



Original Article

Sleep disorders and executive function in children and adolescents with chronic kidney disease



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ARTICLE INFO

Article history:

Received 1 September 2018

Received in revised form

7 November 2018

Accepted 14 November 2018

Available online 14 December 2018

Keywords:

Children

Chronic kidney disease

Sleep-related breathing disorder

Insomnia

Executive function

ABSTRACT

Objective: The impact of sleep-related disorders in children and adolescents with chronic kidney disease on executive function performance has been scarcely studied. The aims of the present study were to assess the prevalence of sleep-related disorders in chronic kidney disease pediatric patients, and to examine possible correlations with measures of executive function.

Methods: We performed a case–control study including 51 children with chronic kidney disease stages 2–5, aged 5–18 years, and 51 healthy controls. The parents of both patients and controls completed the Pediatric Sleep Questionnaire (PSQ), and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire.

Results: Children with chronic kidney disease presented lower executive performance with higher scores in scales of executive function, and an increased risk of presenting a sleep-related disorder (odds ratio (OR) = 7.58, 95% confidence interval (CI) 2.36–24.31, $p < 0.005$) compared to controls. In the patient group, age of chronic kidney disease onset correlated with Behavior Regulation Index T-score ($r = 0.32$, $p < 0.05$). In multivariate analysis, differences between patients and controls for Metacognition Index T-scores did not persist after adjustment for sleep-related breathing disorder and insomnia scores, while differences in Behavior Regulation Index T-scores remained significant (54.15 vs 49.14, $p < 0.02$). Moreover, mediational analyses showed that sleep-related disorders mediated the effect of chronic kidney disease on metacognition, but not on behavioral regulation.

Conclusion: Sleep-related disorders may in part explain the lower executive function performance during everyday life in chronic kidney disease pediatric patients. However, additional disease-related factors may influence executive function, especially in the domains of behavior regulation.

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1. Introduction

Executive function denotes a set of interrelated cognitive abilities and behaviors allowing individuals to purposefully identify goals, to develop plans, to regulate behaviors, emotions, and cognitions to attain these goals [1]. Chronic kidney disease (CKD) has been shown to impact the brain development during early developmental years [2,3]. The uremic milieu may induce structural brain changes, atrophy and silent infarcts, resulting in

accelerated cognitive decline. A recent meta-analysis on neurocognitive outcomes in children and adolescents with CKD showed lower intellectual functioning in patients compared to children without CKD with the most apparent deficits in global intelligence [4]. Given that survival for children with CKD has dramatically improved, focusing research efforts on understanding executive function changes that may affect educational outcomes and quality of life are gaining increasing interest [5–7].

Although sleep-related disorders during childhood have been reported to be quite common, ranging from 25 to 43% [8,9], and their consequences on neurodevelopment and behavior are well known [10–13], it appears that sleep problems are frequently overlooked [14,15]. Uremia, edema, acidosis, altered sleep–awake rhythms, anemia and inadequate iron stores, malnutrition and obesity have been implicated in the pathogenesis of sleep disorders

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in children with CKD [16–18]. However, a recent review identified only seven papers dealing with sleep disorders in children with CKD [16], and thereafter only two relevant papers have been published [19,20]. Moreover, sleep-related disorders have been associated with lower quality of life, as well as disease comorbidities [16], but to our knowledge no previous study has assessed the effect on cognitive function. A recent systematic review, that examined the influence of sleep on developing brain functions and structures in children and adolescents, highlighted the importance of sleep for the developing brain of children and adolescents, although no firm conclusions could be drawn due to the diversity of sleep measures and outcomes [21]. Similarly, a systematic review on the cognitive and behavioral effects of obstructive sleep apnea syndrome showed that children's intellectual abilities may be impaired by obstructive sleep apnea syndrome, but remain within the normal range, and emphasized the low levels of evidence, conflicting findings, and heterogeneity of measures used to assess these domains [22]. Therefore, it is clear that there is a paucity of data on this topic and additional research is needed [16].

The aims of the present study were to assess the prevalence of sleep-related disorders in children with CKD, and to investigate possible correlations of sleep-related disorders scales' scores with measures of different domains of executive function, examining whether sleep disorders contribute to lower executive functioning in CKD pediatric patients.

