REVIEW

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Genetic and circulating biomarkers of cognitive dysfunction and dementia in CKD

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ABSTRACT

Chronic kidney disease (CKD) is commonly accompanied by cognitive dysfunction and dementia, which, in turn, increase the risk of hospitalization, cardiovascular events and death. Over the last 30 years, only four studies focused on genetic markers of cognitive impairment in CKD and kidney failure (KF), indicating a significant gap in research. These studies suggest potential genetic predispositions to cognitive decline in CKD patients but also underscore the necessity for more comprehensive studies. Seventeen reports have established connections between cognitive function and kidney disease markers such as estimated glomerular filtration rate (eGFR), Cystatin C and albuminuria. A rapid eGFR decline has been associated with cognitive deterioration and vascular dementia, and mild to moderate eGFR reductions with diminished executive function in elderly men. Various biomarkers have been associated to Alzheimer's disease or dementia in CKD and KF. These include amyloid beta and phosphorylated tau proteins, uremic toxins, gut microbiota, metabolic indicators, hypertension, endothelial dysfunction, vitamins and inflammation. However, the causal relevance of these associations remains unclear. Overall, the available evidence points to a complex interplay between the different biomarkers and cognitive health in CKD patients, underscoring the need for more research to elucidate these relationships.

Keywords: circulating biomarkers, CKD, cognitive impairment, dementia, genetic biomarkers

INTRODUCTION

Chronic kidney disease (CKD) stands as a formidable challenge to global health, affecting an estimated 10% of the adult population worldwide [1]. This insidious condition is marked by a gradual loss of kidney function, which in turn heralds a host of complications that significantly worsen patient outcomes. The trajectory of CKD often leads to increased morbidity and mortality, making it a silent yet potent threat to public health [2].

One of the most concerning aspects of CKD is its association with cognitive impairment, including both subtle cognitive problems and overt dementia. Cognitive impairment is a broad term that describes any condition affecting an individual's ability to think, concentrate, remember or make decisions. It can range from mild to severe and may affect various cognitive domains such as memory, attention, language and executive function. Mild cognitive impairment (MCI) is a condition where cognitive decline is noticeable but not severe enough to interfere significantly with daily life and activities. MCI can be a precursor to more serious conditions like dementia. Dementia is a syndrome characterized by a significant decline in cognitive function that interferes with daily life and activities. It involves deterioration in memory, thinking, behavior and the ability to perform everyday activities. Studies suggest that cognitive issues may affect between 30% and 60% of patients with CKD, which is a concerningly high prevalence rate compared with the general population [3]. These cognitive comorbidities are not merely incidental because they are linked to an increased risk of negative health outcomes.

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Patients with cognitive dysfunction are more likely to experience frequent hospitalizations, suffer from cardiovascular events and face a higher risk of mortality [4, 5]. These associations underline the critical need for a better understanding and management of cognitive health within the CKD patient population.

However, it is important to note that not all studies have found a consistent association between CKD and cognitive impairment or dementia. In a population-based study by Stocker *et al.* [6] of community-dwelling adults, reduced kidney function was associated with increased levels of dementia-related blood biomarkers but not increased dementia risk, indicating that kidney function might influence the accuracy of dementia-related blood biomarkers, an observation that should be considered in clinical translation.

The pathophysiology of cognitive decline in CKD patients is complex and multifactorial. Vascular disease secondary to old age, hypertension and diabetes is a primary driver [6, 7], contributing to a range of cerebrovascular alterations. White matter hyperintensities, silent brain infarcts and microbleeds are common findings in these patients, particularly those undergoing dialysis treatment [8, 9]. Such cerebral changes indicate underlying vascular damage and are closely associated with cognitive impairment.

Moreover, the retention of uremic solutes, commonly referred to as uremic toxins, exacerbates the problem by having direct neurotoxic effects. These toxins accumulate as the kidneys fail to filter and excrete waste products from the body adequately. The neurotoxicity of these solutes can lead to further cognitive decline, compounding the already significant impact of vascular issues.

Additionally, there is growing evidence to suggest that CKD may contribute to the accumulation of amyloid beta (Aβ) peptides which are hallmark biomarkers of Alzheimer's disease (AD) [8]. The presence of Aβ amyloid in the circulation of patients with CKD adds another layer to the already complex interplay between kidney disease and cognitive health. This accumulation may not only signal an increased risk for developing AD but might also suggest that CKD-related cognitive decline may share some pathophysiological mechanisms with neurodegenerative diseases.

The relationship between CKD and cognitive dysfunction is thus a critical area of study, with significant implications for patient care and outcomes. As researchers continue to unravel the intricate connections between renal impairment and brain health, it becomes increasingly clear that a holistic approach to managing CKD must include strategies to preserve and enhance cognitive function.

