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Research Article

# Neurocognitive and Adaptive Functioning in Young Patients with Severe Chronic Kidney Disease

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## Abstract

**Background:** To assess the association between neurocognitive functioning, adaptive functioning, and health-related quality of life (HRQoL), in Children and Young Adults with Severe Chronic Kidney Disease (CKD).

**Methods:** We included patients with severe CKD (stages 4 and 5), aged 8-30 years, on different therapy modalities (pre-dialysis, dialysis, and transplanted) and healthy controls matched on age, sex, and parental education. All patients and healthy controls performed tasks to assess neurocognitive functioning (WISC/WAIS and a comprehensive neuropsychological test battery), and completed questionnaires to assess adaptive functioning (WFIRS or WHODAS) and HRQoL (PedsQL). Group differences were explored using MANCOVA. Mediation analyses were done to explore whether the relation between neurocognitive functioning and HRQoL was mediated by adaptive functioning.

**Results:** 28 patients with severe CKD and 21 healthy matched controls were included. CKD patients had worse HRQoL ($p < .001$) than healthy controls. Adaptive functioning problems increased with age in the CKD patient group but not in the healthy control group (significant interaction effect: $p = .024$). Significant mediation effects were found, where impaired adaptive functioning mediated the relation between both low estimated Full Scale Intelligence Quotient (eFSIQ) and worse Processing Speed & Working Memory, and impaired HRQoL (eFSIQ: 95% confidence interval = .01-.58; Processing Speed & Working Memory: 95% confidence interval = 2.31-16.36).

**Conclusion:** We found that impaired neurocognitive functioning is associated with worse HRQoL, which is conditional to impaired adaptive functioning. Especially towards young adulthood problems in adaptive functioning are more likely to be reported than when patients are younger.

## Introduction

Children, adolescents, and young adults with severe CKD, especially those on kidney replacement therapy are at risk for structural neurological abnormalities, particularly disruption of white matter integrity [1,2]. These structural abnormalities may underpin the development of impaired neurocognitive functioning, such as lower levels of intellectual functioning, mental slowing, impaired attention, (working) memory, and poor executive functioning [3-8].

Severe CKD and its treatment have physical and psychosocial sequelae that may adversely impact health-related quality of life (HRQoL) in children and young adults with CKD [9-19]. HRQoL ratings in children and adolescents with severe CKD are often lower than in healthy peers and also compared to children and adolescents with other chronic illnesses (e.g. diabetes and asthma) [15,20]. Young adults who were diagnosed with kidney failure in childhood often face challenges in obtaining stable employment, finishing their education, establishing intimate relationships, and achieving independent living [26-33].

In children and adolescents with other chronic health conditions specific cognitive functions – attention, working memory, and processing speed are sensitive to particular treatments and have a downstream impact on functional skills [21,22]. A way to measure these functional skills is to assess adaptive functioning. Adaptive functioning is the ability to engage in and perform activities of daily living and function independently at an age-appropriate level, both socially and practically. These activities often require specific cognitive skills and can be a proxy measure for broader life outcomes [23]. Adaptive functioning is considered to be of particular interest in children with chronic health conditions including severe CKD since demands associated with self-care (including physical, professional, practical, relational, and emotional) are assumed to require adequate adaptive functioning. Children and young adults with severe CKD live longer, due to better outcomes, and therefore might encounter more problems early in life.

Although some of the domains of self-care and social consequences (*e.g.* missing out on social events, not being able to attend school) of CKD in children have been addressed previously [24], data on the overarching construct of adaptive functioning in children and young adults with severe CKD are sparse. In a group of 124 pre-school aged children with mild to moderate CKD low average to average scores on adaptive behavior scales were found [13]. Yet, the relation between neurocognitive functioning, adaptive functioning, and HRQoL in our patient group (children and young adults with severe CKD) is, unknown.

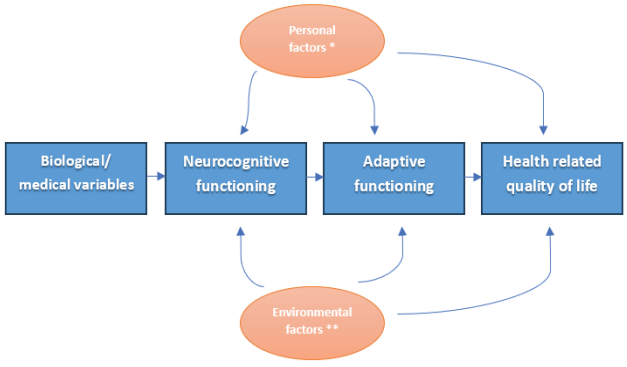
The current study aims to assess adaptive functioning in children and adolescents with severe CKD and to explore how cognitive functioning, HRQoL, and adaptive functioning are associated. Given the vulnerability of this population and the potential impact on daily life functioning with consequences throughout their adult life, a better understanding of this relation could be of great importance. To conceptualize this hypothesis we used the integrated model for health outcomes by Valderas and Alonso [25]. This model is used to systematically study the relationship between neurocognitive functioning, adaptive functioning, and HRQoL in severe CKD along a continuum (Figure 1). This model is based on the International Classification of Functioning, Disability and Health (ICF) [26] and the well-established bio-psycho-social model by Wilson and Cleary [34].

## Methods

### Participants and setting

Patients with CKD stage 4+ were recruited from the Amsterdam University Medical Center, Erasmus Medical Center (the Netherlands), and the University Hospital Antwerp (Belgium). The inclusion and exclusion criteria have previously been described in detail (1). In short, we included patients aged 8-30 years with eGFR<30 on conservative therapy, chronic dialysis, or transplanted patients with a stable transplant function. We excluded patients who had [1] previously established severe intellectual impairment and/or overt learning disability; (2) insufficient mastery of the Dutch language; (3) insufficient hearing and visual acuity; (4) established skull or brain abnormalities not related to CKD; or (5) co-existing or primary mental disorder or disease with primary or secondary central nervous system involvement interfering with the impact of CKD (e.g. depression or genetic abnormalities). This study (recruitment and assessment phase) took place from June 2017 until September 2019.

We divided the patient group into 3 treatment subgroups: (1) a pre-dialysis group ($n$ = 8) with estimated glomerular filtration rate <30 ml/min/1.73m$^2$ (eGFR<30) on conservative treatment at time of assessment; (2) a dialysis group ($n$ = 8); and (3) a transplanted group ($n$ = 12) of patients with a stable graft function and GFR>30 for at least two years [35].




* characteristics of the individual (e.g. symptom modulation, personal motivation, value preferences)
** characteristics of the environment (e.g. psychological, social and economic supports)

**Figure 1:** Simplified and modified version of the integrated model for health outcomes.

For patients and healthy controls, each session involved the completion of questionnaires, where participants and their parents (for participants under the age of 18 only) completed the online questionnaires on socio-demographics (i.e., age, sex, parental educational level), adaptive functioning, and HRQoL through the online KLIK portal [36]. Additionally, all patients (not healthy controls) also performed a 90-minute neurocognitive assessment administered by a trained neuropsychologist in a designated assessment room.

