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Kidney Disease and Cognitive Function

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Abstract

We provide a brief review of research on chronic kidney disease and cognitive performance, including dementia. We touch briefly on the literature relating end-stage-renal disease to cognitive function, but focus on studies of modest and moderate forms of chronic kidney disease (CKD) that precede dialysis and transplantation. We summarize previous reviews dealing with case control studies of patients but more fully examine community-based studies with large samples and necessary controls for demographic risk factors, cardiovascular variables, and other confounds such as depression.

In addition we suggest potential biological and social-psychological mediators between CKD and cognition. Studies follow in two categories of design: (1) cross-sectional studies; (2) longitudinal studies. In each, CKD is related to a wide range of deficits in cognitive functioning including, verbal and visual-memory and organization, and components of executive functioning and fluid intellect. In general, prior to the need to treat with hemodialysis (HD) or kidney transplant (KT), magnitude of effect with relation to CKD and function are small or modest in persons free from acute stroke and dementia. However, HD and KT can result in major impairment. We discuss needed controls, the greater demand on controls after HD and KT begin, and suggest that mechanisms intervening relations between hypertension, or diabetes, and cognitive performance may be similar to those intervening between hypertension and cognitive performance and the hypertension and diabetes literature on cognition provides a good model for the study of early stage kidney disease and cognitive ability. We posit that the mechanisms linking CKD and cognition may be similar to those linking hypertension or diabetes to cognition.

We identify the need for more studies with multiple cognitive test batteries, measures of every-day cognitive abilities relevant to patient understanding of the disease and treatments, and more studies with prevalent and incident dementia outcomes.

Descriptors

kidney disease; chronic kidney disease; cognitive function; dementia; cardiovascular risk factors

A new case of dementia occurs every four seconds world-wide, which is equivalent to 7.7 million cases each year, and mild cognitive impairment is even more prevalent [1]. Chronic kidney disease (CKD) is a risk factor (RF) for dementia and cognitive impairment [2, 3–5].

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Cognitive impairment detracts from quality of life and is a risk factor for dialysis-related mortality [6]. In this brief review we summarize the literature on CKD in relation to cognitive function, discuss intervening mechanisms, and comment on some methodological issues, but refer the reader to other reviews of the many studies comparing treatments such as hemodialysis (HD), peritoneal dialysis (PD) and transplantation. We emphasize a pre-treatment stage of CKD, but include studies examining modest to severe CKD.

Renal Functioning Predictors of Cognitive Function

Renal disease is well-defined in previous reviews [2,3–5,7]. Table 1 summarizes commonly used predictor variables in cognitive studies and the measurement metrics used to define them. Common predictors are estimated glomerular filtration rate (eGFR), serum creatinine (sCR) and far less commonly stages of renal disease [2] involving measures such as proteinuria, biopsy or structural imaging.

Cognitive Outcomes in Renal Studies

A previous review provides a list of tests commonly used in the renal literature [3] and other reviews illustrate how multiple tests should be used where the goal is to infer the locus of brain impairment from one or more specific cognitive deficits [8,9]. Studies designed to examine which abilities do and do not relate to a disease must examine a wide range of different abilities [8,9]. Definitions of terms used in the psychometric literature are given in Table 2. Outcome variables can be dichotomous (i.e., dementia, impairment, deficit), ordinal categories of performance level, or continuously distributed test scores representing performance level. We use the term cognitive impairment only if this cognitive status has been established by clinical criteria, i.e., neuropsychological (NP) evaluation and/or normative data. The term deficit is used as a comparative term indicating a lower average level of performance relative to a reference group or groups. The term decline is only used for longitudinal change in performance.

Overview: End Stage Renal Disease (ESRD) and Treatment

We refer to the reader to previous reviews [2,3–5] for a summary of this literature. However, it is important to note that an estimated 70% of hemodialysis (HD) patients over age 55 exhibit moderate to severe cognitive impairment [5] with a similar prevalence for peritoneal dialysis (PD) patients [10]. Griva et al. [6] reported that two-thirds of a community-dwelling sample of 145 PD, home-dialysis and in-center HD patients in London, UK suffered from what the authors defined as mild or moderate cognitive impairment: 1.00–1.99 and 2–2.99 SD below the mean, respectively. We agree with Murray and Knopman [5] that performance 2.00 SD below the mean (3% of the population fall here) is not moderate, but is reflective of clinically significant cognitive dysfunction. Comprehensive reviews of this literature indicate that HD, PD and transplantation are associated with wide ranging deficits in attention, memory, speed of performance, and components of executive functioning (EF) [4,5], although it is clear that adverse cognitive outcomes are attenuated when cognitive testing is timed properly in relation to dialysis treatment [2].

