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Executive Functioning, Caregiver Monitoring, and Medication Adherence Over Time in Adolescents with Chronic Kidney Disease

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Abstract

Objective: To evaluate associations between executive functioning and caregiver adherence monitoring with objective antihypertensive medication adherence over 24 months in adolescents with chronic kidney disease (CKD).

Methods: Adolescents (N = 97, 11–20 years old) with CKD taking antihypertensive medication and their caregivers were recruited from three pediatric nephrology clinics. At baseline, adolescents and caregivers reported on adolescents' executive functioning and caregivers reported on their adherence monitoring. Antihypertensive medication adherence was objectively assessed via electronic monitoring at baseline and every 6 months after for 24 months. Associations between executive functioning, caregiver monitoring, and longitudinal adherence were evaluated with linear mixed models.

Results: Up to 38% of adolescents had elevated executive functioning scores indicating more severe impairments, with rates varying by scale and reporter (adolescent versus caregiver). Caregiver monitoring showed a significant, negative association with adherence, but adolescents' executive functioning was not significantly associated with adherence. Neither variable was associated with the rate of change in adherence over time.

Conclusions: Given that adolescents' executive functioning was not associated with antihypertensive medication adherence or changes in adherence over time, adherence to daily pill-form medications may involve less cognitive effort than more complex medical regimens. Higher levels of caregiver monitoring were unexpectedly associated with lower adherence levels. This unanticipated finding may reflect increased caregiver monitoring efforts when faced with

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adolescents' medication nonadherence, but this finding warrants further investigation. Adolescents with CKD who are nonadherent may benefit from medication adherence-promoting strategies beyond increasing caregiver monitoring.

Keywords

adherence; executive functioning; caregiver monitoring; kidney diseases

Hypertension and proteinuria are major risk factors for chronic kidney disease (CKD) progression in children (Fathallah-Shaykh, 2017; Wühl & Schaefer, 2008). Lowering blood pressure and decreasing urinary protein excretion with antihypertensive medications are renal protective strategies that reduce the risk for disease progression and the development of end stage renal disease (ESRD; Wühl & Schaefer, 2008; Wühl et al., 2009). Among children with CKD, adherence to antihypertensive medications is suboptimal, with one-quarter to one-third not regularly taking their prescribed medication, depending on adherence assessment method (electronic monitoring of medication self-administration or pharmacy refill adherence, respectively; Pruette et al., 2019). Inconsistent antihypertensive medication adherence may contribute to accelerated CKD progression in youth.

Executive functioning, which includes the subdomains of behavior regulation (ability to shift one's mindset and use emotional control to meet one's goals) and metacognition (ability to monitor, plan, organize, and sustain future-oriented problem solving; Gioia, Isquith, Guy, & Kenworthy, 2000), is associated with medication adherence in children with other chronic illnesses. In adolescents with solid organ transplants, including kidney, approximately 25% had clinically significant levels of broad executive function impairment, and more severe caregiver proxy-reported impairments in metacognition were cross-sectionally associated with higher levels of adolescent-reported medication nonadherence (Gutiérrez-Colina et al., 2016). Similarly, in children and adolescents with type 1 diabetes (T1D), caregiver proxy-reported impairments in behavior regulation were associated with decreased adolescent-reported self-management skills over 2 years (Miller et al., 2012). Further, as youth with T1D emerge into adulthood, better broad executive functioning abilities have been associated with less rapid increases in blood glucose levels over 2 years (reflecting better disease management), even after controlling for intellectual functioning (Berg et al., 2018).

Despite evidence of these associations in adolescents with T1D or transplants, little work has examined the influence of executive function impairments on adherence in youth with CKD. Children and adolescents with CKD generally exhibit lower executive functioning abilities, particularly within metacognition (scoring approximately .5–1 standard deviations higher in an index of metacognitive impairment than the general population; Chen et al., 2018). Up to 40% of children in the Chronic Kidney Disease in Childhood (CKiD) cohort study had parent-reported and objectively-assessed executive functioning levels ≥1 standard deviation (*SD*) below the mean of an age-adjusted normal population (Hooper et al., 2011; Mendley et al., 2015). Further, increased blood pressure variability, a risk factor for renal function decline and ESRD (Sethna et al., 2017), was associated with higher levels of executive functioning impairments in children and adolescents with CKD (Lande et al., 2016). These findings suggest that adolescents with CKD may have higher incidence of executive

functioning impairments compared to the general population, which likely confers greater risk for medication nonadherence and disease progression over time. However, these associations have yet to be empirically evaluated.

Caregiver monitoring, which includes a caregiver's awareness of their child's location, behaviors, goals, and activities and involvement in helping their child reach his/her goals (Stattin & Kerr, 2000), may also be related to children's adherence. Higher levels of caregiver monitoring have been associated cross-sectionally and longitudinally with better glycemic control in youth with T1D (Berg et al., 2017; Ellis et al., 2007; Robinson et al., 2016), suggesting that caregiver monitoring may facilitate completion of appropriate disease self-management behaviors. Among adolescents with epilepsy, higher levels of caregiver involvement in managing antiepileptic drugs (AEDs) were associated with higher AED adherence over time (Holbein, Smith, Peugh, & Modi, 2019) but caregiver involvement in their children's daily lives in general was not (Smith, Mara, & Modi, 2018). Similarly, among adolescents and young adults with T1D, individuals with higher levels of executive functioning impairments demonstrated lower (better) blood glucose levels when caregiver involvement in diabetes care was higher (Berg et al., 2019). Hence, caregiver monitoring of medical management tasks may offset negative contributions of executive functioning impairments on adolescents' adherence.

