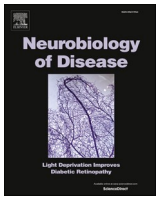
Neurobiology of Disease 200 (2024) 106626

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



Review

Kidney-brain axis in the pathogenesis of cognitive impairment

Qianqian Yan [a,1], Mengyuan Liu [b,1], Yiling Xie [a], Yimi Lin [a], Ping Fu [a], Yaoyu Pu [c,*], Bo Wang [a,*]

[a] Department of Nephrology, Institute of Kidney Diseases, West China Hospital of Sichuan University, Chengdu 610041, China
[b] Department of Anesthesiology, Air Force Hospital of Western Theater Command, PLA, Chengdu 610011, China
[c] Department of Rheumatology and Immunology, West China Hospital of Sichuan University, Chengdu 610041, China

A B S T R A C T

The kidney-brain axis is a bidirectional communication network connecting the kidneys and the brain, potentially affected by inflammation, uremic toxin, vascular injury, neuronal degeneration, and so on, leading to a range of diseases. Numerous studies emphasize the disruptions of the kidney-brain axis may contribute to the high morbidity of neurological disorders, such as cognitive impairment (CI) in the natural course of chronic kidney disease (CKD). Although the pathophysiology of the kidney-brain axis has not been fully elucidated, epidemiological data indicate that patients at all stages of CKD have a higher risk of developing CI compared with the general population. In contrast to other reviews, we mentioned some commonly used medicines in CKD that may play a pivotal role in the pathogenesis of CI. Revealing the pathophysiology interactions between kidney damage and brain function can reduce the potential risk of future CI. This review will deeply explore the characteristics, indicators, and potential pathophysiological mechanisms of CKD-related CI. It will provide a theoretical basis for identifying CI that progresses during CKD and ultimately prevents and treats CKD-related CI.

1. Introduction

The intricate connection between the kidneys and the nervous system plays a crucial role in maintaining overall homeostasis within the body. The kidneys participate in the processes that impact the systemic acid-base balance, electrolyte concentrations, volume states, and toxin levels, all of which have implications for the brain. At the same time, the functions of the kidneys are regulated by the brain. However, once various pathogenic factors disrupt the balance, it can lead to diseases affecting both the nervous system and the kidneys (Fig. 1).

Chronic kidney disease (CKD) refers to kidney structure or function abnormalities lasting at least three months, which have health implications and can result in end-stage renal disease (ESRD) (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2024). According to the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) project, there were approximately 697.5 million all-stage CKD cases worldwide in 2017, with a global prevalence of 9.1% (GBD Chronic Kidney Disease Collaboration , 2020Global, Regional, and National Burden of Chronic Kidney Disease, 1990-2017). A substantial number of patients with CKD suffer from neurological disorders, including cerebrovascular disease and cognitive impairment (CI). In a 6-year follow-up study, the effect of CKD on the risk of CI and dementia was ahead of genetic factors (Lipnicki et al., 2017). The research from the Suita Study showed an association between mild to moderate reductions in estimated glomerular filtration rate (eGFR, in ml/min/1.73 m^2) and CI (Arafa et al., 2024). Furthermore, results from the National Health and Nutritional Examination Survey (NHANES) suggested the risk of CI was higher in patients with CKD than non-CKD patients, and CKD patients with worse kidney function were associated with lower global cognitive function (Chu et al., 2022; Li et al., 2024; Zhou et al., 2024). Not only CKD, acute kidney injury (AKI) could lead to uremic encephalopathy and is associated with the risk of stroke and CI as well (Grams and Rabb, 2012; Husain-Syed et al., 2023; Tsai et al., 2017). Additionally, autosomal dominant polycystic kidney disease (ADPKD) has numerous systemic manifestations and cardiovascular complications, including aneurysmal subarachnoid hemorrhage, which tends to result in cognitive deficits (Rinkel and Ruigrok, 2022).

A recent study also highlighted a significant bidirectional relationship between previous strokes and the development of ESRD, emphasizing the interplay between brain and kidney injuries (Tollitt et al., 2019). Brain injury can affect the kidneys by elevating sympathetic activity, which modifies renal circulation, filtration in the glomeruli, and vasopressin secretion, leading to altered sodium and fluid homeostasis (Udy et al., 2017).As a predictor of impaired cognitive function and stroke, silent brain infarction (SBI) also presents a predictive ability of renal function progression in patients with CKD (Kobayashi et al., 2010). The brain's effects on the kidney, not just on CKD, but on both acute and chronic kidney diseases. In a study of 37,851 American

* Corresponding author.
E-mail addresses: puyaoyu@scu.edu.cn (Y. Pu), kingwave@scu.edu.cn (B. Wang).
[1] These authors contributed equally

https://doi.org/10.1016/j.nbd.2024.106626
Received 24 June 2024; Received in revised form 31 July 2024; Accepted 2 August 2024
Available online 8 August 2024

patients who suffered from traumatic brain injury (TBI), severe AKI was observed in 2.1% of cases, which was linked to increased mortality rates in hospitals, higher instances of morbidity, and extended durations of hospital stay (Luu et al., 2021).

The brain and kidneys are connected in various diseases. This review will mainly focus on the current knowledge of the relationship between CKD and CI. Understanding the communication mechanisms between the nervous system and the kidneys is crucial for developing strategies to ameliorate neurological conditions associated with kidney diseases and designing clinical interventions.

2. Characteristics of CKD-related CI

CKD is categorized by cause, glomerular filtration rate (GFR) category (G1-G5), and albuminuria category (A1-A3) (2). Research focusing on CI predominantly uses the GFR classification. As mentioned above, renal function is closely associated with CI. It is generally observed that the incidence of CI is higher in patients with more severe renal impairment (G4-G5) (Arafa et al., 2024; Chu et al., 2022; Foster et al., 2016), and individuals with severe kidney disease (eGFR<30 ml/min/1.73m^2) exhibited more serious CI (Burns et al., 2018). Female participants with CKD ≥ G2 stage showed consistently worse on the longitudinal cognitive and functional condition than those with a CKD of G1 stage (Iwata et al., 2018). Contrary to expectations, a study including 2306 participants (≥ 60 years) showed that early CKD stages (G1–2) increased the risk of immediate memory impairment by 47.4% and CI by 122.4%, while CKD of G3-G5 stages were not associated with CI (Huang et al., 2023). Moreover, cognitive performance contains multiple domains, including memory, attention, information processing, executive functioning, visuospatial skills, and language abilities, and certain studies have concentrated on particular aspects. CKD patients showed a higher risk of CI in the immediate learning ability, processing speed, sustained attention, and working memory (Li et al., 2023). Severe CKD-related CI was observed in most cognitive domains, including global cognition, verbal memory, attention, naming, and executive function, but not for verbal fluency (Elias et al., 2009; Yaffe et al., 2010). Moderate CKD was linked to diminished learning and concentration abilities, as well as visual attention impairments, but not reaction time (Hailpern et al., 2007). In a study of 4887 older adults (73.9 ± 8.3 years), a decline in eGFR was associated with a greater likelihood of error on the cognitive tests such as Mini Mental State Examination (MMSE)/Frontal Assessment Battery (FAB) and poorer overall performance on the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). Additionally, eGFR <45 ml/min/1.73 m^2 related to poorer performance on all five RBANS domains, with the greatest effect sizes for immediate memory, delayed memory, and attention (Dyer et al., 2022). This study reliably assessed cognitive function in patients with kidney injury using MMSE, one of the commonly used methods for assessing CI in CKD patients, combined with methods for measuring domain-specific cognitive function (Dyer et al., 2022).

The impact of CKD on cognitive function may vary depending on the etiology, unfortunately, research in this field is scarce. A limited number of studies have investigated CI caused by diabetes mellitus (DM) and lupus nephritis. The prevalence of CI in DM patients (80.6%) was significantly higher than in non-DM patients (67.9%). Furthermore, they had substantially lower visuospatial/executive function scores, naming, language, delayed recall, and orientation (Huang et al., 2021). In another study, the prevalence of CI was 17.7% in the DM group compared to 14.9% in the non-DM group (Moon et al., 2019). These outcomes are largely attributed to the more significant impact of diabetes on the vascular system compared to CKD alone. However, children with lupus nephritis exhibit cognitive functions comparable to or better than other children with CKD, which is reassuring considering the multiorgan and lifelong complications associated with lupus (Knight et al., 2017).

3. Indicators of CKD-related CI

A comprehensive understanding of the indicators associated with CKD-related CI can enhance early screening efforts and timely intervention (Table 1). Current evidence suggests that baseline renal insufficiency is a pivotal risk factor for CI. Several studies reported that eGFR decline could be a possible predictor for CI (Arafa et al., 2024; Levassort et al., 2024; Murray et al., 2016; Peng et al., 2021). Over a median follow-up of 5.4 years, participants with a severe decline in eGFR (>20% annually) had an increased risk of CI compared to those with stable

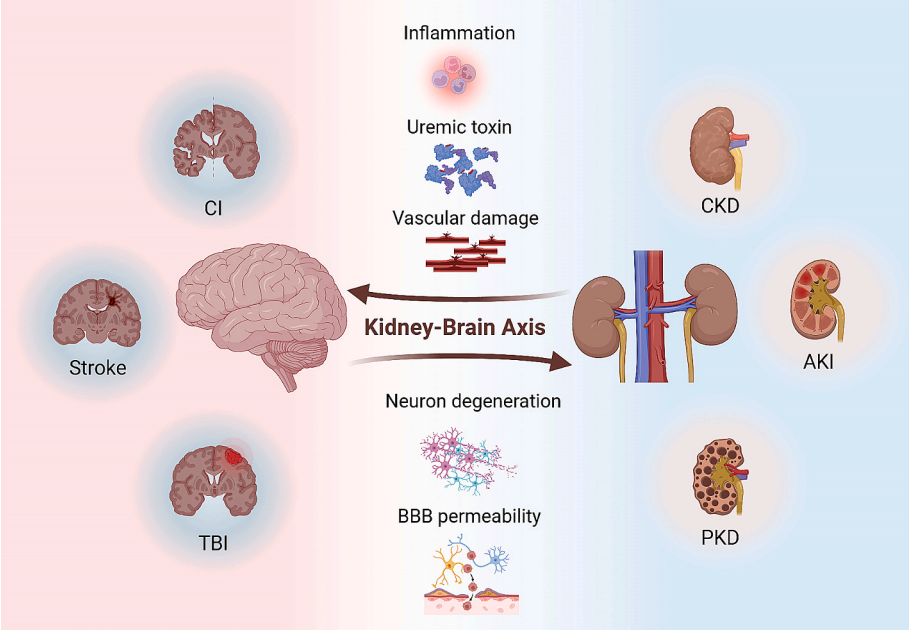


Fig. 1. The kidney-brain axis. The kidneys and brain communicate with each other in different diseases, mainly through a complex network including inflammation, uremic toxin, vascular damage, neuron degeneration, BBB permeability, and so on. Abbreviations: AKI, acute kidney disease; BBB, blood brain barrier; CI, cognitive impairment; CKD, chronic kidney disease; PKD, polycystic kidney disease; TBI, traumatic brain injury.

Table 1
Indicators of CKD-related CI.

Indicators	Inclusion of population	Outcomes	References
eGFR	6215 participants (from Japan)	-Each increment of eGFR by 10 mL/min/1.73m^2 was associated with 4.8% lower odds of CI.	(Arafa et al., 2024)
	3003 participants (from mainland France)	-eGFR was associated with changes in orientation, attention and calculation, language and praxis domain scores.	(Levassort et al., 2024)
	554 participants (from Minneapolis)	-Baseline cognitive performance was significantly associated with eGFR in all domains except language.	(Murray et al., 2016)
	33,654 participants (from China)	-Severe eGFR decline could be a possible predictor for cognitive deterioration or death among the elderly.	(Chen et al., 2017)
Albuminuria	237 participants (from Italian)	-Higher levels of albumin in the urine were associated with lower cognitive performance.	(Santulli et al., 2024)
	4128 participants (from Australia)	-An independent association of albuminuria with memory performance at 12 years of follow-up.	(Sacre et al., 2019)
	18,650 participants (from Australia and the United States)	-Screening cognitive tests for older persons with a urine albumin-creatinine ratio $\geq$ 3 mg/mmol could identify those at elevated risk of cognitive decline and dementia.	(Murray et al., 2022)
UACR	19,399 participants (from the United States)	-UACR 30–299 and $\geq$ 300 mg/g were independently associated with 31% and 57% higher risk for CI, respectively, relative to individuals with UACR <10 mg/g.	(Kurella Tamura et al., 2011)
β2M	100 participants (from China)	-Urinary β2-MG levels in older patients with CKD and cognitive dysfunction were significantly increased.	(Wang et al., 2023b)
SBP	3768 participants (from the United States)	-Among CKD, higher baseline SBP was associated with a higher risk of incident CI specifically in those individuals with eGFR>45 ml/min/1.73m^2.	(Babroudi et al., 2023)
Orthostatic blood pressure	160 participants (from China)	-Exaggerated orthostatic blood pressure reduction is a possible explanation for ESRD-associated memory deficits.	(Liu et al., 2019)
PEW	364 participants (from China)	-PEW was a possible independent risk factor for consciousness dysfunction in MHD patients.	(Yang et al., 2023)
TNF-α	132 participants	-Serum level of TNF-α is associated with the severity of cognitive decline: higher serum levels of TNF-α were found in patients with worse cognitive function.	(Guenzani et al., 2019)
IGF-1	93 participants	-IGF-1 can be considered a novel biomarker for the assessment of cognitive functioning in CKD patients.	(Prelevic et al., 2018)
BLL	412 participants (from the United States)	-Environmental lead exposure is associated with neurocognitive dysfunction in children with CKD.	(Ruebner et al., 2019)
CKD stages	385 participants (from Canadian)	-CKD of G4-G5 stages scored lower in all domains of cognition, with the most pronounced deficits observed in recall, attention, and visual/executive function.	(Foster et al., 2016)
Educational level	232 participants (from Ethiopia)	-Independent predictors of CI among CKD patients were proteinuria, age >65 years, and educational level of grade 8 or less.	(Gela et al., 2021)
Sleep duration	3215 participants (from the United States)	-Longer sleep duration is associated with worse cognitive function only among persons with CKD.	(Warsame et al., 2023)
Alcohol consumption	3005 participants (from the United States)	-Alcohol-heavy drinkers were significantly associated with a higher risk of CI in patients with hypertension and CKD compared with light drinkers.	(Yen et al., 2022)
Depression or anxiety	250 participants (from the United Kingdom)	-The prescription of psychodynamic medications and depression or anxiety were independent risk factors for CI.	(Tollitt et al., 2021)
Use of smartphone	416 participants (from China)	-Age, educational level, occupational status, use of smartphones, sleep disorder, and hemoglobin were independent influencing factors of MCI.	(Yang et al., 2024)
Marriage, history of living alone	200 participants (from China)	-The risk factors affecting cognitive dysfunction are age, education, marital status, divorced or widowed, payment method, self-funded, hypertension, and CKD.	(Wang et al., 2024)

CKD: chronic kidney disease; CI: cognitive impairment; eGFR: estimated glomerular filtration rate; β2M: beta-2 microglobulin; PEW: protein-energy wasting; TNF-α: tumor necrosis factor-α; SBP: systolic blood pressure; ESRD: end-stage renal disease; MHD: maintenance hemodialysis; CI: cognitive impairment; MCI: mild cognitive impairment; UACR: urea albumin/creatinine ratio; IGF-1: insulin growth factor 1; BLL: blood lead level.

eGFR (Chen et al., 2017). A study including CKD stages 3–4 patients over five years revealed that diminished eGFR correlated with inferior cognitive performance (Pépin et al., 2023b). However, another research showed that lower eGFR was associated with poorer cognitive function only among adults who manifested the gait phenotype (Koren et al., 2021). Albuminuria, an additional indicator of abnormal kidney function, which is also connected with CI, can be a predictor of the Alzheimer's disease subtype (Kelly et al., 2024; Sacre et al., 2019; Santulli et al., 2024). Notably, the utility of urinary albumin/creatinine ratio (UACR, in mg/g) as a biomarker is underscored by its ability to more

accurately reflect kidney disease's impact on the brain than eGFR, particularly in the elderly (Santulli et al., 2024). This population is prone to reduced muscle mass due to chronic illness, which can lead to an overestimation of GFR when based on creatinine levels. A longitudinal cohort study of older persons showed that baseline eGFR was not related to performance on any cognitive tests. Still, baseline UACR ≥26.6 mg/g was significantly associated with lower baseline scores and larger declines in cognition (Murray et al., 2022). A 10% increase in UACR, not a 10% change in eGFR, was associated with lower cortical thickness in all lobes except for the occipital lobe and lower hippocampal volume (Vemuri et al., 2017). Elevated UACR and reduced eGFR levels were significantly associated with total brain atrophy (Sink et al., 2015), while only higher UACR levels were closely related to higher white matter lesion volume (Maki et al., 2023). During an average 3.8 ± 1.5-year follow-up, UACR ranges of 30–299 and ≥ 300 mg/g were independently linked to 31% and 57% increased risks of CI, respectively, compared to individuals with UACR <10 mg/g (Kurella Tamura et al., 2011).

