

Review Article

Insights into Cognitive Brain Health in Chronic Kidney Disease

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Received: June 30, 2022; **Accepted:** July 29, 2022;**Published:** August 05, 2022**Abstract**

Cognitive impairment and Chronic Kidney Disease (CKD) are common in older adults. With advances in medicine, the average lifespan is expected to increase, further increasing the prevalence of both conditions. The mechanisms underlying cognitive impairment in CKD are unclear. While mild-moderately low estimated glomerular filtration rate (eGFR) may not be associated with cognitive impairment, severely decreased eGFR and albuminuria do. Patients on dialysis have a high prevalence of cognitive impairment. Cognitive function improves after kidney transplantation. However, some residual cognitive deficits persist after transplantation, indicating that restoring the kidney function alone may not be enough to restore cognitive function, and other etiological factors may play a role. Albuminuria, another marker of CKD is also associated with cognitive impairment. However, albuminuria is often undiagnosed. Improving early identification and management of patients with albuminuria may be a good population-based dementia prevention strategy. Other factors associated with cognitive impairment in CKD include anemia and other metabolic derangements commonly observed in CKD. In this article, we reviewed the prevalence of cognitive impairment in CKD, the potential mechanisms underlying cognitive impairment in CKD, and the current evidence on the association between cognitive impairment and eGFR and albuminuria.

Keywords: Albuminuria; Cognitive impairment; Chronic kidney disease; Dementia; eGFR; End stage kidney disease

Abbreviations

CKD: Chronic Kidney Disease; Egfr: Estimated Glomerular Filtration Rate; ESKD: End Stage Kidney Disease; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; Moca: Montreal Cognitive Assessment; DSST: Digit Symbol Substitution Test; PTH: Parathyroid Hormone

Introduction

Cognitive impairment is common in patients with Chronic Kidney Disease (CKD) [1,2] and negatively impacts daily activities, quality of life, morbidity, mortality, and access to kidney transplantation [3-7]. Despite these adverse consequences, cognitive problems in patients with CKD are often unrecognized and untreated [6]. CKD itself remains under diagnosed limiting interventions to prevent dementia in this high-risk population. Even when diagnosed with CKD, patients remain unaware of their higher risk for cognitive impairment and dementia. The understanding of mechanisms underlying cognitive impairment in CKD is also limited, contributing to the lack of early preventive and management strategies. While there is growing interest in cognitive impairment in CKD, clear guidelines on diagnosis and management of CKD at risk for future dementia are lacking. In this review, we discuss the prevalence, pathophysiology, and future directions in cognitive impairment in CKD.

Epidemiology of Cognitive Impairment in CKD

CKD defined by an estimated glomerular filtration rate of <60mL/

min/1.73m², affects ~37 million adults in the United States [8] and has a prevalence of 38% in people 65 years or older. Similarly, dementia is also highly prevalent in the old, affecting ~6.2 million individuals, with a prevalence of 11% in people 65 years or older. With advances in medicine and increase in average life expectancy, the prevalence of both CKD and dementia is expected to increase further [9-11]. There is a wide variation in prevalence of cognitive impairment in CKD, partly due to different methodologies and thresholds used for defining cognitive impairment and dementia. A uniform approach to diagnosis and detect cognitive impairment in CKD is lacking. Cognitive function is affected in 27-62% of patients with CKD compared to 11-26% in age matched general population [12,14]. Furthermore, cognitive function worsens as the estimated glomerular filtration rate (eGFR) decreases [15-17] and patients with End Stage Kidney Disease (ESKD) have the highest prevalence of cognitive impairment of up to 87% [2,6,18-20]. Compared to the prevalence of dementia of 5% in the general population [21], patients with ESKD are 3-5 times more likely to have dementia with a prevalence of 10-40% [6,22,23].

Just as cognitive impairment increases with age in the general population, cognitive impairment in CKD also increases with age. However, unlike the general population, cognitive impairment in CKD affects younger adults also [6,7]. The domains of cognition affected also seem to be different in CKD; common cognitive domains affected include executive function, attention, and memory [24,27]. These are different from other common etiologies of dementia such as Alzheimer's disease that tends to affect memory more than some

other domains. Furthermore, while cognitive impairment is often progressive and irreversible in the general population, cognitive function in CKD improves with kidney transplantation [28,29]. Despite this improvement, however, the prevalence of cognitive impairment in kidney transplant recipients is about 58%, much higher than the general population [30]. This indicates that factors other than impaired kidney function and low eGFR are at play. While the kidney function is restored after a kidney transplant, other factors such as vascular disease from longstanding hypertension or diabetes causing cognitive impairment may not be reversed with kidney transplantation. Conversely, it is possible that transplant associated factors such as surgery associated delirium or post-transplant immune suppression also affect post-transplant cognitive function.

Cognitive Impairment, eGFR and Albuminuria

Cognitive impairment in CKD increases with declining eGFR [15-17]. With over 20,000 participants, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is the largest cross-sectional study evaluating the association between eGFR and cognitive function. Participants were 64.9 ± 9.6 years old, with a mean eGFR of 85.9 ± 23.7 mL/min/1.73m² (mean eGFR 47.7 ± 10.4 mL/min/1.73m² for the 11% with CKD). Each 10 mL/min/1.73 m² decrease in eGFR below 60 mL/min/1.73 m² was associated with an 11% increase in prevalence of cognitive impairment [31]. Table 1 summarizes some other cross-sectional studies showing similar associations. Some prospective studies also indicated a similar association between eGFR and cognitive impairment. The Cardiovascular Health Cognition Study included 3,349 participants without dementia and followed them for 6 years. A serum creatinine of >1.3mg/dl in women and >1.5mg/dl in men was associated with 37% increased risk of dementia

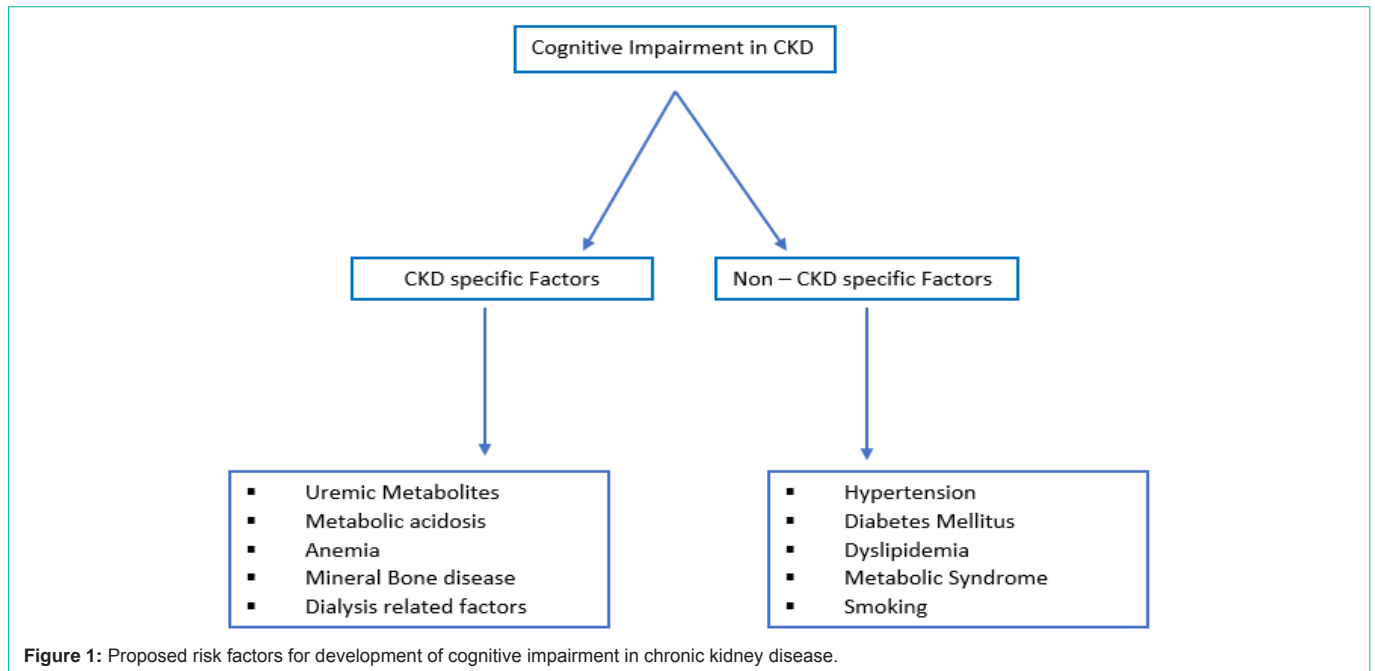
[17]. The Rush Memory and Aging Project showed a higher rate of cognitive decline with a baseline eGFR of 15 mL/min/1.73 m² or lower; an effect similar to being additional 3 years older [32]. The INVADE study [33], the Northern Manhattan Study [34], and the Singapore Longitudinal Aging Study [35] also associated baseline kidney function with increased risk of cognitive decline.