The interplay of caregiver factors (including caregiver monitoring of medical regimens) and child cognitive processes and associated behavior processes (including executive functioning) are theorized as being critical in predicting adherence outcomes in youth with chronic medical conditions (Lansing & Berg, 2014), suggesting similar associations will be observed among adolescents with CKD. However, associations of adolescent executive functioning and caregiver monitoring with adherence have predominately been examined in the T1D literature or relied on self-reported adherence. Hence, this study used linear mixed models to examine associations of executive functioning and caregiver monitoring of medication adherence with objectively- and longitudinally-assessed antihypertensive medication adherence in adolescents with CKD. We hypothesized that higher levels of adolescents' executive functioning impairments (baseline) and lower levels of caregiver monitoring (baseline) would be associated with lower antihypertensive medication adherence measured over 24 months (between-person effects).

Methods

Procedures

Recruitment occurred at three pediatric nephrology clinics in the mid-Atlantic United States. Each site's Institutional Review Board (Johns Hopkins School of Medicine, University of Maryland School of Medicine, Children's National Health System) approved study procedures. Adolescents (ages 11–19 years at informed consent) with a physician-verified diagnosis of CKD (stages 1–5) and current prescription for an antihypertensive medication were included. Adolescents who had a sibling participating in the study, were unable to understand spoken English, had a developmental delay or significant cognitive impairment that would preclude their ability to complete study procedures (as reported by their pediatric nephrologist or primary caregiver), or declined to use electronic medication monitoring

devices during study participation were excluded. Caregivers of eligible adolescents <18 years old were invited to participate; caregivers of eligible adolescents ≥18 years old were invited to participate if they actively participated in adolescents' medical care. By reviewing clinic rosters and electronic medical records, trained research assistants (RAs) identified adolescents who appeared to meet eligibility criteria. Potentially eligible adolescents were mailed a letter describing the study and providing the opportunity to opt out of recruitment. Individuals who did not opt out of study recruitment were contacted via telephone and invited to join the study. For adolescents and caregivers who agreed to participate, written informed consent and assent were completed at the first study visit, which occurred at adolescents' homes or a family-preferred location.

Adolescents and caregivers completed surveys (detailed below) at baseline administered with audio-enhanced computer-assisted self-interviewing (audio CASI). Given the inter-relation between executive functioning and intellectual functioning, we assessed adolescents' general cognitive abilities with an intellectual functioning screener (WASI-II) at baseline. Antihypertensive medication adherence was measured continuously via electronic monitoring for two weeks at baseline and 6-, 12-, 18-, and 24-months after baseline. Families received $100 for completing full assessments at baseline, 12- and 24-months and $50 for completing shorter assessments at 6- and 18-months after baseline.

Surveys

Demographic and medical information.—Adolescents ≥18 years old and caregivers of adolescents <18 years old reported demographic information (e.g., race, family income) at baseline. Electronic medical record (EMR) review identified those with co-morbid hypertension diagnoses and allowed for calculating estimated glomerular filtration rate (eGFR) to determine CKD disease stage ((0.413*height/creatinine; Schwartz et al., 2009).

Executive functioning.—The 80-item Behavior Rating Inventory of Executive Function-Self-Report (BRIEF-SR; Guy, Gioia, & Isquith, 2004) and the 86-item Behavior Rating Inventory of Executive Function-Parent Form (BRIEF-P; Gioia et al., 2000) evaluated adolescents' executive functioning abilities at baseline. Adolescents and caregivers rated how much an item was problematic in the last 6 months using a 3-point Likert scale ranging from *Never* to *Often* (e.g., "I don't plan ahead for future activities"; "[My child] Has a short attention span"). The BRIEF-SR and BRIEF-P contain 8 scales comprising the Behavioral Regulation Index (BRI; i.e., ability to exert inhibitory control over one's behaviors and emotions) and the Metacognition Index (MCI; i.e., ability to initiate, plan, organize, self-monitor, and sustain working memory). The BRI and MCI comprise the Global Executive Composite (GEC) score reflecting overall executive functioning impairments. Raw scores were converted to age- and gender-normed T-scores. For adolescents ≥19 years at baseline (n = 8), the highest available age and gender norms were used to determine T-scores. Higher scores indicate more severe executive functioning impairments. The majority of responses were *Acceptable* on the Negativity scale (99% on the BRIEF-SR and -P) and the Inconsistency scale (97% on the BRIEF-SR and -P). In this study, α = .95 on the BRIEF-SR and α = .98 on the BRIEF–P.

Caregiver Monitoring

Caregiver monitoring of adolescents' adherence to antihypertensive medications was assessed via caregivers' responses to three items modified from the Parental Monitoring of Diabetes Care scale (Ellis et al., 2007). Items were modified to evaluate taking antihypertensive medications rather than performing diabetes care tasks. The following three items were selected for face validity in evaluating the extent to which caregivers monitored how their adolescent took their medicine: "How often did you watch your child take his/her antihypertensive medication?" "How often did you ask your child if he/she took his/her antihypertensive medication?" and "How often do you have to remind your child to take his/her antihypertensive medication?" Each item was rated on a 5-point Likert scale ranging from *Never* (0) to *Every time* (4). Item ratings were summed to create a total score with higher scores indicating higher levels of caregiver monitoring. Regarding internal consistency, $\alpha = .62$ in the current sample.

