HHS Public Access

Author manuscript

Pediatr Nephrol. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

Pediatr Nephrol. 2022 April ; 37(4): 765–775. doi:10.1007/s00467-021-05158-w.

Overview of the Findings and Advances in the Neurocognitive and Psychosocial Functioning of Mild to Moderate Pediatric CKD: Perspectives from The Chronic Kidney Disease in Children (CKiD) Cohort Study

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Authors' contributions: Authors from the CKiD Neurocognitive Committee contributed equally to this educational review.

Declarations

Conflicts of interest/Competing interests: None of the authors have any conflicts of interest to report with respect to the content of this paper.

Availability of data and material: Data in this manuscript were collected by the Chronic Kidney Disease in children prospective cohort study (CKiD) with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital and the University of Missouri - Kansas City and Children's Hospital of Philadelphia, Central Biochemistry Laboratory at the University of Rochester Medical Center, and data coordinating center at the Johns Hopkins Bloomberg School of Public Health. Additionally, data for approximately the first 13 years of this study are available in the form of a public use data base.

Code availability: Not applicable.

Ethics approval: All studies included in this educational review were approved via the study site institutional review board.

Consent to participate: All participants were enrolled into CKiD as per their institutional review board requirements.

Consent for publication: Not applicable.

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Abstract

The Chronic Kidney Disease in Children (CKiD) prospective cohort study was designed to address the neurocognitive, growth, cardiovascular, and disease progression of children and adolescents with mild to moderate CKD. The study has had continuous funding from NIDDK for 17 years and has contributed significant advances in pediatric CKD. The goals of this Educational Review are threefold: (1) To provide an overview of the neurocognitive and psychosocial studies from CKiD to date; (2) To provide best practice recommendations for those working with the neurocognitive and psychosocial aspects of pediatric CKD based on CKiD findings; and (3) To help chart future goals and directives for both research and clinical practice. This collection of 22 empirical studies has produced a number of key findings for children and adolescents with mild to moderate CKD. While various studies suggest a relatively positive presentation for this population as a whole, without evidence of significant impairment or deterioration, findings do indicate the presence of neurocognitive dysfunction, emotional-behavioral difficulties, and lower quality of life for many children with CKD. These findings support the promotion of best practices that are accompanied by additional future clinical and research initiatives with this patient population.

Keywords

pediatric CKD; CKiD Study; neurocognition; quality of life; emotional-behavioral

Introduction

Interest in the relationship between neurocognitive and psychiatric functioning in children with chronic kidney disease (CDK) spans the past 30 years. The general consensus from published work is that there is a well-recognized association between kidney disease and neurocognitive dysfunction in children and adolescents [1] as well as the potential for psychiatric manifestations in pediatric CKD [2]. Most of this work has been devoted to small samples of children with mixed disease severity and complicated by confounders that have clouded these relationships. Furthermore, there are few pediatric longitudinal studies with a focus on neurodevelopmental outcomes in children with mild to moderate CKD. The Chronic Kidney Disease in Children (CKiD) prospective cohort study provides a vehicle to address many of these issues [3].

CKiD Study Description

The CKiD Study was designed to address a number of key scientific questions through the recruitment of a large number of subjects ranging from 12 months to age 16 years across 54 different sites in the United States and Canada, and utilizing common data elements across all of the sites. This study, funded continuously by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for the past 17 years, has yielded a number of key contributions to the field of pediatric nephrology to include advances in our understanding of estimated glomerular filtration rate (eGFR) and factors associated with its progression [4], growth [5], and cardiovascular health [6]. One of the additional primary study goals was to delineate and advance our understanding of the neurocognitive and psychosocial manifestations in early pediatric CKD prior to the presence of significant kidney dysfunction.

The goals of this review are threefold: (1) To provide an overview of the 22 neurocognitive and psychosocial studies that have been conducted by CKiD to date, with a particular focus on new findings advanced by these studies. These studies are summarized in Table 1. (2) To provide clinical recommendations for those working with the neurocognitive and psychosocial aspects of pediatric CKD based on the findings generated by CKiD. (3) To help chart future goals and directives for both research and clinical practice.