## Measures

**Socio-demographic and clinical CKD parameters:** We collected age, sex, and parental education level for patients and healthy controls and divided parental educational level into three categories: (1) low education (primary and lower vocational education up to middle general secondary education); (2) middle education (middle vocational education up to pre-university education); and (3) high education (higher vocational education and university) [37]. We also collected clinical CKD parameters from patients including age at diagnosis of eGFR<30, current eGFR, duration of severe CKD (ratio of the time interval between the date of first eGFR<30 ml/min/1.73m$^2$ and assessment-date, expressed as % of life), dialysis duration (dialysis duration to calendar age ratio, i.e. % of life), and time since transplantation (ratio of time interval between date eGFR>30 after transplantation and assessment-date to calendar age, i.e. % of life).

**Neurocognitive functioning:** We assessed full-scale Intelligence Quotient (eFSIQ) by using the short form of the Wechsler (Adult) Intelligence Scale (WISC/WAIS)-III and specific neurocognitive functions by applying a comprehensive neurocognitive test battery, as previously described, in all CKD patients [1,38]. For these latter tests, we calculated age-standardized scaled scores by comparing the patients' individual scores to normative data and transformed them into z-scores; a lower score corresponded with worse performance. This was described in more detail in our previous study. In short, we could label five neurocognitive domains: processing speed and working memory, verbal memory, fluency, switching, and processing speed, switch and control [1]. In this study, we choose to only use the neurocognitive functioning domains with observed sensitivity to CKD (e.g. eFSIQ, and Processing Speed & Working Memory) [1].

## Adaptive functioning

**WFIRS (self and parent report) [39,40] & WHODAS [41] (self report):** To assess adaptive functioning the Weiss Functional Impairment Rating Scale (WFIRS) was used for pediatric participants and the World Health Organization Disability Assessment Schedule (WHODAS 2.0) for adults. Higher adaptive functioning scores indicate more severe functional impairment. The WFIRS questionnaire was originally designed to measure ADHD-specific functional impairment via self and parent reports. We used the parent form for children aged between 8 and 11 years old, as no self-report is available for this age group. For children aged between 12 and 18 years old, the self-report was used, as self-reports are more reliable for actual well-being than parent reports [40,42,43]. The questionnaire consists of 50 items, grouped into six functional domains: family [10], school & learning [10], life skills [10], child's self-concept [3], social activities [7] and risky activities [10]. For our analysis, we have used the total score only. The WHODAS 2.0 is a generic assessment instrument measuring disability and functional impairment at the population level or in clinical practice. The questionnaire consists of 36 items and captures the level of functioning in six domains: cognitive functioning, mobility, self-care, getting along, life activities, and participation. We used "item-response-theory" (IRT) based scoring. Again, for our analysis we have used the total score only.

A continuous adaptive functioning variable was created from WFIRS and WHODAS total scores by calculating a z-score for each CKD patient using our healthy control participants as the reference group. This is due to a lack of normative data in our specific population.

**HRQoL PedsQL [44]:** To evaluate the HRQoL we used the Pediatric Quality of Life inventory self-report [45] (PedsQL) in all participants aged 8-30 years using age-appropriate versions. The PedsQL is a valid, practical, standardized, and generic assessment tool to measure HRQoL for children, adolescents, and young adults over the past month. The questionnaire comprises 23 items, rated on a 5-point scale, across four domains: physical functioning, emotional functioning, social functioning, and school functioning. A psychosocial functioning scale score was derived by computing the mean of the items answered in the emotional, social, and school functioning scales. The total scale score was obtained by calculating the mean across all 23 items. To calculate age-standardized scaled scores (*i.e.* percentiles) we compared the patients' individual scores to normative data [46,47].

## Data analysis

**Socio-demographic and clinical characteristics:** Statistical analyses were performed using SPSS 28.0 (IBM Corp., 2021). In instances of missing data in the neurocognitive outcomes (M = 2%, range: 0-7%), multiple imputation was employed to address the gaps [45]. We conducted a comparison of all groups (CKD group, healthy control group, and treatment subgroups) regarding age, sex parental educational level, and clinical parameters using Multivariate Analysis of Variance (MANOVA). Sociodemographic variables (age, sex, and parental educational level) were added as covariates to all analyses.

**Adaptive functioning and HRQoL in CKD patients, treatment subgroups, and healthy control group:** Group

differences in adaptive functioning were evaluated using the General Linear Model, where an interaction effect between age and group was added to investigate the relation between age and adaptive functioning for the CKD group and healthy control group. Subgroup differences in adaptive functioning, as well as group and subgroup differences in HRQoL outcome variables (*i.e.* total score, domain scores, psychosocial score), were investigated using MANCOVAs

**The association between neurocognitive functioning, adaptive functioning, and HRQoL in patients with CKD:** Finally, the potentially mediating role of adaptive functioning on the association between neurocognitive functioning (i.e. eFSIQ and Processing speed & Working Memory) and HRQoL in young patients with CKD was explored using mediation models with PROCESS version 4.0 using 5,000 bootstrap samples [48]. To limit the amount of comparisons, only the neurocognitive outcomes with previously observed sensitivity to CKD (i.e. eFSIQ and Processing speed & Working Memory) were evaluated in this mediation analysis [1]. The data on eFSIQ Processing speed & Working Memory was previously determined in our study on neurocognitive functioning in this CKD sample [1].

All statistical testing was two-sided and alpha was set at .05. Cohen's *d* effect sizes are reported where appropriate and were interpreted as small ($d$ <0.5), medium (0.5 < $d$ < 0.8), or large ($d > 0.8$).

The Medical Ethics Committee of the Amsterdam UMC approved the study protocol (NL61708.018.17) and all procedures were executed according to the Declaration of Helsinki.

## Results

### Study participants

We enrolled 28 patients with severe CKD aged 8.0-30.9 years and 21 healthy controls matched on age, sex, and parental educational level. CKD patients were recruited from the Amsterdam University Medical Centre ($n$ = 25), Erasmus Medical Centre, the Netherlands ($n$ = 1), and the University Hospital Antwerp, Belgium ($n$ = 2).

Table 1 displays the socio-demographic and clinical characteristics of the sample. The age at diagnosis was significantly higher in the dialysis group compared to the transplanted group ($p$ = .010, $d$ = 1.34). Seven of the 15 adults were diagnosed at age <18y with severe CKD and thus underwent transition to the adult nephrology department. Specific traumatic experiences were checked with the nephrologists in service of the participating patients. There were no specific traumatic experiences recorded, apart from experiences connected to their disease state. Subgroups based on treatment showed significant differences in terms of eGFR, blood urea, and time since successful transplantation.

