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## Duration of chronic kidney disease reduces attention and executive function in pediatric patients

Susan R. Mendley, MD<sup>1</sup>, Matthew Matheson, MS<sup>2</sup>, Shlomo Shinnar, MD, PhD<sup>3</sup>, Marc Lande, MD<sup>4</sup>, Arlene C. Gerson, PhD<sup>5</sup>, Robert Butler, PhD<sup>6</sup>, Bradley A. Warady, MD<sup>7</sup>, Susan L. Furth, MD<sup>8</sup>, and Stephen R. Hooper, PhD<sup>9</sup>

<sup>1</sup>University of Maryland School of Medicine

<sup>2</sup>Johns Hopkins University School of Public Health

<sup>3</sup>Albert Einstein College of Medicine

<sup>4</sup>University of Rochester School of Medicine

<sup>5</sup>Johns Hopkins University School of Medicine

<sup>6</sup>Neurocognitive Consultants, Happy Valley, OR

<sup>7</sup>Children's Mercy Hospitals and Clinics

<sup>8</sup>Children's Hospital of Philadelphia

<sup>9</sup>University of North Carolina School of Medicine

### Abstract

Chronic kidney disease (CKD) in childhood is associated with neurocognitive deficits. Affected children show worse performance on tests of intelligence than their unaffected siblings and skew toward the lower end of the normal range. Here we further assessed this association in 340 pediatric patients (ages 6 to 21) with mild-moderate CKD in The Chronic Kidney Disease in Childhood cohort from 48 pediatric centers in North America. Participants underwent a battery of age-appropriate tests including Conner's Continuous Performance Test-II (CPT-II), Delis- Kaplan Executive Function System Tower task, and the Digit Span Backwards task from the age-appropriate Wechsler Intelligence Scale. Test performance was compared across the range of estimated GFR and duration of CKD with relevant covariates including maternal education, household income, IQ, blood pressure and preterm birth. Among the 340 patients, 35% had poor performance (below the mean by 1.5 or more standard deviations) on at least one test of executive function. By univariate nonparametric comparison and multiple logistic regression, longer duration of CKD was associated with increased odds ratio for poor performance on the CPT-II Errors of Commission, a test of attention regulation and inhibitory control. Thus, in a population

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Corresponding author: Susan R. Mendley, MD, University of Maryland Children's Hospital, 22 South Greene Street – N5W67, Baltimore, MD 21201-1595, Telephone (410) 328-5303, Fax (410) 328-3835, [smendley@peds.umaryland.edu](mailto:smendley@peds.umaryland.edu).

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with mild to moderate CKD, the duration of disease rather than estimated GFR was associated with impaired attention regulation and inhibitory control.

## Keywords

Neurocognitive Function; Renal Disease; CKD; Connor's Continuous Performance Test

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## Introduction

Chronic kidney disease (CKD) in adults is associated with cognitive impairment which may be related to kidney function as measured by glomerular filtration rate (GFR) and the presence of albuminuria [1–5]. Possible mechanisms for cognitive impairment include accelerated cerebrovascular disease with ischemia, subclinical stroke and subcortical atrophy [6–8] mimicking the pattern of age-related cognitive decline. However, the effects of CKD on cognitive function in childhood are clearly different. Childhood and adolescence are periods of brain growth and the development of neural pathways responsible for comprehension, memory, planning, problem solving, abstract reasoning and attentional control; decreased GFR or other effects of chronic illness may adversely affect these normal developmental processes [9,10]. Measuring these effects in children needs to be approached differently than is done in adults.