2. Methods

2.1. Participants

The study population included children and adolescents with CKD stages 2–5, aged 5–18 years, and healthy controls with similar age and sex distribution. Between November 2015 and March 2017, CKD patients were recruited from the Pediatric Nephrology Unit in a tertiary care affiliated institution. The diagnosis of CKD was based on the National Kidney Foundation Disease Outcomes Quality Initiative (K/DOQI) criteria [23,24]. The control group consisted of healthy children and adolescents visiting pediatric outpatient clinics for well-child visits, who volunteered to participate in the study. For each CKD patient a healthy non-obese child of similar age and the same sex was recruited. Exclusion criteria were autistic spectrum disorders, attention deficit hyperactivity disorder, any neurocognitive delay, epilepsy, cerebral palsy, treatment with sedative or hypnotic medications, severe obesity, enlarged adenoids, and initiation of dialysis or transplantation within the last three months. Informed consent to participate in the study was obtained from the children's parents, and in the adolescent age range from both the parents and the adolescents. All individuals fulfilling the inclusion and exclusion criteria that were approached consented to participate in the study. The study was performed in accordance with the declaration of Helsinki and the institutional review board approved the human research protocol.

2.2. Sleep-related disorders, executive function measures and other measurements

Parents completed two validated pediatric questionnaires, the Pediatric Sleep Questionnaire (PSQ), and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire, which were translated and validated in the Greek language following previously published methodology by the investigators after permission [25]. For the BRIEF questionnaire, translation and validation into the Greek language was previously described [26]. Two independent native-Greek translators translated the PSQ questionnaire from English into Greek. The two translations were

synthesized into one, and two native English translators performed two backward translations from Greek into English. Following this translation, a review committee including the four translators and a pediatric sleep expert, reached in a consensus regarding the final Greek translation. Further assessment of the Greek translation internal consistency with Cronbach's α -coefficient greater than 0.70 was performed in 111 children. The final Greek translation was deposited with the copyright owners (Regents of the University of Michigan) (http://inventions.umich.edu/technologies/3766_pediatic-sleep-questionnaire-designed-as-research-screen-for-symptoms-of-obstructive-sleep-apnea-and-other-sleep-disorders-in-children).

The PSQ was designed to assess symptoms of sleep disorders in children and it includes multiple scales to evaluate for different sleep disorders, including obstructive sleep-related breathing disorder (SRBD), snoring, daytime sleepiness, insomnia, and restless legs syndrome (RLS) [27]. The scales of obstructive SRBD, snoring, and daytime sleepiness have been validated against laboratory polysomnography and may be used as a valid and reliable alternative when polysomnography is not feasible [15,28,29]. This tool has been widely utilized and has shown adequate psychometric properties [30,31]. Moreover, it is the most frequently used sleep questionnaire in children with CKD [16]. Scores greater than 0.33 are considered suggestive of a sleep-related disorder diagnosis.

The BRIEF questionnaire is an 86-item parent-report designed to evaluate behavioral correlates of executive function in 5- to 18-year-old children during everyday life. It includes eight subscales of executive function performance (Inhibit, Shift, and Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), two composite scales (Behavioral Regulation Index (BRI) and Metacognition Index (MI)) and an overall summary score referred as Global Executive Composite (GEC). Raw scores are converted to T-scores according to previously published normative values. Higher scores indicate greater degrees of dysfunction [32,33]. This inventory is reported to have high internal consistency, good convergent validity, and good test–retest reliability [1,26,33–35].

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the subjects in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg)/height² (m²). BMI z-score was calculated by the least mean squares method. Past medical history and current medications were recorded. Data on CKD primary diagnosis, age of onset, and CKD stage were collected for the CKD patients. Socioeconomic status (SES) was assessed using three questions that were generated for the current study based on previously published guidelines [36]. SES was rated as level 1 (medium–high), level 2 (medium) or level 3 (low) at the time of the questionnaires' administration based on questions on the economic feasibility to visit private office or public hospital outpatient pediatric clinics for well-child visits, parents' employment (yes/no), and occupation (non-manual/manual).