Neurocognitive and Psychosocial Contributions

Neurocognitive Findings—There have been 14 studies examining the neurocognitive functioning of the CKiD sample to date (see Table 1). In one of the first studies to emerge from the CKiD Study on neurocognitive functioning in mild to moderate CKD, Hooper et al [7] demonstrated that while the cognitive functioning for this sample of 368 school-age children, ages 6 to 16, was within the average range, about 21% to 40% of participants were deemed to be at-risk (i.e., > 1 standard deviation below the test mean) for neurocognitive dysfunction as defined by measures of intelligence, attention regulation, selected executive functions, and overall academic achievement. In this initial study, the presence of elevated proteinuria was associated with lower intelligence (IQ) and increased attention regulation problems, while higher eGFR was associated with preserved executive functioning (EF). Similarly, when neurocognitive functioning was examined in 124 preschool children with CKD, Hooper et al [8] reported an overall average level of functioning, but a distribution skewed toward lower cognitive performance. Here, 27% of subjects were at least one standard deviation below the mean on IQ, 20% showed significant attention dysregulation, and 30% had parental ratings of heightened executive dysfunction compared to peers. As with the school-age study, few kidney disease-related variables were associated with neurocognitive dysfunction; however, again, higher eGFR and lack of anemia were associated with more intact cognitive abilities. Neither of these cross-sectional studies revealed any major neurocognitive difficulties in the sample, although in both studies the overall findings showed generally higher rates of subtle neurocognitive dysfunction present within those with CKD compared to normative data.

Longitudinal findings from CKiD have also revealed no major deterioration in neurocognitive abilities over at least an 8-year time period, but significant changes in eGFR,

as defined by 5% change per year, were associated with a lowering of IQ (Hooper et al, unpublished data).

The overall academic achievement of the CKiD sample appears to be relatively intact. Consistent with initial description of the performance of this overall sample [7], about one-third of the sample demonstrated significantly lower skills, particularly in mathematics, and low achievement was related to days of missed school and presence of an individualized education plan. [9].

Association with Disease-Related Variables—In addition to the attention devoted to eGFR and proteinuria, CKiD studies have uncovered several other medical and disease-related correlates to neurocognitive functioning. Mendley et al [10] showed that a longer duration of CKD was associated with poorer attention and associated executive dysfunctions. Further, higher casual blood pressure [11] and highly variable visit-to-visit systolic blood pressure [12] were associated with lower nonverbal IQ and verbal set-shifting capabilities (i.e., efficiently moving from one problem solving strategy to another), respectively. These findings remained present after controlling for a host of sociodemographic and CKD-related variables. Blood pressure variability also was found to significantly interact with low levels of bicarbonate ($CO_2 \leq 20$ mmol/L at baseline) to contribute to lower overall parent ratings of EF, suggesting the need to treat both acidosis and blood pressure as one pathway to addressing neurocognitive functioning in pediatric CKD [13]. Lastly, Yokoyama et al [14] demonstrated that a higher plasma FGF-23 level was associated with lower performance in executive function and attention regulation, particularly with respect to errors of omission and speeded response, and this finding was independent of eGFR.

Furthermore, these neurocognitive findings may be accompanied by brain abnormalities manifested in the form of focal and multifocal white matter injury in the anterior limb of the internal capsule on brain MRI in a subset of CKiD patients [15] as well as by the presence of ischemic stroke [16]. While the former imaging findings require replication and determination of their association with cognitive functioning, the presence of ischemic stroke was associated with uniformly low cognitive functioning with an estimated incidence rate of 36.8 per 100,000 (as compared to the population rate of approximately 3 to 25 per 100,000). The pursuit of an underlying neurological mechanism is an important component to understanding the neurocognitive dysfunction that can be seen in some children with mild to moderate CKD, particularly with the multiple dynamic changes that can be seen in both disease progression and ongoing brain maturity [9]. Such findings have been demonstrated in other pediatric conditions (e.g., Turner Syndrome) [17, 18] and have contributed, in part, to increased understanding of their neurocognitive functioning.

While the CKiD Study has focused on a relatively homogenous group of children and adolescents with respect to disease severity, it is important to note that the sample is a heterogenous group of conditions with the common problem of chronic kidney disease. Verbitsky et al [19] demonstrated that a subset of children with CKD are diagnosed with genomic disorders that predispose them to both kidney abnormalities and neurocognitive impairment. These findings suggest that a microarray can provide additional information

on a molecular diagnosis in children with CKD such that early intervention could be initiated prior to the appearance or worsening of any neurocognitive and/or neuropsychiatric manifestations.

