# NEUROPSYCHOLOGICAL FUNCTIONING IN OLDER ADULTS WITH CHRONIC KIDNEY DISEASE

by

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# ABSTRACT

Chronic Kidney Disease (CKD) is a condition that disproportionately affects older adults and is associated with high prevalence of vascular diseases and increased risk for the development of cognitive impairment. In the current study, we examined global cognition, verbal memory and executive functioning in older adults with CKD and compared their performance to age- and education-matched healthy controls. We also assessed the role of potential mediators/moderators of cognitive impairment in CKD, including metabolic disturbances, psychological distress, subclinical dementia and medication usage. Compared to controls, older adults with CKD exhibited worse executive functioning but relatively intact memory retention, a neuropsychological presentation that is consistent with vascular cognitive impairment. Poor cognitive performance in CKD was not associated with metabolic dysfunction or elevated psychological distress, and persisted after controlling for impaired global cognition and differences in medication usage. Future studies investigating the relationship between cerebrovascular pathology and neuropsychological functioning in CKD are warranted.

**Keywords:** chronic kidney disease; vascular cognitive impairment; aging; global cognition; memory; executive functioning.

# DEDICATION

To my parents - for all they have done to pave the way for my achievements.

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# INTRODUCTION

Chronic Kidney Disease (CKD) is a common chronic illness that affects approximately 10% of the population, and for which prevalence and incidence rates have been increasing over the past few decades, particularly in the older adult population (Levey et al., 2003). From both a theoretical and clinical standpoint, CKD represents an interesting chronic disease framework for neuropsychologists. Recent research findings, while limited in scope, have been converging to suggest that CKD is associated with higher rates of cognitive impairment compared to the general population (Kurella et al., 2005; Kurella, Chertow, Luan, & Yaffe, 2004; Kurella, Yaffe, Shlipak, Wenger, & Chertow, 2005; Thornton, Shapiro, Deria, Gelb, & Hill, in press), and that older age places individuals with CKD at an increased risk for developing dementia (Seliger et al., 2004). However, the nature and extent of cognitive impairment in CKD, as well as the causal mechanisms that underlie cognitive dysfunction in this population have yet to be fully elucidated.

Among the few studies that have investigated cognitive functioning in CKD, most present with methodological limitations, such as lack of an adequate control group and/or inclusion of participants with neurological disorders (e.g. stroke), which restrict interpretation and generalizability of findings (Kurella, Chertow, et al., 2005; Kurella et al., 2004; Kurella, Yaffe, et al., 2005). Efforts aimed at conceptualizing the cognitive presentation of CKD are also complicated by the fact that this illness is associated with several independent risk factors that predispose one to cognitive impairment and dementia. Renal failure itself causes metabolic disturbances including the accumulation of wastes (uremia) and anemia (low hemoglobin) that lead to cognitive deficits (Pliskin, Kiolbasa, Hart, & Umans, 2001). Furthermore, vascular diseases, such as hypertension

and diabetes, are highly comorbid with CKD and are known etiological factors for the development of cognitive impairment and stroke (Knopman, et al., 2001). In addition, psychological distress, which is prevalent in the renal disease population, is often associated with cognitive difficulties (Alexopoulos et al., 2002; Kimmel, 2002). In the context of the aging brain, these negative modifiers may exact more pronounced detrimental effects on the cognitive functioning of older adults with CKD relative to their younger counterparts and healthy peers. Developing a better understanding of the nature and severity of cognitive impairment in older adults with CKD may help to clarify the relative contributions of the various risk factors present in this illness, which would have important implications for prognosis and treatment management.

The aim of the current study was to better characterize the neuropsychological functioning of older adults with CKD and to examine the role of potential mediators and/or moderators of cognitive impairment in this population while addressing some of the limitations in past studies. A summary of the main research findings in CKD and cognition to date, as well as the important issues that remain to be addressed are discussed below.

## Metabolic Disturbances

Adequate renal functioning is essential for the proper regulation of body fluids, blood pressure, excretion of metabolic wastes and control of the endocrine system (Pliskin et al., 2001). When kidney functioning is compromised through damage or disease, these critical processes become impaired, leading to the build up of excess fluid and metabolic toxins in the body (Brown & Brown, 1995; Christensen & Ehlers, 2002). Untreated, the effects of advanced uremia can include behavioural and neurological disturbances such as fatigue, anorexia, delirium, seizures and coma (Burn

& Bates, 1998; Kramer et al., 1996; Pliskin et al., 2001; Yount, Jacobs, Bustamante, & Brickman, 1998). The conventional clinical marker of kidney functioning is the glomerular filtration rate (GFR), which provides a measure of the efficiency with which the kidneys clear substances from the blood. In individuals with normal kidney functioning, GFR levels fall in the 120-130 ml/min per 1.73 $m^2$ range (Levey et al., 2003; Pliskin et al., 2001). CKD is defined as GFR less than 60 ml/min per 1.73 $m^2$, representing loss of half or more of kidney functioning, for at least 3 months (Levey et al., 2003). The clinical course of CKD is characterized by progressive deterioration of kidney functioning, which eventually culminates in complete kidney failure, a stage known as end-stage renal disease (ESRD). Patients with ESRD require renal replacement therapy, in the form of dialysis or transplant, for continued survival (Levin, Stevens, & McCullough, 2002).

Research on the neuropsychological functioning of pre-dialysis and pre-transplant ESRD patients has consistently demonstrated deficits in concentration, sustained attention, memory and psychomotor and processing speed (Bremer, Wert, & Durica, 1997; Brickman, Yount, Blaney, Rothberg, & Kaplan De-Nour, 1996; Griva et al., 2003; Umans & Pliskin, 1998; Yount et al., 1998). To the extent that cognitive dysfunction in ESRD is a consequence of untreated, fluctuating metabolic derangements, then one might expect a return to normative levels of cognitive functioning following institution of renal replacement therapy. Otherwise, it can be postulated that factors other than, or in addition to, metabolic disturbances are accounting for cognitive dysfunction in this population. To date, research examining cognitive functioning in renal disease patients who have undergone replacement treatments has produced inconsistent findings. For example, Fazekas et al. (1995), in comparing the cognitive functioning of 30 hemodialysis patients to matched controls, found that 60% of dialysis patients and none of the controls met criteria for cognitive

impairment on the Mini Mental Status Examination (MMSE score < 24). Sehgal, Grey, DeOreo and Whitehouse (1997) also reported high rates of cognitive impairment in the dialysis population. In their study of 336 dialysis patients, 22% met criteria for mild mental impairment (MMSE: 18-23) and 8% met criteria for moderate to severe mental impairment (MMSE: 0-17). In other studies, comparison of cognitive functioning between dialysis and demographically matched chronically-ill patients have not yielded significant differences between groups on measures of intelligence, memory, language and problem solving (Pliskin, Yurk, Ho, & Umans, 1996) and on measures of attention and mental processing speed (Umans & Pliskin, 1998). Of note, both the dialysis and chronically-ill groups in these latter studies were found to be in the mild cognitive impairment range when compared to published normative data. Thus, a comparison of dialysis patients to matched healthy peers rather than chronically-ill patients may have increased the magnitude of the differences observed and provided a better indication of the neuropsychological functioning of these patients relative to estimated premorbid levels.

Similarly, research investigating cognitive functioning in transplant patients has been inconclusive and relatively sparse. Kramer et al. (1996) examined cognitive functioning as measured by the MMSE and Trail Making Test A (number sequencing) in 15 hemodialysis patients and then one year following their transplant. While pre-transplant hemodialysis patients obtained worse scores on cognitive measures compared to controls, their performance was found to be similar to controls following their transplant. However, there was no demonstrable improvement in performance within the patient group from pre- to post-transplant (Kramer et al., 1996). In a study examining cognitive functioning in 117 transplant patients compared to 145 dialysis patients, transplant patients performed better than dialysis patients on verbal memory,

but performed similar to dialysis patients on measures of attention and psychomotor abilities (Griva et al., 2004). However, given lack of a healthy comparison group, it is not evident how either group was functioning relative to demographically-matched peers.

There are important limitations to many of the studies examining cognitive functioning in transplant and dialysis patients, including limited assessment of cognitive domains, lack or inadequate choice of control groups, as well as inadequate control of confounding variables such as psychological status (Pliskin et al., 2001). These limitations preclude definitive conclusions about the role and potential reversibility of the effects of metabolic disturbances on cognitive functioning following renal replacement therapy.

## Chronic Kidney Disease and Cognition

One of the main challenges in determining whether a return to a baseline level of cognitive functioning is achievable following dialysis or transplant treatment is that what constitutes the 'baseline' in this population is poorly understood. The neuropsychological presentation of early CKD has not been well established as limited research to date has focused on cognitive functioning in patients with mild to moderate renal failure, when metabolic disturbances are less severe (Kurella, Chertow, et al., 2005; Kurella et al., 2004; Kurella, Yaffe, et al., 2005; Thornton et al., in press). However, the few published studies in this area suggest a link between CKD and cognitive impairment. Kurella, Yaffe, et al. (2005) examined cognitive functioning in a sample of 1015 menopausal women with established coronary artery disease and comorbid CKD. These participants performed significantly worse on measures of executive functioning, language, attention and psychomotor skills compared to published norms. Moreover, severity of kidney disease, as measured by GFR levels, was found to correlate significantly with cognitive

performance, such that lower GFR levels were associated with lower scores on tests of global cognition, executive functioning, language, and memory. In a study assessing prevalence of cognitive impairment in CKD (Kurella et al., 2004), 15% of a sample of 80 CKD participants met criteria for global cognitive impairment on the Modified Mini-Mental State Exam (3MS), 28 % met criteria for impairment on executive functioning and 38% met criteria for memory impairment, as compared to published norms. Whereas severity of kidney impairment was a significant predictor of poor performance on global cognitive functioning and delayed memory, interestingly GFR was not a significant predictor of executive dysfunction in this study. Research on the longitudinal course of CKD also suggests that this illness is related to an increased risk for cognitive impairment. In a study of 3034 elderly patients with CKD (Kurella, Chertow, et al., 2005), mean declines in cognitive functioning over a 4-year period, as assessed by the 3MS measure, were significantly correlated with severity of CKD.

Although these past studies provide important insights into the cognitive functioning of individuals with CKD, they are limited by important methodological shortcomings. These limitations, such as the absence of demographically matched comparison groups, inclusion of highly selective CKD samples, and failure to exclude participants with history of dementia or frank cerebrovascular disease (i.e. stroke) confound the interpretation of findings. More recently, Thornton et al. (in press) addressed some of these limitations in a well-controlled study investigating neuropsychological functioning in individuals with CKD. Compared to healthy peers, CKD participants exhibited higher rates of cognitive impairment and deficits in executive functioning and verbal memory. Unlike previous studies however, cognitive performance in this study was found to be independent of kidney disease severity (i.e. GFR and

hemoglobin), suggesting that mechanisms other than metabolic disturbances may be responsible for cognitive impairment in CKD.

## Cerebrovascular Risk Factors

Individuals with CKD have higher rates of comorbidity with vascular diseases compared to the general population (Culleton & Hemmelgarn, 2003; Levin, 2003; Madore, 2003; Uhlig, Levey, & Sarnak, 2003; Varma, Garrick, McClung, & Frishman, 2005; Wheeler, Townend, & Landray, 2003). Indeed, vascular diseases commonly predate the onset of CKD and are themselves risk factors for the development and progression of kidney disease. Diabetes is the leading cause of CKD and accounts for approximately 33% of cases (Christensen & Ehlers, 2002). Hypertension is the second most common etiology of CKD and is often itself complicated by renal failure (Yount et al., 1998). Other vascular diseases with high prevalence in this population include dyslipidemia and coronary artery disease (Madore, 2003; Varma et al., 2005). With recent advances in the quality of renal replacement therapies, vascular diseases now comprise the leading cause of mortality in CKD and account for half of all deaths in this population (Culleton & Hemmelgarn, 2003).

There is evidence to suggest that vascular diseases are an important cause of cognitive impairment and dementia (Knopman, et al., 2001). Several large and prospective epidemiological studies have linked hypertension and diabetes to lowered cognitive functioning (Elias et al., 1997; Elias, Wolf, D'Agostino, Cobb, & White, 1993; Launer et al., 2000). Even in the absence of frank cerebrovascular insults, such as clinical stroke, vascular diseases are thought to be associated with structural cerebral abnormalities that can cause deleterious effects on brain functioning (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003). The specific mechanisms or pathways whereby

cerebrovascular disease risk factors lead to cognitive impairment are not yet fully understood. However, certain cumulative pathological processes, such as silent stroke, atherogenesis, and altered cerebral blood flow have been identified as consequences of vascular disease (Elias et al., 2003; Elias et al., 1993). The aging brain in particular, due to normative reductions in regional cerebral blood flow, has a reduced capacity to compensate for the effects of vascular disease and consequently may be more negatively impacted by the pathogenic effects of ischemia (Raz et al., 2003).