Additionally, markers such as cystatin C or β-2 microglobulin (β2M) may be less affected by such non-GFR determinants of creatinine (Inker et al., 2021; Stevens et al., 2008). Higher urinary β2M levels were relevant to worse cognitive scores at baseline (Miller et al., 2021). When combined with smoking and education data, it can effectively predict CI in CKD patients, with a model sensitivity of 60% and specificity of 90% (Wang et al., 2023b). Unlike creatinine, cystatin C is not modulated by protein intake or muscle mass and serves as a more accurate biomarker of eGFR in the older population, which is often the focus of CI studies (Lau and Fisher, 2023). Studies utilizing cystatin C data have identified an increased risk of CI at lower and higher levels of eGFR (Lau et al., 2020a; Paterson et al., 2021; Scheppach et al., 2023; Yaffe et al., 2014), especially in attention, executive function, and naming (Wang et al., 2023b).

Blood pressure is a critical hemodynamic factor in the process of CKD-related CI. In CKD patients with eGFR>45 ml/min/1.73m^2, a higher baseline systolic blood pressure (BP) was associated with an increased risk of CI (Babroudi et al., 2023). A recent study also showed that exaggerated orthostatic BP reduction has an influence on global cognition and can elucidate memory deficits caused by ESRD (Liu et al., 2019). Similarly, decreased maximum orthostatic systolic BP negatively affects short recall memory in ESRD and dialysis patients (Liu et al., 2019). The dietary factors might influence the CI in CKD patients as well. Protein-energy wasting (PEW), one of the commonest severe complications of ESRD, might be a crucial independent indicator for CI in ESRD and consciousness disturbance in maintenance hemodialysis patients (Yang et al., 2023). In the higher protein intake (protein consumption in >1.2 g/(kg·d) group, CKD of G1 to G2 stages elevated the risk of immediate memory impairment (Huang et al., 2023). Serum levels of tumor necrosis factor-α (TNF-α) and insulin growth factor 1 (IGF-1) can be considered novel biomarkers for assessing cognitive functioning in CKD patients (Guenzani et al., 2019; Prelevic et al., 2018). Moreover, disturbed purine nucleotide metabolism is another indicator of CI in CKD (Mazumder et al., 2018), while, low-level lead exposure is associated with lower intelligence quotient (IQ) and more inattention in children with CKD (Ruebner et al., 2019). Other risk factors include age, educational level, BMI, social support, sex, urea level, anemia, sleep duration, drinkers, family incomes, depression or anxiety, occupational status, use of smartphones, sleep disorders, marriage, history of living alone and comorbidity (Foster et al., 2016; Gela et al., 2021; Tollitt et al., 2021; Viriyapak et al., 2022; Wang et al., 2024; Warsame et al., 2023; Yaffe et al., 2013; Yang et al., 2024; Yen et al., 2022).

4. Mechanisms of CKD-related CI

Although an association between CKD and CI has been found, the underlying mechanisms are still not fully understood. A single theory cannot fully explain the potential link between the two diseases; we summarize several widely recognized mechanisms that may be jointly involved in developing CKD-related CI (Table 2). Notably, we highlight the crucial role of medicines in the pathogenesis of the process (Fig. 2).

4.1. Genetic factors

Distinctions are evident between pediatric and adult CKD populations. In pediatric CKD, up to 30% of cases, such as those with steroid-resistant nephrotic syndrome, are attributed to genetic factors (Landini et al., 2020). In these patients, neurocognitive impairment may result from a genomic disorder that causes both CKD and CI (Verbitsky et al., 2017). Syndromes like Bardet–Biedl, Fabry disease, Joubert syndrome, Schimke immuno-osseous dysplasia, tuberous sclerosis, and Lowe syndrome exemplify conditions that manifest both renal and cognitive impairments (Bökenkamp and Ludwig, 2016; Brancati et al., 2010; Karam et al., 2023; Liu et al., 2020a; Sánchez et al., 2023; Sigurdardottir et al., 2000). Genome-wide association studies (GWAS) of one million adults with CKD have pinpointed single-nucleotide polymorphisms (SNPs) in 147 loci related to kidney function. Notably, several of these SNPs are located in genes also expressed in the brain, hinting at a shared genetic basis for renal function and neurological conditions (Wuttke et al., 2019). Pediatric CKD populations more readily display genetic risk factors for CI, whereas adults may benefit from a comprehensive genetic risk score assessment.

4.2. Impaired vascular function

The kidneys and brain have unique susceptibility to vascular injury, and microvascular regulation in both organs is anatomically and functionally similar: both are high flow and rely on local self-regulation (Hachinski, 2012; Ito et al., 2009). When exposed to the low-resistance end of high-volume blood flow (Lee et al., 2010), their blood vessels are prone to damage, especially during dialysis; acute cerebral ischemia increases the risk of acute cognitive dysfunction due to hemodynamic changes (Stanciu et al., 2020). Harmke et al. employed [^{15}O] H2O PET-CT scans to demonstrate that cerebral blood flow declines rapidly in elderly patients during hemodialysis treatment (Polinder-Bos et al., 2018). A similar situation was also found in peritoneal dialysis patients (Cheng et al., 2019). Interestingly, the cognitive deterioration caused by decreased kidney function was improved after the kidney transplantation (Griva et al., 2006). At the same time, CI was also improved due to hemodynamic changes resulting from hemodialysis (Radić et al., 2011). On the other hand, endothelial dysfunction associated with increased vascular permeability due to blood composition changes induced by dialysis has become universal in dialysis patients with CKD (Gennip et al., 2019; Zhao et al., 2023b). Endothelium greatly influences the tension and structure of blood vessels. Vasodilatory substances produced by endothelial cells, such as nitric oxide, prostacyclin, and hyperpolarized relaxation factors are affected, resulting in reduced inhibition of platelet aggregation and smooth muscle cell proliferation, and the vascular wall is vulnerable to atherosclerotic and thrombotic events (Taddei et al., 2001). Notably, endothelial dysfunction is also accompanied by increased blood brain barrier (BBB) permeability (Lau et al., 2020b).

Vascular impairment plays a crucial part in the cognitive decline of the general population and is a vital factor in mortality for CKD patients (Ali et al., 2019). Small vessel injury was the earliest CKD-related lesion identified in the nervous system, which can induce brainstem and deep white matter of the central nervous system ischemic or hemorrhagic stroke (Yao et al., 2021). Vascular arteries are exposed to high pressure and maintain strong vascular tension, which is prone to endothelial dysfunction and lipid hyaline degeneration (Viggiano et al., 2020). Similar to renal arteriolar sclerosis, cerebrovascular lipid hyaline degeneration impacts brain self-regulation, reduces local cerebral blood flow, and leads to ischemic or hemorrhagic stroke (Bernbaum et al., 2015). Cerebrovascular disease appears to co-occur with

Table 2
Effects of medicines used in patients with CKD on CI.

Medicine classification	Medicine name	Underlying mechanism	Experimental animal/ Inclusion of population	Outcomes	References
Immunosuppressor	CPA	(1) Induces histopathological changes (2) Reduces synaptic plasticity (3) Influences the activity of AChE (4) Induces oxidative damage	Male Wistar rats	-CPA induces CI.	(Morid et al., 2023)
		(1) Enhances oxidative damage (2) Enhances secondary inflammatory (3) Influences AChE activity (4) Induces lipid peroxidation and accumulation of free radicals	Male Wistar rats	-CPA is neurotoxic.	(Rabie et al., 2023)
	Tacrolimus	(1) Leads to cerebrovascular events (2) Impairs brain function (3) Inhibits the cerebral immune system (4) Impairs the cerebral energy metabolism	42 kidney transplant patients	-Tacrolimus is associated with neurological complications.	(Pflugrad et al., 2020)
GCs	DEX	(1) Impairs spatial memory (2) Influences the activity of AChE (3) Induces neurochemical alterations (4) Increases MAO activity	Female Swiss mice	-DEX causes memory deficits.	(Strelow et al., 2023)
	CORT	(1) Bidirectionally modulates NSC proliferation (2) Bidirectionally modulates hippocampal neurogenesis (3) Affects hippocampal neurogenesis	Male C57BL/6 J mice	-Glucocorticoids have a U-shaped effect on hippocampal neuroregulation.	(Liu et al., 2024)
Antibiotics	Ampicillin/ Bacitracin/ Meropenem/ Neomycin/ Vancomycin	(1) Impair novel object recognition memory (2) Alter tight junction protein and cytokine mRNA expression in the amygdala and hippocampus (3) Alter expression patterns of neural signaling-related molecules in the brain (4) Induce gut dysbiosis	Male C57BL/6 N mice	-Antibiotics induce dysbiosis and impair cognitive performance.	(Fröhlich et al., 2016)

CKD: chronic kidney disease; CI: cognitive impairment; CPA: cyclophosphamide; GCs: Glucocorticoids; PRED: prednisone; MP: methylprednisolone; CORT: Corticosterone; AChE: acetylcholinesterase; DEX: dexamethasone; MAO: monoamine oxidase; NSC: neural stem cell.

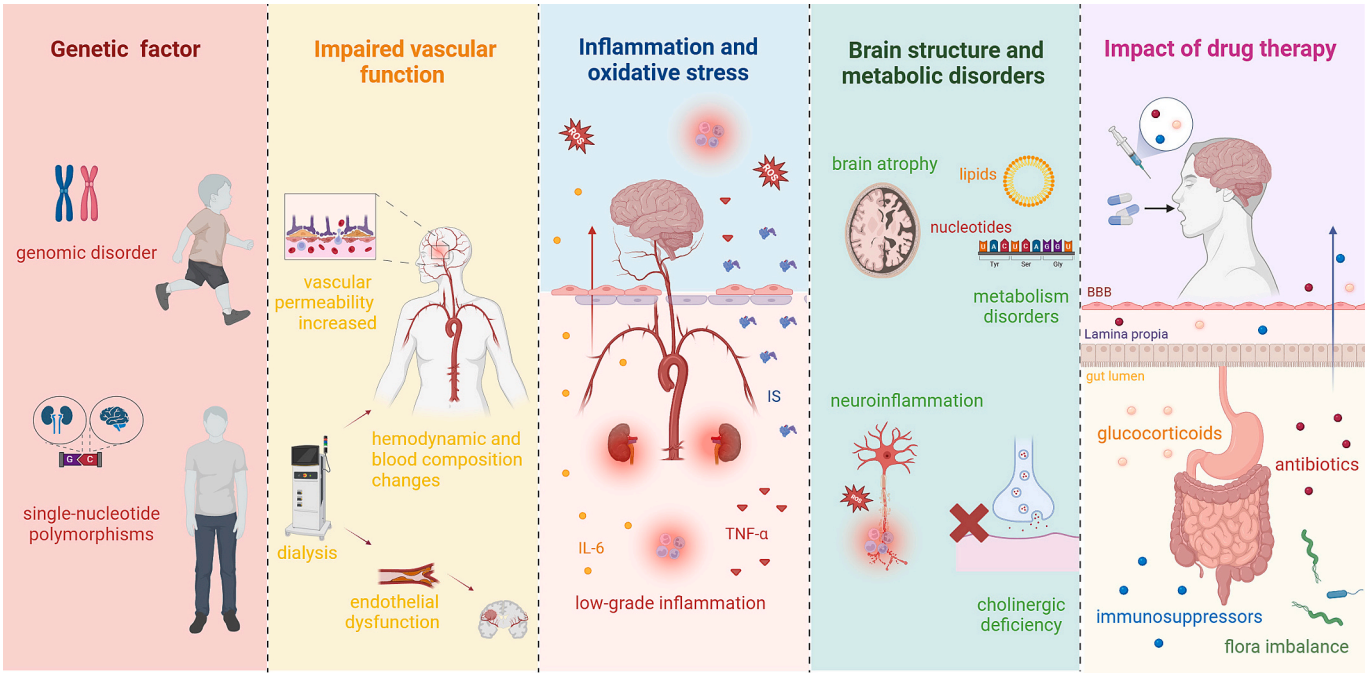


Fig. 2. The mechanisms involved in the crosstalk between chronic kidney disease (CKD) and cognitive impairment (CI). Genetic factor: In pediatric CKD, neurocognitive impairment may result from a genomic disorder that causes both CKD and CI. Unlike pediatric CKD, genetic factors of adult CKD may be related to single nucleotide polymorphisms. Impaired vascular function: During hemodialysis in patients with CKD, changes in hemodynamics and blood composition lead to increased vascular permeability, endothelial dysfunction, and ultimately brain disease and CI. Inflammation and Oxidative Stress: CKD patients are in a state of persistent low-grade inflammation. Inflammatory mediators such as interleukins-6 (IL-6), tumor necrosis factor-α (TNF-α), and uremic toxins such as indoxyl sulfate (IS) can cross the blood-brain barrier (BBB) and lead to a severe excess of reactive oxygen species (ROS) in brain. Brain structure and metabolic disorders: CKD patients may have brain atrophy, lipid and nucleotide metabolism disorders, neuroinflammation, and cholinergic deficiency, all of which may lead to CI. Impact of therapy: Drugs commonly used in CKD patients, such as glucocorticoids and immunosuppressants, can cross the BBB and affect the central nervous system, resulting in CI.

neurodegenerative mechanisms partially promoted by uremic toxins, homocysteine, cystatin C, and creatinine levels (Bugnicourt et al., 2013). Some of these factors are proven to accelerate systemic vascular arteriosclerosis and calcification in CKD patients (Nemcsik et al., 2012). The degree of renal insufficiency is related to the grade of carotid atherosclerosis, which is not only a predictor for future cardiovascular disease but also a direct source of cerebral thrombosis (Hojs Fabjan and Hojs, 2014; Toyoda and Ninomiya, 2014).

