Association of kidney function and brain health: A systematic review and meta-analysis of cohort studies

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ABSTRACT

Objective: This study aimed to evaluate the bidirectional association between the kidney dysfunction and the brain health, including structural and functional abnormalities.

Design: Systematic review and meta-analysis with network meta-analysis for outcomes with different estimated glomerular filtration rate (eGFR) ranges.

Data sources: PubMed, Embase database, Cochrane library and Web of Science (up to Dec. 2021).

Eligibility criteria for selecting studies: Longitudinal studies that provided evidence of the impact of kidney function estimated from eGFR and urine albumin-to-creatinine ratio (UACR) or chronic kidney disease (CKD) on structural and functional brain abnormalities, and those that provided evidence of the opposite relationship. Studies with study population mean age under 18 years old were excluded.

Main outcome measures: Two independent reviewers screened the included studies, extracted the data, and assessed the risk of bias. We performed a random-effects meta-analysis and a network meta-analysis for outcomes with compatible data. We assessed the risk of bias using the Newcastle–Ottawa Quality Assessment Scale criteria (NOS). Subgroup and sensitivity analyses were conducted to explore heterogeneity in the meta-analyses. Inconsistency analyses using the node-splitting method were performed to confirm the results of network meta-analysis.

Results: A total of 53 studies with 3037,357 participants were included in the current systematic review. Among these, 16 provided evidence of structural brain abnormalities, and 38 provided evidence of cognitive impairment and dementia. Analysis of evidence of categorical kidney function showed a positive association between kidney dysfunction and cerebral small vessel disease (cSVD) (relative risk (RR) 1.77, 95% confidence interval (CI) 1.40–2.24, $I^2 = 0.0\%$), but such results were not found in the analyses of evidence where the kidney function was measured as a continuous variable. Meanwhile, analysis of 28 prior longitudinal studies with 194 compatible sets of data showed that the worse kidney function as categorical variables was related to a greater risk of global brain cognitive disorder (RR 1.28, 95% CI 1.20–1.36, $I^2 = 82.5\%$).

Conclusions: In this systematic review and meta-analysis, we found a positive association between CKD and functional brain disorders. However, the relationship between the kidney dysfunction and structural abnormalities in the brain remains controversial. As for the opposite relationship, structural brain abnormalities, especially cerebral microbleeds and silent infarction, but not functional brain abnormalities, are associated with worse renal function. In addition, a higher UACR, but not a lower eGFR, was associated with a higher risk of Alzheimer's disease and vascular dementia.

1. Introduction

Brain health disorders, including structural and functional brain abnormalities and chronic kidney disease (CKD) are growing public health issues. Neurological disorders were the leading cause of disability-adjusted life years (DALYs, 276 million) and the second leading cause of death (9 million) in 2016 globally according to the Global Burden of Diseases study (GBD, Neurology Collaborators, 2016, 2019). Structural brain abnormality, also known as cerebral small vessel disease (cSVD) (Jokinen et al., 2020), is a frequent cause of stroke and the primary subtype of vascular cognitive impairment. The neuroimaging features of SVD include small subcortical infarcts, lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), microbleeds, and brain atrophy (Wardlaw et al., 2013; van Harten et al., 2006). Functional brain abnormalities, including Alzheimer's disease, vascular dementia, and other dementias, are among the largest contributors to neurological DALYs. The age-standardized incidence and mortality rates per 100,000 population were 103.83

(95% UI, 87.93–118.87) and 23.32 (95% UI, 5.66–61.31), respectively, for dementia in 2019 (Gao and Liu, 2021). Approximately 50 million people worldwide were living with dementia in 2018, and this number will more than triple to 152 million by 2050 (World Health Organization, 2012).

CKD is usually characterized by the presence of persistent albuminuria or an estimated glomerular filtration rate (eGFR) of < 60 mL/min/ 1.73 m^2. Notably, the DALYs due to impaired renal function nearly doubled from 1990 to 2019, reaching 76.5 million, with 3.16 million deaths globally in 2019 (Roth et al., 2020). CKD is increasingly recognized as an elevated risk factor for neurological disorders. Research has shown that the prevalence of brain health disorders is high (approximately 50%) in advanced CKD (Murray et al., 2006; Naganuma et al., 2011; Sarnak et al., 2013; Yokoyama et al., 2005), and microvasculopathy has been proposed to link these two conditions (Ito et al., 2009; Knopman, 2010; Weiner, 2008). Therefore, it is vital to target high-risk patients, define a window of opportunity to prevent CKD-induced brain health disorders, and achieve better surveillance.

No consensus has been reached regarding the relationship between CKD and structural or functional brain dysfunction. A study by Vilar et al. supported a positive association between kidney function and the incidence of cSVD (Vilar-Bergua et al., 2016), but these results were disputed in other studies (Aggarwal et al., 2019; Vemuri et al., 2017). Nevertheless, despite reports (Tamura et al., 2011) that worse renal function is a risk factor for dementia and cognitive impairment, another study (Helmer et al., 2011) also identified a null effect. Given this conflicting evidence, the relationship between CKD and structural and functional disorders in the brain remains unclear and requires further investigation. Here, we conducted a systematic review and meta-analysis of published research to elucidate these associations to provide an up-to-date understanding and refine primary prevention strategies.

2. Methods

2.1. Protocol registration

We registered the protocol of this systematic review with PROSPERO (CRD42021293834).

2.2. Study inclusion

The search for the bidirectional relationship between kidney function and brain health was conducted in the PubMed, Embase, Cochrane Library, and Web of Science databases to identify all relevant studies published up to Dec. 2021. Different types of cSVD, cognitive impairment, and dementia as well as their relationship with CKD were investigated in detail. This analysis included four cSVD: brain atrophy, WMH, cerebral microbleeds, and lacunar infarctions. Functional brain abnormalities were referred to as cognitive impairment and dementia, including all-cause dementia, Alzheimer's disease, and vascular dementia. Additional pertinent articles were supplemented by inspecting the references of the included articles. "This study was conducted according to the guidelines set out by Meta-analysis of Observational Studies in Epidemiology (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Knobloch et al., 2011).

2.3. Inclusion and exclusion criteria

Studies meeting the following inclusion criteria were included: (1) an original article published in English with participants' mean age over 18 years, (2) defined kidney function using eGFR, urine albumin-to-creatinine ratio (UACR), creatinine clearance (CCI) or other clearly defined measurements, or used physical diagnosis of kidney function (e. g., ICD-9), (3) defined cSVDs or cognitive impairment and dementia

clearly, (4) measured the structural brain abnormalities using magnetic resonance imaging (MRI), regardless of scanner resolution (1.5 T, 3 T, 7 T), automated assessment/visual assessment, or sequence of scan, (5) cognitive impairment and dementia were identified using generally agreed tests (including the Montreal Cognitive Assessment, MoCA; Mini-Mental State Examination, MMSE; Clinical Dementia Rating score, CDR; Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV etc.), (6) provided quantitative measures of the bidirectional association between kidney function with cSVDs and cognitive impairment and dementia, and (7) prospective cohort epidemiological study designs. The exclusion criteria were as follows: (1) publication was a review, case report, animal study, or letter to the editor, (2) publication did not clearly define clinical outcomes, (3) duplicated data, and (4) the mean age of the study population was under 18 years. For the current analysis, the bidirectional relationships between kidney function and cSVDs, cognitive impairment, and dementia were measured using odds ratios (ORs), relative risks (RRs), incidence rate ratios (IRRs), or hazard ratios (HRs) with 95% confidence intervals (CIs).

2.4. Data extraction and quality assessment

Two investigators (XYT and YPH) independently extracted the data from the enrolled studies using the same method concerning study quality, population characteristics, basic diseases, and outcomes. CKD was defined as eGFR < 60 mL/min per 1.73 m^2 or CCl < 60 mL/min, or UACR > 30 mg/g. Dementia and cognitive impairment were defined based on cognitive tests or related guidelines (Table 1). The data synthesized in our study are available directly from published articles or supplementary materials, and no primary data were collected.

The risk of bias among the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Stang, 2010). Following the NOS guidelines, we rated the quality of the studies by awarding stars in each domain. XYT and YPH independently assessed the risk of bias for each study, which was cross-checked using JBZ and MAC. In case of disagreement, the investigators discussed with other authors to arrive at a consensus. The quality assessment results were scored on a scale of 0–9.

2.5. Statistical analysis

Heterogeneity between studies was evaluated using the I^2 metric and the variance between studies by Tau^2. Random-effects models were used if $I^2 > 50\%$, while the fixed-effects models were used if $I^2 \leq 50\%$. When necessary, we transformed (Qin et al., 2021; Yang et al., 2018) effect metrics derived from different studies to allow for pooled analysis. In this study, we considered OR, RR, IRR, and HR as RR to conduct pooled analyses of bidirectional associations between kidney function and brain health across all the included studies. If the studies had both unadjusted and covariate-adjusted RRs, the latter was selected. For continuous renal function data, we collected estimates and their standard errors (SEs) reported as "per 10 mL/min/1.73 m^2 decrease" when measured by eGFR and "per mg/g increase" when measured by UACR.

To define potentially confounding factors and risk of bias, we conducted subgroup and sensitivity analyses. Sensitivity analyses were conducted to assess the influence of each result on the pooled estimate. The Egger's asymmetry test (Egger et al., 1997) was conducted to evaluate potential publication bias. According to the Cochrane Handbook version 5.1.0 (Cumpston et al., 2019), as a rule of thumb, tests for funnel plot asymmetry should be used only when enough studies are included in the analysis. Thus, in the pooled meta-analyses of evidence with a small number of included studies, the Egger's asymmetry test was not applied. P values were two-tailed, and statistical significance was set at $P < 0.05$. Statistical analyses were performed using Stata version 12.0 (Stata Corporation, College Station, TX, USA).

For the network meta-analysis, studies were included if they provided kidney function measurements as categorical variables. To

Table 1
Study characteristics and main results from studies assessing the association between kidney function and brain health.

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
1	Kurella	2005	4 years	United States	3034	74 (3)	none	CKD was defined as an eGFR < 60 mL/min per 1.73 m^2. Participants with CKD were stratified into two eGFR strata: eGFR 45–59 mL/min per 1.73 m^2 and eGFR < 45 mL/min per 1.73 m^2.	/	Cognitive impairment as a 3MS score < 80 or a decline in 3MS > 5 points at 2 or 4 yr of follow-up among participants with baseline 3MS scores ≥ 80.	A significantly increased risk for cognitive impairment associated with CKD. The risk for impairment varied by the severity of CKD, such that those with a lower eGFR had a greater risk for cognitive impairment but was present even in those with milder levels of CKD.
2	Khatri	2007	6.4 years	United States	615	≥ 55	none	Divided CCl and eGFR into 3 categories: moderate– severe CKD (15–60 mL/min), mild CKD (60–90 mL/min), and normal (>90 mL/min).	All images were acquired using a 1.5-T MRI system (Philips Medical Systems, Best, The Netherlands). White matter hyperintensity volumes (WMHV) were determined using fluid-attenuated inversion recovery images.	/	CKD is associated with a greater burden of WMH and adds to the growing body of evidence that kidney disease is an important, independent risk factor for cerebrovascular disease.
3	Slinin	2008	5 years	United States	5529	≥ 65	none	The category of eGFR between 45 and 59 mL/min per 1.73 m^2 was defined as mild CKD and eGFR less than 45 mL/min per 1.73 m^2 as moderate CKD.	/	Incident cognitive impairment was defined as having a 3MS score of less than 80 or a decline of 5 points or more on the follow up 3MS.	Did not find evidence of an independent association between mild to moderate CKD and likelihood of global cognitive impairment or risk of cognitive decline in older men.
4	Buchman	2009	3.4 years	United States	886	80.6 (7.46)	none	Kidney function was dichotomized into not impaired if eGFR ≥ 60 mL/min/1.73 m^2 vs impaired if eGFR < 60 mL/min/1.73 m^2.	/	Dementia required a history of cognitive decline and evidence of impairment in at least 2 cognitive domains.	Impaired kidney function is associated with a more rapid rate of cognitive decline in old age.
5	Etgen	2009	5 years	German	3679	67.7	none	Defined mild CKD as Ccr between 45 and 59 mL/min/1.73 m^2 and moderate-to-severe CKD as Ccr < 45 mL/min/1.73 m^2	/	Levels of Blessed Information Memory Concentration Scale (6CIT) between 0 and 7 points are considered normal levels and scores > 7 is consistent with cognitive impairment.	In a general elderly population, moderate-to-severe impaired renal function is independently associated with new cognitive impairment after the 2-year follow-up.
6	Bouchi	2010	3.9 years	Finland	366	64 (10)	type 2 diabetes	Normo-, micro- and macroalbuminuria were defined as an ACR < 30, 30–299 and ≥ 300 mg/g, respectively.	SCI was defined by cranial MRI examinations as an area of low-signal intensity measuring at least 3 mm on T1-weighted images, which was also visible as a hyperintense lesion on T2-weighted images	/	SCI may be a predictor of the development and progression of nephropathy in Japanese patients with type 2 diabetes.
7	Kobayashi	2010	2 years	Japan	142	64.7 (12.8)	chronic kidney disease	eGFR was classified in the following ranges: 30–59 mL/min/1.73 m^2 (stage 3), 15–29 mL/min/ 1.73 m^2 (stage 4), and < 15 mL/min/1.73 m^2 (stage 5)	SBI was defined as a focal area ≥ 3 and < 20 mm in diameter in both T1- and T2-weighted scans that was visible as a low-intensity	/	SBI was an important independent prognostic factor for the progression of kidney disease in patients with CKD.