Vascular diseases also cause insidious cerebral damage through ischemic white matter lesions (De Leeuw et al., 2002). Chronic hypertension, for instance, has been shown to be associated with the presence of cerebral white matter pathology in subcortical and periventricular regions (De Leeuw et al., 2002; Raz, Rodrigue, & Acker, 2003). White matter is thought to be particularly vulnerable to the effects of transient decreases in cerebral blood flow associated with vascular disease, as it is poorly irrigated and blood supply to this region is low under normal physiological conditions (De Leeuw et al., 2002; Raz et al., 2003). Moreover, the vasolidatory capacity of white matter in the cerebral prefrontal area is lower than in other regions of the brain (Raz et al., 2003). Consequently, the cognitive functions mediated by the prefrontal cortex and underlying white matter have been posited to be preferentially affected by vascular diseases. These cognitive functions, known as executive functions, are defined as higher-level cognitive functions that allow an individual to independently and successfully carry out purposeful, goal-directed behaviors (Lezak, 1995). Executive functions include abilities such as initiation of problem-solving behaviour, mental flexibility, set shifting, inhibition of overlearned behaviour, inhibition of response to salient stimuli, and abstract reasoning (Kramer, Reed, Mungas, Weiner, & Chui, 2002).

The neuropsychological presentation linked to cerebrovascular disease risk factors is known as vascular cognitive impairment (VCI) (Hachinski, 1994; Garrett et al., 2004). VCI has been conceptualized by some as an earlier stage, and sometimes prodromal form, of vascular dementia, and is thought to be more strongly linked to frontal lobe changes and deficits in executive functioning rather than to severe memory impairment as seen in Alzheimer's dementia (AD) (Baldo, Delis, Kramer, & Shimamura, 2002; Baldo & Shimamura, 2002; Bowler, 2002; Desmond et al., 1999; Hachinski, 1994; Garrett et al., 2004; Sachdev et al., 2004; Vanderploeg, Yuspeh, & Schinka, 2001; Yuspeh, Vanderploeg, Crowell, & Mullan, 2002). In contrast to normal aging and VCI, AD is associated with deterioration of medial temporal lobe and/or diencephalic structures (Bowler, 2002; Vanderploeg et al., 2001), is classically linked with dysfunction in the consolidation of information into long-term memory, and is characterized by rapid forgetting of information over time (Vanderploeg et al., 2001).

Research indicates that renal disease patients undergoing dialysis exhibit significantly higher rates of cerebrovascular lesions than demographically matched peers as evidenced by the presence of multiple lacunes and white matter hyperintensities on magnetic resonance imaging (MRI) (Fazekas et al., 1995; Pereira, Weiner, Scott, & Sarnak, 2005). There is also evidence to suggest that brain abnormalities are present in individuals with mild to moderate CKD, not yet requiring renal replacement therapies. In a recent study (Martinez-Vea et al., 2006), presence of subcortical and periventricular white matter lesions was found to be significantly more prevalent in CKD participants compared to controls. Approximately 33% of participants with CKD evidenced cerebral white matter lesions compared to 6% of controls. Increased age and greater history of vascular disease were both associated with white matter lesions in the CKD group. However, duration of kidney disease was not related to

the presence of white matter lesions in this study. This lack of relationship may be explained in the context of the early course associated with vascular diseases (e.g. hypertension, diabetes) in CKD, which implies that the risk burden for the development of cerebrovascular disease is present in patients at all stages of CKD, including those in the early stages (Levin, 2003; Uhlig et al., 2003; Wheeler et al., 2003). Given these findings of high rates of cerebral vascular damage in individuals with kidney disease, it may be that cerebrovascular pathology is in part mediating the association between CKD and cognitive impairment. This hypothesis has support in a longitudinal study by Seliger et al. (2004) examining older adults free of dementia at baseline who were followed over a 6-year period. Older adults with CKD were found to have an elevated risk for incident dementia as determined by neurological testing. In particular, CKD was associated with the development of vascular dementia, but not with Alzheimer's dementia (AD) (Seliger et al., 2004).

## Psychological Factors

Psychological difficulties represent an additional factor that can contribute to poor cognitive and functional outcome in CKD (Kimmel, 2001; Kimmel, Thamer, Richard, & Ray, 1998). Compared to the general population, the prevalence of psychiatric disorders has been found to be substantially higher in patients with ESRD (Yount et al., 1998) and those undergoing dialysis (Maugeri et al., 1999). Indeed, depression and affective disorders are among the most common psychiatric disorders associated with kidney disease (Kimmel, 2002). Estimates of prevalence in the dialysis population suggest that approximately 25% meet criteria for psychiatric disorders (Kimmel, 2001; Kimmel, 2002). The prevalence of depression in the CKD population is unknown due to lack of epidemiological studies in patient groups who have yet to undergo renal replacement

treatments (Kimmel, 2001; Kimmel, 2002). Depression is widely reported to be associated with cognitive impairment, particularly in older adults (Alexopoulos et al., 2002) and executive dysfunction is a common manifestation of geriatric depression (Alexopoulos et al., 2000; Lockwood, Alexopoulos, & van Gorp, 2002). Given the association between depression and cognitive compromise in older adults, as well as the high comorbidity of psychological disorders in kidney disease, it seems imperative that the assessment of cognitive functioning in CKD also includes an evaluation of the potential role of psychological distress in mediating any observed cognitive deficits.

## Chronic Kidney Disease and Aging

CKD is a condition that affects mostly older adults; the mean age of individuals with CKD is approximately 60 years (Kurella et al., 2004). The implication of this fact is that a substantial proportion of individuals with CKD present with an additional independent risk factor for the development of cognitive impairment and dementia - older age (Tuokko & Frerichs, 2000). Findings from the cognitive aging literature indicate that normal aging is associated with systematic declines on measures of processing speed, working memory and directed, effortful memory tasks (e.g. free recall) (Park, 2000) as well as on measures of executive functioning (Rhodes, 2004). In contrast, measures dependent on overlearned skills and crystallized abilities such as knowledge (e.g. vocabulary) evidence relative stability with aging (Park, 2000). These cognitive findings are corroborated by neuroimaging studies of aging. Cerebral white matter lesions are commonly observed on brain scans of healthy older adults and are thought to be involved in normal age-related cognitive declines (Gunning-Dixon & Raz, 2000; Gunning-Dixon & Raz, 2003). Moreover, the presence of white matter lesions is differentially associated with declines in certain cognitive functions such as processing

speed, executive functioning and explicit memory, but not with others such as intelligence (Gunning-Dixon & Raz, 2000).

In older adults with CKD, cognitive functions exhibiting normal age-related declines may be compounded by the presence of multiple negative modifiers (e.g. metabolic, vascular and psychological disturbances), particularly as there is overlap in the detrimental effects that some of these conditions and aging exact on cognition. This may result in a neuropsychological presentation consistent with accelerated cognitive decline in older adults with CKD. Support for this hypothesis is found in a recent study where age was determined to be a significant moderator of cognitive functioning in CKD (Thornton et al., in press). Older CKD participants performed significantly worse on measures of memory and executive functioning compared to both younger CKD participants and age-matched controls. While these findings suggest a relationship between worsening cognition and older age in CKD, many questions still remain about the cognitive presentation of this patient population. For instance, it remains to be determined whether the reported declines in memory and executive functions observed in CKD are specific to these functions or part of a general decline in overall cognition. Moreover, few studies have examined the extent to which executive dysfunction in CKD reflects primary deficits in these functions as opposed to deficits in lower-level cognitive abilities that support executive functioning (e.g. attention and processing speed) (Kurella et al., 2004; Kurella, Yaffe, et al., 2005). Similarly, the extent to which the reported memory deficits in older adults with CKD reflect an amnestic disorder characterized by rapid forgetting or whether these deficits are more subtle and perhaps secondary to deficits in executive functioning (e.g. failure in utilizing memory strategies, susceptibility to interference; Baldo & Shimamura, 2002) is not clear.

To summarize, the development of cognitive impairment in older adults with CKD is associated with multi-factorial risk, consisting of increased rates of vascular diseases, metabolic disturbances, psychological distress as well as increased age. Nonetheless, few studies to date have systematically investigated the nature and extent of cognitive impairment in older adults with CKD while employing an adequate comparison group and utilizing a cognitive-process approach to the evaluation of neuropsychological functioning (Kurella, Chertow, et al., 2005; Kurella et al., 2004; Kurella, Yaffe, et al., 2005; Thornton et al., in press).

## Objectives

Given that previous research findings suggest that increasing age is a potentially important risk factor and moderator of the cognitive presentation in CKD, the objective of the current study was to further characterize the nature and extent of cognitive impairment in older adults with CKD prior to their initiation into renal replacement treatments. Toward this end, we compared the neuropsychological functioning of a consecutively drawn outpatient sample of older CKD adults who were pre-dialysis/transplant with that of an age- and education-matched sample of healthy controls. In an effort to expand on prior findings linking CKD to memory and executive deficits, we conducted a more comprehensive evaluation of these functions than previously attempted (e.g. examining cognitive process variables and accounting for lower-level cognitive abilities that may underlie deficits in memory and executive functions) and also assessed differences in global cognition between groups. Moreover, to ascertain the extent of cognitive impairment in CKD, we determined the percentage of participants whose performance met established criteria for impairment on these cognitive functions.

A second objective of this study was to investigate the role of potential mediators and/or moderators that may negatively impact cognitive performance in CKD. Factors of interest included psychological distress, metabolic disturbances (as indexed by GFR, hemoglobin and illness duration), medications with known central nervous system (CNS) effects, and subclinical dementia (defined as impaired global cognition on our cognitive screening measure). Toward these ends, we examined (a) the bivariate association between cognitive performance and psychological distress, as well as between cognitive performance and indices of metabolic disturbances in the CKD group, (b) the predictive utility of psychological distress, group and their interaction in accounting for differences in cognitive functioning (c) the performance between groups before and after removing participants on medications with known CNS effects and those meeting criteria for impaired global cognition.

## Hypotheses

1. We predicted that older CKD participants would evidence greater rates of cognitive impairment as compared to age and education matched controls.
2. We predicted that the neuropsychological presentation of CKD participants would be consistent with that of a vascular cognitive impairment (VCI) presentation given the increased cerebrovascular risk factors associated with this population. Specifically, it was proposed that CKD participants would evidence significant deficits in executive functioning while exhibiting relatively preserved memory retention as compared to healthy controls.
3. We also predicted that CKD would be associated with a VCI presentation even after controlling for participant variables (i.e. psychological distress, medication usage and subclinical dementia). Based on findings from previous well-controlled

research (Thornton et al., in press), it was hypothesized that illness variables (GFR, Hemoglobin, illness duration) would not solely account for the cognitive presentation associated with CKD. Finally, it was hypothesized that CKD would be associated with worse performance on frontally-mediated cognitive processes involved in learning and memory (e.g. ability to organize information, susceptibility to intrusions).

# METHOD

## Participants

The current study design was prospective and consisted of a consecutively drawn sample of 54 participants with CKD (age range: 56-89) and 42 healthy controls (age range: 56-89). CKD participants were recruited from the Vancouver General Hospital (VGH) Renal Clinic. CKD candidates were outpatients whose illness had been managed by the Renal Clinic for at least 6 months to permit adequate stabilization of acute illness factors. All had a current diagnosis of chronic kidney disease (i.e. estimated GFR less than 60ml/min/1.73m$^2$), but had yet to be initiated into renal replacement therapy (i.e. dialysis or transplant treatment). Control participants were age- and education-matched volunteers with no history of renal disease. Controls were recruited from senior/community centers around the Vancouver mainland area (e.g. Oakridge Senior Centre) and through local advertisement. Inclusion criteria for both groups required that participants (a) have adequate fluency in English (b) be at least 56 years old (as this is the lower age cutoff for one of the main cognitive tests in this study) and (c) have completed a minimum grade 9 level education (to allow for adequate matching of groups). Participants in both groups were excluded from this study if they had a history of (a) terminal or systemic illness (other than renal disease for the CKD group) (b) neurological disorder (e.g. stroke, traumatic brain injury, dementia) or (c) major psychiatric illness. Given the dependence on vision for many tests, participants with corrected vision of less than 20/50 acuity on the Snellen eye chart were also excluded from this study.

# Measures

## *Global Cognitive Functioning*

The Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001) is a 36-item instrument that assesses cognitive impairment in older adults (ages 56 and above). The DRS-2 total score provides an index of global cognitive functioning (range: 0-144) and five subscale scores provide estimates of functioning in specific cognitive domains: Attention (range: 0-37), Initiation/Perseveration (range: 0-37), Construction (range: 0-6), Conceptualization (range: 0-39) and Memory (range: 0-25). The Initiation/Perseveration and Conceptualization subscales of the DRS-2 demonstrate convergent and discriminant validity with established tests of executive functioning (e.g. perseverative responses of the Wisconsin Card Sorting Test) (Jurica et al., 2001). As such, they were considered indices of executive functioning in the current study. Higher scores on the total and subscale scores indicate better cognitive functioning. The traditional cutoff for cognitive impairment on the DRS-2 total score is $\leq$ 123 (Montgomery & Costa, 1983). However, an alternative cutoff point of $\leq$ 134 has been recommended by van Gorp et al. (1999) for its maximized discriminative power. The latter cutoff point was used to quantify cognitive impairment on the DRS-2 total score in this study. The psychometric properties of the DRS-2 are well established; the test-retest reliability coefficient for the total score is .97 and reliability coefficients for the subscale tests range from .61 to .94.

