain MRI was done by readers blinded to all clinical data. However, this study also has a number of limitations. First, FHS participants are of predominantly White, European descent, which limits generalizability of our findings to similar populations. Second, although it is standard practice in large scale population studies, using a single-void urine sample for the assessment of albuminuria can lead to measurement or misclassification bias as there can be diurnal variability in albumin excretion and some patients may have only transient or intermittent albuminuria. Third, we did not have sufficient data to allow analysis of the associations between CMB, CKD, and albuminuria. Although these has previously been described [40, 52], it is not known whether these relationships are independent of longitudinal BP control since the pattern of distribution in kidney disease is typically deep rather than lobar [53], and this requires further study. Fourth, it is not clear why we did not find an association between impaired kidney function and extensive WMH but it may relate to this specific measure of WMH as both CKD and albuminuria have previously been shown to associate with WMH volume [54, 55]. Fifth, unfortunately we were unable to perform a detailed examination of the risk of CSVD markers and dementia according to various eGFR and albuminuria categories as the numbers were too small within individual categories. Similarly, we were underpowered for analysis of the dementia subtype associations. However, our results are preliminary and further analyses using larger samples in partnership with other CHARGE cohorts are underway.

Using a longitudinal population-based cohort study, we have shown that impaired kidney function, particularly as assessed by

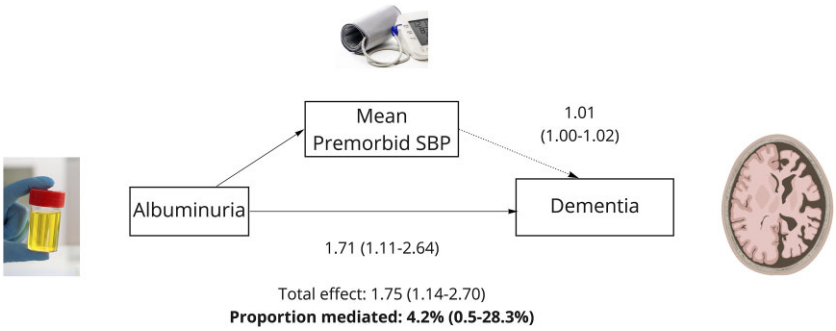


Figure 4: Mediation analysis for MCI and dementia with albuminuria as the exposure and mean SBP (exams 6–8) as the potential mediator.

albuminuria, is associated with both CSVD markers and cognitive disorders independent of premorbid BP. Further studies are needed to disentangle shared pathogenic mechanisms and causal relationships between impaired kidney function and cognitive disorders. By understanding the mechanisms underpinning this relationship, we will be better able to prevent and treat dementia in this high-risk, vulnerable group. Clinical trials are required to determine if reduction of albuminuria may modify cerebrovascular and cognitive risk.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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DATA AVAILABILITY STATEMENT

Data from this manuscript may be shared with qualified investigators following FHS data sharing procedures.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. C.D.A. has received sponsored research support from Bayer AG and has consulted for ApoPharma.

REFERENCES

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl (2011)* 2022;**12**:7–11. https://doi.org/10.1016/j.kisu.2021.11.003
2. Coresh J, Astor BC, Greene T *et al.* Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003;**41**:1–12. https://doi.org/10.1053/ajkd.2003.50007
3. Kurella M, Chertow GM, Fried LF *et al.* Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol* 2005;**16**:2127–33. https://doi.org/10.1681/ASN.2005010005
4. Kurella Tamura M, Tam K, Vittinghoff E *et al.* Inflammatory markers and risk for cognitive decline in chronic kidney disease: the CRIC Study. *Kidney Int Rep* 2017;**2**:192–200. https://doi.org/10.1016/j.ekir.2016.10.007
5. Xu H, Garcia-Ptacek S, Trevisan M *et al.* Kidney function, kidney function decline, and the risk of dementia in older adults: a registry-based study. *Neurology* 2021;**96**:e2956–65
6. Bugnicourt JM, Godefroy O, Chillon JM *et al.* Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol* 2013;**24**:353–63. https://doi.org/10.1681/ASN.2012050536
7. Kelly D, Rothwell PM. Disentangling the multiple links between renal dysfunction and cerebrovascular disease. *J Neurol Neurosurg Psychiatry* 2020;**91**:88–97. https://doi.org/10.1136/jnnp-2019-320526
8. McGrath ER, Beiser AS, DeCarli C *et al.* Blood pressure from mid- to late life and risk of incident dementia. *Neurology* 2017;**89**:2447–54. https://doi.org/10.1212/WNL.0000000000004741
9. Kelly DM, Rothwell PM. Does chronic kidney disease predict stroke risk independent of blood pressure?: A systematic review and meta-regression. *Stroke* 2019;**50**:3085–92. https://doi.org/10.1161/STROKEAHA.119.025442
10. Toyoda K. Cerebral small vessel disease and chronic kidney disease. *J Stroke* 2015;**17**:31–37. https://doi.org/10.5853/jos.2015.17.1.31
11. Naganuma T, Uchida J, Tsuchida K *et al.* Silent cerebral infarction predicts vascular events in hemodialysis patients. *Kidney Int* 2005;**67**:2434–9. https://doi.org/10.1111/j.1523-1755.2005.00351.x
12. Yao H, Araki Y, Takashima Y *et al.* Chronic kidney disease and subclinical brain infarction increase the risk of vascular cognitive impairment: the Sefuri Study. *J Stroke Cerebrovasc Dis*