Similarly, the presence of relatively small amounts of lead in the blood was related to lower IQ and heightened inattention in pediatric CKD [20], and this also could contribute to early intervention efforts when suspected and detected. In contrast, in studies examining more disease-specific subgroups of children with CKD – specifically, children with autosomal recessive polycystic kidney disease [21] and lupus nephritis [22] - relatively minimal neurocognitive or social-behavioral impairment has been demonstrated. Finally, there also could be a number of environmental factors that contribute to neurocognitive functioning that include early intervention, formal school experiences including attendance, quality of instruction and access to special services, family functioning, and other associated stressors that go beyond having a child with a chronic illness. While the CKiD Study has been able to address many of these confounding variables, there remain a significant number of other variables (e.g., family functioning) that should be explored.

Emotional-Behavioral Functioning—The CKiD Study has also provided insight to the emotional-behavioral and social functioning among children with early CKD, with two studies focusing on these outcomes and several others addressing these issues as part of a larger set of questions. Johnson et al [23] examined parent ratings of children's emotional-behavioral functioning and adaptive behavior utilizing a standardized parent rating measure. The sample included 845 participants, ages 2 to 18 at study entry. The sample was 61% male and 22% African American, with about 40% having a high school degree or less. After adjusting for these variables, longitudinal ratings for this sample indicated that parents' perceptions of their children's functioning were largely within normal limits, with median scores being in the average range. Similar to the neurocognitive findings, a higher proportion of children than expected had parent ratings one standard deviation or more above or below the mean on several scales, indicating an increased risk of difficulty in one or more emotional-behavioral or adaptive domains. This included 28% of subjects at risk (i.e., ≥1 standard deviation below the mean) for parent ratings of attention problems, and a higher-than-expected percentage of patients at risk on adaptive scales including leadership skills, activities of daily living, and functional communication.

In the Hooper et al preschool study noted above [8], median scores on parent ratings of social-behavioral functioning were within the average range. In contrast, parent ratings of adaptive behavior (e.g., home living, self-care, health, and safety) were in the low average to average range. For this group, a greater percentage than expected placed in the "at risk" range for adaptive behavior problems (37%). Increased risk was not observed for social-behavioral parent-ratings for the preschool children. Similarly, for the subsamples of children with autosomal recessive polycystic kidney disease and lupus nephritis, parent ratings did not reveal any significant emotional-behavioral concerns [21, 22].

Association with Disease-Related Variables—When evaluating disease-specific variables, change in kidney function (eGFR) was not associated with emotional-behavioral or adaptive skills. Conversely, proteinuria and persistent hypertension were associated with

increased parent-reported attention problems and history of seizures was associated with more internalizing symptoms (e.g., anxiety, depressive symptoms). Glomerular disease status (versus non-glomerular) was associated with fewer internalizing symptoms which may be due to a shorter disease course at study entry for those with glomerular disease (i.e., median duration of disease status: Glomerular = 3.5 yrs., non-glomerular = 7.6 yrs.). Additionally, for the subsample of children with lupus nephritis, few emotional-behavioral problems were reported; however, an interaction was observed between current prednisone use and lupus nephritis for internalizing problems, with worse parent-reported internalizing problems in children with lupus nephritis on prednisone [22].

Consistent with the above findings, Kogon et al [24] evaluated the self-reported depressive symptoms of 344 school-age children and found that depressive symptoms were not associated with change in eGFR. However, a small percentage (5%) reported elevated depressive symptoms, which is slightly higher than the national prevalence rate of 3.2%, and another 2% reported concurrent treatment for depression. Despite these relatively lower rates of depression, depressive symptoms were associated with lower IQ, lower academic achievement, and poor self- and parent-reported health-related quality of life, suggesting that targeting depressive symptoms for treatment may lead to improved school achievement and overall quality of life. In fact, there is available literature indicating the importance of nurturing caregiving and peer support as potential protective factors against depression [25], and this becomes a needed area of scientific inquiry in the study of pediatric CKD.