There have been few studies of practical every-day cognitive tasks and kidney disease. Numeracy skills are critical to advance planning necessary to comply with treatment regimens and disease understanding [11]. Numeracy refers to the degree that one can apply statistical, graphical and numerical skills in such a way as to effectively understand and comply with health information [11]. Abdel-Kader et al. [11] found that the majority of 187 ESRD patients (mean age=52 years) exhibited low numeric efficiency on a 3-item scale. Grubbs et al. [12] reported a 32.3% prevalence of inadequate health care literacy in a sample of 62 dialysis patients. Gelb and colleagues [13], in a study of 108 kidney transplant

recipients, reported that lower levels of performance on every-day problem solving tests and number of depressive symptoms were associated with poor medication adherence, but found no association with multiple NP measures and adherence. These studies were not prospective and thus the direction of these associations needs to be defined in future studies.

In summary, the history of cognitive deficit and impairment begins prior to the transition to ESRD [5]. Once ESRD status has been reached and dialysis has begun, the demands on design and control become increasingly complex and thus the early or pre-treatment stages of CKD provide an important window of investigation.

Cross-Sectional Community-Based Studies

We have chosen to focus on the community-based studies given the very much larger samples, statistical adjustment for CVD and absence of sample bias introduced by multiple exclusions in order control for differences in health factors among uremic samples, healthy controls and patient groups.

Table 5 summarizes methodological detail and results for the community-based studies which began to appear in 2005. Earlier investigations emphasized case-control type studies that compared uremic patients to other diagnostic groups, e.g., medical and psychiatric patients or healthy controls [2]. A major review of this case-control literature [2] indicates that uremic patients, compared to general medical and psychiatric groups, performed better on measures of motor speed, auditory alertness and crystallized intelligence and performed more poorly on measures of cognitive flexibility and other components of EF, verbal memory and learning, visual attention and fluid intelligence. In 3 of the case-control studies reviewed by Koushik et al. [2], levels of performance were not below average when compared to normative data. In some case-control studies exclusion for health factors were extensive, e.g. [14], but often the major controls were for age, education, and sex [2].

In each of the community-based studies (Table 3) there were controls (exclusion or adjustment) for demographic variables, CVD risk factors, or health factors, and other confounders. Estimated eGFR levels <60, versus ≥60 were associated with deficits in global cognitive performance. Studies prior to 2009 reported that higher levels of eGFR were associated with deficits in language, memory, components of EF [15,16], learning and concentration [15], visual attention [15], psychomotor efficiency and processing speed [17], and global impairment on a telephone interview scale [18]. While sample sizes were impressive, the cognitive batteries were limited, sometimes involving only one or a few tests.

To address this issue, Elias et al. [19] using the Maine Syracuse Longitudinal Study (MSLS), employed 923 dementia-free community-dwelling individuals and 19 widely-used clinical cognitive tests in a factor analysis leading to the identification of the following outcome variables: (1) a global composite test score; (2) four composite scores or factors: visual-spatial organization and memory, scanning and tracking (a component of executive function), verbal memory, and working memory and (3) a single measure of abstract reasoning (WAIS Similarities) which loaded with approximately equal strength on each composite. Persons undergoing dialysis (n=4) and/or diagnosed with dementia (n=9) were excluded. For an analysis adjusting for demographic factors, CVD, and acute stroke, higher sCR values were associated with lower levels of performance for global performance, verbal episodic memory and scanning and tracking. For example increments in creatinine of 2 mg/dL were associated with a decrement of 0.12 SD in performance level. Moreover, the odds ratios (ORs) associated with poor global performance (defined as the lowest quartile of the distribution of test scores) were OR=2.27 with control for age, sex, education, and race and OR=1.97 with additional adjustment for CVD and stroke.