While these older studies indicated an association between eGFR and cognitive impairment, emerging evidence suggests that this association may not be true for older adults with mild to moderate CKD [12,16,36-41]. This may be related to the limited ability of eGFR to accurately identify kidney disease in older adults and differentiate age related decrease in eGFR from an actual kidney 'disease' [42-46]. Moreover, serum creatinine varies with muscle mass, and serum creatine-based equations widely used to calculate eGFR can be misleading in older adults with lower muscle mass. Age associated decline in eGFR [47] is prognostically different from disease related decline in eGFR, the risk of progression to ESKD and adverse cardiovascular outcomes with age associated decline in GFR is low [48-50]. Brain health may follow a similar course where the age associated decrease in eGFR may not adversely affect cognitive function. We recently analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to understand the association between cognitive function and eGFR. The unadjusted analysis showed increased risk of cognitive impairment with lower eGFR, however, we found no such association when adjusted for confounding variables such as age [39,40]. Similarly, eGFR >30 mL/min/1.73m² was not associated with cognitive impairment in older adults in the BRain IN Kidney disease (BRINK) study [51]. The 3C study [37], the HUNT [52], and Hisayama [53] studies also did not show an increased risk of cognitive decline or dementia with low baseline eGFR. The Adult Changes in

Table 1: Key cross-sectional studies assessing the association between CKD and Cognitive Impairment.

Study, Year, and Sample size	Age (years)	Assessment of cognitive function	Results summary
Kurella et al., 2004, n=80 [134]	62.5 ± 14.3	3MS, Trails B, CVLT	Cognitive impairment was associated with the severity of CKD
NHANES III, 2007 n=4849 [15]	20-59	Simple Reaction Time Test, DSST, Serial Digit Learning Test	Moderate CKD (eGFR 30-59ml/min/1.73m ²) associated with poorer performance in visual attention and learning/concentration
REGARDS, 2008 n=23,405 [31]	64.9 ± 9.6	6-Item NP Test	Higher prevalence of cognitive impairment in CKD
Elias et al., 2009 n=923 [135]	control: 62.3 ± 11.7 CKD: 68.5 ± 11.6	Battery of 17 NP tests	CKD affects global cognitive function
CRIC-COG, 2010, n=825 [136]	64.9 ± 5.6	Battery of NP tests	Higher prevalence of global cognitive impairment with lower eGFR
CRIC, 2011, n=3591 [14]	58.2 ± 11.0	3MS	Higher prevalence of cognitive impairment with eGFR <30 ml/min/1.73m ² compared eGFR 45-59 ml/min/1.73m ²
Szerlip et al., 2015, n=437 [137]	61.2 ± 8.3	A battery of NP tests	Lower cognitive function in Mexican Americans with lower eGFR. eGFR <45 ml/min/1.73m ² associated with impaired processing speed, executive function, visuospatial skills, delayed memory, and global cognitive function.
Torres et al; 2017, n=898 [138]	controls: 61.6 ± 11.3 CKD: 70.8 ± 11.1	A battery of NP tests	Lower cognitive function with lower eGFR
The Maastricht Study, 2017, n=2987 [64]	59.6 ± 8.2 years	A battery of NP tests	Lower processing speed with albuminuria. No association between eGFR _{cr-lys} and cognitive function
Gupta et al., 2020, n=1181 [39]	73.7 ± 7.1	ADNI-Memory and ADNI-Executive Function	No association between eGFR and cognitive function in mild-moderate CKD
SCOPE Study, 2020, n=2256 [139]	79.5	MMSE	No difference in eGFR across the MMSE categories
Gela et al., 2021, n=232 [140]	54.1 ± 17	MMSE	Cognitive impairment more prevalent with eGFR <60 ml/min/1.73m ² and proteinuria.

ADNI: Alzheimer's Disease Neuroimaging Initiative; CVLT: California Verbal Learning Test; eGFR: estimated Glomerular Filtration Rate; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; SPPB: DSST: Symbol Digit Substitution Test; NP: Neuropsychological



Thought study did not find the average eGFR or the trajectory of eGFR to be associated with dementia in older adults [54]. The Sydney Memory and Ageing Study [55] found kidney disease to be protective against decline in memory; this may however be due to the falsely high eGFR from low muscle mass associated with cognitive impairment. The association between cognitive function and eGFR may differ in the young vs the old. For example, the sub-group analysis of the health ABC study [16] showed that in participants >73 years of age, eGFR 45-60 ml/min/1.73m² was not associated with an increase in cognitive decline when compared to participants with eGFR >60 ml/min/1.73m². However, in participants <73 years, eGFR 45-60 ml/min/1.73m², and <45 ml/min/1.73m² were associated with cognitive decline. In addition, mild-moderately low eGFR is not associated with brain structural changes such as brain atrophy [56].

Due to problems with accurately measuring eGFR with serum creatinine, some studies have used Cystatin C based eGFR (eGFR_{cys}) with cognitive decline [57-59]. However, cystatin C is also a marker of inflammation, and it remains unclear if it was the lower kidney function or inflammation that was responsible for the increased Cystatin C in these studies.

While a low eGFR may not predict cognitive decline, the association between albuminuria and cognitive function seems more robust [60-64]. The Maastricht Study [64] included ~3000 participants aged 59.6 ± 8.2 years, with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine -cystatin C equation (eGFR_{cr-cys}) based eGFR of 88.4 ± 14.6 mL/min/1.73m². While eGFR was not associated with cognitive impairment, albuminuria (urine albumin excretion ≥30 mg/24 hours) present in 8% of the cohort was associated with lower processing speed [64]. In the prospective analysis of 19,399 adults in the REGARDS study who were followed for 3.8+1.5 years, UACR of 30-299mg/g and >300 mg/g with preserved eGFR was independently associated with 31% and 57% higher risk of cognitive impairment respectively [65]. The

HUNT [52], ARIC [66], Honolulu-Asia Aging [67] and Hisayama [53] studies also found an independent association of albuminuria with cognitive decline. The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study, the longest prospective study assessing the association between CKD and cognitive function followed 4,128 participants for 12 years. Albuminuria at baseline was associated with a faster decline in memory [68]. (Table 2) presents a summary of these key prospective studies.