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
									area on the T1-weighted image and a high-intensity area on the T2-weighted image.		
8	Oksala	2010	12 years	Finland	378	70.7 (7.6)	stroke	Patients were divided into those with normal or mildly impaired eGFR ($\geq$60 mL/min/1.73 m^2) and those with low to moderate eGFR (30–60 mL/min/1.73 m^2)	WMLs were rated on proton density-weighted images in accordance with the Leukoaraiosis and Disability in the Elderly rating as no to mild, moderate, and severe degree.	/	Cerebral small vessel disease is connected to kidney function as estimated by eGFR in patients hospitalized for acute stroke.
9	Uzu	2010	7.5 years	Japan	608	30–75 years	type 2 diabetes	The ACR level in each measurement was classified as follows: < 30 mg/g Cr, normoalbuminuria; 30–299 mg/g Cr, microalbuminuria; $\geq$ 300 mg/g Cr, overt proteinuria. ESRD was defined as the initiation of long-term renal replacement therapy.	Infarcts were defined as focal lesions of at least 3 mm in diameter with low signal intensity on T1-weighted images and hyperintensity on T2-eighted images.	/	The presence of SCI increased the risk of ESRD.
10	Wang	2010	4 years	China	1243	58.8 (9.6)	none	eGFR was calculated using the equation developed from data based on Chinese patients with CKD. eGFR as categorical variable: $\geq$ 90 (reference), 60–89, and 30–59 mL/min/1.73 m^2.	/	Mini-Mental State Examination (MMSE) was used to evaluate the cognitive function. The MMSE score ranges from 0 to 30, with higher scores denoting better cognitive function.	Kidney function is associated with cognitive decline in Chinese population, and the relation is independent of urinary albumin excretion.
11	Helmer	2011	7 years	France	7839	73.9 (5.4)	none	Initial eGFR was considered both as continuous variable (for 10 additional units of eGFR) and categorical variable (<45, [45–60] vs $\geq$60). eGFR decline was expressed as the annual slope in mL/min/1.73 m^2/y, and considered both as continuous variable (for 1 additional unit of eGFR decline) and categorical variable (decline of more than 4 mL/min/1.73 m^2/y vs less, corresponding to the decile of the distribution). Proteinuria was defined as an albumin/creatinine ratio (ACR) > 30 mg albumin/g creatinine, a proteinuria > 300 mg/g was retained in the absence of leukocyturia.	/	Cognitive function was assessed using MMSE. Etiology was based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for Alzheimer disease (AD) and the National Institute of Neurological Disorders and Stroke– Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia.	This analysis failed to find any increased risk of dementia associated with low eGFR, except a borderline significant increased risk of DVC.
12	Sasaki	2011	5 years	Japan	222	80.5 (7.6)	none	CKD was defined as a condition with an eGFR less than 60 mL/min per 1.73 m^2 or continuous presence of kidney impairment.	/	The Mini-Mental State Examination (MMSE) was used to assess general cognitive function for all participants.	The results demonstrated a relationship between impaired kidney function and cognitive decline.
13	Tamura	2011	3.8 years	United States	19399	64.1	none	eGFRs were categorized as $\geq$ 90, 60-< 90, 45-< 60, and < 45 mL/min/1.73 m^2. UACR was categorized as <	/	Scores on the 6-Item Screener range from 0 to 6. The incident cognitive	Albuminuria and low eGFR were complementary, but not

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
								10, 10-< 30, 30-< 300, and ≥ 300 mg/g.		impairment was defined as a score ≤ 4.	additive, risk factors for the development of cognitive impairment.
14	Cheng	2012	2 years	China	111147	57.8	none	Inpatients with at least one CKD diagnosis or outpatients with twice CKD service claims were included in the CKD cohort.	/	Dementia with no specific definition mentioned.	Patients with CKD are at a significantly higher risk of dementia than those without CKD.
15	Feng	2012	4 years	Singapore	1315	65.6 (7.2)	none	CKD was defined as an eGFR less than 60 mL/min per 1.73 m^2.	/	The MMSE was administered to measure global cognitive function. Lower MMSE scores (maximum score 30) indicate poorer performance. Cognitive decline at follow-up assessment was defined as a drop of 2 points or more from baseline.	Impaired kidney function and mild to moderate CKD were found to be significantly associated with cognitive and functional declines in older adults.
16	Ohare	2012	6 years	United States	2968	74 (70–80)	none	Three exposure constructs were defined to capture dynamic changes in eGFR over time: eGFR, eGFR trajectory, and short-term variability of eGFR.	/	Diagnoses of incident dementia were then assigned at consensus diagnostic conferences according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.	In community-dwelling older adults followed prospectively for the development of clinical dementia over a median of 6 years, measures of kidney disease severity and progression were not strongly associated with dementia risk.
17	Sajjad	2012	2 years	United States	1764	74 (72.3–75.8)	none	An eGFR < 60 mL/min per 1.73 m^2 was defined as chronic kidney disease. The cut-off value was defined as ACR ≥ 5 mg/g.	/	A global composite score was calculated by averaging the z scores from the six tests: TICS, East Boston Memory Test Immediate Recall, EBMT, verbal fluency, TICS 10-word list delayed recall and digit span backward.	A urinary ACR ≥ 5 mg/g, a level not traditionally considered clinically significant, was independently associated with more rapid decline in cognitive functioning over 4–6 years of follow-up in older community-dwelling women.
18	Davey	2013	5 years	United States	590	62.1	none	Renal impairment was defined as an eGFR < 60 mL/ min/1.73 m^2 and clinically relevant change in renal functioning was defined as a decline > 3 mL/min/1.73 m^2/year.	/	Clinical diagnosis of dementia was based on cognitive data and medical records and a multidisciplinary dementia review for each patient using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.	Early detection of mild to moderate kidney disease is an important public health concern with regard to cognitive decline.
19	Kuriyama	2013	5 years	Japan	291	66.9 (6.1)	none	CKD was defined as an eGFR < 60 mL/min per 1.73 m^2. EGFR was analyzed as a categorical variable: ≥ 60 and < 59 mL/min/1.73 m^2.	T2-weighted and FLAIR images were used for the evaluations of the DWLs, which were graded semi-	MMSE is considered insensitive as a global screening test for mild to	CKD was found to be a risk factor for DWL and DWLP with lower cognitive scale scores, and measuring

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
									quantitatively from Grade 0 (none) to Grade 3 (severe).	moderate cognitive impairment	eGFR is also a surrogate marker for DWL and associated cognitive impairment.
20	Darise	2014	5.3 years	United States	3907	74.6	none	Cystatin C– based estimated glomerular filtration rate (eGFR$_{cys}$) was used as the measure of kidney function. Kidney function was classified as eGFR$_{cys}$ of less than 60, 60–89.9, or $\geq$ 90 mL/minute/1.73 m^2.	/	Cognitive function was measured using the Modified Mini-Mental State (3MS) Examination and the Digit Symbol Substitution Test (DSST). Incident cognitive impairment was defined as a score of less than 80 on the 3MS Examination during 2 consecutive visits, a score of less than 80 on the 3MS Examination and then amassing score on the next visit, or missing 3MS Examination scores for 4 consecutive years.	Kidney function is associated with change in cognitive function over time in older adults.
21	Miwa	2014	7.5 years	Japan	600	68 (8.3)	none	CKD was defined as eGFR < 60 mL/min/1.73 m^2. eGFR was divided into 3 categories: moderate-severe CKD (<45), mild CKD (45–59), and no CKD ($\geq$60 mL/min).	/	The Mini-Mental State Examination (MMSE) Dementia Rating (CDR) scale and the Clinical were used in all patients to screen suspected cases of cognitive decline. Clinically significant cognitive impairment was defined as MMSE score < 24 or a decline $\geq$ 1.5 SD of change scores. Dementia was diagnosed according to DSM-III-R.	CKD was independently related to incident dementia in patients with vascular risk factors. CKD per se can be considered as a marker of an individual's vulnerability to the increased risk of dementia and therefore could be a potential therapeutic target for prevention of dementia.
22	Auriel	2016	1 year	German	368	67 (9.9)	stroke	Participants were subdivided according to their renal function: not impaired if CCl $\geq$ 60 mL/min vs impaired or CKD if CCl < 60 mL/min (defined by National Kidney Foundation guidelines).	Ischemic infarct identification, white matter hyperintensities score, diffusion tensor imaging (DTI) analysis, tissue segmentation and volumetric measure of the hippocampi, hippocampi MD analysis were using MRI.	Cognitive impairment before the stroke was determined as Informant Questionnaire on Cognitive Decline in the Elderly score $\geq$ 3.3. Patients with cognitive impairment were diagnosed with either mild cognitive impairment (MCI) or dementia (DSM-IV-TR).	Decreased renal function is associated with radiologic markers of CSVD and loss of white matter integrity as well as hippocampal volume, and found to be a predictor for lower performance in cognitive tests 2 years following stroke/TIA.
23	Barzilay	2016	3.5 years	United States	502	62.2 (5.7)	diabetes	Albuminuria was defined as $\geq$ 30 mg albumin/g creatinine. eGFR levels at baseline were categorized into $\geq$ or < 90 mL/min/1.73 m^2. Participants with albuminuria at baseline and on all the follow-up urine tests were considered to have persistent albuminuria. Those with no albuminuria at baseline or on any of	T1-weighted volumetric MRI scans were first preprocessed according to a standardized protocol for alignment, removal of extra-cerebral tissue, and segmentation of brain parenchyma into gray	/	Albuminuria was not associated with significant independent differences in brain volume measurements cross-sectionally or prospectively as compared with those without albuminuria.

