Neurocognitive Functioning of Children and Adolescents with Mild-to-Moderate Chronic Kidney Disease

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Summary

Background and objectives Few data exist on the neurocognitive functioning of children with mild-to-moderate chronic kidney disease (CKD). The primary objectives of this paper are (*1*) to determine the neurocognitive status in this population and (*2*) to identify sociodemographic and health-status variables associated with neurocognitive functioning.

Design, setting, participants, & measurements This was a cross-sectional study of 368 children, aged 6 to 16 years, from the Chronic Kidney Disease in Children (CKiD) cohort. Median iGFR was 43 ml/min per 1.73 m^2, and the median duration of CKD was 8.0 years. Approximately 26% had underlying glomerular disease. Measures of intelligence, academic achievement, attention regulation, and executive functioning were obtained at study entry. The prevalence of neurocognitive deficits was determined by comparing participant scores on each measure of neurocognitive functioning with normative data. The association between hypothesized predictors of neurocognitive dysfunction was evaluated using multivariate regression analyses.

Results Neurocognitive functioning was within the average range for the entire group; however, 21% to 40% of participants scored at least one SD below the mean on measures of intelligence quotient (IQ), academic achievement, attention regulation, or executive functioning. Higher iohexol-based GFR (iGFR) predicted a lesser risk for poor performance on measures of executive function. Participants having elevated proteinuria (*i.e.*, urine protein/creatinine >2) scored lower on verbal IQ, full-scale IQ, and attention variability than those without elevated proteinuria.

Conclusions Whereas most children with mild-to-moderate CKD have no major neurocognitive deficits, a substantial percentage did show neurocognitive dysfunction that places them at risk for poor long-term educational and occupational outcomes.

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Introduction

The relationship between chronic kidney disease (CKD) and neurodevelopmental dysfunction in children is well recognized (1,2). Early studies showed high rates of developmental delay and encephalopathy in children with severe CKD and called attention to the neurologic impairments that can occur secondary to kidney disease (3). Whereas early studies showed that many infants with CKD were at increased risk for intellectual disabilities, microcephaly, and seizures (4), recent reports show a more favorable neurocognitive and rehabilitation potential (5). Increased disease severity, longer duration of disease, and younger age of onset have been found to increase the risk of neurocognitive deficits in older cohorts (6), including difficulties in language, visual-spatial ability, memory, and executive functioning (1). Nearly all of the published studies have focused on youth with ESRD and/or samples of mixed severity, and few data exist on the neurocognitive functioning of children with mild-to-moderate CKD.

The Chronic Kidney Disease in Children (CKiD) prospective cohort study is a multicenter longitudinal investigation of children with mild-to-moderate CKD. One of the major questions posed by the CKiD study relates to the effect of CKD on neurocognitive functioning and, as such, is designed to address a key void in the literature (7,8). This study provides the first large-scale evaluation of neurocognitive functioning in children and adolescents with pre–end stage kidney disease. We hypothesized that (*1*) the prevalence of children with mild-to-moderate kidney disease who have neurocognitive dysfunction will be higher than the prevalence of such problems in the general

population; (2) kidney disease severity, as defined by the iohexol-based GFR (iGFR), will be associated with lower neurocognitive functioning; and (3) increased disease duration and low socioeconomic status will be associated with lower neurocognitive functioning.

Materials and Methods

Participants

This is a cross-sectional assessment of a subgroup of participants enrolled in the National Institutes of Health–funded multicenter CKiD study. Eligibility criteria for enrollment in CKiD included an estimated GFR as calculated by the Schwartz formula (9) of 30 to 90 ml/min per 1.73 m^2, and exclusion criteria included solid organ, bone marrow, or stem cell transplant; cancer/leukemia; or HIV (7). Participants for this report were between the ages of 6 and 17 years and had completed neurocognitive testing at study entry. The study protocol was approved by the institutional review boards at all 46 sites, and informed consent was obtained from all caregivers.

Measures of Neurocognitive Functioning

Age-specific measures of intellectual functioning (Wechsler Abbreviated Scales of Intelligence [WASI]) (10), academic achievement (Wechsler Individual Achievement Test-II-Abbreviated [WIAT-II-A]) (11), attention regulation (Conners' Continuous Performance Test-II [CPT-II]) (12), and executive functioning (Behavior Rating Inventory of Executive Functions-Parent [BRIEF]) (13) were administered to each study participant.