General Cognitive Abilities

The Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II; Wechsler, 2011) were used as a general cognitive abilities screener at baseline. Subtests were administered as part of this study by trained RAs who were supervised by licensed clinical psychologists on the study team. Raw scores were converted to age-normed T-scores to determine adolescents' general cognitive abilities with the Full Scale Intellectual Quotient-2 Subtests (FSIQ-2).

Objective Antihypertensive Medication Adherence

Medication Event Monitoring System (MEMS 6) TrackCap monitors (AARDEX Ltd. Union City, CA) assessed daily antihypertensive medication administration. The MEMS cap records the time and date of each bottle opening and closure. Before each study visit, the RA obtained adolescents' antihypertensive medication regimens (EMR and physician confirmed) including the names of their antihypertensive medication(s), dosages, and schedules. The RA placed the medication in the MEMS bottle. If more than one antihypertensive medication was prescribed, each medication was monitored with a separate MEMS cap and bottle. Adherence was calculated as the number of MEMs cap openings / the total number of expected openings based on the prescribed regimen and the number of days observed. If multiple medications were monitored, average adherence was calculated for each individual medication and then averaged across medications to create a single composite adherence score. The intraclass correlation indicated that 44% of the variance in adherence measurements was between-persons.

Analysis Plan

Descriptive statistics (e.g., mean, *SD*, range) were calculated for primary study variables. Proportions of adolescents in the Clinically Significant (T-score ≥65), At-risk (T-score ≥60), and Sub-clinical ranges (T-score <60) for the BRIEF-SR and –P scales were calculated.

Linear mixed models (PROC MIXED; SAS 9.4 Software, Cary, NC) were used to evaluate associations between baseline executive functioning and baseline caregiver monitoring in predicting level of adherence as well as the rate of change in adherence over 24 months. An

alpha level of $p<.05$ was used to test statistical significance. The restricted maximum likelihood estimation and autoregressive covariance structure were used to allow for some missingness in the data and to account for expected correlations between repeated measures within individuals over time. There was 2% missingness in caregiver proxy-reported survey scale scores, 3% missingness in adolescent-reported survey scale scores, and 16% missingness across all five MEMS cap measurement time points. The fully observed dataset was analyzed. Sensitivity analyses assessed potential patterns of missingness in adherence data based on whether adolescents' antihypertensive medications were discontinued by their prescribing nephrologist after baseline ($n = 13$). Associations between key study variables were similar when adolescents with discontinued medications were excluded. Hence, adolescents whose medications were discontinued during the study were included in final analyses to enhance generalizability. Given that the BRIEF-SR and -P were administered to adolescents ≥19 years old and their caregivers at baseline, we also conducted sensitivity analyses to assess the pattern of effects when these individuals were excluded. The pattern of effects were similar when adolescents ≥19 years old and their caregivers were excluded and, therefore, these individuals were included in final analyses.

Preliminary analyses to evaluate change in adherence over time informed whether time was modeled as a linear or quadratic effect with a subject-level random intercept and random slope. Akaike Information Criterion (AIC) values were used to select the best fitting model (if the difference in AIC values were ≤2, the more parsimonious random intercept fixed slope model was selected; Hilbe, 2011).

To evaluate associations of baseline executive functioning (grand mean centered) and baseline caregiver monitoring (grand mean centered) with adherence over time, BRIEF-SR BRI, MCI, and GEC scales (T-scores) were entered in three separate models with caregiver monitoring (sum scores) and an interaction term between the predictors and time. The same analytic approach was used to evaluate whether the BRIEF-P scales (T-scores) and caregiver monitoring (sum scores) predicted adherence over time. The following covariates (baseline) were included in each model: adolescent age, gender (1 = female, 0 = male), race (1 = Caucasian, 0 = non-Caucasian), FSIQ-2, regimen complexity (number of antihypertensive medications prescribed [1 = one medication prescribed, 0 = >1 medication prescribed], prescribed number of daily antihypertensive medication doses [1 = one daily dose, 0 = >1 daily dose]), and disease characteristics (transplant status [1 = transplant, 0 = no transplant], ESRD status [1 = ESRD, 0 = no ESRD]). Consistent with prior research investigating executive functioning and adherence, the FSIQ-2 was included as a covariate to account for potential contributions of cognitive abilities to executive functioning (Wiebe et al., 2018). All other covariates were based on factors commonly associated with pediatric adherence (Hommel, Ramsey, Rich, & Ryan, 2017).

Results

Participants

A total of 130 adolescents with CKD enrolled in this study; two adolescents were excluded after enrollment due to extremely low FSIQ-2 scores on the WASI-II from which it was determined that study participation would not be appropriate (would preclude completion of

surveys), resulting in 128 adolescent participants. There were no differences in age, gender, or race between those who participated and those who declined to participate (N = 134). Of those who declined to participate, 10 stated an unwillingness to use the MEMS cap to electronically monitor antihypertensive medication adherence as their reason for not enrolling.