4.3. Inflammation and oxidative stress

Persistent low-grade inflammation presents at all stages of CKD, which accounts for cardiovascular and all-cause mortality to some extent (Yan and Shao, 2024), and the inflammation promotes neuroinflammation of brain tissue, leading to CI (Chen et al., 2023). According to mounting data, inflammatory processes impair neurodegenerative cascades, and various mediators related to inflammation can modulate brain function and track the disease's severity and progression (Zhou et al., 2023). In the early stages of CKD, levels of various mediators such as pro-inflammatory cytokines, interleukins-6 (IL-6), and TNF-α in the blood are elevated (Amdur et al., 2016). As the disease progresses, these mediators become favorable predictors of clinical adverse outcomes and death (Alves et al., 2018). At the same time, they can also cross the BBB, causing neuropsychiatric alterations (Miranda et al., 2017). However, some uremic toxins with neuroprotective effects do not cross the BBB under basic situations, and they are unlikely to directly contact neurons to protect the nerve (Viggiano et al., 2020). Uremic toxins have dual effects on neurons: neuroprotective and neurotoxic effects. For instance, uremic toxin can promote the phenotyping of macrophages into harmful pro-inflammatory M1 and activate microglia to facilitate brain injury after stroke, as well as oxidative stress and endothelial dysfunction in CKD patients (Assem et al., 2018; Yu et al., 2011).

Indoxyl sulfate (IS), one of the uremic toxins, plays a significant role in inducing renal-cerebral dysfunction (Li et al., 2021b) and is associated with the pathogenesis of neurological diseases in CKD patients (Karbowska et al., 2020). For example, IS can directly disrupt central nervous system homeostasis and neuronal damage by increasing oxidative stress (OS) and inflammation in glial cells (Adesso et al., 2017). IS not only accelerates the progression of CKD but may lead to vascular disease by inducing OS; it is also involved in endothelial dysfunction via inducing endothelial cell senescence (Yu et al., 2011). OS, a key inducer of vascular dysfunction, refers to a state of stress in which the body has a serious excess of reactive oxygen species (ROS) and active nitrogen substances (RNS) and a lack of antioxidants (Wang et al., 2023a). Kiichiro et al. established a stable mouse model of uremic CKD and demonstrated that antioxidant drugs could alleviate CI in CKD mice, thus proving that OS is related to CI in CKD (Fujisaki et al., 2014). In addition to the accumulation of neurotoxic metabolites, hormonal disturbances, and imbalances in excitatory and inhibitory neurotransmitters (Brouns and De Deyn, 2004; De Deyn et al., 2001), reactive oxygen species production is considered the main contributor to uremic encephalopathy (Deng et al., 2001). It may be explained by the damaging effects of ROS on the cerebrovascular system through enhancing vasodilation, modifying vascular reactivity, and disrupting the BBB (Yu et al., 2018). Similar to IS, ROS intensifies the number of inflammatory mediators in neurodegenerative disease patients, contributing to neuroinflammation and eventually promoting neuronal degeneration (Bishir et al., 2020; Guo et al., 2002).

4.4. Brain structure and metabolic disorders

CI is associated with abnormalities in brain structure, and the structure of the cerebral cortex, especially cortical thickness, is considered a neuroimaging biomarker for predicting cognitive decline (Chen et al., 2021; Yin et al., 2018). The conceivable cause of CI in CKD is that multiple cortical regions and subcortical regulatory neurons are damaged, resulting in dysregulation of some brain functional domains (Kim et al., 2022). Passer et al., who first depicted structural alterations in the cerebral cortex of CKD patients in 1977, reported a high prevalence of brain atrophy in end-stage uremia using computed tomography (Passer, 1977). The existence of the kidney-brain axis and the hypothesis that brain structure is affected by the progression of CKD are further supported. Large-scale Mendelian randomization was used by Chen et al. to prove that CKD, eGFR, and albuminuria may affect the cerebral cortex, indicating a pathophysiological role between kidney injury and brain function (Chen et al., 2021). Frontal and occipital lobes were the most relevant thinning regions of the cerebral cortex affected by proteinuria, which Cho et al. found through the retrospective study of 1215 normal elderly individuals (Cho et al., 2016). The results of the appeal experiments seem to imply that albuminuria may have neuronal toxicity, causing structural changes in the brain. However, other views suggest that damaged white matter integrity appears to be the major reason for CI in CKD patients, which plays a crucial role in harmonizing interactions between different brain regions and normal brain function (Liu et al., 2020b; Tuladhar et al., 2015). Unfortunately, no consensus exists on the location and extent of white matter integrity degradation, and studies hold diverse views (Jiang et al., 2021). An observational cohort study comparing magnetic resonance imaging images pre- and post-renal transplant suggests that nerve bundles associated with memory and executive function, such as the corpus callosum and cingulate gyrus may be related to white matter integrity (Gupta et al., 2016).

Diabetes mellitus, the main cause of CKD (Zhao et al., 2023c), can lead to cognitive decline, a process that is associated with brain metabolism disorders (Zheng et al., 2017). Compared to the control group, type 1 diabetes mice with cognitive decline (T1DCD) showed higher levels of lipid peroxidation and nucleotide metabolism disorders in the brain, higher levels of oxidative stress and neuroinflammation in the frontal cortex, and decreased energy metabolism (Xiong et al., 2023). Nucleotides and lipids are important components in maintaining cell homeostasis. Their metabolism disorders in the brain can lead to neuronal damage and, eventually, CI. Similarly, disturbances in brain energy metabolism can also cause CI in neurodegenerative diseases (Liu et al., 2021). At the same time, disruption of neurotransmitter metabolism was also observed in the brain of T1DCD mice. One of the most significant neurotransmitters in the central cholinergic system, acetylcholine functions in learning and memory and is vital in maintaining consciousness (Lai et al., 2022). The behavior and motor function of the nervous system are influenced by the cholinergic system and its neurotransmitter acetylcholine (ACh), and cholinergic deficiency can cause cognitive decline (Mazumder et al., 2019; Smogorzewski and Massry, 2008). Muhammed reported a general change in acetylcholinesterase (AChE) activity in CKD mice's brain, according to estimations from brain tissue homogenate and histoenzymological study (Mazumder et al., 2019). Moreover, Catalase activity alteration, mitochondrial dysfunction, and calcium dysregulation were found in the brain tissue of CKD mice (Mazumder et al., 2019). Other studies have further discovered that AChE activity change in the hypothalamus, cerebral cortex, and hippocampus may be the mechanism of CI in patients with CKD (Bohnen et al., 2005; Smogorzewski and Massry, 2008). Neuropeptide Y (NPY), regulating metabolism, is produced by certain neurons in the brain and nerve endings in the periphery, and can easily cross the BBB (Baker et al., 2013; Kastin and Akerstrom, 1999). Once the BBB is destroyed, inflammatory infiltration happens, and the production of NPY is affected; finally, a chain of neurometabolic dysfunction occurs (Li et al., 2021a). A recent study applied Mendelian randomization showed that elevated plasma NPY levels are a risk factor for the progression of CKD, supporting the hypothesis that NPY is implicated in kidney progression (Spoto et al., 2024). Coincidentally, NPY mRNA-expressing cells' quantity and silver grain density was increased in the brain, which was observed in some neurodegenerative diseases (Tanaka et al., 2021), and the increased signaling of NPY may contribute to the CI

(Rokot et al., 2021). Therefore, NPY is suspected to be a possible participant in expedited cognitive decline in patients with CKD (Zoccali et al., 2021). However, the effects of elevated NPY in CKD patients on CI and the specific mechanisms are unknown, and further research is needed.

4.5. Impact of drug therapy

Due to the prevalence of substantial comorbidities, CKD patients have a greater burden of polypharmacy and experience extensive adverse drug reactions (ADRs) (Pépin et al., 2023a). Among these ADRs, cognitive adverse reactions are common in CKD patients and may be modifiable by different classes of factors associated with CI (Pépin et al., 2023a). After these drugs enter the body, they are digested into small molecules, some of which can cross the BBB and affect the central nervous system, altering cognitive function (Hafez et al., 2023). Several drugs often included in therapeutic schedules for CKD patients are associated with CI, such as immunosuppressors, glucocorticoids, and antibiotics (Table 2).

4.5.1. Immunosuppressor

An important cause of CKD is immune-mediated glomerular disease, in which the inflammatory immune mechanism plays an important role. Immunosuppressants have become the main treatments for most chronic glomerular diseases but can cause plenty and continual neurological complications (Ponticelli and Campise, 2005). Immunosuppressants can affect the central nervous system through direct or indirect neurotoxicity (Piotrowski et al., 2017). The commonly used drugs for CKD, tacrolimus (TAC) and cyclophosphamide are immunosuppressants highly correlated with neurological complications (Jurgensen et al., 2020). Normally, these drugs do not cross the BBB easily, but CKD can affect the BBB permeability, thereby making immunosuppressants more prone to poison the nervous system (Stolp et al., 2005). Cyclophosphamide affects the structure and function of synapses, a process linked to CI (Morid et al., 2023). According to the report, the rats injected with cyclophosphamide showed histopathological changes in the hippocampus and prefrontal cortex, manifesting as neuron phagocytosis, apoptosis, neuronal disorders, and degeneration, ultimately leading to memory decline in rats (Morid et al., 2023). On the other hand, cyclophosphamide affects the production of ACh (Morid et al., 2023; Rabie et al., 2023), whose deficiency can cause cognitive decline. As early as 15 years ago, a study found that organ transplant patients developed CI after treatment with tacrolimus (Aridon et al., 2009). Ten years later, this conclusion was confirmed again in 42 patients who received kidney transplants and took tacrolimus (Pflugrad et al., 2020). Researchers found that these patients showed structural and metabolic changes in the brain after taking tacrolimus, suggesting that tacrolimus may cause neurodegenerative changes by suppressing the brain's immune system (Pflugrad et al., 2020).

4.5.2. Glucocorticoids

One of the most popular glomerular diseases all over the world is immunoglobulin A nephropathy (IgAN), a vital reason for CKD (Yan et al., 2024), which is often treated with glucocorticoids (GCs) (Zhao et al., 2023a). Due to their powerful anti-inflammatory and immunosuppressive effects, GCs have been widely used for treating kidney diseases in recent years and have become one of the basic drugs for improving renal function. GCs are steroid hormones secreted by the adrenal cortex and also play roles in nervous tissue, involved in the pathophysiological processes of neurodevelopment, cognition, and neurodegenerative disorders (Tsimpolis et al., 2024). Studies have shown that aberrant swings of GCs may induce serious CI (Cao et al., 2023) and even affect brain structure, leading to brain atrophy (De Alcubierre et al., 2023). For instance, patients who received high doses of GCs in the short term experienced brain atrophy (Rao et al., 2002), and some patients recovered their brain structure after stopping GCs treatment (Bentson et al., 1978). Meanwhile, research found that GCs influence the activity of AChE in the prefrontal lobe of Swiss mice, which may be a factor that affects CI (Strelow et al., 2023). However, other studies suggest that GCs may alleviate CI, enhance synaptic function, and protect neurons (De Alcubierre et al., 2023). The differing views of these studies may be due to differences in the dose and type of GCs used on laboratory animals, as well as the timing of administration (De Alcubierre et al., 2023). Liu et al. discovered that GCs can facilitate neural stem cell (NSC) proliferation and adult hippocampal neurogenesis at a physiological level; however, the stress level of GCs has the opposite effect and may even result in NSC apoptosis (Liu et al., 2024). In conclusion, more research is needed to elucidate the effects of GCs on CI and the pathophysiological mechanisms involved.

4.5.3. Antibiotics

Patients with CKD are susceptible to infection because of malnutrition, low immunity, and frequent use of GCs and immunosuppressants, so the possibility of using antibiotics is high (Wang and Liu, 2022). People usually notice the common side effects of antibiotics on the digestive and cardiovascular systems, such as vomiting, diarrhea, and arrhythmia; in fact, these substances seriously affect the peripheral and central nervous systems (Bhattacharyya et al., 2014). Because of the reduced renal excretion function in patients with CKD, antibiotics are more likely to cause antibiotic-associated encephalopathy (AAE) through direct neurotoxicity or interaction with other drugs (Wang and Liu, 2022). The mechanism by which antibiotics are toxic to the nervous system includes affecting the delivery of neurotransmitters (Hafez et al., 2023). Mice that developed cognitive deficits after antibiotic use had changes in specific brain regions associated with the expression of cognition-relevant signaling molecules, especially brain-derived neurotrophic factor and the NPY system (Fröhlich et al., 2016). It is worth mentioning that antibiotics can cause intestinal flora imbalance, affect microbial metabolism, and change intestinal microbiota-brain communication, which leads to significant alterations in molecular expression related to brain function (Fröhlich et al., 2016). At present, few studies have been conducted on CI caused by antibiotic use in patients with CKD, but studies about the effect of antibiotics on cognition are often reported. Therefore, we have reason to suspect that antibiotics are involved in the development of CI in CKD patients.

4.5.4. Other potential drugs

Drug therapy is one of the main treatments for patients with CKD. In addition to the three types mentioned above, drugs commonly used to treat patients with CKD include sodium-glucose co-transporter 2 inhibitors (SGLT2i), antidiabetic agents, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). It is worth mentioning that SGLT2i, a novel drug for treating CKD, has underlying cardiorenal protection effects and has become an effective means to treat CKD (Terzo et al., 2024). The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for Evaluation and Management of Chronic Kidney Disease offers a 1 A recommendation for adult patients with CKD (2). Recently, researchers have found that SGLT2i has neuroprotective effects, including decreasing neuroinflammation, improving synaptic plasticity, and promoting neuron survival (Mancinetti et al., 2023). The multiple mechanisms of action of antidiabetic agents, ACEIs, and ARBs also suggest that some may have neuroprotective effects in addition to their renoprotection (Cohen et al., 2022; Müller et al., 2023; Tian et al., 2023). The treatment of CKD is a long and comprehensive treatment process. Most drugs are completely or partially metabolized and cleared by the kidneys, and the reduction of GFR in CKD patients can cause changes in their pharmacokinetics and pharmacodynamics. Therefore, more studies need to confirm the specific role of these drugs in CKD-related CI.