The WASI is a standardized measure of intelligence that provides estimates of full-scale intelligence quotient (FSIQ), verbal IQ (VIQ; vocabulary and similarities), and performance IQ (PIQ; block design and matrix reasoning). The WIAT-II-A is a standardized measure that provides estimates of reading recognition, math calculations, spelling, and overall achievement. The CPT-II is a computerized measure of attention that requires the individual to touch the mouse or space bar in conjunction with visual stimuli (*i.e.,* letters) that are presented at the rate of about one per second over approximately 14 minutes. Scores include omission and commission error rates, response variability, and reaction time. The BRIEF is a parent completed scale that provides ratings of eight subscales (*e.g.,* Inhibition) and indices for metacognition, behavior regulation, and a global executive composite. Order effects were controlled via counterbalancing blocks of tasks. All of the tasks were administered/supervised by a licensed psychologist.

Predictor variables were chosen *a priori* on the basis of clinical considerations to avoid Type I errors resulting from preliminary tests of significance targeted disease-related predictor variables for the multivariate analyses included CKD diagnosis category (*i.e.,* glomerular *versus* nonglomerular), duration of CKD (*i.e.,* percentage of life with CKD), presence of hypertension (casual systolic or diastolic pressure $\geq 95^{th}$ percentile for age, gender, and height; or current use of any antihypertensive medication and self-report of hypertension), anemia ($<5^{th}$ percentile of normal for age and gender or taking an erythropoiesis-stimulating agent), iGFR (GFR determined by plasma disappearance of infused iohexol) (14), and elevated proteinuria (urine protein/creatinine >2). Selected demographic variables (age, gender, and maternal education) and low birth weight (<2500 g) were included.

Data Analyses

Descriptive statistics for the demographic, neurocognitive, and health-status variables were generated to characterize the study sample. Performance on each test was calculated and compared with age-appropriate norms observed in the general population. The at-risk status for each assessment was defined as performance that was ≥1 SD below the mean. The association between hypothesized predictors of neurocognitive function was evaluated with multivariate regression models. Each regression included an examination of residuals as a check on the required assumptions of normally distributed errors with constant variance. In the event that the required assumptions were violated, data transformations were considered. On the basis of the findings, selected interactions between clinical and sociodemographic variables were examined with respect to the neurocognitive outcomes. Logistic regression was used to determine which CKD-related predictor variables were associated with neurocognitive risk as defined by scores on major assessment indices falling ≥1 SD below the normative mean. The odds ratios were calculated to estimate the relative risk associated with each predictor.

Results

Group Characteristics

The study sample comprised 368 participants. Median iGFR was 42.7 ml/min per 1.73 m^2, and the median duration of CKD was about 8.0 years (IQR = 4 to 12). Approximately 26% had underlying glomerular disease (*e.g.,* focal segmental glomerulosclerosis) and 74% had structural urologic disease (*e.g.,* obstructive uropathy). About 51% met the definition for hypertension, with about 68% of this subgroup using antihypertensive agents. For 116 children, a wide range of other health conditions was represented (*e.g.,* asthma, diabetes, and lung disease), but the frequency for most of these comorbid conditions was quite small. The sample did permit examination of two comorbid conditions with sufficient numbers: asthma (n = 61) and seizures (n = 43). Using unequal-variance t tests, we did not find differences on any of the neurocognitive outcomes for those with and without asthma. In contrast, significant differences were noted between those with and without seizures on all of the IQ and achievement variables, and this necessitated the addition of seizures as a predictor variable in our regression analyses. Table 1 shows these group characteristics.