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
								the follow-up urine tests were considered to have no albuminuria. Participants with no albuminuria at baseline who developed albuminuria on at least one follow-up test were considered progressors. Those with albuminuria at baseline but none on follow-up were considered remitters.	matter, white matter, and cerebrospinal fluid.		
24	Gronewold	2016	2 years	German	120	63.6	none	Chronic kidney disease stages 3–5 with no specific definition mentioned.	/	In order to obtain a score for global cognition, z-scores were calculated for all 10 neuropsychological tests on the basis of norm values generated in the control group.	Cognitive performance did not decrease during the observation period in CKD patients over a 2-year follow-up.
25	Peng	2016	14 months	China	500	59.7 (9.94)	ischemic stroke	Impaired kidney function was defined as eGFR < 60 mL/min/1.73 m^2. Progression of CKD is defined as a drop in eGFR category accompanied by a 25% or greater drop in eGFR from baseline.	CMB were defined as small foci of signal loss or hypointensity on T2 * -weighted MRI. Patients with ≥ 1 deep or infartentorial microbleeds were counted as having deep or infratentorial microbleeds regardless of whether they had lobar microbleeds.	/	Decreased eGFR was significantly associated with a higher presence of CMB in patients with ischemic stroke.
26	Shima	2016	2.3 years	Japan	404	60.2 (16.4)	chronic kidney disease	The eGFR values were stratified into the following ranges according to the KDIGO classification and staging system: ≥ 90 mL/min/1.73 m^2, 60–89 mL/min per 1.73 m^2, 30–59 mL/min per 1.73 m^2, 15–29 mL/min per 1.73 m^2, and 15 mL/min per 1.73 m^2.	MBs were defined as focal areas of signal loss on T2 * -weighted images without a history of stroke or transient ischemic attack.	/	The presence of MBs is a strong predictor for composite outcome, which included poor kidney outcome and CVD events, in patients with predialysis CKD.
27	Tamura	2016	6.1 years	United States	3883	57.7 (11.0)	none	Participants met age-based estimated glomerular filtration rate (eGFR) criteria: 20–70, 20– 60, and 20–50 mL/min/1.73 m^2 for ages 21–44, 45–64, and 65–74 years, respectively.	/	Cognitive impairment was defined as 3MS scores < 85, < 80, and < 75 for participants aged younger than 65, 65–79, and 80 years or older, respectively.	Among adults with CKD, cognitive impairment was not significantly associated with a higher risk of progression of CKD after accounting for traditional risk factors.
28	van Overbeek	2016	2 years	Netherlands	89	64.9 (11.1)	lacunar stroke	eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.	CMBs were defined as punctate hypointense lesions on gradient-echo images with a diameter < 10 mm, in lobar, deep and infratentorial regions.	/	Found an independent association between lower eGFR and CMBs progression after two years of follow-up in lacunar stroke patients.
29	Vilar-Bergua	2016	1 month	Spain	975	64 (59–67)	none	The absence of microalbuminuria was defined as albumin:creatinine ratio > 21 mg/g in men and > 30 in women. Patients were dichotomized using the cut-off value of 60 mL/min/1.73 m^2 to classify those with chronic kidney disease (CKD).	CSVD: (1) ≥ 1 lacunes; (2) WMH rated at FLAIR sequences and scoring 3 points at periventricular areas or 2–3 points in the deep WM, according to the Fazekas scale; (3) moderate	/	The UACR was independently associated with the presence of an increasing number of different CSVD markers, whereas kidney function measured by the

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
									to extensive (>10) basal ganglia EPVS assessed on T2-weighted MRI; and (4) ≥ 1 deep brain microbleeds		creatinine-estimated GFR was not.
30	Bai	2017	3.3 years	China	247	83.5 (2.6)	none	All participants had an eGFR > 30 mL/min/1.73 m^2. Early-stage CKD was defined as an eGFR of 30–59 mL/min/1.73 m^2. eGFR was calculated as three categories: ≥ 60 mL/min/1.73 m^2, 45–59 mL/min/1.73 m^2, and 30–44 mL/min/1.73 m^2. eGFR as a continuous variable (per 10 mL/min/1.73 m^2 increase).	/	Cognitive function was assessed with the Mini-Mental State Examination (MMSE) at both the baseline and annual visits. The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function.	Early-stage CKD is associated with cognitive decline in an oldest-old Chinese population.
31	Ben Assayag	2017	2 years	Israel	575	67.4 (9.7)	stroke	Participants whose eCCl < 60 mL/min were considered as having CKD.	Ischemic infarct identification, white matter hyperintensities score, diffusion tensor imaging (DTI) analysis, tissue segmentation and volumetric measure of the hippocampi, small vessel disease (chronic lacunar infarcts, cerebral microbleeds and enlarged perivascular spaces) were using MRI.	Patients with cognitive impairment were diagnosed as having either mild cognitive impairment (impaired on at least 1 cognitive domain on the Montreal Cognitive Assessment score) or dementia (DSM IV-TR).	T2DM and impaired renal function are independently associated with abnormal brain structure, as well as poorer performance in cognitive tests, 2 years after stroke. T2DM and lower eCCl have an independent and additive effect on brain atrophy and the risk for cognitive decline.
32	Chen	2017	5.4 years	China	33654	75.4	none	a 20% annual eGFR change was used as the cutoff point of renal function progression. The percentage change of renal function per year was categorized into 3 groups: "severe decline" (decline in the eGFR with a > 20% decrease per year), "stable" (an increase or decrease of ≤ 20% per year in the eGFR), and "increase" (rise in the eGFR with a > 20% increase per year).	/	The SPMSQ scores of cognitive function as follows: a score with 0–2 errors indicates intact cognition, 3–4 errors indicates mild impairment, 5–7 errors indicates moderate impairment, and 8–10 errors indicates severe impairment. The primary end point of cognitive deterioration was ≥ 3 errors among the elderly on the SPMSQ.	Severe eGFR decline is a significant factor associated with cognitive deterioration in a community elderly population.
33	Gronewold	2017	2 years	German	54	65.0 (11.2)	none	Control patients were included when having an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 for ≥ 3 months. CKD stages 3–5 with no specific definiton mentioned.	/	The summary score of global cognitive performance was formed by computing mean values of ten standardized tests z-scores.	eGFR was not associated with cognitive decline.
34	Vemuri	2017	3 years	United States	240	69 (9)	chronic kidney disease	Divided eGFR into three categories: eGFR < 45 (moderate to severe CKD), 45–59 (mild CKD), or > 60 (minimal or no CKD) mL/min/1.73 m^2.	Cortical thickness, hippocampal volume, brain infarcts, white matter hyperintensities and microhemorrhages using MRI.	/	Both eGFR and UACR as biomarkers of kidney disease were associated with brain changes, even after accounting for vascular risk factors.
35	Li	2018	67 months	China	216	54.2	type 2 diabetes	A UAER of < 20 mg/minute was normal, a UAER of ≥ 20 to < 200 mg/	/	Mini-Mental State Examination (MMSE) and	A positive correlation between cognitive

8

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
								minute was considered to indicate microalbuminuria, and a UAER of $\geq$ 200 mg/minute was consistent with macroalbuminuria.		Montreal Cognitive Assessment Scale (MoCA) assessments were performed. The maximum MoCA score is 30 points. A score of $\leq$ 26 points is considered to indicate cognitive impairment.	impairment and renal microangiopathy in patients with T2DN.
36	Sedaghat	2018	5.2 years	Iceland	2671	74.7 (4.9)	none	Large eGFR was defined as decline as > 3 mL/min per 1.73 m^2/year. Log base 2 transformed values was used to obtain values per 2-fold higher urine ACR. Incident albuminuria was defined as urine ACR > 30 mg/g at follow-up among individuals with urine ACR < 30 mg/g at baseline.	Cerebral microbleeds were defined as focal areas of signal void within the brain parenchyma visible on T2 * -weighted gradient-echo type echo planar scans. New lesions were defined as appearance of MRI-detected infarcts or microbleeds in the follow-up scans that were not present in the baseline images. White matter hyperintensity volume progression was defined as percentage change in the volume of white matter hyperintensity between 2 visits.	/	Changes in kidney measures over time are associated with risk of subclinical brain pathology in an elderly population.
37	Takae	2018	10 years	Japan	1562	71	none	UACR was categorized as normoalbuminuria (UACR <30 mg/g) and albuminuria (UACR $\geq$30 mg/g). UACR in the normoalbuminuria range was further divided into the following tertile categories: low-normal ($\leq$6.9 mg/g), medium-normal (7.0–12.7 mg/g), and high-normal (12.8– 29.9 mg/g). Low eGFR was defined as eGFR < 60 mL/min per 1.73 m^2.	/	The guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, were used to define the diagnosis of dementia. AD was diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and VD was diagnosed using the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences.	Albuminuria was significantly associated with higher risk for the development of all-cause dementia, AD, and VD. Subjects with a lower eGFR level tended to have a higher risk of incident VaD. Albuminuria and low eGFR mutually increased the risk of VaD, but not AD.
38	Agarwal	2019	3.7 years	United States	3017	62.8 (10.8)	lacunar stroke	The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR.	Intracerebral hemorrhage	/	Baseline eGFR of < 60 mL/min (versus $\geq$60 mL/min) was not associated with intracerebral hemorrhage.

Table 1 (continued)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
39	Fandler-Hofler	2019	15 months	Australia	101	60.2 (10.7)	stroke	CKD: either eGFR < 60 mL/min/1.73 m^2 and/or albuminuria/ACR > 30 mg/g). High-risk RD patients were defined as eGFR < 45 mL/min/1.73 m^2, eGFR < 60 mL/min/1.73 m^2 with albuminuria/ACR > 30 mg/g or any GFR with albuminuria/ACR > 300 mg/g	Follow-up MRI scans were specifically analysed with regard to changes in cerebrovascular lesions (such as new infarcts, lacunes and WMH progression). WMH were rated according to the Fazekas scale. Progression of WMH was defined the as occurrence of new white matter hyperintensities or transition to a higher Fazekas scale score	/	Early renal dysfunction was found in a quarter of recent small subcortical infarcts patients and associated with WMH severity, but not cerebral small vessel disease progression.
40	Gabin	2019	15 years	Norway	48508	49.5 (16.7)	none	Categorical cutoffs with eGFR: > 90, 60–89.9, 30–59.9, and < 30 mL/min/1.73 m^2. ACR was also examined categorically as quartiles: 0–0.53,0.54–0.87,0.88–1.77, and ≥ 1.78 mg/mmol.	/	The ICD-10 classification system was thereafter applied for diagnoses of AD, VD, a mixture of AD and VD.	Vascular mechanisms may affect both kidney and brain as an association between MA, VaD, and Combined AD/VaD was found. However, eGFR was not significantly associated with dementia independent of DM or HTN.
41	Koop-Nieuwelink	2019	11.6 years	Netherland	5993	69.0 (8.2)	none	First, the eGFR was calculated based on creatinine (eGFRcr). Second, the eGFR was calculated based on cystatin-C (eGFRcys). Third, the eGFR was calculated based on both creatinine and cystatin-C (eGFRcrcys).	/	All patients finished MMSE. Dementia was diagnosed using DSM-III-R, AD was diagnosed using NINCDS-ADRDA and VD was diagnosed using NINDS-AIREN.	Impaired kidney function was associated with a higher risk of stroke, but not with dementia during 12 years of follow-up.
42	Chen	2020	2 years	China	244	71.6 (4.9)	none	A participant would be classified as having KD if he/she had either GFR< 60 mL/min/1.73 m^2 or presence of proteinuria (≥1 +).	/	Global cognitive function was assessed by MoCA-T, in which a total score ranged from 0 to 30 and a higher score indicates better cognitive function.	Presence of both kidney dysfunction and cortical thinning had detrimental effects on several cognitive domains in non-demented, community dwelling older adults.
43	Guerville	2020	5 years	France	1334	75 (71–78)	none	The cutoff used for the binary variable was 60 mL/min/1.73 m^2 because it is part of the definition of CKD.	/	The composite Z-score of MAPT, the CDR score and conversion to dementia were used as cognitive outcomes.	The results did not indicate that a mild to moderate renal insufficiency to be associated with brain imaging features of AD, and the results did not support the involvement of AD mechanisms in cognitive and functional decline associated with CKD.
44	Hiramatsu	2020	3 years	United Kingdom	468399	75.1	none	Patients with CKD at stages 3–5 were identified based on two consecutive measurement of eGFR < 60 mL/ min/1.73 m^2, > 3 months apart. eGFR	/	Dementia here includes Alzheimer's disease, vascular dementia and other types of dementia such as	A co-occurrence of the detection of CKD and dementia in real-world clinical practice in the

(continued on next page)

