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Investigating Medication Adherence on Neuropsychological & Psychosocial Functioning in Adolescents with Chronic Kidney Disease Using the Chronic Kidney Disease in Children Cohort

Elizabeth A. Fiest

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INVESTIGATING MEDICATION ADHERENCE ON NEUROPSYCHOLOGICAL &

PSYCHOSOCIAL FUNCTIONING IN ADOLESCENTS WITH CHRONIC KIDNEY

DISEASE USING THE CHRONIC KIDNEY DISEASE IN CHILDREN COHORT

A Dissertation

Submitted to the School of Graduate Studies and Research

in Partial Fulfillment of the

Requirements for the Degree

Doctor of Psychology

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Title: Investigating Medication Adherence on Neuropsychological & Psychosocial
          Functioning in Adolescents with Chronic Kidney Disease Using the Chronic Kidney
          Disease in Children Cohort

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Pediatric chronic kidney disease (CKD) is associated with several comorbidities, including hypertension, anemia, and growth hormone deficiency. Thus, treatment of CKD requires a complex medical regimen to manage the disease process, even within the mild to moderate stages. Previous research has focused its efforts on examining children with CKD who have progressed to end stage renal disease (ESRD), and less research has been conducted within the mild to moderate CKD pediatric population. As such, the Chronic Kidney Disease in Children (CKiD) study was developed to examine physical, neurocognitive, and psychosocial functioning in children and adolescents with mild to moderate CKD. Previous research has shown that proper management of CKD and its comorbidities can improve neurocognitive and psychosocial functioning within this population. The aim of the present study was to better understand the effects of medication burden (number of unique medications prescribed) and medication adherence on executive (EF) and psychosocial functioning in adolescents with CKD. Adolescent participants from the CKiD cohort prescribed any medication, antihypertensives, and erythropoiesis-stimulating agents (ESAs) were used within the analyses. Results suggested that higher medication burden is predictive of poorer psychosocial functioning. However, this result is likely not clinically significant as medication burden explained only 3% of the change in psychosocial functioning. Medication burden was not predictive of EF, which is likely due to parent-reported EF falling within age-appropriate ranges and low medication burden within this

population. Similarly, there was a lack of effect between adherence to antihypertensives and ESAs and EF and psychosocial functioning. Participants within the present study reported high adherence and there was little variability among reported adherence. Additionally, parent-reported EF fell generally within age-appropriate ranges. Together, this likely explained the lack of effect between medication adherence and EF and psychosocial functioning. It is also possible there was too little variability in adherence to truly examine the impact of medication adherence on EF and psychosocial functioning within the present study.

ACKNOWLEDGMENTS

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CHAPTER I

LITERATURE REVIEW

Introduction

Research and medical treatments in the pediatric population have advanced to a point

where we can focus not only on the advanced stages of diseases, such as end stage renal disease

(ESRD), but also on the stages leading to it such as the mild to moderate stages of chronic

kidney disease (CKD). Turning the focus to the mild to moderate stages of CKD helps

researchers to better understand the mechanistic processes occurring during these stages that lead

to ESRD, and provides insight into the risk factors for advancing to ESRD. Rising numbers of

pediatric CKD cases has made this area of research a timely and relevant endeavor as it aims to

better understand the risk factors associated with the progression to ESRD and to develop

preventative treatments.

The kidneys serve an important function within the body as it maintains homeostasis.

When functioning of the kidneys is disturbed, it disrupts homeostasis and has consequences for

other systems and functions within the body. Kidney dysfunction impacts cardiovascular

functioning, blood pressure, hemoglobin levels, and growth hormones. There is now evidence

that improper kidney functioning can also have an impact on neurocognitive functioning as well

as aspects of psychosocial functioning (Gerson et al., 2006).

Because of the consequences that improper kidney functioning can have on individuals,

multiple research cohorts have been formed in the adult and pediatric populations to better

understand the earlier stages of CKD, namely the mild to moderate stages. Researching

specifically children with mild to moderate CKD is the Chronic Kidney Disease in Children

(CKiD) study. The CKiD cohort is comprised of children between ages 1-16 years-old who have

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been diagnosed with mild to moderate CKD. The CKiD cohort was gathered from 57 clinical sites across the United States, and participants within the cohort undergo yearly physical examinations and questionnaires that track the progression of CKD as well as bi-yearly neuropsychological assessments (Furth et al., 2006).