In summary, community-based, large sample, cross-sectional studies support the generalization that mild and modest kidney disease is related to modest deficits in multiple cognitive abilities. As in the hypertension literature, crystallized intellect appears to be spared in studies of dementia-free samples [19]. The limitation of each of these studies is that they were cross-sectional and only two studies specifically reported excluding of dialysis patients [19,20] or those with eGFR<30 [15].

Longitudinal Studies

Longitudinal studies of community-based samples after 2004 are summarized in Table 4. These studies measure change in cognitive functioning over time. Studies are arranged by outcomes: (1) level of cognitive performance, (2) binary levels of performance where decline in performance is based on poor performance at followup defined arbitrarily or in terms of normative data; (3) binary or gradations of certainty with regard to probable dementia. The first two categories are important to the third because lower cognitive performance in persons free from acute stroke and dementia is a risk factor for dementia [21]. The studies cited have relatively good controls as defined by adjustment for age, sex, education, and race, where relevant, and extended models which consider health variables, cardiovascular risk factors or events (e.g. stroke). Table 5 provides a check-list summary of results for papers summarized in Table 4. Each of the studies [20,22–28, Note 1] reported that baseline levels for at least one predictor was related to cognitive decline, impairment or dementia, except for Slinin et al. [29] who obtained negative results with adjustment for age. Davey et al. [Note 1] with the smallest longitudinal sample (N= 590), but with a comprehensive cognitive test battery, did not find longitudinal change in cognitive performance from baseline to followup. However, a *decline in renal function* over time (indicated by eGFR or sCR) was related to decline in global cognitive performance, verbal memory and abstract reasoning. Negative findings relative to decline in cognitive performance relative to baseline levels of renal function are not readily explained by study length or number of cognitive measures. Relative to other studies, Davey et al. [Note 1] featured the largest number of cognitive outcomes and a fairly long followup of 4 to 5 years. But the sample was relatively well-educated and change in renal function may be more sensitive in terms of cognitive change than baseline levels. Following 2406 participants over 4 years, Helmer et al. [23] also found that change in renal function over 4 years but not baseline renal function was related to longitudinal decline (incident dementia).

None of the longitudinal studies used an every-day measure of cognitive performance or employed numeracy as a predictor or covariate and only 5 of the 16 studies summarized in Tables 4 and 5 adjusted for clinical depression or depressed mood.

Obviously there is a need for more studies with comprehensive test batteries, longer longitudinal followup periods and stratification by education level and/or numeracy skill, and with explicit exclusion of renal dialysis patients. Yet considering these studies collectively, it is clear that depending on severity of renal disease and the general health of the study population, various indices of CKD prevalence are related to decline in cognitive performance over time and dementia in samples over 65 years of age. What is not known from current studies is the prevalence, incidence or rate of cognitive decline prior to dementia.

Note 1 Davey, A, Elias, MF, Robbins, A, Seliger, SL, Dore GA. Decrease in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning, and verbal memory. Unpublished Manuscript, Submitted to Nephrol Dial Transplant, revised and under re-review.

It is encouraging to find that in the study of relatively well-educated non-demented community-based subjects, dialysis excluded, decline in performance levels over 4 to 5 years was modest and not such that they would interfere with understanding and adherence necessary to the treatment of renal disease [Note 1].

Mechanisms Relating Kidney Disease to Cognition

Table 6 lists variables that may mediate between renal disease and cognitive function. One may hypothesize, among other models, direct paths in which CKD affects brain function and morphology and hence cognition. An alternative, and not mutually exclusive, possibility is that risk factors shared by brain and kidney lead to cognitive deficit, decline and impairment [30]. This parallel risk factor model is appealing because “both kidney and brain are low resistance end-organs and are exposed and re-exposed to high-volume blood flow though the cardiac cycle” [30 p.5]. Thus the brain and kidney very likely share common risk factors for cognitive deficit and impairment. It is clear that the issue of mediating variables becomes complex once treatment is initiated for ESRD. Thus we refer the reader to a comprehensive model by Murray & Knopman [5] and in Table 6 summarize the many candidate mechanisms. In pre-treatment forms of renal disease it makes some sense that the search for mechanisms should begin with the strongest risk factors for kidney disease, i.e., hypertension and diabetes. However, few if any mediation studies have been undertaken.

