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CRITICAL REVIEW

A Systematic Review of Cognitive Impairments Associated With Kidney Failure in Adults Before Natural Age-Related Changes

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Abstract

Objectives: Recognition of cognitive impairment in chronic kidney disease (CKD) and its impact on functioning in adults is growing. The vast majority of studies to date have been conducted in older populations where CKD is more pronounced; however, the degree to which age-related cognitive changes could be influencing these findings remains unaddressed. This current study thus aimed to review cognitive impairment findings by stage in non-elderly CKD samples. **Methods:** PubMed and Medline *via* Scopus were searched for cross-sectional or cohort studies and randomized controlled trials that assessed cognitive function in individuals with CKD in any research setting. CKD studies including patients at any illness stage were included providing participants were below 65 years old, were not on peritoneal dialysis and had not undergone a kidney transplant. **Results:** Fifteen studies, with a total of 9304 participants, were included. Cognitive function broadly deteriorated from stage 1 to stage 5. Early stage CKD was associated with a drop in speed of processing, attention, response speed, and short-term memory abilities. Moderate stage CKD was associated with deficits in executive functioning, verbal fluency, logical memory, orientation and concentration. People with end stage kidney disease manifested significant deficits in all previous cognitive domains, along with cognitive control, delayed and immediate memory, visuospatial impairment, and overall cognitive impairment. **Conclusions:** Cognitive impairment is evident across the stages of CKD, independent of age-related changes, for both lower-order and higher-order cognitive abilities. These impairments also increase between the stages, suggesting a cumulative effect. Future directions for research are discussed. (*JINS*, 2019, *25*, 101–114)

Keywords: Chronic renal disease, End stage kidney disease, Cognition, Cognitive impairment, Executive function

INTRODUCTION

The prevalence of chronic kidney disease (CKD) has rapidly increased in the past decade, with current estimates suggesting that 1 in 10 people will develop the condition during their lifetimes (Chen & Harris, 2015). Incidence is predicted to continue growing due to rising rates of related comorbid disorders which contribute to kidney failure such as obesity, hypertension, and diabetes (Tucker, Kingsley, Morton, Scanlan, & Dalbo, 2014). When kidney filtration rates are reduced, uremic toxins are not removed from the body and this build-up of toxins can negatively affect the central nervous system (Arnold, Issar, Krishnan, & Pussell, 2016). This leads to a greater susceptibility to changes in cognitive functionality with decreased kidney function. Understanding cognitive dysfunction is critical, as it impacts overall functioning and quality of life in both mental (Fujino et al., 2016; Tan, Thomas, & Rossell, 2014) and physical disorders (Orbo et al., 2015; Schuurs & Green, 2013), and specifically CKD (Seidel et al., 2014; Weiner & Seliger, 2014).

Kidney disease is categorized into stages, which are determined by the degree of impaired kidney filtration rates. The most commonly used measure is the estimated glomerular filtration rate (eGFR), which is an estimate of how well the kidneys filter waste from the blood: early stage CKD consists of stages 1 (eGFR $\geq$ 90 mL/min per 1.73 m^2) and 2 (eGFR between 60 and 89 mL/min per 1.73 m^2), moderate stage CKD consists of stages 3 (eGFR between 30 and 59 mL/min per 1.73 m^2), and 4 (eGFR between 15 and 29 mL/min

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per 1.73 m^2), and end stage CKD consists of stage 5 (eGFR of <15 mL/min per 1.73 m^2) (Thomas, Kanso, & Sedor, 2008).

Cognitive Impairment in CKD

Cognitive impairment is defined as poorer cognitive function beyond that expected through normal aging and has been observed in both mental and physical disorders. It is a significant phenomenon in CKD specifically (Etgen, Chonchol, Forstl, & Sander, 2012), affecting numerous patients and is exacerbated with worsening kidney function, independent of other confounding factors (Kurella Tamura et al., 2008). Investigations of neurocognitive changes in end stage CKD have highlighted domains of cognition such as memory, concentration, and speed of processing (Berger et al., 2016; Kaltsatou et al., 2015). The vast majority of these studies have been conducted in older populations in line with the higher CKD prevalence and severity among older adults (Zhang & Rothenbacher, 2008); consequently, there is less of a focus on the earlier CKD stages.

This raises three issues for consideration. First, kidney disease is evident across the adult lifespan, affecting individuals from aged 18 onward. In a systematic review of studies totaling 65,181 adult participants, 5% of the population under the age of 30 had a CKD diagnosis, 7.2% were diagnosed in the range of 30–44 compared with 23.4% in those over 64 (Zhang & Rothenbacher, 2008). A common assertion is that kidney disease is relatively asymptomatic until the end stages (Levey et al., 2003); however, there is evidence that deficits in executive and higher neurocognitive functions are already present in the earlier stages of renal impairment (Berger et al., 2016; Sanchez-Roman et al., 2011). Therefore, the characterization of neurocognitive change across the disease trajectory, particularly the profile of neurocognitive impairment in the earlier stages of CKD, is incomplete and requires better understanding.

The second issue is delineating the specific pattern of neurocognitive impairment in kidney disease. Studies to date have used a variety of different tasks to assess cognition in kidney disease with a focus on confirming neurocognitive impairment, but with less attention being paid to what aspects are impacted and at what disease-stage. A recent review (Berger et al., 2016) has raised this issue, finding a range of neurocognitive deficits, with orientation, attention, and language being most impaired. A careful delineation of the neurocognitive profile in CKD, along with a mapping across illness stages, could help to advance the field, improve prognostic accuracy, and to identify areas of possible cognitive remediation.

Third, and arguably most importantly, the predominance of older populations in neurocognitive studies of CKD to date makes it difficult to determine whether reported findings of neurocognitive impairment are consequent upon the disease itself, or conflated with natural age-related cognitive changes. While cognitive change does vary by domain and between individuals across the life span, it is generally considered to significantly accelerate when an individual is in their 60s (Salthouse, Atkinson, & Berish, 2003). Kidney filtration efficiency naturally falls with age and has been associated with impaired neurocognitive function (Khatri et al., 2009), and this would be exacerbated in healthy aging (Ziegler et al., 2010). It is, therefore, important to understand how failing kidney function affects cognition before aging processes impact in order to characterize better the specific influence of CKD itself. Previous reviews in this field have not accounted for this (Berger et al., 2016; Elias, Dore, & Davey, 2013; Etgen et al., 2012).

Presently, cognitive studies in elderly CKD populations have primarily revealed significant general cognitive deficits (Chang et al., 2017; König et al., 2018; Romijn, van Marum, Emmelot-Vonk, Verhaar, & Koek, 2015). This is largely due to the wide use of the Mini-Mental State Examination (MMSE) in this group (Folstein, Folstein, & McHugh, 1975), which only provides a measure of general cognition. These deficits compound normal cognitive aging (Buchman et al., 2009), are exacerbated with CKD progression (Romijn et al., 2015) and are related to an increased risk for mortality (Sharma et al., 2016) and comorbid conditions such as dementia (Bugnicourt, Godefroy, Chillon, Choukroun, & Massy, 2013; Weng et al., 2012).

CKD is also associated with other comorbid conditions, particularly for older individuals, such as stroke (Seliger, Gillen, Longstreth, Kestenbaum, & Stehman-Breen, 2003) and cardiovascular disease (Stenvinkel & Herzog, 2010). Risk for these comorbid conditions have been observed to rise with decreasing kidney function and these conditions have been invariably associated with cognitive deficits themselves. This adds to the complexity of specifying CKD-related cognitive dysfunction in older individuals.

To this end, this systematic review sought to address these three issues with the objectives of (1) specifying the areas of neurocognitive impairment in CKD; (2) characterizing neurocognitive impairment in CKD across all stages; and (3) examining neurocognitive impairment in CKD among individuals while minimizing the effects of age-related cognitive change (<65 years).