5. The influence of CI on kidney function

As we mentioned above, CKD and CI share many common risk factors; therefore, patients with CKD have a high probability of developing CI. Similarly, damage to the brain appears to affect kidney function and promote the development of kidney disease. In developing certain diseases, bidirectional communication between the brain and kidneys may exist (Xie et al., 2022). The nervous system communicates with the kidneys in the physiological state to maintain the homeostasis of the internal environment. When the balance is disrupted, the nervous system can directly or indirectly influence the process of CKD through neuroimmunomodulation (Tanaka and Okusa, 2020). Possible causes include the renal vascular system and tubular epithelial cells directly affected by neurotransmitters released from sympathetic nerve endings (Tanaka and Okusa, 2020). As mentioned earlier, the kidneys and the brain have similar hemodynamic properties. When a patient develops small blood vessel disease in the brain, such as a silent cerebral infarction (SCI), small blood vessel damage may also be present in the kidneys (Uzu et al., 2010). In addition, cerebral microvascular disease can predict the occurrence and progression of kidney disease in diabetic patients (Bouchi et al., 2010). In a study of 608 patients with type 2 diabetes, Takashi et al. found that patients who also suffer from SCI had an increased risk of developing ESRD or elevated serum creatinine concentrations (Uzu et al., 2010). Japanese researchers further demonstrated that diabetic patients with SCI have a higher risk of kidney disease development and progression than those with diabetes alone through 366 type 2 diabetes patients (Bouchi et al., 2010). Similarly, it has been suggested that impaired cognitive function can identify patients with systemic microvascular disease who are at risk of progressing to CKD (Kurella Tamura et al., 2016). Particularly, experts assume impairment of executive function is associated with vascular risk factors, so it is more strongly linked with CKD progression than in other cognitive areas (Hachinski et al., 2006; Kurella Tamura et al., 2016). One advantage of the vascular connection between the two organs is that microvascular disease in the kidneys needs to be evaluated by biopsy, while microvascular disease in the brain can be detected by non-invasive imaging to minimize patient harm (Kurella Tamura et al., 2016). Although the current number of studies on CI causing kidney damage is small, this potential link has attracted the attention of researchers, hoping that more studies will clarify the underlying mechanisms.

6. Treatment strategies and preventive measures

At present, the effectiveness of treating or improving CI symptoms in CKD patients is limited (Viggiano et al., 2020). The core strategy to combat CKD-related CI lies in prevention (Drew et al., 2019). Therefore, blocking the common pathophysiological mechanism of the occurrence and development of CKD and CI may be the key to prevention (Drew et al., 2019), mainly including treatment of CKD and its complications, prevention of vascular risk factors, and lifestyle modification (Pépin et al., 2023a). At the same time, we need to identify and screen high-risk patients who may develop CI in CKD as early as possible, such as elderly patients with CKD, especially those who start dialysis treatment and those with cerebrovascular diseases and diabetes (Drew et al., 2019; Drew et al., 2017). In addition, given that the medicines used by CKD patients have different effects on CI, reevaluating medicine prescribing in CKD patients may be an important step in preventing or improving CKD-related CI (Hafez et al., 2023). The literature recommends CKD patients to use drugs that may impede CI progression in addition to treating kidney diseases, such as ACEIs/ARBs, SGLT2i, antidiabetic agents, and antihypertensive agents (Drew et al., 2019); reduce or avoid the use of medicines that may promote the progression of CI, such as antibiotics, immunosuppressants, anticholinergics, and opioids (Hafez et al., 2023). Finally, extending dialysis time, lowering the dialysate temperature, taking melatonin, and regular exercise were all considered protective factors for CI (Tsuruya and Yoshida, 2024). Given the bidirectional communication between the brain and the kidneys, renal function monitoring in patients with CI may be necessary (Pépin et al., 2023a).

7. Discussion

CKD and CI are closely related, but there are still many unsolved problems, including the crosstalk mechanism, the early identification of the diseases, and the specific treatment and prevention measures. In addition, we did not find relevant studies comparing the risk of CI in different pathological types or at all stages of CKD. In the future, more studies should focus on the specific pathological and stage classification of CKD patients, exploring the relationship between these two and the risk of CI. The connection between the kidneys and the brain is complex, multifaceted, and bidirectional, and clinicians need to understand the potential links better to enable early diagnosis and treatment. Especially in this accelerating aging society, the phenomenon of CKD causing CI is becoming more and more common, and early prevention is particularly important. In addition to the oft-mentioned mechanisms between CKD and CI, we also summarize the possible effects of drugs commonly used in CKD patients on the development of CI, hoping to assist clinicians when prescribing drugs. We are the first to note and summarize the possible effects of generally used medicines on the pathogenesis of CI in the treatment of CKD. Although there are few reports about CI directly caused by drug use in CKD patients, given the frequency of prescription in CKD patients and the exact effects of drugs on CI, it is reasonable to infer that some common drugs for CKD patients can cause CI, and play a certain role in the crosstalk process of CKD and CI. Due to the problems of polypharmacy, pharmacokinetic changes, and BBB damage in patients with CKD, it is crucial to use drugs carefully and monitor adverse reactions. Early detection of drug-induced CI and discontinuation of risk drugs are essential, which may improve patient outcomes and significantly reduce patient mortality. Certainly, we can not only focus on the unilateral impact of the kidneys on the brain; CI patients should also undergo a comprehensive assessment of renal function, especially in elderly patients. Finally, we call on clinicians to pay more attention to the crosstalk relationship between organs, especially brain-body communication, which may bring unexpected benefits to the treatment process of diseases.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 82300840 to BW; Grant No. 82101616 to YYP), the Natural Science Foundation of Sichuan Province (Grant No. 2024NSFSC1503 to BW; Grant No. 2 023NSFSC1703 to YYP), and the 1.3.5 project for disciplines of excellence from West China Hospital of Sichuan University (Grant No. ZYGD23015 to PF). The figures were created with a free version of Biorender.com under agreement number YK272LNCYA and UH272LNDYU.

CRediT authorship contribution statement

Qianqian Yan: Writing – original draft. **Mengyuan Liu:** Writing – original draft. **Yiling Xie:** Software. **Yimi Lin:** Software. **Ping Fu:** Investigation. **Yaoyu Pu:** Supervision, Funding acquisition. **Bo Wang:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2024.106626.

References

Adesso, S., Magnus, T., Cuzzocrea, S., Campolo, M., Rissiek, B., Paciello, O., Autore, G., Pinto, A., Marzocco, S., 2017. Indoxyl sulfate affects glial function increasing oxidative stress and Neuroinflammation in chronic kidney disease: interaction between astrocytes and microglia. Front. Pharmacol. 8, 370. https://doi.org/10.3389/fphar.2017.00370.

Ali, S., Dave, N., Virani, S.S., Navaneethan, S.D., 2019. Primary and secondary prevention of cardiovascular disease in patients with chronic kidney disease. Curr. Atheroscler. Rep. 21, 32. https://doi.org/10.1007/s11883-019-0794-6.

Alves, F.C., Sun, J., Qureshi, A.R., Dai, L., Snaedal, S., Bárány, P., Heimbürger, O., Lindholm, B., Stenvinkel, P., 2018. The higher mortality associated with low serum albumin is dependent on systemic inflammation in end-stage kidney disease. PLoS ONE 13, e0190410. https://doi.org/10.1371/journal.pone.0190410.

Amdur, R.L., Feldman, H.I., Gupta, J., Yang, W., Kanetsky, P., Shlipak, M., Rahman, M., Lash, J.P., Townsend, R.R., Ojo, A., Roy-Chaudhury, A., Go, A.S., Joffe, M., He, J., Balakrishnan, V.S., Kimmel, P.L., Kusek, J.W., Raj, D.S., 2016. Inflammation and progression of CKD: the CRIC study. Clin. J. Am. Soc. Nephrol. 11, 1546–1556. https://doi.org/10.2215/cjn.13121215.

Arafa, A., Kawachi, H., Matsumoto, C., Teramoto, M., Yasui, Y., Kato, Y., Matsuo, M., Nakao, Y.M., Kashima, R., Kokubo, Y., 2024. The association between the estimated glomerular filtration rate and cognitive impairment: the Suita study. Hypertens. Res. 47, 672–676. https://doi.org/10.1038/s41440-023-01476-8.

Aridon, P., Ragonese, P., Di Benedetto, N., Grasso, G., Conaldi, P.G., D'amelio, M., Savettieri, G., 2009. Progressive necrotic encephalopathy following tacrolimus therapy for liver transplantation. Neurol. Sci. 30, 527–529. https://doi.org/10.1007/s10072-009-0149-0.

Assem, M., Lando, M., Grissi, M., Kamel, S., Massy, Z.A., Chillon, J.M., Hénaut, L., 2018. The impact of uremic toxins on cerebrovascular and cognitive disorders. Toxins 10. https://doi.org/10.3390/toxins10070303.

Babroudi, S., Tighiouart, H., Schrauben, S.J., Cohen, J.B., Fischer, M.J., Rahman, M., Hsu, C.-Y., Sozio, S.M., Weir, M., Sarnak, M., Yaffe, K., Tamura, M.K., Drew, D., 2023. Blood pressure, incident cognitive impairment, and severity of CKD: findings from the chronic renal insufficiency cohort (CRIC) study. Am. J. Kidney Dis. 82 https://doi.org/10.1053/j.ajkd.2023.03.012.

Baker, D.G., Bertram, T.M., Patel, P.M., Barkauskas, D.A., Clopton, P., Patel, S., Geracioti Jr., T.D., Haji, U., O'connor, D.T., Nievergelt, C.M., Hauger, R.L., 2013. Characterization of cerebrospinal fluid (CSF) and plasma NPY levels in normal volunteers over a 24-h timeframe. Psychoneuroendocrinology 38, 2378–2382. https://doi.org/10.1016/j.psyneuen.2013.04.020.

Bentson, J., Reza, M., Winter, J., Wilson, G., 1978. Steroids and apparent cerebral atrophy on computed tomography scans. J. Comput. Assist. Tomogr. 2, 16–23. https://doi.org/10.1097/00004728-197801000-00003.

Bernbaum, M., Menon, B.K., Fick, G., Smith, E.E., Goyal, M., Frayne, R., Coutts, S.B., 2015. Reduced blood flow in normal white matter predicts development of leukoaraiosis. J. Cereb. Blood Flow Metab. 35, 1610–1615. https://doi.org/10.1038/jcbfm.2015.92.

Bhattacharyya, S., Darby, R., Berkowitz, A.L., 2014. Antibiotic-induced neurotoxicity. Curr. Infect. Dis. Rep. 16, 448. https://doi.org/10.1007/s11908-014-0448-3.

Bishir, M., Bhat, A., Essa, M.M., Ekpo, O., Ihunwo, A.O., Veeraraghavan, V.P., Mohan, S. K., Mahalakshmi, A.M., Ray, B., Tuladhar, S., Chang, S., Chidambaram, S.B., Sakharkar, M.K., Guillemin, G.J., Qoronfleh, M.W., Ojcius, D.M., 2020. Sleep deprivation and neurological disorders. Biomed. Res. Int. 2020, 5764017 https://doi.org/10.1155/2020/5764017.

Bohnen, N.I., Kaufer, D.I., Hendrickson, R., Ivanco, L.S., Lopresti, B., Davis, J.G., Constantine, G., Mathis, C.A., Moore, R.Y., Dekosky, S.T., 2005. Cognitive correlates of alterations in acetylcholinesterase in Alzheimer's disease. Neurosci. Lett. 380, 127–132. https://doi.org/10.1016/j.neulet.2005.01.031.

Bökenkamp, A., Ludwig, M., 2016. The oculocerebrorenal syndrome of Lowe: an update. Pediatr. Nephrol. 31, 2201–2212.

Bouchi, R., Babazono, T., Yoshida, N., Nyumura, I., Toya, K., Hayashi, T., Hanai, K., Tanaka, N., Ishii, A., Iwamoto, Y., 2010. Silent cerebral infarction is associated with the development and progression of nephropathy in patients with type 2 diabetes. Hypertens. Res. 33, 1000–1003. https://doi.org/10.1038/hr.2010.122.

Brancati, F., Dallapiccola, B., Valente, E.M., 2010. Joubert syndrome and related disorders. Orphanet J. Rare Dis. 5, 20. https://doi.org/10.1186/1750-1172-5-20.

Brouns, R., De Deyn, P.P., 2004. Neurological complications in renal failure: a review. Clin. Neurol. Neurosurg. 107, 1–16. https://doi.org/10.1016/j.clineuro.2004.07.012.

Bugnicourt, J.M., Godefroy, O., Chillon, J.M., Choukroun, G., Massy, Z.A., 2013. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J. Am. Soc. Nephrol. 24, 353–363. https://doi.org/10.1681/asn.2012050536.

Burns, C.M., Knopman, D.S., Tupper, D.E., Davey, C.S., Slinin, Y.M., Lakshminarayan, K., Rossom, R.C., Pederson, S.L., Gilbertson, D.T., Murray, A.M., 2018. Prevalence and risk of severe cognitive impairment in advanced chronic kidney disease. J. Gerontol. A Biol. Sci. Med. Sci. 73, 393–399. https://doi.org/10.1093/gerona/glx241.

Cao, Y., Song, Y., Ding, Y., Ni, J., Zhu, B., Shen, J., Miao, L., 2023. The role of hormones in the pathogenesis and treatment mechanisms of delirium in ICU: the past, the present, and the future. J. Steroid Biochem. Mol. Biol. 233, 106356 https://doi.org/10.1016/j.jsbmb.2023.106356.

Chen, Y.-C., Weng, S.-C., Liu, J.-S., Chuang, H.-L., Hsu, C.-C., Tarng, D.-C., 2017. Severe decline of estimated glomerular filtration rate associates with progressive cognitive deterioration in the elderly: a community-based cohort study. Sci. Rep. 7, 42690 https://doi.org/10.1038/srep42690.

Chen, X., Kong, J., Pan, J., Huang, K., Zhou, W., Diao, X., Cai, J., Zheng, J., Yang, X., Xie, W., Yu, H., Li, J., Pei, L., Dong, W., Qin, H., Huang, J., Lin, T., 2021. Kidney damage causally affects the brain cortical structure: a Mendelian randomization study. EBioMedicine 72, 103592. https://doi.org/10.1016/j.ebiom.2021.103592.

Chen, X., Xia, Y., Shen, S., Wang, C., Zan, R., Yu, H., Yang, S., Zheng, X., Yang, J., Suo, T., Gu, Y., Zhang, X., 2023. Research on the current application status of magnesium metal stents in human luminal cavities. J. Funct. Biomater. 14 https://doi.org/10.3390/jfb14090462.

Cheng, B.C., Chen, P.C., Chen, P.C., Lu, C.H., Huang, Y.C., Chou, K.H., Li, S.H., Lin, A.N., Lin, W.C., 2019. Decreased cerebral blood flow and improved cognitive function in patients with end-stage renal disease after peritoneal dialysis: an arterial spin-labelling study. Eur. Radiol. 29, 1415–1424. https://doi.org/10.1007/s00330-018-5675-9.