Of the 128 who participated, 97 adolescents (M age = 14.87 years, SD = 2.32, Range = 11 to 20) completed adherence monitoring and surveys at baseline and had a caregiver participating in the study who completed proxy-reported executive functioning and caregiver monitoring surveys at baseline (N = 97; Figure 1). Only 3 participants refused to continue in the study over the course of data collection. The majority of adolescents (n = 58) completed adherence monitoring on all 5 assessment opportunities. The average number of adherence assessments was 4.22 (SD = 1.16). The most frequent reason for missing MEMS data was provider discontinuation of antihypertensive medication prescription (6 months n = 6; 12 months n = 6; 18 months n = 9; 24 months n = 12). There were no demographic differences between adolescents with all 5 adherence assessments versus adolescents missing ≥1 adherence assessments.

The majority of the final sample were male, African American (n = 40) or Caucasian (n = 41), and had private health insurance. Most adolescents took one antihypertensive medication at baseline and less than half had a hypertension diagnosis (Table 1). The sample was diverse in terms of CKD stage and family income. The majority of caregivers were female (72%; n = 70) and the adolescent's biological parent (99%; n = 96).

Descriptive Data on Primary Study Variables

Descriptive statistics for adherence, executive functioning, and caregiver monitoring appear in Table 2. The prevalence of adolescents in the Clinically Significant (T-score ≥65), At-risk (T-score ≥60), and Sub-clinical ranges (T-score <60) of the BRIEF-SR and -P appear in Table 3. Adolescent responses to the BRIEF-SR indicated 8–11% fell in the Clinically Significant range and 18–22% fell in the At-risk range for problems with executive functioning. Caregiver responses to the BRIEF-P indicated 18–24% of adolescents fell in the Clinically Significant range and 27–38% fell in the At-risk range for problems with executive functioning.

Preliminary Analyses to Assess Changes in Adherence Over Time

Adherence decreased linearly over time ($\beta = -2.71$, SE = .77, $t = -3.53$, $p < .001$); there was a significant random intercept for subject (variance estimate = 291.51, $p < .001$) but not a random slope (variance estimate = 4.30, p = .28). There was no quadratic effect of time ($\beta = -1.02$, SE = .59, $t = -1.73$, p = .08). Based on the AIC, the linear random intercept fixed slope model (AIC = 3730.3) was selected over the linear random intercept and random slope model (AIC = 3732.0).

Are Executive Functioning and Caregiver Monitoring Associated with Adherence Over Time?

In the linear mixed models (Table 4) analyzing associations between baseline adolescent-reported executive functioning and adherence over time, there were no significant main effects for the BRIEF-SR BRI, MCI, or GEC scales. Baseline caregiver monitoring was negatively associated with adherence in each model (βs = −2.80 to −2.87, ps = .03). None of the Time × predictor interactions in any of the models were statistically significant.

In the caregiver proxy-reported executive functioning linear mixed models (Table 4), there were no significant main effects for the baseline BRIEF-P BRI, MCI, or GEC scales. Baseline caregiver monitoring was negatively associated with adherence in the model including the BRI (β = −2.73, p = .04) but not the MCI or GEC. None of the Time × predictor interactions were statistically significant.

Post-Hoc Analyses

Due to unexpected negative associations between caregiver monitoring and adherence, we conducted post-hoc analyses to further evaluate this association. First, we conducted a linear mixed model excluding the BRIEF-SR or –P subscales. In this model, caregiver monitoring continued to show a significant negative association with adherence (β = −2.93, p = .02).

Due to lower internal consistency for the caregiver monitoring scale, we evaluated our models with caregiver monitoring as a binary cutpoint score rather than a sum score. We calculated the binary variable as 1 = caregiver rated ≥1 item as 3 (Most times) or 4 (Every time) and 0 = caregiver rated all three items ≤2 (Sometimes or less frequently). When this variable was included in the models, caregiver monitoring showed a negative association with adherence which did not reach statistical significance for the models including the BRIEF-SR (βs = −6.49–−8.07, ps = .30–.24) or the BRIEF-P (βs = −2.87–−6.05, ps = .38–.69).

We also calculated the binary caregiver monitoring variable as 1 = caregiver rated ≥1 item as 4 (Every time) and 0 = caregiver rated all three items as ≤3 (Most times or less frequently). When this variable was included in the models, the same negative, non-statistically significant association with adherence was found in the models including the BRIEF-SR (βs = −5.16–−5.26, ps = .36–.38) or the BRIEF-P (βs = −2.92–−4.31, ps = .45–.61).

Discussion

This study examined associations of baseline self- and caregiver proxy-report measures of executive functioning (BRIEF-SR and -P) and caregiver monitoring with electronically-monitored antihypertensive medication adherence over a 24 month period of time in adolescents with CKD. Contrary to hypotheses, lower adherence was significantly associated with higher levels of caregiver monitoring sum scores in all but two of the linear mixed models (the opposite direction than expected) and was not significantly associated with executive functioning. Neither caregiver monitoring nor executive functioning were associated with the rate of change in adherence over time. However, when caregiver monitoring was examined in the models as a cutpoint score in post-hoc analyses, none of the

associations with adherence remained statistically significant. These unexpected findings may reflect our community-based sample of adolescents with CKD who did not have significant cognitive delays and for whom the majority did not present with significantly impaired executive functioning. The findings may suggest that caregivers monitor medication adherence more in response to adolescents not consistently taking their antihypertensive medicine. However, the unexpected findings and potential psychometric limitations of the caregiver monitoring scale indicate that further investigation of these associations is warranted.