Cognitive Function after Kidney Transplantation

Kidney transplantation is the treatment of choice in ESKD. In addition to improving survival and quality of life [69,70], kidney transplantation also improves cognitive function [29,71]. Despite improvement, the prevalence of cognitive impairment in transplant recipients remains as high as 58% [30,72]. In addition, the middle cerebral artery kinetics response profile during moderate-intensity exercise is altered in kidney transplant recipients [73]. These data along with the high prevalence of vascular risk factors, and brain alterations in CKD indicate that vascular factors, independent of eGFR may also play an important role in cognitive impairment in ESKD. In addition, the transplant surgery, post-surgery delirium, and immunosuppression can also affect cognitive function in transplant recipients [74].

Diagnosis of Cognitive Impairment

Several tests are available to screen for cognitive impairment. Most were developed for screening of Alzheimer disease. The common tests clinically used include the Mini Mental State Examination (MMSE), the Modified Mini Mental State Examination (3MS), the Montreal Cognitive Assessment (MoCA), the Trail making B, the Mini-Cog test, and the Digit Symbol Substitution Test (DSST). Drew et al. compared the predictive ability of these screening tests in patients on maintenance hemodialysis and found the MoCA to be the best

Table 2: Key longitudinal studies assessing the relationship between CKD and Cognitive Impairment.

Study, Year, and Sample Size	Age (years)	Measures of cognitive function	Follow up (years)	Results summary
Seliger et al., 2004 n= 3349 [17]	75	Battery of NP tests	6	Creatinine ≥ 1.3 mg/dl for women and ≥ 1.5 mg/dl for men) associated with an increased risk of incident dementia
The Health ABC study, 2005 n= 3034 [16]	74 \pm 3	3MS	4	eGFR <45 ml/min/1.73m ² associated with an increased risk for cognitive impairment
Slinin et al., 2008 n=5529 [36]	73.6 \pm 5.9	3MS and Trail Making test B	5	Reduction in eGFR (<45 ml/min/1.73m ²) associated with poor executive function at baseline, but not a risk factor for cognitive decline
The INVADE Study, 2009 n=3154 [33]	75	6-Item Cognitive Impairment Test	2	Creatinine clearance eGFR <45 -59 mL/min/1.73m ² and <45 mL/min/1.73m ² associated with incident cognitive impairment after the 2-years
The Northern Manhattan Study, 2009 n=2172 [34]	66	TICS-m	2.9	Creatinine clearance <90 ml/min/1.73m ² associated with worse global cognitive function
The Rancho Bernardo Study, 2010 n= 759 [141]	75	MMSE, Trails B, and Category fluency test	6-7	Albuminuria ≥ 30 mg/g (but not low eGFR) associated with cognitive decline.
REGARDS study, 2011 n=19,399 [65]	≥ 65	6-Item NP Test	3.8 \pm 1.5	With preserved eGFR, albuminuria >30 mg/g associated with cognitive impairment. Low eGFR (<60 mL/min/1.73m ²) without albuminuria (<10 mg/g) also associated with cognitive impairment
The 3C Study, 2011 n= 7839 [37]	>65	MMSE	7	Low baseline eGFR(<60 mL/min/1.73m ²) not associated with cognitive impairment. Rapid decline in eGFR associated with cognitive impairment
O'Hare et al., 2012 n=2968 [54]	>65	CASI	6.0 (3.1-10.1)	No association between eGFR and dementia
The Singapore longitudinal aging study, 2012 n= 1315 [35]	65 \pm 7.2	MMSE IADL	4	CKD (eGFR <60 mL/min/1.73m ²) in older individuals predicted cognitive and functional decline
The Cardiovascular Health Study, 2014 n=3907 [142]	>65	3MS DSST	7	eGFR _{cr} (<60 mL/min/1.73 m ²) is associated with higher risk of worsening cognition
Honolulu-Asia Aging Study, 2016 n=3734 [67]	77-78	CASI	8	Midlife dipstick proteinuria predicted cognitive decline over 8 years
BRINK Study, 2016 n=554 [51]	69.3	Battery of NP tests	3	eGR <30 mL/min/1.73 m ² associated with decline in cognitive function
Ekblad et al., 2018 n=3687 [143]	49.3	Battery of NP tests	11	Albuminuria >3 mg/mmol associated with cognitive impairment
Hisayama study, 2018 n= 1562 [53]	>60	Dementia based on DSM-III definition, clinical and imaging data	10	Albuminuria >30 mg/g associated with dementia. eGFR (after adjustment for albuminuria) not associated with dementia
Aus Diab Study, 2019 n=4128 [68]	>25	CVLT SDMT	12	Albuminuria ≥ 3.5 mg/mmol in women and ≥ 2.5 mg/mmol in men associated with memory impairment. eGFR <60 ml/min/1.73 m ² not associated with worsening of cognitive function
The HUNT Study, 2019 n=48508 [52]	49.5 \pm 16.7	Dementia diagnoses based on history, clinical exam and brain imaging	7	Albuminuria > 1.78 mg/mmol associated with increased vascular dementia. No association between eGFR and dementia.
The Rancho Bernado Study, 2021 n= 1634 [144]	71.7 years	MMSE, Trails B, Buschke total recall	8.1	Albuminuria ≥ 30 mg/g was associated with rapid cognitive decline. No such association found with eGFR and cognitive function.
Grasing et al., 2021 n=1127 [40]	74 \pm 7	ADNI-Memory and ADNI-Executive Function	6 \pm 2.6	Mild-moderately low eGFR was not associated with cognitive decline.

ADNI: Alzheimer's Disease Neuroimaging Initiative; CVLT: California Verbal Learning Test; CASI: Cognitive Abilities Screening Instrument; eGFR: estimated Glomerular Filtration Rate; MMSE: Mini Mental State Examination; 3MS: Modified Mini Mental State Examination; SPPB: Short Physical Performance Battery; UACR: Urine Albumin-Creatinine Ratio; DSST: Symbol Digit Substitution Test; TICS- m: Modified Telephone Interview for Cognitive Status; NP: Neuropsychological; SDMT: Symbol Digit Modalities Test; IADL: Instrumental Activities of Daily Living

performing screening test [75]. While screening tests are helpful, they have limited ability to confirm the diagnosis or grade the level of cognitive impairment. After a low score on a screening test, a follow up detailed neuropsychological assessment is still recommended to confirm diagnosis and identify the domains of cognition affected. These tools while widely used in geriatric clinics are often not readily available in a nephrology clinic. In addition, perceived cognitive status is not a reliable assessment of actual cognitive status [76]. Thus, cognitive impairment, especially in younger patients with CKD remains largely undiagnosed.

Pathophysiology of Cognitive Impairment in CKD

The mechanisms underlying cognitive impairment in CKD are complex and multifactorial. While several CKD specific factors can

be implicated, it is important to recognize that patients with CKD have confounding factors such as multiple comorbidities, older age, and low physical activity that can independently increase the risk of cognitive impairment. For simplicity, we will categorize the possible etiological factors of cognitive impairment in CKD into two broad entities, i.e., CKD specific and non-CKD specific risk factors (Figure 1).