Cho, E.B., Shin, H.Y., Park, S.E., Chun, P., Jang, H.R., Yang, J.J., Kim, H.J., Kim, Y.J., Jung, N.Y., Lee, J.S., Lee, J., Jang, Y.K., Jang, E.Y., Kang, M., Lee, J.M., Kim, C., Min, J.H., Ryu, S., Na, D.L., Seo, S.W., 2016. Albuminuria, cerebrovascular disease and cortical atrophy: among cognitively Normal elderly individuals. Sci. Rep. 6, 20692 https://doi.org/10.1038/srep20692.

Chu, N.M., Hong, J., Harasemiw, O., Chen, X., Fowler, K.J., Dasgupta, I., Bohm, C., Segev, D.L., Mcadams-Demarco, M.A., 2022. Chronic kidney disease, physical activity and cognitive function in older adults-results from the National Health and nutrition examination survey (2011-2014). Nephrol. Dial. Transplant. 37, 2180–2189. https://doi.org/10.1093/ndt/gfab338.

Cohen, J.B., Marcum, Z.A., Zhang, C., Derington, C.G., Greene, T.H., Ghazi, L., Herrick, J. S., King, J.B., Cheung, A.K., Bryan, N., Supiano, M.A., Sonnen, J.A., Weintraub, W.S., Scharfstein, D., Williamson, J., Pajewski, N.M., Bress, A.P., 2022. Risk of mild cognitive impairment or probable dementia in new users of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors: a secondary analysis of data from the systolic blood pressure intervention trial (SPRINT). JAMA Netw. Open 5, e2220680. https://doi.org/10.1001/jamanetworkopen.2022.20680.

De Alcubierre, D., Ferrari, D., Mauro, G., Isidori, A.M., Tomlinson, J.W., Pofi, R., 2023. Glucocorticoids and cognitive function: a walkthrough in endogenous and exogenous alterations. J. Endocrinol. Investig. 46, 1961–1982. https://doi.org/10.1007/s40618-023-02091-7.

De Deyn, P.P., D'hooge, R., Van Bogaert, P.P., Marescau, B., 2001. Endogenous guanidino compounds as uremic neurotoxins. Kidney Int. Suppl. 78, S77–S83. https://doi.org/10.1046/j.1523-1755.2001.59780077.x.

Deng, G., Vaziri, N.D., Jabbari, B., Ni, Z., Yan, X.X., 2001. Increased tyrosine nitration of the brain in chronic renal insufficiency: reversal by antioxidant therapy and angiotensin-converting enzyme inhibition. J. Am. Soc. Nephrol. 12, 1892–1899. https://doi.org/10.1681/asn.V1291892.

Drew, D.A., Weiner, D.E., Tighiouart, H., Duncan, S., Gupta, A., Scott, T., Sarnak, M.J., 2017. Cognitive decline and its risk factors in prevalent hemodialysis patients. Am. J. Kidney Dis. 69, 780–787. https://doi.org/10.1053/j.ajkd.2016.11.015.

Drew, D.A., Weiner, D.E., Sarnak, M.J., 2019. Cognitive impairment in CKD: pathophysiology, management, and prevention. Am. J. Kidney Dis. 74, 782–790. https://doi.org/10.1053/j.ajkd.2019.05.017.

Dyer, A.H., Laird, E., Hoey, L., Hughes, C.F., Mcnulty, H., Ward, M., Strain, J.J., O'kane, M., Tracey, F., Molloy, A.M., Cunningham, C., Sexton, D.J., Mccarroll, K., 2022. Reduced kidney function is associated with poorer domain-specific cognitive performance in community-dwelling older adults. Int. J. Geriatr. Psychiatry 37. https://doi.org/10.1002/gps.5771.

Elias, M.F., Elias, P.K., Seliger, S.L., Narsipur, S.S., Dore, G.A., Robbins, M.A., 2009. Chronic kidney disease, creatinine and cognitive functioning. Nephrol. Dial. Transplant. 24, 2446–2452. https://doi.org/10.1093/ndt/gfp107.

Foster, R., Walker, S., Brar, R., Hiebert, B., Komenda, P., Rigatto, C., Storsley, L., Prasad, B., Bohm, C., Tangri, N., 2016. Cognitive impairment in advanced chronic kidney disease: the Canadian frailty observation and interventions trial. Am. J. Nephrol. 44, 473–480.

Fröhlich, E.E., Farzi, A., Mayerhofer, R., Reichmann, F., Jačan, A., Wagner, B., Zinser, E., Bordag, N., Magnes, C., Fröhlich, E., Kashofer, K., Gorkiewicz, G., Holzer, P., 2016. Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. Brain Behav. Immun. 56, 140–155. https://doi.org/10.1016/j.bbi.2016.02.020.

Fujisaki, K., Tsuruya, K., Yamato, M., Toyonaga, J., Noguchi, H., Nakano, T., Taniguchi, M., Tokumoto, M., Hirakata, H., Kitazono, T., 2014. Cerebral oxidative stress induces spatial working memory dysfunction in uremic mice: neuroprotective effect of tempol. Nephrol. Dial. Transplant. 29, 529–538. https://doi.org/10.1093/ndt/gft327.

Gela, Y.Y., Getu, A.A., Adane, A., Ayal, B.M., Akalu, Y., Ambelu, A., Diress, M., Yeshaw, Y., 2021. Cognitive impairment and associated factors among chronic kidney disease patients: a comparative cross-sectional study. Neuropsychiatr. Dis. Treat. 17, 1483–1492. https://doi.org/10.2147/NDT.S304543.

Gennip, A., Broers, N.J.H., Meulen, K.J.T., Canaud, B., Christiaans, M.H.L., Cornelis, T., Gelens, M., Hermans, M.M.H., Konings, C., Net, J.B.V., Sande, F.M.V., Schalkwijk, C. G., Stifft, F., Wirtz, J., Kooman, J.P., Martens, R.J.H., 2019. Endothelial dysfunction and low-grade inflammation in the transition to renal replacement therapy. PLoS ONE 14, e0222547. https://doi.org/10.1371/journal.pone.0222547.

Global, Regional, and National Burden of Chronic Kidney Disease, 1990-2017. A systematic analysis for the global burden of disease study 2017. Lancet 395, 709–733. https://doi.org/10.1016/S0140-6736(20)30045-3.
Grams, M.E., Rabb, H., 2012. The distant organ effects of acute kidney injury. Kidney Int. 81, 942–948. https://doi.org/10.1038/ki.2011.241.
Griva, K., Thompson, D., Jayasena, D., Davenport, A., Harrison, M., Newman, S.P., 2006. Cognitive functioning pre- to post-kidney transplantation–a prospective study. Nephrol. Dial. Transplant. 21, 3275–3282. https://doi.org/10.1093/ndt/gfl385.
Guenzani, D., Buoli, M., Caldiroli, L., Carnevali, G.S., Serati, M., Vezza, C., Armelloni, S., Messa, P., Vettoretti, S., 2019. Malnutrition and inflammation are associated with severity of depressive and cognitive symptoms of old patients affected by chronic kidney disease. J. Psychosom. Res. 124, 109783 https://doi.org/10.1016/j.jpsychores.2019.109783.
Guo, J.T., Yu, J., Grass, D., De Beer, F.C., Kindy, M.S., 2002. Inflammation-dependent cerebral deposition of serum amyloid a protein in a mouse model of amyloidosis. J. Neurosci. 22, 5900–5909. https://doi.org/10.1523/jneurosci.22-14-05900.2002.
Gupta, A., Lepping, R.J., Yu, A.S., Perea, R.D., Honea, R.A., Johnson, D.K., Brooks, W.M., Burns, J.M., 2016. Cognitive function and White matter changes associated with renal transplantation. Am. J. Nephrol. 43, 50–57. https://doi.org/10.1159/000444334.
Hachinski, V., 2012. Staging and natural history of cerebrovascular pathology in dementia. Neurology 79, 107. https://doi.org/10.1212/01.wnl.0000416262.36658.49.
Hachinski, V., Iadecola, C., Petersen, R.C., Breteler, M.M., Nyenhuis, D.L., Black, S.E., Powers, W.J., Decarli, C., Merino, J.G., Kalaria, R.N., Vinters, H.V., Holtzman, D.M., Rosenberg, G.A., Wallin, A., Dichgans, M., Marler, J.R., Leblanc, G.G., 2006. National Institute of Neurological Disorders and Stroke-Canadian stroke network vascular cognitive impairment harmonization standards. Stroke 37, 2220–2241. https://doi.org/10.1161/01.Str.0000237236.88823.47.
Hafez, G., Malyszko, J., Golenia, A., Klimkowicz-Mrowiec, A., Ferreira, A.C., Arıcı, M., Bruchfeld, A., Nitsch, D., Massy, Z.A., Pépin, M., Capasso, G., Mani, L.Y., Liabeuf, S., 2023. Drugs with a negative impact on cognitive functions (part 2): drug classes to consider while prescribing in CKD patients. Clin. Kidney J. 16, 2378–2392. https://doi.org/10.1093/ckj/sfad239.
Hailpern, S.M., Melamed, M.L., Cohen, H.W., Hostetter, T.H., 2007. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: third National Health and nutrition examination survey (NHANES III). J. Am. Soc. Nephrol. 18, 2205–2213.
Hojs Fabjan, T., Hojs, R., 2014. Stroke and renal dysfunction. Eur. J. Intern. Med. 25, 18–24. https://doi.org/10.1016/j.ejim.2013.08.710.
Huang, X., Yi, C., Wu, M., Qiu, Y., Wu, H., Ye, H., Peng, Y., Xiao, X., Lin, J., Yu, X., Yang, X., 2021. Risk factors and clinical outcomes of cognitive impairment in diabetic patients undergoing peritoneal Dialysis. Kidney Blood Press. Res. 46, 531–540. https://doi.org/10.1159/000514172.
Huang, J., Yu, Y., Li, H., Wei, Y., Sun, M., 2023. Effect of dietary protein intake on cognitive function in the elderly with chronic kidney disease: analysis of the National Health and nutrition examination survey 2011-2014. Ren. Fail. 45, 2294147 https://doi.org/10.1080/0886022X.2023.2294147.
Husain-Syed, F., Takeuchi, T., Neyra, J.A., Ramírez-Guerrero, G., Rosner, M.H., Ronco, C., Tolwani, A.J., 2023. Acute kidney injury in neurocritical care. Crit. Care 27, 341. https://doi.org/10.1186/s13054-023-04632-1.
Inker, L.A., Eneanya, N.D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., Crews, D.C., Doria, A., Estrella, M.M., Froissart, M., Grams, M.E., Greene, T., Grubb, A., Gudnason, V., Gutiérrez, O.M., Kalil, R., Karger, A.B., Mauer, M., Navis, G., Nelson, R.G., Poggio, E.D., Rodby, R., Rossing, P., Rule, A.D., Selvin, E., Seegmiller, J.C., Shlipak, M.G., Torres, V.E., Yang, W., Ballew, S.H., Couture, S.J., Powe, N.R., Levey, A.S., 2021. New creatinine- and cystatin C-based equations to estimate GFR without race. N. Engl. J. Med. 385, 1737–1749. https://doi.org/10.1056/NEJMoa2102953.
Ito, S., Nagasawa, T., Abe, M., Mori, T., 2009. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens. Res. 32, 115–121. https://doi.org/10.1038/hr.2008.27.
Iwata, A., Iwatsubo, T., Ihara, R., Suzuki, K., Matsuyama, Y., Tomita, N., Arai, H., Ishii, K., Senda, M., Ito, K., Ikeuchi, T., Kuwano, R., Matsuda, H., 2018. Effects of sex, educational background, and chronic kidney disease grading on longitudinal cognitive and functional decline in patients in the Japanese Alzheimer's disease neuroimaging initiative study. Alzheimers Dement. 4, 765–774. https://doi.org/10.1016/j.trci.2018.06.008.
Jiang, Y., Liu, Y., Gao, B., Che, Y., Lin, L., Jiang, J., Chang, P., Song, Q., Wang, N., Wang, W., Miao, Y., 2021. Segmental abnormalities of White matter microstructure in end-stage renal disease patients: an automated Fiber quantification Tractography study. Front. Neurosci. 15, 765677 https://doi.org/10.3389/fnins.2021.765677.
Jurgensen, A., Qannus, A.A., Gupta, A., 2020. Cognitive function in kidney transplantation. Curr. Transplant. Rep. 7, 145–153. https://doi.org/10.1007/s40472-020-00284-0.
Karam, A., Delvallée, C., Estrada-Cuzcano, A., Geoffroy, V., Lamouche, J.-B., Leuvrey, A.-S., Nourisson, E., Tarabeux, J., Stoetzel, C., Scheidecker, S., Porter, L.F., Génin, E., Redon, R., Sandron, F., Boland, A., Deleuze, J.-F., Le May, N., Dollfus, H., Muller, J., 2023. WGS revealed novel BBS5 pathogenic variants, missed by WES, causing ciliary structure and function defects. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24108729.
Karbowska, M., Hermanowicz, J.M., Tankiewicz-Kwedlo, A., Kalaska, B., Kaminski, T.W., Nosek, K., Wisniewska, R.J., Pawlak, D., 2020. Neurobehavioral effects of uremic toxin-indoxyl sulfate in the rat model. Sci. Rep. 10, 9483. https://doi.org/10.1038/s41598-020-66421-y.
Kastin, A.J., Akerstrom, V., 1999. Nonsaturable entry of neuropeptide Y into brain. Am. J. Phys. 276, E479–E482. https://doi.org/10.1152/ajpendo.1999.276.3.E479.
KDIGO, 2024. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 105, S117–S314. https://doi.org/10.1016/j.kint.2023.10.018.
Kelly, D.M., Pinheiro, A.A., Koini, M., Anderson, C.D., Aparicio, H., Hofer, E., Kern, D., Blacker, D., Decarli, C., Hwang, S.-J., Viswanathan, A., Gonzales, M.M., Beiser, A.S., Seshadri, S., Schmidt, R., Demissie, S., Romero, J.R., 2024. Impaired kidney function, cerebral small vessel disease and cognitive disorders: the Framingham heart study. Nephrol. Dial. Transplant. https://doi.org/10.1093/ndt/gfae079.
Kim, D.S., Kim, S.W., Gil, H.W., 2022. Emotional and cognitive changes in chronic kidney disease. Korean J. Intern. Med. 37, 489–501. https://doi.org/10.3904/kjim.2021.492.
Knight, A., Kogon, A.J., Matheson, M.B., Warady, B.A., Furth, S.L., Hooper, S.R., 2017. Cognitive function in children with lupus nephritis: a cross-sectional comparison with children with other glomerular chronic kidney diseases. J. Pediatr. 189 https://doi.org/10.1016/j.jpeds.2017.06.044.
Kobayashi, M., Hirawa, N., Morita, S., Yatsu, K., Kobayashi, Y., Yamamoto, Y., Saka, S., Toya, Y., Yasuda, G., Umemura, S., 2010. Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. Am. J. Kidney Dis. 56, 468–476. https://doi.org/10.1053/j.ajkd.2010.03.018.
Koren, M.J., Blumen, H.M., Ayers, E.I., Verghese, J., Abramowitz, M.K., 2021. Cognitive dysfunction and gait abnormalities in CKD. Clin. J. Am. Soc. Nephrol. 16, 694–704. https://doi.org/10.2215/CJN.16091020.
Kurella Tamura, M., Muntner, P., Wadley, V., Cushman, M., Zakai, N.A., Bradbury, B.D., Kissela, B., Unverzagt, F., Howard, G., Warnock, D., Mcclellan, W., 2011. Albuminuria, kidney function, and the incidence of cognitive impairment among adults in the United States. Am. J. Kidney Dis. 58, 756–763. https://doi.org/10.1053/j.ajkd.2011.05.027.
Kurella Tamura, M., Yaffe, K., Hsu, C.Y., Yang, J., Sozio, S., Fischer, M., Chen, J., Ojo, A., Deluca, J., Xie, D., Vittinghoff, E., Go, A.S., 2016. Cognitive impairment and progression of CKD. Am. J. Kidney Dis. 68, 77–83. https://doi.org/10.1053/j.ajkd.2016.01.026.
Lai, J.Q., Shi, Y.C., Lin, S., Chen, X.R., 2022. Metabolic disorders on cognitive dysfunction after traumatic brain injury. Trends Endocrinol. Metab. 33, 451–462. https://doi.org/10.1016/j.tem.2022.04.003.
Landini, S., Mazzinghi, B., Becherucci, F., Allinovi, M., Provenzano, A., Palazzo, V., Ravaglia, F., Artuso, R., Bosi, E., Stagi, S., Sansavini, G., Guzzi, F., Cirillo, L., Vaglio, A., Murer, L., Peruzzi, L., Pasini, A., Materassi, M., Roperto, R.M., Anders, H.-J., Rotondi, M., Giglio, S.R., Romagnani, P., 2020. Reverse phenotyping after whole-exome sequencing in steroid-resistant nephrotic syndrome. Clin. J. Am. Soc. Nephrol. 15 https://doi.org/10.2215/CJN.06060519.
Lau, W.L., Fisher, M., 2023. New insights into cognitive decline in chronic kidney disease. Nat. Rev. Nephrol. 19, 214–215. https://doi.org/10.1038/s41581-022-00656-y.
Lau, W.L., Fisher, M., Greenia, D., Floriolli, D., Fletcher, E., Singh, B., Sajjadi, S.A., Corrada, M.M., Whittle, C., Kawas, C., Paganini-Hill, A., 2020a. Cystatin C, cognition, and brain MRI findings in 90+−year-olds. Neurobiol. Aging 93, 78–84. https://doi.org/10.1016/j.neurobiolaging.2020.04.022.
Lau, W.L., Nunes, A.C.F., Vasilevko, V., Floriolli, D., Lertpanit, L., Savoj, J., Bangash, M., Yao, Z., Shah, K., Naqvi, S., Paganini-Hill, A., Vaziri, N.D., Cribbs, D.H., Fisher, M., 2020b. Chronic kidney disease increases cerebral microbleeds in mouse and man. Transl. Stroke Res. 11, 122–134. https://doi.org/10.1007/s12975-019-00698-8.
Lee, M., Saver, J.L., Chang, K.H., Liao, H.W., Chang, S.C., Ovbiagele, B., 2010. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ 341, c4249. https://doi.org/10.1136/bmj.c4249.
Levassort, H., Boucquemont, J., Alencar De Pinho, N., Lambert, O., Helmer, C., Metzger, M., Teillet, L., Frimat, L., Combe, C., Fouque, D., Laville, M., Jacquelinet, C., Liabeuf, S., Stengel, B., Massy, Z.A., Pépin, M., 2024. A new approach for cognitive impairment pattern in chronic kidney disease. Nephrol. Dial. Transplant. 39, 848–859. https://doi.org/10.1093/ndt/gfad244.
Li, C., Xu, J.J., Hu, H.T., Shi, C.Y., Yu, C.J., Sheng, J.Z., Wu, Y.T., Huang, H.F., 2021a. Amylin receptor insensitivity impairs hypothalamic POMC neuron differentiation in the male offspring of maternal high-fat diet-fed mice. Mol. Metab. 44, 101135 https://doi.org/10.1016/j.molmet.2020.101135.
Li, L.C., Chen, W.Y., Chen, J.B., Lee, W.C., Chang, C.C., Tzeng, H.T., Huang, C.C., Chang, Y.J., Yang, J.L., 2021b. The AST-120 recovers uremic toxin-induced cognitive deficit via NLRP3 Inflammasome pathway in astrocytes and microglia. Biomedicines 9. https://doi.org/10.3390/biomedicines9091252.
Li, F., Chen, H., Mao, N., Liu, H., 2023. Dietary fiber intake and cognitive impairment in older patients with chronic kidney disease in the United States: a cross-sectional study. PLoS ONE 18, e0291690. https://doi.org/10.1371/journal.pone.0291690.
Li, T., Hu, Z., Qiao, L., Wu, Y., Ye, T., 2024. Chronic kidney disease and cognitive performance: NHANES 2011-2014. BMC Geriatr. 24, 351. https://doi.org/10.1186/s12877-024-04917-2.
Lipnicki, D.M., Crawford, J., Kochan, N.A., Trollor, J.N., Draper, B., Reppermund, S., Maston, K., Mather, K.A., Brodaty, H., Sachdev, P.S., 2017. Risk factors for mild cognitive impairment, dementia and mortality: the Sydney memory and ageing study. J. Am. Med. Dir. Assoc. 18, 388–395. https://doi.org/10.1016/j.jamda.2016.10.014.
Liu, W., Wang, L., Huang, X., Yuan, C., Li, H., Yang, J., 2019. Orthostatic blood pressure reduction as a possible explanation for memory deficits in dialysis patients. Hypertens. Res. 42, 1049–1056. https://doi.org/10.1038/s41440-019-0236-4.
Liu, A.J., Staffaroni, A.M., Rojas-Martinez, J.C., Olney, N.T., Alquezar-Burillo, C., Ljubenkov, P.A., La Joie, R., Fong, J.C., Taylor, J., Karydas, A., Ramos, E.M., Coppola, G., Boxer, A.L., Rabinovici, G.D., Miller, B.L., Kao, A.W., 2020a.