A meta-analysis and systematic review showed that children and adolescents with CKD may have more severe executive functioning impairments (i.e., scoring 3.50–5.90 points higher on BRIEF indexes compared to the general population; Chen et al., 2018). Our sample's levels of executive functioning impairment were more variable and largely dependent on the rater. Adolescents rated themselves only 1.45 to 2.44 points above the mean on BRIEF indexes, with 8–11% of adolescents endorsing clinically significant impairments. In contrast, caregivers rated adolescents from 4.20 to 7.33 points above the mean on BRIEF-P indexes (greatest impairments noted in metacognition), with 18–24% endorsing clinically significant impairments. The differences in BRIEF-SR and –P rates are consistent with the tendency for adolescents to report fewer impairments than caregiver proxy-reports (Cassidy et al., 2015). Our sample's BRIEF-P ratings are similar to those reported in prior literature (Chen et al., 2018). The proportion of our sample that had BRIEF-SR and -P scores in the At-risk range of impairment ($SD \geq 1$; 18%–38%) are also comparable to the BRIEF-P scores in the CKiD cohort (Hooper et al., 2011).

The lack of association between executive function domains and time interactions with adherence contrasts with prior longitudinal and cross-sectional findings from samples of adolescents and young adults with T1D (Miller et al., 2012) and solid organ transplant (Gutierrez-Colina et al., 2016). Average BRIEF-SR and -P scores were similar between the current sample and those reported in prior investigations of executive functioning and self-reported adherence or glycemic control (Berg et al., 2018; Gutierrez-Colina et al., 2016; Miller et al., 2012). Our study exclusively measured adherence to antihypertensive medications via electronic monitoring and most adolescents only took one antihypertensive medication per day. Taking one daily medication that does not require precise dosage timing may involve fewer executive functions than more complex regimens (e.g., self-managing T1D or following specifically timed immunosuppressive medication regimens). Alternatively, the lack of associations we describe may be due to small sample size and lower incidence of executive functioning impairments limiting power to detect significant effects.

Contrary to hypotheses, higher levels of caregiver monitoring sum scores were associated with significantly lower antihypertensive medication adherence in models including the BRIEF-SR and the model including the BRIEF-P BRI scale. There were no time by predictor interactions. Given psychometric limitations of the caregiver monitoring tool, we further investigated the unexpected results using binary cutpoint scores. In these post-hoc analyses, the directionality of the associations continued to be negative but were no longer statistically significant. The current findings diverge from those reported in youth with T1D

in which higher levels of caregiver monitoring were associated with higher self-reported adherence (Berg et al., 2017; Ellis et al., 2007; Robinson et al., 2016). T1D involves self-managing a range of domains (e.g., blood glucose monitoring, insulin administration, medication adherence, meal planning), which may benefit from increased caregiver monitoring in completing these complex, multi-step tasks. In contrast, adherence to daily oral medication, such as antihypertensive medicine in the current study, is a singular behavior for which caregivers may not monitor intensely unless there is evidence that the adolescent is not consistently taking their medicine. Differences between our findings and those recently reported in adolescents with epilepsy (Holbein et al., 2019) may reflect that we measured whether caregivers monitor adolescents' antihypertensive medication regimens (e.g., watching and asking if their child took the medicine, reminding their child to take the medicine) rather than whether caregivers are personally responsible for managing and administering the medications. In light of the discrepant findings about the role of caregiver monitoring in adolescent adherence and our measure's psychometric limitations, more research is needed to understand how caregivers may optimally monitor adolescents' adherence.

The current findings do not suggest that caregivers should become less involved in adherence monitoring. Rather, they suggest that balancing caregiver monitoring, adolescents' growing independence, and adherence is likely challenging for adolescents with chronic illnesses. For example, results of a pilot study of a text messaging and app-based adherence intervention for adolescents with epilepsy showed that caregiver involvement in the 1-month intervention did not improve adherence rates (Modi, Mann, Urso, & Peugh, 2016). This further highlights the complexity of balancing caregiver monitoring and involvement in promoting adolescents' medication adherence. Adolescents with CKD who do not regularly take their antihypertensive medications may benefit from other strategies to improve adherence. Technological advances with Bluetooth-enabled pill bottles, for example, may allow caregivers to consistently, but unobtrusively, monitor adolescents' real time adherence. This approach could help caregivers intervene promptly and seek resources from providers to improve adolescents' adherence before it becomes an ongoing concern. Technology-based monitoring allows for passive observation, which may help caregivers scaffold gradually increased adolescent independence for medication management and minimize potential caregiver-adolescent conflict. Additionally, our prior research shows that medication self-efficacy (believing one can be adherent to a medication regimen) and positive and negative beliefs about medications are associated over time with antihypertensive medication adherence in adolescents with CKD (Eaton et al., 2019). Providers may consider targeting these areas via motivational interviewing and cognitive restructuring approaches to improve long-term adherence among typically developing adolescents with CKD.