Research into genetic and circulating biomarkers of cognitive dysfunction or dementia in CKD is crucial since it can lead to early detection and targeted interventions, potentially slowing or preventing cognitive decline. Understanding the genetic predispositions and biomarkers could clarify the pathophysiological mechanisms underlying cognitive impairments in CKD, paving the way for personalized medicine approaches. This research could also help stratify patient risk profiles, allowing for more efficient allocation of healthcare resources and better patient outcomes.

In this review, we discuss the current knowledge on genetic variants and body fluid biomarkers associated with cognitive dysfunction and dementia, peculiarly in the pathophysiological context of CKD, and integrate this information with knowledge at the population level.

KIDNEY FUNCTION AND COGNITIVE PROBLEMS IN CKD

Seventeen studies described the relationship between kidney biomarkers and cognitive dysfunction or dementia and CKD, and six studies were conducted in kidney failure (KF) patients on dialysis (Box 1). The link between cognitive function and kidney disease was coherently observed in several cross-sectional studies that adopted the estimated glomerular filtration rate (eGFR) estimated by creatinine-based methods [10–18] or Cystatin C [19–24], or indicators of kidney damage like albuminuria [22, 25].

Box 1: Brain alterations in CKD and KF patients.

- **MRI studies** indicate increased cerebral small-vessel disease and changes in grey matter volume in KF patients on dialysis.
- **Functional MRI** studies show alterations in neural networks and improvements in cognitive impairment post-hemodialysis.
- **NIRS** studies suggest that nutritional status and kidney function impact cerebral oxygen saturation.
- **Brain health correlation**: higher eGFR correlates with better cognition and slower progression of mild cognitive impairment, while albuminuria is linked to hippocampal atrophy.

In a large cohort study of 7839 elderly subjects [26], low eGFR at baseline did not predict an excess incident risk of cognitive decline or dementia, while faster eGFR decline during the first 4 years of the study was associated with global cognitive decline and incident dementia with a vascular component, suggesting that vascular mechanisms may mediate this association. On the other hand, lower eGFR was associated with worse cognitive performance and incident cognitive events, independently of demographics, cardiovascular risk factors and depression in 3033 patients with CKD stages 3–4, followed for 5 years included in the CKD-Renal Epidemiology and Information Network (CKD REIN) cohort [27]. In the same cohort, a lower eGFR in CKD patients was associated with early impairments in praxis, language and attention before an obvious cognitive decline [28]. In contrast, in another longitudinal study of over 5000 community-level elderly men, mild to moderate reductions in eGFR were associated with poor executive function at baseline but not with global cognitive impairment or risk of cognitive decline in older men [17].

In KF patients, the link between kidney diseases and dementia was more solidly established. Indeed, in a study of over 300 000 KF patients included in the US Renal Data System [29], the 5-year risk of incident dementia was 16% in women and 13% in men, and older patients with dementia had more than double risk of mortality as compared with dialysis patients without dementia. Similarly, cognitive dysfunction by the Mini-Mental State Examination (MMSE) predicted mortality in another study of 137 hemodialysis patients in Italy [30]. The risk of dementia was also high in two small studies, one in the late 1970s [31] and another in 2018 [32], and in a case series in pediatric patients [33].

GENETIC MARKERS OF COGNITIVE DYSFUNCTION AND DEMENTIA: STUDIES IN CKD PATIENTS AND IN OTHER POPULATIONS

As alluded to before, cognitive dysfunction and dementia are increasingly recognized as key features of CKD. Identifying genetic variants associated with cognitive decline in CKD patients is of obvious relevance for improving etiologic, prognostic and therapeutic knowledge of this critical alteration. At least in principle, genetic variants can facilitate early diagnosis and development of targeted therapies in this population. Until now, only four studies [34–37] have specifically discussed genetic markers of cognitive dysfunction and dementia.

Li *et al.* [34] retrieved gene expression datasets in 327 patients with AD and CKD and 318 normal individuals from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) to find shared genetic biomarkers. In this analysis, among 150 candidate genes, JunD Proto-Oncogene (a member of the JUN family, functioning as a crucial component of the activating protein, AP-1, a transcription factor with a wide range of actions, from immunological to cell growth and differentiation, and gene expression in response to extracellular signals), ALF transcription elongation factor 1 (a protein that plays a crucial role in transcription elongation, i.e. the process of RNA synthesis during gene expression) and zinc finger protein 36 homolog (ZFP36) Like 1 (an RNA-binding protein that plays a crucial role in post-transcriptional control) are potential co-diagnostic markers for AD and CKD. The findings in this relatively small study still need external validation. The findings are contingent upon a distinct patient cohort and did not consider crucial factors such as age, gender, medication utilization and co-existing medical conditions.