Methodological Issues

Controls

Controls for age, education, sex, and where relevant, race and ethnic composition are imperative, and controls for prevalent CVD risk factors, including depressed mood or clinical depression, and CVD events (e.g. acute stroke) are very important. But inspection of Table 6 indicates that many other potential confounders exist even where the focus is pre-ESRD kidney disease. Polypharmacy is highly prevalent in the elderly. Moreover, many social psychological factors that are correlated with renal disease are especially important when patient groups or non-patients are employed as control groups.

Cognitive Measurement

The finding that renal disease is related to multiple cognitive abilities, with few exceptions (e.g. over-learned crystallized intelligence), may be related to the fact that renal disease has a diffuse effect on brain function. However, it is important to recognize that the clinical cognitive tests traditionally employed in research on disease are impure, i.e., they measure a mixture of intended and unintended cognitive *constructs*. Clinical cognitive tests are highly correlated with each other and with tests of general intellectual functioning [9]. There are two solutions: (1) factor analyses that identify theoretically-relevant cognitive domains, e.g. [19], and (2) utilization of more precise information processing tasks [9]. The latter method increases measurement purity but also increases performance difficulty for poorly educated study participants, makes significant demands on study time, and is less clinically interpretable.

Clinical Implications

In general, pre-dialysis and pre-transplant levels of cognitive deficit are relatively modest in well cared for and relatively highly educated, dementia- and stroke-free community samples, e.g., [19,22]. This is good news and suggests that intervention might possibly be effective in preventing or delaying more serious ESRD and ESRD-treatment related cognitive deficit and impairment [4,5]. This conclusion is tentative pending more studies and clinical trials.

Summary

Prior to ESRD and treatment, kidney disease can result in global and multiple, specific-cognitive deficits, often mild, but sometimes associated with dementia. Treatment methods are improving but the physiological consequences of treatment can lead to more severe deficit. Biological factors intrinsic to renal disease, psychosocial factors, and polypharmacy are candidate intervening mechanisms, but formal studies identifying mediators between mild and modest levels of kidney disease and cognition have not been done.

We are starting down the path of a complex and challenging area of research and have a long way to go. We are in a descriptive phase of research, albeit we need more studies with comprehensive batteries of cognitive tests and tests of every-day cognitive function. To our knowledge, there have been no randomized-to-treatment clinical trials addressing improvement in cognitive performance with treatment for CVD risk factors. The clinical trial literature on hypertension provides a good model for this important next step.

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Table 1

Definitions of terms used in this review.

Tern	Definition
Construct	The theoretical mental process that tests attempt to measure or index.
Decline	Change in performance level from better to worse over time.
Deficit	A relative decrement in performance that does not rise to the level of impairment, e.g. mean level of performance in a group is lower than mean level of performance in another group, but individual differences in performance may overlap among groups.
Dementia	A progressive cognitive impairment characterized by decline in memory ability and impairment in one or more other cognitive domains, e.g., language, orientation, reasoning, attention and executive functioning (EF). Represents a decline from a previous level of functioning and interferes with activities of daily living and independence. Alzheimer's Disease (AD) is the most common form and a major risk factor is amnesic MCI.
Domain	A composite set of skills measured (indexed) by more than one test of specific ability as may be identified by factor analysis.
Every-Day ability	A test that measures real-life activities such as map reading, check balancing, following directions, organizing medications.
Executive Function	The ability to anticipate, plan and organize and to reject old inappropriate responses for new appropriate responses when confronted with a new problem. Difficult to separate from fluid intelligence and often and erroneously used as isomorphic with frontal lobe function, although frontal lobe damage is associated with poorer EF.
Fluid Intelligence	Ability with regard to dealing with new and novel tasks as opposed to crystallized (verbal intelligence) ability, often with demands on speed of performance. Many reviews of the literature have emphasized the extreme difficulty of separating fluid intelligence from executive functioning [EF] given their significant overlap in abilities measured [ref number here]
Global Ability	Overall ability which is the synergistic combination of specific abilities, e.g. overall score on an intelligence test.
Impairment	Poor performance reaching a clinically important level of deficit as defined by neuropsychological assessment and/or normative data.
Impurity	Failure of a test to measure only abilities it was designed to measure.
Level of Performance	An average or median level of performance based on the entire distribution of test scores or normative data.
Mental Status	Ability measured by screening measures such as the Mini Mental Status Examination (MMSE), often described as a test of global ability but lacking in sensitivity and specificity relative to intelligence test measures.
Mild Cognitive Impairment	Mild Cognitive Impairment (MCI) is a level of performance that indicates decline from a previous level of performance and impairment by clinical/normative criteria, but does not rise to the level of dementia. Individuals with MCI typically remain in the community and do not necessarily exhibit general intellectual decline. There are at least 30 different definitions formal clinical definitions in the literature.
Short Form	A shorter form of a test designed to retain validity and reliability but normally loses both to some extent.
Specific Ability	Ability in a relatively narrow range of specialized functioning as opposed to global cognitive ability or general intelligence.
Vascular Dementia (VaD)	Memory decline may be present but not necessarily predominant and other cognitive domains are affected early in the disease process and in the MCI that precedes it. Progress of VaD is more varied over time than is the progress of AD and a history of CVD risk factors and events are common. AD has a vascular component and mixed dementias are common.