Association of Cognitive and Behavioral Features between Adults with Tuberous Sclerosis and frontotemporal dementia. JAMA Neurol. 77, 358–366. https://doi.org/10.1001/jamaneurol.2019.4284.
Liu, M., Wu, Y., Wu, X., Ma, X., Yin, Y., Fang, H., Huang, S., Su, H., Jiang, G., 2020b. White matter microstructure changes and cognitive impairment in the progression of chronic kidney disease. Front. Neurosci. 14, 559117 https://doi.org/10.3389/fnins.2020.559117.
Liu, M., Jiao, Q., Du, X., Bi, M., Chen, X., Jiang, H., 2021. Potential crosstalk between Parkinson's disease and energy metabolism. Aging Dis. 12, 2003–2015. https://doi.org/10.14336/ad.2021.0422.
Liu, M.Y., Fan, Y., Ni, N., Yu, T., Mao, Z., Huang, H., Zhang, J., Tang, Y., He, H., Meng, F., You, Y., Zhou, Q.G., 2024. TERT mediates the U-shape of glucocorticoids effects in modulation of hippocampal neural stem cells and associated brain function. CNS Neurosci. Ther. 30, e14577 https://doi.org/10.1111/cns.14577.
Luu, D., Komisarow, J., Mills, B.M., Vavilala, M.S., Laskowitz, D.T., Mathew, J., James, M.L., Hernandez, A., Sampson, J., Fuller, M., Ohnuma, T., Raghunathan, K., Privratsky, J., Bartz, R., Krishnamoorthy, V., 2021. Association of Severe Acute Kidney Injury with mortality and healthcare utilization following isolated traumatic brain injury. Neurocrit. Care. 35, 434–440. https://doi.org/10.1007/s12028-020-01183-z.
Maki, K., Ohara, T., Hata, J., Shibata, M., Hirabayashi, N., Honda, T., Sakata, S., Furuta, Y., Akiyama, M., Yamasaki, K., Tatewaki, Y., Taki, Y., Kitazono, T., Mikami, T., Maeda, T., Ono, K., Mimura, M., Nakashima, K., Iga, J.-I., Takebayashi, M., Ninomiya, T., 2023. CKD, brain atrophy, and White matter lesion volume: the Japan prospective studies collaboration for aging and dementia. Kidney Med. 5, 100593 https://doi.org/10.1016/j.xkme.2022.100593.
Mancinetti, F., Xenos, D., De Fano, M., Mazzieri, A., Porcellati, F., Boccardi, V., Mecocci, P., 2023. Diabetes-Alzheimer's connection in older age: SGLT2 inhibitors as promising modulators of disease pathways. Ageing Res. Rev. 90, 102018 https://doi.org/10.1016/j.arr.2023.102018.
Mazumder, M.K., Phukan, B.C., Bhattacharjee, A., Borah, A., 2018. Disturbed purine nucleotide metabolism in chronic kidney disease is a risk factor for cognitive impairment. Med. Hypotheses 111, 36–39. https://doi.org/10.1016/j.mehy.2017.12.016.
Mazumder, M.K., Paul, R., Bhattacharya, P., Borah, A., 2019. Neurological sequel of chronic kidney disease: from diminished acetylcholinesterase activity to mitochondrial dysfunctions, oxidative stress and inflammation in mice brain. Sci. Rep. 9, 3097. https://doi.org/10.1038/s41598-018-37935-3.
Miller, L.M., Rifkin, D., Lee, A.K., Kurella Tamura, M., Pajewski, N.M., Weiner, D.E., Al-Rousan, T., Shlipak, M., Ix, J.H., 2021. Association of Urine Biomarkers of kidney tubule injury and dysfunction with frailty index and cognitive function in persons with CKD in SPRINT. Am. J. Kidney Dis. 78 https://doi.org/10.1053/j.ajkd.2021.01.009.
Miranda, A.S., Cordeiro, T.M., Santos Lacerda Soares, T.M., Ferreira, R.N., Simões, E.S.A. C., 2017. Kidney-brain axis inflammatory cross-talk: from bench to bedside. Clin. Sci. 131, 1093–1105. https://doi.org/10.1042/cs20160927.
Moon, S., Roh, Y.K., Yoon, J.L., Jang, K.U., Jung, H.J., Yoo, H.J., Jang, H.C., 2019. Clinical features of geriatric syndromes in older Koreans with diabetes mellitus. Ann. Geriatr. Med. Res. 23, 176–182. https://doi.org/10.4235/agmr.19.0041.
Morid, O.F., Menze, E.T., Tadros, M.G., George, M.Y., 2023. L-carnitine modulates cognitive impairment induced by doxorubicin and cyclophosphamide in rats; insights to oxidative stress, inflammation, synaptic plasticity, liver/brain, and kidney/brain axes. J. NeuroImmune Pharmacol. 18, 310–326. https://doi.org/10.1007/s11481-023-10062-1.
Müller, J.A., Giacobe, L.J., Grassi, V., Palmeira, A.L.R., 2023. The use of angiotensin receptor blockers in dementia prevention. Dement. Neuropsychol. 17, e20233006 https://doi.org/10.1590/1980-5764-dn-2023-3006.
Murray, A.M., Bell, E.J., Tupper, D.E., Davey, C.S., Pederson, S.L., Amiot, E.M., Miley, K. M., Mcpherson, L., Heubner, B.M., Gilbertson, D.T., Foley, R.N., Drawz, P.E., Slinin, Y., Rossom, R.C., Lakshminarayan, K., Vemuri, P., Jack, C.R., Knopman, D.S., 2016. The brain in kidney disease (BRINK) cohort study: design and baseline cognitive function. Am. J. Kidney Dis. 67, 593–600. https://doi.org/10.1053/j.ajkd.2015.11.008.
Murray, A.M., Thao, L.T.P., Ryan, J., Wolfe, R., Wetmore, J.B., Woods, R.L., Polkinghorne, K.R., 2022. CKD biomarkers, cognitive impairment, and incident dementia in an older healthy cohort. Kidney360 3, 435–445. https://doi.org/10.34067/KID.0005672021.
Nemcsik, J., Kiss, I., Tislér, A., 2012. Arterial stiffness, vascular calcification and bone metabolism in chronic kidney disease. World J. Nephrol. 1, 25–34. https://doi.org/10.5527/wjn.v1.i1.25.
Passer, J.A., 1977. Cerebral atrophy in end-stage uremia. Proc. Clin. Dial. Transplant Forum 7, 91–94.
Paterson, E.N., Maxwell, A.P., Kee, F., Cruise, S., Young, I.S., Mcguinness, B., Mckay, G. J., 2021. Association of renal impairment with cognitive dysfunction in the Northern Ireland cohort for the longitudinal study of ageing (NICOLA). Nephrol. Dial. Transplant. 36, 1492–1499. https://doi.org/10.1093/ndt/gfab182.
Peng, S.-Y., Wu, I.W., Sun, C.-C., Lee, C.-C., Liu, C.-F., Lin, Y.-Z., Yeung, L., 2021. Investigation of possible correlation between retinal neurovascular biomarkers and early cognitive impairment in patients with chronic kidney disease. Transl. Vis. Sci. Technol. 10, 9. https://doi.org/10.1167/tvst.10.14.9.
Pépin, M., Klimkowicz-Mrowiec, A., Godefroy, O., Delgado, P., Carriazo, S., Ferreira, A. C., Golenia, A., Malyszko, J., Grodzicki, T., Giannakou, K., Paolisso, G., Barbieri, M., Garneata, L., Mocanu, C.A., Liabeuf, S., Spasovski, G., Zoccali, C., Bruchfeld, A., Farinha, A., Arici, M., Capasso, G., Wiecek, A., Massy, Z.A., 2023a. Cognitive disorders in patients with chronic kidney disease: approaches to prevention and treatment. Eur. J. Neurol. 30, 2899–2911. https://doi.org/10.1111/ene.15928.
Pépin, M., Levassort, H., Boucquemont, J., Lambert, O., Alencar De Pinho, N., Turinici, M., Helmer, C., Metzger, M., Cheddani, L., Frimat, L., Combe, C., Fouque, D., Laville, M., Ayav, C., Liabeuf, S., Jacquelinet, C., Teillet, L., Stengel, B., Massy, Z.A., 2023b. Cognitive performance is associated with glomerular filtration rate in patients with chronic kidney disease: results from the CKD-REIN cohort. J. Neurol. Neurosurg. Psychiatry 94, 457–466. https://doi.org/10.1136/jnnp-2022-330347.
Pflugrad, H., Nösel, P., Ding, X., Schmitz, B., Lanfermann, H., Barg-Hock, H., Klempnauer, J., Schiffer, M., Weissenborn, K., 2020. Brain function and metabolism in patients with long-term tacrolimus therapy after kidney transplantation in comparison to patients after liver transplantation. PLoS ONE 15, e0229759. https://doi.org/10.1371/journal.pone.0229759.
Piotrowski, P.C., Lutkowska, A., Tsibulski, A., Karczewski, M., Jagodziński, P.P., 2017. Neurologic complications in kidney transplant recipients. Folia Neuropathol. 55, 86–109. https://doi.org/10.5114/fn.2017.68577.
Polinder-Bos, H.A., García, D.V., Kuipers, J., Elting, J.W.J., Aries, M.J.H., Krijnen, W.P., Groen, H., Willemsen, A.T.M., Van Laar, P.J., Strijkert, F., Luurtsema, G., Slart, R., Westerhuis, R., Gansevoort, R.T., Gaillard, C., Franssen, C.F.M., 2018. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. J. Am. Soc. Nephrol. 29, 1317–1325. https://doi.org/10.1681/asn.2017101088.
Ponticelli, C., Campise, M.R., 2005. Neurological complications in kidney transplant recipients. J. Nephrol. 18, 521–528.
Prelevic, V., Radunovic, D., Antunovic, T., Ratkovic, M., Gligorovic-Bahranovic, N., Gledovic, B., Vujosevic, S., Nedovic-Vukovic, M., Basic-Jukic, N., 2018. Increased serum level of IGF-1 correlates with better cognitive status in end-stage renal disease patients undergoing hemodialysis. Ther. Apher. Dial. 22, 118–123. https://doi.org/10.1111/1744-9987.12610.
Rabie, O., El-Nashar, H.A.S., George, M.Y., Majrashi, T.A., Al Warhi, T., Hassan, F.E., Eldehna, W.M., Mostafa, N.M., 2023. Phytochemical profiling and neuroprotective activity of Callistemon subulatus leaves against cyclophosphamide-induced chemobrain. Biomed. Pharmacother. 167, 115596 https://doi.org/10.1016/j.biopha.2023.115596.
Radić, J., Ljutić, D., Radić, M., Kovačić, V., Dodig-Ćurković, K., Šain, M., 2011. Kidney transplantation improves cognitive and psychomotor functions in adult hemodialysis patients. Am. J. Nephrol. 34, 399–406. https://doi.org/10.1159/000330849.
Rao, A.B., Richert, N., Howard, T., Lewis, B.K., Bash, C.N., Mcfarland, H.F., Frank, J.A., 2002. Methylprednisolone effect on brain volume and enhancing lesions in MS before and during IFNbeta-1b. Neurology 59, 688–694. https://doi.org/10.1212/wnl.59.5.688.
Rinkel, G.J., Ruigrok, Y.M., 2022. Preventive screening for intracranial aneurysms. Int. J. Stroke 17, 30–36. https://doi.org/10.1177/17474930211024584.
Rokot, N.T., Ataka, K., Iwai, H., Suzuki, H., Tachibe, H., Kairupan, T.S., Cheng, K.C., Amitani, H., Inui, A., Asakawa, A., 2021. Antagonism for NPY signaling reverses cognitive behavior defects induced by activity-based anorexia in mice. Psychoneuroendocrinology 126, 105133. https://doi.org/10.1016/j.psyneuen.2021.105133.
Ruebner, R.L., Hooper, S.R., Parrish, C., Furth, S.L., Fadrowski, J.J., 2019. Environmental lead exposure is associated with neurocognitive dysfunction in children with chronic kidney disease. Pediatr. Nephrol. 34, 2371–2379. https://doi.org/10.1007/s00467-019-04306-7.
Sacre, J.W., Magliano, D.J., Zimmet, P.Z., Polkinghorne, K.R., Chadban, S.J., Anstey, K. J., Shaw, J.E., 2019. Associations of chronic kidney disease markers with cognitive function: a 12-year follow-up study. J. Alzheimers Dis. 70, S19–S30. https://doi.org/10.3233/JAD-180498.
Sánchez, R., Ripoll-Vera, T., López-Mendoza, M., De Juan-Ribera, J., Gimeno, J.R., Hermida, Á., Ruz-Zafra, M.A., Torregrosa, J.V., Mora, A., García-Pinilla, J.M., Fortuny, E., Aguinaga-Barrilero, A., Torra, R., 2023. The Spanish Fabry women study: a retrospective observational study describing the phenotype of females with GLA variants. Orphanet J. Rare Dis. 18, 8. https://doi.org/10.1186/s13023-022-02599-w.
Santulli, G., Visco, V., Ciccarelli, M., Ferrante, M.N.V., De Masi, P., Pansini, A., Virtuoso, N., Pirone, A., Guerra, G., Verri, V., Macina, G., Taurino, A., Komici, K., Mone, P., 2024. Frail hypertensive older adults with prediabetes and chronic kidney disease: insights on organ damage and cognitive performance - preliminary results from the CARYATID study. Cardiovasc. Diabetol. 23, 125. https://doi.org/10.1186/s12933-024-02218-x.
Scheppach, J.B., Wu, A., Gottesman, R.F., Mosley, T.H., Arsiwala-Scheppach, L.T., Knopman, D.S., Grams, M.E., Sharrett, A.R., Coresh, J., Koton, S., 2023. Association of Kidney Function Measures with Signs of neurodegeneration and small vessel disease on brain magnetic resonance imaging: the atherosclerosis risk in communities (ARIC) study. Am. J. Kidney Dis. 81 https://doi.org/10.1053/j.ajkd.2022.07.013.
Sigurdardottir, S., Myers, S.M., Woodworth, J.M., Raymond, G.V., 2000. Mental retardation and seizure disorder in Schimke immunoosseous dysplasia. Am. J. Med. Genet. 90, 294–298.
Sink, K.M., Divers, J., Whitlow, C.T., Palmer, N.D., Smith, S.C., Xu, J., Hugenschmidt, C. E., Wagner, B.C., Williamson, J.D., Bowden, D.W., Maldjian, J.A., Freedman, B.I., 2015. Cerebral structural changes in diabetic kidney disease: African American-diabetes heart study MIND. Diabetes Care 38, 206–212. https://doi.org/10.2337/dc14-1231.
Smogorzewski, M.J., Massry, S.G., 2008. Altered acetylcholine metabolism of brain in uremia: role of secondary hyperparathyroidism. J. Ren. Nutr. 18, 122–126. https://doi.org/10.1053/j.jrn.2007.10.025.
Spoto, B., Mallamaci, F., Politi, C., Parlongo, R.M.T., Leonardis, D., Capasso, G., Tripepi, G., Zoccali, C., 2024. Neuropeptide Y gene polymorphisms and chronic