In a two-sample Mendelian randomization study [35] investigating the causal relationship between renal function and various neurodegenerative diseases, this study found no causative relationship with AD and Lewy body or frontotemporal dementia and amyotrophic lateral sclerosis but found an association between multiple sclerosis and reduced eGFR.

Similarly, another Mendelian randomization study [36] found no large causal impact of human gut microbiota features on cardiometabolic traits, chronic diseases or longevity.

Finally, a genome-wide association study [37] based on a large database by an international consortium aimed to identify shared genetic mechanisms between kidney function and cerebrovascular disease found that reduced kidney function is potentially causally related to an increased risk of large artery stroke and that certain genetic loci are associated with both kidney function traits and cerebrovascular disease phenotypes.

Given the limited knowledge of genetic factors in the general population and disease states and the minuscule information on CKD, several areas warrant further investigation to better understand the genetic basis of cognitive dysfunction and dementia in CKD (Table 1). Despite significant advancements, several gaps remain in understanding the genetic underpinnings of cognitive dysfunction in CKD. Current studies often suffer from limited sample sizes, which restricts the ability to identify novel genetic markers and validate existing ones. Additionally, the complex interplay between genetic and environmental factors in cognitive decline among CKD patients is largely unknown, necessitating comprehensive investigations into gene–gene and gene–environment interactions. The role of epigenetic modifications, such as DNA methylation and histone modifications, has been scarcely explored in this context. To address these gaps, leveraging advances in genomics and bioinformatics is crucial. This includes conducting larger and more diverse genome-wide association studies (GWAS) and promoting interdisciplinary collaborations between experts in nephrology, neurology, genetics and other relevant fields. Furthermore, incorporating genetic markers into personalized medicine approaches and fostering international collaborations and data sharing will be essential for advancing our understanding and developing targeted interventions for CKD-related cognitive complications. Research on cognitive resilience and cognitive reserve in CKD patients is still in its infancy. Cognitive resilience, the capacity to maintain or recover cognitive function despite neuropathological changes or other risk factors, has not been extensively studied in relation to genetic markers. Similarly, the role of genetic factors in cognitive reserve, which involves the ability to withstand neuropathological changes and maintain cognitive function through compensatory neural networks and cognitive strategies, remains underexplored. Identifying genetic factors associated with cognitive resilience and reserve, and understanding their molecular pathways, could provide valuable insights for potential therapeutic strategies. Additionally, investigating genetic markers linked to specific cognitive domains, such as memory and executive function, will help elucidate diverse neurobiological mechanisms underlying cognitive decline in CKD patients.

The influence of demographic factors, such as sex and age, on the relationship between genetic markers and cognitive dysfunction in CKD patients is not well understood. Investigating how these demographic factors interact with genetic markers is crucial for developing a more nuanced understanding of cognitive decline in this population. This research could reveal important insights into the differential impact of genetic factors across various demographic groups, ultimately informing more personalized approaches to prevention and treatment.

Mitochondrial genetics and pharmacogenetics represent promising but underexplored areas in the study of cognitive dysfunction in CKD. Variations in mitochondrial DNA (mtDNA) may contribute to cognitive decline and mitochondrial dysfunction in CKD patients, yet this area has received limited attention. Additionally, the role of non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in the pathogenesis of cognitive dysfunction in CKD warrants further investigation. Understanding how genetic factors influence the response to medications for cognitive dysfunction could optimize personalized treatment plans. Research in these areas could enhance our understanding of the molecular mechanisms driving cognitive decline and lead to more effective therapeutic strategies.

The integrity of the blood–brain barrier and its role in cognitive decline in CKD patients is another critical area that requires further exploration. Genetic factors affecting blood–brain barrier integrity and cerebrovascular function could provide insights into the mechanisms underlying cognitive dysfunction. Additionally, the potential of gene therapy as a novel approach to prevent or treat cognitive dysfunction in CKD based on genetic markers is an exciting avenue for future research. Investigating these aspects could lead to innovative strategies for preserving brain health in individuals with CKD.

Translating genetic findings into clinical practice remains a significant challenge. Assessing the practical application of genetic markers for risk prediction, early diagnosis and monitoring cognitive decline in CKD patients is essential for advancing personalized medicine. Moreover, increasing public awareness about the genetic factors involved in CKD-related cognitive decline and the

Table 1: Overview of the problems and needed investigations in the field of cognitive dysfunction and dementia in CKD research.