Quality of Life Findings—Interest in quality of life runs high in most pediatric chronic illness populations and these functions have been examined in six CKiD studies to date. In the largest study examining quality of life in children and adolescents with mild to moderate CKD (n = 402), Gerson et al [26] found that parent and youth reported ratings in the physical, school, social, and emotional domains were significantly more impaired when compared to parent and youth reports from healthy children after adjusting for a host of sociodemographic and CKD-related factors. Contrary to what might be expected, better scores in the physical, emotional, and social domains were significantly associated with longer disease duration and older age, perhaps secondary to having a longer time for the child and caregivers to adjust and make accommodations for the chronic illness. This presumed adaptation also could indicate significant resiliency in this population pertaining to their perception of physical, social, and emotional functioning, an area that remains relatively unexplored in pediatric CKD. Additionally, Gerson et al reported that older age, regardless of age of diagnosis, also was significantly related to lower school quality of life ratings, and short stature was significantly related to poorer physical functioning. In contrast, higher family socioeconomic status was associated with higher quality of life ratings in physical, school, and social domains.

Longitudinal analyses show trends similar to the neurocognitive and emotional-behavioral findings with little change in perceived quality of life over time [27]. Despite the hypothesis that there would be deterioration over time, longer duration of CKD was associated with higher, not lower, child-rated health-related quality of life (HRQOL) although quality of life for the CKiD sample remained well below the values seen in unaffected children. Even among children at highest risk for poor quality of life, including those who started

at lower ratings, the large majority show positive trajectories in child-reported HRQOL. In contrast, parent-proxy reports of their child's HRQOL did not reflect improvement with longer duration of their child's CKD, with only a minority of parents reporting an increasing trajectory.

Association with Disease-Related Variables—Carlson et al [27] found anemia (i.e., hemoglobin < 5th percentile for age, sex, race) to be associated with significantly lower quality of life as defined by physical functioning by the child rating and on emotional functioning by the parent ratings. Anemia that was resolved or persistent did not manifest changes, either positive or negative, in any area of HRQOL when compared to CKD patients without anemia. So, despite the relationship of anemia with selected areas of quality of life ratings, parent and child quality of life ratings do not appear to deteriorate over time. Disease severity, as defined by eGFR, was not related to HRQOL, although Wong et al [28] did show a significant, but modest relationship between elevated blood pressure and lower parent and child ratings of HRQOL. Similarly, Roumelioti et al [29] showed that severity of CKD was associated with increased reporting of weakness, fatigue, daytime sleepiness, and lower quality of life ratings, and Ferris et al [30] demonstrated that while the average quality of life scores reported by parents of younger children with CKD were higher than those of their older counterparts, these ratings decreased significantly more in the younger age group as the number of medications increased when compared to older children with CKD. Finally, Al-Uzri et al [31] showed growth in height and use of growth hormone to be related to better parent report of physical and social functioning in children with CKD.

Best Practices Based on CKiD Findings—This collection of 22 empirical studies has produced a number of key findings from this large sample of children and adolescents with mild to moderate CKD. While the results of the various studies suggest a relatively positive presentation of this sample as a whole, with some associated conditions wherein cognitive functioning appears to be relatively intact (e.g., autosomal-recessive polycystic kidney disease, lupus nephritis), there are still findings that indicate the presence of problems across neurocognitive, emotional-behavioral, and quality of life domains, particularly in the presence of high or variable blood pressure, anemia, and low bicarbonate. Taken together, these findings support the promotion of several best practices that should drive both clinical and research initiatives in the pediatric nephrology population.

- Our findings to date suggest that children and adolescents with mild to moderate CKD do not have significant cognitive deterioration over time with progression of CKD from mild-moderate toward end stage. While we did find a higher percentage of children and adolescents with lower IQ, academic deficits, poorer attention regulation, executive dysfunction, emotional dysregulation, and lower quality of life ratings compared to healthy children, the overall profile for this CKD sample with mild to moderate disease severity appears to be relatively intact with no evidence of deterioration over the time spanned studied to date. This is positive news for providers, parents, and the patients themselves.
- Given that there is a significantly high percentage of the population who will experience neurocognitive, emotional-behavioral, and quality of life