## *Verbal Learning and Memory*

The California Verbal Learning Test-Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) is an instrument designed to evaluate verbal learning and memory in individuals ages 16 to 89. During the first five trials of the CVLT-II, a list of 16

words (List A; 4 semantic categories comprising 4 words each) was presented to the examinee and he/she was tested on recall immediately following each trial. An interference list (List B) was then presented during one trial for which the examinee was tested on recall. This was followed by testing of short delay free-recall and cued-recall of List A. A 20-minute delay was then implemented, followed by testing of long delay free-recall and cued-recall of List A. The examinee was then tested on their recognition memory (ability to distinguish target words from distractor words) for List A. The CVLT-II provides numerous parameters of learning and memory. In the present study, variables of interest were selected as to inform on functioning in the areas of attention, learning and memory retention. Auditory attention was assessed by level of correct recall on the first immediate trial of List A (raw scores: 0-16). Verbal learning ability was indexed by level of correct recall on List A Trials 1-5 (raw scores: 0-80). Retention rate was determined by the amount of information retained from List A Trial 5 to the Long Delay-Recall trial. This score was computed by (1) transforming raw scores on each trial into a z-score standardized on the control group's respective mean (2) subtracting participants' z-scores on List A Trial 5 from their z-scores on the Long-Delay Free Recall trial. Retention rate was computed in this manner to allow participants to be compared to their baseline levels of recall without disproportionately penalizing those with low initial levels of recall (Delis et al., 2000). Higher raw and z scores on these CVLT-II measures reflected better performance. The CVLT-II has good psychometric properties; the test-retest reliabilities of the variables of interest are as follows: Trial 1: $r^2 = .57$; Trials 1-5: $r^2 = .82$; Retention comprises Long-Delay Free recall: $r^2 = .88$ and Trial 5: $r^2 = .76$.

***Learning and Memory: Process Variables***

Besides the amount of information learned and retained, to better understand *how* learning occurred, we examined two process variables that may underlie

performance on verbal learning and memory: CVLT-II Semantic Clustering and CVLT-II Intrusion Errors. Semantic clustering informs the extent to which the examinee adopts an organizational strategy during the learning process (i.e. grouping words based on semantic features). Intrusion errors refer to the recall of words that are not target words on the lists. The test-retest reliability of these process variables are as follows: Semantic clustering (chance-adjusted raw score): $r^2 = .74$ and Total Intrusions: $r^2 = .63$.

## *Executive Functioning*

The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) consists of a battery of standardized tests that assess executive abilities in individuals up to the age of 89. We selected three measures from this battery to allow for breadth in the assessment of executive functions. In order to better understand whether poor performance on these measures was related to a deficit in executive functioning and/or to impairment in a more fundamental, underlying ability (e.g. attention, processing speed), we contrasted performance on an executive task with that on a respective baseline task for each of the three measures (Delis et al., 2001). Descriptions of the selected tests, the executive abilities they are thought to assess and their psychometric properties are presented below.

### *The Trail Making Test*

The D-KEFS Trail Making test contains several timed visual tasks that require an examinee to connect items in a particular sequence. The two tasks that were assessed from this test were Number Sequencing and Number-Letter Switching. Number Sequencing (also known as Trails A) requires that participants connect numbers that are randomly placed on a booklet in an ascending sequence (e.g.1→ 2→ 3→ 4, etc). Performance on this task is thought to rely on visuospatial, attention, psychomotor and

numerical processing skills and was considered the baseline condition. Number-Letter Switching (also known as Trails B) requires that examinees connect a series of numbers and letters, which are randomly placed on a booklet, in an alternating, sequential manner (e.g. 1→A→2→B→3→C, etc). In addition to the cognitive demands required of the previous task, this task introduces a cognitive shifting component and was considered the executive functioning task. For both tasks, completion time (in seconds) determined level of performance, with longer completion times denoting worse performance. We contrasted performance on the baseline and executive tasks by computing a difference score. This was done by subtracting each participant's score on Number Sequencing from their score on Number-Letter Switching. Higher difference scores suggested difficulty in cognitive flexibility beyond that accounted for by problems in the more fundamental cognitive abilities. The test-retest reliability coefficients for these tasks are as follows: Number-Sequencing: $r^2 = .59$ and Number-Letter Switching: $r^2 = .38$.

***The Verbal Fluency Test***

The D-KEFS Verbal Fluency Test contains several timed tasks that require examinees to generate words according to designated criteria. The two tasks that were assessed from this test were Category Fluency and Category Switching. In Category Fluency, participants are asked to produce as many words as possible that belong to a specified semantic category during a 60 s trial. Two trials are presented, one for each of two designated semantic categories (Animals and Boy's Names). Performance on this task relies on the ability to generate responses fluently and was considered a relative baseline condition. In Category Switching, participants are asked to say words from two specified semantic categories (Fruits and Furniture) in an alternating manner (e.g. Apple, Chair, Banana, Table, etc.). One trial with a 60 s time limit was presented. In addition to

the cognitive demands of the previous task, performance on this task requires that participants' shift attention between concepts (cognitive shifting), and was considered an executive function task. For both tasks, number of words generated determined level of performance, with higher scores denoting better performance. Performances on the baseline and executive tasks were contrasted by computing a difference score. However because the two tasks were not equated on number of trials presented, first we averaged the number of words produced for the two trials of Category Fluency to allow for direct comparison with the one trial that was presented for Category Switching. Then, participants' score on Category Switching was subtracted from their average score on Category Fluency. Higher difference scores suggested difficulty in cognitive flexibility beyond that accounted for by problems in response generation (fluency). The test-retest reliability coefficients for these tasks are as follows: Category Fluency: $r^2 = .79$ and Category Switching: $r^2 = .52$.

***The Color-Word Interference Test***

The two tasks selected from the D-KEFS Color-Word Interference test were Color Naming and Inhibition. In Color Naming, participants are required to name the color of randomly presented stimuli (rectangular color patches) as quickly as possible (e.g. red, green, blue). Performance on this task relies on attention and processing speed and was considered the baseline condition. The Inhibition task (also known as the traditional Stroop interference task) requires that participants inhibit reading words denoting colors in order to identify the dissonant ink color in which words are displayed (e.g. when the word 'red' is printed in green ink, the examinee is required to say "green"). This task assesses a participant's ability to inhibit an automatic response in favor of a more controlled response, and was considered an executive functioning task. For both tasks, completion time (in seconds) determined level of performance, with

longer completion times denoting worse performance. We contrasted performance on the baseline and executive tasks by computing a difference score. This was done by subtracting each participant's score on Color Naming from their score on Inhibition. Higher difference scores suggested difficulty in cognitive inhibition beyond that accounted for by problems in the more fundamental cognitive abilities. The test-retest reliability coefficients for these tasks are as follows: Color Naming: $r^2 = .76$ and Inhibition: $r^2 = .75$.

### *Composite Executive Functioning*

The three executive functioning contrast measures described above assess functioning in the areas of cognitive shifting and cognitive inhibition. As we did not have specific predictions about differential performance on these measures, in order to initially minimize the number of analyses, we created a composite executive functioning contrast score. This composite score was a weighted average of the three executive functioning contrast scores and obtained by 1) transforming each test's raw contrast score into a z-score standardized on the control group's mean and *SD* and 2) computing the average z-score of the three contrast z-scores.

## *Vocabulary*

A multiple-choice vocabulary test from the Education Testing Service kit (Ekstrom, French, Harman, & Dermen, 1976) provided an index of semantic knowledge or vocabulary level, and was used as a matching variable between groups. The version employed in this study contained 18-items from Vocabulary V-2. This test was administered without time constraints. A total score was obtained by subtracting 25% of incorrect responses from the number of correct responses. Higher scores represented better vocabulary. The test-retest reliability of this measure is .80 (Ekstrom et al., 1976).

### *Psychological Distress*

Level of psychological distress was assessed with two instruments. The Center for Epidemiological Studies Depression (CES-D; Radloff, 1977) scale is a measure of depression severity. This test consists of 20 items, rated on a 4-point Likert-type scale, on which respondents report the frequency of depressive symptoms (e.g. depressed mood, sleep/appetite disturbances, feelings of hopelessness, etc) over the previous week. Total scores on the CES-D range from 0-60, with higher scores signifying more severe symptomatology. The test-retest reliability of the CES-D total score is .57 (Radloff, 1977), and use of this measure has been validated in the older adult population (Beekman et al., 1997). The Multidimensional Anxiety Questionnaire (MAQ; Reynolds, 1999) is a measure of anxiety severity. This test consists of 40 items, rated on a 4-point Likert-type scale, on which respondents report the frequency of anxiety symptoms (e.g. feelings of panic, worry, difficulty concentrating, etc) over the previous month. Total scores on the MAQ range from 40-160, with higher scores representing more severe symptomatology. The test-retest reliability of the MAQ total score is .95 (Reynolds, 1999).

There is evidence to suggest that anxiety and depression are highly comorbid in older populations, particularly in those with physical illnesses (Lenze et al., 2000; Sheikh, 1991). Given this past finding, in conjunction with the fact that participants' scores on the CES-D and MAQ were highly correlated in the current sample ($r^2$=. 793 for entire sample, $r^2$ =. 703 for CKD, and $r^2$ =. 901 for Controls; all $p$'s < .01), we opted to derive a single index of 'psychological distress', as has been proposed by some researchers (Jorm, 2000). We derived this composite score by (1) transforming participants' raw scores on each test into T-scores (standardized on the control group's

respective mean score) and (2) computing the average of the two T-scores. All analyses examining psychological distress were based on this composite score only.

### *Demographic and Health Status*

Demographic information and clinical characteristics of participants were assessed with the Health Questionnaire. This self-report measure has demonstrated utility in past cognitive aging studies (Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Thornton & Raz, 2006; Thornton et al., in press). The demographic variables selected for inclusion in this study were age, gender, ethnicity, education and handedness. Clinical variables of interest included those conditions thought to be associated with increased cerebrovascular risk, e.g. history of hypertension, diabetes mellitus and hypercholesterolemia. Medications prescribed to treat these conditions (e.g. antihypertensives, insulin/oral hypoglycemic agents and anti-cholesterol agents) as well as those with known CNS effects (namely anti-depressants, benzodiazepines and opiates) were also recorded. For CKD participants, additional biological indices pertaining to metabolic integrity were obtained through medical chart review. CKD participants' most recent monthly GFR and hemoglobin levels were used to characterize the severity of renal functioning and anemia, respectively.

The Instrumental Activities of Daily Living (IADL; Lawton & Brody, 1969) provided an indication of participants' level of independent functioning. Scores on this test range from 0-8, with higher scores denoting greater independence.

## Procedure

Testing of participants was conducted between January 2003 and October 2005. Participants in both groups were administered a similar testing battery consisting of the

cognitive and psychological measures outlined above. However, initial evaluation of participants involved cognitive screening with the DRS-2 measure while additional measures were introduced into the battery at a later time (September 2003) to allow for a more comprehensive evaluation of neuropsychological functioning. Consequently, data for the DRS-2 measure are available for the entire sample (i.e. all 54 CKD and 42 control participants) whereas complete data for the CVLT-II and D-KEFS measures are available only for participants tested after September 2003. Of the total 54 CKD participants, 30 present with complete CVLT-II and D-KEFS data. The 30 CKD participants who were administered these additional neuropsychological tests did not differ from the 24 CKD participants without data on these measures, on age, education, vocabulary level and performance on the DRS-2 measures (see Appendix A). For controls, complete data for the CVLT-II and D-KEFS measures were available for 39 out of 42 participants. The testing battery was individually administered by formally trained research assistants according to standardized procedures. Administration time for the battery was approximately two hours and participants were remunerated for time and travel expenses. CKD participants were tested in a quiet testing room at the VGH Renal Clinic. Control participants were tested at the Human Neuropsychology lab at Simon Fraser University or at community locations (e.g. senior centers, library rooms) that met adequate testing standards (e.g. minimal noise, well-lit). Informed written consent was obtained from all participants and the study protocol was approved by Simon Fraser University's Office of Research Ethics and the University of British Columbia's Behavioural Research Ethics Board.

## Data Analyses

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) Version 14.0 for Windows. Two-tailed *p*-values were reported for all descriptive tests. An alpha level of .05 was used as the criterion for significance, and Bonferroni corrections were made where appropriate. The data were assessed for outliers, defined as data points 3 or more *SD*'s from their respective group mean, and corrected according to guidelines from Tabachnick and Fidell (2007), i.e. assigning an outlier a value that is one unit from the most extreme inlying (non-outlier) value in its distribution. In total, 13 outliers were identified and corrected for the 17 measures in this study (an average of less than 1 outlier per measure). Extreme deviations from normality (defined as skewness/kurtosis values above 1 or below –1) led to examination of transformed data. The DRS-2 Attention, Initiation-Perseveration, Conceptualization and Memory subscales were associated with negative skewness and data for these measures were transformed through reflect & square root or reflect & logarithmic transformations, as appropriate. The scaled scores (ss) for these subscales, relatively more normally distributed than the raw scores, were also analyzed. Given that results were consistent for all three types of scores, raw scores were reported for ease of interpretation. The Color-Word Interference and Psychological Distress measures were associated with positive skewness, which led to square root and logarithmic transformations, respectively. Given that results for the raw and transformed scores on both these measures were consistent for all analyses, raw scores were reported for ease of interpretation.