This study has many strengths including the use of objectively monitored medication adherence over 24 months, adolescent and caregiver perspectives, and a proactively recruited community-based sample. However, limitations regarding measurement, exclusion criteria, and generalizability are worth noting. We relied on the BRIEF for measuring executive functioning, which has low (McAuley, Chen, Goos, Schachar, & Crosbie, 2010) to moderate (Toplak, Bucciarelli, Jain, & Tannock, 2008) relations with performance-based executive

function assessments. Fortunately, the BRIEF has been shown to better predict disease management compared to performance-based executive functioning assessments in other pediatric samples (e.g., T1D; Suchy et al., 2015), suggesting that our use of the BRIEF may have increased our predictive validity. However, our use of audio CASI in administering the BRIEF may have reduced attentional demands normally accompanying paper-and-pencil completion of the BRIEF and contributed to executive functioning levels observed in our sample. Further, the BRIEF-SR and –P forms were used with eight adolescents ≥19 years at baseline, though we found that excluding these participants resulted in a similar pattern of effects to those observed in the full sample. Future work involving mixed methods of performance-based and self-report measurements (including paper-and-pencil administration) of executive function will allow for greater exploration of associations between executive function and medication adherence in youth with CKD, while also allowing for comparability across administration types. We also noted limitations related to our measurement of caregiver monitoring, which was assessed with three face valid items adapted from a measure with strong internal consistency originally validated in adolescents with T1D (Ellis et al., 2007). Our adaptations may have contributed to the lower internal consistency observed in our study, which led to our decision to also analyze the scale as a cutpoint, rather than a sum score. Additionally, only caregiver report of caregiver monitoring was obtained to reduce adolescent burden, though we acknowledge the benefit of assessing adolescents' perspectives of caregiver involvement. Future research is needed to validate a caregiver monitoring scale for adolescents with CKD, both caregiver and adolescent report, to help clarify associations between caregiver monitoring and antihypertensive medication adherence.

Further, our recruitment strategies and exclusionary criteria may have impacted the results and generalizability of the study. Individuals unwilling to use the MEMS cap and those with significant developmental delay or cognitive impairment were excluded, which may have resulted in excluding adolescents with more disease management struggles. Future researchers may choose to expand inclusion criteria to allow for greater variability in study samples, particularly to enhance representation of adolescents with CKD and significant executive functioning impairments, which may increase power to detect effects. Finally, although our participants were recruited from three pediatric nephrology clinics, these sites were in the same geographical region and our sample was relatively small. Future researchers may consider broadening recruitment strategies to include additional sites in different geographic locations to increase sample sizes and statistical power and to enhance the generalizability of findings.

Among a community-based sample of adolescents with CKD, baseline executive functioning abilities did not appear to be associated with longitudinal, electronically-monitored adherence to daily pill-based antihypertensive medication regimens. Caregivers may increase their levels of monitoring because the adolescent has demonstrated nonadherence. For healthcare providers of adolescents with CKD, there may be utility in assessing caregiver monitoring practices to identify how much caregivers monitor adherence, whether their level of monitoring is helping to support adherence, and what additional strategies may be implemented to most effectively enhance adolescents' adherence when indicated. Other future directions include evaluating the use of technology to help caregivers unobtrusively

monitor adolescents' adherence and evaluating how targeting adolescents' self-efficacy, thoughts, and feelings about medications may provide added support of long-term adherence.

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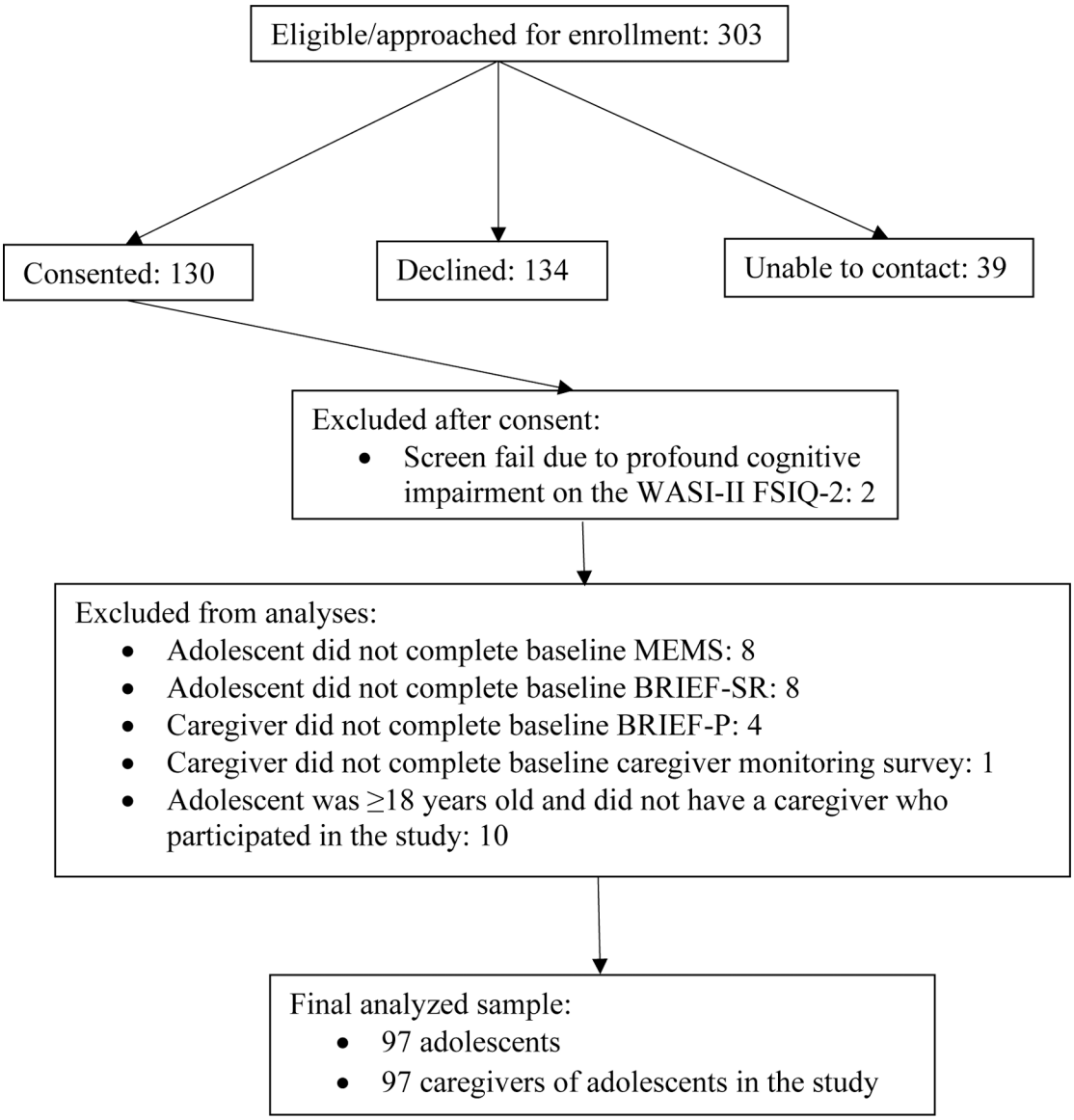