difficulties, it remains important to include regular, systematic neurocognitive and psychosocial monitoring as part of standard follow-up care. This does not have to entail a full complement of assessment procedures; but, rather, routine screening for such concerns as part of their regular medical treatment. The studies have revealed indicators of subtle problems with IQ, particularly nonverbal IQ, attention regulation, and overall executive functioning capabilities, in addition to some sense of emotional-behavioral and quality of life issues, and it will be important for the first signs of these concerns not to be missed. Indeed, these types of difficulties have been demonstrated in a number of pediatric chronic disease conditions, such as cancer, sickle cell disease, and hepatic disease, particularly with respect to a lower IQ; however, this is not a universal finding across pediatric chronic conditions, as in several conditions, such as hemophilia, cystic fibrosis, and even conditions within CKD (e.g., ARPKD), there does not appear to be any additional neurocognitive burden secondary to chronic illness per se [32]. What is remarkable about this corpus of CKiD findings is that they have been identified in children with mild to moderate illness severity. Thus, it is imperative for these subtle differences to be identified and subsequently managed as part of the child's medical care. Additionally, while it remains unclear how kidney disease directly affects neurodevelopment in children and adolescents, it is clear from emergent neuroimaging studies for children with CKD that underlying neural structure is different and, as such, may contribute to different (e.g., does plasticity occur?) or abnormal (e.g., do modified and/or malformed myelination patterns emerge?) neural contributions to neurocognitive functioning. These neurodevelopmental differences, when compared to adults, continue to reflect the need for systematic follow-up regarding the integrity and change of neurocognitive functioning over the dynamic course of development. Given that we did not find major neurocognitive, emotional-behavioral, or quality of life impairments through the first 16 years of this study, though, the question remains as to when deterioration will occur as suggested by the kidney replacement literature [33], and ongoing neurodevelopmental surveillance will be particularly important with the progression of CKD toward kidney failure and subsequent kidney replacement therapies.

- As part of standard of care, assessment practices should include measures of IQ, attention, and executive functions. Specific measurements for these domains of function will vary across site and availability, with a wide range of direct assessment and behavior ratings scales available for use by psychologists and other providers (e.g., pediatricians, mental health providers, etc.). At this juncture there is no clear sense of the timing of when these assessments should occur over the course of disease progression (e.g., CKD Stage 1, CKD Stage 3, etc.), though given the subtle risks present it would be prudent to have a neurodevelopmental assessment every couple of years. In the CKiD Study, such assessments occurred once every two years. In addition to the areas of dysfunction identified by the CKiD Study, Chen et al [1] noted that assessment of other cognitive functions, such as memory, also may prove

useful as part of a larger assessment. Given the importance of neurocognitive functioning to academic achievement, measures of academic skills should be included, particularly math skills, as should assessment of emotional-behavioral functioning and quality of life perceptions.

- Findings from this collection of studies have demonstrated the complexities inherent in pediatric CKD by showcasing the importance of co-morbid or co-occurring conditions that have been shown to be independently associated with neurocognition. These factors include high blood pressure, blood pressure variability, the interaction of blood pressure variability and low levels of bicarbonate, blood lead, and the presence of genetic conditions that may affect both the brain and the kidney. Such knowledge has the potential to improve screening and intervention strategies aiming to decrease exposure to chronic disease (primary prevention), limit resulting pathology (secondary prevention), and help those already suffering effects (tertiary prevention). More specifically, assessing for these factors in pediatric CKD could inform CKD-specific treatment approaches (e.g., the need to treat both acidosis and blood pressure to address neurocognitive functioning; focused treatment of hypertension [34]) that may ultimately affect both the course of CKD progression as well as improve neurocognitive and psychosocial functioning.

Future Directions

Findings from the scientific endeavors in the CKiD Study provide a more positive outlook on cognition and psychosocial outcomes than initially expected at the inception of the study, but our CKiD studies have shown that there remains a large percentage of the mild to moderately involved population who will still experience neurocognitive and psychosocial difficulties that will require attention. Going forward, we will continue to examine our extensive database, particularly with respect to the interactions of various factors and potential subgroups, and have now advanced into CKiD-IV. For this phase of the study, we have incorporated new cognitive measures (e.g., NIH Cognitive Toolbox) [35] that should permit the collection of common data elements across different studies beyond CKiD.

Additionally, given our preliminary findings with respect to the presence of genomic disorders, a further exploration of genotype-phenotype linkages may be warranted. Similarly, given the preliminary findings in the literature with respect to brain structure, increased attention to the brain-based functions in pediatric CKD also are in order and will assist in guiding the field with respect to neurological mechanisms inherent in pediatric CKD [9]. Perhaps most importantly, with CKiD-IV we have begun following participants into their kidney replacement therapies and have the opportunity to examine neurocognitive and psychosocial functioning post-RRT where we will have one of the largest samples in the world with pre- and post-RRT data. Similarly, with the aging of our sample, we also have the opportunity to track older adolescents and young adults into their adult clinical services. Future work also should include measures of family functioning and peer support, to include assessment of caregiver and sibling quality of life and general functioning status, in order to examine factors of risk and resiliency in this population as well as provide more detailed information on family factors that could be contributing to the neurocognitive

and psychosocial functioning of children with CKD. Ultimately, findings from the CKiD Study should drive evidence-based treatment programs to address the neurocognitive and the psychosocial needs of this population of children and adolescents [36]. Methodologically, the CKiD Study is an observational study, which can only provide associations, but a strategically planned randomized clinical treatment trial could lead to increased cause-and-effect relationships and propel the field forward with respect to evidence-based treatment efforts.