To compare the CKD and control groups on demographic, clinical and cognitive variables, we conducted independent-samples *t* tests for continuous data when homogeneity of variance was assumed and Welch's *t*-tests when homogeneity of

variance was not assumed. In addition, two-way ANOVA's with gender and group as fixed factors were conducted to compare performance on the DRS-2 measures due to unequal gender distribution for the sample of participants who present with data for these measures. Pearson's chi-square tests were conducted to compare groups on categorical data. Analyses of the bivariate relationships between cognitive and clinical variables of interest were conducted using Pearson *r* product-moment correlation coefficients. Sequential (hierarchical) regression was employed to examine the contribution of three variables (psychological distress, group and their interaction) in predicting cognitive functioning. In order to reduce multicollinearity with the interaction term, the continuous independent variable (psychological distress) was centered (i.e. converted to a deviation score) in the regression analyses (Tabachnick & Fidell, 2007).

Effect size estimates (Cohen's *d*), computed by subtracting the two group means and dividing by their pooled standard deviation, were reported to permit comparisons across measures and samples. By convention, effect sizes are defined as small when $d = .2$, medium when $d = .5$ and large when $d = .8$ (Cohen, 1992).

# RESULTS

## Part I: Global Cognition

### *Demographic Characteristics*

Information regarding the demographic characteristics of the 54 CKD and 42 control participants comprising this sample is presented in Table 1. The CKD and control groups were matched on age ($t(94) = 1.52$, $p = .13$), education ($t(94) = -1.66$, $p = .10$) and vocabulary level (ETS; $t(94) = -1.61$, $p = .11$). Also, there were no significant differences between groups on handedness ($\chi^2$ (2, $N = 96$) = 1.66, $p = .44$) or ethnicity ($\chi^2$ (2, $N = 96$) = 2.62, $p = .27$). However, there were significantly more females in the control group than in the CKD group ($\chi^2$ (1, $N = 96$) = 10.90, $p < .001$).

***Table 1:***
***Demographic Characteristics of CKD and Control Participants for Full Sample.***

| Demographic Characteristics | CKD (n=54) | Controls (n=42) | *p* |
|---|---|---|---|
| Age (mean ± SD) | 72.13 ± 8.71 | 69.14 ± 10.53 | ns |
| Education (mean ± SD) | 13.56 ± 2.94 | 14.48 ± 2.35 | ns |
| Vocabulary (mean ± SD) | 12.07 ± 3.48 | 13.13 ± 2.80 | ns |
| Female | 23 (42.6%) | 32 (76.2%) | <.001 |
| Right handedness | 49 (90.7%) | 39 (92.9%) | ns |
| Ethnicity | | | ns |
| Caucasian | 44 (81.5%) | 39 (92.9%) | |
| Asian | 7 (13.0%) | 2 (4.8%) | |
| Other | 3 (5.6%) | 1 (2.4%) | |

### *Clinical Characteristics*

Information regarding the clinical characteristics of participants is presented in Table 2. For the CKD group, the mean years of illness duration was 4.53 (*SD* = 5.53). In terms of parameters of metabolic functioning for this group, the mean GFR (ml/min/1.73m$^2$) was 21.15 (*SD* = 8.62) and the mean Hemoglobin concentration (g/L) was 124.39 (*SD* = 11.58). Compared to controls, the CKD group had significantly higher rates of all vascular risk factors evaluated in this study; they had higher prevalence of hypertension ($\chi^2$ (1, *N* = 96) = 28.29, $p < .001$), diabetes ($\chi^2$ (1, *N* = 96) = 17.23, $p < .001$) and hypercholesterolemia ($\chi^2$ (1, *N* = 96) = 5.18, $p < .05$). Accordingly, CKD participants were more likely to be on medications that treat vascular-related illnesses: anti-hypertensives ($\chi^2$ (1, *N* = 96) = 36.42, $p < .001$), anti-diabetic medications ($\chi^2$ (1, *N* = 96) = 13.83, $p < .001$) and anti-cholesterol agents ($\chi^2$ (1, *N* = 96) = 13.95, $p < .001$).

The difference between groups on reported levels of psychological distress was marginally significant ($t(91) = 2.00$, $p = .05$), with the CKD group associated with higher levels of distress. There were no significant differences between the groups on the use of anti-depressant ($\chi^2$ (1, *N* = 96) = .10, $p = .75$) or opiate ($\chi^2$ (1, *N* = 96) = 1.59, $p = .21$) medications. However, use of benzodiazepines was significantly higher in the CKD group compared to controls ($\chi^2$ (1, *N* = 96) = 4.98, $p < .05$).

The mean score on the IADL was 7.84 (*SD* = .44) for the CKD group (range: 7-8) and all controls obtained 8/8 on this measure. These scores are indicative of autonomous levels of functioning for participants in both groups of this study.

***Table 2:***
***Clinical Characteristics of CKD and Control Participants for Full Sample.***

| Clinical Characteristics | CKD (n=54) | Controls (n=42) | *p* |
|---|---|---|---|
| Duration of renal disease (years) | 4.53 ± 5.53 | n/a | - |
| GFR (ml/min/1.73m$^2$) | 21.15 ± 8.62 | n/a | - |
| Hemoglobin (g/L) | 124.39 ± 11.58 | n/a | - |
| Hypertension | 50 (92.6%) | 18 (42.9%) | <.001 |
| Diabetes mellitus | 18 (33.3%) | 0 (0%) | <.001 |
| Hypercholesterolemia | 22 (40.7%) | 8 (19.0%) | <.05 |
| Anti-hypertensives | 52 (96.3%) | 17 (40.5%) | <.001 |
| Anti-diabetic medications | 15 (27.8%) | 0 (0%) | <.001 |
| Oral agents | 8 (14.8%) | 0 (0%) | |
| Injectable agents | 9 (16.7%) | 0 (0%) | |
| Anti-cholesterol agents | 24 (44.4%) | 4 (9.5%) | <.001 |
| Benzodiazepines | 6 (11.1%) | 0 (0%) | <.05 |
| Opiates | 2 (3.7%) | 0 (0%) | ns |
| Anti-depressants | 3 (5.6%) | 3 (7.1%) | ns |
| Psychological Distress[a] | 53.38 ± 8.59 | 49.70 ± 9.00 | .05 |
| IADL (maximal score = 8) | 7.84 ± .44 | 8.00 ± 0 | - |

Note: a: Psychological Distress (T-score) = Average of anxiety (MAQ) and depression (CES-D) scores.

## *Global Cognitive Functioning*

As there was unequal gender distribution across groups in this sample (i.e. more females in the control group), 2-way ANOVAs were conducted with gender and group as fixed factors and the DRS-2 measures as dependent variables. The Construction

subscale, however, was not subjected to analysis because there was no variability in performance on this measure for the control group (all achieved the maximal score of 6) and CKD participants obtained scores of 5 or 6 (mean 5.96, *SD* = 1.91). In order to reduce the risk of Type I errors resulting from the multiple comparisons performed on the other subscale scores, a Bonferroni correction was made by adjusting the alpha level of .05 to .0125 (divided by the number of subscale tests for which analyses were conducted: 4). This alpha level was set as the new critical value for significance on the subscale measures.

Table 3 presents DRS-2 total and subscale performances for the CKD and control groups. Participants with CKD performed significantly worse than controls on a measure of global cognition (DRS-2 total score; ($F(1, 94) = 8.69$, $p < .005$, $d = -.71$). Analyses of the subscale scores revealed no group differences on the Attention ($F(1, 94) = 1.71$, $p = .20$, $d = .23$) and Memory subscales ($F(1, 94) = 1.55$, $p = .22$, $d = -.29$). Consistent with predictions, CKD participants performed significantly worse than controls on a measure of executive functioning, the Conceptualization subscale ($F(1, 94) = 11.21$, $p < .005$, $d = -.73$). While a significant group difference did not emerge for the other executive functioning task, the Initiation/Perseveration subscale ($F(1, 94) = 3.51$, $p = .06$, $d = -.50$), the strength of the magnitude of this difference was in the moderate range.

Gender did not emerge as a significant main effect for any of the DRS-2 measures: DRS-2 Total Score: ($F(1, 94) = 1.60$, $p = .21$); Attention subscale ($F(1, 94) = .23$, $p = .63$); Initiation/Perseveration subscale ($F(1, 94) = 1.74$, $p = .19$); Conceptualization subscale ($F(1, 94) = .04$, $p = .85$) and Memory subscale ($F(1, 94) = .66$, $p = .42$). Moreover, there were no significant Gender by Group interactions for any of the measures: DRS-2 Total Score: ($F(1, 94) = 1.53$, $p = .22$); Attention subscale ($F(1,$

94) = .62, $p$ = .43); Initiation/Perseveration subscale ($F$(1, 94) = .39, $p$ = .54); Conceptualization subscale ($F$(1, 94) = 1.17, $p$ = .28) and Memory subscale ($F$(1, 94) = 1.70, $p$ = .20).

***Table 3:***
***Descriptive Statistics for the DRS-2 Measures.***

| Cognitive Measures (maximal score) | CKD (n=54) (mean ± SD) | Controls (n=42) (mean ± SD) | *p* | *d* |
|---|---|---|---|---|
| DRS-2 Total Score (144) | 137.26 ± 4.78 | 140.12 ± 2.90 | <.005 | -.71 |
| Attention (37) | 36.30 ± .82 | 36.10 ± .96 | ns | .23 |
| Initiation/Perseveration (37) | 35.33 ± 2.80 | 36.48 ± 1.40 | .06 | -.50 |
| Construction (6) | 5.96 ± .19 | 6.00 ± 0 | - | - |
| Conceptualization (39) | 36.15 ± 2.27 | 37.60 ± 1.52 | <.005 | -.73 |
| Memory (25) | 23.56 ± 1.65 | 23.98 ± 1.18 | ns | -.29 |

Note: The significant findings reported above were also maintained when vocabulary (ETS) or education were added as covariates.

## *Rates of Cognitive Impairment*

Table 4 presents rates of cognitive impairment for the CKD group on the DRS-2 total and subscale scores. The percentage of participants considered to meet criteria for cognitive impairment on the DRS-2 total score was based on the recommended cutoff of ≤ 134 (van Gorp et al., 1999). As there are no established cutoff points for the subscales, the percentage of participants considered to meet criteria for cognitive impairment on these measures was based on a conventional cutoff point of scores falling 1.5 or more *SD*'s below the control mean (Tuokko, Frerichs, & Kristjansoon, 2001). As can be seen on Table 4, approximately 24% of CKD participants met criteria for global cognitive impairment (DRS-2 total score), whereas only 7% of controls (3 out

42 participants) met criteria for impaired global cognition. On the subscale scores, the largest performance differences were noted on the executive functioning measures, Initiation/Perseveration and Conceptualization subscales, for which rates of impairment were estimated at 27.78% and 37.04% respectively. On the Memory subscale, 22.20% of participants in the CKD group met criteria for impairment. Rates of impairment were lowest for the Attention and Construction subscales, with estimates at 0% and 3.70%, respectively.

***Table 4:***
***Rates of Cognitive Impairment on the DRS-2 Measures.***

| Cognitive Variables | CKD (n=54) Impaired: n (%) |
|---|---|
| DRS-2 Total Score[a] | 13 (24.07%) |
| Attention | 0 (0%) |
| Initiation/Perseveration | 15 (27.78%) |
| Construction | 2 (3.70%) |
| Conceptualization | 20 (37.04%) |
| Memory | 12 (22.20%) |

Note: % Impaired = percentage falling 1.5 or more *SD*'s below the control mean.
a: DRS-2 total score: % Impairment on this variable is based on an established cutoff point of ≤ 134 (van Gorp et al., 1999).

### *Psychological Distress: Potential Mediating Effects on DRS-2 Performance*

Pearson *r* correlation coefficients between psychological distress and performance on the DRS-2 measures for the CKD group are presented in Table 5. The association between psychological distress and cognitive performance did not reach statistical significance for any of the DRS-2 measures (all *p*'s > .05). However, it should

be noted that for the CKD group, there was a trend for better global cognitive functioning to be associated with higher levels of reported psychological distress.

***Table 5:***
***Correlations between Psychological Distress, Illness Parameters and Cognitive Performance for the CKD Group (n=54).***

| Cognitive Variables | Psychological Distress | GFR | Hemoglobin | Illness Duration |
|---|---|---|---|---|
| DRS-2 Total Score | .26 | .01 | .05 | .03 |
| Attention | .09 | .16 | .12 | .13 |
| Initiation/Perseveration | .23 | -.01 | .02 | .09 |
| Construction | .00 | .05 | .08 | .05 |
| Conceptualization | .08 | -.06 | .00 | -.02 |
| Memory | .27 | .07 | .01 | -.06 |

Note: *$p < .05$ (2-tailed).

To further examine the relative contributions of psychological distress, group (CKD vs. controls) and their interaction in predicting performance on the DRS-2 measures, we conducted a series of three-step hierarchical regressions, the results of which are presented in Table 6. The first step of the model included psychological distress (centered), the second, group (CKD vs. Controls) and the third included the interaction of these variables. The outcome variables of interest were the cognitive measures for which significant differences (or marginally significant differences) emerged between the groups (i.e. DRS-2 Total, Conceptualization and Initiation/Perseveration scores). As can be seen on Table 6, after controlling for psychological distress (which was not a significant predictor of performance for any of the DRS-2 measures) group emerged as a significant predictor for all three DRS-2 measures. Specifically, CKD was associated with worse performance on the three DRS-

2 measures. Group accounted for 13% of the variance in global cognition (DRS-2 total score), 12% of the variance in performance on the Conceptualization subscale and 7.5% of the variance in performance on the Initiation/Perseveration subscale. The interaction term of group by psychological distress was non-contributory in predicting performance on the cognitive measures ($R^2$ change = .02, .009 and .006 for the DRS-2 Total, Conceptualization and Initiation/Perseveration scores, respectively).