CKD Specific Factors

Uremic metabolites: Impairment of glomerular filtration and/or tubular secretion leads to accumulation of several metabolites in CKD. More than 150 such compounds have been identified and many others remain unknown. Many uremic metabolites adversely affect the central nervous system [77]. Although high serum levels of several uremic metabolites should not cross the blood brain barrier

and affect the brain, CKD causes vascular endothelial dysfunction and disruption of the blood brain-brain-barrier [78] allowing a higher-than-normal concentration of these metabolites into the brain. These uremic metabolites may also lead to alterations in brain neurochemicals, cerebral blood flow, and white matter integrity [71].

Metabolic acidosis: Metabolic acidosis is common in CKD. Hydrogen ions can cause neural excitotoxicity and modulation of N-methyl-D aspartate- activated currents leading to hyperexcitable state [79,80]. In the cross-sectional analysis of 2,853 participants from the Systolic BP Intervention Trial (SPRINT) study, low serum bicarbonate level was independently associated with cognitive impairment [81]. Longitudinal studies are needed to assess causality and explore this association further.

Anemia: Anemia is common in CKD. Both anemia and its treatment with erythropoietin stimulating agents are associated with increased risk of cerebrovascular disease and cognitive impairment [82]. It remains unclear if these associations are related hypoperfusion and hypoxia or due to increased risk of cerebrovascular events [14,83].

Mineral Bone Disease: Secondary hyperparathyroidism commonly found in advanced CKD and characterized by elevated Parathyroid (PTH), low calcium, and low vitamin D levels is also associated with cognitive impairment [84,85]. It is hypothesized that PTH crosses the blood-brain barrier and increases the release of vasopressin. Vasopressin increases vasoconstriction, causing hypoperfusion in cortical areas of the brain involved in memory and learning processes [86,87]. Furthermore, cognitive function improves after parathyroidectomy, implicating that high PTH levels may be associated with cognitive impairment independent of the severity of CKD [88]. Additional supporting data for this association and the role of vitamin D needs further exploration.

Dialysis procedure related Factors: Dialysis is a lifesaving procedure in ESKD. Initiation of dialysis clears neurotoxic uremic metabolites and improves uremic encephalopathy. However, initiation of dialysis is also associated with increase in stroke [89]; an independent risk factor for cognitive impairment and dementia. While dialysis inadequacy may affect cognitive function [20], increasing dialysis frequency or dose does not improve cognitive function [90]. Sudden fluid shifts commonly seen with in-center hemodialysis can decrease cerebral blood flow causing cerebral stunning, ischemia, and eventual atrophy [91-95]. Indeed, high ultra filtration volumes during hemodialysis reduce cerebral blood flow [96]. In addition, infarctions in watershed areas of the brain are reported in hemodialysis patients [97]. Cerebral ischemia in ESKD is independent of systemic blood pressure indicating that disruption of cerebral auto regulation and blood brain barrier may play a role in ischemic brain injury [91]. Dialysate temperature may also affect cerebral blood flow. However, the increase in fractional anisotropy at 12 months with normal dialysate temperature (37 degrees C) and a lack of improvement in fractional anisotropy with a lower dialysate temperature indicates otherwise [98]. Unlike hemodialysis, peritoneal dialysis has less hemodynamic shifts and may preserve cognitive function better [99]. Despite this theoretical advantage of peritoneal dialysis over hemodialysis in preserving cognitive function, comparative studies are lacking.

Non- CKD Specific Risk factors

Hypertension, diabetes, dyslipidemia, obesity, metabolic syndrome, and smoking; common risk factors for dementia are common in CKD. CKD is also associated with endothelial dysfunction, atherosclerosis, vascular stiffness, and vascular calcifications. These changes may explain the higher risk of cerebrovascular events, lacunar infarcts, white matter disease, and brain atrophy; (common features of vascular dementia; in CKD) [100-102]. These risk factors lead to endothelial dysfunction. Endothelial dysfunction within the renal vasculature is a key feature in progression of kidney disease. Inflammation, oxidative stress, and possibly hyperphosphatemia increase endogenous inhibitors of endothelial nitric oxide synthase [103]. Endothelial dysfunction is a well described risk factor of vascular dementia [104]. Aging itself can affect vascular endothelial function [105], and coupled with other traditional risk factors seen in CKD, this effect can be additive.

Diabetes, the leading cause of CKD in the United States [8], is an independent risk factor for vascular disease and cognitive impairment [106,107]. Hyperglycemia induces oxidative stress and over expression of cytokines increasing inflammation and lipid accumulation. This causes a pro thrombotic state largely responsible for small vessel (retinopathy, nephropathy, neuropathy) and large vessel (cardiovascular, cerebrovascular, and peripheral vascular) diseases [108,109]. An anti-inflammatory effect of metformin, an oral hypoglycemic agent is hypothesized to be neuroprotective and may delay the progression of cognitive decline [110-114]. Due to safety concerns, metformin use is however restricted in advanced CKD [115].

Hypertension, the second leading cause of CKD is also an independent risk factor for cognitive impairment in the general population [8]. Hypertension is a known risk factor for both clinical disease such as stroke and transient ischemic attacks [116] as well as subclinical disease such as lacunar infarcts and white matter disease [101,102]. Higher blood pressures are associated with higher incident dementia [117,118] and lowering blood pressure reduces cognitive decline and probable dementia [119,120].

Several other confounding risk factors are commonly present in individuals with CKD. Smoking is a risk factor for both cognitive impairment and CKD [121]. While nicotine may improve cognition in the short-term, long-term smoking is detrimental for cognitive function [122-125]. Visceral obesity is also associated with increased risk for CKD [126-130] as well as dementia [131-133].

Conclusion

Cognitive impairment in CKD is common but remains largely undiagnosed. It remains debatable whether a low eGFR is independently associated with cognitive impairment especially in older patients with mild-moderate reduction in eGFR. Albuminuria may be a better predictor of cognitive decline than eGFR. Confounding variables such as age and co-morbidities such as diabetes and hypertension make the relationship between CKD and cognitive function hard to interpret.

Normalization of brain alterations and improvement in some cognitive domains with kidney transplantation indicates reversibility in CKD associated cognitive impairment. This reversibility is

promising and can guide strategies for management of patients who are unable to receive a kidney transplant. These strategies may include lowering ultrafiltration and preserving residual kidney function and tubular secretion even on dialysis.

Careful evaluation and management of risk factors, and screening for cognitive impairment can improve patient care. Standardization of cognitive function assessment tools in CKD and frequency of screening will also be beneficial. Importantly, without any effective pharmaceutical treatment for cognitive impairment in CKD, prevention may be the best strategy to lower incident dementia. Thus, lifestyle modifications, dietary changes, better management of comorbidities such as hypertension, dyslipidemia, and diabetes, smoking cessation, and increasing physical activity may be critical. Early identification of patients at risk for future dementia can help prioritize these efforts. Future research should include the effects of early identification and aggressive management of risk factors on dementia prevention in CKD.