Table 2

Common predictor variables in studies of renal disease and cognitive performance,

Predictor	Metric or Type of Measurement	Type of Variable
Uremic Patient ¹ vs Controls	Diagnostic criteria	Categorical
eGFR ²	mL/min per 1.73m ² body surface	Categorical ⁴ or continuous.
Serum Creatinine (sCR)	mg/dL or μ mol/L	Continuous ⁵
Stage of Kidney Disease ³	Standard Diagnostic Criteria	Categorical

¹Uremia defined as the accumulation of urinary waste products in the urine or the constellation of signs and symptoms indicating kidney disease or failure.

²eGFR (estimated glomerular filtration rate) be estimated via different formulae: Modification of Diet in Renal Disease (MDRD) study equation Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation Mayo Clinic Quadratic equation

³See reference 5 for definitions and criteria.

⁴Studies often use eGFR ≥ 60 (mL/min/1.73m²) versus <60 , or, for example, normal (≥ 90); mildly decreased (60 to 89); moderate CKD (30–59), severe CKD (15 to 29) and kidney failure (<15), or clinical criteria, tertiles, quartiles, quintiles etc.

⁵Continuously distributed such as eGFR in units (ml/min/1,73m²) or sCR in units (1 mg/dL) expressed as 1/sCR due to skew. [see reference 26 as example].

Table 3

Community-based studies published after 2004 arranged by date of publication.

Authors	Design	Outcomes	Control or Adjustment	Summary of Findings
Kurella et al. (2005) [16]	1,105 community-dwelling post-menopausal women (<80 years) with established coronary artery disease (no hysterectomy) enrolled in the Estrogen/Progestin Replacement Study. CKD estimated using eGFR as mild (45–59), moderate (30–44) and severe (eGFR < 30); eGFR 60 was referent group.	Multiple tests including 3MS, Trail Making Part B, Boston Naming, Verbal Fluency, Word List Memory and Recall.	Adjustment for age, race, education, lifestyle factors, stroke, diabetes, and other variables related to kidney disease.	eGFR was associated with deficits in global cognition, executive function, language, and memory (15 to 25% increment in risk for deficit per 10 mL/min/1.73m ² decrement in eGFR.
Hailpern et al. (2007)[15] Level expressed as quartiles, referent group is quartile with the poorest performance.	Younger, healthy and ethnically diverse community-based adults recruited from the NHANES III (age range 20–59; N range 4721 to 4865 depending on the test used). Moderate CKD was defined as eGFR 30 to 59 with eGFR > 60 as the reference group.	Simple visual-motor reaction time, visual attention and learning and concentration tests.	Ordinal regression analysis, adjustment for demographic variables and self-reported health variables. Diabetes excluded in sensitivity analyses.	Moderate CKD was associated with poorer learning and concentration (OR= 2.4) and visual attention (OR= 2.7) when adjusted for age, gender, education, race, and self-reported general health and other variables related to CKD.
Jassal et al. (2008) [17] Performance level (test scores).	99 uremic patients (mean age 65, with 50% > 65 years) with stage 3 to 5 kidney disease on optimized medical treatment at a pre-dialysis clinic. Renal function defined as eGFR calculated as a continuously distributed variable.	Multiple cognitive tests with composite scores measuring three domains: attention and working memory; psychomotor efficiency and processing speed; learning efficiency	Adjustment for age, education and sex, comorbid diseases, hemoglobin, PTH, and number of neurodepressor drugs, anti-depression medication, parathyroid diseases. Sensitivity analysis with ESPS. Exclusions: head injury, learning disabilities, history of acute stroke and TIA, and depressed mood.	Renal function (eGFR) was related to poorer performance on test of psychomotor efficiency and processing speed with statistical adjustment for covariates, but was not associated with performance scores for attention and working memory or learning ability.
Kurella Tamura, et al. (2008)[18]	23,405 community – dwelling participants (>44 years) from the REGARDS Study. CKD defined as < 60. eGFR in 10- ML/min/1.73m ² increments.	A six item telephone screening test with cognitive impairment (sic. deficit) defined as a score of <4.	Excluded eGFR <10. Adjusted for age, education, sex, race, recruitment location, CVD and CVD risk factors.	CKD <60 was associated with higher risk of cognitive deficit (OR= 1.23). Each 1-mL/min 1.73m ² was associated with an increment in cognitive impairment (OR=1.11).
Elias et al. ¹ (2009) [19] Performance decrement defined as the lowest quartile and also performance level	923 community dwelling participants (> 40 years of age); comparisons between eGFR > 60 and < 60; increment in sCR from 1 to 2 mg/dL, and 1/sCR as a continuously distributed variable.	Based on 19 tests submitted to factor analysis. Composite scores were formed for verbal episodic memory (VEM), visual-spatial memory and organization, (VSOM) scanning and tracking (ST), working memory (WM), and a global composite of all scores.	Adjusted for age, education, sex, race, diabetes, systolic blood pressure, BMI, smoking, HDL, and stroke and other risk factors in sensitivity analyses. Exclusions: dialysis, dementia, <40 years of age.	Comparisons of persons with eGFR < 60 with eGFR > 60 indicated decrement for the latter group for the global composite, OR= 1.25, VSOM; OR= 1.88), and ST (components of EF), OR= 1.56. Same associations for performance level outcomes. Higher levels of creatinine were associated with lower levels of performance on the global composite, WM, and ST.