***Table 6:***
***Hierarchical Regression Results Predicting Performance on the DRS-2 Total, Conceptualization and Initiation/Perseveration Measures for the CKD and Control Participants (n=96).***

| Predictors | *B* | *SE* | *β* | *p* | $R^2$ |
|---|---|---|---|---|---|
| DRS-2 Total Score (Global Cognition) – Step 1 | | | | | |
| Psychological Distress | .04 | .05 | .09 | ns | .008 |
| DRS-2 Total Score (Global Cognition) – Step 2 | | | | | |
| Psychological Distress | .08 | .05 | .16 | ns | |
| Group (CKD/Controls) | 3.14 | .84 | .37 | <.001 | |
| $R^2$* | | | | | .137 |
| DRS-2 Conceptualization – Step 1 | | | | | |
| Psychological Distress | -.01 | .03 | -.05 | ns | .003 |
| DRS-2 Conceptualization – Step 2 | | | | | |
| Psychological Distress | .00 | .02 | .02 | ns | |
| Group (CKD/Controls) | 1.46 | .42 | .35 | .001 | |
| $R^2$* | | | | | .119 |
| DRS-2 Initiation/Perseveration – Step 1 | | | | | |
| Psychological Distress | .04 | .03 | .13 | ns | .017 |
| DRS-2 Initiation/Perseveration – Step 2 | | | | | |
| Psychological Distress | .05 | .03 | .19 | ns | |
| Group (CKD/Controls) | 1.32 | .48 | .28 | <.01 | |
| $R^2$* | | | | | .092 |

Note: * Step 3 did not result in a significant increase in $R^2$.

### *Metabolic Disturbances: Potential Mediating Effects on DRS-2 Performance*

None of the illness parameters investigated in this study (GFR, hemoglobin and illness duration) were significantly correlated with performance on the DRS-2 measures (all $p$'s > .20). Table 5 presents Pearson $r$ correlations between illness parameters and performance on the DRS-2 measures for the CKD group.

### *Medication Usage & Subclinical Dementia: Potential Mediating Effects on DRS-2 Performance*

Benzodiazepines were the only class of psychopharmacological agents examined for which usage differed significantly between groups ($\chi^2$ (1, $N$ = 96) = 4.98, $p$ < .05). In this sample, 6 CKD participants and none of the controls were on Benzodiazepines. Given that Benzodiazepines have known CNS effects and have been linked with cognitive dysfunction (Barker, Greenwood, Jackson, & Crowe, 2004), it was of interest to investigate the possible role of this medication in contributing to the cognitive differences observed between groups. Furthermore, given the higher rate of impairment in global cognition (DRS-2 total score) present in the CKD group compared to controls, it was of interest to determine whether the observed significant differences between groups would be maintained with removal of individuals with impaired global cognition (i.e. possible subclinical dementia). Toward these ends, we re-examined performance between groups on the DRS-2 measures with exclusion of participants on Benzodiazepines and those meeting criteria for impaired global cognition (DRS-2 total score $\leq$ 134) in both groups.

The CKD (N= 36) and control (N=39) groups in this sample were matched on age ($t$(73) = 1.06, $p$ = .29), education ($t$(73) = -1.04, $p$ = .30), vocabulary level (ETS; $t$(73) = -.83, $p$ = .41), handedness ($\chi^2$ (2, $N$ = 75) = 1.21, $p$ = .55) and ethnicity ($\chi^2$ (2, $N$ = 75) =

2.26, $p$ = .32). However, as with the above sample there were significantly more females in the control group than in the CKD group ($\chi^2$ (1, $N$ = 75) = 4.75, $p$ < .05). Analyses indicated that the previously significant finding of worse performance associated with the CKD group on the DRS-2 Conceptualization subscale was maintained ($F$(1, 73) = 8.18, $p$ < .01, $d$ = -.68) with removal of participants on Benzodiazepines and of those with impaired global cognition. In fact, the largest effect size was observed with this measure. The difference in performance between the groups on the DRS-2 total raw score did not reach statistical significance which is expected given exclusion of individuals with impaired global cognition, of which there were more CKD participants ($F$(1, 73) = 2.17, $p$ = .15, $d$ = -.44). Nonetheless, the magnitude of this difference was in the moderate range. Furthermore, a marginally significant group difference emerged on the Attention subscale, with CKD associated with better performance ($F$(1, 73) = 4.12, $p$ = .05, $d$ = .43). Differences between groups on the other subscales remained non-significant: Initiation/Perseveration ($F$(1, 73) = .07, $p$ = .79, $d$ = -.17) and Memory ($F$(1, 73) = .02, $p$ = .88, $d$ = -.06). As with the larger sample, there were no significant gender main effects or significant group by gender interaction effects for any of the measures (all $p$'s > .05). Appendix C provides descriptive statistics on the DRS-2 measures for this sample.

## Part II: Verbal Memory & Executive Functioning

### *Demographic Characteristics*

As described above, complete data on the verbal memory and executive functioning measures were available for 30 CKD and 39 control participants. Information regarding the demographic characteristics of participants comprising this sample is

presented in Table 7. The CKD and control groups were matched on age ($t(67) = .96$, $p = .34$), education ($t(67) = -1.63$, $p = .11$) and vocabulary level (ETS score; ($t(67) = -1.96$, $p = .054$). Moreover, there were no significant differences between groups on gender ($\chi^2$ (2, $N = 69$) = 2.29, $p = .13$), handedness ($\chi^2$ (2, $N = 69$) = 1.46, $p = .48$) or ethnicity ($\chi^2$ (2, $N = 69$) = 2.47, $p = .29$) in this sample.

***Table 7:***
***Demographic Characteristics of CKD and Control Participants for Sub-Sample.***

| Demographic Characteristics | CKD (n=30) | Controls (n=39) | *p* |
|---|---|---|---|
| Age (mean ± SD) | 70.73 ± 8.08 | 68.59 ± 9.94 | ns |
| Education (mean ± SD) | 13.50 ± 3.07 | 14.56 ± 2.36 | ns |
| Vocabulary (mean ± SD) | 11.68 ± 3.96 | 13.29 ± 2.83 | ns |
| Female | 18 (60.0%) | 30 (76.9%) | ns |
| Right handedness | 26 (86.7%) | 36 (92.3%) | ns |
| Ethnicity | | | ns |
| Caucasian | 24 (80.0%) | 36 (92.3%) | |
| Asian | 3 (10.0%) | 2 (5.1%) | |
| Other | 3 (10.0%) | 1 (2.6%) | |

## *Clinical Characteristics*

Information regarding the clinical characteristics of participants in this sample is presented in Table 8. For the CKD group, the mean years of illness duration was 3.45 ($SD = 3.62$), the mean GFR (ml/min/1.73m$^2$) was 23.75 ($SD = 7.86$) and the mean Hemoglobin concentration (g/L) was 124.00 ($SD = 13.15$). As with the complete sample, the CKD group had significantly higher rates of vascular risk factors including

hypertension ($\chi^2$ (1, $N$ = 69) = 18.50, $p$ < .001), diabetes ($\chi^2$ (1, $N$ = 69) = 13.46, $p$ < .001) and hypercholesterolemia ($\chi^2$ (1, $N$ = 69) = 6.61, $p$ < .05). CKD participants were also more likely to be on medications to treat these illnesses: anti-hypertensives ($\chi^2$ (1, $N$ = 69) = 23.14, $p$ < .001), anti-diabetic medications ($\chi^2$ (1, $N$ = 69) = 11.76, $p$ < .005) and anti-cholesterol agents ($\chi^2$ (1, $N$ = 69) = 7.00, $p$ < .005).

The difference between groups on reported levels of psychological distress was marginally significant ($t$(65) = 1.85, $p$ = .07), with the CKD group associated with higher levels of distress. There were no significant differences between the groups on the use of anti-depressant ($\chi^2$ (1, $N$ = 69) = .03, $p$ = .87) or opiate ($\chi^2$ (1, $N$ = 69) = 2.68, $p$ = .10) medications. However, as with the full sample, use of benzodiazepines was significantly higher in the CKD group compared to controls ($\chi^2$ (1, $N$ = 69) = 5.52, $p$ < .05).

***Table 8:***
***Clinical Characteristics of CKD and Control Participants for Sub-Sample.***

| Clinical Characteristics | CKD (n=30) | Controls (n=39) | *p* |
|---|---|---|---|
| Duration of renal disease (years) | 3.45 ± 3.62 | n/a | - |
| GFR (ml/min/1.73m$^2$) | 23.75 ± 7.86 | n/a | - |
| Hemoglobin (g/L) | 124.00 ± 13.15 | n/a | - |
| Hypertension | 28 (93.3%) | 17 (43.6%) | <.001 |
| Diabetes mellitus | 9 (30.0%) | 0 (0%) | <.001 |
| Hypercholesterolemia | 14 (46.7%) | 7 (17.9%) | <.05 |
| Anti-hypertensives | 29 (96.7%) | 16 (41.0%) | <.001 |
| Anti-diabetic medications | 8 (26.7%) | 0 (0%) | <.005 |
| Oral agents | 5 (16.7%) | 0 (0%) | |
| Injectable agents | 5 (16.7%) | 0 (0%) | |
| Anti-cholesterol agents | 14 (46.7%) | 4 (10.3%) | <.005 |
| Benzodiazepines | 4 (13.3%) | 0 (0%) | <.05 |
| Opiates | 2 (6.7%) | 0 (0%) | ns |
| Anti-depressants | 2 (6.7%) | 3 (7.7%) | ns |
| Psychological Distress[a] | 53.37 ± 7.11 | 49.67 ± 8.89 | .07 |

Note: a: Psychological Distress (T-score) = Average of anxiety (MAQ) and depression (CES-D) scores.

### *Verbal Memory*

Participants with CKD performed significantly worse than controls on a measure of auditory attention (CVLT-II Trial 1; ($t(67) = -3.16$, $p < .005$, $d = -.77$) and on a measure of learning across repeated trials (CVLT-II Trials 1-5; ($t(67) = -4.18$, $p < .001$, $d = -1.01$). The CKD and control groups, however, did not significantly differ in their ability to retain

information following a delay after baseline levels of recall were accounted for (CVLT-II retention: ($t(67) = -.52$, $p = .61$, $d = -.13$). Appendix B presents performance of groups on the two trials (Trial 5 and Long-Delay Free Recall) that comprised the Retention scores.

Further examination of learning parameters revealed that CKD participants obtained significantly lower scores on their ability to organize information in related 'chunks' (CVLT-II semantic clustering; ($t(59.48) = -2.85$, $p < .01$, $d = -.64$) but did not differ significantly from controls on the number of intrusion errors they committed during recall (CVLT-II Intrusion errors; $t(67) = .23$, $p = .82$, $d = -.06$). Of note, corrections for multiple analyses were not made for the CVLT-II measures because they were conceptualized as representing distinct theoretical constructs. However, an adjustment set at alpha level of .01 for the 5 analyses conducted would not have negated any of the significant results reported above. Table 9 presents means and *SD*'s on the CVLT-II measures for the CKD and control groups.

### *Executive Functioning*

Consistent with predictions, the CKD group performed significantly worse than controls on executive functioning as measured by the composite contrast score of the three D-KEFS tests ($t$ (67) = -2.94, $p < .01$, $d = -.71$). To explore the possibility of differential performance on the three tests, secondary analyses were undertaken to compare groups on each contrast score. To control the family-wise error rate, a Bonferroni correction was made by adjusting the alpha level from .05 to .017 (divided by the number of tests: 3). Analyses revealed that the CKD group performed significantly worse than controls on a measure of cognitive inhibition (D-KEFS Color-Word Interference test contrast score ($t(67) = 3.03$, $p < .005$, $d = -.74$). While group differences

on the two measures of cognitive shifting did not reach statistical significance (Verbal Fluency test contrast score ($t(67) = -.36$, $p = .72$, $d = .09$); Trail Making test contrast score ($t(67) = 2.03$, $p = .046$, $d = -.49$)), the magnitude of the difference on one of these measures (Trail Making test) was noted to be in the moderate range. Table 9 presents performance of the CKD and control groups on the D-KEFS measures. Appendix B presents performance of groups on the D-KEFS subtests that comprised the contrast scores. Appendix D presents the inter-correlations among the cognitive variables that were examined in this study.

***Table 9:***
***Descriptive Statistics for the CVLT-II and D-KEFS Measures.***

| Cognitive measures (maximal score) | CKD (n=30) mean ± SD | Controls (n=30) mean ± SD | *p* | *d* |
|---|---|---|---|---|
| CVLT-II Trial 1 (16) | 4.57 ± 1.57 | 6.00 ± 2.06 | <.005 | -.77 |
| CVLT-II Trials 1-5 (80) | 38.23 ± 8.49 | 47.64 ± 9.83 | <.001 | -1.01 |
| CVLT-II Retention (z-score) | -.09 ± .66 | .00 ± .76 | ns | -.13 |
| CVLT-II Semantic clustering | .34 ± .88 | 1.24 ± 1.70 | <.01 | -.64 |
| CVLT-II Intrusion errors* | 4.57 ± 4.66 | 4.33 ± 3.72 | ns | -.06 |
| D-KEFS Composite Contrast Score (z-score) | -.46 ± .65 | .00 ± .65 | <.01 | -.71 |
| D-KEFS Trail Making (Contrast Score)* | 76.67 ± 36.33 | 59.54 ± 33.52 | .05 | -.49 |
| D-KEFS Verbal Fluency (Contrast Score)* | 5.58 ± 4.13 | 5.94 ± 4.07 | ns | .09 |
| D-KEFS Color-Word Interference (Contrast Score)* | 39.27 ± 18.07 | 28.62 ± 10.99 | <.005 | -.74 |

Note: *: For these measures, higher scores = worse performance. The significant findings reported above were also maintained when vocabulary (ETS) or education were added as covariates.