Multiple-choice questions (answers are provided following the reference list)

1. In the CKiD Study, a relatively high percentage of children with mild to moderate CKD can manifest mild neurocognitive difficulties in:
   - **a.** Impulsivity
   - **b.** Verbal IQ
   - **c.** Parent ratings of executive functions
   - **d.** Anxiety
2. From the CKiD Study, there are a variety of factors that have been associated with neurocognitive functioning including:
   - **a.** Low bicarbonate and low blood pressure variability
   - **b.** High bicarbonate and high blood pressure variability
   - **c.** Low bicarbonate and high blood pressure
   - **d.** High bicarbonate and low blood pressure
3. Children with mild to moderate CKD show:
   - **a.** Rates of depression that are slightly higher than that found in the normal population
   - **b.** Extremely high rates of depression
   - **c.** Extremely high rates of behavior problems
   - **d.** Extremely low rates of depression
4. On quality-of-life ratings, parents and youth reported:
   - **a.** Ratings in the physical and emotional domains to be significantly more impaired when compared to similar reports from healthy children.
   - **b.** Ratings in the physical domain to be significantly more impaired when compared to similar reports from healthy children.
   - **c.** Ratings in the physical, school, social, and emotional domains to be equivalent to those from healthy children.
   - **d.** Ratings in the school and social domains to be significantly higher when compared to similar reports from healthy children.

5. From the CKiD Study, best practices would dictate:
   a. The need for annual comprehensive assessments.
   b. No need for any comprehensive assessments in this population.
   c. Appreciation for the various factors contributing to neurocognitive and psychosocial outcomes, including increased consideration for brain imaging and genetic testing strategies, and consideration for routine monitoring of neurocognitive and psychosocial functioning.
   d. A focus on neurocognitive assessments at more frequent intervals than emotional-behavioral assessments.

Acknowledgements

Data in this manuscript were collected by the Chronic Kidney Disease in children prospective cohort study (CKiD) with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital and the University of Missouri - Kansas City (Bradley Warady, MD) and Children's Hospital of Philadelphia (Susan Furth, MD, PhD), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and data coordinating center (Alvaro Muñoz, PhD and Derek Ng, PhD) at the Johns Hopkins Bloomberg School of Public Health. The CKiD Study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01 DK066143, U01 DK066174, U24 DK082194, U24 DK066116). The CKiD website is located at https://statepi.jhsph.edu/ckid and a list of CKiD collaborators can be found at https://statepi.jhsph.edu/ckid/site-investigators/. Investigators can access the publication acknowledgment on the Investigator Resources page on the CKiD website: https://statepi.jhsph.edu/ckid/investigator-resources/. The acknowledgment is also included in the concept sheet submission form and Publication Policy. Both documents have been updated with the new publication acknowledgement and have been reposted on the Investigator Resources page.

Funding: The CKiD Study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U24-DK-082194, U24-DK-66116).

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Key Summary Points

- A significant number of children and adolescents with mild to moderate CKD can show neurocognitive, emotional-behavioral, and quality of life difficulties.
- Despite these difficulties, the overall profile of children with mild to moderate CKD does not indicate the presence of severe impairments.
- The neurocognitive, emotional-behavioral, and quality of life of children with mild to moderate CKD do not show significant deterioration over time, even as their kidney disease worsens and progresses, at least until the point of kidney replacement therapies.
- Neurocognitive and psychological monitoring should be part of a routine standard of care for developmental surveillance of this population, with formal assessments being indicated at the sign of neurocognitive and/or psychosocial difficulties, particularly given the relatively higher rates of risk for negative neurodevelopmental outcomes that have been uncovered.
- In addition to CKD, there are numerous other possible contributors to neurocognitive and psychosocial impairment including sociodemographic (e.g., family functioning, peer support) and disease-related factors (e.g., seizures, hypertension, anemia, elevated proteinuria) that could be independent contributors to the presence of these impairments as well as potential resilience.