The early literature on childhood CKD shows its association with encephalopathy and developmental delay, especially of gross motor skills and language acquisition [11–14]. Case series show that when the uremic milieu coincides with critical periods of brain development, it can cause non-specific EEG abnormalities [15,16] as well as structural changes including atrophy and infarcts [17–19]. Such severe deficits have become less common with the elimination of oral and dialytic aluminum intake and the avoidance of uncontrolled uremia [20,21]. Nonetheless, there remains evidence for subtle neurocognitive deficits in children with advanced chronic kidney disease. Children with CKD perform less well on standardized tests of intelligence and academic achievement than their unaffected siblings [22]. Prospective studies have demonstrated that cognitive deficits can improve after kidney transplantation [23,24]. Lawry et al showed better neurocognitive function and school performance among transplant patients when compared to chronic dialysis patients[25].

Neurocognitive impairment has been described in other chronic diseases of childhood, including systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis (JRA), inflammatory bowel disease (IBD) and cancer chemotherapy. Estimates of neurocognitive impairment in childhood SLE vary depending upon the test battery used, the cohort and controls studied and the categorization of cognitive impairment. Two studies demonstrated incidences of impairment ranging from 59–71% of small study groups [26, 27]. In a prospective study with age- and ethnicity-matched controls in addition to standardized norms, SLE subjects and controls performed similarly [28]. Subjects with renal disease were over-represented in the group with neurocognitive impairment, but this did not reach statistical significance. A study of 31 subjects with systemic JRA showed no difference in

WISC-R and WAIS-R, information processing speed, memory and verbal learning when compared with an age and socio-economically matched control group [29]. Adolescents with IBD made more errors in tests of verbal learning than a comparable group with JRA, yet performed similarly on other tests of memory, intelligence and executive function[30].

The neurotoxic effects of chemotherapy for childhood cancer have been extensively studied. Risk factors for neurocognitive sequelae after acute lymphoblastic leukemia (ALL) include younger age at diagnosis, female sex and intensity of treatment, particularly systemic high dose methotrexate [Buizer31]. Cranial radiation was used in earlier studies of ALL to prevent central nervous system relapse but effects on IQ and academic performance have driven protocols toward chemotherapy alone.

Subjects with advanced renal failure have more often been reported, but the effects of early chronic kidney disease on neurocognitive function remain incompletely elucidated. Published results from the NIH-sponsored Chronic Kidney Disease in Children Study (CKiD) have shown that IQ and academic achievement in children with mild-to-moderate CKD cluster at the lower end of the normal range and the distribution is skewed downward[32]. Whether the severity of CKD or the duration of exposure to low GFR during brain development is of greater importance is not fully understood.

Executive function (EF) is the central cognitive process that controls problem solving to permit goal-directed behavior. Various conceptual and empirical models of EF have been proposed, but most include: inhibition of prepotent responses, shifting mental sets, monitoring and regulating performance, planning and problem solving, and working memory capacity. Control of attention is included in a construct linking EF and working memory capacity. [33–39] Additionally, executive processes are considered critical to the integrity of many learning and social-behavioral functions [35] and each of these functions has a developmental basis that will exert effects on learning and behavior at different times, with a sequential unfolding of executive functions from infancy into early adulthood [40, 41]. Consequently, brain injury or toxic exposure during this period of developmental ascendancy would be expected to have an effect on the integrity of EF [42].

Several assessments of EF were incorporated into the CKiD study to determine if EF is particularly sensitive to perturbation in a uremic milieu [43] and if abnormalities of performance could be detected early in the course of CKD. The objective of the current study was to estimate the prevalence of EF deficits in children with mild-to-moderate CKD and to investigate what disease and patient characteristics are associated with executive dysfunction.

## Results

### Sample Description

Subjects were enrolled in the CKiD study at ages 1–16 and followed prospectively. The neurocognitive testing in this cross-sectional analysis was administered to 340 subjects age 6–21 years. Characteristics of this study sample are shown in Table 1. With a median age of 13, the group was 61% male and 83% Caucasian, and the median parent-reported duration

of CKD diagnosis was 10 years. One quarter of the study group had blood pressure measured  $>90^{\text{th}}$  percentile (for age, height, and gender) on the day of cognitive testing. Because of the age of the subjects, there were no diabetics; SLE was present in only 2% and depression in 7%. Median estimated GFR (eGFR) for the group was 43 ml/min/1.73m<sup>2</sup> (interquartile range, 31–53). As reported for the entire cohort [32], IQ clustered at the low range of normal and 22% of the study sample had IQ scores  $<85$ ; this was incorporated into statistical models. All subjects attended school and the median grade level at the time of testing was 6<sup>th</sup> (IQR 3, 9). Forty percent of subjects were below expected grade level. The median number of days absent from school for medical reasons was 4 (IQR 2, 8) and 11% of the study group was absent 18 or more days in the preceding school year.