Problem	Needed investigation
Research approaches	
In general, studies of limited sample size	- Conduct larger and diverse GWAS studies to identify novel genetic markers and validate existing ones
Gene–gene and gene–environment interactions largely unknown	- Investigate the complex interplay between genetic and environmental factors in cognitive decline among CKD patients
The impact of epigenetic factors has been scarcely investigated	- Explore the role of epigenetic modifications (e.g. DNA methylation, histone modifications) in CKD-related cognitive dysfunction
Leveraging advances in genomics and bioinformatics	- Utilize advanced genomics technologies and bioinformatics to comprehensively understand genetic and environmental factors contributing to cognitive decline in CKD
Interdisciplinary collaborations	- Promote collaborations between experts in nephrology, neurology, genetics and other relevant fields to advance understanding and translation of genetic findings into interventions for CKD-related cognitive complications
Incorporating genetic markers into personalized medicine approaches	- Develop and validate genetic risk prediction models for personalized interventions in CKD patients at risk of cognitive decline
Fostering international collaborations and data sharing	- Promote global collaborations and data sharing to conduct well-powered studies and accelerate discoveries in CKD-related genetic markers
Cognitive resilience and cognitive reserve and domain-specific investigations	
The role of genetic markers in cognitive resilience, i.e. the capacity to maintain or recover cognitive function despite the presence of neuropathological changes or other risk factors (the ability to recover from cognitive challenges)—scarcely investigated	- Identify genetic factors associated with cognitive resilience in CKD patients and explore molecular pathways underlying resilience for potential therapeutic strategies
Genetic markers in different cognitive domains	- Identify genetic markers linked to specific cognitive domains (e.g. memory, executive function) to understand diverse neurobiological mechanisms
Genetic factors in cognitive reserve, i.e. the ability to withstand neuropathological changes and maintain cognitive function through the recruitment of compensatory neural networks and cognitive strategies (the capacity to compensate for cognitive decline)	- Investigate the role of genetic factors in the development and maintenance of cognitive reserve in CKD patients
Demographics and genetics	
Understanding the influence of sex and age on the relationship between genetic markers and cognitive dysfunction	- Investigate the impact of demographic factors (sex and age) on how genetic markers interact with cognitive dysfunction in CKD
Mitochondrial genetics and pharmacogenetics	
Investigating the role of mitochondrial genetics	- Examine the contribution of mtDNA variations to cognitive decline in CKD and their role in mitochondrial dysfunction
Assessing the role of genetic markers in neuroimaging and other biomarkers	- Investigate associations between genetic markers and neuroimaging or biomarker findings to enhance diagnostic tools for cognitive dysfunction in CKD
Exploring the role of non-coding RNAs	- Investigate the involvement of non-coding RNAs (e.g. miRNAs, lncRNAs) in the pathogenesis of cognitive dysfunction in CKD
Evaluating the impact of pharmacogenetics	- Study how genetic factors influence the response to medications for cognitive dysfunction in CKD, optimizing personalized treatment plans
Blood–brain barrier and gene therapy	
Investigating the role of genetic markers in the blood–brain barrier	- Explore genetic factors affecting blood–brain barrier integrity and cerebrovascular function in cognitive decline in CKD
Examining the impact of gene therapy	- Explore the potential of gene therapy as a novel approach to prevent or treat cognitive dysfunction in CKD based on genetic markers
Clinical application and public awareness	
Evaluating the utility of genetic markers in clinical practice	- Assess the practical application of genetic markers for risk prediction, early diagnosis and monitoring cognitive decline in CKD patients
Promoting public awareness and education	- Increase public awareness about genetic factors in CKD-related cognitive decline and the importance of early detection and intervention

importance of early detection and intervention is crucial. Public education efforts can help promote early diagnosis and timely intervention, ultimately improving outcomes for CKD patients at risk of cognitive decline. Addressing these diverse research areas will help identify novel genetic markers, elucidate molecular mechanisms underlying cognitive decline, and develop targeted interventions to prevent or treat cognitive dysfunction and dementia in CKD patients. Ultimately, these efforts will improve the overall quality of life for individuals affected by CKD and its associated complications.

IMAGING STUDIES IN CKD

Fourteen studies based on standard magnetic resonance imaging (MRI) [38–41] functional magnetic resonance [42–45], diffusion kurtosis imaging [46, 47], evoked potentials [48, 49], near infrared spectroscopy (NIRS) [50] and electroencephalographic and radionuclide [51] focused on brain alterations in CKD and KF (Box 2).

Box 2: Kidney biomarkers and cognitive dysfunction/dementia.