METHODS

Search Strategy

This review conforms to the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) current statement (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group 2009). The electronic databases PubMed and Medline *via* Scopus were searched for articles up to December 2017 using the following Medical Subject Heading (MeSH) terms: "Chronic renal insufficiency", "kidney diseases", "renal disease", "chronic kidney failure", "cognition", "cognitive dysfunction", "executive function", "executive dysfunction" in either the title, abstract or keywords. The initial search yielded 642 results. All relevant literature examining the association between CKD and cognitive task performance was considered in the search. A flow chart of the search strategy is presented in Figure 1. Within the final 11 studies, reference lists were searched manually to find any additional studies that were not found in

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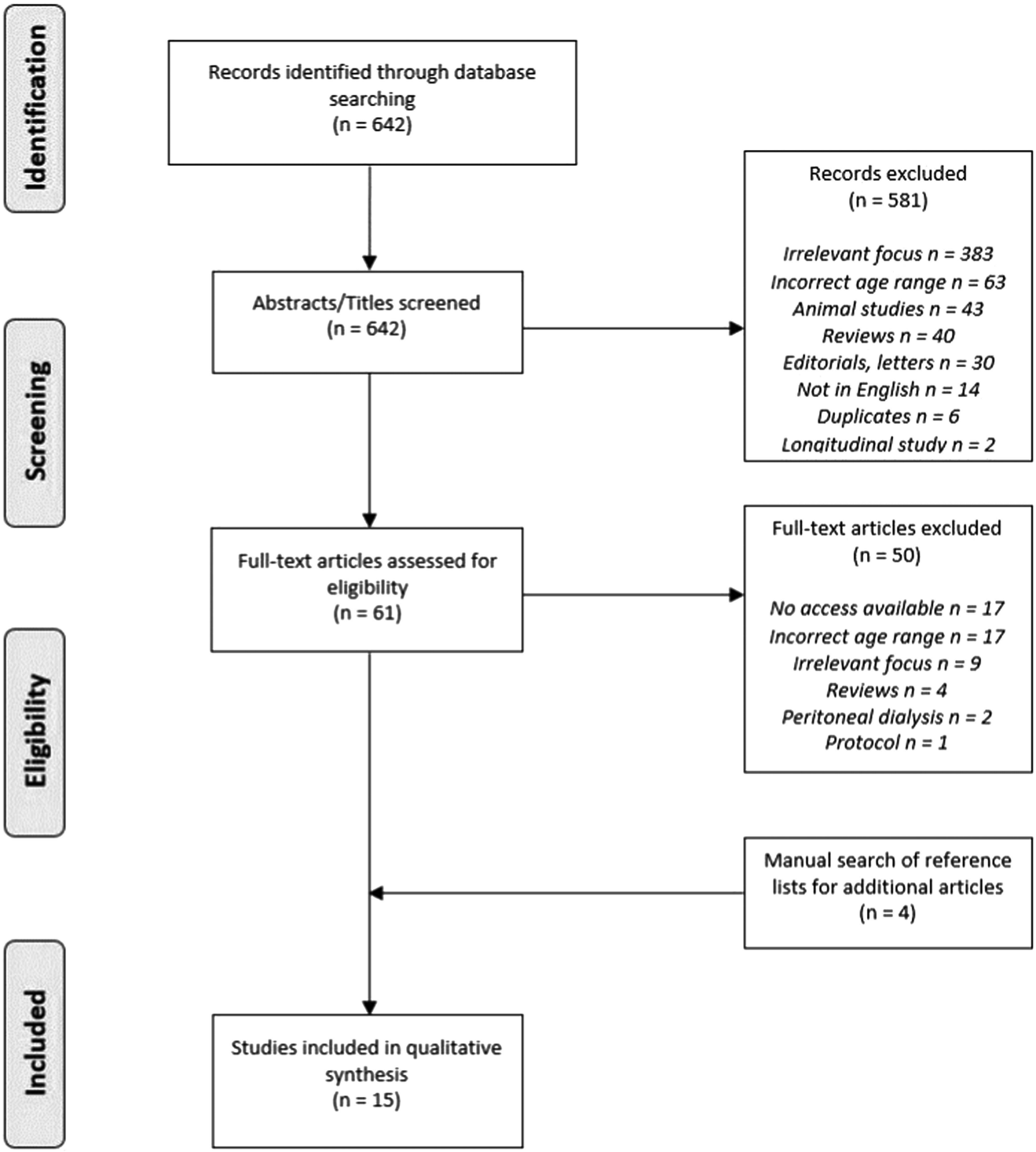

Fig. 1. Flowchart of search strategy, including reasons for exclusion and inclusion of studies.

the database output; this produced an additional 4 studies, making a total of 15 studies.

Study Selection

Articles were included if they were peer-reviewed, published in English and included a clinical CKD sample undergoing hemodialysis who were not post-transplant. Articles were excluded based on demographic criteria if the samples had a history of stroke or neurological disorder, or consisted primarily of children, adolescents (<18 years) or the elderly (>65 years). However, studies comparing different age groups which encompassed our target age demographics were included, provided that the control groups were age-matched or age was controlled for in the analyses. In cases where only group mean ages were provided, studies were included if the mean

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age was below 65 years. Case studies, reviews, and studies without group comparisons were also excluded.

Abstracts were screened for relevance and any which focused on post transplantation or patients undergoing peritoneal dialysis were excluded as long-term kidney function would not be reliably represented *via* eGFR in such individuals. These conditions differ in their cognitive impact compared to haemodialysis, which is still the most common dialysis method. Studies where the connection between cognitive impairment and CKD were due to extraneous conditions and variables (e.g., anemia, hypertension, dementia) were also excluded. After reviewing abstracts, the full text of the remaining articles were reviewed.

RESULTS

Search Summary

The online search yielded 642 items. From the initial search six duplicate items were removed. The abstracts of the remaining 636 items were screened, and 581 were excluded, *inter alia*, due to irrelevant focus, incorrect demographics, non-human subjects, reviews and papers not written in English. Following this, 61 full-text articles were retrieved and assessed for eligibility. Among the full-text articles, 17 were inaccessible, 17 contained aging or pediatric populations, 9 did not focus on the association between the stages of CKD and cognitive impairment, 4 were reviews, 2 focused on peritoneal dialysis, and 1 was a study protocol. This resulted in 11 papers being included in the qualitative synthesis. A manual search of the reference lists from the 11 eligible studies yielded an additional 4 studies, totaling 15 articles included in the final qualitative synthesis. Two researchers (J.B. and E.J.T.) found 100% agreement for the studies that met inclusion criteria.

Study Characteristics

A descriptive summary of the articles included in this review is presented in Table 1. Four studies were conducted in North America, four in Africa, five in Asia, and one each in Europe and South America. In this review, 12 cross-sectional studies and one population based cohort design were included. Two studies did not specify their study design. Nine studies consisted of participants at more than one CKD stage.

In terms of comorbid conditions, seven studies (Dixit et al., 2013; Egbi, Ogunrin, & Oviasu, 2015; Madan, Agarwal, Kalra, & Tandon, 2007; Madan, Kalra, Agarwal, & Tandon, 2007; Nasser, Shawki, El Shahawy, & Sany, 2012; Owolabi et al., 2016; Pi et al., 2016) excluded individuals with diabetes mellitus and/or cardiac risk or history. Five studies did not exclude these and reported rates of presentation (Hailpern, Melamed, Cohen, & Hostetter, 2007; Owolabi et al., 2016; Sanchez-Roman et al., 2011; Thornton, Shapiro, Deria, Gelb, & Hill, 2007; Tsai, Wang, & Fuh, 2010), with three conducting analyses comparing them between the groups and all finding no significant differences. One other study reporting diabetes controlled for its presence in their analyses (Silverwood et al., 2014). Several other studies (Bae & Park, 2008; Dixit et al., 2013; Egbi et al., 2015; Madan, Agarwal, et al., 2007; Madan, Kalra, et al., 2007; Nasser et al., 2012; Owolabi et al., 2016; Pi et al., 2016; Sanchez-Roman et al., 2011; Thornton et al., 2007) also excluded participants with other comorbidities such as history of Parkinson's disease and/or cerebrovascular diseases, hypertension, and head injuries. Two studies (Chen et al., 2015; Gad, Ramzy, Abdelhamid, ElMassry, & Masoud, 2012) did not report any related conditions to CKD.