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
								45–60 mL/min/1.73 m^2 (namely, CKD stage 3a); eGFR 30–44 mL/min/1.73 m^2 (namely, CKD stage 3b) and eGFR < 30 mL/min/1.73 m^2 (namely, CKD stage 4 or 5).		Lewy body dementia according to UK Clinical Practice Research Datalink.	first 6 months after CKD detection, while a weak association was suggested in the long run. There was no positive association between CKD severity and dementia diagnosis.
45	Jimenez-Balado	2020	4.1 years	Spain	360	65 (61–68)	none	A significant eGFR decline was defined as the lowest quintile of change (−10.57 mL/min/1.73 over the 4 years of follow-up). Microalbuminuria (MAU) was determined using previously described cutoffs (defined as ACR >21 mg/g in men and >30 in women) at the baseline and follow-up.	White matter hyperintensities (WMH) were measured using the Fazekas scale at deep (DWMH) and periventricular areas (PVH). Fazekas scores at each area (0–3) were dichotomized into non-extensive (0–1) and extensive (2–3).	Those patients over the cut-off of DRS-2 or those who did not meet MCI criteria, were considered as normal aging (NA) patients. Four possible transitions in cognitive status were observed: stable NA (NA at both visits), reversion to normal (MCI at the baseline and NA at the follow-up visit), stable MCI (MCI at both visits), and incident MCI (NA at the baseline and MCI at the follow-up visit).	Subjects with MAU at the follow-up were at higher risk of progression of PVH. Decline in eGFR related to incident MCI, independently of the progression of cSVD. The decline in kidney function —due to microvascular lesions— may reflect the same process in the brain, probably due to shared etiologies and risk factors.
46	Kang	2020	3.13 years	Finland	2244582	58.5	none	The reference group was defined as the subjects with eGFR levels between the 50th and 64th percentile in each group. Hyperfiltration was defined as eGFR ≥ 95th percentile in each group.	/	The primary outcome was the development of all types of dementia, which included vascular dementia, Alzheimer's dementia, and other kinds of dementia according to ICD-10.	Glomerular hyperfiltration may be a predictor of dementia, especially vascular dementia, not Alzheimer's dementia.
47	Kurella Tamura	2020	5.1 years	United States	9361	67.9	none	Analysis categorized baseline eGFR as ≥ 60 mL/min per 1.73 m^2 versus < 60 mL/min per 1.73 m^2, and baseline UACR as,30 mg/g versus ≥ 30 mg/g.	/	The primary outcome was probable (all-cause) dementia, and secondary outcomes were MCI, defined as two consecutive adjudicated classifications of MCI, and a composite outcome of MCI or probable dementia using the Montreal Cognitive Assessment and the Functional Assessment Questionnaire.	Declining eGFR may be a marker for those at higher risk for dementia or MCI, but it did not appear to modify or attenuate the effects of intensive hypertension treatment.
48	Lau	2020	1.5 years	United States	27	56.8	none	Pre-dialysis CKD (n = 8) and chronic hemodialysis patients (n = 9), and controls with normal kidney function (n = 10), which were manually matched to the hemodialysis CKD patients by gender and age ± 5 years.	Microbleeds were counted by an attending neuroradiologist and analyzed for progression over time. Layer thickness for SWI sequences was performed at 2 mm, with an interlayer interval of 0. Microbleeds were counted based on 2-mm axial SWI. FLAIR was performed to detect white matter lesions at 3 mm slice thickness, also with an interlayer interval of 0.	/	Human brain MRI studies confirmed increased prevalence of microbleeds in CKD patients compared with age-matched non-CKD controls, and hemodialysis patients in particular were noted to develop new microbleeds over a 1.5-year follow-up period.

Table 1 (*continued*)

number	study	year	follow up	country	sample	age	basic disease	kidney function measurement	measurement of structural brain abnormalities	measurement of cognitive impairment/dementia	main results
49	Scheppach	2020	18.4 years	United States	4626	75.5 (5.2)	none	The exposures of interest were UACR and eGFR at ARIC visits 4 and 5. No specific definition mentioned.	/	Dementia was ascertained using surveillance based on a prior discharge hospitalization International Classification of Diseases-9 (ICD-9).	An increased risk of dementia among participants with higher levels of UACR and lower levels of GFR, but only when GFR estimation is based on novel kidney markers.
50	Tseng	2020	5.05 years	China	35434	71.07 (5.63)	none	Categorical cutoffs with eGFR: > 75, 60–75, 45–59, and < 45 mL/min/ 1.73 m^2.	/	The health examination data included the AD8 questionnaire—an eight-item questionnaire assessing early dementia.	Among the older individuals in the present study, elevated mild albuminuria and low eGFR were associated with early dementia.
51	Grasing	2021	6 years	United States	1127	74 (7)	none	Four categories of baseline eGFR: < 45, 45–60, 61–90 and > 90 mL/min/ 1.73 m^2.	/	Cognition was measured via previously validated composite scores for memory (ADNI-Mem) and executive function (ADNI-EF) based on the ADNI's battery of neuropsychological testing.	In this cohort from the ADNI study, there was no association between baseline eGFR and cognitive decline in older adults with mild-moderately low eGFR.
52	Tollitt	2021	2 years	United Kingdom	250	66 (53–74)	chronic kidney disease	Fast progression of CKD was defined as an eGFR decline > 3 mL/min/1.73 m^2/year. Alternative methods of rapid decline in renal function were also used and included > 20% decline in eGFR within the 12months antecedent to the cognitive assessment and > 20 and > 50% decline in eGFR from baseline during the study.	/	The cognitive outcome measures used in this study were as follows: cognitive impairment (binary and continuous output from MoCA); cognitive impairment (binary and continuous output from TMT A or TMT B); related cognitive impairment continuous and binary.	A faster eGFR decline was not associated with the presence of cognitive impairment measured by three independent cognitive assessments in moderate to severe CKD.
53	Wang	2021	5.3 years	China	1412	70.69 (6.85)	none	Characteristics of participants were presented stratified by baseline GFRcrcys tertiles (GFRcrcys <67, 67 ≤ GFR$_{crcys}$ <80, GFR$_{crcys}$ ≥ 80 mL/ min/1.73 m^2).	/	A consensus diagnosis for dementia using DSM-IV criteria. Alzheimer's disease (AD) was diagnosed by NINCDS-ADRDA criteria.	Low GFR$_{crcys}$ was independently associated with high risk of incident dementia and AD in community-dwelling older adults. GFR$_{crcys}$ may be considered as a marker of an individual's vulnerability to the increased risk of cognitive decline.

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; CCI, creatinine clearance; CKD, chronic kidney disease; MCI, mild cognitive impairment; SCI, silent cerebral infarction; CMB, cerebral microbleed; AD, Alzheimer dementia; VD, vascular dementia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; 6CIT, 6-Item Cognitive Impairment Test; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating score; DRS-2, the Dementia Rating Scale 2nd version; ICD, International Classification of Diseases; AD8, an eight-item questionnaire assessing early dementia; MoCA, the Montreal Cognitive Assessment; eGFRcys, cystatin C–based estimated glomerular filtration rate; DVC, dementia with vascular component; MAPT, the Multidomain Alzheimer's Preventive Trial; TMT, Trail Making Test; TICS, Telephone Interview for Cognitive Status; EBMT, East Boston Memory Test; NINCDS-ADRDA, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).

compare the direct and indirect estimates for each comparison, the inconsistency of our results was confirmed using the node-splitting method (Dias et al., 2010) and its Bayesian *P* value. If the *P* value was less than 0.05, an inconsistency was considered to be detected. Rank probabilities of the effects of all available eGFR ranges were calculated and are shown visually using the bar plots of ranking probability for the network (Salanti et al., 2011). Network meta-analyses using Bayesian methods (Lumley, 2002) for indirect treatment comparisons were performed using JAGS and R software (version 3.3.3) with the gemtc package (version: 0.8–2) and rjags package (version: 4–6) in a random-effect model, as most of the head-to-head comparisons only included one set of data providing direct evidence. When a meta-analysis was not feasible, we reported the results of the narrative review.

3. Results

3.1. Literature search outcomes and validity assessment

In the analysis of evidence on the bidirectional relationship between kidney function and cSVDs, we identified 534 potentially relevant reports, of which 197 were excluded because they were duplicates. The remaining 337 articles were subjected to title and abstract screening. A further 252 studies were removed, as they did not met the inclusion criteria (reviews, letters, conference abstracts, and independent studies). A total of 85 articles were found eligible for the full-text review and data assessment. Further, 16 studies (Agarwal et al., 2019; Barzilay et al., 2016; Bouchi et al., 2010; Fandler-Höfler et al., 2019; Jiménez-Balado et al., 2020; Khatri et al., 2007; Kobayashi et al., 2010; Lau et al., 2020; Oksala et al., 2010; Peng et al., 2016; Sedaghat et al., 2018; Shima et al., 2016; Uzu et al., 2010; van Overbeek et al., 2016; Vemuri et al., 2017; Vilar-Bergua et al., 2016) were included in the current meta-analysis and literature review, of which 12 (Agarwal et al., 2019; Barzilay et al., 2016; Fandler-Höfler et al., 2019; Jiménez-Balado et al., 2020; Khatri et al., 2007; Lau et al., 2020; Oksala et al., 2010; Peng et al., 2016; Sedaghat et al., 2018; van Overbeek et al., 2016; Vemuri et al., 2017; Vilar-Bergua et al., 2016) focused on the association between decreased kidney function and cSVDs and 4 (Bouchi et al., 2010; Kobayashi et al., 2010; Shima et al., 2016; Uzu et al., 2010) described the effect of cSVDs on kidney function (Fig. 1).

In the analysis of evidence on the bidirectional relationship between kidney function and cognitive impairment and dementia, our search strategy targeted 4728 relevant studies. After removing duplicates, 2645 articles were screened according to the title and abstract. A total of 258 studies were searched for full text, and 38 studies (Auriel et al., 2016; Bai et al., 2017; Ben Assayag et al., 2017; Buchman et al., 2009; Chen et al., 2017, 2020; Cheng et al., 2012; Darsie et al., 2014; Davey et al., 2013; Etgen et al., 2009; Feng et al., 2012; Gabin et al., 2019; Grasing et al., 2021; Gronewold et al., 2016, 2017; Guerville et al., 2020; Helmer et al., 2011; Hiramatsu et al., 2020; Jiménez-Balado et al., 2020; Kang et al., 2020; Koop-Nieuwelink et al., 2019; Kurella et al., 2005; Kurella Tamura et al., 2020; Kuriyama et al., 2013; Li et al., 2018; Miwa et al., 2014; O'Hare et al., 2012; Sajjad et al., 2012; Sasaki et al., 2011; Scheppach et al., 2020; Slinin et al., 2008; Takae et al., 2018; Tamura et al., 2011, 2016; Tollitt et al., 2021; Tseng et al., 2020; Wang et al., 2010, 2021) were included in the current meta-analysis and literature review. Here, 37 articles (Auriel et al., 2016; Bai et al., 2017; Ben Assayag et al., 2017; Buchman et al., 2009; Chen et al., 2017, 2020; Cheng et al., 2012; Darsie et al., 2014; Davey et al., 2013; Etgen et al., 2009; Feng et al., 2012; Gabin et al., 2019; Grasing et al., 2021; Gronewold et al., 2016, 2017; Guerville et al., 2020; Helmer et al., 2011; Hiramatsu et al., 2020; Jiménez-Balado et al., 2020; Kang et al., 2020; Koop-Nieuwelink et al., 2019; Kurella et al., 2005; Kurella Tamura et al., 2020; Kuriyama et al., 2013; Li et al., 2018; Miwa et al., 2014; O'Hare et al., 2012; Sajjad et al., 2012; Sasaki et al., 2011; Scheppach et al., 2020; Slinin et al., 2008; Takae et al., 2018; Tamura et al., 2011; Tollitt et al., 2021; Tseng et al.,

2020; Wang et al., 2010, 2021) focused on the association between kidney function and cognitive impairment and dementia, while one article (Tamura et al., 2016) focused on the effect of cognitive impairment and dementia on kidney function (Fig. 2).

In summary, 53 studies were included in the current study, of which one study (Jiménez-Balado et al., 2020) focused on kidney function changes and their relationship with the progression of cSVDs and cognitive decline. Table 1 provides an overview of the 53 eligible studies, and all studies were scored 5–9 in NOS quality assessment (supplementary material 3, table 1).