- **Cross-sectional studies**: various studies using eGFR (creatinine-based and Cystatin C methods) and albuminuria as markers consistently associated cognitive dysfunction with kidney disease.
- **Longitudinal studies**: low eGFR did not predict cognitive decline, but a rapid decline was associated with dementia, particularly with a vascular component. Mild to moderate eGFR reductions were linked to poor executive function but not global cognitive impairment in elderly men.
- A solid link has been observed between KF and dementia, and KF patients also showed a significant risk of dementia and increased mortality in KF patients with dementia.
- Various biomarkers related to AD and dementia, such as Aβ peptides, tau proteins, NfL and others, are altered in CKD patients, suggesting potential mechanisms linking CKD to cognitive impairment. However, studies performed so far are observational and, as such, merely hypothesis-generating.

These studies provide insights into the relationship between kidney function and brain health. The MRI-based studies showed that individuals with KF on dialysis have an increased prevalence of cerebral small-vessel disease, as indicated by the presence of cerebral microbleeds and white matter hyperintensity [41]. These patients exhibit increased grey matter volume in certain brain regions, such as the bilateral caudate and thalamus, particularly in secondary hyperparathyroidism [39].

Biomarkers of kidney disease, such as eGFR and urinary albumin-to-creatinine ratio, have been independently associated with brain changes and microstructural alterations observed through diffusion tensor imaging [46].

Functional magnetic resonance studies documented that KF patients have alterations in multiple neural networks associated with cognitive scores and indicators of kidney function [43] and hemodialysis improves these patients' cognitive impairment and neurovascular coupling [44]. It is important to reconcile these findings with the notion that hemodynamic instability during hemodialysis sessions may alter cerebral blood flow and cause ischemia, potentially leading to cognitive dysfunction. The observed improvements in cognitive impairment and neurovascular coupling post-hemodialysis suggest that while hemodialysis may pose risks, it also has the potential to ameliorate some of the adverse effects on brain function. Therefore, the relationship between hemodialysis, cerebral blood flow and cognitive outcomes is likely multifaceted, involving both detrimental and beneficial effects. Further research is needed to elucidate the precise mechanisms and to optimize hemodialysis protocols to minimize hemodynamic instability and its impact on cerebral health.

In a study involving individuals without or with mild cognitive impairment and normal renal function, higher eGFR was associated with larger hippocampal volume and better cognition [39]. Additionally, individuals with mild cognitive impairment in the highest eGFR group had a lower disease progression rate compared with those in the intermediate eGFR group. However, another study found that albuminuria, not the eGFR, was associated with hippocampal atrophy [45].

NIRS has revealed associations between cerebral regional saturation of oxygen and energy intake, serum albumin concentration and haemoglobin levels in predialysis CKD patients [50]. This suggests that nutritional status and kidney function may influence cerebral oxygen saturation.

In a study involving individuals without or with mild cognitive impairment and normal renal function, higher eGFR was associated with larger hippocampal volume and better cognition [40]. Additionally, individuals with mild cognitive impairment in the highest eGFR group had a lower disease progression rate compared with those in the intermediate eGFR group. However, another study found that albuminuria, not the eGFR, was associated with hippocampal atrophy [46].

Interestingly, mild to moderate renal insufficiency was not found to be related to brain imaging features of AD in a study involving community-dwelling older adults without dementia [42].

These studies highlight the complex relationship between kidney function and brain health and indicate that further research is needed to understand the mechanisms underlying these associations and to develop strategies for preserving brain health in individuals with kidney disease.

CIRCULATING AND BODY FLUIDS BIOMARKERS OF AD IN CKD

Eighteen studies in CKD and KF patients [52–68] focused on the relationship between biomarkers of AD/dementia and CKD. These biomarkers (Fig. 1) include (i) plasma Aβ1–42 and 40 [69]—the dominant peptide in vascular dementia and the soluble circulating form of the same peptide (Aβ40), which is raised in KF patients [52], (ii) P-tau181 and P-tau217 [70], i.e. two phosphorylated tau proteins that have been associated with AD and that are increased in CKD [53, 55], (iii) neurofilament light (NfL) [71], a biomarker of axonal injury that is associated with the prevalent and incident risk for CKD in the Gothenburg H70 Birth Cohort Study [54] and, independently of CKD, with cognitive impairment and a high risk of death in the general population [59], (iv) S100B [72], a marker for glial dysfunction and blood–brain barrier disruption that attains high levels and associates with cognitive impairment in KF patients [64], (v) glycogen synthase kinase-3β