Overall Group Performance on the Neurocognitive Measures

Overall FSIQ was in the average range (mean = 96.4, SD = 16.5), as were VIQ and PIQ and their associated subtests. The WIAT-II-A total achievement score also was within the average range (mean = 95.2, SD = 17.8), with basic reading recognition, spelling, and arithmetic skills being evenly developed within that range. Measures of attention regulation (*i.e.,* CPT-II errors of omission, errors

Table 1. Demographic characteristics of study participants ≥6 years of age (n = 368)

Characteristic	Value
Age (median, IQR)	13 (10, 15)
6 to 9 years (n = 102)	
10 to 13 years (n = 123)	
14 to 17 years (n = 143)	
Male (%, n)	59% (217)
Race (%, n)	
Caucasian	69% (255)
African American	14% (53)
Asian	2% (8)
other	14% (51)
Hispanic ethnicity (%, n)	14% (50)
Maternal education (median, IQR)	14 (12, 16)
High school or less (%, n)	41% (149)
13 to 15 years of education (%, n)	27% (99)
≥16 years of education (%, n)	31% (114)
Primary CKD diagnosis (%, n)	
Glomerular (*e.g.* focal segmental glomerulosclerosis)	26% (94)
Nonglomerular (*e.g.* obstructive uropathy)	74% (274)
CKD duration, years (median, IQR)	8 (4, 12)
% of life with CKD (median, IQR)	88% (34, 99)
Iohexol-based GFR, ml/min per 1.73 m^2 (median, IQR)	43 (33, 54)
Elevated proteinuria (>2 SDs) (%, n)	15% (54)
Anemia (%, n)	43% (154)
Hypertension (%, n)	51% (187)
Low birth weight (<2500 g) (%, n)	18% (65)
Learning disability (%, n)	15% (55)
ADHD by parent report (%, n)	12% (43)
Seizures (%, n)	12% (43)

IQR, interquartile range; CKD, chronic kidney disease; ADHD, attention deficit and hyperactivity disorder.

of commission, variability, and reaction time) were age-appropriate. Parental ratings of executive functions revealed few overall problems, with the three major BRIEF indices reflecting age-appropriate functioning. These findings can be seen in Table 2.

Percentage of Participants Manifesting Neurocognitive Risk. Table 2 shows the percentage of at-risk children, defined as test performance ≥1 SD below the normative mean for age, to range from 21% to 33% on IQ; 26% to 33% on achievement; 15% to 23% on attention regulation; and 27 to 40% on executive functioning. Compared with normal curve expectations (*i.e.,* about 16%), these percentages demonstrated that a large portion of children with mild-to-moderate CKD are at risk for neurocognitive dysfunction. Rates of study participants scoring ≥1 SD below the norm were more than double the normative expectation on WASI block design (33%), WIAT-II-A numerical operations (33%), BRIEF metacognition (35%), BRIEF working memory (40%), BRIEF planning (36%), and BRIEF global executive composite (33%).

Predictors of Neurocognitive and Academic Achievement Outcomes

Intellectual Functioning. Participants with elevated proteinuria scored 7.2 points lower on VIQ (95% confidence interval [CI] = −11.99, 2.39) and 6.1 points lower on FSIQ (95% CI = −10.73 to −1.44) than patients without this condition (Table 3). No other disease-related variables served as significant predictors of intellectual functioning.

Maternal education was associated with intelligence, with participants whose mothers attained 13 to 15 years of education scoring 7.2 points higher on VIQ, 4.2 points higher on PIQ, and 6.7 points higher on FSIQ than participants whose mothers had attained a high school education or less. This effect was more than doubled when maternal education was ≥16 years (Table 3). Participants who were identified as having low birth weight scored 4 to 6 points lower on IQ than participants having a normal birth weight. Similarly, those having comorbid seizure disorder also scored 8 to 10 points lower across the IQ scores than those without seizures. Girls scored 3 to 4 points lower on IQ than boys, and African Americans scored about 5 to 8 points lower than non–African Americans on IQ (Table 3). Selected interactions between elevated proteinuria and African American status (P = 0.24), elevated proteinuria and female gender (P = 0.92), and elevated proteinuria and maternal education (P = 0.25) on WASI FSIQ were NS.

Academic Achievement. iGFR (per 10 ml/min per 1.73 m^2) was a significant predictor of overall academic achievement skills, with a 1.4-point (95% CI = 0.02 to 2.68) increase in skills being associated with each 10 ml/min per 1.73 m^2 change in iGFR. None of the other disease-related variables were significant predictors of achievement after controlling for all of the other variables in the model.

As expected, participants' mothers who had 13 to 15 years of education scored about 5 to 6 points higher on overall academic achievement than those whose mothers had a high school education or less, and this rate doubled when participants' mothers had ≥16 years of education. African Americans scored about 6 points lower than non–African Americans. Participants with low birth weight scored 6 to 7 points lower than those with normal birth weight, and those with seizures scored nearly 9 points lower than those without seizures (Table 3).