References

- Hannan M, Collins EG, Phillips SA, Quinn L, Steffen A, Bronas UG. Cognitive and vascular function in older adults with and without CKD. *Aging Clinical and Experimental Research*. 2020; 33: 1885-1894.
- Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Advances in chronic kidney disease*. 2008; 15: 123-132.
- Bremer BA, Wert KM, Durica AL, Weaver A. Neuropsychological, physical, and psychosocial functioning of individuals with end-stage renal disease. *Annals of Behavioral Medicine*. 1997; 19: 348-352.
- Lopez-Vargas PA, Tong A, Phoon RK, Chadban SJ, Shen Y, Craig JC. Knowledge deficit of patients with stage 1-4 CKD: a focus group study. *Nephrology (Carlton)*. 2014; 19: 234-43.
- Drew DA, Weiner DE, Tighiouart H, Scott T, Lou K, Kantor A, et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2015; 65: 303-311.
- Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006; 67: 216-223.
- Gupta A, Montgomery RN, Bedros V, Lesko J, Mahnken JD, Chakraborty S, et al. Subclinical Cognitive Impairment and Listing for Kidney Transplantation. *Clinical journal of the American Society of Nephrology : CJASN*. 2019; 14: 567-575.
- Chronic kidney disease in the United States, 2021. US Department of Health and Human Services, Centers for Disease Control and Prevention.
- Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two Novel Equations to Estimate Kidney Function in Persons Aged 70 Years or Older. *Annals of Internal Medicine*. 2012; 157: 471.
- Stevens LA, Viswanathan G, Weiner DE. Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. *Advances in chronic kidney disease*. 2010; 17: 293-301.
- Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2020; 16: 391-460.
- Burns CM, Knopman DS, Tupper DE, Davey CS, Slinin YM, Lakshminarayan K, et al. Prevalence and Risk of Severe Cognitive Impairment in Advanced Chronic Kidney Disease. *The Journals of Gerontology: Series A*. 2018; 73: 393-399.
- Otobe Y, Hiraki K, Hotta C, Nishizawa H, Izawa KP, Taki Y, et al. Mild cognitive impairment in older adults with pre-dialysis patients with chronic kidney disease: Prevalence and association with physical function. *Nephrology (Carlton)*. 2019; 24: 50-5.
- Tamura MK, Xie D, Yaffe K, Cohen DL, Teal V, Kasner SE, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. *Clinical journal of the American Society of Nephrology: CJASN*. 2011; 6: 248-256.
- Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *Journal of the American Society of Nephrology: JASN*. 2007; 18: 2205-2213.
- Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *Journal of the American Society of Nephrology: JASN*. 2005; 16: 2127-2133.
- Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. *Journal of the American Society of Nephrology: JASN*. 2004; 15: 1904-1911.
- Murray AM, Knopman DS. Cognitive impairment in CKD: no longer an occult burden. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2010; 56: 615-618.
- Salazar-Félix NA, Martin-del-Campo F, Cueto-Manzano AM, Romo-Flores ML, Velázquez-Vidaurre AL, Sánchez-Soriano A, et al. Prevalence of mild cognitive impairment in automated peritoneal dialysis patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2021; 36: 2106-2111.
- Shin DJ, Kim T, Jung D, Moon J, Jeon D, Kim S, et al. Association between Dialysis Adequacy and Cognition in Patients with Peritoneal Dialysis. *Psychiatry Investigation*. 2020; 17: 1143-1148.
- Kim HW, Jhee JH, Joo YS, Yang KH, Jung JJ, Shin JH, et al. Dialysis Adequacy and Risk of Dementia in Elderly Hemodialysis Patients. *Frontiers in Medicine*. 2021; 8.
- Cheung KL, LaMantia MA. Cognitive Impairment and Mortality in Patients Receiving Hemodialysis: Implications and Future Research Avenues. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2019; 74: 435-437.
- Kalirao P, Pederson S, Foley RN, Kolste A, Tupper D, Zaun D, et al. Cognitive impairment in peritoneal dialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2011; 57: 612-620.
- Drew DA, Weiner DE, Sarnak MJ. Cognitive Impairment in CKD: Pathophysiology, Management, and Prevention. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2019; 74: 782-790.
- Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: impact of uremic toxins on cognitive function. *Neurotoxicology*. 2014; 44: 184-193.
- Franco DO, Starosta RT, Roriz-Cruz M. The specific impact of uremic toxins upon cognitive domains: a review. *Jornal Brasileiro de Nefrologia*. 2019; 41: 103-111.
- Viggiano D, Wagner CA, Martino G, Nedergaard M, Zoccali C, Unwin R, et al. Mechanisms of cognitive dysfunction in CKD. *Nature Reviews Nephrology*. 2020; 16: 452-469.
- Chu NM, Gross AL, Shaffer AA, Haugen CE, Norman SP, Xue Q, et al. Frailty and Changes in Cognitive Function after Kidney Transplantation. *Journal of the American Society of Nephrology : JASN*. 2019; 30: 336-345.
- Gupta A, Lepping RJ, Yu AS, Perea RD, Honea RA, Johnson DK, et al. Cognitive Function and White Matter Changes Associated with Renal Transplantation. *American Journal of Nephrology*. 2016; 43: 50-57.
- Gupta A, Mahnken JD, Johnson DK, Thomas TS, Subramaniam D, Polshak T, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. *BMC Nephrology*. 2017; 18.
- Tamura MK, Wadley V, Yaffe K, McClure LA, Howard G, Go R, et al. Kidney