3.2. Meta-analyses and systematic review of the relationship between kidney function and cSVDs

3.2.1. Continuous kidney function and cSVD

Six studies (Agarwal et al., 2019; Jiménez-Balado et al., 2020; Sedaghat et al., 2018; van Overbeek et al., 2016; Vemuri et al., 2017; Vilar-Bergua et al., 2016) with 7532 participants were included in the analysis, where the association of chronic kidney disease and the incidence of cSVD were measured as continuous variables (supplementary material 3, table 2) The overall pooled analysis for continuous eGFR and cSVD demonstrated a null effect (RR 1.03, 95% CI 0.99–1.06, I^2 = 25.9%) (Fig. 3A). Heterogeneity among studies was substantial, with low risk of bias (supplementary material 3, Fig. 1A). Further results of the sub-group analysis are shown in Table 3. Four studies (Jiménez-Balado et al., 2020; Sedaghat et al., 2018; Vemuri et al., 2017; Vilar-Bergua et al., 2016) with 4246 participants provided eight sets of data using continuous UACR as the CKD measurement. The analysis of these data generally reported a null effect (RR 1.01, 95% CI 0.99–1.02, I^2 = 57.8%) (Fig. 3B). Heterogeneity among studies and the risk of bias was moderate and low, respectively (supplementary material 3, Fig. 1B). Further subgroup analysis is shown in supplementary material 3, table 3.

3.3. Categorical kidney function and cSVD

The analysis of CKD as a categorical variable included four studies (Agarwal et al., 2019; Oksala et al., 2010; Peng et al., 2016; Vilar-Bergua et al., 2016) of 4870 participants (supplementary material 3, table 4), which showed a positive association between kidney dysfunction and cSVD (RR 1.77, 95% CI 1.40–2.24, I^2 = 0.0%) (Fig. 4A). Moreover, the outcome of subgroup analysis in different kidney function measurements remained consistent with an increased risk of cSVD was found in CKD status categorized by both eGFR (RR 1.63, 95% CI 1.25–2.12, I^2 = 0.0%) and UACR (RR 2.40, 95% CI 1.44–3.99) (Fig. 4B). These four studies were reported to have a low risk of bias (supplementary material 3, Fig. 2).

Previous studies have established a null association during the examination of the effect of CKD progression as dichotomous variable on cSVD (Peng et al., 2016; Sedaghat et al., 2018) of 3171 participants (RR 1.18, 95% CI 0.85–1.63, I^2 = 70.3%). However, these results might be biased because of the substantial heterogeneity among the studies. The results of subgroup analysis are shown in supplementary material 3, table 5.

3.4. The association between kidney function and cerebral volume

Data regarding the association between renal function and cerebral atrophy were incompatible with the meta-analyses, although four studies provided longitudinal evidence. Jiménez-Balado et al. (Jiménez-Balado et al., 2020) reported in 2020 that worsening eGFR had a null effect on deep WMH volume change during a 4.1 years follow-up of 360 Spanish participants (β − 0.21, 95% CI −0.67 to 0.25). Barzilay (Barzilay et al., 2016) et al. also found that the baseline eGFR and eGFR change in patients with type 2 diabetes mellitus were not associated with any significant differences in the brain volume measurements. However, on the other hand, Khatri et al. (Khatri et al., 2007) reported in
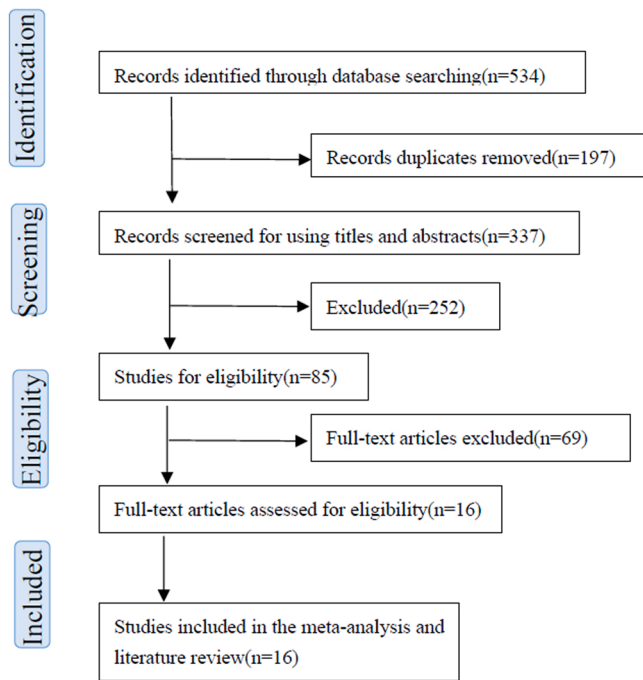
Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of studies about the association between kidney function and structural brain abnormalities.

2007 that both the baseline creatinine clearance (15–60 mL/min) and eGFR (15–60 mL/min) were connected to increased log-WMH volume (β 0.322, 95% CI 0.095–0.550; β 0.322, 95% CI 0.080–0.564 respectively). In addition, Vemuri et al. (Vemuri et al., 2017) showed that a 10% worsening in eGFR or in UACR was related to increasing WMH volume (β 2.849, SE 0.94; β 0.323, SE 0.10, respectively).
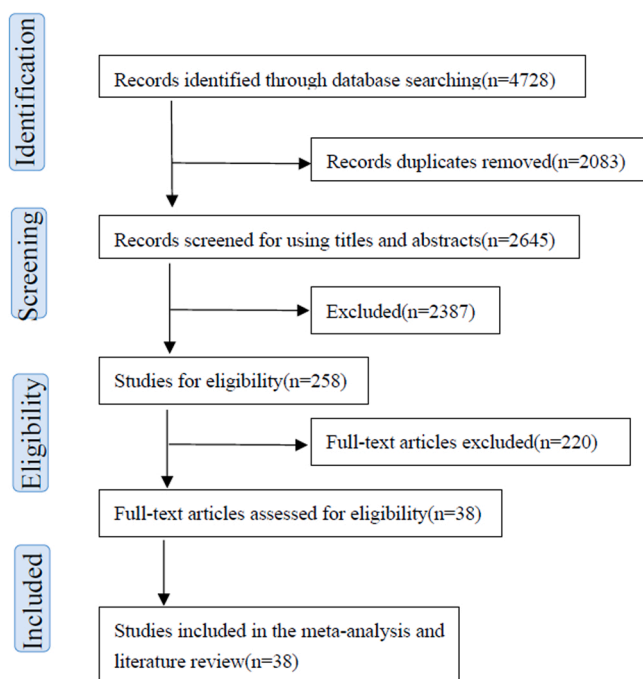

Fig. 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of studies about the association between kidney function and cognitive impairment and dementia.

3.5. Meta-analysis and literature review of relationship between kidney function and cognitive impairment/ dementia

3.5.1. Continuous kidney function and cognitive impairment/ dementia

Ten studies (Bai et al., 2017; Feng et al., 2012; Guerville et al., 2020; Helmer et al., 2011; Jiménez-Balado et al., 2020; Koop-Nieuwelink et al., 2019; Scheppach et al., 2020; Tamura et al., 2011; Tollitt et al., 2021; Tseng et al., 2020) consisting of 77013 individuals provided evidence of kidney function and cognitive impairment or dementia scaled by continuous eGFR (supplementary material 3, table 6). Five (Guerville et al., 2020; Helmer et al., 2011; Jiménez-Balado et al., 2020; Koop-Nieuwelink et al., 2019; Tollitt et al., 2021), three (Bai et al., 2017; Feng et al., 2012; Tseng et al., 2020), and two (Scheppach et al., 2020; Tamura et al., 2011) of these studies analyzed European, Asian, and American populations, respectively. As continuous variables, a decline in eGFR was linked to an increased risk of overall brain functional impairment (RR 1.04, 95% CI, 1.00–1.08; $I^2 = 66.9\%$). In subgroup analyses of cognitive impairment (Bai et al., 2017; Feng et al., 2012; Guerville et al., 2020; Jiménez-Balado et al., 2020; Tamura et al., 2011; Tollitt et al., 2021) where we excluded datasets concerning any type of dementia, the pooled RR was 1.12 (95% CI 1.02–1.22, $I^2 = 67.8\%$), indicating a positive association. However, with respect to all-cause dementia (Helmer et al., 2011; Koop-Nieuwelink et al., 2019; Scheppach et al., 2020; Tseng et al., 2020) and Alzheimer's disease (Helmer et al., 2011; Koop-Nieuwelink et al., 2019), our subgroup analyses reported negative results (RR 1.01, 95% CI 0.97–1.06, $I^2 = 70.7\%$; RR 0.96, 95% CI 0.92–1.02, $I^2 = 0.0\%$ respectively) (Fig. 5). The results of the sensitivity analysis were consistent with those of the primary analysis. Further subgroup analysis is shown in supplementary material 3, table 7. These studies were reported to have a low risk of bias (supplementary material 3, Fig. 3).

Three studies (Jiménez-Balado et al., 2020; Scheppach et al., 2020; Tamura et al., 2016) utilized the continuous UACR as a measure of kidney function. Scheppach et al. (Scheppach et al., 2020) found that the UACR increase was linked to a higher incidence of all-cause dementia in both 54–74-year-old midlife and 70–90-year-old elderly participants. In addition, Tamura et al. (Tamura et al., 2016) also indicated that the UACR doubling was associated with the risk of developing cognitive impairment in a national (the United States) sample of 19,399 adults. On the contrary, a study of 976 middle-aged adults from Jiménez-Balado et al. (Jiménez-Balado et al., 2020) revealed a null effect of the UACR incline on mild cognitive impairment (RR 1.54, 95% CI 0.92–2.58). The overall pooled risk ratio of the three studies was 1.02 (95% CI 1.00–1.04, $I^2 = 77.1\%$), and the small number of included studies might have biased these findings (Fig. 6). Further subgroup analysis is shown in supplementary material 3, table 7.