Attention-related Variables. For the CPT-II omissions score, log transformations were required given the uneven distribution of the scores. Using these transformations, those with hypertension scored 1.0 (95% CI = 0.92 to 0.99) point worse on errors of omission but 2.7 points (95% CI = −5.20 to −0.18) better on attention variability than those without hypertension (Table 3). Individuals with elevated proteinuria score 1.1 points (95% CI = 1.00 to 1.13) worse on errors of omission.

The errors of omission score increased (*i.e.,* worsened) by about 1 point for every 2-year increase in age, but the variability score improved by 1 to 2 points. This pattern indicated that older age was associated with poorer attention but less variability in performance. African Americans obtained better scores on errors of commission by 5 to 6 points but were about 1 point lower on errors of omission and 5 points lower on variability. Low birth weight was associated with a 1-point increase in the errors of omission, indicating that low birth weight contributed to increased inattention after controlling for all other variables in the model. Selected interactions between hypertensive and Af-

Table 2. Descriptive statistics for the neurocognitive variables for the participants ≥6 years of age

Measure	Mean	SD	Confidence Interval Range (5^{th} Percentile; 95^{th} Percentile)	% >1 SD below Mean[a]
WASI				
verbal IQ	98.0	17.0	70; 123	21
vocabulary	47.6	12.0	26; 66	27
similarities	48.7	11.9	27; 66	24
performance IQ	95.4	16.3	70; 120	27
block design	46.3	11.3	29; 64	33
matrix reasoning	47.6	11.2	26; 63	26
full-scale IQ	96.4	16.5	68; 121	25
WIAT-II-A				
basic reading	96.5	17.1	66; 120	26
spelling	96.2	16.8	68; 122	26
numerical operations	93.7	20.2	60; 126	33
total achievement	95.2	17.8	67; 126	31
CPT-II				
omissions[b]	51.7	13.5	42; 79	15
commissions	51.7	11.0	32; 66	23
variability	50.1	11.0	35; 68	22
reaction time	48.2	11.9	31; 70	17
BRIEF-P				
behavioral regulation index[b]	53.5	11.1	39; 74	28
inhibition	52.9	11.3	40; 75	27
shift of set	53.0	10.9	38; 74	28
emotional control	53.2	11.1	38; 75	29
metacognition index	55.9	11.5	39; 76	35
initiation	55.1	11.2	38; 76	30
working memory	56.8	12.2	40; 79	40
planning	55.7	11.8	38; 77	36
organization	53.4	9.7	37; 69	27
monitoring	54.0	11.5	36; 73	30
global executive composite	55.2	11.6	39; 76	33

Wechsler Abbreviated Scales of Intelligence (WASI) intelligence quotients (IQ) and Wechsler Individual Achievement Test-II-Abbreviated (WIAT-II-A) scores are reported as standard scores with means of 100 and a standard deviation of 15, and WASI subtests have a mean of 50 and a standard deviation of 10. For these tasks, higher scores reflect more intact abilities. Conners' Continuous Performance Test-II (CPT-II) and Behavior Rating Inventory of Executive Functions (BRIEF) scores are reported as standard scores with a mean of 50 and a standard deviation of 10, and higher scores reflect more impaired abilities.
[a]≤1 SD below mean for WASI and WIAT-II-A variables and ≥1 SD above mean for CPT-II and Behavior Rating Inventory of Executive Functions-Parent (BRIEF-P) variables.
[b]Log transformations were required.

rican American status ($P = 0.75$) and hypertensive and chronological age ($P = 0.12$) on CPT-II variability were NS.

Executive Function Ratings. For the BRIEF score distributions, log transformations were required. Using these transformations, participants classified as hypertensive scored 1.1 (95% CI = 1.01 to 1.11) points higher (*i.e.,* more impaired) on the BRIEF behavioral regulation index than did those who were not hypertensive (Table 3).

Participants with mothers having ≥16 years of education received significantly worse ratings on the behavioral regulation index by about 1 point, but significantly better scores by nearly 4 points on the global executive composite than those participants whose mothers had a high school degree or less. Chronological age was significantly associated with the metacognitive index, with each 2-year increment in age generating nearly a 1-point worsening of the score. Participants with low birth weight received higher scores (*i.e.,* poorer performance) by nearly 4 points on the BRIEF metacognitive index and global executive composite than those with normal birth weight. The selected interactions between hypertension and maternal education for BRIEF behavioral regulation index were NS.