**Adaptive functioning in CKD patients, treatment subgroups, and healthy control group:** The interaction effect between age and group (CKD vs. healthy controls) on adaptive functioning was significant (Table 2). The significant interaction effect revealed that higher age was significantly related to more problems in total adaptive functioning in the CKD patient group and not in the healthy control group (Figure 2).

Regarding treatment subgroup analyses, the dialysis group reported significantly more adaptive functioning problems compared to the pre-dialysis, transplanted, and healthy control group (Table 3). Raw data on subscales of adaptive functioning for CKD patients and healthy controls are shown in Supplementary Table 2.

Estimated marginal means (mean standard error is .043) of total adaptive functioning scores are shown, taking covariates gender and parental educational level into account.

**HRQoL in CKD patients, treatment subgroups, and healthy control group:** CKD patients had significantly lower total HRQoL, than healthy controls **(Table S1).** More specifically, had lower HRQoL in the psychosocial, physical, social, and school domains. Exploratory analyses comparing treatment subgroups showed a significant main effect of treatment type for total HRQoL and HRQoL on specific domains (i.e. psychosocial, physical, social, and school domains). In general, the healthy controls reported the highest HRQoL scores and the dialysis group reported lower scores than the transplanted and pre-dialysis group **(for more details see supplement, Table S1)**.

**The association between neurocognitive functioning, adaptive functioning, and HRQoL in patients with CKD:** The potential mediating role of adaptive functioning on the association between neurocognitive functioning with observed sensitivity of CKD (i.e. eFSIQ and Processing speed & Working Memory, as assessed in our previous study in this sample [1]) and HRQoL in young CKD patients was investigated using mediation analysis (Figure 3). There were no direct associations between eFSIQ or Processing Speed & Working memory on adaptive functioning. There were significant indirect associations; more adaptive functioning problems in CKD patients significantly mediated the relation between eFSIQ and HRQoL (95% confidence interval = .01 to .58). Additionally, more adaptive functioning problems in CKD patients significantly mediated the relation between Processing Speed & Working Memory and HRQoL (95% confidence interval = 2.31 to 16.36).

## Discussion

We found that children and young adults with severe CKD report more adaptive functioning problems compared to their healthy peers and the older the patients are the more

**Table 1:** Demographic and clinical CKD parameters in the CKD and treatment subgroups.

| | Group | | Contrasts | | CKD treatment group | | | Statistics | |
|---|---|---|---|---|---|---|---|---|---|
| | CKD | Healthy control | *p* | *d* | Pre-dialysis | Dialysis | Transplanted | *p* | contrasts |
| ***n*** | **28** | **20** | | | **8** | **8** | **12** | | |
| Age (years) | 18.5 (9.1 - 30.5) | 19.8 (9.0-29.2) | .967 | .02 | 15.7 (9.1-26.6) | 23.0 (9.6-27.1) | 17.8 (9.1-30.5) | .192 | |
| Male, *n* (%) | *n* = 18 (64%) | *n* = 13 (61.9%) | .768 | -.08 | *n* = 6 (75%) | *n* = 4 (50%) | *n* = 8 (67%) | .595 | |
| Educational level parents[b] | 2.0 (1.0-3.0) | 2.0 (1.0 - 3.0) | .610 | .02 | 2.0 (2.0-3.0) | 2.0 (1.0-3.0) | 2.0 (1.0-3.0) | .493 | |
| eFSIQ (mean) | 99 | n.a. | | | 112 | 94 | 92 | .078 | |
| Age at CKD diagnosis (years) | 14.3 (0.0-24.7) | - | | | 14.6 (1.9-24.7) | 19.9 (9.3-24.0) | 8.1 (0.0-22.8) | .030 | D > Tx |
| Primary disease[c]<br>• CAKUT[1]<br>• Renovascular[2]<br>• Cortical necrosis[3]<br>• Acquired Glomerulopathy[4]<br>• Inherited nephropathy[5]<br>• Other & unknown cause[6] | <br>8<br>3<br>3<br>4<br>7<br>3 | | | | <br>3<br>0<br>0<br>2<br>2<br>1 | <br>0<br>0<br>2<br>2<br>3<br>1 | <br>5<br>3<br>1<br>0<br>2<br>1 | | |
| History of relevant comorbidities<br>• Extreme prematurity (<32 weeks)<br>• Malignant hypertension[d]<br>• Convulsions/history of epilepsy | <br>1<br>5<br>2 | | | | <br>0<br>0<br>0 | <br>0<br>2<br>1 | <br>1<br>3<br>1 | | |
| eGFR (ml/min/1.73 m$^2$)[e] | 26.6 (10.0-90.0) | | | | 23.7 (11.3-29.0) | 10.0 (10.0-10.0) | 51.6 (31.0-90.0) | **<0.001** | Tx > PD & D |
| Urea (mmol/L)[f] | 14.9 (5.1-28.8) | | | | 16.2 (13.7-20.7) | 21.4 (16.8-28.8) | 8.0 (5.1-14.5) | **<0.001** | D > PD > Tx |
| Duration of severe CKD (% of life) | 12% (0-81%) | | | | 7% (0-81%) | 11% (3-45%) | 20% (4-78%) | .585 | |
| Ever treated by dialysis (n)<br>Hemodialysis<br>Peritoneal dialysis<br>Both | 16<br>7<br>8<br>1 | | | | 3<br>3<br>-<br>- | 8<br>3<br>5<br>- | 5<br>1<br>3<br>1 | | |
| Duration dialysis (% of life) | 1% (0-49%) | | | | 0% (0-6%) | 4% (1-40%) | 0% (0-49%) | .391 | |
| Ever treated by renal transplantation (n)<br>Pre-emptive<br>Nonpre-emotive | 16<br>8<br>8 | | | | 2<br>1<br>1 | 2<br>-<br>2 | 12<br>5<br>7 | | |
| Time since renal transplantation (% of life) | 6% (0-75%) | | | | 0% (0-6%) | 0 (0-10%) | 23% (13-75%) | <.001 | Tx > PD & D |