### *Rates of Cognitive Impairment*

Table 10 presents rates of cognitive impairment for the CKD group. As there are no established cutoff points for the CVLT-II and D-KEFS measures, the percentage of participants considered to meet criteria for cognitive impairment was based on a conventional cutoff point of scores falling 1.5 or more *SD*'s below or above the control mean (Tuokko et al., 2001). Specifically, for measures where higher scores denoted better performance, scores falling 1.5 or more *SD's* below the control mean were classified as being in the impaired range. And for those measures where higher scores denoted worse performance, scores falling 1.5 or more *SD's* above the control mean were classified as being in the impaired range.

As can be seen on Table 10, 10% of CKD participants were impaired on a measure of auditory attention (CVLT-II Trial 1) and 26.67% showed impaired learning ability following repeated presentation of information (CVLT-II Trials 1-5). However, after accounting for each group's baseline level of recall, only 2.56% of CKD participants demonstrated impaired retention ability. None of the CKD participants met criteria for impairment on their ability to organize information according to categories (CVLT-II Semantic Clustering). However, 13.33% of CKD participants were impaired on the number of intrusion errors committed during recall (CVLT-II intrusion errors). In the area of executive functioning, 26.67% of CKD participants demonstrated impairment as assessed by the D-KEFS composite contrast score. Analyses of the distinct D-KEFS measures revealed rates of impairment ranging from 3.33% (D-KEFS Verbal Fluency Test) to 16.67% (D-KEFS Trail Making test) on measures of cognitive shifting. On the

other hand, 26.67% of CKD participants met criteria for impairment on a measure of cognitive inhibition (D-KEFS Color-Word Interference test).

***Table 10:***
***Rates of Cognitive Impairment on the CVLT-II and D-KEFS Measures.***

| Cognitive Measures | CKD (n=30) Impaired: n (%) |
|---|---|
| CVLT-II Trial 1 (Auditory Attention) | 3 (10.00%) |
| CVLT-II Trials 1-5 (Learning) | 8 (26.67%) |
| CVLT-II Retention | 0 (0%) |
| CVLT-II Semantic clustering | 0 (0%) |
| CVLT-II Intrusion errors* | 4 (13.33%) |
| D-KEFS Composite contrast score | 8 (26.67%) |
| D-KEFS Trail Making Test (contrast score)* | 5 (16.67%) |
| D-KEFS Verbal Fluency Test (contrast score)* | 1 (3.33%) |
| D-KEFS Color-Word Interference Test (contrast score)* | 8 (26.67%) |

Note: % Impaired = percentage falling 1.5 or more *SD*'s below the mean (*M*) of controls. *However, for these measures, higher mean scores denote worse performance thus % impaired = percentage falling 1.5 or more *SD*'s above the mean (M) of controls.

## *Psychological Distress: Potential Mediating Effects on Verbal Memory and Executive Functioning*

Pearson *r* correlations between psychological distress and cognitive variables for the CKD group are presented in Table 11. Psychological distress was significantly correlated with performance on the cognitive inhibition task (D-KEFS Color-Word Interference test). Of note, the direction of this relationship was negative (Pearson $r = -.47$), as a higher level of psychological distress was associated with shorter completion time on this task (i.e. better performance on cognitive inhibition). It was noted that this

relationship may reflect the finding that better global cognition was also marginally associated with increased reporting of psychological distress (Pearson $r$ = .26, see Table 5). Indeed, after controlling for global cognition (DRS-2 total score) through partial correlation, the relationship between psychological distress and cognitive inhibition was reduced to non-significance ($pr$ = -.34). None of the other verbal memory and executive functioning measures were significantly correlated with psychological distress in the CKD group.

***Table 11:***
***Correlations between Psychological Distress, Illness Parameters and Cognitive Performance for the CKD Group (n=30).***

| Cognitive Measures | Psychological Distress | GFR | Hemoglobin | Illness Duration |
|---|---|---|---|---|
| CVLT-II Trial 1 (Auditory Attn.) | .22 | .04 | -.33 | .13 |
| CVLT-II Trials 1-5 (Learning) | .12 | .02 | -.25 | .02 |
| CVLT-II Retention | -.14 | -.07 | .00 | .08 |
| CVLT-II Semantic Clustering | .30 | .32 | -.12 | -.30 |
| CVLT-II Intrusion errors | -.18 | -.01 | .08 | .29 |
| D-KEFS Composite score | .23 | -.02 | -.11 | .00 |
| D-KEFS Trail Making Test | .00 | .23 | .25 | -.09 |
| D-KEFS Verbal Fluency Test | .31 | .22 | -.11 | -.20 |
| D-KEFS Color-Word Interference Test | -.47** | -.27 | .04 | .18 |

Note: * $p < .05$ level (2-tailed); ** $p < .01$ level (2-tailed).

As with the full sample, to further examine the relative contributions of psychological distress, group (CKD vs. controls) and their interaction in predicting performance on the verbal memory and executive functioning measures, we conducted

a series of three-step hierarchical regressions, the results of which are presented in Table 12. The first step of the model included psychological distress (centered), the second, group (CKD vs. Controls), and the third included the interaction of these variables. The outcome variables of interest were the verbal memory and executive functioning measures for which significant differences emerged between the groups. For verbal memory, these measures were: CVLT-II Trial 1, CVLT-II Trials 1-5, CVLT-II Semantic Clustering, and for executive functioning, these measures were: the D-KEFS Composite contrast score and the D-KEFS Color-Word Interference contrast score.

As can be seen on Table 12, after controlling for psychological distress (which was not a significant predictor of performance for any of the verbal memory measures) group emerged as a significant predictor for all three CVLT-II measures. Specifically, CKD was associated with poor performance on all these measures and predicted 12% of the variance in auditory attention (CVLT-II Trial 1), 20% of the variance in recall of information across repeated trials (CVLT-II Trials 1-5) and 10% of the variance in the ability to strategically organize information (CVLT-II Semantic Clustering). The interaction term of group by psychological distress did not make a significant contribution in predicting performance on the verbal memory measures ($R^2$ change = .02, .01 and .01 for the CVLT-II Trial 1, Trials 1-5 and Semantic Clustering, respectively; all $p$'s > .05).

After controlling for psychological distress (which was not a significant predictor), CKD was associated with worse performance on overall executive functioning (D-KEFS Composite score), accounting for 12% of the variance in performance. The interaction term of group by psychological distress was not a significant predictor of overall executive functioning ($R^2$ change = .01).

With respect to the D-KEFS Color-Word Interference task, initially results indicated that elevated psychological distress and CKD were associated with worse

performance in cognitive inhibition. In addition, results suggested that performance decrements on this task were differentially exacerbated in CKD participants with lower levels of psychological distress (see Table 12). However, given the above reported finding that global cognition may, in part, be mediating the relationship between psychological distress and cognitive inhibition, we re-examined the predictive utility of group, psychological distress and their interaction in accounting for differences in cognitive inhibition after controlling for global cognition. Indeed, after controlling for this variable, only CKD emerged as a significant predictor of poor performance on the D-KEFS Color-Word Interference task, accounting for 6% of the variance in performance. Elevated psychological distress was only marginally associated with better performance on this measure ($p$ = .051) and the interaction term of group by psychological distress was non-contributory ($R^2$ change = .02, $p$ > .10).

***Table 12:***
***Hierarchical Regression Results Predicting Verbal Memory and Executive Functioning Performance for the CKD and Control Participants (n=69).***

| Predictors | *B* | *SE* | *β* | *p* | $R^2$ |
|---|---|---|---|---|---|
| CVLT-II Trial 1 (Auditory Attention) – Step 1 | | | | | |
| Psychological Distress | -.02 | .03 | -.09 | ns | .007 |
| CVLT-II Trial 1 (Auditory Attention) – Step 2 | | | | | |
| Psychological Distress | .00 | .03 | .00 | ns | |
| Group (CKD/Controls) | 1.42 | .47 | .36 | <.005 | |
| $R^2$* | | | | | .130 |
| CVLT-II Trials 1-5 (Verbal Learning) – Step 1 | | | | | |
| Psychological Distress | -.10 | .15 | -.08 | ns | .007 |
| CVLT-II Trials 1-5 (Verbal Learning) – Step 2 | | | | | |
| Psychological Distress | .03 | .14 | .03 | ns | |
| Group (CKD/Controls) | 9.53 | 2.33 | .46 | <.001 | |
| $R^2$* | | | | | .207 |
| CVLT-II Semantic Clustering – Step 1 | | | | | |
| Psychological Distress | .00 | .02 | .01 | ns | .00 |

| Predictors | *B* | *SE* | *β* | *p* | $R^2$ |
|---|---|---|---|---|---|
| CVLT-II Semantic Clustering – Step 2 | | | | | |
| Psychological Distress | .01 | .02 | .08 | ns | |
| Group (CKD/Controls) | .96 | .35 | .33 | <.01 | |
| $R^2$* | | | | | .10 |
| D-KEFS Composite Contrast Score – Step 1 | | | | | |
| Psychological Distress | .002 | .01 | .03 | ns | .001 |
| D-KEFS Composite Contrast Score – Step 2 | | | | | |
| Psychological Distress | .01 | .01 | .11 | ns | |
| Group (CKD/Controls) | .50 | .16 | .36 | <.005 | |
| $R^2$* | | | | | .125 |
| D-KEFS Color-Word Interference (Contrast Score) – Step 1 | | | | | |
| Psychological Distress | -.36 | .23 | -.19 | ns | .04 |
| D-KEFS Color-Word Interference (Contrast Score) – Step 2 | | | | | |
| Psychological Distress | -.53 | .21 | -.28 | .02 | |
| Group (CKD/Controls) | -12.55 | 3.48 | -.41 | .001 | |
| $R^2$* | | | | | .20 |
| D-KEFS Color-Word Interference (Contrast Score) – Step 3 | | | | | |
| Psychological Distress | -1.20 | .35 | -.64 | .001 | |
| Group (CKD/Controls) | -13.33 | 3.38 | -.43 | <.001 | |
| Group x Psyc. Distress | 1.02 | .43 | .44 | .02 | |
| $R^2$ | | | | | .26 |

Note: * Step 3 did not result in a significant increase in $R^2$.

## *Metabolic Disturbances: Potential Mediating Effects on Verbal Memory and Executive Functioning*

Table 11 presents Pearson *r* correlations between illness parameters and cognitive variables for the CKD group. None of the illness parameters investigated in this study (GFR, hemoglobin and illness duration) were significantly correlated with performance on the verbal memory and executive functioning measures (all *p*'s > .05).

### *Medication Usage & Subclinical Dementia: Potential Mediating Effects on Verbal Memory and Executive Functioning*

As with the full sample, for reasons described above, we re-examined performance between groups on the verbal memory and executive functioning measures with exclusion of participants on Benzodiazepines (4 CKD participants) and those meeting criteria for impaired global cognition (DRS-2 total score $\leq$ 134) in both groups. The CKD (N= 22) and control (N=37) groups comprising this sub-sample were matched on age ($t(57) = .50$, $p = .62$), education ($t(57) = -1.40$, $p = .17$), vocabulary level (ETS; $t(57) = -.79$, $p = .44$), gender ($\chi^2$ (1, $N = 59$) = .39, $p = .53$), handedness ($\chi^2$ (2, $N = 59$) = .02, $p = .90$) and ethnicity ($\chi^2$ (2, $N = 59$) = 1.54, $p = .46$).

Analyses revealed that all previously reported significant and non-significant findings between groups on the verbal memory and executive functioning measures were maintained with removal of these participants, with Bonferroni corrections applied as appropriate: CVLT-II Trial 1: ($t(57) = -2.43$, $p < .05$, $d = -.65$); CVLT-II Trials 1-5: ($t(57) = -2.92$, $p < .01$, $d = -.79$; CVLT-II retention: ($t(57) = -1.28$, $p = .21$, $d = -.35$); CVLT-II semantic clustering; ($t(56.62) = -2.00$, $p = .05$, $d = -.47$); CVLT-II Intrusion errors; ($t(57) = .46$, $p = .65$, $d = .12$); D-KEFS Composite contrast score ($t(57) = -2.31$, $p < .05$, $d = -.62$); D-KEFS Trail Making contrast score ($t(57) = 1.58$, $p = .12$, $d = .42$); D-KEFS Verbal Fluency contrast score($t(57) = -.09$, $p = .93$, $d = -.02$) and D-KEFS Color-Word Interference contrast score ($t(57) = 2.53$, $p = .01$, $d = -.68$). Appendix C provides descriptive statistics on the CVLT-II and D-KEFS measures for this sample.