- function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2008; 52: 227-234.
32. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. *Neurology*. 2009; 73: 920-927.
 33. Etgen T, Sander D, Chonchol M, Briesenick C, Poppert H, Förstl H, et al. Chronic kidney disease is associated with incident cognitive impairment in the elderly: the INVADE study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2009; 24: 3144-3150.
 34. Khatri M, Nickolas T, Moon YP, Paik MC, Rundek T, Elkind MSV, et al. CKD associates with cognitive decline. *Journal of the American Society of Nephrology: JASN*. 2009; 20: 2427-2432.
 35. Feng L, Yap KB, Yeoh LY, Ng TP. Kidney Function and Cognitive and Functional Decline in Elderly Adults: Findings from the Singapore Longitudinal Aging Study. *Journal of the American Geriatrics Society*. 2012; 60: 1208-1214.
 36. Slinin Y, Paudel ML, Ishani A, Taylor BC, Yaffe K, Murray AM, et al. Kidney Function and Cognitive Performance and Decline in Older Men. *Journal of the American Geriatrics Society*. 2008; 56: 2082-2088.
 37. Helmer C, Stengel B, Metzger M, Froissart M, Massy Z, Tzourio C, et al. Chronic kidney disease, cognitive decline, and incident dementia. *Neurology*. 2011; 77: 2043-2051.
 38. Tamura MK, Gaussoin SA, Pajewski NM, Chelune GJ, Freedman BI, Gure TR, et al. Kidney Disease, Intensive Hypertension Treatment, and Risk for Dementia and Mild Cognitive Impairment: The Systolic Blood Pressure Intervention Trial. *Journal of the American Society of Nephrology : JASN*. 2020; 31: 2122-2132.
 39. Gupta A, Kennedy K, Perales-Puchalt J, Drew D, Beddhu S, Sarnak M, et al. Mild-moderate CKD is not associated with cognitive impairment in older adults in the Alzheimer's Disease Neuroimaging Initiative cohort. *PLoS One*. 2020; 15: e0239871.
 40. Grasing M, Kenned K, Sarnak MJ, Burns JM, Gupta A. Mild to moderate decrease in eGFR and cognitive decline in older adults. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2021.
 41. Gupta A, Burns JM. A Single Point-in-Time eGFR Is Not Associated with Increased Risk of Dementia in the Elderly. *Journal of the American Society of Nephrology: JASN*. 2020; 31: 2965-2965.
 42. Glasscock R, Delanaye P, Nahas ME. An Age-Calibrated Classification of Chronic Kidney Disease. *JAMA*. 2015; 314: 559.
 43. Kremers WK, Denic A, Lieske JC, Alexander MP, Kaushik V, Elsherbiny HE, et al. Distinguishing age-related from disease-related glomerulosclerosis on kidney biopsy: the Aging Kidney Anatomy study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2015; 30: 2034-2039.
 44. Glasscock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney international*. 2012; 82: 270-277.
 45. Lindeman RD, Tobin J, Shock NW. Longitudinal Studies on the Rate of Decline in Renal Function with Age. *Journal of the American Geriatrics Society*. 1985; 33: 278-285.
 46. Wetzels JFM, Kiemeneij LALM, Swinkels DW, Willems HL, Heijer MD. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney international*. 2007; 72: 632-637.
 47. Douville P, Martel AR, Talbot J, Desmeules S, Langlois S, Agharazii M. Impact of age on glomerular filtration estimates. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2009; 24: 97-103.
 48. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. *Journal of the American Society of Nephrology: JASN*. 2007; 18: 2758-2765.
 49. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012; 308: 2349.
 50. Obi Y, Kimura T, Nagasawa Y, Yamamoto R, Yasuda K, Sasaki K, et al. Impact of age and overt proteinuria on outcomes of stage 3 to 5 chronic kidney disease in a referred cohort. *Clinical journal of the American Society of Nephrology: CJASN*. 2010; 5: 1558-1565.
 51. Murray AM, Bell EJ, Tupper DE, Davey CS, Pederson SL, Amiot EM, et al. The Brain in Kidney Disease (BRINK) Cohort Study: Design and Baseline Cognitive Function. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2016; 67: 593-600.
 52. Gabin JM, Romundstad S, Saltvedt I, Holmen J. Moderately increased albuminuria, chronic kidney disease and incident dementia: the HUNT study. *BMC Nephrology*. 2019; 20.
 53. Takae K, Hata J, Ohara T, Yoshida D, Shibata M, Mukai N, et al. Albuminuria Increases the Risks for Both Alzheimer Disease and Vascular Dementia in Community-Dwelling Japanese Elderly: The Hisayama Study. *J Am Heart Assoc*. 2018; 7.
 54. O'Hare AM, Walker R, Haneuse S, Crane PK, McCormick WC, Bowen JD, et al. Relationship Between Longitudinal Measures of Renal Function and Onset of Dementia in a Community Cohort of Older Adults. *Journal of the American Geriatrics Society*. 2012; 60: 2215-2222.
 55. Lipnicki DM, Sachdev PS, Crawford J, Reppermund S, Kochan NA, Trollor JN, et al. Risk Factors for Late-Life Cognitive Decline and Variation with Age and Sex in the Sydney Memory and Ageing Study. *PLoS ONE*. 2013; 8: e65841.
 56. Grasing M, Sharma P, Lepping RJ, Honea R, Burns JM, Brooks WM, et al. Association between the Estimated Glomerular Filtration Rate and Brain Atrophy in Older Adults. *American journal of nephrology*. 2022; 53: 176-181.
 57. Yaffe K, Kurella-Tamura M, Ackerson L, Hoang TD, Anderson AH, Duckworth M, et al. 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. *Journal of the American Geriatrics Society*. 2014; 62: 1623-1629.
 58. Murray AM, Barzilay JI, Lovato JF, Williamson JD, Miller ME, Marcovina S, et al. Biomarkers of Renal Function and Cognitive Impairment in Patients With Diabetes. *Diabetes Care*. 2011; 34: 1827-1832.
 59. Madero M, Sarnak MJ. Association of cystatin C with adverse outcomes. *Current Opinion in Nephrology and Hypertension*. 2009; 18: 258-263.
 60. Sedaghat S, Cremers LGM, Groot MD, Hoorn EJ, Hofman A, Lugt AVD, et al. Kidney function and microstructural integrity of brain white matter. *Neurology*. 2015; 85: 154-161.
 61. Tamura MK, Pajewski NM, Bryan RN, Weiner DE, Diamond M, Buren PV, et al. Chronic kidney disease, cerebral blood flow, and white matter volume in hypertensive adults. *Neurology*. 2016; 86: 1208-1216.
 62. Cho EB, Shin H, Park SE, Chun P, Jang HR, Yang J, et al. Albuminuria, Cerebrovascular Disease and Cortical Atrophy: among Cognitively Normal Elderly Individuals. *Scientific Reports*. 2016; 6.
 63. Vemuri P, Knopman DS, Jack CR, Lundt ES, Weigand SD, Zuk SM, et al. Association of Kidney Function Biomarkers with Brain MRI Findings: The BRINK Study. *Journal of Alzheimer's disease : JAD*. 2017; 55: 1069-1082.
 64. Martens RJ, Kooman JP, Stehouwer CD, Dagnelie PC, van der Kallen CJ, Koster A, et al. Estimated GFR, Albuminuria, and Cognitive Performance: The Maastricht Study. *Am J Kidney Dis*. 2017; 69: 179-91.
 65. Tamura MK, Muntner P, Wadley V, Cushman M, Zakai NA, Bradbury BD, et al. Albuminuria, kidney function, and the incidence of cognitive impairment among adults in the United States. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2011; 58: 756-763.
 66. Scheppach JB, Coresh J, Wu A, Gottesman RF, Mosley TH, Knopman