Note: Values are displayed as median (range) unless otherwise indicated.
Abbreviations: CKD: Chronic Kidney Disease; D: Dialysis Group; eFSIQ: Estimated Full-Scale Intelligence Quotient; eGFR: Estimated Glomerular Filtration Rate; GA: Gestational Age; PD: Pre-Dialysis group; Tx: Transplanted Group.
CKD patients who previously underwent a kidney transplantation, but had an eGFR<30 at the time of assessment were allocated to either the pre-dialysis or dialysis group, according to their current treatment mode.
[b]1.0 = low education, 2.0 = middle education, 3.0 = high education. Clinical CKD parameters were extracted from the patient's medical file, specifications are as follows:
[c] Primary diseases: 1 urethral valves (*n* = 7), dysplasia (*n* = 1), 2 atypical hemolytic uremic syndrome (*n* = 1), malignant hypertension (*n* = 2), 3 due to asphyxia (*n* = 1), due to septicemia (*n* = 2); 4 primary Focal Segmental Glomerulosclerosis (*n* = 2), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA) vasculitis (*n* = 1), LE-nephritis (*n* = 1); 5 branchiootorenal (BOR-) syndrome (*n* = 1), NHPH1 mutation (*n* = 1), Autosomal dominant polycystic kidney disease (ADPKD) (*n* = 1), Alport's syndrome (*n* = 1), inherited FSGS due to INF2 mutation (*n* = 2), Pax-2 mutation (*n* = 1); 6 Tubulointerstitial Nephritis (*n* = 1), unknown cause (*n* = 2).
[d]malignant hypertension was defined as extremely high blood pressure resulting in organ damage.
[e]creatinine levels were obtained closest to the date of study participation (range: -51 days to +4 days relative to participation date), of which eGFR was calculated using Schwarz formula for patients aged <18 years [49] and the abbreviated Modification of Diet in Renal Disease formula was used for patients aged >18 [50]. Due to large fluctuations in eGFR before and after dialysis, the eGFR of patients receiving dialysis was conservatively set at 10 [51].
[f] urea blood levels were obtained closest to the date of study participation (range: -51 days to +4 days relative to participation date).

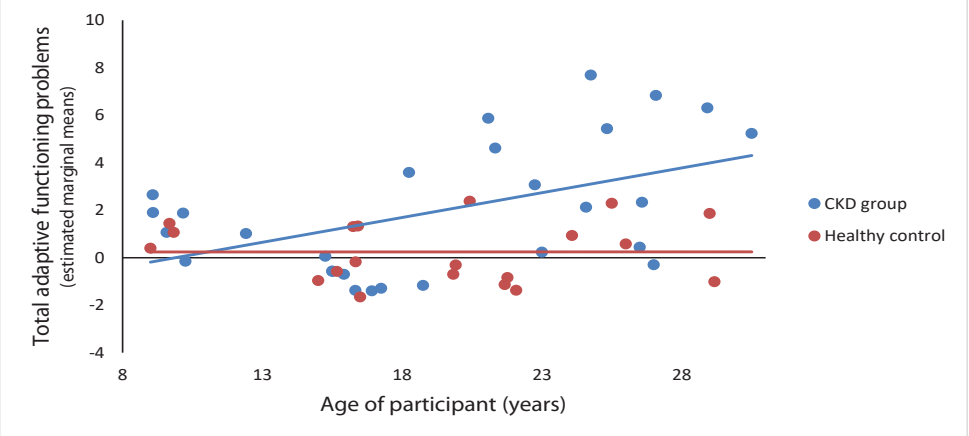



**Figure 2:** Visualization of the interaction effect showed that higher age was significantly associated with more adaptive functioning problems in the CKD patient group (blue line) and not in the healthy control group (orange line).

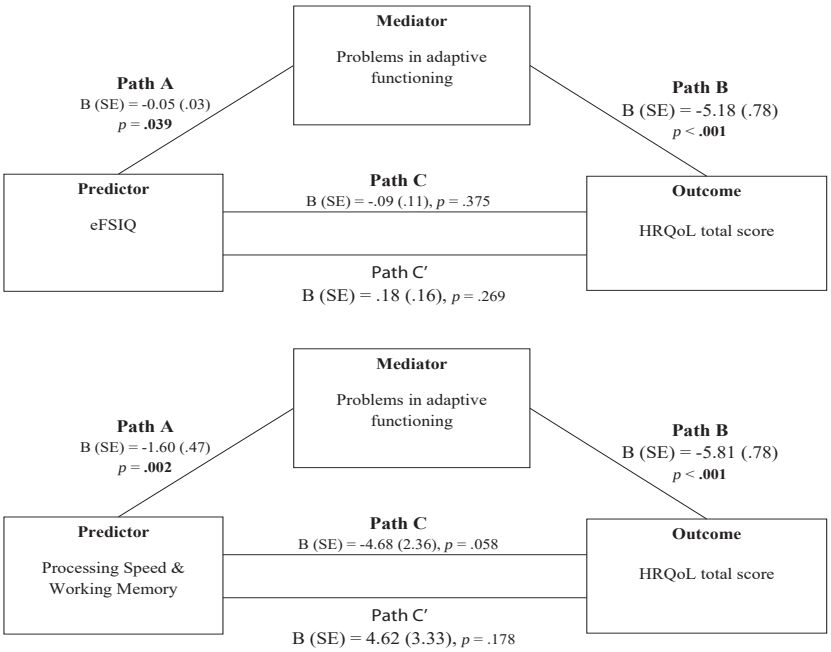



**Figure 3:** Mediation model. Mediation models testing the impact of problems in adaptive functioning in CKD patients in the association between neurocognitive functioning (i.e. eFSIQ and Processing Speed & Working Memory) and HRQoL. Illustration of the indirect (Path A and B), direct (Path C), and total effects (Path C'), showing that the effect of neurocognitive functioning (i.e. eFSIQ and Processing Speed & Working Memory) on HRQoL is mediated by problems in adaptive functioning.
Note. B: Unstandardized Regression Coefficient; eFSIQ: estimated Full-Scale Intelligence Quotient; HRQoL: Health-Related Quality of Life; SE: Standard Error.

**Table 2:** Comparison of adaptive functioning in the CKD and HC group. An interaction term and sociodemographics as covariates were added to the model.

| | Statistics | | | |
|---|---|---|---|---|
| | *B* | *SE* | *t* | *p* |
| Group (CKD vs. HC) | 2.481 | 1.932 | 1.284 | 0.206 |
| Age (years) | .248 | .057 | 4.313 | **< .001** |
| Age * group (CKD vs. HC) | -.226 | .096 | -2.346 | **.024** |
| Sex | -1.152 | .597 | -1.929 | .060 |
| Parental education level | -.264 | .508 | -.520 | .606 |

*Note.* Abbreviations: *B:* Unstandardized Regression Coefficient; CKD: Chronic Kidney Disease group; HC: Healthy Control Group; *t:* t-score; SE: Standard Error.