2.3. Statistical analysis

The IBM SPSS 24.0 (SPSS Inc, Chicago, IL, USA) statistical package was used to analyze the data. Standard descriptive statistics, *t*-test or non-parametric methods (Mann–Whitney test, χ^2 test) were used as appropriate for the comparison between the groups. Bivariate and partial correlation tests were used to assess relationships among PSQ and BRIEF scales. Logistic regression analysis was performed to determine the risk of having a sleep disorder. General Linear Model multivariate analysis of covariance was used to examine the effect of PSQ scores on BRIEF composite rates and to assess differences between the CKD and the control group after adjustment for possible covariates (SES, SRBD, insomnia). A *p*-value <0.05 was considered statistically significant.

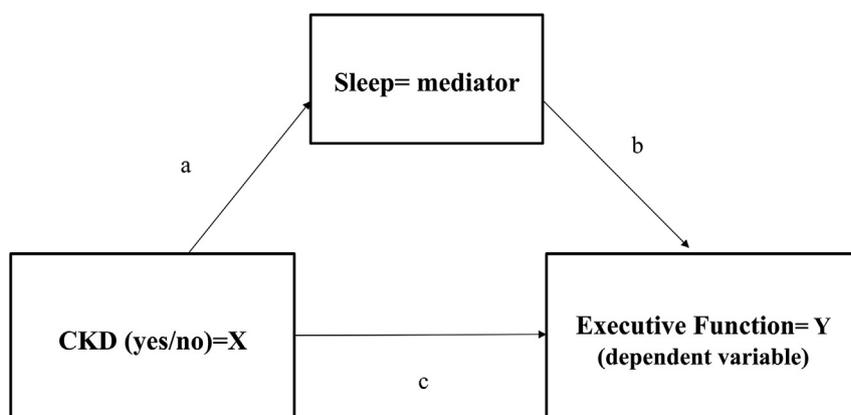


Fig. 1. Statistical model for the mediational analyses: M, mediator (sleep-related breathing disorder (SRBD) or Insomnia); X = chronic kidney disease (CKD) status (yes/no); Y = dependent variable (Behavioral Regulation Index (BRI) T-score, Metacognition Index (MI) T-score); Direct effect of X on M = a; Direct effect of M on Y = b; Direct effect of X on Y = c.

Bootstrap mediation analyses using bootstrap conditional effects procedures were used to examine the effect of CKD (no = 2, yes = 1) on BRI and MI T-scores, and whether sleep scales (SRBD, insomnia) mediated the effect of CKD on executive function (no = 2, yes = 1). The statistical model for the mediation analyses is illustrated in Fig. 1 [37].

3. Results

3.1. Demographic characteristics

The study population included 51 children and adolescents with CKD, and 51 controls of the same sex and of similar age, and SES. The most common cause of CKD was congenital anomalies of the kidney and urinary tract. All children were Caucasian. Demographic, anthropometric, and clinical data are summarized in Table 1. Mothers answered the questionnaires in most of cases (77.5%), followed by fathers in 14.5% of the cases. In CKD patients a significantly higher percentage of fathers completed the questionnaires compared to controls.

3.2. Group differences in sleep disorders scales

The CKD group presented statistically significant higher scores in SRBD, insomnia, and daytime sleepiness scales than the control group (Table 2). The prevalence of SRBD (score ≥ 0.33) between CKD patients and controls was not significant. The prevalence of insomnia, daytime sleepiness, and arousals during the night was significantly higher in CKD patients than in controls (Fig. 2). CKD patients presented an increased risk to present insomnia (odds ratio (OR) = 7.53, 95% confidence interval (CI) 1.59–35.69, $p < 0.05$), and daytime sleepiness (OR = 13.75, 95% CI 1.70–111.04, $p < 0.05$). CKD patients also had an increased risk of presenting arousals during the night (OR = 15.71, 95% CI 1.93–127.32, $p < 0.05$) compared to controls. CKD patients compared to controls had an increased risk of presenting any sleep disorder (OR = 7.58, 95% CI 2.36–24.31, $p < 0.005$).

3.3. Associations between executive function, sleep disorders, and CKD-related parameters

The SRBD score correlated with all BRIEF scales T-scores (Supplementary Table S1). The correlations between SRBD score and BRI, MI, GEC scales T-scores remained significant after

correction for participant group (CKD-control). Insomnia score correlated only with MI scale T-score, and the relation remained significant after correction for participant group. The other sleep scales did not correlate with BRIEF scales.