- DS, et al. Albuminuria and Estimated GFR as Risk Factors for Dementia in Midlife and Older Age: Findings From the ARIC Study. *American Journal of Kidney Diseases*. 2020; 76: 775-83.
67. Higuchi M, Chen R, Abbott RD, Bell C, Launer L, Ross GW, et al. Mid-Life Proteinuria and Late-Life Cognitive Function and Dementia in Elderly Men: The Honolulu-Asia Aging Study. *Alzheimer Disease & Associated Disorders*. 2015; 29: 200-205.
68. Sacre JW, Magliano DJ, Zimmet PZ, Polkinghorne KR, Chadban SJ, Anstey KJ, et al. Associations of Chronic Kidney Disease Markers with Cognitive Function: A 12-Year Follow-Up Study. *Journal of Alzheimer's Disease*. 2018; 70: S19-S30.
69. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney international*. 2000; 57: 307-313.
70. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic Review: Kidney Transplantation Compared With Dialysis in Clinically Relevant Outcomes. *American Journal of Transplantation*. 2011; 11: 2093-2109.
71. Lepping RJ, Montgomery RN, Sharma P, Mahnken JD, Vidoni ED, Choi I, et al. Normalization of Cerebral Blood Flow, Neurochemicals, and White Matter Integrity after Kidney Transplantation. *Journal of the American Society of Nephrology: JASN*. 2020; 32: 177-187.
72. Radić J, Ljutić D, Radić M, Kovačić V, Dodig-Čurković K, Šain M. Kidney Transplantation Improves Cognitive and Psychomotor Functions in Adult Hemodialysis Patients. *American Journal of Nephrology*. 2011; 34: 399-406.
73. Ward J, Ramakrishnan M, Jurgensen A, Billinger S, Gupta A. Cerebrovascular Response during Acute Exercise in Kidney Transplant Recipients. *Clinical journal of the American Society of Nephrology: CJASN*. 2021; 17: 111-113.
74. Jurgensen A, Qannus AA, Gupta A. Cognitive Function in Kidney Transplantation. *Current Transplantation Reports*. 2020; 7: 145-153.
75. Drew DA, Tighiouart H, Rollins J, Duncan S, Babroudi S, Scott T, et al. Evaluation of Screening Tests for Cognitive Impairment in Patients Receiving Maintenance Hemodialysis. *Journal of the American Society of Nephrology: JASN*. 2020; 31: 855-864.
76. Gupta A, Thomas TS, Klein JA, Montgomery RN, Mahnken JD, Johnson DK, et al. Discrepancies between Perceived and Measured Cognition in Kidney Transplant Recipients: Implications for Clinical Management. *Nephron*. 2017; 138: 22-28.
77. Lin Y, Wu P, Liang S, Mubanga M, Yang Y, Hsu Y, et al. Protein-bound uremic toxins are associated with cognitive function among patients undergoing maintenance hemodialysis. *Scientific Reports*. 2019; 9(1).
78. Bobot M, Thomas L, Moyon A, Fernandez S, McKay N, Balasse L, et al. Uremic Toxic Blood-Brain Barrier Disruption Mediated by AhR Activation Leads to Cognitive Impairment during Experimental Renal Dysfunction. *Journal of the American Society of Nephrology: JASN*. 2020; 31: 1509-1521.
79. DiNicolantonio JJ, O'Keefe J. Low-grade metabolic acidosis as a driver of chronic disease: a 21st century public health crisis. *Open Heart*. 2021; 8: e001730.
80. Zhao H, Cai Y, Yang Z, He D, Shen B. Acidosis leads to neurological disorders through overexciting cortical pyramidal neurons. *Biochemical and biophysical research communications*. 2011; 415: 224-228.
81. Dobre M, Gaussoin SA, Bates JT, Chonchol MB, Cohen DL, Hostetter TH, et al. Serum Bicarbonate Concentration and Cognitive Function in Hypertensive Adults. *Clinical journal of the American Society of Nephrology: CJASN*. 2018; 13: 596-603
82. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *The New England journal of medicine*. 2006; 355: 2085-2098.
83. Abramson JL, Jurkovic CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney international*. 2003; 64: 610-615.
84. Bjorkman MP, Sorva AJ, Tilvis RS. Does elevated parathyroid hormone concentration predict cognitive decline in older people?. *Aging Clin Exp Res*. 2010; 22: 164-9.
85. Lourida I, Thompson-Coon J, Dickens CM, Soni M, Kuźma E, Kos K, et al. Parathyroid Hormone, Cognitive Function and Dementia: A Systematic Review. *PLoS ONE*. 2015; 10: e0127574.
86. Khudaverdyan D, Asratyan A. Effect of the parathyroid hormone—Calcium system on functional activity of the hypothalamus-neurohypophysis complex. *Bulletin of experimental biology and medicine*. 1996; 122: 1069-71.
87. Çermik TF, Kaya M, Uğur-Altun B, Bedel D, Berkarda, Yiğitbaşı N. Regional cerebral blood flow abnormalities in patients with primary hyperparathyroidism. *Neuroradiology*. 2006; 49: 379-385.
88. Caron NR, Pasięka JL. What Symptom Improvement Can Be Expected After Operation for Primary Hyperparathyroidism?. *World Journal of Surgery*. 2009; 33: 2244-2255.
89. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. *Journal of the American Society of Nephrology: JASN*. 2013; 24: 1166-1173.
90. Tamura MK, Unruh ML, Nissenson AR, Larive B, Eggers PW, Gassman J, et al. Effect of more frequent hemodialysis on cognitive function in the frequent hemodialysis network trials. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2013; 61: 228-237.
91. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between Hypotension and Cerebral Ischemia during Hemodialysis. *Journal of the American Society of Nephrology: JASN*. 2017; 28: 2511-2520.
92. McIntyre CW. Recurrent Circulatory Stress: The Dark Side of Dialysis. *Seminars in Dialysis*. 2010; 23: 449-451.
93. Mizumasa T, Hirakata H, Yoshimitsu T, Hirakata E, Kubo M, Kashiwagi M, et al. Dialysis-Related Hypotension as a Cause of Progressive Frontal Lobe Atrophy in Chronic Hemodialysis Patients: A 3-Year Prospective Study. *Nephron Clinical Practice*. 2004; 97: c23-c30.
94. Polinder-Bos HA, García DV, Kuipers J, Elting JWW, Aries MJH, Krijnen WP, et al. Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in Elderly Patients. *Journal of the American Society of Nephrology: JASN*. 2018; 29: 1317-1325.
95. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2001; 38: S11-S17.
96. Findlay MD, Dawson J, Dickie DA, Forbes KP, McGlynn D, Quinn T, et al. Investigating the Relationship between Cerebral Blood Flow and Cognitive Function in Hemodialysis Patients. *Journal of the American Society of Nephrology: JASN*. 2019; 30: 147-158.
97. Davenport A, Buscombe JR. Watershed cerebral infarction in a hemodialysis patient. *Kidney international*. 2010; 77: 1140.
98. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *Journal of the American Society of Nephrology: JASN*. 2015; 26: 957-965.
99. Neumann D, Mau W, Wienke A, Girndt M. Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. *Kidney international*. 2018; 93: 430-438.
100. Lepping RJ, Montgomery RN, Sharma P, Mahnken JD, Vidoni ED, Choi I, et al. Normalization of Cerebral Blood Flow, Neurochemicals, and White Matter Integrity after Kidney Transplantation. *Journal of the American Society of Nephrology: JASN*. 2020; 32: 177-187.
101. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, Lugt AVD, Breteler MM. Kidney Function Is Related to Cerebral Small Vessel Disease. *Stroke*. 2008; 39: 55-61.
102. Drew DA, Bhadelia R, Tighiouart H, Novak V, Scott TM, Lou KV, et al. Anatomic brain disease in hemodialysis patients: a cross-sectional study. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2013; 61: 271-278.