2017;**26**:420–4. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.002
13. Ito S, Nagasawa T, Abe M *et al.* Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res* 2009;**32**:115–21. https://doi.org/10.1038/hr.2008.27
14. Coresh J, Astor BC, McQuillan G *et al.* Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002;**39**:920–9. https://doi.org/10.1053/ajkd.2002.32765
15. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis* 2014;**63**:820–34. https://doi.org/10.1053/j.ajkd.2013.12.006
16. Levey AS, Stevens LA. Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010;**55**:622–7. https://doi.org/10.1053/j.ajkd.2010.02.337
17. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.
18. Jeerakathil T, Wolf PA, Beiser A *et al.* Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004;**35**:1857–61. https://doi.org/10.1161/01.STR.0000135226.53499.85
19. DeCarli C, Massaro J, Harvey D *et al.* Measures of brain morphology and infarction in the Framingham Heart Study: establishing what is normal. *Neurobiol Aging* 2005;**26**:491–510. https://doi.org/10.1016/j.neurobiolaging.2004.05.004
20. Wardlaw JM, Smith EE, Biessels GJ *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;**12**:822–38. https://doi.org/10.1016/S1474-4422(13)70124-8
21. Duering M, Biessels GJ, Brodtmann A *et al.* Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol* 2023;**22**:602–18. https://doi.org/10.1016/S1474-4422(23)00131-X
22. Pinheiro A, Demissie S, Scruton A *et al.* Association of apolipoprotein e ε4 allele with enlarged perivascular spaces. *Ann Neurol* 2022;**92**:23–31. https://doi.org/10.1002/ana.26364
23. Potter GM, Chappell FM, Morris Z *et al.* Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. *Cerebrovasc Dis* 2015;**39**:224–31. https://doi.org/10.1159/000375153
24. Satizabal CL, Beiser AS, Chouraki V *et al.* Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med* 2016;**374**:523–32. https://doi.org/10.1056/NEJMoa1504327
25. Seshadri S, Beiser A, Au R *et al.* Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-part 2. *Alzheimers Dement* 2011;**7**:35–52. https://doi.org/10.1016/j.jalz.2010.12.002
26. Jak AJ, Preis SR, Beiser AS *et al.* Neuropsychological criteria for mild cognitive impairment and dementia risk in the Framingham Heart Study. *J Int Neuropsychol Soc* 2016;**22**:937–43. https://doi.org/10.1017/S1355617716000199
27. American Psychatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Press Inc., 2000.
28. McKhann G, Drachman D, Folstein M *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 1984;**34**:939–44. https://doi.org/10.1212/WNL.34.7.939
29. Bachman DL, Wolf PA, Linn R *et al.* Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham study. *Neurology* 1992;**42**:115–9. https://doi.org/10.1212/WNL.42.1.115
30. Román GC, Tatemichi TK, Erkinjuntti T *et al.* Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. *Neurology* 1993;**43**:250–60. https://doi.org/10.1212/WNL.43.2.250
31. Elosua R, Ordovas JM, Cupples LA *et al.* Association of APOE genotype with carotid atherosclerosis in men and women: the Framingham heart study. *J Lipid Res* 2004;**45**:1868–75. https://doi.org/10.1194/jlr.M400114-JLR200
32. Hertzmark E, Pazaris MSD. The SAS Mediate Macro. https://cdn1.sph.harvard.edu/wp-content/uploads/sites/271/2012/08/mediate.pdf (7 June 2022, data last accessed).
33. Lin DY, Fleming TR, De Gruttola V Estimating the proportion of treatment effect explained by a surrogate marker. *Stat Med* 1997;**16**:1515–27. https://doi.org/10.1002/(SICI)1097-0258(19970715)16:13%3c1515::AID-SIM572%3e3.0.CO;2-1
34. Kobayashi M, Hirawa N, Yatsu K *et al.* Relationship between silent brain infarction and chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**:201–7. https://doi.org/10.1093/ndt/gfn419
35. Kelly DM, Li L, Rothwell PM. Etiological subtypes of transient ischemic attack and ischemic stroke in chronic kidney disease: population-based study. *Stroke* 2020;**51**:2786–94. https://doi.org/10.1161/STROKEAHA.120.030045
36. Liu B, Lau KK, Li L *et al.* Age-specific associations of renal impairment with magnetic resonance imaging markers of cerebral small vessel disease in transient ischemic attack and stroke. *Stroke* 2018;**49**:899–904. https://doi.org/10.1161/STROKEAHA.117.019650
37. Marini S, Georgakis MK, Chung J *et al.* Genetic overlap and causal inferences between kidney function and cerebrovascular disease. *Neurology* 2020;**94**:e2581–91. https://doi.org/10.1212/WNL.0000000000009642
38. Kobayashi M, Hirawa N, Morita S *et al.* Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. *Am J Kidney Dis* 2010;**56**:468–76. https://doi.org/10.1053/j.ajkd.2010.03.018
39. Penton AA, Lau H, Babikian VL *et al.* Chronic kidney disease as risk factor for enlarged perivascular spaces in patients with stroke and relation to racial group. *Stroke* 2020;**51**:3348–51. https://doi.org/10.1161/STROKEAHA.119.028688
40. Georgakis MK, Chatzopoulou D, Tsivgoulis G *et al.* Albuminuria and cerebral small vessel disease: a systematic review and meta-analysis. *J Am Geriatr Soc* 2018;**66**:509–17. https://doi.org/10.1111/jgs.15240
41. Jung KH, Stephens KA, Yochim KM *et al.* Heterogeneity of cerebral white matter lesions and clinical correlates in older adults. *Stroke* 2021;**52**:620–30. https://doi.org/10.1161/STROKEAHA.120.031641
42. Takae K, Hata J, Ohara T *et al.* Albuminuria increases the risks for both Alzheimer disease and vascular dementia in community-dwelling Japanese elderly: the Hisayama study. *J Am Heart Assoc* 2018;**7**:e006693. https://doi.org/10.1161/JAHA.117.006693
43. Scheppach JB, Coresh J, Wu A *et al.* Albuminuria and estimated GFR as risk factors for dementia in midlife and older age: findings from the ARIC study. *Am J Kidney Dis* 2020;**76**:775–83 https://doi.org/10.1053/j.ajkd.2020.03.015