**Table 3:** Mean adaptive functioning scores in the CKD and treatment subgroups. Statistical comparisons of adaptive functioning in treatment subgroups.

| | Group | | Treatment subgroups | | | Statistics[a] | | |
|---|---|---|---|---|---|---|---|---|
| | CKD | Healthy control | Pre-dialysis | Dialysis | Transplanted | *p* | contrasts | Significant covariates |
| n | 28 | 20 | 8 | 8 | 12 | | | |
| Adaptive functioning Total score | 2.0 (2.88) | .14 (.98) | .61 (1.68) | 4.74 (2.47) | 1.08 (2.61) | **<.001** | D > PD, Tx, HC | Age: .004 |

**Note:** Means and standard deviations are displayed. Abbreviations: CKD: Chronic Kidney Disease; HC: Healthy Controls; PD: Pre-Dialysis Group; D: Dialysis Group; Tx: Transplanted Group.
[a] *p* values and Cohen's *d* effect sizes for treatment group comparisons using MANCOVA are provided and post hoc contrasts of MANOVA are used.

problems they report. In the CKD group, dialysis patients report significantly more adaptive functioning problems than pre-dialysis and transplanted patients. We also found that the impact of impaired neurocognitive functioning on HRQoL was conditional to its impact on adaptive functioning in CKD patients. More specifically, our data showed no direct relationship between neurocognitive functioning and HRQoL, but they do suggest at the same time that impaired neurocognitive functioning (both eFSIQ and Processing Speed and Working memory), may lead to impaired adaptive functioning, which in that case hurts HRQoL in children and young adults with severe CKD.

Contrary to HRQoL, data on adaptive functioning in CKD patients are scarce. In our study group, we found age to be linearly inversely associated with adaptive functioning in CKD patients. The more a patient grows into adulthood, the worse their adaptive functioning scores. We found no age effect in healthy controls on adaptive functioning. Our data suggest young adults experience problems within the domains of mobility, life activities, and participation **(Table S2)**. For example, they report having trouble getting out of their homes, and difficulties with household activities, work, and school activities.

There are several explanations why older patients, such

as adolescents and young adults, experience more problems with adaptive functioning compared to younger patients. First, adolescents start seeking for autonomy. Younger children with a chronic illnesses still highly depend on their caregivers and are often carefully guarded [27]. As they grow older, demands to take responsibility for their health, self-management of their disease and activities of daily living and independently executing day-to-day activities will increase. Second, younger patients have a relatively short duration of illness and/or treatment compared to older patients. Possibly, younger patients may not have been faced yet with some of the potential consequences of longer exposure to the treatment of the disease. Thirdly, another explanation for this difference could lie in the use of different coping strategies by children and adults. Children are known to adapt in another way to new situations compared to adults [28,29]. Subsequently, they may rate their HRQoL significantly higher than adults. This observation mimics the outcomes of a study where the HRQoL of patients (mean age of 29 years) with pediatric CKD/dialysis onset was compared to the HRQoL of patients with adult-onset; the latter groups had very significantly worse scores [30]. The explanation for this observation was that children and adults may have different expectations of life and subsequent different health perceptions [31,32]. To delve deeper into this phenomenon, empirical research should focus on understanding how children with CKD manage their chronic illness and to what degree various coping strategies may have an impact later in life. Lastly, we are aware that age might also have an impact on cognitive functioning. This could contribute to the association we have found between age and adaptive functioning.

Our findings on adaptive functioning and HRQoL are in line with the sparse existing data on this topic. In a group of 124 pre-school aged children with mild to moderate CKD low average to average scores on adaptive behavior scales were found, which is similar to our findings. However, this study did not look at the young adult population and also the disease severity cannot be compared. Contrary to some other studies (in various populations), we did not find a direct relationship between neurocognitive functioning and HRQoL [24,33,52-55]. However, using a mediation analysis, we did see that more problems in adaptive functioning in CKD patients significantly mediated the relation between neurocognitive functioning (i.e. intelligence, processing speed, and working memory) and HRQoL. A mediation model explains whether an independent variable affects the dependent variable through one or more other variables [56]. More specifically, our findings imply that problems in neurocognitive functioning in CKD patients may subsequently lead to worse adaptive functioning which may in turn lead to worse HRQoL. This suggests that previously identified risk factors for impaired neurocognitive functioning in CKD patients (such as longer dialysis duration and longer time since kidney transplantation) may also contribute to worse daily life functioning and subsequently HRQoL. The negative impact of inadequate adaptive functioning on HRQOL has been demonstrated in other conditions. Studies in children with attention deficit disorder (ADD) and epilepsy [54,57] also showed that inadequate adaptive functioning in those patients predicted an impaired HRQoL. Examining adaptive functioning should be therefore an important aspect of clinical neuropsychological evaluations.

We speculate that certain protective factors might account for the observed indirect effects, even in the absence of direct effects. These factors were not explored in our study. We suggest factors such as having the drive to catch up with peers, feeling encouraged/motivated by family and friends, and growing up in a safe environment could potentially improve their adaptive functioning skills, which may in turn lower the risk for loss of HRQoL. In a few studies, not in our population, they found that neurocognitive dysfunction may be associated with lower adaptive functioning or HRQoL, but none looked at the mediating role [58-60].

## Strengths and limitations

This is the first study to examine adaptive functioning and analyze its relation to neurocognitive functioning and HRQoL in both children and young adults with severe CKD using a mediation model. Additionally, it is the study the first to evaluate adaptive functioning in children and young adults with CKD. Despite these strengths, several limitations require mentioning. First, we recognize our small sample size. Severe CKD is a rare disease in young patients and much effort was made to establish a collaboration with (inter)national child nephrology centers to reach as many Dutch-speaking patients as possible. Due to the small sample size cautious interpretation is necessary, especially within the group comparisons. Since small sample size is an inevitable issue in pediatric nephrology research it is recommended to further investigate the neuropathology in dialysis and transplanted patients in a prospective, longitudinal design with multiple repeated measurements to increase power and to follow the course of CKD. A second limitation is the heterogeneity of our sample in terms of socio-demographic (e.g. wide age range) and illness characteristics, which is inevitable due to the low prevalence of severe CKD in children and young adults. Careful matching of the healthy control group on age, sex, and parental education partly accounted for this, and confounding analyses showed that sociodemographic factors did not account for reported group differences. Another limitation is the variety of questionnaires between children and adults. To measure adaptive functioning we have used different questionnaires for the children and the adult population, mostly because there is a lack of validated, age-appropriate questionnaires to assess adaptive functioning over the full age range. Although both questionnaires are validated and we performed thorough analyses to ensure that the questionnaires are reliable, careful interpretation

is needed. Finally, we have to apply nuance to our concept of neurocognitive functioning. Neurocognitive functioning refers to multiple mental abilities. In our previous study, it was seen that especially intellectual skills, processing speed, and working memory were affected by CKD [1]. For this reason and to limit the number of statistical comparisons, we focused on these specific neurocognitive abilities, and the relevance of other neurocognitive domains for adaptive functioning and HRQoL may have been undetected.