103. Lind L, Sarabi M, Millgård J, Kahan T, Edner M. Endothelium-dependent vasodilation and structural and functional changes in the cardiovascular system are dependent on age in healthy subjects. *Clinical physiology*. 1999; 19: 400-409.
104. Zuliani G, Cavalieri M, Galvani M, Passaro A, Munari MR, Bosi C, et al. Markers of endothelial dysfunction in older subjects with late onset Alzheimer's disease or vascular dementia. *Journal of the Neurological Sciences*. 2008; 272: 164-170.
105. Lakatta EG. Arterial and Cardiac Aging: Major Shareholders in Cardiovascular Disease Enterprises: Part III: Cellular and Molecular Clues to Heart and Arterial Aging. *Circulation: Journal of the American Heart Association*. 2003; 107: 490-497.
106. Werhane ML, Thomas KR, Bangen KJ, Weigand AJ, Edmonds EC, Nation DA, et al. Arterial Stiffening Moderates the Relationship Between Type-2 Diabetes Mellitus and White Matter Hyperintensity Burden in Older Adults With Mild Cognitive Impairment. *Frontiers in Aging Neuroscience*. 2021; 13.
107. Andrews RM, Shpitser I, Lopez O, Longstreth WT, Chaves PHM, Kuller L, et al. Examining the causal mediating role of brain pathology on the relationship between diabetes and cognitive impairment: the Cardiovascular Health Study. *Journal of the Royal Statistical Society. Series A, (Statistics in Society)*. 2020; 183: 1705-1726.
108. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *European Heart Journal*. 2013; 34: 2436-2443.
109. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World journal of diabetes*. 2015; 6: 1246.
110. Teng Z, Feng J, Qi Q, Dong Y, Xiao Y, Xie X, et al. Long-Term Use of Metformin Is Associated With Reduced Risk of Cognitive Impairment With Alleviation of Cerebral Small Vessel Disease Burden in Patients With Type 2 Diabetes. *Frontiers in Aging Neuroscience*. 2021; 13.
111. Zhang Q, Li W, Liu Z, Zhang H, Ba Y, Zhang R. Metformin therapy and cognitive dysfunction in patients with type 2 diabetes. *Medicine*. 2020; 99: e19378.
112. Gorgich EAC, Parsaie H, Yarmand S, Baharvand F, Sarbishegi M. Long-term administration of metformin ameliorates age-dependent oxidative stress and cognitive function in rats. *Behavioural Brain Research*. 2021; 410: 113343.
113. Kodali M, Attaluri S, Madhu LN, Shuai B, Upadhyay R, Gonzalez JJ, et al. Metformin treatment in late middle age improves cognitive function with alleviation of microglial activation and enhancement of autophagy in the hippocampus. *Aging Cell*. 2021; 20.
114. Samaras K, Makkar S, Crawford JD, Kochan NA, Wen W, Draper B, et al. Metformin Use Is Associated With Slowed Cognitive Decline and Reduced Incident Dementia in Older Adults With Type 2 Diabetes: The Sydney Memory and Ageing Study. *Diabetes Care*. 2020; 43: 2691-2701.
115. Rhee CM, Kalantar-Zadeh K. Restricting Metformin in CKD: Continued Caution Warranted. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2015; 66: 1101-1102.
116. Wang H, Hung S, Sung J, Hung K, Wang J. Risk of stroke in long-term dialysis patients compared with the general population. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2014; 63: 604-611.
117. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, et al. Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. *JAMA*. 2019; 322: 535.
118. Schrader B, Schrader J, Elsässer A, Bünker A, Hillmann B, Vaske B, et al. Influence of cardiovascular risk factors on arterial hypertension and mild cognitive impairment in 4602 participants of the ELITE study. *Journal of Hypertension*. 2020; 38: 2475-2481.
119. Gupta A, Perdomo S, Billinger S, Beddhu S, Burns J, Gronseth G. Treatment of hypertension reduces cognitive decline in older adults: a systematic review and meta-analysis. *BMJ Open*. 2020; 10: e038971.
120. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA*. 2019; 321: 553.
121. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients-absence of evidence or evidence of absence?. *Clinical journal of the American Society of Nephrology: CJASN*. 2008; 3: 226-236.
122. Campos MW, Serebrisky D, Castaldelli-Maia JM. Smoking and Cognition. *Current drug abuse reviews*. 2016; 9: 76-79.
123. Okusaga O, Stewart MCW, Butcher I, Deary I, Fowkes FGR, Price JF. Smoking, hypercholesterolaemia and hypertension as risk factors for cognitive impairment in older adults. *Age and ageing*. 2013; 42: 306-311.
124. Pascoe M, Ski CF, Thompson DR, Linden T. Serum cholesterol, body mass index and smoking status do not predict long-term cognitive impairment in elderly stroke patients. *Journal of the Neurological Sciences*. 2019; 406: 116476.
125. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology*. 2005; 184: 523-539.
126. Pinto-Sietsma S, Navis G, Janssen WMT, Zeeuw DD, Gans ROB, Jong PED. A central body fat distribution is related to renal function impairment, even in lean subjects. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2003; 41: 733-741.
127. Foster MC, Hwang S, Massaro JM, Hoffmann U, DeBoer IH, Robins SJ, et al. Association of Subcutaneous and Visceral Adiposity With Albuminuria: The Framingham Heart Study. *Obesity*. 2011; 19: 1284-1289.
128. Chang A, Horn LV, Jacobs DR, Liu K, Muntner P, Newsome B, et al. Lifestyle-related factors, obesity, and incident microalbuminuria: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2013; 62: 267-275.
129. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. *Journal of the American Society of Nephrology: JASN*. 2006; 17: 1695-1702.
130. Hsu C, McCulloch C, Iribarren C, Darbinian J, Go A. Body Mass Index and Risk for End-Stage Renal Disease. *Annals of Internal Medicine*. 2006; 144: 21.
131. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008; 71: 1057-1064.
132. Dobbins S, Beiser A, Hoffmann U, Decarli C, O'Donnell CJ, Massaro JM, et al. Visceral fat is associated with lower brain volume in healthy middle-aged adults. *Ann Neurol*. 2010; 68: 136-44.
133. Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R. Central Obesity in the Elderly is Related to Late-onset Alzheimer Disease. *Alzheimer Disease & Associated Disorders*. 2012; 26: 101-105.
134. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive Impairment in Chronic Kidney Disease. *Journal of the American Geriatrics Society*. 2004; 52: 1863-1869.
135. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2009; 24: 2446-2452.
136. Yaffe K, Ackerson L, Tamura MK, Blanc PL, Kusek JW, Sehgal AR, et al. Chronic Kidney Disease and Cognitive Function in Older Adults: Findings from the Chronic Renal Insufficiency Cohort Cognitive Study. *Journal of the American Geriatrics Society*. 2010; 58: 338-345.
137. Szerlip HM, Edwards ML, Williams BJ, Johnson LA, Vintimilla RM, O'Bryant SE. Association Between Cognitive Impairment and Chronic Kidney Disease in Mexican Americans. *Journal of the American Geriatrics Society*. 2015; 63: 2023-2028.

138. Torres RV, Elias MF, Seliger S, Davey A, Robbins MA. Risk for cognitive impairment across 22 measures of cognitive ability in early-stage chronic kidney disease. *Nephrology Dialysis Transplantation*. 2017; 32: 299-306.
139. Britting S, Artzi-Medvedik R, Fabbietti P, Tap L, Mattace-Raso F, Corsonello A, et al. Kidney function and other factors and their association with falls. *BMC Geriatrics*. 2020; 20.
140. Gela YY, Getu AA, Adane A, Ayal BM, Akalu Y, Ambelu A, et al. Cognitive Impairment and Associated Factors Among Chronic Kidney Disease Patients: A Comparative Cross-Sectional Study. *Neuropsychiatric Disease and Treatment*. 2021; 2021: 1483-1492.
141. Jassal SK, Kritz-Silverstein D, Barrett-Connor E. A prospective study of albuminuria and cognitive function in older adults: the Rancho Bernardo study. *American journal of epidemiology*. 2010; 171: 277-286.
142. Darsie B, Shlipak MG, Sarnak MJ, Katz R, Fitzpatrick AL, Odden MC. Kidney function and cognitive health in older adults: the Cardiovascular Health Study. *American journal of epidemiology*. 2014; 180: 68-75.
143. Ekblad LL, Toppala S, Johansson JK, Koskinen S, Sundvall J, Rinne JO, et al. Albuminuria and microalbuminuria as predictors of cognitive performance in a general population: an 11-year follow-up study. *Journal of Alzheimer's Disease*. 2018; 62: 635-48.
144. Richard EL, McEvoy LK, Oren E, Alcaraz JE, Laughlin GA, LaCroix AZ, et al. Markers of Kidney Function and Longitudinal Cognitive Ability Among Older Community-Dwelling Adults: The Rancho Bernardo Study. *Journal of Alzheimer's disease: JAD*. 2021; 83: 319-331.