Longitudinal studies of relations between kidney function and cognitive function organized by type of outcome (see italics): levels, impairment, dementia.

Table 4

Authors, Outcome and Time to Followup	Predictor(s)	Controls: adjustments or exclusions	Sample	Cognitive Tests or Diagnostic Category	Major statistically significant findings ¹
Buchman et al. (2009)[22] <i>Decline</i> in performance over 3-4 years.	Continuous eGFR (MDRD) at baseline and trichotomized impaired kidney function at baseline defined as <45, >45 to <60, > 60.	eGFR at baseline, age, sex, education, BMI, hemoglobin, physical activity, social activity, vascular risk factors, vascular diseases, depressive symptoms. Exclusions: Dementia	886 community-dwelling participants (mean age=80.6) from the Rush Memory and Aging Project who participated in both baseline and followup analyses.	5 subscale composites and a global composite derived from 19 individual measures. Subscales were: episodic memory, semantic memory, working memory, perceptual speed, visuospatial abilities.	Lower eGFR and impaired kidney function associated with rate of decline in global composite, episodic memory, semantic memory, and working memory.
Jassal et al. (2010)[24] Annual <i>decline</i> in performance level over mean follow-up of 6.6 years.	eGFR categorized as 60 or <60 and albuminuria (ACR 30 mg/g) versus no-albuminuria.	Stratified by sex. Covariates: age, SBP, HbA1C, education, strenuous exercise, alcohol consumption, current estrogen for women, eGFR, depressed mood, antihypertensive meds, lipid-lowering meds, Exclusions: <50 years of age, stroke	759 community dwelling men and women (mean age=74.9 years) at baseline who returned for repeat testing.	MMSE, Trails B, and Animals Naming Category Fluency test performance levels, both continuous and using cut points.	For men but not women, baseline albuminuria, but not eGFR, was associated with decline in MMSE and category fluency scores with adjustment for all covariates.
Wang et al. (2010)[28] <i>Decline</i> in performance (yes/no) in relation to baseline eGFR.	Categories of eGFR: 90 (reference), 60-89, 30-59; continuous eGFR in secondary analyses; albuminuria defined as 25 mg/g for males and 17 mg/g for females.	Basic: age, sex, education, BMI Additional: SBP, diabetes, urinary ACR. Exclusions: stroke	1,243 community-based Chinese participants (< 40 years of age) with an eGFR> 30; and 66 cases of during a 4-year followup.	A fall in MMSE of 2 points from baseline was defined as cognitive decline.	Relative to the reference group, risk of decline was higher for those with eGFR of 30-59
Davey et al. [Note 1] <i>Decline</i> in level of performance (over 4-5 years).	Continuously distributed eGFR and 1/sCR and change in eGFR baseline to followup.	Basic controls: age, education, sex race/ethnicity, eGFR at baseline. Additional controls: diabetes, depressed mood, alcohol consumption, diabetes and hypertension, APOE genotype, smoking, and cardiovascular disease. Exclusions, stroke at baseline dementia and renal dialysis.	590 Maine- Syracuse Longitudinal Study participants who participated at baseline and followup.	Decline in performance level for abstract reasoning and 4 major domains of functioning based on factor analysis of 19 separate test scores.	Baseline levels of eGFR and 1/sCR were unrelated to longitudinal change but change in renal function (eGFR) longitudinally was associated with change in cognitive performance for the global composite, verbal memory controls employed.
Kurella et al. (2005)[25] <i>Incident impairment</i> (yes/no) with followup at 2 and 4 years.	Categories of eGFR: 60 (reference), 45- 59, <45. Also used estimated creatinine clearance (Cockcroft-Gault) and gender-specific creatinine cut-points (top 1 and 10 percent of distributions).	Basic: age, race, gender, education Additional: baseline CVD, diabetes, BP, lipids, inflammatory markers, hematocrit concentration, incident stroke Exclusions: baseline cognitive impairment; ADL difficulties; life-threatening illness; intention of moving before follow-up	2406 elderly persons in the Health ABC Study (mean age = 74 years).	Modified Mini- Mental State Exam (3MS) with incident "impairment" defined as 3MS <80 or decline in 3MS >5 at either followup exam.	eGFR levels <60 were associated with greater odds of cognitive impairment, with adjustment for the full model. Creatinine levels in the top 10% and 1% were associated with higher odds of cognitive impairment, with adjustment for the basic model.