Predictors of Neurocognitive and Academic Achievement At-risk Status

Using at-risk status in the logistic regressions produced similar results to the linear regressions noted above for the intellectual functioning and academic skills; however, several additional findings were noteworthy. First, the logistic regression revealed that higher iGFR predicted a lesser chance of being at risk for overall executive dysfunction. Here, for every 10 ml/min per 1.73 m^2 increase in iGFR, the risk for falling ≥1 SD below the mean on the global executive composite was significantly decreased (odds ratio [OR] = 0.82; 95% CI = 0.69 to 0.097).

Second, having low birth weight was associated with a two-fold (95% CI = 1.07 to 3.73) risk for overall executive dysfunction and also served to increase the chances of being at risk for errors of omission by 3.54 times (95% CI = 1.55 to 8.06) the odds of those with normal birth weight.

Table 3. Adjusted multivariable linear regressions to determine predictors of neurocognitive outcomes

Characteristic	WASI Point Estimates (95% CI)			WIAT-II-A Point Estimates (Achievement, 95% CI)	CPT-II Point Estimates (95% CI)			BRIEF-P Point Estimates (95% CI)		
	Verbal IQ	Performance IQ	Full-scale IQ		Commissions	Omissions[a]	Variability	Behavior Regulation Index[a]	Metacognitive Index	Global Executive Composite
Female	−3.5 (−6.91 to −0.06)[b]	−4.0 (−7.45 to −0.51)[b]	−4.00 (−7.32 to −0.69)[b]	−2.1 (−6.11 to 1.82)	1.9 (−0.74 to 4.48)	1.0 (0.98 to 1.06)	1.0 (−1.63 to 3.52)	1.0 (0.92 to 1.00)	−0.8 (−3.52 to 1.87)	−2.5 (−5.12 to 0.22)
African American	−5.9 (−10.68 to −1.06)[b]	−8.8 (−13.69 to −3.95)[b]	−8.1 (−12.77 to −3.45)[c]	−6.1 (−11.71 to −0.41)[b]	−5.7 (−9.62 to −1.73)[c]	1.1 (1.04 to 1.18)[c]	5.2 (1.28 to 9.11)[c]	1.1 (0.99 to 1.14)	2.1 (−1.82 to 5.96)	2.1 (−1.71 to 5.94)
Maternal Education										
13 to 15 years	7.2 (3.19 to 11.25)[c]	4.2 (0.16 to 8.32)[b]	6.7 (2.82 to 10.63)[c]	5.6 (0.99 to 10.23)[b]	−0.7 (−3.69 to 2.38)	1.0 (0.99 to 1.09)	0.7 (−2.27 to 3.74)	1.0 (0.92 to 1.03)	1.1 (−2.09 to 4.27)	−0.6 (−3.75 to 2.55)
>16 years	14.6 (10.64 to 18.47)[c]	10.2 (6.25 to 14.19)[c]	13.7 (9.89 to 17.48)[c]	14.5 (9.94 to 19.07)[c]	−2.1 (−5.13 to 0.97)	1.0 (0.94 to 1.03)	−2.5 (−5.53 to 0.50)	0.9 (0.87 to 0.97)[c]	−3.00 (−6.12 to 0.13)	−4.0 (−7.06 to −0.87)[b]
Age per 2 years	−0.3 (−1.37 to 0.75)	−0.8 (−1.83 to 0.33)	−0.5 (−1.54 to 0.52)	−0.7 (−1.89 to 0.59)	−0.3 (−1.13 to 0.52)	1.0 (0.96 to 0.99)[c]	−1.6 (−2.45 to −0.83)[c]	1.00 (0.99 to 1.02)	0.9 (0.05 to 1.74)[b]	0.7 (−0.12 to 1.55)
Low birth weight	−6.2 (−10.36 to −2.01)[c]	−4.3 (−8.50 to −0.05)[b]	−5.9 (−9.96 to −1.88)[c]	−6.7 (−11.57 to −1.78)[c]	2.9 (−0.34 to 6.16)	1.1 (1.03 to 1.14)[c]	2.4 (−0.74 to 5.60)	1.0 (0.96 to 1.08)	3.9 (0.53 to 7.28)[b]	3.9 (0.60 to 7.27)[b]
Glomerular diagnosis	3.6 (−1.12 to 8.28)	3.8 (−0.96 to 8.57)	4.1 (−0.47 to 8.64)	2.9 (−2.57 to 8.32)	−0.6 (−4.15 to 2.97)	1.1 (0.99 to 1.11)	−0.1 (−3.62 to 3.49)	1.0 (0.91 to 1.04)	−3.1 (−6.76 to 0.59)	−2.1 (−5.71 to 1.58)
iGFR per 10 ml/min per 1.73 m^2	0.7 (−0.32 to 1.75)	0.8 (−0.27 to 1.82)	0.8 (−0.22 to 1.79)	1.4 (0.02 to 2.68)[b]	−0.1 (−0.84 to 0.71)	1.0 (0.98 to 1.00)	−0.5 (−1.27 to 0.26)	1.0 (0.97 to 1.00)	−0.7 (−1.54 to 0.11)	−0.7 (−1.49 to 0.15)
% of life with CKD to per 10%	0.2 (−0.37 to 0.74)	−0.1 (−0.64 to 0.48)	0.1 (−0.46 to 0.61)	0.2 (−0.44 to 0.84)	0.1 (−0.37 to 0.46)	1.00 (0.99 to 1.01)	0.2 (−0.22 to 0.61)	1.00 (0.99 to 1.01)	0.03 (−0.40 to 0.46)	0.1 (−0.30 to 0.56)
Elevated proteinuria	−7.2 (−11.99 to −2.39)[c]	−3.9 (−8.71 to 1.01)	−6.1 (−10.73 to −1.44)[b]	−0.5 (−6.01 to 4.96)	1.5 (−2.32 to 5.22)	1.1 (1.00 to 1.13)[b]	1.8 (−1.95 to 5.62)	1.0 (0.91 to 1.04)	−1.1 (−4.85 to 2.66)	−1.5 (−5.27 to 2.18)
Hypertensive	1.2 (−2.08 to 4.51)	−0.1 (−3.40 to 3.28)	0.5 (−2.65 to 3.74)	1.4 (−2.40 to 5.27)	−0.6 (−3.11 to 1.97)	1.0 (0.92 to 0.99)[b]	−2.7 (−5.20 to −0.18)[b]	1.1 (1.01 to 1.11)[b]	1.0 (−1.66 to 3.60)	2.0 (−0.59 to 4.63)
Seizures	−8.5 (−13.53 to −3.37)[c]	−10.1 (−15.20 to −4.90)[c]	−10.2 (−15.15 to −5.30)[c]	−8.8 (−14.58 to −2.93)[c]	0.7 (−3.25 to 4.60)	1.0 (0.92 to 1.05)	−0.6 (−4.54 to 3.25)	1.1 (0.99 to 1.14)	3.2 (−0.98 to 7.34)	3.5 (−0.61 to 7.64)