In anticipation of potential confounders, such as fatigue secondary to order effects, the tests were separated into two blocks, and the blocks were administered in a counterbalanced format across subjects. Additionally, we obtained validity ratings by the psychologists to determine the quality of the test administration and test data. All tests had excellent reliability; 93% of CPT, 96% of Digit Span Backward and 94% of D-KEFS had the highest validity rating of 1.0. Given the critical impact of fatigue on attention regulation and associated executive functions, we also assessed fatigue using the Peds QL [44]; 17% of the group indicated low energy often or almost always on either the parent or child report on the day of EF testing.

Thirty-five percent of the study group (119 subjects; 95% confidence interval [CI]: 30–41%) performed poorly (  $1.5$  SD below mean) on at least one test of EF. Of these subjects, 79 performed poorly on only one test, 30 on two tests and 10 performed poorly on 3 or more tests. Some subjects were unable to complete the tasks or had missing values on at least one test in the battery.

### Factors Associated with Poor EF Performance

Table 2 displays the median and IQR of duration of CKD and eGFR for each poor-performance group and its complement. By nonparametric comparison, longer duration of disease was associated with poor performance on the Connor's Continuous Performance test (CPT-II) Errors of Commission ( $p=0.004$ ). No other comparisons approached statistical significance.

Multiple logistic regression models used to examine the association of duration of CKD and impairment of GFR on the likelihood of deficient performance on EF tests are shown in Table 3. After controlling for race, maternal education, household income, IQ, blood pressure, premature birth and proteinuria, which were defined as relevant covariates in previous publications from this cohort [32, 45], the level of eGFR was not associated with increased odds of poor performance on any of the EF tasks. By contrast, longer duration of CKD was associated with increased odds of poor performance on the CPT-II Errors of Commission, with an odds ratio of 1.16 ( $p = 0.013$ ; 95% CI: 1.03–1.31). This estimate can be interpreted as a doubling of the odds of poor performance for every 4.6 years of CKD exposure. Additional logistic regression analysis showed elevated BP ( $>90^{\text{th}}$  percentile for age, height and gender) was associated with a greater degree of variability in CPT performance (less consistent performance of the task,  $p<0.01$ ), while higher household

income was protective, associated with a lesser degree of CPT variability ( $p < 0.05$ ). However, poor performance in planning and problem solving on the D-KEFS Tower Task was not predicted either by severity or duration of CKD. Working memory as assessed by Digit Span Backward was not affected by either the duration of known CKD or the level of GFR; however, the highest level of maternal education (college degree or higher) was protective against poor performance in working memory (OR 0.20,  $p = 0.049$ ; 95% CI 0.04–0.99).

Multiple linear regression with correction for multiple testing showed no significant association with eGFR, duration of CKD, elevated blood pressure, proteinuria, or preterm birth on performance of any of the EF tasks as continuous variables across the full range of performance (data not shown). As expected, low IQ (full scale IQ  $< 85$ ) had a significant deleterious effect on performance and subjects with IQ  $< 85$  were over-represented in the poor performing group for each task. For that reason our logistic regression model incorporated IQ as a relevant covariate (see below). Higher maternal education (college degree or more) was associated with improved performance only on Digit Span Backward (estimate of effect size 1.07). The EF composite score did not improve the predictive value of any variable on the likelihood of deficient performance.