Table 1.

Summary of CKiD Neurocognitive and Psychosocial Studies from 2010–2021 (n = 22 Studies)

Study	Sample	Measures	Findings
Neurocognitive			
Hooper et al, 2011	n = 368 children, ages 6–16 yrs.	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), selected tasks from D-KEFS	21% to 40% deemed to be at risk for neurocognitive dysfunction. Elevated proteinuria was associated with lower IQ and increased attention problems. Higher eGFR was associated with preserved executive functions.
Lande et al, 2011	n = 383; 132 (34%) had elevated blood pressure.	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), D-KEFS (selected tasks)	Higher casual blood pressure associated with lower nonverbal IQ.
Hartung et al, 2014	n = 22 ARPKD patients compared to n = 44 children with other causes of CKD matched on eGFR, age at study entry, and age at diagnosis.	WASI or WPPSI-R or MSEL, WIAT-II Screening, CPT-II or K-CPT, BRIEF (parent), BASC-2 (parent)	Children with ARPKD in the CKiD sample showed intact neurocognitive abilities and average parent ratings of social- behavioral when compared to normative expectations and other children with CKD.
Mendley et al, 2015	n = 340, ages 6 to 21 yrs. (median age = 13.0 yrs.); median duration of CKD = 10 yrs.	CPT-II, D-KEFS Tower Task, Digit Span Backward task from the age-appropriate Wechsler Intelligence Scale	Longer duration of CKD associated with lower attention and executive functions.
Hooper et al, 2016	n = 124 children, ages 12 to 68 months (median = 3.7 years)	WPPSI-III, MSEL, K-CPT, ABAS-II	Average level of development/IQ, but distribution was skewed toward lower cognitive abilities. 20% to 30% performed in the at-risk range on the neurocognitive measures, and 37% received ratings in the at- risk range for adaptive behavior problems. Higher eGFR associated with higher cognitive functioning.
Lande et al, 2016	n = 650, with a mean follow-up period of 4.0 yrs.	D-KEFS Category Switching	More variable visit-to-visit systolic blood pressure associated with verbal set-shifting abilities.
Verbitsky et al, 2017	n = 389 noncarriers and n = 31 children with genomic disorders	WASI-II, WIAT-II Screening, BRIEF (Parent), BASC-2 (parent)	A subset of children with CKD are diagnosed with genomic disorders that predispose them to both kidney abnormalities and neurocognitive impairment.
Knight et al, 2017	n = 34 children with lupus nephritis; n = 171 children with other forms of glomerular disease	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), D-KEFS (selected tasks), BASC-2 (parent)	Children with lupus nephritis showed intact neurocognitive abilities when compared to other children with CKD. Current prednisone use related to poorer attention and better adaptive skills. An interaction between current prednisone use and lupus nephritis for internalizing problems was noted, with worse parent-reported internalizing problems in children with lupus nephritis on prednisone.
Matsuda-Abedini et al, 2018	n = 49, 29 with CKD, including kidney transplant (mean age 14.4 yrs.) and 20 healthy controls (mean age 13.7 yrs.)	sMRI using fractional anisotropy maps calculated from diffusion tensor imaging X V	Brain abnormalities demonstrated by focal and multifocal white matter injury in the anterior limb of the internal capsule.
Harshman et al, 2019	n = 319; median age = 12.7 yrs.; median duration of CKD = 10.2 yrs.	WIAT-II Screening	Low total academic achievement in 34% percent of the sample. No significant effect of CKD-related medical variables on academic achievement. Mathematics had the lowest scores. Low achievement was related to days of missed school and presence of individualized education plan.