In the CKD group, age of CKD onset correlated with emotional control scale T-score ($r = 0.35$, $p = 0.01$), and BRI scale T-score ($r = 0.32$, $p < 0.05$). Duration of CKD correlated with inhibit scale T-score ($r = 0.30$, $p < 0.05$). There were no associations between BRI, MI, GEC scales T-scores and CKD stage, duration of disease, or

Table 1
Demographic and clinical characteristics.

	CKD group N = 51 (mean \pm SD or %)	Control group N = 51 (mean \pm SD or %)	p
Age (years)	12.13 \pm 4.03	11.64 \pm 3.75	0.52
Sex (male)	29 (57%)	27 (53%)	0.69
Height (m)	1.48 \pm 0.22	1.53 \pm 0.19	0.21
Height z-score	-0.39 \pm 1.20	0.97 \pm 0.86	<0.001
BMI z-score	0.09 \pm 1.06	0.29 \pm 0.83	0.35
Relative			
Mother	68.6%	92.2%	<0.05
Father	23.5%	5.9%	<0.05
Both	3.9%	2.9%	
Brother	3.9%	0	
SES ^a			
Level 1	80.4%	90.2%	0.37
Level 2	11.8%	5.9%	0.37
Level 3	7.8%	3.9%	0.37
CKD stage			
2	47.1%	–	
3–4	27.4%	–	
5	25.5%	–	
Primary diagnosis			
CAKUT	37.3%	–	
Cystic kidney disease	21.6%	–	
Glomerulonephritis	15.7%	–	
HUS	11.8%	–	
Tubulointerstitial nephritis	7.8%	–	
Neonatal AKI	5.9%	–	
Age of CKD onset (years)	3.97 \pm 3.87	–	
CKD duration (years)	8.41 \pm 3.74	–	

AKI, acute kidney injury; BMI, body mass index; CAKUT, Congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; HUS, hemolytic-uremic syndrome, SD, standard deviation; SES, socioeconomic status.

^a SES rated as level 1 (medium-high), level 2 (medium) or level 3 (low) at the time of questionnaires' administration based on questions on the economic feasibility to visit private office or public hospital outpatient pediatric clinics for well-child visits, parents' employment, and occupation.

Table 2
Differences in Pediatric Sleep Questionnaire scales.

Sleep scale	CKD group mean \pm SD/median (IQR)	Control group Mean \pm SD/median (IQR)	<i>p</i>
SRBD	0.16 \pm 0.11/0.14 (0.06–0.24)	0.08 \pm 0.11/0.05 (0.00–0.10)	<0.001 ^a
Snoring	0.09 \pm 0.19/0.00 (0.00–0.12)	0.12 \pm 0.20/0.00 (0.00–0.25)	0.40 ^a
Restless legs syndrome	0.12 \pm 0.18/0.00 (0.00–0.18)	0.10 \pm 0.14/0.00 (0.00–0.16)	0.73 ^a
Insomnia	0.18 \pm 0.26/0.00 (0.00–0.29)	0.08 \pm 0.13/0.00 (0.00–0.25)	<0.05 ^a
Daytime sleepiness	0.16 \pm 0.25/0.00 (0.00–0.25)	0.02 \pm 0.09/0.00 (0.00–0.00)	<0.005 ^a
Sleep duration – school days (h)	8.98 \pm 0.86	8.99 \pm 1.11	0.94 ^b
Sleep duration – weekends (h)	9.93 \pm 0.90	10.05 \pm 1.15	0.54 ^b

IQR, interquartile range; SD, standard deviation.

^a Mann–Whitney test.

^b *t*-test.

primary diagnosis. Controlling for age of CKD onset attenuated the correlations of SRBD with BRI and GEC scales T-score. However, correlations between SRBD and MI scale T-score ($r = 0.33$, $p < 0.05$), as well as insomnia and MI scale T-score ($r = 0.39$, $p < 0.05$) in the CKD group persisted even after controlling for age of CKD onset.

3.4. Multivariate analysis of group differences in executive function

CKD patients presented higher T-scores in nearly all BRIEF scales compared to controls (Table 3). Multivariate analysis of covariance with dependent variable BRI, MI and GEC scales T-scores, and covariates SRBD, Insomnia, and CKD-control group are shown in Table 4. In multivariate analysis differences between CKD patients and controls for MI and GEC T-scores did not persist after adjustment for SRBD and insomnia scores. However, differences in BRI T-scores between controls and CKD patients remained significant in the multivariate analysis (BRI T-score 54.15 vs 49.14, $p < 0.02$). The differences in BRI T-score persisted even after adjustment for SES.