## Discussion

Our data show that longer CKD duration is associated with an increased likelihood of poor performance in inhibitory control and visual vigilance as measured by errors of commission on the Connors' CPT-II, which suggests abnormal attention regulation. This observation was supported by both univariate analysis and multiple logistic regression. However, we did not demonstrate an effect of GFR on CPT-II performance. Attention is only one component of executive function; the risk of poor performance on tasks which tap other aspects of EF, including the Delis-Kaplan Executive Function System Tower Task (DKEFS) and the Wechsler Intelligence Scale for Children Fourth Edition (WISC) or Wechsler Adult Intelligence Scale Fourth Edition (WAIS) Digit Span Backwards, was not associated with either duration of CKD or GFR.

Our current finding is concordant with the work of Fennell [46], who reported poorer attention regulation in children with CKD when compared to age-matched controls. Another prospective study of children with ESRD showed that inhibitory control, as measured by CPT-II, appeared to be sensitive to uremia [23]. When these subjects were restudied (within-subject comparison) after kidney transplant with near-normal GFR, they demonstrated improved performance on the CPT-II, with fewer errors of commission [23]. Those publications, along with the findings from the present study, support an effect of CKD on attention and inhibitory control, and also support the use of the CPT-II as a relevant tool in this setting and the CKD population in general.

Our results suggest that we have identified a specific area of poor neurocognitive performance in this population and may provide a mechanistic insight into the effect of CKD. The CPT-II specifically assesses attention regulation and requires sustained focus on a repeated task and the ability to consistently suppress incorrect responses. If a subject allows

attention to waver, he will miss correct responses (errors of omission); if he fails to suppress a response to an incorrect stimulus (i.e. lack of inhibitory control) he will exhibit errors of commission. If a subject's reaction time performance varies through a test session as he tires or fails to sustain attention, he will manifest increased response variability. In this study, our subjects demonstrated poor performance in both aspects: longer duration of CKD was associated with errors of commission and increased variability of performance was associated with elevated blood pressure.

It is notable that our cross-sectional findings show duration of disease to be more relevant than the level of GFR, and suggest that CKD may have a subtle but persistent effect on neurodevelopmental processes. Further complicating our understanding of this effect are the multiple comorbid events and their sequelae which may occur in the course of childhood chronic disease. The literature documents developmental impairment in infants and toddlers with CKD and those requiring dialysis in infancy [11–13], and we may be able to detect a more subtle but still relevant effect in children who have had a milder but longer exposure to renal disease. Some children with congenital urologic abnormality have a long duration of known disease and one could postulate an early impact on neurodevelopment at a critical early period or that their early diagnosis may skew the analysis. However the comparison of non-glomerular and glomerular renal disease grouping has not yielded important differences in neurocognitive function.

Low IQ was clearly associated with poor EF performance on all tasks and we are left with the theoretical question as to whether low IQ leads to poor EF or whether poor EF leads to low IQ. It is equally likely that causes of CKD and numerous comorbid events affect both EF and IQ and these may not be separable in a heterogeneous population like ours. We controlled for low IQ in the logistic regression model, but must consider if that was sufficient. Removing low IQ subjects entirely from the analysis limited the statistical power too much to allow meaningful conclusions. We also considered the option of not controlling for IQ, given that it tends to be a summary variable for a number of cognitive functions[47], but elected to control for this variable given the number of cases with low IQ in the sample. At a minimum, these findings reflect a conservative approach to our data analyses and increase confidence in the associations uncovered.

The CKiD study was prospectively designed to provide a systematic assessment of numerous aspects of childhood CKD. We have focused our analysis on attention and executive functions in the study population which spans a wide spectrum of age and GFR. Unlike some studies in adult cohorts which, by necessity, used widely available but more rudimentary tools for assessing cognitive abilities, experienced child psychologists designed and performed an age appropriate battery of EF tests.