44. Ekblad LL, Toppala S, Johansson JK *et al.* Albuminuria and microalbuminuria as predictors of cognitive performance in a general population: an 11-year follow-up study. *J Alzheimers Dis* 2018;**62**:635–48. https://doi.org/10.3233/JAD-170972
45. Kelly DM, Rothwell PM. Proteinuria as an independent predictor of stroke: systematic review and meta-analysis. *Int J Stroke* 2020;**15**:29–38. https://doi.org/10.1177/1747493019895206
46. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K *et al.*, Albuminuria reflects widespread vascular damage. The steno hypothesis. *Diabetologia* 1989;**32**:219–26. https://doi.org/10.1007/BF00285287
47. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004;**5**:347–60. https://doi.org/10.1038/nrn1387
48. Marnane M, Hsiung GY. Could better phenotyping small vessel disease provide new insights into alzheimer disease and improve clinical trial outcomes? *Curr Alzheimer Res* 2016;**13**:750–63. https://doi.org/10.2174/1567205013666160222112634
49. Weller RO, Subash M, Preston SD *et al.* Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. *Brain Pathol* 2008;**18**:253–66. https://doi.org/10.1111/j.1750-3639.2008.00133.x
50. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. *Vasc Health Risk Manag* 2008;**4**:363–81.
51. Sedaghat S, Ji Y, Hughes TM *et al.* The association of kidney function with plasma amyloid-β levels and brain amyloid deposition. *J Alzheimers Dis* 2023;**92**:229–39. https://doi.org/10.3233/JAD-220765
52. Shima H, Ishimura E, Naganuma T *et al.* Cerebral microbleeds in predialysis patients with chronic kidney disease. *Nephrol Dial Transplant* 2010;**25**:1554–9. https://doi.org/10.1093/ndt/gfp694
53. Laible M, Horstmann S, Möhlenbruch M *et al.* Renal dysfunction is associated with deep cerebral microbleeds but not white matter hyperintensities in patients with acute intracerebral hemorrhage. *J Neurol* 2015;**262**:2312–22. https://doi.org/10.1007/s00415-015-7840-2
54. Khatri M, Wright CB, Nickolas TL *et al.* Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). *Stroke* 2007;**38**:3121–6. https://doi.org/10.1161/STROKEAHA.107.493593
55. Weiner DE, Gaussoin SA, Nord J *et al.* Cognitive function and kidney disease: baseline data from the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis* 2017;**70**:357–67. https://doi.org/10.1053/j.ajkd.2017.04.021

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