3.5. Meditational analysis

The results from this analysis did not reveal mediation for BRI T-scores (Fig. 3). Although children with CKD had higher SRBD

scores ($a = 0.08$, $p < 0.01$), SRBD did not significantly influence BRI ($b = 15.22$, $p < 0.07$). The indirect effect did not reach significance, but there was no evidence that the presence of CKD influenced BRI independent of its effect on SRBD ($c' = 3.62$, $p = 0.08$), suggesting that at least part of the variance in BRI may be due to SRBD score levels. Although children with CKD had higher insomnia scores ($a = 0.12$, $p < 0.01$), insomnia did not significantly influence in BRI ($b = 2.63$, $p = 0.56$). The indirect effect reached significance, providing evidence that the presence of CKD influenced BRI independent of its effect on insomnia ($c' = 4.73$, $p = 0.02$).

The results from this analysis confirmed a mediation model with the presence of CKD indirectly influencing MI through its effects on sleep (Fig. 3). Children with CKD had higher SRBD scores ($a = 0.08$, $p < 0.01$), and children with higher SRBD scores demonstrated greater impairments in MI ($b = 27.41$, $p < 0.001$). There was no evidence that the presence of CKD influenced MI independent of its effects on SRBD ($c' = 2.33$, $p = 0.20$). Children with CKD had higher insomnia scores ($a = 0.12$, $p < 0.01$), and children with higher insomnia scores demonstrated greater impairments in MI ($b = 11.12$, $p < 0.001$). There was also no evidence that the presence of CKD influenced MI independent of its effects on insomnia ($c' = 3.47$, $p = 0.06$).

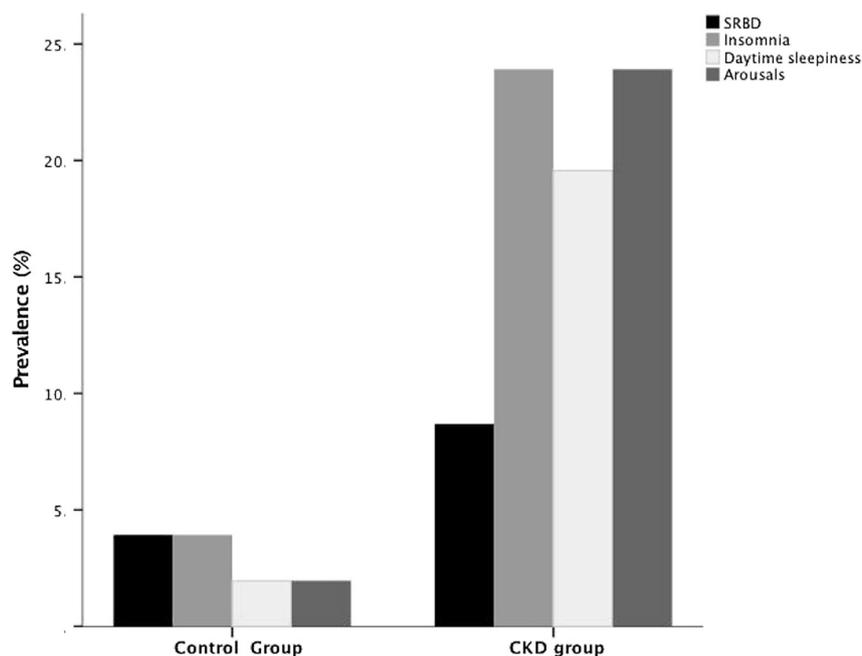


Fig. 2. Prevalence of sleep-related disorders in the chronic kidney disease (CKD) and control groups; Insomnia, Daytime sleepiness, and Arousal were significantly more prevalent in the CKD group (23.5% in CKD vs 3.9% in controls, $p < 0.01$, 21.6% in CKD vs 2% in controls, $p < 0.01$, and 23.9% in the CKD vs 2% in controls $p < 0.005$, respectively), sleep-related breathing disorder (SRBD) prevalence between CKD patients and controls was not significant (7.8% in CKD vs. 3.9% in controls, $p = 0.33$).