Figure 1.

Consort diagram of screening, recruitment, enrollment, and inclusion in final sample. Information on reasons for adolescent ineligibility has been previously published (Eaton et al., 2019).

Table 1

Adolescent Demographic Information

Demographic variable	%	*n*
Gender		
Male	57	55
Female	43	42
Race		
African American	41	40
Caucasian	42	41
Asian/Pacific Islander	4	4
Multiracial	8	8
Other	4	4
Annual household income		
<$50,000	34	33
$50,000–99,999	30	29
≥$100,000	35	34
Not reported	1	1
Health insurance		
Public	43	42
Private	55	53
Not reported	2	2
CKD stage		
1	21	20
2	28	27
3	23	22
4–5	10	10
Not available during study time frame	18	18
Number of prescribed antihypertensive medications (baseline)		
1	74	72
2	20	19
3–4	6	6
Hypertension diagnosis		
Yes	40	39
No	60	58

Note. $N = 97$.

Table 2

Descriptive Data for Primary Study Variables

Variable	*M*(*SD*)	Range	*n*
Antihypertensive Medication Adherence (% MEMS cap openings/expected openings)			
Baseline	77.68 (23.02)	4.55 – 100	97
6 months	79.63 (25.01)	11.11 – 100	80
12 months	78.42 (28.06)	1.05 – 100	83
18 months	72.88 (29.77)	2.96 – 100	77
24 months	69.29 (27.08)	5.00 – 100	72
Adolescent-Reported Executive Functioning (BRIEF-SR; Baseline)			
BRI	51.45 (10.91)	33 – 94	95
MCI	52.44 (11.19)	31 – 97	95
GEC	52.23 (11.62)	30 – 100	93
Caregiver Proxy-Reported Executive Functioning (BRIEF-P; Baseline)			
BRI	54.20 (10.32)	37 – 88	97
MCI	57.33 (10.08)	36 – 82	93
GEC	56.72 (10.39)	36 – 86	93
Caregiver Monitoring (Baseline)	7.30 (2.11)	3 – 12	97

Note. Higher BRIEF-SR and –P T-scores reflect more problems with executive functioning. Higher scores on Caregiver Monitoring reflect higher levels of adherence monitoring.

Table 3

Descriptive Data for Ranges of Executive Functioning Impairments

	Sub-clinical (T-score<60)	At-risk (T-score≥60)	Clinically Significant (T-score≥65)
	% (n)	% (n)	% (n)
Adolescent-Reported Executive Functioning (BRIEF-SR)			
BRI	82 (78)	18 (17)	8 (8)
MCI	82 (78)	18 (17)	9 (9)
GEC	78 (73)	22 (20)	11 (10)
Caregiver Proxy-Reported Executive Functioning (BRIEF-P)			
BRI	73 (71)	27 (26)	18 (14)
MCI	62 (58)	38 (35)	22 (20)
GEC	66 (61)	34 (32)	24 (22)

Note. At-risk and Clinically Significant ranges are based on the recommendations from the BRIEF manual (Gioia et al., 2000; Guy et al., 2004). Sub-clinical denotes any scores that fell below the At-risk cut-off score (T-score<60).