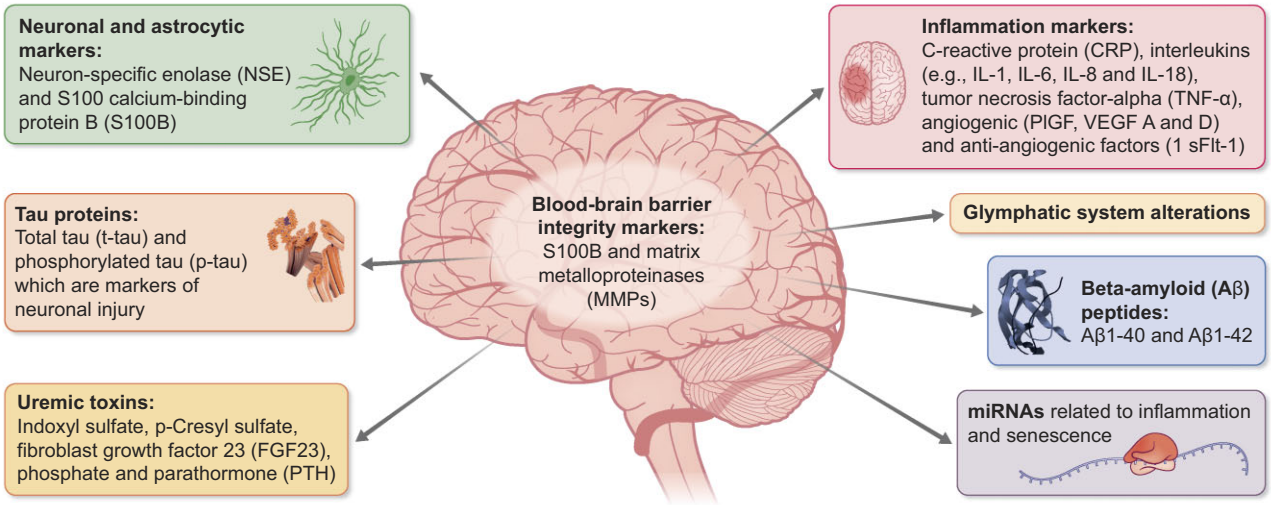

Figure 1: The figure shows a series of biomarkers of AD, which are suspected causal risk factors for cognitive dysfunction and dementia in the CKD and KF populations. See also comments in the main text.

(GSK3β), a serine/threonine protein kinase involved in regulating glycogen metabolism implicated in AD [73] that shows high levels in CKD [65], (vi) amyloid precursor protein (APP), a biomarker that is reduced both in AD [74] and in CKD patients [66], (vii) ADAM10, the main α-secretase that participates in the non-amyloidogenic cleavage of APP and is increased in AD [75] but paradoxically decreased in CKD patients [66], (viii) BACE1, the β-secretase enzyme reflecting Aβ peptides production in AD [76] that is increased in CKD [66], (ix) presenilin 1 (PS1), a key component of the gamma-secretase complex that cleaves APP and contributes to the production of Aβ peptides in AD [77] and in CKD patients [66] and (x) lipid peroxidation (LPO) products that are raised both in AD [78] and in CKD patients [66]. Finally, miRNA related to inflammation and senescence are deranged in CKD and KF patients [79], but their role in cognitive problems has not been specifically investigated in these patients.

Overall, these studies should be inherently considered hypothesis-generating rather than hypothesis-testing because their design was purely observational. Furthermore, the diagnostic value of the same biomarkers remains unknown because none of the studies summarized here reported information on the diagnostic discrimination of the biomarkers being investigated.

MISCELLANEOUS BIOMARKERS

Nineteen miscellaneous biomarkers—including gut microbiota [80, 81], CKD metabolic bone disorder (CKD-MBD) biomarkers [82–85] metabolic biomarkers, hypertension [86–88], endothelial dysfunction [89], vitamins [90, 91], inflammation [92, 93], and uremic toxins and other biomarkers [94–96]—have been associated with cognitive dysfunction and dementia in the CKD population (Box 3).

Box 3: Miscellaneous biomarkers and cognitive dysfunction in CKD.

- **Gut microbiota**: differences in gut microbiome composition may impact cognitive function in CKD patients.
- **CKD-MBD biomarkers**: certain biomarkers, such as serum Klotho and FGF23, are associated with cognitive performance and the risk of dementia, respectively.
- **Metabolic biomarkers**: high IGF-1 levels correlate with better cognitive status; uncontrolled hypertension impacts AD biomarkers.
- **Endothelial dysfunction**: implicated in cognitive impairment in KF patients on dialysis.
- **Inflammation**: inflammation markers like CRP are associated with attention impairment.
- **Vitamins**: vitamin imbalances are not clearly linked to cognitive impairment.