Table 3
Differences in Behavior Rating Inventory of Executive Function (BRIEF) scales.

BRIEF scale	CKD group (mean ± SD)	Control group (mean ± SD)	<i>p</i>
Inhibit T-score	52.84 ± 8.59	49.78 ± 9.10	0.10
Shift T-score	54.76 ± 9.89	48.19 ± 8.89	0.001
Emotional control T-score	54.22 ± 10.06	50.23 ± 10.51	0.06
BRI T-score	54.39 ± 8.98	49.46 ± 9.76	<0.05
Initiate T-score	53.84 ± 8.88	49.13 ± 9.96	<0.05
Working memory T-score	50.97 ± 9.26	48.50 ± 8.40	0.19
Plan/organize T-score	51.55 ± 9.40	47.38 ± 8.76	<0.05
Organization of material T-score	50.54 ± 10.36	45.68 ± 9.17	<0.05
Monitor T-score	52.25 ± 10.06	46.76 ± 9.34	<0.01
MI T-score	51.47 ± 8.80	46.82 ± 8.39	<0.05
GEC T-score	53.00 ± 8.59	47.22 ± 8.02	<0.005

BRI, Behavioral Regulation Index; CKD, chronic kidney disease; GEC, Global Executive Composite; MI, Metacognition Index.

4. Discussion

The present study adds data in two fields that have been under investigated in pediatric patients with CKD: sleep-related disorders and executive function. Current evidence on sleep disorders or executive function in pediatric CKD patients is characterized by few, methodologically heterogeneous, papers including different populations and various questionnaires [16]. In the present case–control study, CKD patients presented lower performance in nearly all domains of executive function compared with healthy children. Higher scores in sleep-related disorders scales were shown to mediate in part this lower performance.

Patients with CKD in the present study had an increased risk of presenting clinically significant sleep disturbance. Insomnia was prevalent in 23.5% of the CKD children. Sinha et al., had previously found that 10% of non-dialysis CKD patients suffered from insomnia [38]. The 23.9% prevalence of arousals in the present study is lower compared to previous studies that used the PSQ, ranging from 37.5% to 76% [19,39]. Using the PSQ, the prevalence of daytime sleepiness has been reported 12% in non-dialysis pediatric patients [38], and 56% in patients on dialysis [39]. Overall the 21% prevalence of daytime sleepiness in the present study lies intermediate to the extremes of 10–60% reported in the existing literature [40,41]. In the present study CKD patients presented statistically significant higher scores in SRBD scale compared to controls, but the prevalence of SRBD did not differ between the two groups. In the largest available study using the PSQ, the investigators reported SRBD in 23.3% of 159 patients on different CKD stages, but there was no control group [42]. Sinha et al., reported SRBD in 6% of non-dialysis CKD patients [38] similar to the 7.8% prevalence of SRBD in our CKD population. The discrepancies between the studies may be attributed to differences in the population characteristics and the tools used to assess sleep disorders.

Previous studies in non-CKD pediatric populations have also shown relations between BRIEF scales and sleep. In healthy adolescents, sleepiness has been associated with GEC performance [43]. Children having SRBD assessed by polysomnography had increased rates of impaired BRI performance [44]. In children with type 1 diabetes mellitus the impact of disease on sleep and the resulting sleep disruption has been associated with neurocognitive and behavioral deficits [45]. In the present study, using parent-reported BRIEF scores, we demonstrated that children with CKD compared to controls had lower performance in nearly all the scales of executive function except working memory. Our findings are in concert with those of Mendley et al., who reported that 35% of children with mild to moderate CKD had poor executive function performance, but their working memory was not affected [46]. Gipson et al., studied four executive function domains in CKD pediatric patients. They reported that the CKD group performed lower than the control group on both initiation and sustaining, while the two groups did not differ on set-shifting and inhibition [6]. In previous studies using the BRIEF parent questionnaire children with mild to moderate CKD stage presented higher scores in BRI, MI, and GEC composite scales compared to control group or general population [4,47,48]. The lack of associations between BRIEF scores and most CKD-related parameters, including primary diagnosis, CKD stage, and duration of CKD have been previously reported [48]. Notably, Hooper et al., found an association of GEC with Iohexol GFR calculation in children with moderate CKD providing evidence that more precise assessment of CKD status could provide hints of increased risk for poor executive function performance [48].