A total of 9304 participants were examined with a mean age varying from 31.8 to 63.24 years and an age range of 18 to 65 years. The results are discussed corresponding to the findings for each stage of CKD. Across studies, 46 individual cognitive tasks have been used, covering 13 domains of neurocognition (see Table 2). In presenting the results below, domains of difference are presented with the relevant cognitive tasks reported in brackets. Effect sizes of significant differences (Cohen's *d*) were calculated and presented where permissible.

Early Stage CKD (Stages 1–2)

Three studies examined patients with early stages of CKD. The third national health and nutrition examination survey (NHANES III) study (Hailpern et al., 2007) included comparisons between an early and a moderate stage group, as defined by eGFR (mL/min per 1.73 m^2) of ≥60 or <60. Early stage patients performed better than moderate stage patients ($d = 0.25$ to 0.9) in tasks associated with processing speed [Simple Reaction Time tests, Digit Symbol Substitution (D-SYM) and serial digit learning tests]. The second study investigated cognitive changes between early and moderate stage women, also defined by an eGFR (mL/min per 1.73 m^2) of ≥60 or <60 (Tsai et al., 2010).

A significant difference in scores ($d = 0.31$ to 0.52) was observed in verbal learning and working memory [the Rey Auditory Verbal Learning Test (RAVLT) delayed recall, backward digit span (DSB)] between early and moderate stage patients, with the latter performing worse. No significant differences were observed for long term verbal memory or processing speed (RAVLT recognition score, continuous recognition, categorical verbal fluency, Trail Making Test [TMT] A and B, forward digit span [DSF]). The final study examined cognitive function in stage 1–2 participants approaching retirement age (Silverwood et al., 2014). A significant, negative, linear relationship ($d = 0.14$ to 0.15) was observed between cognitive performance and declining eGFR for verbal memory and processing speed (choice reaction time tasks).

Moderate Stage CKD (Stages 3–4)

Patients with moderate stage CKD were included in nine studies. Two of these studies have been discussed above

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Table 1. Summary of studies of cognitive change across different chronic kidney disease stages

Study	Country	Design	No. of participants	Age range (years)	CKD stage	Measure of cognition	Result summary
Madan et al. 2007	USA	Cross-sectional	45	21–50	3, 4, 5	MMSE	Decrease in MMSE total score between each stage, no significance within groups
Owolabi et al. 2016	Nigeria	Cross-sectional	80 Controls, 80 ESKD patients.	Not specified, mean age HD = 49.85, Controls = 49.84	5	Simple reaction time task, Binary choice reaction time, computerized visual scanning task, recognition memory task,	Significantly poorer performance for ESKD group across each measure compared to controls
Silverwood et al. 2014	England, Scotland and Wales	Cross-sectional	2229	60–64	1	Verbal memory task, letter search task, simple reaction time task, choice reaction time task.	Significant decrease in verbal memory and choice reaction time with decrease of GFR
Dixit et al. 2013	India	Not mentioned	30 Controls, 30 ESKD patients.	18–60	5	MMSE, digit-symbol substitution test, letter cancellation test (1 + 3)	MMSE was significantly greater in controls than in ESKD patients overall. Letter cancellation tasks were significantly poorer in ESKD patients
Thornton et al. 2007	Canada	Cross-sectional	55 Controls, 51 CKD patients	38–60	3–5	CVLT-II, TMT-B, Color-word interference test	Decrease in score for all measures for CKD group compared to controls. Significant decline in scores for CVLT-II delayed recall.
Madan et al. 2007	USA	Cross-sectional	15 Controls, 15 ESKD patients	21–50	5	MMSE	Minor decrease in MMSE score for ESKD group compared to controls
Chen et al. 2015	China	Cross-sectional	32 Controls, 32 ESKD patients	Not specified, mean age HD = 36.5, Controls = 32.7	5	NCT-A, Digit span task, Line-tracing test, Serial dotting test	Significant decline in performance for all cognitive measures
Bae et al. 2008	South Korea	Not specified	15 Controls, 15 ESKD	Not specified, mean age ESKD = 53.2, Controls = 45.2	5	MMSE, TMT (A + B)	Minor decline in MMSE for ESKD patients, significant decline for TMT A and B for ESKD patients compared to controls
Gad et al. 2012	Egypt	Cross-sectional	100	40–55	3–4	MMSE, Color Trail (A + B), COWA, Logical memory (A + B)	Significant decrease in performance across each measures between controls and 3–4 CKD patients
Tsai et al. 2010	Taiwan	Population-based cohort design	1023	40–54	1–2, 3	RAVLT Delayed recall, learning score, recognition score, CRPOK. Category verbal fluency: animal, trail making test, A + B, forward + backward digit span	Decrease in all scores for stage 3 compared to stage 1–2, significant decrease in RAVLT delayed ($p = .001$) and backward digit span ($p < .001$)

Table 1. (*Continued*)

Study	Country	Design	No. of participants	Age range (years)	CKD stage	Measure of cognition	Result summary
Egbi et al. 2015	Nigeria	Cross-sectional	290	45–54	3, 4, 5	Six-item cognitive impairment test (6ICT)	CI Stage 3 = 20.00% CI stage 4 = 33.71% CI Stage 5 = 46.15%
Hailpern et al. 2007	USA	Cross-sectional	4849	27–45	1–2, 3–5	SRTT(ms), SDST(s), SDLT (errors)	Significant decrease between stage 1–2 and 3–4 in SRTT ($p = .04$), SDS ($p < .001$), and SDLT errors ($p = .04$)
Pi et al. 2016	China	Cross-sectional	120	Not specified, mean age HD = 56 CKD = 53.4	3–5, 5	3MS, TMT A + B, Immediate memory, Delayed memory, Visuospatial ability, language ability	Cognitive impairment (CI %) was significantly poorer for ESKD compared to undialyzed stage 3–5 group in executive function, delayed memory, visuospatial ability, and overall CI
Nasser et al. 2012	Egypt	Cross-sectional	120	22–60	3–4, 5	MMSE, TMT-B, D-SYM, D-SPAN	Significant decrease between ESKD and control group for MMSE, TMT-B, D-SYM, and D-SPAN
Sanchez-Roman et al. 2011	Mexico	Prospective cross-sectional study compared to a healthy cohort	78	Not specified, mean age control = 34.32 CKD = 37.38	3–4, 5	Attention/Executive Functions Index(AEFI), Memory index	Decline in both attention/executive function index and memory index between control and stage 5

Note. 3MS = Modified MMSE; CI = cognitive impairment; CKD = chronic kidney disease; COWA = Controlled Oral Word Association Test; CRPOK = Continuous Recognition Paradigm of Kimura; CVLT-II = California Verbal Learning Test – Second Edition; D-SPAN = Digit Span Test; D-SYM = Digit Symbol Test; ESKD = end stage kidney disease; HD = hemodialysis; MMSE = Mini Mental State Exam; NCT-A = Number Connection Test-A; RAVLT = Rey Auditory Verbal Learning Test; SDLT = Serial Digit Learning Tests; SDST = Serial Digit Learning Tests; SRTT = Simple Reaction Time Tests; TMT-B = Trail Making Test Part B.