Higher intelligence quotient (IQ) and achievement scores reflect better performance, whereas higher Conners' Continuous Performance Test-II (CPT-II) and Behavior Rating Inventory of Executive Functions (BRIEF) scores reflect poorer performance. CI, confidence interval; CKD, chronic kidney disease; iGFR, iohexol-based GFR; WASI, Wechsler Abbreviated Scales of Intelligence; WIAT-II-A, Wechsler Individual Achievement Test-II-Abbreviated.

[a]The variables were log transformed for analyses, and the regression coefficients and confidence limits were exponentiated. These values correspond to the ratio of the means.

[b]$P < 0.05$.

[c]$P < 0.01$.

Having comorbid seizures also significantly increased the chances of an individual falling in the at-risk range for FSIQ (OR = 3.62; 95% CI = 1.62 to 8.11), academic achievement (OR = 3.71; 95% CI = 1.67 to 8.25), and BRIEF metacognitive index (OR = 2.63; 95% CI = 1.22 to 5.65).

Finally, increased maternal education (≥16 years of education) diminished the chances of having at-risk status on the BRIEF metacognitive index (OR = 0.51; 95% CI = 0.28 to 0.94) and global executive composite (OR = 0.50; 95% CI = 0.27 to 0.94); every 2 years of chronological age lessened the likelihood of an individual being at risk for errors of omission (OR = 0.75; 95% CI = 0.58 to 0.97) and variability (OR = 0.68; 95% CI = 0.55 to 0.83), and being African American decreased the odds of being at risk for commission errors (OR = 0.09; 95% CI = 0.01 to 0.68).