The lower executive function performance in the CKD group in the present study could be in part attributed to sleep-related disorders. Sleep-related disorders have been previously reported to be significant confounders of impaired executive function in

Table 4
Multivariate analysis of covariance for the effect of sleep-related disorders scores on BRIEF composite scales.

	<i>B</i>	<i>p</i>	<i>B</i> ^a	<i>p</i>
BRI T-score				
SRBD	15.84 (−1.76 to 33.44)	0.07	17.04 (−1.44 to 35.54)	0.07
Insomnia	−0.34 (−9.62 to 8.94)	0.94	0.33 (−9.45 to 10.13)	0.94
CKD vs controls	5.00 (0.94–9.06)	<0.05	4.52 (0.35–8.68)	<0.05
MI T-score				
SRBD	22.14 (6.12–38.17)	<0.01	23.94 (7.95–39.93)	<0.005
Insomnia	6.58 (−1.86 to 15.04)	0.12	5.44 (−3.02 to 13.91)	0.20
CKD vs controls	2.10 (−1.59 to 5.80)	0.26	2.92 (−0.67 to 6.52)	0.11
GEC T-score				
SRBD	22.17 (6.38–37.96)	<0.01	24.12 (8.26–39.98)	<0.005
Insomnia	3.26 (−5.06 to 11.59)	0.43	2.88 (−5.51 to 11.28)	0.49
CKD vs controls	3.62 (−0.02 to 7.26)	0.05	3.98 (0.40–7.55)	<0.05

BRI, Behavioral Regulation Index; CKD, chronic kidney disease; GEC, Global Executive Composite; MI, Metacognition Index; SRBD, obstructive sleep-related breathing disorder; SES, socioeconomic status.

^a Adjusted for SES.