# DISCUSSION

Despite evidence from recent studies suggesting that CKD is associated with higher rates of cognitive impairment compared to the general population and that increasing age in CKD confers an added risk for the development of dementia (Kurella et al., 2004; Seliger et al., 2004; Thornton et al., in press), the nature and scope of cognitive impairment in this population have yet to be established. Moreover, whether cognitive dysfunction in CKD is a result of renal disease factors (i.e. metabolic disturbances) or due to the effects of other co-morbid conditions associated with this illness is poorly understood. The aim of the current study was to better characterize the neuropsychological functioning of older adults with CKD and to examine the role of potential mediators and/or moderators that may compromise cognitive functioning in this population, such as elevated psychological distress, metabolic disturbances, differences in medication usage with CNS effects and presence of subclinical dementia. An additional goal of this study was to address some of the limitations in previous research by comparing the cognitive performance of older adults with CKD to age and education matched healthy controls and by examining cognitive processes that may be accounting for the previously reported deficits in memory and executive functioning.

Results from the current study are consistent with previous findings suggesting that CKD is associated with significant cognitive impairment (Kurella, Chertow, et al., 2005; Kurella et al., 2004; Kurella, Yaffe, et al., 2005; Thornton et al., in press). Although individuals with histories of dementia were excluded from this study and all participants were rated as functionally independent on the IADL, older adults with CKD nonetheless presented with lowered global cognitive functioning, as assessed by the DRS-2 total score, compared to controls. Moreover, the difference in global cognition between

groups was approximating a large magnitude ($d$ = -.71; Cohen, 1992). Further comparison between groups on distinct cognitive domains (DRS-2 subscales) revealed some dissociation in deficits as the largest performance differences were observed on the executive functioning measures (Conceptualization and Initiation/Perseveration subscales), with CKD associated with worse performance on these abilities.

In the current study, whereas only 7% of controls met criteria for global cognitive impairment, this was the case for nearly one quarter of participants in the CKD group. The rate of global impairment for the CKD group in this study was higher than in a recent study reporting a 15% rate, as determined by scores of < 80 on the 3MS, in a sample of 80 CKD participants (Kurella et al., 2004). The discrepancy in rates of impairment between studies may be explained by differences in the sensitivity of the measures employed. Use of a cut-off point of $\leq$ 134 on the DRS-2 total score, as adopted in the present study, is associated with 93% sensitivity in detecting dementia (van Gorp et al., 1999), compared to 88% sensitivity for the 3MS with the standard cut-off point of $\leq$ 77 (Bland & Newman, 2001). Furthermore, given that poor performance was most pronounced on executive functioning indices for the CKD group, it may be that screening measures that include evaluation of these functions, as in the DRS-2, are more discerning at detecting overall impairment in this population.

Additionally, differences in the demographic characteristics of participants between studies may have contributed to the variability in rates of global impairment. The study by Kurella et al. (2004) comprised both younger and older adults, with the age of CKD participants ranging from 24-92 years and the mean age at 64.2 years ($SD$ = 14.2). In contrast, consistent with the goals of this study, inclusion of participants was limited to those adults above age 55 years and thus, the average age of CKD participants was relatively higher, at 72.13 years ($SD$ = 8.71). Given previous findings

suggesting that increasing age in CKD is associated with elevated risk for developing dementia (Seliger et al., 2004), it is not unexpected that the prevalence of global cognitive impairment would be higher in a sample consisting mostly of older adults with CKD.

With respect to verbal learning and memory, older adults with CKD exhibited significant deficits in their auditory attention as well as in their ability to learn and recall verbal information after repeated presentations, compared to controls. Moreover, the magnitude of the difference in performance between groups was large for these abilities ($d$ = -.77 and -1.01, respectively). Previous research studies have reported that CKD is associated with deficits in memory as indexed by measures of delayed recall (e.g. CVLT-II Long-delay free recall; Kurella et al., 2004; Thornton et al., in press). However, past studies have not evaluated whether poor performance on delayed memory measures reflects true decrements in CKD participants' recall over time or rather differences in baseline levels of recall between groups. This point is particularly relevant in light of the current finding of decreased levels of initial learning and recall associated with the CKD group. To better address this question, we adopted a more nuanced approach to examining delayed memory in the current study by controlling for participants' baseline levels of recall. Our findings indicate that, after accounting for baseline levels of recall, older adults with CKD evidence comparable rates of memory retention relative to their healthy peers.

Examination of the qualitative processes involved in learning and memory revealed that older adults with CKD demonstrated significant deficits in their ability to utilize memory strategies during learning of information (i.e. spontaneously organize information according to semantic categories), however, they did not differ from controls in their susceptibility to interference during recall as evidenced by comparable rates of

intrusion errors between groups. This latter finding is notable as some studies have reported that individuals with frontal lobe lesions and executive dysfunction are susceptible to increased intrusion errors during recall tasks (Baldo, Delis, et al., 2002; Baldo & Shimamura, 2002). There is also research, however, linking increased rates of intrusion errors to AD and memory impairment (Delis, Massman, Butters, & Salmon, 1991; Fox, Olin, Erblich, Ippen, & Schneider, 1998). Interestingly, research comparing memory performance in AD to subtypes of vascular dementia has found that increased error rates on memory tasks are linked to dementias with cortical pathology, independent of diagnostic etiology (Vanderploeg et al., 2001). That is, both AD and cortical vascular dementia were found to be associated with increased susceptibility to intrusions while subcortical vascular dementia was not (Vanderploeg et al., 2001). Similarly, within vascular dementia, intrusion errors on recall tasks have been found to be significantly correlated with greater cortical atrophy (Lafosse et al., 1997). Thus, perhaps the failure to find significant differences between groups on intrusion errors reflects the composition of the CKD group in the present study, which included individuals free of histories of clinical stroke and, presumably, other neurological diseases with cortical involvement.

Overall, the current results on verbal learning and memory extend previous findings by suggesting that the pattern of memory impairment observed in older adults with CKD does not appear to be consistent with an amnestic presentation characterized by rapid forgetting, but rather that memory problems in this population may be related to deficits in attention and executive functioning, such as the ability to organize information in ways that enhance learning and recall.

In terms of executive functioning, older adults with CKD demonstrated significant deficits in these abilities as indicated by worse performance on the D-KEFS composite

executive functioning score. In this study, approximately 27% of older adults with CKD met criteria for impairment on this composite measure. Also, the difference in overall executive functioning between groups was nearing a large magnitude ($d$ = -.71). More detailed analysis of performance on individual executive functioning measures revealed that compared to controls, older adults with CKD exhibited significantly worse performance in response inhibition (Color-Word Interference contrast score) whereas differences between groups in mental set shifting/switching were somewhat mixed. Specifically, a marginally significant finding emerged on one measure of cognitive switching (Trail Making contrast score), which was associated with a moderate effect size ($d$ = -.49) and worse performance for the CKD group. On the other hand, no significant group difference emerged on the other cognitive switching measure (Verbal Fluency contrast score), which was associated with a small effect size ($d$ = .09).

One potential explanation for the finding of a significant group difference, favouring controls, on cognitive response inhibition but not on measures of cognitive set shifting is that this dissociation in performance reflects differences in the neuroanatomical underpinnings of these functions. Although we did not directly examine brain functioning in this study, it is interesting to note that these two types of executive functions are thought to be mediated by different neuroanatomical subregions of the prefrontal cortex (Tekin & Cummings, 2002). The anterior cingulate cortex (ACC), for instance, is thought to mediate inhibition of response, whereas the dorsolateral prefrontal cortex (DLPFC) is thought to be involved in cognitive set shifting (Tekin & Cummings, 2002). The DLPFC, however, is also thought to be involved in the regulation of other executive functions, such as new learning, abstract reasoning, response generation (i.e. fluency) and the ability to form organizational strategies (Tekin & Cummings, 2002). Thus, the possible explanation that CKD preferentially disrupts ACC

functions (i.e. response inhibition) while relatively sparing DLPFC functions (i.e. cognitive switching) does not appear to be substantiated in this study as evidenced by the equally robust findings linking CKD to worse performance on other DLPFC functions, e.g. on measures of abstract reasoning (i.e. DRS-2 Conceptualization subscale), new learning (i.e. CVLT-II learning) and formation of organizational strategies (i.e. CVLT-II semantic clustering). Moreover, there is no evidence based on extant literature suggesting that either CKD or its associated comorbid conditions (e.g. vascular diseases, depression, etc) show specificity for the disruption of executive functions mediated by the ACC over other executive functions. In fact, there is research to show that age-related differences in cognitive performance are pronounced on tasks with DLPFC involvement (MacPherson, Phillips, & Della Sala, 2002) and that white matter pathology in the DLPFC is linked to depression in older age (Thomas et al., 2003).

Given that performance between groups on one of the cognitive switching measures was associated with a moderate effect size yet only marginally significant, another possible explanation for failure to find a significant difference may be a statistical power limitation. Although we had sufficient power to detect a large effect size in this study ($d$ = .80; Cohen, 1992), detecting a medium effect size with 80% power at .05 significance level would have required 64 participants in each group. As a result, it is possible that with a larger sample size, a statistically significant difference between the CKD and control groups on the D-KEFS Trail Making contrast score would have been detected.

As for the lack of significant finding between groups on the Verbal Fluency contrast score, it is notable that performance on the baseline condition (Category Fluency) comprising this contrast score is also thought to rely on frontally-mediated processes (e.g. strategic retrieval) (Baldo & Shimamura, 1998; Delis et al., 2001) and

has been shown to be associated with age-related decline (Brickman et al., 2005). Thus, an important consideration of these results is that while older adults with CKD may not be evidencing difficulties in cognitive switching above and beyond their difficulties in fluency, they may nonetheless be presenting with problems in cognitive switching. Examination of group performances on this task (see Appendix B) shows some support for this possibility as the category switching condition was associated with a moderate effect size ($d$ = -.55), with the CKD group performing worse than controls.

Besides sample size, a related factor that may have affected power to detect a significant finding is the reliability of the measures. It may not be a coincidence that of the three D-KEFS measures examined, the one for which significant group differences emerged, the Color-Word Interference test, also presented with the best reliability for the individual measures that comprised its contrast score ($r^2$ = .75 and .76). On the other hand, both the Verbal Fluency and Trail Making contrast scores comprised at least one measure with relatively poorer reliability (i.e. Category Switching: $r^2$ = .52, Number Sequencing: $r^2$ = .59 and Number-Letter Switching task: $r^2$ = .38). This may have increased the error variability of these measures and as a result, decreased the sensitivity in detecting significant differences when present.

In order to elucidate the factors that may be contributing to poor cognitive functioning in CKD, a second objective of this study was to examine potential mediators and/or moderators of performance in the CKD group. With respect to indices of illness severity, we found no evidence linking poor performance in global cognition, memory or executive functioning to metabolic dysfunction as measured by levels of GFR and hemoglobin or to duration of CKD. While the neurological and cognitive deficits in advanced, untreated renal disease are understood to largely reflect direct CNS effects of the disease (i.e. metabolic encephalopathy) (Pliskin et al., 2001), the CNS effects

associated with mild to moderate renal dysfunction are less well defined as research investigating these relationships have produced mixed findings. For instance, in a recent study evaluating cognitive functioning in younger and older adults with CKD, measures of GFR and hemoglobin were found to be unrelated to reported cognitive deficits (Thornton et al., in press). On the other hand, there is research suggesting that CKD illness factors (i.e. metabolic disturbances) are linked to increased risk for developing dementia (Seliger et al., 2004). Complicating matters, other findings suggest that metabolic disturbances may not be uniformly associated with deficits across cognitive domains, as in the study by Kurella et al. (2004), whereby decreased GFR was a significant predictor of poor performance in global cognition and delayed memory, but not of executive dysfunction.

In the current study, CKD was associated with higher levels of psychological distress relative to controls. Interestingly, among CKD participants, the direction of this relationship was such that individuals with lower cognitive functioning were reporting better emotional functioning as evidenced by their endorsement of fewer psychological distress symptoms. This association was relatively more robust for executive functioning, specifically response inhibition, compared to other domains. Further analyses suggested that global cognitive impairment might, in part, be mediating the relationship between executive dysfunction and decreased reporting of psychological distress.

A possible explanation for the results on psychological distress is that older adults with CKD who presented with cognitive deficits underestimated their difficulties on self-report measures due to lack of adequate insight or self-awareness into their functioning. Indeed, there is some support for this explanation as decreased awareness has been linked to general cognitive impairment and more specifically, to executive dysfunction (Ecklund-Johnson & Torres, 2005), and there is some research to indicate

that lack of awareness in dementia is inversely related to depressed mood (Ecklund-Johnson & Torres, 2005; Harwood, Sultzer, & Wheatley, 2000). Regardless of the basis for this relationship, however, the finding of a positive association between cognitive functioning and distress allows us to rule out elevated psychological distress as an underlying cause of cognitive impairment in older adults with CKD for this study.

Other factors that could potentially contribute to cognitive impairment in CKD that were examined in this study included usage of medications with known CNS effects and the presence of subclinical dementia. We observed that the reported pattern of memory and executive deficits in CKD persisted after controlling for differences in medication usage with CNS effects and global cognitive impairment. These findings expand upon previous research by demonstrating that the cognitive deficits reported in older adults with CKD are not accounted for by generalized cognitive impairment or dementia. Rather, findings point to specificity for deficits in executive functioning over memory retention, and indicate that even older CKD adults with intact global cognition exhibit significant executive functioning difficulties.