Gut microbiota

In a recent study [80], differences in gut microbiome abundance (the 16S rRNA analysis) and structure between peritoneal dialysis and non-dialysis KF patients have been reported, and differences among patients with and without cognitive impairment within the peritoneal dialysis group. Other observations [81] identified alterations in gut microbiota profiles and serum metabolites in haemodialysis patients with mild cognitive decline. Specific gut bacteria were significantly different in patients with mild cognitive dysfunction than healthy controls or those with normal cognitive function. Twenty-one serum metabolites were altered in those with cognitive dysfunction, indicating their potential as biomarkers for this alteration in these patients.

CKD-MBD biomarkers

A recent study [11] described a positive relationship between serum α-Klotho and cognitive function in older CKD patients with albuminuria. This suggests that higher α-Klotho levels may favorably impact cognitive performance in this population. In contrast, the co-receptor of α-Klotho, fibroblast growth factor 23 (FGF23), was directly associated with an increased risk of incident dementia and AD [82] in a large cohort of dementia-free individuals in the Framingham offspring study. Low 25-hydroxyvitamin D, a key

alteration in the CKD-MBD scenario, had an unfavorable impact on cognitive function in a cross-sectional study in 255 KF patients on hemodialysis [85]. Hypothetically, serum phosphate has also been implicated in cognitive dysfunction in CKD [97].

Metabolic biomarkers, hypertension and endothelial dysfunction

High levels of serum Insulin Growth Factor 1 (IGF-1), an important growth hormone mediating the protein anabolic effect of pituitary growth hormone, correlated with better cognitive status, in KF patients on dialysis [88]. Uncontrolled hypertension, dyslipidemia, diabetes and CKD all impact biomarkers of AD, including Aβ40, Aβ42, total tau and NfL chain [86].

Endothelial dysfunction, an alteration that can lead to reduced blood flow to the brain, is another biomarker implicated in cognitive impairment in KF patients on dialysis [89]. High homocysteine, an amino acid that alters endothelial function, is associated with cognitive dysfunction in middle-aged and older adults with CKD [98] and in diabetic patients [99].

Vitamins

Deficiencies or imbalances in certain vitamins and other nutrients may affect brain health and cognitive performance. However, neither vitamin B12, folate [90] nor vitamin K [91] were linked to cognitive impairment in CKD patients.

Inflammation and angiogenesis

Inflammation plays a crucial role in the pathophysiology of CKD [100] and cognitive dysfunction [101]. In analyses made in the Chronic Renal Insufficiency Cohort (CRIC), raised high sensitivity C-reactive protein (hs-CRP), fibrinogen and interleukin (IL)-1b signaled an independent risk of impairment in attention compared with participants with lower levels of the same biomarkers [99].

In a recent analysis in the Swedish BioFINDER study [102], the rate of fall in cognitive function tests was higher in 247 patients with mild cognitive impairment at baseline than in a group of 497 individuals with normal cognitive function. At baseline, higher levels cerebrospinal fluid (CSF) of Placental Growth Factor (PlGF, a marker of angiogenesis), lower levels of soluble fms-related tyrosine kinase (1 sFlt-1, an anti-angiogenic marker) and higher levels of IL-8 were associated with more white matter lesions in individuals without cognitive problems, while in patients with mild cognitive impairment higher levels of PlGF, IL-16, IL-6 and IL-8, and the angiogenic factors Vascular Growth Factor A and D, were all associated with the same outcome measure. Longitudinal analyses over an 8-year follow-up showed independent effects of CSF inflammatory markers and white matter lesions on cognition, especially in people without cognitive impairment at baseline, indicating a continuum in the normal range of the link between these biomarkers and cognitive function.

Uremic toxins

Uremic toxins such as indoxyl sulphate and paracresyl sulphate might in theory influence the increased prevalence of cerebrovascular and neurological signs and symptoms in patients with CKD. However, the clinical studies that have evaluated the correlation between neurologic symptoms and uremic toxin levels are rather scarce and inconclusive [94].

It is important to note that the biomarkers discussed above are not mutually exclusive and may interact with each other and with other factors to influence cognitive function in CKD patients. Understanding their individual and combined contributions to cognitive impairment fully and developing targeted interventions for preserving cognitive health in this population remains a challenge for future studies in CKD.

An open question is why dementia is so often accelerated in CKD patients and whether CKD patients exhibit an increased risk of Aβ aggregation. In the last decade, the glymphatic system has emerged as the most important export route for Aβ and protein waste, such as tau and synuclein involved in neurodegenerative diseases [103]. The glymphatic system transports CSF along perivascular spaces from where the water channel, aquaporin-4, supports the concept that CSF infiltrates the brain's extracellular spaces. The excess fluid and waste proteins leave the parenchyma along perivenous spaces and cranial nerves, from where meningeal and cervical lymphatic vessels drain into the venous system. The glymphatic system is primarily active during sleep, raising the hypothesis that sleep disturbances that are common in CKD patients contribute to the progressive loss of cognitive function [104]. Glymphatic function was analysed using the diffusion tensor image analysis—a technique that measures the rate and direction of water diffusion in the brain—along the perivascular space (DTI-ALPS), and the DPTI-ALPS index was significantly reduced in patients with KF compared with aged-matched controls [105].