Pediatric studies cited previously [14] focused on children with advanced CKD, but the goals of the CKiD study are to follow subjects with mild to moderate renal dysfunction to find the earliest effects of the disease and permit longitudinal reassessments. As such, many disturbances of cognitive and intellectual function described in children with advanced CKD are expected to be more subtle or not yet apparent in our subjects who are still early in their disease course. Yet, it is notable that more than a third of our subjects performed poorly on

at least one test of EF. While we did not demonstrate a correlation of EF abilities with level of GFR, this observation is consistent with some well-controlled adult studies [2,5]. There are significant lifelong implications of diminished EF that may limit full rehabilitation from childhood CKD, including medication adherence, performance at higher levels of schooling and employment.

The current study has several limitations. The range of GFRs in the study population may not have been wide enough to detect the full effects on EF. Subjects with longer duration of disease may have had other coexisting conditions which our analysis did not reveal, but which may have impacted cognition or cognitive development. That the effect of duration of CKD on CPT errors of commission was demonstrated by logistic regression but not by linear regression may reflect the variable disease course or the milder degree of renal impairment in the study population; however, we must consider that the effect may be quite weak. Further, only one component score of the CPT test reached significance and again we must consider whether the effect is real or spurious. In fact, poor performance on the CPT may be the result of lack of engagement in the task rather than a true deficit of attention regulation, although it is important to note that we counterbalanced our tasks and ratings of the quality of the administrations/data were excellent. The cross-sectional study design limits the ability to make inferences regarding the cause of the decreased EF found in some subjects and the effect sizes were relatively small. Our interpretation of the impact of uremia on EF is limited by the early stage of CKD, with only modestly decreased GFR in many subjects. It will be important to track this relationship over time; the CKiD study will re-evaluate each subject's performance longitudinally in relation to change in GFR.

The CKiD study is an ambitious attempt to capture the full impact of chronic kidney disease in an evolving cohort of children who are experiencing progression of renal dysfunction, ongoing somatic growth, cardiovascular changes, and coincident cognitive and emotional development. Separating the overlapping effects of all these variables remains a challenge well worth pursuing. We provide early results with the clear intention to continue investigations.

## Materials/Methods

CKiD is a prospective cohort study of children ages 1–16 years at recruitment with chronic kidney disease (estimated GFR 30–90 ml/min/1.73m<sup>2</sup>) which is conducted at 48 pediatric nephrology centers in North America. Details of the study design and methods have been published previously [48]. In this analysis we have looked at all subjects aged 6 and older and results are limited to ages for which there are normative data. Children with intellectual disabilities and those with genetic syndromes with central nervous system manifestations were excluded by study design. The protocol was approved by the Institutional Review Boards of all centers.

## Kidney Function

The CKiD study includes a reliable method of GFR measurement by iohexol clearance at defined study timepoints [49]. However we separated neurocognitive testing dates from clearance studies to avoid the distraction of iohexol infusion and phlebotomy. Previous

analysis of the iohexol clearance data has allowed generation of a validated, accurate method to estimate GFR (eGFR) using serum creatinine, cystatin C and blood urea nitrogen measurements [49, 50] and this was used to provide a contemporaneous eGFR at the time of neurocognitive assessment.

### **Assessment of Attention and Executive Function**

The study protocol includes a battery of age-appropriate tests of EF performed by child psychologists at defined intervals (6 months after study entry, 1.5 years later and then every 2 years). This analysis contains data from the first visit at which each subject had the complete EF battery done, so some subjects were more than 16 years of age by the time of testing. EF measures included the Conner's Continuous Performance Test-II (CPT-II) which is a computer-based task that requires the subject to touch the mouse or space bar in response to visual stimuli (i.e., letters on computer screen) that are presented at the rate of about one per second over approximately a 14 minute testing period. The CPT-II provides information about the child's omission and commission error rates, reaction time and response variability which represent an assessment of sustained attention and inhibitory control. The CPT-II measures are scaled to a mean = 50, SD = 10; higher scores indicate worse performance.