Table 2. Summary of the examined cognitive domains within the reviewed studies

Cognitive domain assessed	Test
Orientation	Mini Mental State exam (MMSE)
	Six-Item Cognitive Impairment Test (6CIT)
	Modified Mini Mental State Exam (3MS)
Attention	Colour Trail A, B
	Serial Digit Learning test
	Symbol Digit Substitution Test
	Line-Tracing Test
	Digit Detection from the NEUROPSI Attention and Memory Battery
	Mental Control test from the NEUROPSI Attention and Memory Battery
Verbal ability	Controlled Oral Word Association Test (COWAT)
	Category Verbal fluency: Animal
	California Verbal Learning Test – 2nd Edition
Memory	Logical memory A, B from the Wechsler Memory Scale – 3rd Edition (WMS-III).
	Delayed Recall and recognition test from the Rey Auditory Verbal Learning Test (RAVLT)
	Continuous Recognition paradigm of Kimura
	Serial Digit Learning Test
	List learning and story memory test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Recall and Recognition Tests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Learning	Learning Test from the Rey Auditory Verbal Learning Test (RAVLT)
	California Verbal Learning Test – 2nd Edition
Speed of processing	Trail Making Test (TMT) A
	Simple Reaction Time Test
	Symbol Digit Substitution Test
	Digit symbol Coding Test from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)
	Number Connection Test
	Serial Dotting Test
Visuospatial ability	Figure copy test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Forward Spatial Span Test from the NEUROPSI Attention and Memory Battery
	Visual Search Test from the NEUROPSI Attention and Memory Battery
	Backward Spatial Span test from the NEUROPSI Attention and Memory Battery
Sequencing (EF)	Color Trail Test A, B
Working memory	Forward Digit Span test from the Wechsler Adult Intelligence Scale – fourth edition (WAIS-IV)
	Backward Digit Span test from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)
	Motor Function Tests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Verbal Paired Associates and Logical Memory test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Flexible thinking/set shifting/ switching (EF)	Trail Making test (TMT) B
	Symbol Digit Substitution Test
	Motor Function Tests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Language	Picture naming test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Semantic Fluency test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
General executive functioning (EF)	Verbal and Design Fluency tests from the test from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Rey-Osterrieth Complex Figure
Inhibition (EF)	Stroop test

Note. EF indicates domains that represent executive function cognitive processes.

(Hailpern et al., 2007; Tsai et al., 2010). Of the remaining seven studies, four compared the differences between two groups; a healthy cohort and a clinical group of patients with both stage 3 and 4 CKD inclusive (Gad et al., 2012; Nasser et al., 2012; Sanchez-Roman et al., 2011), and a healthy cohort and a clinical group of patients with stage 3 to 5 CKD (Thornton et al., 2007). Gad et al (2012) found that a moderate CKD group performed significantly worse than the

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healthy control group ($d = 2.44$ to 3.45) in general cognition, processing speed, switching, logical and semantic memory, and initiation (MMSE, color TMT A and B, logical memory TMT A and B, COWAT).

In a separate study, Nasser et al. (2012), reported moderate CKD participants to have significantly poorer scores ($d = 3.34$ to 6.33) than healthy controls in general cognition, processing speed, switching, and working memory (MMSE, TMT-B, D-SYM, and digit span). The third study (Thornton et al., 2007) showed that moderate stage participants performed poorer on verbal learning, switching, and inhibition (California Verbal Learning Test - 2nd Edition (CVLT-II), TMT-B, Color-word Interference Test); however, only scores on the CVLT-II delayed recall trial were significantly impaired between groups ($d = 0.55$). Contrastingly, Sanchez-Roman et al. (2011) found that a moderate stage CKD group had no significant performance differences than a healthy cohort on attentional, executive function, and memory tasks.

Of the remaining studies that examined moderate CKD, two included a 3-group comparison of neuropsychological performance between stage 3, 4, and a control group (3-4-C) (Egbi et al., 2015; Madan, Kalra, et al., 2007). The first study found that there was no significant differences between groups in general cognition (MMSE) (Madan, Kalra, et al., 2007). The second three-group comparison study used the six-item cognitive impairment test (6CIT), designed to examine cognitive impairment in memory, orientation and concentration (Egbi et al., 2015). Six percent of the controls had cognitive impairment, compared to 24.0% of stage 3 patients ($d = 0.08$) and 41.6% of the stage 4 patients ($d = 0.1$).

End-Stage CKD (Stage 5)

Ten studies included in this review examined cognitive impairment in end stage CKD patients. Six of these studies examined an independent cohort of end stage CKD patients compared to a healthy control group (Bae & Park, 2008; Chen et al., 2015; Dixit et al., 2013; Madan, Agarwal, et al., 2007; Nasser et al., 2012; Owolabi et al., 2016). A further three studies compared cognitive function across four separate groups, that is, healthy and stages 3, 4, and 5 (Egbi et al., 2015; Madan, Kalra, et al., 2007; Sanchez-Roman et al., 2011). One study compared differences between an end stage CKD group on hemodialysis against a moderate end stage group who were not on dialysis (Pi et al., 2016). The remaining study compared differences in cognitive function between a control group and an end stage CKD group, and has been discussed under the "moderate stage" subheading above (Nasser et al., 2012).

Three studies used only one measure of cognition to determine cognitive impairment. Two of the studies only used the MMSE as a measure of cognitive impairment, as the primary focus was electrophysiological monitoring (Madan, Agarwal, et al., 2007; Madan, Kalra, et al., 2007). In those studies, it was found that general cognition (MMSE) was reduced across all CKD stages compared to controls (Madan, Kalra, et al., 2007). There was a minor reduction in MMSE scores between end stage CKD and control group (Madan, Agarwal, et al., 2007), but these differences did not reach significance. The third study (Egbi et al., 2015) found a significant difference ($d = 0.26$) in general cognition performance (6CIT) between the control group (6.00%), stage 3 (20.00%), 4 (33.71%), and end stage groups (46.15%).

Among the independent cohort studies that examined cognitive performance between end stage CKD and controls, the first (Chen et al., 2015) found significant deficits in processing speed and visuospatial attention (Number Connection Test-A, D-SYM, Line-Tracing Test, Serial-Dotting Test) compared to the healthy control group ($d = 0.56$ to 1.58). The second study (Bae & Park, 2008) found that end stage CKD groups had significantly poorer processing speed and switching (TMT A and B) compared to controls ($d = 2.04$ to 2.64). The third study (Owolabi et al., 2016) noted a significant reduction in performance for the end stage CKD group for overall auditory and visual processing speed, recognition memory, and attention ($d = 0.88$ to 2.46). The final study examined cognitive performance in end stage CKD patients before and after dialysis, compared to a control group (Dixit et al., 2013). For this review, only data in the pre-dialysis stage was considered, to account for the effects of hemodialysis on cognition, and to be consistent with the other reviewed studies. End stage CKD groups performed significantly poorer than controls for general cognition and attention [MMSE, Letter cancellation tasks (one and three letter), D-SYM] ($d = 1.13$ to 2.82).

In the study by Nasser et al. (2012), comparing cognitive dysfunction between end stage CKD patients and controls, there was poorer cognitive performance between control and end stage CKD groups in general cognition, switching, and working memory (MMSE, TMT-B, D-SYM and digit span) ($d = 2.26$ to 3.83). Performance on these tasks was also significantly more impaired in the end stage CKD group compared to moderate CKD patients ($d = 0.61$ to 1.44), but with reduced effect size against the control comparison. Another study (Sanchez-Roman et al., 2011) established significant differences between end stage CKD and healthy controls on measures of attention, executive function, and memory ($d = 0.49$ to 0.64). End stage CKD patients also had significantly poorer memory performance when compared to moderate stage CKD patients ($d = 0.54$).

The final study in this section contrasted the performance of end stage CKD patients against an un-dialyzed mixed stage 3–5 group (Pi et al., 2016). The CKD group had significantly greater impairment compared to the stage 3–5 group on overall CI, executive function, immediate memory, delayed memory, and visuospatial performance ($d = 0.41$ to 1.17). No significant group differences were observed for language performance.