Taken together, the current results seem to implicate factors other than psychological distress, illness severity, usage of medications with CNS effects and dementia as the etiological bases for diminished cognitive functioning in older adults with CKD. Given that CKD is associated with increased rates of cerebrovascular risk factors, as corroborated by the significantly higher rates of hypertension, diabetes and hypercholesteromia in the present sample, it may be that cerebrovascular pathology is mediating the relationship between CKD and cognitive impairment. There is evidence to suggest that individuals undergoing dialysis exhibit significantly higher rates of cerebrovascular lesions relative to their peers, as evidenced by the presence of multiple lacunes and white matter pathology on MRI (Fazekas et al., 1995; Pereira et al., 2005).

Recent research has shown that cerebrovascular pathology is also present earlier in the course of this disease as individuals with mild to moderate CKD who are not yet requiring renal replacement therapies have also been shown to have higher prevalence of subcortical and periventricular white matter pathology (Martinez-Vea et al., 2006). In that study, approximately 33% of participants with CKD evidenced silent cerebral white matter lesions compared to 6% of controls, and presence of white matter lesions was associated with both increased age and greater history of vascular disease but not with severity of CKD (Martinez-Vea et al., 2006). The hypothesis that cognitive impairment in CKD is due to cerebrovascular etiology has support in the current study, as the neuropsychological presentation of the CKD group, characterized by executive dysfunction and relatively intact memory retention, is consistent with vascular cognitive impairment (VCI) (Hachinski, 1994; Sachdev et al., 2004). This hypothesis also has corresponding support in longitudinal research examining cognitive functioning in CKD whereby older adults with CKD were found to have an elevated risk for the development of incident dementia (Seliger et al., 2004) and specifically, for vascular dementia but not for Alzheimer's dementia. Unlike VCI, AD is characterized by poor retention and rapid forgetting of information over time (Baldo, Delis, et al., 2002; Baldo & Shimamura, 2002; Bowler, 2002; Vanderploeg et al., 2001; Yuspeh et al., 2002), a pattern of memory impairment that was not a distinguishing feature of the current sample of older adults with CKD.

## Limitations

There are some potential limitations to the current study that are worthy of consideration. As described above, power limitations may have precluded detection of some statistically significant findings. Given that group differences on some measures

were associated with moderate effect sizes but did not reach statistical significance (e.g. DRS-2 Initiation/Perseveration subscale and D-KEFS Trail Making Test contrast score), it is possible that a larger sample size would have resulted in significant results. The fact that the CKD sample in this study consisted of participants with no histories of neurological impairments (e.g. stroke), major psychiatric illnesses, sensory impairments (e.g. visual), etc., can be considered a limitation insofar as this may limit the generalizability of findings to the larger population of older adults with CKD. However, this possibility would only suggest that the current findings underestimate the extent of cognitive difficulties in a larger population with a higher risk burden for cognitive impairment. Finally, as we did not directly examine the presence or extent of cerebrovascular pathology in CKD in this study, a causative link to the reported cognitive deficits cannot be made. Future studies examining the neuropsychological correlates of cerebrovascular disease in CKD are necessary before establishing cerebrovascular pathology as a putative mechanism for cognitive impairment in this population.

## Conclusions

In conclusion, findings from the current study indicate that functionally independent, community-residing older adults with CKD exhibit higher rates of cognitive impairment compared to their healthy peers, and evidence a neuropsychological presentation that is consistent with vascular cognitive impairment. In this study, the pattern of cognitive deficits observed in CKD was not accounted for by metabolic disturbances, elevated psychological distress, differences in usage of medications with CNS effects or generalized cognitive decline. These findings have important implications in clarifying the mechanisms that may be contributing to cognitive deficits in CKD and point to the significance of adequately treating cerebrovascular risk factors to reduce the

risk for cognitive impairment in this population. Current findings also illustrate the importance of using measures that incorporate the assessment of executive functions when screening for cognitive impairment in older adults with CKD. Finally, given that individuals with CKD are required to self-manage elaborate medical and dietary treatments, it will be of significance to investigate whether the cognitive problems observed in CKD are associated with difficulties in managing this illness and if so, to determine the level and types of support patients will require in order to improve outcome.

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# APPENDICES

# Appendix A:

# Descriptive Statistics for Variables of Interest

**Comparison of CKD Participants administered the CVLT-II and D-KEFS measures vs. CKD Participants not administered these measures.**

| Variables | CKD (n=30)[a] mean ± SD | CKD (n=24)[b] mean ± SD | *p* |
|---|---|---|---|
| Age (mean ± SD) | 70.73 ± 8.08 | 73.88 ± 9.30 | ns |
| Education (mean years ± SD) | 13.50 ± 3.07 | 13.63 ± 2.83 | ns |
| Vocabulary (mean ± SD) | 11.68 ± 3.96 | 12.55 ± 2.78 | ns |
| Female | 18 (60.0%) | 5 (20.8%) | <.005 |
| Duration of renal disease (years) | 3.45 ± 3.62 | 5.89 ± 7.10 | ns |
| GFR (ml/min/1.73m$^2$) | 23.75 ± 7.86 | 17.89 ± 8.57 | <.05 |
| Hemoglobin (g/L) | 124.00 ± 13.15 | 124.88 ± 9.51 | ns |
| DRS-2 Total Score | 138.10 ± 3.75 | 136.21 ± 5.68 | ns |
| DRS-2 Attention | 36.33 ± .71 | 36.25 ± .94 | ns |
| DRS-2 Initiation/Perseveration | 35.83 ± 2.34 | 34.71 ± 3.22 | ns |
| DRS-2 Construction | 6.00 ± 0 | 5.92 ± .28 | - |
| DRS-2 Conceptualization | 36.07 ± 2.26 | 36.25 ± 2.33 | ns |
| DRS-2 Memory | 23.90 ± 1.45 | 23.13 ± 1.80 | ns |

Note: a: CKD (n=30) participants who present with complete data on the CVLT-II and D-KEFS measures. b: CKD (n=24) participants who do not present with complete data on the CVLT-II and D-KEFS measures.

# Appendix B:

## Performance on the D-KEFS and CVLT-II Contrast Measures

| Cognitive measures | CKD (n=30) mean ± SD | Controls (n=39) mean ± SD | *p* | *d* |
|---|---|---|---|---|
| D-KEFS Trail Making Test | | | | |
| Number Sequencing | 49.33 ± 20.09 | 40.51 ± 14.17 | <.05 | -.52 |
| Number-Letter Switching | 126.00 ± 45.43 | 100.03 ± 40.57 | <.05 | -.61 |
| D-KEFS Verbal Fluency Test | | | | |
| Category Fluency | 17.98 ± 4.83 | 19.78 ± 4.23 | ns | -.40 |
| Category Switching | 12.40 ± 2.08 | 14.00 ± 3.43 | <.05 | -.55 |
| D-KEFS Color-Word Interference Test | | | | |
| Color Naming | 31.60 ± 4.84 | 30.46 ± 5.87 | ns | -.21 |
| Inhibition | 70.87 ± 19.71 | 59.08 ± 13.45 | <.005 | -.72 |
| CVLT-II Retention Score | | | | |
| Trial 5 | 9.43 ± 2.52 | 11.59 ± 2.34 | <.001 | -.89 |
| Long-Delay free Recall | 7.80 ± 3.12 | 11.28 ± 3.23 | <.001 | -1.09 |

Note: All above scores represent raw scores. For the D-KEFS Trail Making and Color-Word Interference tests, lower score = better performance and for the CVLT-II measures and D-KEFS Verbal Fluency test, higher score = better performance. Also note, for the Trail Making and Verbal Fluency tests, the differences between the individual contrast scores presented above are slightly different than the computed contrast scores presented on Table 9. These small discrepancies are due to outlier corrections, as some data points were identified as outliers for the contrast scores but not for the individual scores, and vice versa.

# Appendix C:

# Descriptive Statistics for Cognitive Measures

**Exclusion of Participants on Benzodiazepines and Participants Meeting Cut-off for Global Cognitive Impairment on the DRS-2 Total Score (Raw Score ≤ 134)**

| Cognitive measures (maximal score) | CKD mean ± SD | Controls mean ± SD | *p* | *d* |
|---|---|---|---|---|
| DRS-2 Total Score (144) | 139.56 ± 2.70 | 140.64 ± 2.27 | ns | -.44 |
| Attention (37) | 36.47 ± .70 | 36.10 ± 1.00 | .05 | .43 |
| Initiation/Perseveration (37) | 36.39 ± 1.48 | 36.62 ± 1.27 | ns | -.17 |
| Construction (6) | 6.00 ± 0 | 6.00 ± 0 | - | - |
| Conceptualization (39) | 36.58 ± 1.98 | 37.74 ± 1.37 | <.01 | -.68 |
| Memory (25) | 24.11 ± 1.26 | 24.18 ± .89 | ns | -.06 |
| CVLT-II Trial 1 (16) | 4.82 ± 1.47 | 6.05 ± 2.09 | <.05 | -.65 |
| CVLT-II Trials 1-5 (80) | 40.73 ± 7.56 | 47.89 ± 9.90 | .005 | -.79 |
| CVLT-II Retention (z-score) | -.21 ± .66 | .04 ± .74 | ns | -.35 |
| CVLT-II Semantic clustering | .51 ± .94 | 1.21 ± 1.74 | .05 | -.47 |
| CVLT-II Intrusion errors* | 4.86 ± 5.23 | 4.32 ± 3.81 | ns | -.12 |
| D-KEFS Composite Contrast Score (z-score) | -.37 ± .63 | .03 ± .65 | <.05 | -.62 |
| D-KEFS Trail Making (Contrast Score)* | 74.27 ± 37.17 | 59.24 ± 34.41 | ns | -.42 |
| D-KEFS Verbal Fluency (Contrast Score)* | 5.89 ± 3.67 | 5.97 ± 3.81 | ns | -.02 |
| D-KEFS Color-Word Interference (Contrast Score)* | 36.09 ± 15.52 | 27.62 ± 10.25 | .01 | -.68 |

Note: *For these measures, higher scores = worse performance. For the DRS-2 measures: CKD: n=36 and Controls n=39. For the CVLT-II and D-KEFS measures: CKD: n= 22 and Controls: n= 37. Separate analyses examining performance between groups following the exclusion of only those on Benzodiazepines or only those meeting criteria for cognitive impairment yielded the same findings.

# Appendix D:

## Inter-correlations between Cognitive Variables

| | Cognitive Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| 1 | DRS-2 Total Score (144) | - | | | | | | |
| 2 | Attention (37) | .35** | - | | | | | |
| 3 | Initiation/Perseveration (37) | .68** | .08 | - | | | | |
| 4 | Conceptualization (39) | .66** | .17 | .06 | - | | | |
| 5 | Memory (25) | .61** | .03 | .31** | .19 | - | | |
| 6 | CVLT-II Trial 1 (16) | .33** | .14 | .10 | .29* | .17 | - | |
| 7 | CVLT-II Trials 1-5 (80) | .46** | .06 | .27 | .33** | .25* | .76** | - |
| 8 | CVLT-II Retention (z-score) | .05 | .07 | .01 | .10 | -.09 | -.02 | -.10 |
| 9 | CVLT-II Semantic clustering | .35** | .16 | .15 | .35** | .06 | .55** | .60** |
| 10 | CVLT-II Intrusion errors[a] | -.28* | .00 | -.11 | -.29* | -.13 | -.04 | -.16 |
| 11 | D-KEFS Composite Contrast Score (z-score) | .36** | .15 | .10 | .41** | .07 | .27* | .36** |
| 12 | D-KEFS Trail Making (Contrast Score)[a] | -.26* | -.03 | .03 | -.43** | -.02 | -.35** | -.41** |
| 13 | D-KEFS Verbal Fluency (Contrast Score)[a] | .21 | -.09 | .23 | .06 | .22 | .20 | .28* |
| 14 | D-KEFS Color-Word Interference (Contrast Score)[a] | -.49** | -.14 | -.33** | -.32** | -.24* | -.28* | -.42** |

Table continued on next page.

| | Cognitive Variable | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|
| 1 | DRS-2 Total Score (144) | | | | | | | |
| 2 | Attention (37) | | | | | | | |
| 3 | Initiation/Perseveration (37) | | | | | | | |
| 4 | Conceptualization (39) | | | | | | | |
| 5 | Memory (25) | | | | | | | |
| 6 | CVLT-II Trial 1 (16) | | | | | | | |
| 7 | CVLT-II Trials 1-5 (80) | | | | | | | |
| 8 | CVLT-II Retention (z-score) | - | | | | | | |
| 9 | CVLT-II Semantic clustering | -.03 | - | | | | | |
| 10 | CVLT-II Intrusion errors[a] | -.17 | -.30* | - | | | | |
| 11 | D-KEFS Composite Contrast Score (z-score) | .03 | .30* | -.17 | - | | | |
| 12 | D-KEFS Trail Making (Contrast Score)[a] | -.11 | -.25* | .13 | -.70** | - | | |
| 13 | D-KEFS Verbal Fluency (Contrast Score)[a] | .01 | -.05 | .05 | -.28* | -.10 | - | |
| 14 | D-KEFS Color-Word Interference (Contrast Score)[a] | .03 | -.23 | .11 | -.75** | .35** | -.23 | - |

Note: a: Higher scores = worse performance for these measures. The DRS-2 Construction subscale was not included in above analyses due to lack of variability. Also note, for the inter-correlations between the DRS-2 measures: $n = 96$ and for the inter-correlations between the DRS-2, CVLT-II and D-KEFS measures, $n = 69$.

* $p < .05$

** $p < .01$