Authors, Outcome and Time to Followup	Predictor(s)	Controls; adjustments or exclusions	Sample	Cognitive Tests or Diagnostic Category	Major statistically significant findings ¹
Slinin et al. (2008)[29] <i>Incident impairment</i> (yes/no) in followup 4.6 years.	eGFR (MDRD) categories: 60-45-59 (mild CKD) <45 (moderate CKD)	Basic: age, education, race Additional: health status, IADL impairments, alcohol use, diabetes, hypertension, stroke, CVD, BMI, PAD Exclusions: unable to walk; bilateral hip replacement; severe medical conditions, dialysis excluded in secondary analyses	3722 community-based men (65 years) from the Osteoporotic Fractures in Men Study who provided baseline and followup data.	3MS and Trails B Impairment defined as an 3MS score < 80 or decline > 5; or increase in Trails B time 1 SD above mean change	Odds of incident impairment in relation to CKD was observed but was attenuated and not significant with adjustment for age.
Eigen et al. (2009)[20] <i>Incident impairment</i> over 2 years (yes/no) from in relation to baseline eGFR.	Baseline normal (>60) mild (45-59), and moderate-severe (<45) CKD based on eGFR (Cockcroft-Gault standardized for body surface area)	Basic: age, sex Additional: depression, physical activity, alcohol, diabetes, IHD/stroke, hyperlipidemia, hypertension, smoking Exclusions: cognitive impairment at baseline; CKD at baseline in secondary analyses.	3154 INVADE study participants (>54 years) (396 with cognitive impairment at baseline and 194 with incident cognitive impairment at followup.)	Blessed Information Memory Concentration Scale (6CIT). A score > 7 defined as impairment	eGFR <45 associated with cognitive impairment with adjustment for all covariates. With exclusion of CKD at baseline, incident CKD (eGFR < 60) was associated with incident cognitive impairment (covariates not reported).
Seliger et al. (2004)[27] <i>Incident dementia</i> (AD & VaD); followup median 6 years.	Primary: 1/sCR; Secondary: Renal insufficiency: sCR 1.3 mg/dl for women and 1.5 mg/dl for men.	Basic: Adjustment for age, sex, race and body weight, education, coronary heart disease, diabetes, hypertension, smoking status, and ApoE genotype; Exclusions: prevalent dementia at baseline	3349 participants of the Cardiovascular Health Cognition Study (age > 64 yrs). Incident dementia= 477 cases. Stratification by health status at baseline: poor, good and excellent	Diagnosis of dementia based on multiple test scores and clinical review. Type of dementia assessed with MRI.	Associations between elevated creatinine and incident dementia, but only non-dementia participants in good to excellent health at baseline; higher sCR associated with increased risk of VaD, but not "pure" AD-type dementia.
Helmer et al. (2011)[23] <i>Incident dementia</i> (AD, vascular) and change in level of performance on the MMSE; followup median 6.8 yrs.	eGFR (CKD-EPI) at baseline and change in eGFR over time, proteinuria	Basic: Adjustment for study center, age, sex, education, APOE genotype. Additional: hypertension, CVD, stroke, high lipid levels, diabetes, smoking, BMI, baseline eGFR. Exclusions: prevalent dementia at baseline	7,839 participants of the 3C Study (baseline eGFR); 2,382 multiple eGFR 1,040 proteinuria (Age > 65 yrs).	Diagnosis of dementia; based on NP examination and review by neurologist (DSM- IV criteria). Etiology based on NINCDS-ADIRDA and NINDS-AIREN criteria	No increased risk of cognitive decline or incident dementia in relation to eGFR at baseline. However, eGFR decline was associated with decline in global cognition (MMSE) and eGFR decline >4/year and proteinuria were related to increased risk for incident vascular dementia (with adjustment for extended covariate set).
Sasaki et al. (2011)[26] <i>Incident dementia</i>	CKD present/absent based on eGFR and albuminuria	Age, sex, education, hypertension, diabetes, dyslipidemia, ischemic heart disease, anemia.	256 community-dwelling participants from the Osaki-Tajiri Project (Northern Japan) (65 years).	Dementia: NINCDS-ADIRDA and NINDS-AIREN criteria	Association between CKD and conversion to dementia from a normal or questionable state at baseline with adjustment for all covariates.