DISCUSSION

The current review examined cognitive changes across the lifespan in non-elderly adults with CKD, while minimizing

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the effects of natural age-related changes. The evidence suggests a significant deterioration in cognitive function across the illness course of CKD in line with existing conceptualizations. These observations are strengthened by a targeted focus on studies with a non-elderly adult population. From the 15 articles reviewed, significant differences were found between the patient and control groups in 13 studies (Bae & Park, 2008; Chen et al., 2015; Dixit et al., 2013; Egbi et al., 2015; Gad et al., 2012; Hailpern et al., 2007; Nasser et al., 2012; Owolabi et al., 2016; Pi et al., 2016; Sanchez-Roman et al., 2011; Silverwood et al., 2014; Thornton et al., 2007; Tsai et al., 2010). Across all controlled studies, individuals with any stage of CKD scored lower on cognitive testing compared to controls. Overall cognitive performance diminished between each stage, from early to end. The pattern and extent of this deficit differed across cognitive domains.

Cognitive Impairment Across Disease Course

Early stage CKD

The progression from early to moderate CKD seems to be associated with significant decreases in speed of processing, response speed, attention, short-term memory, and set shifting ability. This is indicative that the bulk of cognitive deficits in the earlier stages of CKD comprise of the more basic abilities (e.g., speed of processing, attention). This is also aligned with findings for decreased mental sharpness as an early CKD symptom (Levey et al., 2003), and contrasts with assumptions of early CKD being relatively asymptomatic. Over 90% of individuals with CKD are unaware that they have the condition (Australian Bureau of Statistics, 2013). Critically, evidence of a significant linear relationship between eGFR and cognitive performance (speed of processing, verbal memory), inclusive of early CKD stage participants (Silverwood et al., 2014), improves our understanding of early symptoms or indicators of CKD. This has the potential to advance early detection and targeted treatments. Improved early detection has been shown to reduce the debilitation associated with declining kidney function by up to 50% (Johnson, 2004).

Moderate stage CKD

Moderate stage CKD patients were found to have significantly poorer speed of processing, verbal fluency, logical memory, recall memory, sequencing, short-term memory, orientation, and concentration compared to healthy comparison cohorts (Egbi et al., 2015; Gad et al., 2012). Inhibition and switching deficits were also observed in this group, although these domains were not more severely impaired than in earlier stages of renal impairment (Thornton et al., 2007). Cognitive performance was also substantially poorer in stage 4 patients compared to stage 3, with almost double the severity of memory and concentration deficits (Egbi et al., 2015). These findings show that, as CKD progresses, memory and speed of processing continue to deteriorate. Additionally, difficulties in concentration and orientation begin to emerge. These latter abilities are considered more complex and higher-order in nature, demonstrating and confirming that cognitive faculties are degrading and the profile of impairment expands with poorer renal function.

End stage CKD

End stage CKD patients demonstrate significantly poorer attention, concentration, speed of processing, executive function, visuospatial abilities, delayed memory and immediate memory compared to controls (Bae & Park, 2008; Dixit et al., 2013; Nasser et al., 2012; Owolabi et al., 2016; Pi et al., 2016; Sanchez-Roman et al., 2011). Additionally, most cognitive impairments that initially manifest in early or moderate stage CKD continued to exacerbate with progression into end stage CKD, with significant reductions noted in executive function, memory and global cognition measures (Nasser et al., 2012; Pi et al., 2016). Not all cognitive domains are impaired to equal levels of severity, as language was found to be the least impacted area of cognitive impairment.

General cognition was poorer at stage 5 compared to stage 4, although this difference was less pronounced than between stage 3 and 4 (Egbi et al., 2015). As found between the early and moderate stages, speed of processing and memory continued to decay with disease progression (Nasser et al., 2012), as do attention and executive function (Sanchez-Roman et al., 2011) which further highlights the difference in impairment profile between CKD stages. With the recognized role of cognitive abilities in better functioning (Rispaud, Rose, & Kurtz, 2016), this suggests potential pathways on intervention to improve patient quality of life, particularly at specific stages of the illness.

CKD-Related Versus Age-Related Cognitive Change

In the majority of previous work, the cognitive impairment observed in end stage CKD patients has potentially been confounded with natural age-related cognitive changes due to primarily elderly samples being assessed. The results of the current, more targeted, review are, however, aligned with those of previous reviews, that is, that individuals with CKD exhibit poorer cognitive performance compared to those without CKD (Etgen et al., 2012), and that the extent of these differ between individual cognitive domains (Berger et al., 2016).

Notably, not all previously identified cognitive deficits have been demonstrated in CKD samples under the age of 65. Language impairments were not observed in the studies reviewed here, suggesting that these may be conflated with age-related cognitive changes. That being said, language is a multi-faceted domain and further investigations of other language components are required to better understand this. Additionally, the severity of cognitive impairment observed here among younger patients could plausibly be exacerbated in patients above 65 years of age, although this has yet to be directly investigated.

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Consequently, more empirical work is needed to advance characterization of the cognitive effects of CKD.

Mechanisms of CKD-Related Cognitive Impairment

The mechanisms by which CKD leads to cognitive impairment are yet to be clearly defined, with a vast majority relating to a build-up of substances in the blood from inefficient kidney function and associated comorbid conditions. We briefly describe a few here and discuss how they might relate to the stages of impairment in CKD. Several vascular problems are associated with CKD, such as diabetes mellitus, hypertension, and cardiovascular disease (Schiffrin, Lipman, & Mann, 2007), that may contribute to a higher risk for and severity of cognitive impairment. Poorer levels of sleep observed in CKD patients have also been implicated (Madero, Gul, & Sarnak, 2008).

Cognitive impairment may also result from higher levels of inflammation, oxidative stress, anemia, and uremic toxins that rise with decreasing kidney function (McClellan et al., 2004; Oberg et al., 2004; Watanabe, Watanabe, & Nakayama, 2014). With inflammation in particular, increased levels of interleukin-6, interleukin-1β, fibrinogen, and C-reactive protein in CKD patients have been associated with increased cognitive impairment (Kalsatou, 2016; Kurella Tamura et al., 2017). There is also evidence that the parathyroid hormone is linked to greater cognitive deficits (Roman et al., 2011).

The linear associations between these vascular and physiological problems and decreasing kidney function supports the progression of cognitive impairment observed in the stages of CKD. These could then plausibly be compounded by the subsequent emergence of the comorbid conditions, such as stroke and dementia, and lead to the typically most severe cognitive impairment profiles of later stage CKD (Berger et al., 2016). As it stands, more specificity for these proposed mechanisms regarding the individual contributions to cognitive impairment in CKD is needed. This is critical given the recognized role of comorbidities such as cardiovascular infarctions and diabetes in poorer CKD outcomes (Anderson et al., 2009; Prichard, 2000). Improved understanding of these would help clarify the direct effects of kidney failure itself and its antecedents.

Additional studies of kidney failure in younger populations, accounting for general aging effects, would further specify these relationships. With greater clarity, remediation of these comorbid conditions thus potentially could improve prognoses for future CKD patients. Future studies should consider the collection of biological markers of the disease and comprehensive information on comorbidities alongside cognitive tests to permit such examinations and advance our collective understanding.

Measures of Cognitive Impairment

It is noteworthy that a variety of cognitive measures have been used in the extant literature, with little consistency across disease stages. Increased coordination and consistency in cognitive measures used would improve the generalizability and comparability of findings in the field. The MMSE was the only measure that has been used across all stages, displaying a minor continuous decrease, with end stage CKD groups reporting the lowest values (Madan, Kalra, et al., 2007; Nasser et al., 2012). However, some inconsistencies were identified, and it should be noted that the MMSE also produced inconclusive results between different studies. Clinical participants in the study by Madan et al. (2007), although demonstrating significantly reduced performance compared to healthy controls, could still be considered within the normal cognitive range. Comparatively, Gad et al. (2012) found that their moderate CKD group scores reflected mild cognitive impairment.