Included in the battery was the Delis-Kaplan Executive Function System Tower Task (DKEFS) in which subjects are asked to move a set of disks from one peg to another; only one disk can be moved at a time and a larger disk cannot be placed over a smaller disk. The task becomes more complicated as the number of disks increases and it draws upon skills of planning, reasoning, problem solving, and inhibitory control. Age-based norms for the Total Achievement Score (representing time required to complete the task correctly) are available for subjects age 8 years and older and only that age group is included in analysis. The DKEFS scores are scaled to a mean = 10, SD = 3; lower scores indicate worse performance.

Also included was an assessment of working memory using the Wechsler Intelligence Scale for Children Fourth Edition (WISC) or Wechsler Adult Intelligence Scale Fourth Edition (WAIS, for those subjects over age 16 at testing) Digit Span Backwards tasks, in which subjects are asked to repeat a list of verbally-presented numbers in reverse order. Age-based standardized norms for Digit Span Backward have a mean = 10, SD = 3 and lower scores indicate worse performance. In addition to the EF measures, we determine the estimated level of IQ for each subject using Full-4 from the Wechsler Abbreviated Scale of Intelligence.

### **Statistical Analysis**

Performance on tests of executive function was compared across the range of GFR and CKD duration. Duration of CKD was determined by parent report of the child's medical history and onset of disease at the first study visit and then corroborated with nephrologist's records.

To address the primary research question, we identified subjects with poor performance on a test of EF, which was defined as a score  $\geq 1.5$  SD below the normal population mean on any of the five EF measures. On DKEFS and Digit Span Backward, poor performance corresponds to a scaled score  $\leq 5.5$ ; on CPT measures, poor performance corresponds to a T



score of 65. We stratified our sample by performance on each EF measure and examined the distributions of the primary exposures, duration of CKD and eGFR, testing for differences with Wilcoxon rank-sum tests. We used logistic regression to predict the likelihood of executive dysfunction by level of GFR or duration of CKD, adjusting for a targeted group of covariates or potential confounders including age, race, maternal education, household income, IQ, blood pressure, premature birth, and proteinuria. These covariates were selected from a wide range of potentially relevant patient characteristics based upon previously published neurocognitive findings from the CKiD study [32, 45]. To clarify the impact of renal disease on neurocognitive function, eGFR and duration of CKD were examined in separate models. We also explored adjusted linear regression models to assess potential effects on the continuous EF scales across the full range of performance.

We considered whether a global assessment might be a useful tool to identify relevant exposures affecting EF in this population. To test this, we created a composite score of the five EF measures by rescaling the scores to have the same mean and directionality and accounting for within- and between-measure variance, allowing an overall score of “poor” and “not poor”.

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**Table 1**

Characteristics of study participants (N=340) at time of first executive function testing

Characteristic	% (n) or Median [IQR]
Age, years	13 [10, 17]
Male	61% (206)
African-American	17% (57)
Maternal Education	
High school or less	41% (136)
Some college	28% (91)
College or more	31% (103)
Household Income	
<\$36,000/year	38% (127)
\$36,000/year	62% (204)
IQ < 85	22% (73)
Elevated Blood Pressure <sup>a</sup>	26% (78)
Premature Birth	12% (37)
Urine Protein:Creatinine <sup>2</sup>	12% (38)
Duration of CKD, years	10 [6, 13]
eGFR, ml/min 1.73m <sup>2</sup>	43 [31, 53]
D-KEFS Total Achievement	10 [8, 11]
Digit Span Backward	9 [7, 11]
CPT-II Errors of Commission	54 [44, 60]
CPT-II Hit Reaction Time	47 [40, 54]
CPT-II Variability	49 [43, 59]

<sup>a</sup>Defined as systolic or diastolic blood pressure 90<sup>th</sup> percentile for age, sex and height.

Table 2

Duration of CKD and estimated GFR by performance on EF tasks.