¹ Negative results are not summarized (see variables column).

Table 5

Summary check sheet for essential methods and findings with eGFR Serum Creatinine, Albuminuria as outcome variables with studies ordered as in Table 4.

First Author	eGFR	Creatinine	Albuminuria (Alb)	MMSE/3MS (Global)	Composite of Tests (Global)	Number of Tests used As Outcomes	Dementia	Decline on any test or Incident Dementia	
								Relative to baseline renal function	Relative to change in renal function
Buchman	✓			✓	✓	19		✓ eGFR	
Jassal	✓		✓	✓		2		✓ Alb male	
Wang	✓		✓	✓				✓ eGFR	
Davey	✓	✓			✓	19			✓ eGFR/sCR
Kurella	✓	✓		✓				✓	
Slinin	✓			✓		1			
Eigen ¹	✓					1		✓ eGFR	
Seliger ^{2,3}	✓	✓					✓	✓ eGFR/sCR	
Helmer	✓						✓		✓
Sasaki	✓						✓	✓	

¹ Based on Cockcroft-Gault formula, standardized for body surface area.

² Renal insufficiency, defined differently for men (1.5mg/dl) and women (1.3 mg/dl), was related incident dementia.

³ Only for dementia free persons in good or excellent health at baseline.

Table 6

Some candidate mechanisms mediating between kidney disease and cognitive functioning on order of discussion in text.¹

CVD Risk Factors	Hypertension, chronic hypotension, diabetes mellitus, hyperlipidemia, cardiovascular disease, including myocardial infarction, arterial fibrillation, cigarette smoking, elevated homocysteine, hemostatic abnormalities, hypercoagulation, oxidative stress, inflammation, acute stroke,
Biologic Intrinsic	Vascular changes in brain; anemia, white matter lesions, anemia, cortical atrophy, hyperparathyroidism, microalbuminuria, subclinical atherosclerosis
Psychosocial/Treatment	Clinical depression and depressed mood and other psychosocial variables, polypharmacy, malnutrition,
Dialysis- related	Hypotensive episodes, chronic microembolism, subclinical increases in brain edema, acute stroke, silent and asymptomatic stroke, hemodynamic changes and fluid shifts, microalbuminuria, recurrent cerebral ischemia, acute dynamic cardiovascular changes, lacunar infarcts, microbleeds

¹See reviews of the literature including references 3–5.