As a tool designed for broad use and not tailored specifically to CKD, the MMSE may have limited utility as a tool for assessing cognitive impairment in this population. The MMSE is less sensitive to variations in cognitive impairment levels, and so may have reduced efficacy for the early stages of CKD. In addition, it has no capacity to support the assessment of individual domains of cognitive function, an aspect of significant variation in CKD. The MMSE is also known to suffer from ceiling effects (Spencer et al., 2013). Reduced utility of the MMSE is evident in other medical cohorts as well (Ringdal et al., 2011; Scazufca, Almeida, Vallada, Tasse, & Menezes, 2009).

Alternative assessment tools that address some of these limitations include the widely recognized and established Repeatable Battery for the Assessment of Neurological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998) and the Cambridge Neuropsychological Test Automated Battery [CANTAB (Cognitive assessment software], 2017]) that have more robust psychometric properties and permit the examination of multiple cognitive domains. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is another quick cognitive assessment tool that has demonstrated good utility in CKD populations (Tiffin-Richards et al., 2014).

Despite the large number of measures used and cognitive domains investigated, the domain of executive function remains relatively less explored with only three studies thus far specifically investigating this. Executive functions are higher-order cognitive abilities, such as problem solving, planning and organization, that are more strongly related to real-world functioning (Cahn-Weiner, Boyle, & Malloy, 2002). There is evidence that impairments in higher-order cognitive functions are related to deficits in more fundamental, or lower-order, cognitive abilities such as processing speed and attention (Neill & Rossell, 2013). As demonstrated in this review, these lower-order cognitive functions are impaired in CKD. It follows then that executive functions should be more thoroughly investigated in CKD to (1) extend the neurocognitive impairment profile of the disease, and (2) better understand how functional deficits manifest.

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Limitations and Future Directions

This review carries several caveats. The number of included studies is small, largely due to the age-related exclusion criteria. However, accounting for age-related cognitive change is a necessary step to clarifying CKD-related cognitive change. Future studies should, therefore, adopt this criterion and expand the breadth of work to improve the characterization of CKD-related cognitive impairment. The mean age cutoff used here maintains the possibility that some individuals above 65 years old are in the included studies. However, it was considered practical for minimizing the impact of older age on cognitive performance while sufficiently maximizing the number of representative papers included. Non-English language and peritoneal dialysis studies were also excluded, although these resulted in just 16 omissions, far fewer than the 79 excluded for age.

The generalizability of some study findings here are limited by their design, such as when moderate and end stage CKD patients are grouped and considered together. The severity of cognitive impairment varies between moderate and end stage CKD patients, and future research should examine CKD groups independently to more effectively evaluate cognitive changes. The development of a consensus cognitive assessment approach would provide added benefit, particularly through the inclusion of at least two tasks per cognitive domain examined to improve the validity and sensitivity of assessment.

Furthermore, future studies should include comparisons against healthy control groups, particularly in studies of the earlier CKD stages to improve characterization and interpretability. This will assist in the recognition of cognitive symptoms that can be suitable as early markers for CKD diagnosis. Longitudinal studies that track individuals from the early stage to end stage CKD would also be beneficial for improving current understanding of CKD-related cognitive change.

The current review also included studies that controlled for comorbid conditions (e.g., diabetes, cardiovascular disease). Given high comorbidity rates for these conditions in CKD (Collins et al., 2003; Whaley-Connell et al., 2008), the reduced generalizability of the findings to more general CKD groups should be noted. It is, however, appropriate for our stated aim of examining how decreasing renal function specifically affects cognition.

CONCLUSIONS

This review is the first to examine the impact of CKD on cognition across the disease course while considering age-related cognitive changes. The evidence supports changes in cognitive impairment across the stages of CKD, independent of age, for both lower- and higher-order cognitive abilities. Speed of processing, response speed, attention and short-term memory, and set shifting abilities were the first cognitive domains to be affected in early stages, which are not entirely asymptomatic. Executive function, concentration, sequencing, orientation, working memory changes emerged in moderate stages, and verbal fluency, visuospatial abilities, and further memory impairment progressed in end stage CKD. Cognitive impairment in CKD is thus broad, transcends stages, and may be a useful marker, in conjunction with other measures, for early identification of CKD.

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REFERENCES

Anderson, S., Halter, J.B., Hazzard, W.R., Himmelfarb, J., Horne, F. M., Kaysen, G.A., . . . Workshop Participants. (2009). Prediction, progression, and outcomes of chronic kidney disease in older adults. *Journal of the American Society of Nephrology*, *20*(6), 1199–1209. doi:10.1681/asn.2008080860

Arnold, R., Issar, T., Krishnan, A.V., & Pussell, B.A. (2016). Neurological complications in chronic kidney disease. *JRSM Cardiovascular Disease*, *5*, 2048004016677687. doi:10.1177/2048004016677687

Australian Bureau of Statistics. (2013). *Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12.* Canberra: Australian Bureau of Statistics. Retrieved from http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4364.0.55.005Chapter4002011-12

Bae, J.S., & Park, S.S. (2008). Contingent negative variation before and after hemodialysis among patients with end-stage renal disease. *Journal of the Neurological Sciences*, *267*(1–2), 70–75. doi:10.1016/j.jns.2007.09.039

Berger, I., Wu, S., Masson, P., Kelly, P.J., Duthie, F.A., Whiteley, W., . . . Webster, A.C. (2016). Cognition in chronic kidney disease: A systematic review and meta-analysis. *BMC Medicine*, *14*(1), 206. doi:10.1186/s12916-016-0745-9

Buchman, A.S., Tanne, D., Boyle, P.A., Shah, R.C., Leurgans, S.E., & Bennett, D.A. (2009). Kidney function is associated with the rate of cognitive decline in the elderly. *Neurology*, *73*(12), 920–927. doi:10.1212/WNL.0b013e3181b72629

Bugnicourt, J.-M., Godefroy, O., Chillon, J.-M., Choukroun, G., & Massy, Z.A. (2013). Cognitive disorders and dementia in CKD: The neglected kidney-brain axis. *Journal of the American Society of Nephrology*, *24*(3), 353–363. doi:10.1681/asn.2012050536

Cahn-Weiner, D.A., Boyle, P.A., & Malloy, P.F. (2002). Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Applied Neuropsychology*, *9*(3), 187–191. doi:10.1207/s15324826an0903_8

CANTAB [Cognitive assessment software]. (2017). In: Cambridge Cognition. All rights reserved. Retrieved from www.cantab.com.

Chang, C.Y., Lin, C.C., Tsai, C.F., Yang, W.C., Wang, S.J., Lin, F.H., & Fuh, J.L. (2017). Cognitive impairment and hippocampal atrophy in chronic kidney disease. *Acta Neurologica Scandinavica*, *136*(5), 477–485. doi:10.1111/ane.12753

Chen, H.J., Qi, R., Kong, X., Wen, J., Liang, X., Zhang, Z., . . . Zhang, L.J. (2015). The impact of hemodialysis on cognitive dysfunction in patients with end-stage renal disease: A resting-state functional MRI study. *Metabolic Brain Disease*, *30*(5), 1247–1256. doi:10.1007/s11011-015-9702-0

Chen, T., & Harris, D.C. (2015). Challenges of chronic kidney disease prevention. *The Medical Journal of Australia*, *203*(5), 209–210.