Discussion

Findings from this study are noteworthy in that they represent one of the largest multisite investigations of mild-to-moderate kidney disease in a pediatric nephrology population. Consistent with earlier investigations of children with severe CKD or mixed severity sample (15–18), findings from this study revealed that, in general, children with mild-to-moderate kidney disease fall within age-appropriate expectations for IQ, academic achievement, and attention/executive functioning. When individual patients were examined, however, there was a large percentage of children who evidenced risk for dysfunction. This was especially noteworthy for the parent ratings of executive functioning, where percentages ranged from 27% to 40%, and would be consistent with previous work showing executive dysfunction in mixed-severity samples of children with CKD using laboratory assessments (19). Although executive impairments are certainly not unique to kidney disease, their appearance in children with mild-to-moderate CKD severity is noteworthy, particularly given that this disease undoubtedly will worsen over time.

Whereas we found the expected relationships between maternal education and neurocognitive functioning (20), the relative lack of association between the CKD-related variables and neurocognitive functions was striking. After controlling for other variables in the model, the presence of glomerular diagnosis and the percentage of life with CKD did not relate to performance on any of the neurocognitive outcomes, and iGFR was a significant predictor only for academic achievement. These findings suggest that there may be a particular threshold for disease burden before observing specific neurocognitive impairment. Conversely, we found higher iGFR to be associated with lower risk for executive dysfunction, and this finding gives us the first hint that the neurocognitive effects of early CKD might be delineated with more precise measurement.

The results did show that participants with elevated proteinuria had lower VIQ and FSIQ and poorer attention after controlling for other variables in the model; moreover, the subgroup with elevated proteinuria had several distinct characteristics worth noting. Specifically, they were older (14.6 *versus* 12.6 years) and more likely to have glomerular disease (52% *versus* 21%), hypertension (63% *versus* 49%), and immunosuppressive medication use (20% *versus* 11%) than the nonproteinuric group. Previous analysis of this dataset has shown a racial disparity in proteinuria and cause of CKD (21), for which we likely could not adjust completely. Consequently, although proteinuria may serve as a potential biologic index for neurocognitive dysfunction, it remains an ongoing question as to whether it is an independent effect beyond race and socioeconomic factors.

Hypertension also was not clearly related to neurocognitive function. Having hypertension contributed to more impairment on the BRIEF behavior regulation index, which rates the individual's ability to shift cognitive set and modulate emotions and behavior via appropriate inhibitory controls; however, the one T-score point difference is likely of little clinical significance. Similar findings were noted for the CPT-II errors of omission and variability. Others have shown that individuals with hypertension evidenced decreased neurocognitive abilities when compared with normotensive controls (22) and that subsequent pharmacologic treatment had positive effects on neurocognitive abilities (23,24); however, our findings may have been constrained by the fact that 67% of our sample was already taking hypertensive medications.

Finally, the consistency with which low birth weight related to both at-risk status and lower IQ, academic achievement, attention, and executive capabilities was noteworthy, particularly given that only 18% of the sample was identified as having low birth weight. Although the influence of low birth weight on later neurocognitive functioning is well documented (25), its influence on neurocognitive functioning in this sample persisted even when adjusting for a host of other variables. Furthermore, the 18% rate in our sample is over twice the national prevalence of low birth weight (8.2%) in the United States (26); consequently, children with CKD and low birth weight may have "double jeopardy" with respect to later neurocognitive difficulties and associated learning problems. A similar set of observations could be made for the presence of comorbid seizures in children with mild-to-moderate CKD. Taken together, this would warrant more vigilant neurodevelopmental surveillance by caregivers and clinical providers.

The findings from this large multisite study not only build on work from smaller, single-center samples but also point to the need for ongoing neurodevelopmental surveillance of children with CKD. This will prompt early targeted interventions to improve lifetime rehabilitation potential and quality of life. It also will allow for ongoing examination of the effect of specific disease-related variables that may become increasingly more apparent with disease progression and subsequent increased disease burden.

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Disclosures

None.

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