kidney disease progression. J. Hypertens. 42, 267–273. https://doi.org/10.1097/hjh.0000000000003600.
Stanciu, G.D., Ababei, D.C., Bild, V., Bild, W., Paduraru, L., Gutu, M.M., Tamba, B.I., 2020. Renal contributions in the pathophysiology and neuropathological substrates shared by chronic kidney disease and Alzheimer's disease. Brain Sci. 10 https://doi.org/10.3390/brainsci10080563.
Stevens, L.A., Coresh, J., Schmid, C.H., Feldman, H.I., Froissart, M., Kusek, J., Rossert, J., Van Lente, F., Bruce, R.D., Zhang, Y.L., Greene, T., Levey, A.S., 2008. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am. J. Kidney Dis. 51, 395–406. https://doi.org/10.1053/j.ajkd.2007.11.018.
Stolp, H.B., Dziegielewska, K.M., Ek, C.J., Potter, A.M., Saunders, N.R., 2005. Long-term changes in blood-brain barrier permeability and white matter following prolonged systemic inflammation in early development in the rat. Eur. J. Neurosci. 22, 2805–2816. https://doi.org/10.1111/j.1460-9568.2005.04483.x.
Strelow, D.N., Magalhães, L.S., Paim, M.P., Krüger, L.D., Neto, J.S.S., Brüning, C.A., Bortolatto, C.F., 2023. Depressive-like behavior and cognitive impairment induced by acute administration of dexamethasone: pharmacological effects of 2-phenyl-3-(phenylselanyl)benzofuran in female Swiss mice. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 125, 110772. https://doi.org/10.1016/j.pnpbp.2023.110772.
Taddei, S., Virdis, A., Ghiadoni, L., Sudano, I., Salvetti, A., 2001. Endothelial dysfunction in hypertension. J. Cardiovasc. Pharmacol. 38 (Suppl. 2), S11–S14. https://doi.org/10.1097/00005344-200111002-00004.
Tanaka, S., Okusa, M.D., 2020. Crosstalk between the nervous system and the kidney. Kidney Int. 97, 466–476. https://doi.org/10.1016/j.kint.2019.10.032.
Tanaka, M., Yamada, S., Watanabe, Y., 2021. The role of neuropeptide Y in the nucleus accumbens. Int. J. Mol. Sci. 22 https://doi.org/10.3390/ijms22147287.
Terzo, C., Gembillo, G., Cernaro, V., Longhitano, E., Calabrese, V., Casuscelli, C., Peritore, L., Santoro, D., 2024. Investigational new drugs for the treatment of chronic renal failure: an overview of the literature. Expert Opin. Investig. Drugs 33, 319–334. https://doi.org/10.1080/13543784.2024.2326624.
Tian, S., Jiang, J., Wang, J., Zhang, Z., Miao, Y., Ji, X., Bi, Y., 2023. Comparison on cognitive outcomes of antidiabetic agents for type 2 diabetes: a systematic review and network meta-analysis. Diabetes Metab. Res. Rev. 39, e3673 https://doi.org/10.1002/dmrr.3673.
Tollitt, J., Odudu, A., Flanagan, E., Chinnadurai, R., Smith, C., Kalra, P.A., 2019. Impact of prior stroke on major clinical outcome in chronic kidney disease: the Salford kidney cohort study. BMC Nephrol. 20, 432. https://doi.org/10.1186/s12882-019-1614-5.
Tollitt, J., Odudu, A., Montaldi, D., Kalra, P.A., 2021. Cognitive impairment in patients with moderate to severe chronic kidney disease: the Salford kidney cohort study. Clin. Kidney J. 14, 1639–1648. https://doi.org/10.1093/ckj/sfaa178.
Toyoda, K., Ninomiya, T., 2014. Stroke and cerebrovascular diseases in patients with chronic kidney disease. Lancet Neurol. 13, 823–833. https://doi.org/10.1016/s1474-4422(14)70026-2.
Tsai, H.-H., Yen, R.-F., Lin, C.-L., Kao, C.-H., 2017. Increased risk of dementia in patients hospitalized with acute kidney injury: a nationwide population-based cohort study. PLoS ONE 12, e0171671. https://doi.org/10.1371/journal.pone.0171671.
Tsimpolis, A., Kalafatakis, K., Charalampopoulos, I., 2024. Recent advances in the crosstalk between the brain-derived neurotrophic factor and glucocorticoids. Front. Endocrinol. 15, 1362573 https://doi.org/10.3389/fendo.2024.1362573.
Tsuruya, K., Yoshida, H., 2024. Cognitive impairment and brain atrophy in patients with chronic kidney disease. J. Clin. Med. 13 https://doi.org/10.3390/jcm13051401.
Tuladhar, A.M., Van Norden, A.G., De Laat, K.F., Zwiers, M.P., Van Dijk, E.J., Norris, D. G., De Leeuw, F.E., 2015. White matter integrity in small vessel disease is related to cognition. NeuroImage Clin. 7, 518–524. https://doi.org/10.1016/j.nicl.2015.02.003.
Udy, A.A., Jarrett, P., Lassig-Smith, M., Stuart, J., Starr, T., Dunlop, R., Deans, R., Roberts, J.A., Senthuran, S., Boots, R., Bisht, K., Bulmer, A.C., Lipman, J., 2017. Augmented renal clearance in traumatic brain injury: a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. J. Neurotrauma 34, 137–144. https://doi.org/10.1089/neu.2015.4328.
Uzu, T., Kida, Y., Shirahashi, N., Harada, T., Yamauchi, A., Nomura, M., Isshiki, K., Araki, S., Sugimoto, T., Koya, D., Haneda, M., Kashiwagi, A., Kikkawa, R., 2010. Cerebral microvascular disease predicts renal failure in type 2 diabetes. J. Am. Soc. Nephrol. 21, 520–526. https://doi.org/10.1681/asn.2009050558.
Vemuri, P., Knopman, D.S., Jack, C.R., Lundt, E.S., Weigand, S.D., Zuk, S.M., Thostenson, K.B., Reid, R.I., Kantarci, K., Slinin, Y., Lakshminarayan, K., Davey, C.S., Murray, A., 2017. Association of kidney function biomarkers with brain MRI findings: the BRINK study. J. Alzheimers Dis. 55, 1069–1082.
Verbitsky, M., Kogon, A.J., Matheson, M., Hooper, S.R., Wong, C.S., Warady, B.A., Furth, S.L., Gharavi, A.G., 2017. Genomic disorders and neurocognitive impairment in pediatric CKD. J. Am. Soc. Nephrol. 28, 2303–2309. https://doi.org/10.1681/ASN.2016101108.
Viggiano, D., Wagner, C.A., Martino, G., Nedergaard, M., Zoccali, C., Unwin, R., Capasso, G., 2020. Mechanisms of cognitive dysfunction in CKD. Nat. Rev. Nephrol. 16, 452–469. https://doi.org/10.1038/s41581-020-0266-9.
Viriyapak, E., Chantaratin, S., Sommai, K., Sumboonnanonda, A., Pattaragarn, A., Supavekin, S., Piyaphanee, N., Lomjansook, K., Chaiyapak, T., 2022. Prevalence of cognitive dysfunction and its risk factors in children with chronic kidney disease in a developing country. Pediatr. Nephrol. 37, 1355–1364. https://doi.org/10.1007/s00467-021-05280-9.
Wang, H., Liu, D., 2022. Retrospective case-control study on screening risk factors of antibiotic-associated encephalopathy in patients with chronic kidney disease. BMJ Open 12, e064995. https://doi.org/10.1136/bmjopen-2022-064995.
Wang, X., Wang, X., Han, Q., 2023a. Intelligent detection strategy and bioimaging application of dual-responsive hg(2+) and ONOO(−) using near-infrared probes. Anal. Chim. Acta 1266, 341358. https://doi.org/10.1016/j.aca.2023.341358.
Wang, Y., Hu, L., Zhou, D., Chen, X., Zhou, L., 2023b. Association of Urinary Biomarkers of renal tubular injury with cognitive dysfunction in older patients with chronic kidney disease: a cross-sectional observational study. Brain Sci. 13 https://doi.org/10.3390/brainsci13040551.
Wang, X.-H., He, Y., Zhou, H., Xiao, T., Du, R., Zhang, X., 2024. Risk factors for cognitive impairment in patients with chronic kidney disease. World J. Psychiatry 14, 308–314. https://doi.org/10.5498/wjp.v14.i2.308.
Warsame, F., Chu, N.M., Hong, J., Mathur, A., Crews, D.C., Bayliss, G., Segev, D.L., Mcadams-Demarco, M.A., 2023. Sleep duration and cognitive function among older adults with chronic kidney disease: results from the National Health and nutrition examination survey (2011-2014). Nephrol. Dial. Transplant. 38, 1636–1644. https://doi.org/10.1093/ndt/gfac325.
Wuttke, M., Li, Y., Li, M., Sieber, K.B., Feitosa, M.F., Gorski, M., Tin, A., Wang, L., Chu, A. Y., Hoppmann, A., Kirsten, H., Giri, A., Chai, J.F., Sveinbjornsson, G., Tayo, B.O., Nutile, T., Fuchsberger, C., Marten, J., Cocca, M., Ghasemi, S., Xu, Y., Horn, K., Noce, D., Van Der Most, P.J., Sedaghat, S., Yu, Z., Akiyama, M., Afaq, S., Ahluwalia, T.S., Almgren, P., Amin, N., Ärnlöv, J., Bakker, S.J.L., Bansal, N., Baptista, D., Bergmann, S., Biggs, M.L., Biino, G., Boehnke, M., Boerwinkle, E., Boissel, M., Bottinger, E.P., Boutin, T.S., Brenner, H., Brumat, M., Burkhardt, R., Butterworth, A.S., Campana, E., Campbell, A., Campbell, H., Canouil, M., Carroll, R. J., Catamo, E., Chambers, J.C., Chee, M.L., Chee, M.L., Chen, X., Cheng, C.Y., Cheng, Y., Christensen, K., Cifkova, R., Ciullo, M., Concas, M.P., Cook, J.P., Coresh, J., Corre, T., Sala, C.F., Cusi, D., Danesh, J., Daw, E.W., De Borst, M.H., De Grandi, A., De Mutsert, R., De Vries, A.P.J., Degenhardt, F., Delgado, G., Demirkan, A., Di Angelantonio, E., Dittrich, K., Divers, J., Dorajoo, R., Eckardt, K.U., Ehret, G., Elliott, P., Endlich, K., Evans, M.K., Felix, J.F., Foo, V.H.X., Franco, O.H., Franke, A., Freedman, B.I., Freitag-Wolf, S., Friedlander, Y., Froguel, P., Gansevoort, R.T., Gao, H., Gasparini, P., Gaziano, J.M., Giedraitis, V., Gieger, C., Girotto, G., Giulianini, F., Gögele, M., Gordon, S.D., Gudbjartsson, D.F., Gudnason, V., Haller, T., Hamet, P., Harris, T.B., Hartman, C.A., Hayward, C., Hellwege, J.N., Heng, C.K., Hicks, A.A., Hofer, E., Huang, W., Hutri-Kähönen, N., Hwang, S.J., Ikram, M.A., Indridason, O.S., Ingelsson, E., Ising, M., Jaddoe, V.W.V., Jakobsdottir, J., Jonas, J.B., Joshi, P.K., Josyula, N.S., Jung, B., Kähönen, M., Kamatani, Y., Kammerer, C.M., Kanai, M., Kastarinen, M., Kerr, S.M., Khor, C.C., Kiess, W., Kleber, M.E., Koenig, W., Kooner, J.S., Körner, A., Kovacs, P., Kraja, A.T., Krajcoviechova, A., Kramer, H., Krämer, B.K., Kronenberg, F., Kubo, M., Kühnel, B., Kuokkanen, M., Kuusisto, J., La Bianca, M., Laakso, M., Lange, L.A., Langefeld, C.D., Lee, J.J., Lehne, B., Lehtimäki, T., Lieb, W., Lim, S.C., Lind, L., Lindgren, C.M., Liu, J., Liu, J., Loeffler, M., Loos, R.J.F., Lucae, S., Lukas, M.A., Lyytikäinen, L.P., Mägi, R., Magnusson, P.K.E., Mahajan, A., Martin, N.G., Martins, J., März, W., Mascalzoni, D., Matsuda, K., Meisinger, C., Meitinger, T., Melander, O., Metspalu, A., Mikaelsdottir, E.K., Milaneschi, Y., Miliku, K., Mishra, P.P., Mohlke, K.L., Mononen, N., Montgomery, G.W., Mook-Kanamori, D.O., Mychaleckyj, J.C., Nadkarni, G.N., Nalls, M.A., Nauck, M., Nikus, K., Ning, B., Nolte, I.M., Noordam, R., O'connell, J., O'donoghue, M.L., Olafsson, I., Oldehinkel, A.J., Orho-Melander, M., Ouwehand, W.H., Padmanabhan, S., Palmer, N.D., Palsson, R., Penninx, B., Perls, T., Perola, M., Pirastu, M., Pirastu, N., Pistis, G., Podgornaia, A.I., Polasek, O., Ponte, B., Porteous, D.J., Poulain, T., Pramstaller, P.P., Preuss, M.H., Prins, B.P., Province, M. A., Rabelink, T.J., Raffield, L.M., Raitakari, O.T., Reilly, D.F., Rettig, R., Rheinberger, M., Rice, K.M., Ridker, P.M., Rivadeneira, F., Rizzi, F., Roberts, D.J., Robino, A., Rossing, P., Rudan, I., Rueedi, R., Ruggiero, D., Ryan, K.A., Saba, Y., Sabanayagam, C., Salomaa, V., Salvi, E., Saum, K.U., Schmidt, H., Schmidt, R., Schöttker, B., Schulz, C.A., Schupf, N., Shaffer, C.M., Shi, Y., Smith, A.V., Smith, B. H., Soranzo, N., Spracklen, C.N., Strauch, K., Stringham, H.M., Stumvoll, M., Svensson, P.O., Szymczak, S., Tai, E.S., Tajuddin, S.M., Tan, N.Y.Q., Taylor, K.D., Teren, A., Tham, Y.C., Thiery, J., Thio, C.H.L., Thomsen, H., Thorleifsson, G., Toniolo, D., Tönjes, A., Tremblay, J., Tzoulaki, I., Uitterlinden, A.G., Vaccargiu, S., Van Dam, R.M., Van Der Harst, P., Van Duijn, C.M., Velez Edward, D.R., Verweij, N., Vogelezang, S., Völker, U., Vollenweider, P., Waeber, G., Waldenberger, M., Wallentin, L., Wang, Y.X., Wang, C., Waterworth, D.M., Bin Wei, W., White, H., Whitfield, J.B., Wild, S.H., Wilson, J.F., Wojczynski, M.K., Wong, C., Wong, T.Y., Xu, L., Yang, Q., Yasuda, M., Yerges-Armstrong, L.M., Zhang, W., Zonderman, A.B., Rotter, J.I., Bochud, M., Psaty, B.M., Vitart, V., Wilson, J.G., Dehghan, A., Parsa, A., Chasman, D.I., Ho, K., Morris, A.P., Devuyst, O., Akilesh, S., Pendergrass, S.A., Sim, X., Böger, C.A., Okada, Y., Edwards, T.L., Snieder, H., Stefansson, K., Hung, A. M., Heid, I.M., Scholz, M., Teumer, A., Köttgen, A., Pattaro, C., 2019. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat. Genet. 51, 957–972. https://doi.org/10.1038/s41588-019-0407-x.
Xie, Z., Tong, S., Chu, X., Feng, T., Geng, M., 2022. Chronic kidney disease and cognitive impairment: the kidney-brain Axis. Kidney Dis. 8, 275–285. https://doi.org/10.1159/000524475.
Xiong, F., Gong, K., Xu, H., Tu, Y., Lu, J., Zhou, Y., He, W., Li, W., Li, C., Zhao, L., Gao, H., Zheng, H., 2023. Optimized integration of metabolomics and lipidomics reveals brain region-specific changes of oxidative stress and neuroinflammation in type 1 diabetic mice with cognitive decline. J. Adv. Res. 43, 233–245. https://doi.org/10.1016/j.jare.2022.02.011.
Yaffe, K., Ackerson, L., Kurella Tamura, M., Le Blanc, P., Kusek, J.W., Sehgal, A.R., Cohen, D., Anderson, C., Appel, L., Desalvo, K., Ojo, A., Seliger, S., Robinson, N., Makos, G., Go, A.S., 2010. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. J. Am. Geriatr. Soc. 58, 338–345. https://doi.org/10.1111/j.1532-5415.2009.02670.x.
Yaffe, K., Ackerson, L., Hoang, T.D., Go, A.S., Maguire, M.G., Ying, G.-S., Daniel, E., Bazzano, L.A., Coleman, M., Cohen, D.L., Kusek, J.W., Ojo, A., Seliger, S., Xie, D.,