Collins, A.J., Li, S., Gilbertson, D.T., Liu, J., Chen, S.-C., & Herzog, C.A. (2003). Chronic kidney disease and cardiovascular disease in the Medicare population: Management of comorbidities in kidney disease in the 21st century: Anemia and bone disease. *Kidney International*, *64*, S24–S31. doi:10.1046/j.1523-1755.64.s87.5.x

Dixit, A., Dhawan, S., Raizada, A., Yadav, A., Vaney, N., & Kalra, O.P. (2013). Attention and information processing in end stage renal disease and effect of hemodialysis: A bedside study. *Renal Failure*, *35*(9), 1246–1250. doi:10.3109/0886022X.2013.819768

Egbi, O.G., Ogunrin, O., & Oviasu, E. (2015). Prevalence and determinants of cognitive impairment in patients with chronic kidney disease: A cross-sectional study in Benin City, Nigeria. *Annals of African Medicine*, *14*(2), 75–81. doi:10.4103/1596-3519.149877

Elias, M.F., Dore, G.A., & Davey, A. (2013). Kidney disease and cognitive function. *Contributions to Nephrology*, *179*, 42–57. doi:10.1159/000346722

Etgen, T., Chonchol, M., Forstl, H., & Sander, D. (2012). Chronic kidney disease and cognitive impairment: A systematic review and meta-analysis. *American Journal of Nephrology*, *35*(5), 474–482. doi:10.1159/000338135

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Fujino, H., Sumiyoshi, C., Sumiyoshi, T., Yasuda, Y., Yamamori, H., Ohi, K., . . . Imura, O. (2016). Predicting employment status and subjective quality of life in patients with schizophrenia. *Schizophrenia Research: Cognition*, *3*, 20–25. doi:10.1016/j.scog.2015.10.005

Gad, A.H., Ramzy, G.M., Abdelhamid, Y.M., ElMassry, H.A., & Masoud, M.M. (2012). Cognitive impairment in hemodialysis patients. *Egyptian Journal of Neurology, Psychiatry, & Neurosurgery*, *49*(3), 245–249.

Hailpern, S.M., Melamed, M.L., Cohen, H.W., & Hostetter, T.H. (2007). Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *Journal of the American Society of Nephrology*, *18*(7), 2205–2213. doi:10.1681/asn.2006101165

Johnson, D.W. (2004). Evidence-based guide to slowing the progression of early renal insufficiency. *Internal Medicine Journal*, *34*(1–2), 50–57.

Kalsatou, A. (2016). The Impact of Inflammation on Cognitive Impairment in Chronic Kidney Disease patients. *Journal of Clinical and Experimental Nephrology*, *1*(20). doi:10.21767/2472-5056.100020

Kaltsatou, A., Grigoriou, S.S., Karatzaferi, C., Giannaki, C.D., Stefanidis, I., & Sakkas, G.K. (2015). Cognitive function and exercise training for chronic renal disease patients: A literature review. *Journal of Bodywork and Movement Therapies*, *19*(3), 509–515. doi:10.1016/j.jbmt.2015.04.006

Khatri, M., Nickolas, T., Moon, Y.P., Paik, M.C., Rundek, T., Elkind, M.S., . . . Wright, C.B. (2009). CKD associates with cognitive decline. *Journal of the American Society of Nephrology*, *20*(11), 2427–2432. doi:10.1681/asn.2008101090

König, M., Gollasch, M., Spira, D., Buchmann, N., Hopfenmüller, W., Steinhagen-Thiessen, E., & Demuth, I. (2018). Mild-to-moderate chronic kidney disease and geriatric outcomes: analysis of cross-sectional data from the Berlin Aging Study II. *Gerontology*, *64*(2), 118–126.

Kurella Tamura, M., Tam, K., Vittinghoff, E., Raj, D., Sozio, S.M., Rosas, S.E., . . . Yaffe, K. (2017). Inflammatory markers and risk for cognitive decline in chronic kidney disease: The CRIC Study. *Kidney International Reports*, *2*(2), 192–200. doi:10.1016/j.ekir.2016.10.007

Kurella Tamura, M., Wadley, V., Yaffe, K., McClure, L.A., Howard, G., Go, R., . . . McClellan, W. (2008). Kidney function and cognitive impairment in US adults: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *American Journal of Kidney Disease*, *52*(2), 227–234. doi:10.1053/j.ajkd.2008.05.004

Levey, A.S., Coresh, J., Balk, E., Kausz, A.T., Levin, A., Steffes, M. W., . . . Eknoyan, G. (2003). National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Annals of Internal Medicine*, *139*(2), 137–147.

Madan, P., Agarwal, S., Kalra, O.P., & Tandon, O.P. (2007). Effect of hemodialysis on cognitive function in ESRD patients. *Renal Failure*, *29*(6), 699–703. doi:10.1080/08860220701460103

Madan, P., Kalra, P., Agarwal, S., & Tandon, O.P. (2007). Cognitive impairment in chronic kidney disease. *Nephrology Dialysis Transplantation*, *22*(2), 440–444. doi:10.1093/ndt/gfl572

Madero, M., Gul, A., & Sarnak, M.J. (2008). Review: Cognitive function in chronic kidney disease. *Seminars in Dialysis*, *21*(1), 29–37. doi:10.1111/j.1525-139X.2007.00384.x

McClellan, W., Aronoff, S.L., Bolton, W.K., Hood, S., Lorber, D. L., Tang, K.L., . . . Leiserowitz, M. (2004). The prevalence of anemia in patients with chronic kidney disease. *Current Medical Research and Opinion*, *20*(9), 1501–1510. doi:10.1185/030079904X2763

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. doi:10.1371/journal.pmed.1000097

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. doi:10.1111/j.1532-5415.2005.53221.x

Nasser, M.T., Shawki, S., El Shahawy, Y., & Sany, D. (2012). Assessment of cognitive dysfunction in kidney disease. *Saudi Journal of Kidney Diseases and Transplantation*, *23*(6), 1208–1214. doi:10.4103/1319-2442.103561

Neill, E., & Rossell, S.L. (2013). Executive functioning in schizophrenia: The result of impairments in lower order cognitive skills? *Schizophrenia Research*, *150*(1), 76–80. doi:10.1016/j.schres.2013.07.034

Oberg, B.P., McMenamin, E., Lucas, F.L.E.E., McMonagle, E., Morrow, J., Ikizler, T.A.L.P., & Himmelfarb, J. (2004). Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney International*, *65*(3), 1009–1016. doi:10.1111/j.1523-1755.2004.00465.x

Orbo, M., Aslaksen, P.M., Larsby, K., Schafer, C., Tande, P.M., Vangberg, T.R., & Anke, A. (2015). Relevance of cognition to health-related quality of life in good-outcome survivors of out-of-hospital cardiac arrest. *Journal of Rehabilatation Medicine*, *47*(9), 860–866. doi:10.2340/16501977-1998

Owolabi, L.F., Abdu, A., Ibrahim, A., Owolabi, D.S., Nalado, A., Bappa, A., & Taura, A.A. (2016). Cognitive function assessment

in patients with end- stage renal disease in Nigeria: A single center experience. *Annals of African Medicine*, *15*(3), 138–144. doi:10.4103/1596-3519.188895

Pi, H.C., Xu, Y.F., Xu, R., Yang, Z.K., Qu, Z., Chen, Y.Q., . . . Dong, J. (2016). Cognitive impairment and structural neuroimaging abnormalities among patients with chronic kidney disease. *Kidney and Blood Pressure Research*, *41*(6), 986–996.