### Clinical implication

The primary concern that prompts a patient to seek treatment is often related to issues with functioning. For children and adolescents, these problems may be not feeling fit or having trouble concentrating at school. While this is likely the patient's focus, the physician's focus has historically been on treating symptoms that are typical for a certain disease. Multidimensional assessment that considers both symptoms and functioning promotes effective communication between the clinician's and the patient's perspective. Symptoms, neurocognitive functioning, adaptive skills, and HRQoL describe distinct outcomes but are intertwined. The relation between change in symptoms and change in functioning is of great clinical relevance. Even so, it indicates that for the most optimal adaptive functioning and HRQoL, some patients may need symptom treatment, and others need psychological treatment, all with the ultimate effect of minimizing functional impairment. Also, our findings highlight the importance of physicians being aware of CKD patients at risk for neurological complications leading to more problems in neurocognitive functioning [1], as these problems may affect adaptive functioning and subsequently HRQOL. Our results may help in targeting young patients who are at risk for developing lower adaptive functioning or HRQoL and may give clues for the prevention of these problems and improve their chances in society as young adults. Implementing a comprehensive care model that includes nephrologists, psychologists, social workers, and occupational therapists may enhance awareness and tackle obstacles to life participation. Recognizing and cultivating social networks may motivate and support young patients to develop independence, autonomy, and determination to actively participate in life activities and pursue their goals. Social workers and potentially peer navigators could assist young adults with finding employment and accessing social benefits and housing [52]. It is important to realize that the most vulnerable population is the young adults, especially when they lack a support system. Young adults sometimes receive even less help, due to differences in adult healthcare compared to pediatric healthcare. Making sure this group receives adequate and tailored care for their problems is of great importance.

## Conclusion

In summary, our study revealed that children and young adults with severe CKD experience significantly more adaptive functioning problems compared to their healthy peers, with older patients reporting more problems. Patients undergoing dialysis report most impaired adaptive functioning compared to pre-dialysis and transplanted patients. We are the first to find that impaired neurocognitive functioning indirectly leads to impaired HRQoL through its effect on adaptive functioning in young CKD patients. Our findings underscore the critical impact of adaptive functioning on the well-being of children and young adults with severe CKD. Therefore, comprehensive and multidisciplinary care approaches are essential. This care should address both medical and psychological needs, with a focus on promoting adaptive skills to improve HRQoL and outcomes for these patients. Recognizing the unique challenges faced by CKD patients during the transition to adulthood is crucial for providing tailored support and improving their long-term prospects in life.

### Conflicts of interest

All authors report no real or perceived conflicts of interest that could affect the study design; collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

### Author contribution

SL, KJO, MSS, FJB, and JWG participated in the research design. SL and JK conducted the research and performed data analyses. SL, JK, KJO, and JWG were involved in the data analysis plan. MSS, AB, KH, HJ, FJB, and JWG were treating physicians. All authors participated in the interpretation of outcomes and participated in the writing of the paper.

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## References

1. Lijdsman S, Oostrom KJ, van Sandwijk MS, Bouts AH, van Hoeck K, de Jong H, Oosterlaan J, Bemelman FJ, Königs M, Groothoff JW. Risk factors for neurocognitive impairment and the relation with structural brain abnormality in children and young adults with severe chronic kidney disease. Pediatr Nephrol. 2023 Jun;38(6):1957-1969. doi: 10.1007/s00467-022-05781-1. Epub 2022 Nov 2. PMID: 36322259; PMCID: PMC10154258.

2. Lijdsman S, Königs M, van Sandwijk MS, Bouts AH, van Hoeck K, de Jong H, Engelen M, Oosterlaan J, Bemelman FJ, Oostrom KJ, Groothoff JW. Structural brain abnormalities in children and young adults with severe chronic kidney disease. Pediatr Nephrol. 2022 May;37(5):1125-1136. doi: 10.1007/s00467-021-05276-5. Epub 2021 Nov 20. PMID: 34800137; PMCID: PMC9023396.

3. Groothoff JW, Grootenhuis M, Dommerholt A, Gruppen MP, Offringa M, Heymans HS. Impaired cognition and schooling in adults with end stage renal disease since childhood. Arch Dis Child. 2002 Nov;87(5):380-5. doi: 10.1136/adc.87.5.380. PMID: 12390905; PMCID: PMC1763100.

4. Chen K, Didsbury M, van Zwieten A, Howell M, Kim S, Tong A, Howard K, Nassar N, Barton B, Lah S, Lorenzo J, Strippoli G, Palmer S, Teixeira-Pinto A, Mackie F, McTaggart S, Walker A, Kara T, Craig JC, Wong G.

Neurocognitive and Educational Outcomes in Children and Adolescents with CKD: A Systematic Review and Meta-Analysis. Clin J Am Soc Nephrol. 2018 Mar 7;13(3):387-397. doi: 10.2215/CJN.09650917. Epub 2018 Feb 22. PMID: 29472306; PMCID: PMC5967677.

5. Duquette PJ, Hooper SR, Wetherington CE, Icard PF, Gipson DS. Brief report: intellectual and academic functioning in pediatric chronic kidney disease. J Pediatr Psychol. 2007 Sep;32(8):1011-7. doi: 10.1093/jpepsy/jsm036. Epub 2007 Jun 7. PMID: 17556399.

6. Vanderlinden JA, Ross-White A, Holden R, Shamseddin MK, Day A, Boyd JG. Quantifying cognitive dysfunction across the spectrum of end-stage kidney disease: A systematic review and meta-analysis. Nephrology (Carlton). 2019 Jan;24(1):5-16. doi: 10.1111/nep.13448. PMID: 30094890.

7. Hooper SR, Laney N, Radcliffe J, Moodalbail D, Hartung EA, Ruebner RL, Jawad AF, Furth SL. Executive Functioning in Children, Adolescents, and Young Adults with Chronic Kidney Disease. J Dev Behav Pediatr. 2015 Nov-Dec;36(9):734-42. doi: 10.1097/DBP.0000000000000221. PMID: 26468938.

8. Mendley SR, Matheson MB, Shinnar S, Lande MB, Gerson AC, Butler RW, Warady BA, Furth SL, Hooper SR. Duration of chronic kidney disease reduces attention and executive function in pediatric patients. Kidney Int. 2015 Apr;87(4):800-6. doi: 10.1038/ki.2014.323. Epub 2014 Sep 24. PMID: 25252026; PMCID: PMC4372504.

9. Gerson AC, Wentz A, Abraham AG, Mendley SR, Hooper SR, Butler RW, Gipson DS, Lande MB, Shinnar S, Moxey-Mims MM, Warady BA, Furth SL. Health-related quality of life of children with mild to moderate chronic kidney disease. Pediatrics. 2010 Feb;125(2):e349-57. doi: 10.1542/peds.2009-0085. Epub 2010 Jan 18. PMID: 20083528; PMCID: PMC3663134.

10. Tong A, Tjaden L, Howard K, Wong G, Morton R, Craig JC. Quality of life of adolescent kidney transplant recipients. J Pediatr. 2011 Oct;159(4):670-5.e2. doi: 10.1016/j.jpeds.2011.04.007. Epub 2011 May 31. PMID: 21621222.