3.6. Categorical kidney function and cognitive impairment and dementia

To comprehensively address the connection between kidney dysfunction and brain functional impairment, 28 prior longitudinal studies (Auriel et al., 2016; Bai et al., 2017; Ben Assayag et al., 2017; Cheng et al., 2012; Etgen et al., 2009; Feng et al., 2012; Gabin et al., 2019; Guerville et al., 2020; Helmer et al., 2011; Hiramatsu et al., 2020; Kang et al., 2020; Kurella et al., 2005; Kurella Tamura et al., 2020; Kuriyama et al., 2013; Miwa et al., 2014; O'Hare et al., 2012; Sasaki et al., 2011; Scheppach et al., 2020; Slinin et al., 2008; Takae et al., 2018; Tamura et al., 2011; Tollitt et al., 2021; Tseng et al., 2020; Wang et al., 2010, 2021) with 194 compatible sets of data measuring kidney function as categorical variables were analyzed in our meta-analyses (supplementary material 3, table 8). The results are shown in the forest plot (Fig. 7 and supplementary material 3, Fig. 4). Worse kidney function was related to greater risks of global brain cognitive disorder (RR 1.28, 95% CI 1.20–1.36, $I^2 = 82.5\%$) regardless of different tests of the renal function (eGFR, UACR, CCl, and similar). The combined result of the studies considering cognitive impairment (not dementia)
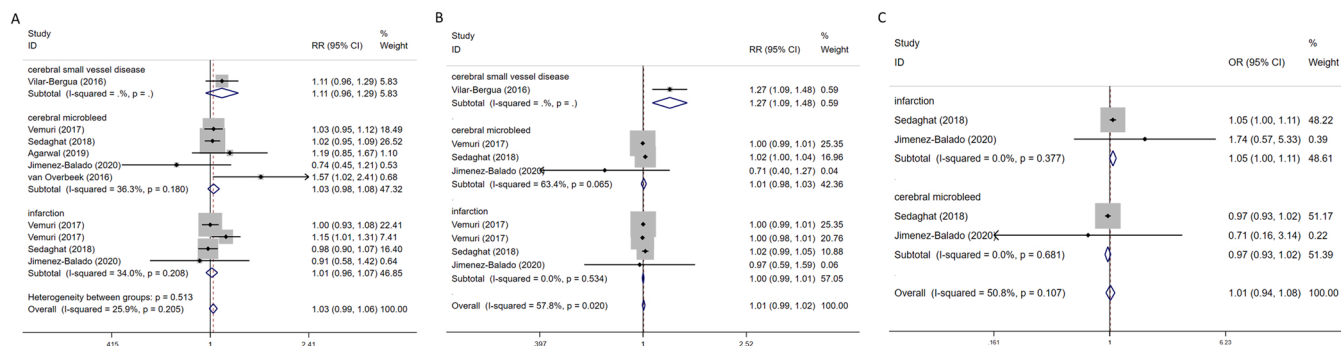
Fig. 3. Meta-analysis of evidence on association between continuous kidney function and cerebral small vessel diseases. A. Meta-analysis of evidence on association between continuous eGFR and cerebral small vessel diseases. B. Meta-analysis of evidence on association between continuous UACR and cerebral small vessel diseases. C. Meta-analysis of evidence on association between continuous eGFR change and cerebral small vessel diseases. **Abbreviation:** eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.
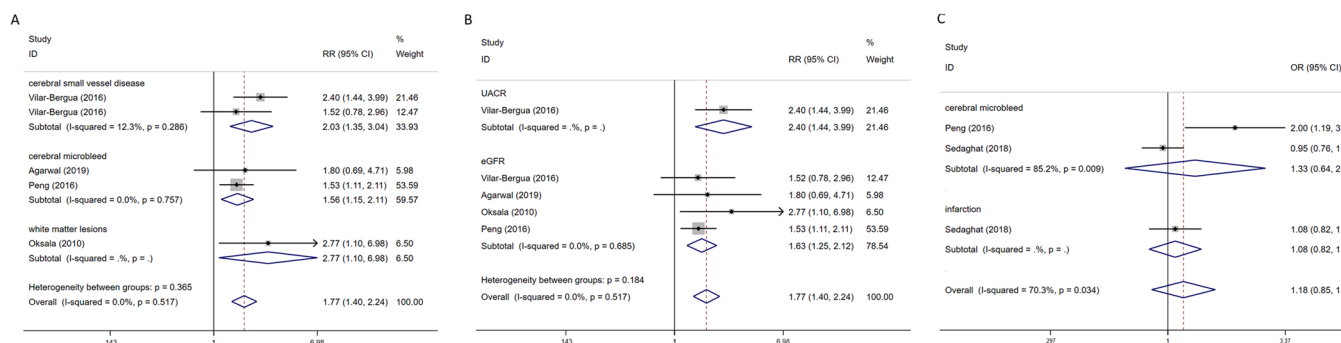

Fig. 4. Meta-analysis of evidence on association between categorial kidney function and cerebral small vessel diseases. A. Meta-analysis of evidence on association between categorial kidney function and cerebral small vessel diseases according to different cerebral small vessel diseases. B. Meta-analysis of evidence on association between categorial kidney function and cerebral small vessel diseases according to kidney dysfunction method. C. Meta-analysis of evidence on association between categorial kidney function change and cerebral small vessel diseases according to different cerebral small vessel diseases. Abbreviation: eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.

demonstrated that the declined renal function might have a harmful effect on individuals' cognitive processes (RR 1.26, 95% CI 1.15–1.39, I^2 = 56.1%) (Fig. 7B). Moreover, diminution of renal function adversely affected not only the all-cause dementia but also each sub-classification of dementia (pooled RR for all-cause dementia, vascular dementia, and Alzheimer's disease were 1.29, 95% CI 1.19–1.40, I^2 = 87.9%, 1.20, 95% CI 1.06–1.37, I^2 = 54.1%, and 1.35, 95% CI 1.20–1.52, I^2 = 14.0%, respectively). Notably, these results might be partially overinterpreted because of the existence of potential publication bias (supplementary material 3, Fig. 5). The sub-group analysis is shown in supplementary material 3, table 8.

Two studies (Helmer et al., 2011; O'Hare et al., 2012) used the eGFR decline over the follow-up years as the categorical variables for CKD assessment. Helmer et al. (Helmer et al., 2011) discovered in a 7-year-follow-up cohort study in 2011 that as compared to the patients with < 4 mL/min/1.73 m², an annual eGFR decline of > 4 mL/min/1.73 m² was a plausible risk factor for all-cause dementia (RR 1.69, 95% CI 1.05–2.73) and vascular dementia (RR 5.35, 95% CI 1.76–16.32), but not Alzheimer's disease (RR 1.29, 95% CI 0.68–2.43) (Fig. 8). On the other hand, in a 2968-participant-cohort study (O'Hare et al., 2012) conducted by O'Hare et al., results claimed a null association between the declining 5-year eGFR trajectory and all-cause dementia (HR 0.92, 95% CI 0.84–1.01) or Alzheimer's disease (HR 0.94, 95% CI 0.85–1.04).

The sub-group analysis is shown in supplementary material 3, table 8.

3.7. Network meta-analysis of the association between different eGFR range and cognitive impairment and dementia

Sixteen cohort studies (Bai et al., 2017; Feng et al., 2012; Gabin et al., 2019; Guerville et al., 2020; Helmer et al., 2011; Hiramatsu et al., 2020; Kurella et al., 2005; Kurella Tamura et al., 2020; Kuriyama et al., 2013; Miwa et al., 2014; Sasaki et al., 2011; Slinin et al., 2008; Takae et al., 2018; Tamura et al., 2011; Tseng et al., 2020; Wang et al., 2010) comprising 607909 participants were included in the network meta-analysis to examine 13 different eGFR ranges. Among these studies, 9 (Bai et al., 2017; Feng et al., 2012; Guerville et al., 2020; Kurella et al., 2005; Kurella Tamura et al., 2020; Kuriyama et al., 2013; Slinin et al., 2008; Tamura et al., 2011; Wang et al., 2010), 8 (Gabin et al., 2019; Helmer et al., 2011; Hiramatsu et al., 2020; Kurella Tamura et al., 2020; Miwa et al., 2014; Sasaki et al., 2011; Takae et al., 2018; Tseng et al., 2020), 4 (Gabin et al., 2019; Helmer et al., 2011; Miwa et al., 2014; Takae et al., 2018), 4 (Gabin et al., 2019; Helmer et al., 2011; Miwa et al., 2014; Takae et al., 2018) were related to cognitive impairment, overall dementia, Alzheimer's disease, and vascular dementia, respectively (S Table 10). The network plot (Fig. 9) shows the association between different ranges of eGFR and the incidence of
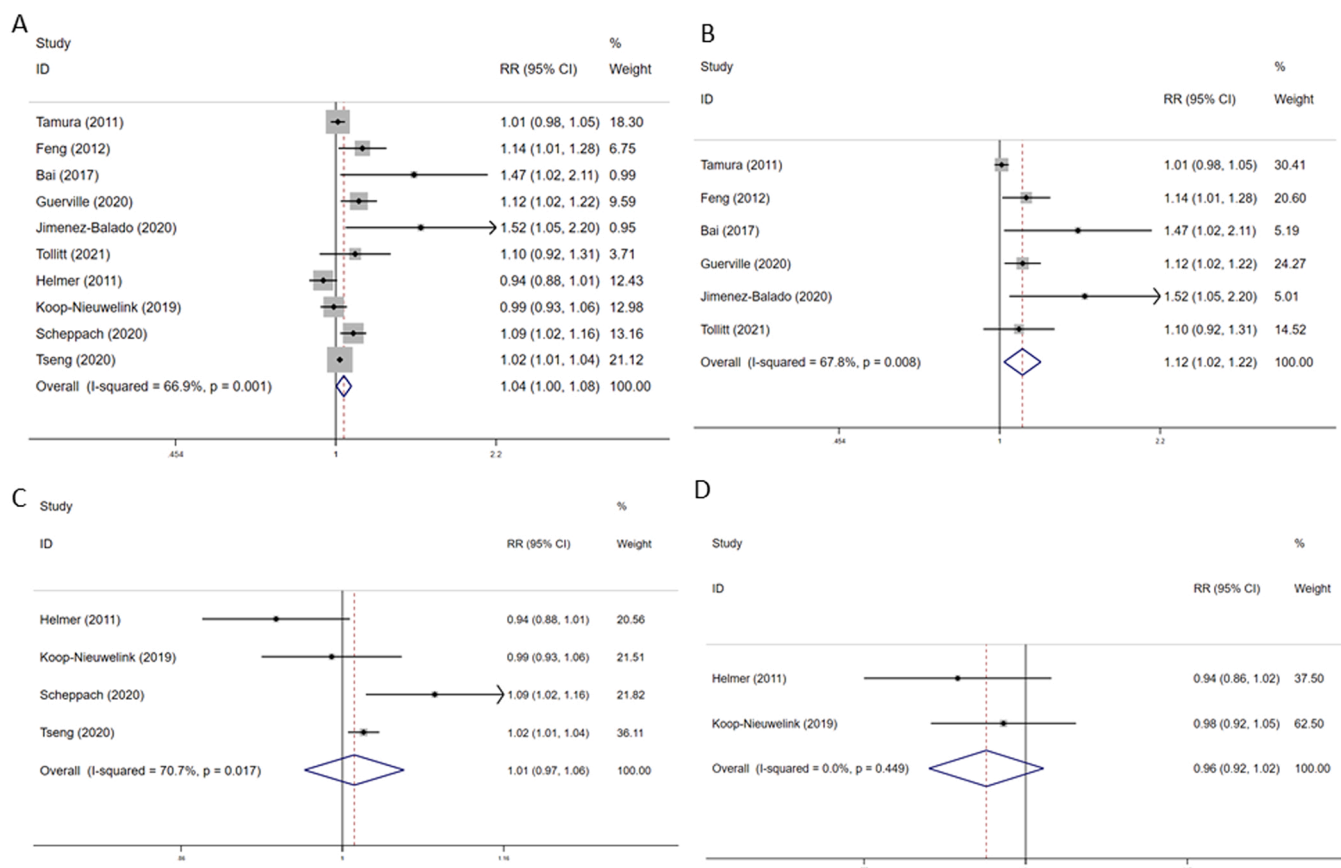
Fig. 5. Meta-analysis of evidence on association between continuous eGFR and cognitive impairment and dementia. A. Meta-analysis of evidence on association between continuous eGFR and cognitive impairment and dementia. B. Meta-analysis of evidence on association between continuous eGFR and cognitive impairment. C. Meta-analysis of evidence on association between continuous eGFR and dementia. **D.** Meta-analysis of evidence on association between continuous eGFR and Alzheimer dementia. Abbreviation: eGFR, estimated glomerular filtration rate; RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.