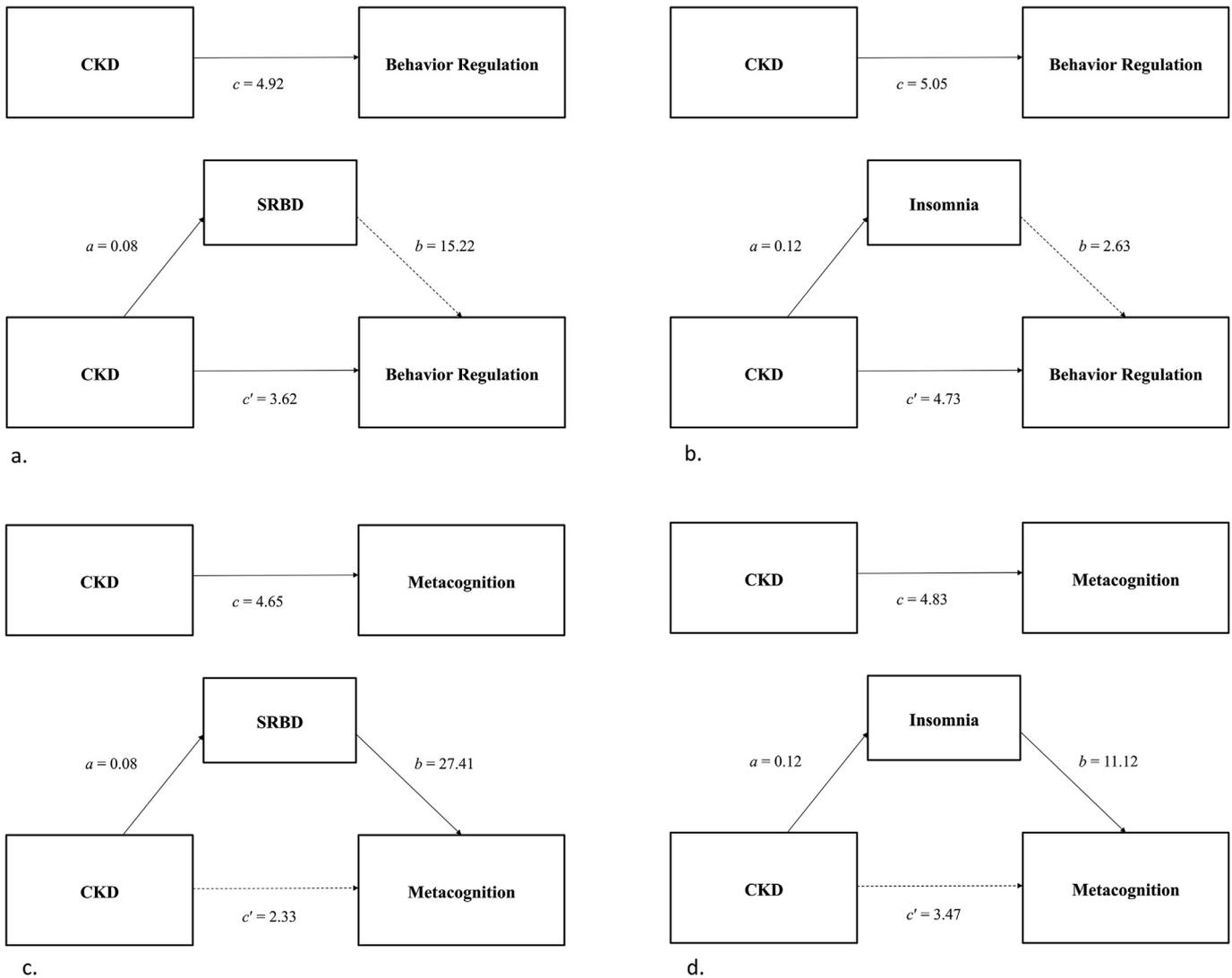


Fig. 3. Coefficients for the effect of chronic kidney disease (CKD) on Behavioral Regulation Index (BRI) and Metacognition Index (MI) through sleep-related disorders. (a) sleep-related breathing disorder (SRBD) did not mediate the effects of CKD on Behavior Regulation. (b) Insomnia did not mediate the effects of CKD on Behavior Regulation. (c) SRBD mediated the effects of CKD on Metacognition. (d) Insomnia mediated the effects of CKD on Metacognition.

children [49]. Impairment of executive function by disordered sleep is also supported by a functional neuroimaging study in adolescents, showing that disordered sleep influences the prefrontal cortex [50]. However, BRI scores in the present study remained elevated in CKD patients compared to controls after adjusting for sleep-related disorders' effects. The mediational analysis also showed that sleep-related disorders in the CKD group fully mediated lower MI T scores, but not the BRI T-scores. This finding implies that additional factors may influence the child's ability to shift cognitive set, modulate emotions and behavior via appropriate inhibitory control [46]. These factors could be attributed to CKD-related factors or may be iatrogenic [4]. BRI scores were associated with age of CKD onset providing evidence of the impact of CKD disarrangements at the early critical neurodevelopmental period.

The results of the present study should be interpreted considering potential strengths and limitations. One limitation of the study population is the relatively small population sample. On the other hand, the study is originated from a single tertiary center, and the sample size is comparable to that of previous multicenter

studies on sleep disorders in pediatric CKD. The inclusion of different CKD stages could be considered as another limitation of the study. The evaluation of both sleep-related disorders and executive functioning relied on parental report with its potential biases (mono-informant bias or common rater effect, using the same informant to determine both sleep and executive function problems may inflate correlations due to item overlap). Ideally, polysomnographic data should be used to evaluate sleep disorders. However, in the present study we used the PSQ that includes scales validated against laboratory polysomnography. Furthermore, inclusion of formal executive function tests would be appropriate in future studies. Finally, the cross-sectional nature of the study does not allow inference as to the causal relation between disordered sleep, CKD, and executive function, although the use of mediational analysis quantified the contribution of sleep and CKD on executive function. Despite these limitations, our findings may add data to under-investigated fields, and to our knowledge, it is the first study that sheds light on the detrimental effects of the sleep-related disorders on executive function in pediatric CKD patients.

5. Conclusions

Sleep-related disorders are more prevalent in children with CKD compared with healthy controls and may have implications on their executive function. The executive function impairment may place children with CKD at educational and occupational disadvantage. Thus, close surveillance of CKD pediatric patients by developmental pediatricians and neuropsychologists, as well as tailoring of educational and prevocational efforts of teachers and physicians to the individual characteristics of these children, is of emerging importance for early interventions to ensure the future well-being of CKD pediatric patients. Finally, assessment and monitoring of sleep disorders is important in CKD, and further studies investigating the impact of SRBD treatment in CKD children are warranted.

Conflict of interest

The authors have no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2018.11.020>.

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