Given the shared risk factors and pathological mechanisms between AD and CKD, the limited knowledge gathered so far and some internal contradictions of the current literature, there is a pressing need to identify and validate novel biomarkers of cognitive dysfunction and dementia in CKD patients. Further research should investigate the role of these potential biomarkers, individually and in combination, in the early diagnosis, prognosis and treatment of cognitive impairment in CKD. Identifying reliable circulating biomarkers will ultimately facilitate timely interventions and improve the quality of life for CKD patients with cognitive dysfunction (Table 2).

FUTURE DIRECTIONS AND CHALLENGES

CKD-related cognitive dysfunction research faces several challenges that remain to be addressed.

Most studies reviewed here were cross-sectional. There is a need for large-scale, longitudinal studies to establish the temporal relationship between CKD progression and cognitive decline. Such studies would enable the identification of at-risk populations and provide insights into the natural history of cognitive dysfunction in this population. A recent large study in the general population with a 20-year longitudinal observation in China [106] showed that CSF and imaging biomarkers in AD, including Aβ42, the ratio of Aβ42 to Aβ40, phosphorylated tau181, total tau, NfL and hippocampal volume diverged from those without cognitive problems 18 (Aβ42) to 9 (hippocampal volume) years before diagnosis. In comparison, measurable cognitive decline was detected only 6 years before the diagnosis of AD.

Combining different types of biomarkers, such as blood-based, CSF, neuroimaging and genetic markers, may provide a more comprehensive understanding of the pathophysiology of cognitive dysfunction in CKD. This integrated approach could lead to the development of more accurate diagnostic and prognostic tools.

There is an urgent need for intervention trials targeting modifiable risk factors such as hypertension, diabetes and dyslipidemia, as well as investigating the efficacy of pharmacological and

Table 2: Research gaps on biomarkers of cognitive function in CKD.

Biomarkers/factors	Key findings	Research gaps
Kidney biomarkers (eGFR, albuminuria)	Coherent link between cognitive function and kidney disease in cross-sectional studies	Lack of information on diagnostic discrimination of biomarkers
Kidney disease and dementia	Increased risk of incident dementia in kidney failure patients	Limited studies on the relationship between kidney disease and cognitive decline in the general population
AD and dementia biomarkers (Aβ, tau proteins, NfL, S100B, GSK3β, APP, ADAM10, BACE1, PS1, LPO products)	Association between AD biomarkers and CKD	Diagnostic value of these biomarkers remains unknown
MRI-based studies	Increased prevalence of cerebral small-vessel disease in dialysis patients	Limited understanding of the mechanisms underlying the association between kidney function and brain health
Functional MRI studies	Alterations in neural networks associated with cognitive scores and kidney function indicators	Need for further research on the impact of hemodialysis on cognitive impairment
NIRS	Associations between cerebral oxygen saturation and nutritional status, serum albumin concentration and hemoglobin levels in CKD patients	Limited research on the influence of kidney function on cerebral oxygen saturation
Miscellaneous biomarkers (gut microbiota, CKD-MBD biomarkers, metabolic biomarkers, hypertension, endothelial dysfunction, vitamins, inflammation)	Gut microbiota composition may impact cognitive function in CKD patients	Need for further research on the individual and combined contributions of these biomarkers to cognitive impairment
Interaction and combined contributions	Biomarkers may interact with each other and other factors to influence cognitive function in CKD patients	Lack of understanding of the complex relationships and mechanisms involved

Population-wide, longitudinal studies are needed to identify markers predicting onset, progression and outcome of cognitive impairment and dementia in CKD and in KF.

non-pharmacological therapies in preventing or slowing cognitive decline in CKD patients.

The identification and validation of reliable circulating biomarkers for cognitive dysfunction and dementia in CKD patients is an important research priority, given the shared risk factors and pathological mechanisms between AD and CKD. Addressing these challenges will not only improve our understanding of the relationship between CKD and cognitive dysfunction but also facilitate the development of targeted interventions to improve the quality of life for CKD patients with cognitive impairment.

CONCLUSION

Cognitive dysfunction and dementia are significant comorbidities in CKD patients, contributing to increased morbidity and mortality. Circulating biomarkers, including inflammatory markers, uremic toxins and metabolic factors, and gut microbiota, offer promising avenues for the early diagnosis and monitoring of cognitive decline in this population.

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DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

APPENDIX

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