Table 4

Adolescent- and Caregiver Proxy-Reported Executive Functioning (Baseline) and Caregiver Monitoring (Baseline) Predicting Adherence Over Time

Dependent variable in all models: Antihypertensive medication adherence (time varying)								
	Adolescent Reported Executive Functioning (BRIEF-SR)				**Caregiver Proxy-Reported Executive Functioning (BRIEF-P)**			
Independent variables: BRI, Caregiver monitoring								
Fixed effects	***β***	***SE***	***t***	***p***	***β***	***SE***	***t***	***p***
Intercept	69.58	5.85	11.89	<.001	69.47	5.93	11.72	<.001
Time	−2.77	.79	−3.53	.001	−2.76	.77	−3.60	<.001
Age	−2.70	.96	−2.83	.005	−2.70	.96	−2.82	.005
Gender	−6.21	4.13	−1.50	.13	−6.63	4.25	−1.56	.12
Race	3.41	4.31	.79	.43	4.02	4.32	.93	.35
Number of antihypertensive medications	1.52	5.65	.27	.79	1.75	5.76	.30	.76
Number of daily antihypertensive doses	11.13	6.17	1.80	.07	11.32	6.33	1.79	.07
Transplant status	4.94	4.86	1.02	.31	4.29	5.02	.85	.39
End-stage renal disease status	−2.72	7.44	−.37	.71	−.73	7.13	−.10	.92
FSIQ-2	.05	.14	.39	.70	.03	.14	.22	.83
BRI	.19	.23	.84	.40	−.14	.26	−.54	.59
Caregiver monitoring	−2.87	1.27	−2.25	.03	−2.73	1.32	−2.07	.04
Time × BRI	−.02	.07	−.23	.82	.08	.08	1.02	.31
Time × Caregiver monitoring	.37	.36	1.03	.30	.25	.37	.68	.50
Random effects	**Variance Estimate**	***SE***	**Z**	***p***	**Variance Estimate**	***SE***	**Z**	***p***
Intercept (Individual)	238.55	66.98	3.56	<.001	246.06	66.01	3.73	<.001
Independent variables: MCI, Caregiver monitoring								
Fixed effects	***β***	***SE***	***t***	***p***	***β***	***SE***	***t***	***p***
Intercept	70.81	5.96	11.88	<.001	68.53	6.00	11.43	<.001
Time	−2.77	.78	−3.57	<.001	−2.36	.76	−3.13	.002
Age	−2.75	.96	−2.87	.004	−2.45	1.03	−2.37	.02
Gender	−6.64	4.15	−1.60	.11	−6.45	4.29	−1.50	.13
Race	4.41	4.34	1.02	.31	3.05	4.40	.69	.49
Number of antihypertensive medications	1.28	5.70	.22	.82	3.15	5.79	.54	.59
Number of daily antihypertensive doses	10.64	6.23	1.71	.09	11.41	6.47	1.76	.08

Transplant status	3.47	4.87	.71	.48	2.72	5.08	.53	.59
End-stage renal disease status	−.63	7.16	−.09	.93	−1.16	7.18	−.16	.87
FSIQ-2	.003	.14	.02	.98	.04	.14	.31	.76
MCI	−.04	.22	−.16	.87	−.25	.26	−.98	.33
Caregiver monitoring	−2.83	1.28	−2.21	.03	−2.17	1.31	−1.66	.10
Time × MCI	−.04	.07	−.52	.60	.01	.08	.14	.89
Time × Caregiver monitoring	.37	.36	1.03	.30	.16	.36	.45	.65
Random effects	**Variance Estimate**	***SE***	**Z**	***p***	**Variance Estimate**	***SE***	**Z**	***p***
Intercept (Individual)	241.91	65.82	3.68	<.001	256.09	66.62	3.84	<.001
Independent variables: GEC, Caregiver monitoring								
Fixed effects	***β***	***SE***	***t***	***p***	***β***	***SE***	***t***	***p***
Intercept	71.02	5.99	11.85	<.001	68.81	6.04	11.38	<.001
Time	−2.80	.79	−3.55	.001	−2.37	.75	−3.14	.002
Age	−2.79	.96	−2.90	.004	−2.55	1.03	−2.48	.01
Gender	−5.80	4.19	−1.38	.17	−6.34	4.37	−1.45	.15
Race	4.01	4.40	.91	.36	3.08	4.43	.69	.49
Number of antihypertensive medications	1.08	5.74	.19	.85	3.20	5.86	.55	.59
Number of daily antihypertensive doses	10.08	6.26	1.61	.11	11.00	6.54	1.68	.09
Transplant status	3.91	4.92	.80	.43	2.41	5.16	.47	.64
End-stage renal disease status	−2.71	7.49	−.36	.72	−1.05	7.22	−.15	.88
FSIQ-2	.02	.14	.15	.88	.05	.14	.35	.73
GEC	.08	.22	.35	.72	−.24	.26	−.91	.36
Caregiver monitoring	−2.80	1.29	−2.16	.03	−2.17	1.32	−1.64	.10
Time × GEC	−.03	.07	−.38	.70	.04	.07	.54	.59
Time × Caregiver monitoring	.38	.36	1.05	.30	.12	.36	.32	.75
Random effects	**Variance Estimate**	***SE***	**Z**	***p***	**Variance Estimate**	***SE***	**Z**	***p***
Intercept (Individual)	242.19	67.61	3.58	<.001	260.11	67.18	3.87	<.001

Note. Higher T-scores on the BRIEF-SR and –P reflect more problems with executive functioning; higher scores on the caregiver monitoring scale reflect higher levels of caregiver adherence monitoring.