Prichard, S.S. (2000). Comorbidities and their impact on outcome in patients with end-stage renal disease. *Kidney International*, *57*, S100–S104. doi:10.1046/j.1523-1755.2000.07417.x

Randolph, C., Tierney, M.C., Mohr, E., & Chase, T.N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, *20*(3), 310–319. doi:10.1076/jcen.20.3.310.823

Ringdal, G.I., Ringdal, K., Juliebo, V., Wyller, T.B., Hjermstad, M. J., & Loge, J.H. (2011). Using the Mini-Mental State Examination to screen for delirium in elderly patients with hip fracture. *Dementia and Geriatric Cognitive Disorders*, *32*(6), 394–400. doi:10.1159/000335743

Rispaud, S.G., Rose, J., & Kurtz, M.M. (2016). The relationship between change in cognition and change in functional ability in schizophrenia during cognitive and psychosocial rehabilitation. *Psychiatry Research*, *244*, 145–150. doi:10.1016/j.psychres.2016.07.033

Roman, S.A., Sosa, J.A., Pietrzak, R.H., Snyder, P.J., Thomas, D. C., Udelsman, R., & Mayes, L. (2011). The effects of serum calcium and parathyroid hormone changes on psychological and cognitive function in patients undergoing parathyroidectomy for primary hyperparathyroidism. *Annals of Surgery*, *253*(1), 131–137. doi:10.1097/SLA.0b013e3181f66720

Romijn, M.D., van Marum, R.J., Emmelot-Vonk, M.H., Verhaar, H. J., & Koek, H.L. (2015). Mild chronic kidney disease is associated with cognitive function in patients presenting at a memory clinic. *International Journal of Geriatric Psychiatry*, *30* (7), 758–765. doi:10.1002/gps.4226

Salthouse, T.A., Atkinson, T.M., & Berish, D.E. (2003). Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *Journal of Experimental Psychology. General*, *132*(4), 566–594. doi:10.1037/0096-3445.132.4.566

Sanchez-Roman, S., Ostrosky-Solis, F., Morales-Buenrostro, L.E., Nogues-Vizcaino, M.G., Alberu, J., & McClintock, S.M. (2011). Neurocognitive profile of an adult sample with chronic kidney disease. *Journal of the International Neuropsychological Society*, *17*(1), 80–90. doi:10.1017/s1355617710001219

Scazufca, M., Almeida, O.P., Vallada, H.P., Tasse, W.A., & Menezes, P.R. (2009). Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: Results from the Sao Paulo Ageing & Health Study. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(1), 8–15. doi:10.1007/s00406-008-0827-6

Schiffrin, E.L., Lipman, M.L., & Mann, J.F.E. (2007). Chronic kidney disease. *Effects on the Cardiovascular System*, *116*(1), 85–97. doi:10.1161/circulationaha.106.678342

Schuurs, A., & Green, H.J. (2013). A feasibility study of group cognitive rehabilitation for cancer survivors: Enhancing cognitive function and quality of life. *Psychooncology*, *22*(5), 1043–1049. doi:10.1002/pon.3102

Seidel, U.K., Gronewold, J., Volsek, M., Todica, O., Kribben, A., Bruck, H., & Hermann, D.M. (2014). Physical, cognitive and emotional factors contributing to quality of life, functional health and participation in community dwelling in chronic kidney disease. *PLoS One*, *9*(3), e91176. doi:10.1371/journal.pone.0091176

Seliger, S.L., Gillen, D.L., Longstreth, W.T. Jr., Kestenbaum, B., & Stehman-Breen, C.O. (2003). Elevated risk of stroke among patients with end-stage renal disease. *Kidney International*, *64*(2), 603–609. doi:10.1046/j.1523-1755.2003.00101.x

Sharma, A., Yabes, J., Al Mawed, S., Wu, C., Stilley, C., Unruh, M., & Jhamb, M. (2016). Impact of cognitive function change on mortality in renal transplant and end-stage renal disease patients. *American Journal of Nephrology*, *44*(6), 462–472. doi:10.1159/000451059

Silverwood, R.J., Richards, M., Pierce, M., Hardy, R., Sattar, N., Ferro, C., . . . data collection, t. (2014). Cognitive and Kidney Function: Results from a British Birth Cohort Reaching Retirement Age. *PLoS One*, *9*(1), e86743. doi:10.1371/journal.pone.0086743

Spencer, R.J., Wendell, C.R., Giggey, P.P., Katzel, L.I., Lefkowitz, D.M., Siegel, E.L., & Waldstein, S.R. (2013). Psychometric limitations of the Mini-Mental State Examination among nondemented older adults: An evaluation of neurocognitive and magnetic resonance imaging correlates. *Experimental Aging Research*, *39*(4), 382–397. doi:10.1080/0361073X.2013.808109

Stenvinkel, P., & Herzog, C.A. (2010). Cardiovascular disease in chronic kidney disease, In J. Floege,. R.J. Johnson, & J. Feehally (Eds.), *Comprehensive clinical nephrology* (4th ed., pp. 935–950). Philadelphia: Mosby.

Tan, E.J., Thomas, N., & Rossell, S.L. (2014). Speech disturbances and quality of life in schizophrenia: Differential impacts on functioning and life satisfaction. *Comprehensive Psychiatry*, *55* (3), 693–698. doi:10.1016/j.comppsych.2013.10.016

Thomas, R., Kanso, A., & Sedor, J.R. (2008). Chronic kidney disease and its complications. *Primary Care*, *35*(2), 329–vii. doi:10.1016/j.pop.2008.01.008

Thornton, W.L., Shapiro, R.J., Deria, S., Gelb, S., & Hill, A. (2007). Differential impact of age on verbal memory and executive functioning in chronic kidney disease. *Journal of the International Neuropsychological Society*, *13*(2), 344–353. doi:10.1017/s1355617707070361

Tiffin-Richards, F.E., Costa, A.S., Holschbach, B., Frank, R.D., Vassiliadou, A., Krüger, T., . . . Reetz, K. (2014). The Montreal Cognitive Assessment (MoCA) – A sensitive screening instrument for detecting cognitive impairment in chronic hemodialysis patients. *PLoS One*, *9*(10), e106700. doi:10.1371/journal.pone.0106700

Tsai, C.F., Wang, S.J., & Fuh, J.L. (2010). Moderate chronic kidney disease is associated with reduced cognitive performance in midlife women. *Kidney International*, *78*(6), 605–610. doi:10.1038/ki.2010.185

Tucker, P.S., Kingsley, M.I., Morton, R.H., Scanlan, A.T., & Dalbo, V.J. (2014). The increasing financial impact of chronic kidney disease in australia. *International Journal of Nephrology*, *2014*, 120537. doi:10.1155/2014/120537

Watanabe, K., Watanabe, T., & Nakayama, M. (2014). Cerebro-renal interactions: Impact of uremic toxins on cognitive function. *NeuroToxicology*, *44*, 184–193. doi:10.1016/j.neuro.2014.06.014

Weiner, D.E., & Seliger, S.L. (2014). Cognitive and physical function in chronic kidney disease. *Current Opinion in Nephrology and Hypertension*, *23*(3), 291–297. doi:10.1097/01.mnh.0000444821.87873.7b

Weng, S.C., Shu, K.H., Tang, Y.J., Sheu, W.H., Tarng, D.C., Wu, M.J., . . . Chuang, Y.W. (2012). Progression of cognitive dysfunction in elderly chronic kidney disease patients in a

veteran's institution in central Taiwan: A 3-year longitudinal study. *Internal Medicine*, *51*(1), 29–35.

Whaley-Connell, A.T., Sowers, J.R., McFarlane, S.I., Norris, K.C., Chen, S.C., Li, S., . . . Collins, A.J. (2008). Diabetes mellitus in CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition and Examination Survey (NHANES) 1999-2004. *American Journal of Kidney Disease*, *51*(4 Suppl. 2), S21–S29. doi:10.1053/j.ajkd.2007.12.013

Zhang, Q.L., & Rothenbacher, D. (2008). Prevalence of chronic kidney disease in population-based studies: Systematic review. *BMC Public Health*, *8*, 117. doi:10.1186/1471-2458-8-117

Ziegler, D.A., Piguet, O., Salat, D.H., Prince, K., Connally, E., & Corkin, S. (2010). Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging*, *31*(11), 1912–1926. doi:10.1016/j.neurobiolaging.2008.10.015