11. Lande MB, Gerson AC, Hooper SR, Cox C, Matheson M, Mendley SR, Gipson DS, Wong C, Warady BA, Furth SL, Flynn JT. Casual blood pressure and neurocognitive function in children with chronic kidney disease: a report of the children with chronic kidney disease cohort study. Clin J Am Soc Nephrol. 2011 Aug;6(8):1831-7. doi: 10.2215/CJN.00810111. Epub 2011 Jun 23. PMID: 21700829; PMCID: PMC3156422.

12. Haavisto A, Korkman M, Holmberg C, Jalanko H, Qvist E. Neuropsychological profile of children with kidney transplants. Nephrol Dial Transplant. 2012 Jun;27(6):2594-601. doi: 10.1093/ndt/gfr650. Epub 2011 Dec 1. PMID: 22140125.

13. Hooper SR, Gerson AC, Johnson RJ, Mendley SR, Shinnar S, Lande MB, Matheson MB, Gipson DS, Morgenstern B, Warady BA, Furth SL. Neurocognitive, Social-Behavioral, and Adaptive Functioning in Preschool Children with Mild to Moderate Kidney Disease. J Dev Behav Pediatr. 2016 Apr;37(3):231-8. doi: 10.1097/DBP.0000000000000267. PMID: 26890559; PMCID: PMC4818179.

14. Thys K, Schwering KL, Siebelink M, Dobbels F, Borry P, Schotsmans P, Aujoulat I; ELPAT Pediatric Organ Donation and Transplantation Working Group. Psychosocial impact of pediatric living-donor kidney and liver transplantation on recipients, donors, and the family: a systematic review. Transpl Int. 2015 Mar;28(3):270-80. doi: 10.1111/tri.12481. Epub 2014 Nov 21. PMID: 25363518.

15. Tjaden LA, Grootenhuis MA, Noordzij M, Groothoff JW. Health-related quality of life in patients with pediatric onset of end-stage renal disease: state of the art and recommendations for clinical practice. Pediatr Nephrol. 2016 Oct;31(10):1579-91. doi: 10.1007/s00467-015-3186-3. Epub 2015 Aug 27. PMID: 26310616; PMCID: PMC4995226.

16. Lopes M, Ferraro A, Koch VH. Health-related quality of life of children and adolescents with CKD stages 4-5 and their caregivers. Pediatr Nephrol. 2014 Jul;29(7):1239-47. doi: 10.1007/s00467-014-2769-8. Epub 2014 Feb 28. PMID: 24577804.

17. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, Simões E Silva AC, Kummer AM. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. Pediatr Nephrol. 2015 Dec;30(12):2153-62. doi: 10.1007/s00467-015-3159-6. Epub 2015 Jul 27. PMID: 26210984.

18. Tong A, Henning P, Wong G, McTaggart S, Mackie F, Carroll RP, Craig JC. Experiences and perspectives of adolescents and young adults with advanced CKD. Am J Kidney Dis. 2013 Mar;61(3):375-84. doi: 10.1053/j.ajkd.2012.09.024. Epub 2013 Jan 10. PMID: 23312724.

19. Tong A, Wong G, McTaggart S, Henning P, Mackie F, Carroll RP, Howard K, Craig JC. Quality of life of young adults and adolescents with chronic kidney disease. J Pediatr. 2013 Oct;163(4):1179-85.e5. doi: 10.1016/j.jpeds.2013.04.066. Epub 2013 Jun 22. PMID: 23800404.

20. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007 Jul 16;5:43. doi: 10.1186/1477-7525-5-43. PMID: 17634123; PMCID: PMC1964786.

21. King TZ, Ailion AS, Fox ME, Hufstetler SM. Neurodevelopmental model of long-term outcomes of adult survivors of childhood brain tumors. Child Neuropsychol. 2019 Jan;25(1):1-21. doi: 10.1080/09297049.2017.1380178. Epub 2017 Sep 28. PMID: 28956496.

22. Wolfe KR, Madan-Swain A, Kana RK. Executive dysfunction in pediatric posterior fossa tumor survivors: a systematic literature review of neurocognitive deficits and interventions. Dev Neuropsychol. 2012;37(2):153-75. doi: 10.1080/87565641.2011.632462. PMID: 22339228; PMCID: PMC3730812.

23. Tassé MJ. Adaptive behavior and functional life skills across the lifespan: Conceptual and measurement issues. Adaptive Behavior Strategies for Individuals with Intellectual and Developmental Disabilities: Evidence-Based Practices Across the Life Span: Springer; 2021; 1-20.

24. Alhamed AA, Toly VB, Hooper SR, Dell KM. The link between executive function, socio-emotional functioning and health-related quality of life in children and adolescents with mild to moderate chronic kidney disease. Child Care Health Dev. 2022 May;48(3):455-464. doi: 10.1111/cch.12946. Epub 2021 Dec 16. PMID: 34893999.

25. Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. Qual Life Res. 2008 Nov;17(9):1125-35. doi: 10.1007/s11136-008-9396-4. Epub 2008 Oct 3. PMID: 18836850.

26. Organization WH. International Classification of Functioning, Disability, and Health: Children & Youth Version: ICF-CY: World Health Organization; 2007.

27. Kerklaan J, Hannan E, Hanson C, Guha C, Cho Y, Christian M, Hamiwka L, Ryan J, Sinha A, Wong G, Craig J, Groothoff J, Tong A. Perspectives on life participation by young adults with chronic kidney disease: an interview study. BMJ Open. 2020 Oct 16;10(10):e037840. doi: 10.1136/bmjopen-2020-037840. PMID: 33067282; PMCID: PMC7569939.

28. Stewart AJ, Sokol M, Healy JM, Chester NL. Longitudinal studies of psychological consequences of life changes in children and adults. Journal of Personality and Social Psychology. 1986; 50(1):143.

29. Stewart JL. Children living with chronic illness: an examination of their stressors, coping responses, and health outcomes. Annu Rev Nurs Res. 2003;21:203-43. PMID: 12858698.

30. Groothoff JW, Grootenhuis MA, Offringa M, Gruppen MP, Korevaar JC, Heymans HS. Quality of life in adults with end-stage renal disease since childhood is only partially impaired. Nephrol Dial Transplant. 2003 Feb;18(2):310-7. doi: 10.1093/ndt/18.2.310. PMID: 12543886.

31. Kim WS, Cho SI, Shin HI, Park JH. Identifying factors associated with self-rated health according to age at onset of disability. Disabil Rehabil. 2012;34(15):1262-70. doi: 10.3109/09638288.2011.641656. Epub 2011 Dec 26. PMID: 22200125.

32. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: Is quality of life determined by expectations or experience? BMJ. 2001 May 19;322(7296):1240-3. doi: 10.1136/bmj.322.7296.1240. PMID: 11358783; PMCID: PMC1120338.

33. Allen TM, Anderson LM, Rothman JA, Bonner MJ. [Formula: see text] Executive functioning and health-related quality of life in pediatric sickle cell disease. Child Neuropsychol. 2017 Nov;23(8):889-906. doi: 10.1080/09297049.2016.1205011. Epub 2016 Jul 21. PMID: 27439898.

34. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995 Jan 4;273(1):59-65. PMID: 7996652.

35. Levin A, Stevens P, Bilous RW, Coresh J, Francisco A, Jong PE, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplements. 2013;3:1-150.

36. Haverman L, van Rossum MA, van Veenendaal M, van den Berg JM, Dolman KM, Swart J, Kuijpers TW, Grootenhuis MA. Effectiveness of a web-based application to monitor health-related quality of life. Pediatrics. 2013 Feb;131(2):e533-43. doi: 10.1542/peds.2012-0958. Epub 2013 Jan 6. PMID: 23296436.

37. Onderwijsindeling S. Standard Educational Classification. Den Haag/Heerlen: Centraal Bureau voor de Statistiek [Statistics Netherlands]. 2016.

38. Kaldenbach Y. De WISC-III anno 2006. Kind & Adolescent Praktijk. 2006;5(3):100.

39. Gajria K, Kosinski M, Sikirica V, Huss M, Livote E, Reilly K, Dittmann RW, Erder MH. Psychometric validation of the Weiss Functional Impairment Rating Scale-Parent Report Form in children and adolescents with attention-deficit/hyperactivity disorder. Health Qual Life Outcomes. 2015 Nov 17;13:184. doi: 10.1186/s12955-015-0379-1. PMID: 26577642; PMCID: PMC4650258.

40. Weiss MD, McBride NM, Craig S, Jensen P. Conceptual review of measuring functional impairment: findings from the Weiss Functional Impairment Rating Scale. Evid Based Ment Health. 2018 Nov; 21(4):155-164. doi: 10.1136/ebmental-2018-300025. Epub 2018 Oct 12. PMID: 30314990; PMCID: PMC6241626.

41. Organisation WH. Measuring health and disability: manual for WHO Disability Assessment Schedule (WHODAS 2.0). 2010. Contract No.: ISBN: 9789241547598.

42. Hope TL, Adams C, Reynolds L, Powers D, Perez RA, Kelley ML. Parent vs. self-report: Contributions toward diagnosis of adolescent psychopathology. Journal of Psychopathology and Behavioral Assessment. 1999; 21:349-63.

43. Phares V, Compas BE, Howell DC. Perspectives on child behavior problems: Comparisons of children's self-reports with parent and teacher reports. Psychological Assessment: A Journal of Consulting and Clinical Psychology. 1989; 1(1):68.

44. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999 Feb;37(2):126-39. doi: 10.1097/00005650-199902000-00003. PMID: 10024117.

45. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007 Jan 3;5:1. doi: 10.1186/1477-7525-5-1. PMID: 17201920; PMCID: PMC1769360.

46. van Muilekom MM, Luijten MAJ, van Oers HA, Conijn T, Maurice-Stam H, van Goudoever JB, Grootenhuis MA, Haverman L; KLIK collaborator group. Paediatric patients report lower health-related quality of life in daily clinical practice compared to new normative PedsQLTM data. Acta Paediatr. 2021 Jul;110(7):2267-2279. doi: 10.1111/apa.15872. Epub 2021 May 6. PMID: 33838052; PMCID: PMC8360011.

47. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. BMC Pediatr. 2009 Nov 3;9:68. doi: 10.1186/1471-2431-9-68. PMID: 19887000; PMCID: PMC2776579.

48. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach: Guilford publications; 2017.

49. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-37. doi: 10.1681/ASN.2008030287. Epub 2009 Jan 21. PMID: 19158356; PMCID: PMC2653687.

50. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007 Apr;53(4):766-72. doi: 10.1373/clinchem.2006.077180. Epub 2007 Mar 1. PMID: 17332152.

51. Okuda Y, Soohoo M, Tang Y, Obi Y, Laster M, Rhee CM, Streja E, Kalantar-Zadeh K. Estimated GFR at Dialysis Initiation and Mortality in Children and Adolescents. Am J Kidney Dis. 2019 Jun;73(6):797-805. doi: 10.1053/j.ajkd.2018.12.038. Epub 2019 Mar 2. PMID: 30833086.

52. Love CE, Webbe F, Kim G, Lee KH, Westerveld M, Salinas CM. The role of executive functioning in quality of life in pediatric intractable epilepsy. Epilepsy Behav. 2016 Nov;64(Pt A):37-43. doi: 10.1016/j.yebeh.2016.08.018. Epub 2016 Oct 8. PMID: 27728901.

53. Schraegle WA, Titus JB. Executive function and health-related quality of life in pediatric epilepsy. Epilepsy Behav. 2016 Sep;62:20-6. doi: 10.1016/j.yebeh.2016.06.006. Epub 2016 Jul 20. PMID: 27448239.

54. Sherman EM, Slick DJ, Eyrl KL. Executive dysfunction is a significant predictor of poor quality of life in children with epilepsy. Epilepsia. 2006 Nov;47(11):1936-42. doi: 10.1111/j.1528-1167.2006.00816.x. PMID: 17116035.

55. Ziengs AL, Buunk AM, van Sonderen L, Eisenga MF, Gomes Neto AW, Annema C, Vlagsma T, Navis GJ, Berger SP, Bakker SJL, Spikman JM. Long-term cognitive impairments in kidney transplant recipients: impact on participation and quality of life. Nephrol Dial Transplant. 2023 Feb 13;38(2):491-498. doi: 10.1093/ndt/gfac035. PMID: 35175356; PMCID: PMC9923696.

56. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986 Dec;51(6):1173-82. doi: 10.1037//0022-3514.51.6.1173. PMID: 3806354.

57. Sikora DM, Vora P, Coury DL, Rosenberg D. Attention-deficit/hyperactivity disorder symptoms, adaptive functioning, and quality of life in children with autism spectrum disorder. Pediatrics. 2012 Nov;130 Suppl 2:S91-7. doi: 10.1542/peds.2012-0900G. PMID: 23118259.

58. Al Shahawy AK, El-Gamasy MA, Elhakeem Seleem MA, Mawlana W, El Sharkaway AH. Assessment of cognitive functions and adaptive behavior in children with end-stage renal disease on regular hemodialysis. Saudi J Kidney Dis Transpl. 2020 Mar-Apr;31(2):395-406. doi: 10.4103/1319-2442.284014. PMID: 32394912.

59. Knight A, Kogon AJ, Matheson MB, Warady BA, Furth SL, Hooper SR. Cognitive Function in Children with Lupus Nephritis: A Cross-Sectional Comparison with Children with Other Glomerular Chronic Kidney Diseases. J Pediatr. 2017 Oct;189:181-188.e1. doi: 10.1016/j.jpeds.2017.06.044. Epub 2017 Jul 19. PMID: 28734655; PMCID: PMC5614831.

60. Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychol. 2002 Jun;8(2):71-82. doi: 10.1076/chin.8.2.71.8724. PMID: 12638061.