Study	Sample	Measures	Findings
Ruebner et al, 2019	n = 412, median age = 15.4 yrs.	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), D-KEFS (selected tasks)	Small amounts of blood lead are detected in the CKiD sample, and these small amounts were associated with lower IQ and poor attention abilities.
Harshman et al, 2020	n = 865, with about 22% with low bicarbonate at study entry.	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), D-KEFS (selected tasks), WISC-IV- Integrated	Blood pressure variability x low levels of bicarbonate contributed to lower parent ratings of executive functions.
Kuperferman et al, 2020	Of 891 subjects, 5 (0.56%) had a confirmed stroke prior to study entry. Median time at risk was 15.7 yrs.	WASI, WIAT-II Screening, CPT- II, BRIEF (parent), D-KEFS (selected tasks)	Incidence rate of approximately 36.8 per 100,000. Presence of ischemic stroke associated with uniformly lower neurocognitive functioning.
Yokoyama et al, 2020	n = 702 for whom baseline plasma FGF-23 and neurocognitive testing were performed; ages 6 to 16 yrs.	WASI, CPT-II, D-KEFS (selected tasks)	Higher plasma FGF-23 level was associated with lower performance in executive function and attention regulation. This finding was independent of eGFR.
Emotional-Behavioral			
Kogon et al, 2016	n = 344 school-age children, ages 6 to 17 yrs., median age = 13 yrs.; 7% carried a prior diagnosis of depression; 8 participants were receiving pharmacological treatment at the time of the visit.	Child Depression Inventory (Child), Pediatric Inventory of Quality of Life Core Scales (parent and youth), WASI-II, WIAT-II Screening	5% rate of elevated depression symptoms, and another 2% were being treated for depression. Depressive symptoms were not associated with change in eGFR, but were related to lower IQ, lower academic achievement, and lower ratings of quality of life.
Johnson et al, 2020	n = 845, ages 2 to 18 yrs.; median age at study entry = 11.8 yrs.	BASC-2 (parent)	Longitudinal parent ratings of behavioral functioning of their children were within the average range for their chronological age, with little change occurring over time. Higher proportions of children were within the at-risk range on one or more clinical or adaptive behavior scale. Proteinuria and persistent hypertension were associated with parent-reported attention, and seizure history was related to internalizing symptoms.
Quality of Life			
Gerson et al, 2010	n = 402, median age = 11 yrs.; mean duration of CKD = 7.4 yrs.	Pediatric Inventory of Quality of Life Core Scales (parent and youth)	Parent and youth ratings were significantly more impaired in physical, school, social, and emotional domains when compared to data from healthy children after adjusting for demographic and CKD-related factors. Better scores in physical, emotional, and social domains were related to longer disease duration and older age. Older age related to lower school quality of life ratings.
Roumelioti et al, 2010	n = 301; median age = 13.9 yrs.	Pediatric Inventory of Quality of Life Core Scales (parent and youth) (selected sleep items)	Severity of CKD was associated with increased reports of weakness, fatigue, daytime sleepiness, and lower overall quality of life ratings.
Al-Uzri et al, 2013	n = 483, median age = 10.4 yrs.	Pediatric Inventory of Quality of Life Core Scales (parent and youth)	Use of growth hormone and subsequent growth in height was significantly related to more positive parent report of physical and social quality of life.
Wong et al, 2016	n = 551 contributing to 2,376 visits; Normotensive n = 384, Elevated Blood Pressure n = 164, with n = 101 on hypertensive medication; median age = 11.5 yrs.; CKD duration = 6.4 yrs.	Pediatric Inventory of Quality of Life Core Scales (parent and youth)	Elevated blood pressure was significantly related to lower parent and child ratings of health-related quality of life.
Carlson et al, 2020	n = 733; median age = 11.0 yrs.; median duration of CKD was 8 years.	Pediatric Inventory of Quality of Life Core Scales (parent and youth)	Longitudinal analysis showed little change in perceived quality of life over time. Longer duration of CKD was associated with higher child-rated quality of life, and anemia was related to lower physical and emotional functioning.

Study	Sample	Measures	Findings
Ferris et al, 2021	n = 734; median age = 11 years; disease duration = 8 years	Pediatric Inventory of Quality of Life Core Scales (parent and youth); medication counts	Average parent quality of life scores for younger children were higher than those for older children, but ratings declined more with increased medication counts than parent ratings for older children.

WASI-II = Wechsler Abbreviated Scale of Intelligence (2nd edition); WIAT-II = Wechsler Individual Achievement Test (2nd edition); CPT-II = Conners' Continuous Performance Test-II; K-CPT = Kiddie Continuous Performance Test; BRIEF = Behavior Rating Inventory of Executive Functions; D-KEFS = Delis-Kaplan Executive Function System; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised; MSEL = Mullen Scale of Early Learning; BASC-2 = Behavior Assessment System for Children (2nd edition); ABAS-II = Adaptive Behavior Assessment Scale (2nd edition); sMRI = structural magnetic resonance imaging; WISC-IV-I = Wechsler Intelligence Scale for Children (4th edition) – Integrated