Grunwald, J.E., 2013. Retinopathy and cognitive impairment in adults with CKD. Am. J. Kidney Dis. 61, 219–227. https://doi.org/10.1053/j.ajkd.2012.10.006.
Yaffe, K., Kurella-Tamura, M., Ackerson, L., Hoang, T.D., Anderson, A.H., Duckworth, M., Go, A.S., Krousel-Wood, M., Kusek, J.W., Lash, J.P., Ojo, A., Robinson, N., Sehgal, A. R., Sondheimer, J.H., Steigerwalt, S., Townsend, R.R., 2014. Higher levels of cystatin C are associated with worse cognitive function in older adults with chronic kidney disease: the chronic renal insufficiency cohort cognitive study. J. Am. Geriatr. Soc. 62, 1623–1629. https://doi.org/10.1111/jgs.12986.
Yan, Z., Shao, T., 2024. Chronic inflammation in chronic kidney disease. Nephron 148, 143–151. https://doi.org/10.1159/000534447.
Yan, Q., Zhao, Z., Liu, D., Li, J., Pan, S., Duan, J., Liu, Z., 2024. Novel immune cross-talk between inflammatory bowel disease and IgA nephropathy. Ren. Fail. 46, 2337288 https://doi.org/10.1080/0886022x.2024.2337288.
Yang, X., Quan, Y., Wu, E., Jiang, Y., Song, Q., Li, Y., Li, Q., Sun, Z., Yuan, J., Zha, Y., Cui, X., 2023. The association of cognition with protein energy wasting and synaptic transmission in chronic kidney disease. Semin. Dial. 36, 326–336. https://doi.org/10.1111/sdi.13146.
Yang, Q., Xiang, Y., Ma, G., Cao, M., Fang, Y., Xu, W., Li, L., Li, Q., Feng, Y., Yang, Q., 2024. A nomogram prediction model for mild cognitive impairment in non-dialysis outpatient patients with chronic kidney disease. Ren. Fail. 46, 2317450 https://doi.org/10.1080/0886022X.2024.2317450.
Yao, T., Song, G., Li, Y., Wang, D., 2021. Chronic kidney disease correlates with MRI findings of cerebral small vessel disease. Ren. Fail. 43, 255–263. https://doi.org/10.1080/0886022x.2021.1873804.
Yen, F.-S., Wang, S.-I., Lin, S.-Y., Chao, Y.-H., Wei, J.C.-C., 2022. The impact of alcohol consumption on cognitive impairment in patients with diabetes, hypertension, or chronic kidney disease. Front. Med. 9, 861145 https://doi.org/10.3389/fmed.2022.861145.
Yin, Y., Li, M., Li, C., Ma, X., Yan, J., Wang, T., Fu, S., Hua, K., Wu, Y., Zhan, W., Jiang, G., 2018. Reduced White matter integrity with cognitive impairments in end stage renal disease. Front. Psychol. 9, 143. https://doi.org/10.3389/fpsyt.2018.00143.
Yu, M., Kim, Y.J., Kang, D.H., 2011. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. Clin. J. Am. Soc. Nephrol. 6, 30–39. https://doi.org/10.2215/cjn.05340610.
Yu, G., Liang, Y., Zheng, S., Zhang, H., 2018. Inhibition of myeloperoxidase by N-acetyl Lysyltyrosylcysteine amide reduces oxidative stress-mediated inflammation, neuronal damage, and neural stem cell injury in a murine model of stroke. J. Pharmacol. Exp. Ther. 364, 311–322. https://doi.org/10.1124/jpet.117.245688.
Zhao, H., Li, Y., Sun, J., Xu, G., Wang, C., Zhou, S., Nie, S., Li, Y., Su, L., Chen, R., Cao, Y., Gao, Q., Hu, Y., Li, H., Yang, Q., Wan, Q., Liu, B., Xu, H., Li, G., Weng, J., Chen, C., Liu, H., Shi, Y., Zha, Y., Kong, Y., Su, G., Tang, Y., Zhou, Y., Guo, A., Gong, M., Xu, X., Hou, F.F., 2023a. Immunosuppression versus supportive care on kidney outcomes in IgA nephropathy in the real-world setting. Clin. J. Am. Soc. Nephrol. 18, 1186–1194. https://doi.org/10.2215/cjn.0000000000000215.
Zhao, H., Wu, D., Gyamfi, M.A., Wang, P., Luecht, C., Pfefferkorn, A.M., Ashraf, M.I., Kamhieh-Milz, J., Witowski, J., Dragun, D., Budde, K., Schindler, R., Zickler, D., Moll, G., Catar, R., 2023b. Expanded hemodialysis ameliorates uremia-induced impairment of vasculoprotective KLF2 and concomitant proinflammatory priming of endothelial cells through an ERK/AP1/cFOS-dependent mechanism. Front. Immunol. 14, 1209464 https://doi.org/10.3389/fimmu.2023.1209464.
Zhao, S., Li, Y., Su, C., 2023c. Assessment of common risk factors of diabetes and chronic kidney disease: a Mendelian randomization study. Front. Endocrinol. 14, 1265719 https://doi.org/10.3389/fendo.2023.1265719.
Zheng, H., Zheng, Y., Zhao, L., Chen, M., Bai, G., Hu, Y., Hu, W., Yan, Z., Gao, H., 2017. Cognitive decline in type 2 diabetic db/db mice may be associated with brain region-specific metabolic disorders. Biochim. Biophys. Acta Mol. basis Dis. 1863, 266–273. https://doi.org/10.1016/j.bbadis.2016.11.003.
Zhou, F., Sun, Y., Xie, X., Zhao, Y., 2023. Blood and CSF chemokines in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. Alzheimers Res. Ther. 15, 107. https://doi.org/10.1186/s13195-023-01254-1.
Zhou, T., Zhao, J., Ma, Y., He, L., Ren, Z., Yang, K., Tang, J., Liu, J., Luo, J., Zhang, H., 2024. Association of cognitive impairment with the interaction between chronic kidney disease and depression: findings from NHANES 2011-2014. BMC Psychiatry 24, 312. https://doi.org/10.1186/s12888-024-05769-1.
Zoccali, C., Ortiz, A., Blumbyte, I.A., Rudolf, S., Beck-Sickinger, A.G., Malyszko, J., Spasovski, G., Carriazo, S., Viggiano, D., Kurganaite, J., Sarkeviciene, V., Rastenyte, D., Figurek, A., Rroji, M., Mayer, C., Arici, M., Martino, G., Tedeschi, G., Bruchfeld, A., Spoto, B., Rychlik, I., Wiecek, A., Okusa, M., Remuzzi, G., Mallamaci, F., 2021. Neuropeptide Y as a risk factor for cardiorenal disease and cognitive dysfunction in chronic kidney disease: translational opportunities and challenges. Nephrol. Dial. Transplant. 37, ii14–ii23. https://doi.org/10.1093/ndt/gfab284.