Fig. 6. Meta-analysis of evidence on association between continuous UACR and cognitive impairment and dementia. Abbreviation: UACR, urine albumin-to-creatinine ratio; RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.
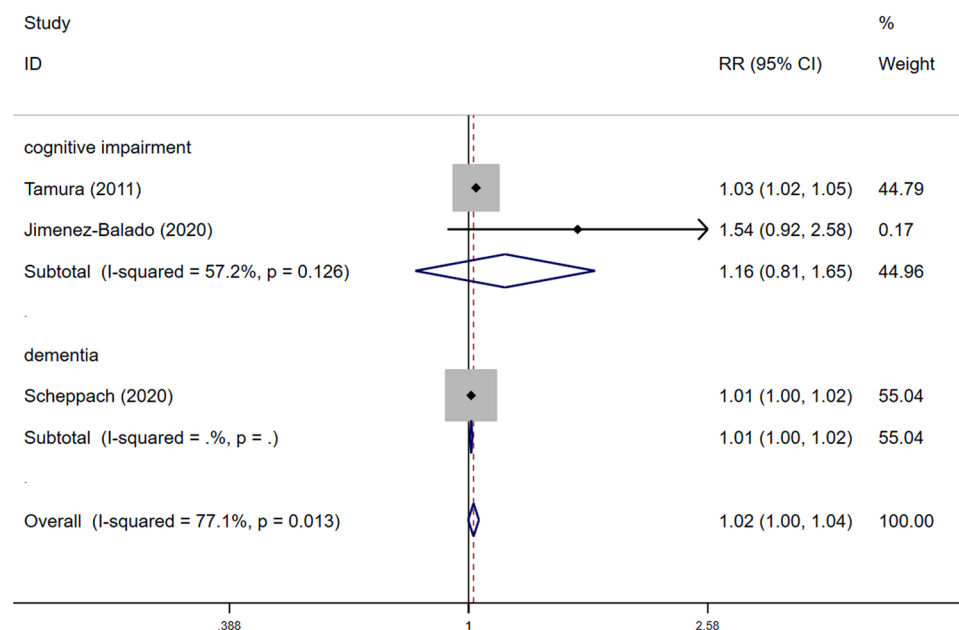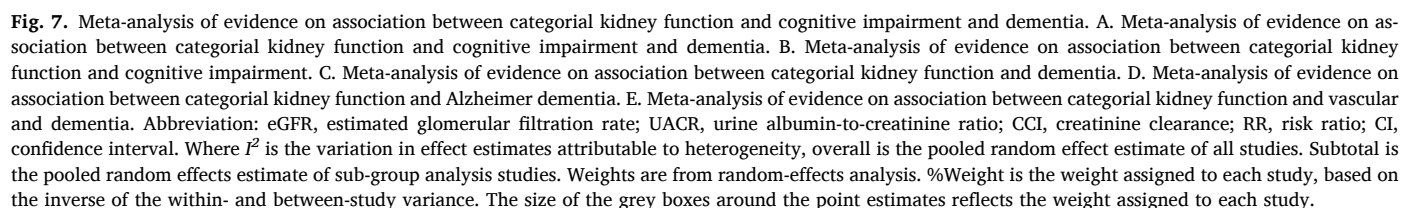
cognitive impairment/dementia.

In this Bayesian network meta-analysis (supplementary material 3 table 1), we found that the eGFR of < 45 mL/min/1.73 m^2 (HR 1.30, 95% CI 1.00–1.80), < 60 mL/min/1.73 m^2 (HR 1.20, 95% CI 1.10–1.50), < 90 mL/min/1.73 m^2 (HR 2.30, 95% CI 1.20–4.50), and 30–60 mL/min/1.73 m^2 (HR 2.00, 95% CI 1.10–4.00) were associated with an increased risk of cognitive impairment/dementia in comparison to the eGFR of ≥ 60 mL/min/1.73 m^2. Furthermore, the eGFR of < 90 mL/min/1.73 m^2 appeared to have a negative impact on patients' cognitive function than that of the eGFR of ≥ 90 mL/min/1.73 m^2 (RR 1.90, 95% CI 1.20–3.20).

Local inconsistency was evaluated by one comparison at a time in the node-splitting analysis of our study by separating the direct evidence of that comparison from the network of indirect evidence. In terms of different eGFR ranges, eight nodes were split, and the P values varied from 0.26 to 0.99, which meant that no statistically significant inconsistencies were detected.

The rank possibilities of different eGFR ranges are shown in supplementary material 3, Fig. 6. The eGFR of < 90 mL/min/1.73 m^2 owned the highest first rank possibility (38.78%), followed by ≥ 45 and 30–60 mL/min/1.73 m^2, while the eGFR of ≥ 75 mL/min/1.73 m^2 showed 50.19% possibility to be the last risk factor of cognitive impairment/ dementia among the other ranges of eGFR (supplementary material 3, table 12). The eGFR range of ≥ 60 mL/min/1.73 m^2 held 25.21% and 29.19% possibility to be the last second and third at risk eGFR range.

3.8. Meta-analysis and literature review of the relationship between the brain health and kidney function

3.8.1. The effect of cSVD on the kidney function

Four studies (Bouchi et al., 2010; Kobayashi et al., 2010; Shima et al., 2016; Uzu et al., 2010) independently reported that the patients with cSVD (supplementary material 3, table 13), especially the silent cerebral infarction or microbleeds, were significantly at risk to develop the renal insufficiency (pooled RR 2.51, 95% CI 1.88–3.36, I^2 = 0.0%) (Fig. 10). Further subgroup analysis is shown in supplementary material 3, table 14. Notably, only few studies are available on evaluation of this opposite relationship, and hence, the robustness of the pooled estimate might be less.

3.9. The effect of cognitive impairment and dementia on kidney function

Currently, only one published article (Tamura et al., 2016) examined the effect of cognitive impairment on CKD progression. The recruited population consisted of 3883 participants from the Chronic Renal Insufficiency Cohort (CRIC) study, and the data revealed that the cognitive impairment had no influence on the incidence of developing end-stage renal disease (HR 1.07, 95% CI 0.87–1.03) or the risk of a 50% decline in baseline eGFR (HR 1.06, 95% CI 0.89–1.27).
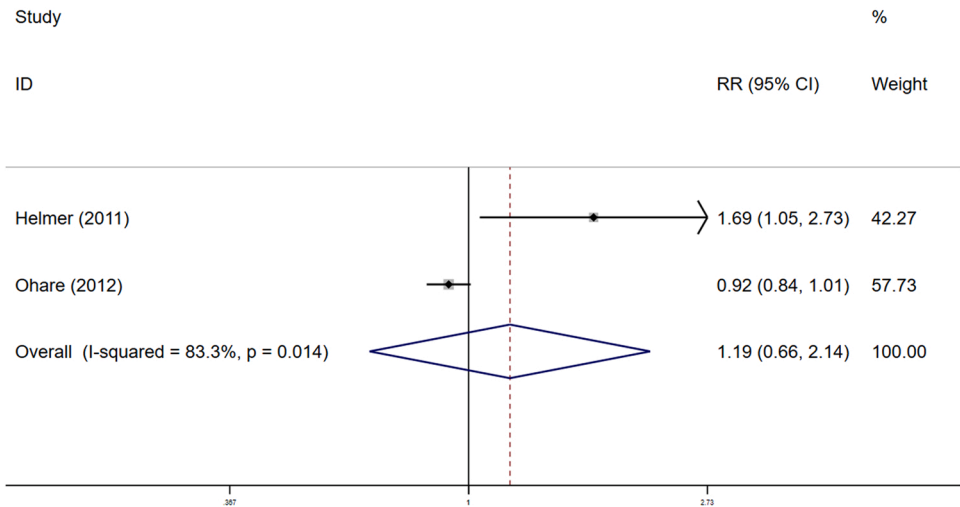

Fig. 7. Meta-analysis of evidence on association between categorial kidney function and cognitive impairment and dementia. A. Meta-analysis of evidence on association between categorial kidney function and cognitive impairment and dementia. B. Meta-analysis of evidence on association between categorial kidney function and cognitive impairment. C. Meta-analysis of evidence on association between categorial kidney function and dementia. D. Meta-analysis of evidence on association between categorial kidney function and Alzheimer dementia. E. Meta-analysis of evidence on association between categorial kidney function and vascular and dementia. Abbreviation: eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; CCI, creatinine clearance; RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.

Fig. 8. Meta-analysis of evidence on association between categorial kidney function change and cognitive impairment and dementia. Abbreviation: RR, risk ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.

4. Discussion

4.1. Principal findings

In this meta-analysis, we comprehensively examined the association between kidney dysfunction and structural and functional brain disorders by assessing accessible, compatible data from the longitudinal cohort studies. Structural brain disorders or cSVD were found to have no statistically significant association with the kidney function. We also found that the kidney dysfunction is related to cognitive impairment and dementia. These findings did not vary in subgroup analyses of older age (≥65 years) or middle-aged participants, consistent with most currently published studies.

In addition, our synthesized evidence showed results similar to those of a previous study (Deckers et al., 2017) that UACR might better reflect cognitive function in CKD patients than eGFR. In the analysis of categorical kidney function and dementia, the categorical eGFR was reported to be associated with cognitive impairment and all-cause dementia but not Alzheimer's disease or vascular dementia, whereas categorical UACR was found to be related to all these types of cognitive

dysfunction. Our results indicate the critical role of UACR as a risk factor for cognitive impairment and dementia compared with eGFR. The feature of GFR estimation could be blamed for this unstable association between eGFR and functional brain health in our meta-analysis. The equation commonly used for GFR estimation is based on creatinine, which is widely used in routine clinical practice but can be substantially influenced by confounding factors, such as unusual muscle mass (Stevens and Levin, 2013), diet with high meat content, or dietary supplements containing creatine. In particular, reduced muscle mass is a concern in elderly patients, which may lead to an overestimation of GFR. Inaccurate determination of the GFR readings (Zaman et al., 2013) may obscure the potential association with dementia.

Intriguingly, evidence of the opposite relationship demonstrated a negative impact of structural brain abnormalities, cerebral microbleeds, and silent cerebral infarction on renal function. However, functional brain abnormalities had a null effect on kidney function in the pooled results of 2 relative longitudinal studies. This might be largely biased by the small amount of synthesized data. Furthermore, our results from the network meta-analysis demonstrated that a lower eGFR had a more statistically significant harmful effect on the brain cognitive function. In
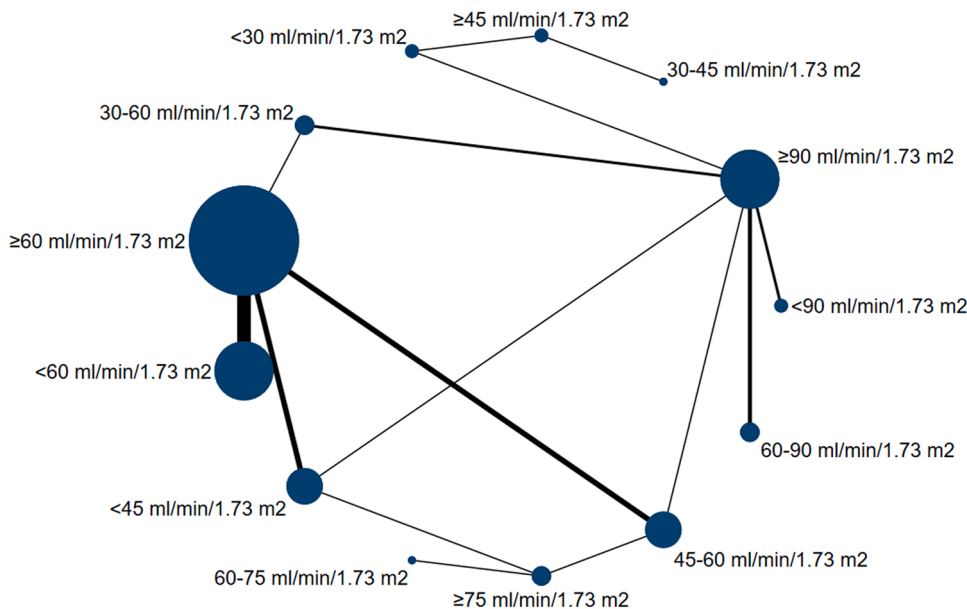

Fig. 9. Network plot for evidence on association between different eGFR range and cognitive impairment and dementia. Abbreviation: eGFR, estimated glomerular filtration rate. Each circle represents one eGFR range, and the size of circle and the thickness of connected lines indicate number of trials for each comparison.

the rank possibility analysis, the results indicated that the riskiest eGFR range would be approximately ≥ 45–60 mL/min/1.73 m². This implies that patients with stage 3 CKD are at a greater risk of developing the brain functional disorders. We also noticed that a few studies with less than three years of follow-up offered irregular findings. This is reasonable because the brain dysfunction usually does not develop within such a short period.