EF Measure <sup>a</sup>	Performance Groupings	N <sup>b</sup>	Measure of CKD Severity					
			Duration of CKD (years)		eGFR (ml/min/1.73m <sup>2</sup> )			
			Median	IQR	p-value <sup>c</sup>	Median	IQR	p-value <sup>c</sup>
D-KEFS Total Achievement	5.5	27	9.4	[5.5, 12.0]	0.109	38.9	[28.5, 56.6]	0.920
	>5.5	261	10.5	[7.3, 14.2]		42.6	[31.8, 52.0]	
Digit Span Backward	5.5	40	9.5	[6.5, 12.4]	0.934	46.4	[35.0, 56.9]	0.318
	>5.5	273	9.6	[6.4, 12.8]		42.7	[30.9, 52.9]	
CPT-II Errors of Commission	65	39	11.4	[8.5, 15.2]	0.004	39.3	[32.3, 50.7]	0.623
	<65	264	9.3	[6.2, 12.6]		43.3	[31.5, 5, 3.7]	
CPT-II Hit Reaction Time	65	24	7.5	[5.6, 11.1]	0.107	46.0	[34.1, 61.1]	0.165
	<65	280	9.7	[6.4, 13.2]		42.7	[31.0, 52.1]	
CPT-II Variability	65	40	9.8	[6.2, 14.6]	0.940	43.3	[31.8, 52.5]	0.949
	<65	265	9.6	[6.4, 12.8]		39.6	[30.8, 57.6]	
<i>Any of the five</i>	Poor	119	9.9	[6.3, 13.0]	0.941	42.4	[32.8, 54.3]	0.259
	Not poor	221	9.6	[6.4, 13.0]		42.6	[30.3, 51.6]	
<i>Composite of the five</i>	Poor	44	8.9	[6.6, 11.4]	0.277	42.3	[32.6, 56.6]	0.692
	Not poor	296	9.8	[6.4, 13.2]		42.6	[31.0, 53.1]	

<sup>a</sup> Poor performance on any test of EF is defined as a score 1.5 SD below the age-adjusted, normal population. On DKEFS and Digit Span Backward, poor performance corresponds to a scaled score 5.5; on CPT measures, poor performance corresponds to a T score of 65.

<sup>b</sup> Differences in numbers are due to missing data for each test.

<sup>c</sup> p-values compare CKD severity measure in poor vs. not poor performing groups by Wilcoxon rank-sum test.

**Table 3**Adjusted<sup>a</sup> Odds Ratios for poor performance on EF tests.

EF Measure	Measure of CKD Severity					
	Duration of CKD (years) <sup>b</sup>			eGFR (ml/min/1.73m <sup>2</sup> ) <sup>b</sup>		
	OR	95% CI	p-value	OR	95% CI	p-value
D-KEFS Total Achievement	0.92	(0.80, 1.05)	0.210	0.85	(0.56, 1.29)	0.452
Digit Span Backward	1.02	(0.90, 1.14)	0.786	1.02	(0.73, 1.43)	0.916
CPT-II Errors of Commission	1.16	(1.03, 1.31)	0.013	1.04	(0.77, 1.42)	0.792
CPT-II Hit Reaction Time	0.96	(0.81, 1.13)	0.594	1.08	(0.74, 1.58)	0.687
CPT-II Variability	1.16	(1.01, 1.33)	0.039	1.04	(0.78, 1.39)	0.807
Any of the five	1.05	(0.98, 1.14)	0.164	1.03	(0.84, 1.25)	0.809
Composite of the five	0.95	(0.84, 1.08)	0.422	0.97	(0.69, 1.35)	0.837

<sup>a</sup> Odds Ratios adjusted for age, African-American race, maternal education, household income, IQ < 85, elevated blood pressure, premature birth, and urine protein:creatinine 2.<sup>b</sup> Odds Ratio estimate for duration of CKD is per 1 year and for eGFR is per 10 ml/min/1.73m<sup>2</sup> increase.