4.2. Underlying mechanisms

The pathophysiological mechanisms of the observed associations between the limited kidney function and global brain health are unclear, and a few plausible theories may, to a certain degree, elucidate these connections. First, scientists have concluded that the microvascular disease may be linked to two conditions. Branches of the anterior, middle, and posterior cerebral arteries (Ito et al., 2009; Knopman, 2010; Weiner, 2008) penetrating the brain tissues and juxtamedullary afferent arterioles in the kidneys are strain vessels that are frequently exposed to high pressure to provide a large pressure gradient over a short distance. Therefore, these vessels strictly rely on their autoregulation (Bugnicourt et al., 2013) to manage hemodynamic stress from the large supplying arteries. Studies using transcranial Doppler ultrasonography (Silvestrini et al., 2006) have proven that the cerebral microvascular hemodynamic impairment is commonly involved in patients with cognitive impairment. Meanwhile in CKD patients, studies have shown a greater risk of developing vascular diseases (Saran et al., 2020), such as arterial hypertension, than that in the healthy population. Therefore, simultaneous occurrence of the kidney and cerebral microvascular diseases may play a key role in these relationships.

Second, assumption had arisen that the blood-brain barrier disruption-induced albumin leakage (Knopman, 2010; Wada et al., 2007; Weiner, 2008) may partly explain the development of WMH. However, this theory has only been proven in animal models (Egashira et al., 2015) but not in humans. Meanwhile, CKD shares a similar pathological basis of gradual alterations in the kidney endothelial cells and glomeruli, leading to a glomerular leakage of serum albumin into the urine. Under these circumstances, it is plausible to hypothesize that the same vascular pathophysiological process that causes albumin leakage in both the cerebrovascular and kidney vasculature would be the main culprit in the correlation between the kidney dysfunction and the brain disorders. Moreover, the kidney function can be regarded as an indicator or window for observation of the pathological process in the brain.

Other potential mechanisms, including direct neuronal injury by uremic toxins, may also be responsible for the connection between the kidney function and the brain health. Elevated homocysteine levels due to CKD or uremia are associated with white matter lesions (Wright et al., 2005) as well as Alzheimer's disease (Seshadri, 2006) through direct prothrombotic effect (Seshadri et al., 2008) and endothelial inflammatory reactions (Hassan et al., 2004). Elevated levels of cystatin-C (Yaffe et al., 2008) in CKD and uremic patients have also been reported to be associated with the development of Alzheimer's disease. Other metabolic toxins accumulate in the renal dysfunction, including phosphorusto-fibroblast growth factor 23 (Fliser et al., 2007) and some guanidine compounds (De Deyn et al., 2009), such as creatinine, guanidine, guanidinosuccinic acid, and methylguanidine could also contribute to the brain function decline.

On the aspect of the opposite relation, structural brain disorders, especially the cerebral microbleeds and silent cerebral infarction, may also predispose patients to progression of the kidney disease. A possible mechanism that may contribute to this involves plasma asymmetric dimethylarginine (Pikula et al., 2009), an endogenous inhibitor of nitric oxide synthase, which was shown to be associated with cSVDs in the Framingham offspring study (Pikula et al., 2009). Studies have consistently hypothesized that the impaired cognitive function may also adversely influence the renal function owing to lower usage or incompliance with the CKD risk reduction strategies. It is plausible to assume that the cognition-deficit CKD patients may have difficulties in adhering to the doctor's orders of dietary potassium restriction or daily medication prescription, which could lead to a more rapid renal function loss. However, further studies are required to explore this opposite relationship.

4.3. Strengths & limitations

The strengths of this meta-analysis include its large sample size, long follow-up period, and the exclusion of all cross-sectional or retrospective studies. This meta-analysis was performed under the protocol in accordance with the PRISMA (Knobloch et al., 2011), with a comprehensive search strategy which was also reproducible. We not merely focused on the global cognitive function, but structural brain abnormalities as well. Moreover, our study added evidence to the difference between UACR and eGFR in revealing CKD patients' brain health. The quality of all studies was rated medium to high, therefore our meta-analysis provided good evidence for the association between kidney function and brain health.
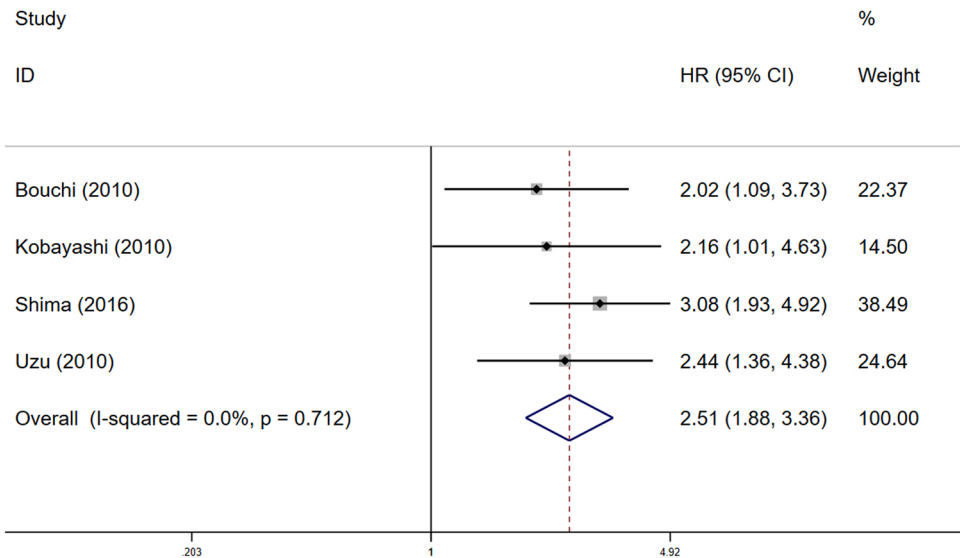
Study ID		HR (95% CI)	% Weight
Bouchi (2010)		2.02 (1.09, 3.73)	22.37
Kobayashi (2010)		2.16 (1.01, 4.63)	14.50
Shima (2016)		3.08 (1.93, 4.92)	38.49
Uzu (2010)		2.44 (1.36, 4.38)	24.64
Overall (I-squared = 0.0%, p = 0.712)		2.51 (1.88, 3.36)	100.00

.203   1   4.92

Fig. 10. Meta-analysis of evidence on the effect of cerebral small vessel disease on kidney function. Abbreviation: HR, hazard ratio; CI, confidence interval. Where I^2 is the variation in effect estimates attributable to heterogeneity, overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of sub-group analysis studies. Weights are from random-effects analysis. % Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the grey boxes around the point estimates reflects the weight assigned to each study.

This meta-analysis was limited by the small number of studies available for comparison and the lack of unadjusted original data from each study. Sociodemographic factors such as age, sex, health behaviors, and vascular risk factors were adjusted among the groups for analysis in each included article. Because the original data were not available for extraction, potential confounding factors, such as gender differences, blood pressure, primary cause of kidney function decline and effect of anemia or malnutrition secondary to CKD, probably biased our estimates. Secondly, The main variables of the kidney function in most studies were eGFR and UACR, while the association of other kidney function markers and brain health, such as serum creatinine, creatinine clearance, beta-2-microglobulin, and cystatin C levels, has not been fully explored in currently published articles. Recent evidence (Scheppach et al., 2020) has shown that the novel kidney markers, such as cystatin C and beta-2-microglobulin, which would not be influenced by non-kidney factors, including muscle mass decline, high meat component diet, and creatinine, could indicate kidney function more stably and better depict the association between the renal function and brain health than that by the eGFR. Therefore, additional studies are required in the future. Moreover, dose-response meta-analyses were not conducted in our study because of the small number of available studies that provided compatible data. In addition, we excluded studies published in languages other than English.

4.4. Future implications

Most of the studies included in our analysis concerning the renal function and the brain cognitive status used eGFR or UACR as categorical measures, and few studies used the continuous renal function markers. In this case, it would be plausible to expect that a nonlinear model might better mirror the relationship between the renal function and the brain cognitive status. Therefore, additional studies are needed to confirm whether the non-significant results in those studies using continuous eGFR/UACR were truly null.

Both the brain and the kidney consist of abundant vascular tissues and also have similar hemodynamic properties that can respond to diseases such as hypertension and diabetes mellitus (O'Rourke and Safar, 2005) in similar ways at the microscopic level. Although analyzed in subgroups of these illnesses, our results could not fully rule out these confounding factors because of the lack of unadjusted original cohort data. Thus, false-positive results might occur in the cause-effect relationship between the kidney function and brain health, as found in our study, due to the existence of probable indirect confounders between the exposure and outcome. As well, other possible confounding factors are of importance to be analyzed in future researches including gender differences, blood pressure, primary cause of kidney function decline and the potential effect of anemia or malnutrition secondary to CKD.etc. Mendelian randomization analysis may be helpful in future studies.

Last but not least, currently commonly used methods or questionnaires for cognitive evaluation in CKD patients may not fully examine the domains of impairment that are frequently found in these patients. The most commonly used cognitive test among our included studies was the MMSE, where 9 (Bai et al., 2017; Feng et al., 2012; Helmer et al., 2011; Koop-Nieuwelink et al., 2019; Kuriyama et al., 2013; Li et al., 2018; Miwa et al., 2014; Sasaki et al., 2011; Wang et al., 2010) of the 37 studies evaluated cognition ability. The MMSE was well validated and thoroughly designed, but may be potentially disadvantaged in detecting early and mild cognitive impairment. However, the results of this meta-analysis showed that the cognitive impairment is more closely related to digressed renal function than dementia. Thus, the use of the MMSE may not properly supervise the mildest stages of cognitive deficits, as it is often found in patients with CKD. The utilization of the MMSE in patients with CKD is also concerning because the MMSE does not assess any aspect of executive function (Hachinski et al., 2006), which is the domain that has been proven to be more strongly associated with CKD progression than the other cognitive domains because its

deficits are linked to vascular risk factors and are often noted in patients with vascular dementia. The trial-making test forms B (TMT B) (Llinàs-Reglà et al., 2017) and the Category Fluency test (Welsh et al., 1994), and tests of executive function are therefore recommended for use in examinations of patients with CKD. However, to date, only one prospective cohort study has provided evidence of TMT B (Tollitt et al., 2021). Further research is needed to identify the most suitable cognitive test to assess cognitive ability in patients with CKD.

4.5. Public Health Implications

As our results proposed, decreased renal function may, to a certain extent, worsen brain cognitive function; thus, our study suggests that the management of modifiable factors in the pathway from the kidney function progression to functional neurodegenerative change is among the keys for prevention. Consequently, preservation of the kidney function to prevent dementia could be just as vital in the clinical care of older patients as it is for middle-aged patients. Given the large burden of structural and functional brain abnormalities in patients with CKD, cognitive screening and brain MRI should be performed for all patients with CKD. It is important for clinicians to select appropriate cognitive screening tests for CKD patients to avoid missing cases, and executive function should be considered as one of the domains assessed in adult CKD patients with suspected cognitive impairment.

5. Conclusion

Our meta-analysis is among the most extensive studies examining the association between the kidney dysfunction and functional and structural brain abnormalities. We conclude that worsening kidney function is associated with a decline in cognitive function, but not with the overall brain structural disorders. In addition, a higher UACR, but not eGFR, was associated with a higher risk of Alzheimer's disease and vascular dementia. Individuals with stage 3 CKD have a higher risk of developing cognitive brain dysfunction. Structural brain abnormalities, especially cerebral microbleeds and silent infarctions, might have harmful effects on the renal function. Further, the effects of brain abnormalities on the kidney function remain unclear. Hence, future longitudinal studies are still needed to elucidate the causal relationships and explore the window of prevention for the occurrence of these brain abnormalities in CKD patients.

Ethical approval

Ethical approval for this evidence synthesis was not required.

Contributors

XT and YPH contributed equally to this work. JBZ is corresponding authors. XT, YPH, YHC, HJG, HX, IP, YSQ and JYZ have full access to all the data in this study and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis. XT and YPH contributed to studies selection, data extraction, data analyses, and manuscript drafting. XT, YPH contributed to data analyses, data interpretation, and manuscript drafting. JBZ, XT and YPH contributed to study design, data interpretation, and final approval of the manuscript.

MAC revised this manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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The authors plan to disseminate these findings to appropriate audiences such as academia, clinicians, policy makers, and the general public through various channels including press release, social media, or e-newsletter.

Transparency statement

The lead author, JBZ, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the National Natural Science Foundation of China for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101762.

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