The CKiD study broadly aims to longitudinally follow children in a prospective, observational manner with mild to moderate CKD in order to better understand the earliest effects of the disease on physical and neurocognitive functioning given the well established poorer overall functioning in those with advanced renal disease (Gipson et al., 2006). Specific aims of the study as explicitly stated by Furth et al. (2006) are to,

> (1) identify novel and traditional risk factors for the progression of CKD; (2) characterize the impact of a decline in kidney function on neurodevelopmental, cognitive abilities, and behavior; (3) identify the prevalence and the evolution of cardiovascular (CV) disease risk factors in children with CKD; and (4) examine the effects of the declining GFR on growth and assess the consequences of growth failure on morbidity in children with CKD (pp. 1007).

One of the aims of the CKiD study is to better understand the association between declining kidney function and neurocognitive functioning as well as its impact on psychosocial functioning. Using measures of neurocognitive functioning, research thus far has shown mild to moderate CKD to impact areas of cognitive functioning such as overall intellectual abilities and executive functioning. The present study will focus on better understanding the effects of medication adherence and medication burden (i.e., number of unique medications prescribed) on children diagnosed with CKD and comorbidities (e.g., cardiovascular disease, anemia, and growth impairment) on neurocognitive and psychosocial functioning.

Structure and Function of the Kidneys

The kidneys are two bean shaped organs with the primary function of maintaining balance and homeostasis such as balancing levels of water and electrolytes, maintaining acid-base homeostasis, and excreting waste. Human kidneys begin to form during the 5th week of gestation. During this time, nephrons, the building blocks of the kidneys, are forming and will continue to form until 32-34 weeks gestation. The kidneys will continue to grow beyond 32-34 weeks gestation, but this growth is represented by the growth and maturation of existing nephrons. New nephrons do not form past 32-34 weeks gestation; therefore, the kidneys are unable to make up for damaged or lost nephrons through the creation of new nephrons beyond this point. Kidney functioning is dependent on the correct structural developmental and the three-dimensional patterning as this encourages nephron development often influencing the number of nephrons present. A normal range of nephrons in a human is between 200,000 and 1.8 million, and the number present at birth has consequences for the future health and well-being of the kidneys. Lower numbers of nephrons present at birth are associated with a higher risk of developing CKD and hypertension (Bates, Ho, & Smis-Lucas, 2016; Gilbert et al., 2014).

The three main functions of the kidneys include maintaining body composition, voiding of metabolic waste products and other substances, including drugs or toxins as well as excreting hormones and enzymes (Gilbert et al., 2014). To be able to complete these functions, the kidneys rely on the development of specific cells in a specialized temporal and spatial pattern in order to produced adequate number of nephrons. Multiple disorders stem from improper development and lack of adequate nephrons including renal malformations namely renal aplasia, dysplasia, and hypoplasia, which represent an absence of the kidney, failure of cells to properly specialize, and small kidneys, respectively. Common urinary tract disorders resulting from developmental

disorders of the kidneys include abnormalities such as vesicoureteral reflux or a duplication of collection systems. Additionally, a failure in the development of this specialized temporal and spatial patterns results in congenital anomalies of the kidney and urinary tract (CAKUT). CAKUT is the most common cause of CKD and end stage renal disease (ESRD) in the pediatric population (Bates et al., 2016; Gilbert et al., 2014).

Chronic Kidney Disease

Kidney Disease is a term that encompasses a myriad of disorders that can affect children in a multitude of ways. Acute kidney injury has a sudden onset that is short-lasting. Treating the underlying causes of acute kidney disease can eradicate it completely in some cases, but other cases have longer-lasting effects. Chronic kidney disease (CKD) has a longer course that is not fully remedied with treatment; the damage done to the kidneys in these cases is often irreversible. CKD typically worsens over time and leads to end stage renal disease (ESRD), which requires more aggressive treatments such as transplantation and dialysis (Harambat, van Stralen, Kim, & Tizard, 2012; NIDDK, 2014; VanDeVoorde, Wong, & Warady, 2016). CKD is recognized as a public health concern with the numbers of those affected by CKD rising even in the pediatric population. The current global reported prevalence rate for the early stages of pediatric CKD is 18.5 to 53.5 per million children (Assadi, 2012; Coresh et al., 2007; Harambat, van Stralen, Espinosa, et al., 2012).

When the kidneys are not functioning properly, toxins and waste products are not filtered correctly from the body. Blood pressure, sodium, and potassium are not well regulated, and there is insufficient hormone production necessary for growth (Gerson et al., 2006; Harambat, van Stralen, Kim, et al., 2012; VanDeVoorde et al., 2016). Children with CKD may not exhibit symptomology of the disease during the early stages; therefore, common comorbidities such as

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cardiovascular disease, hypertension, or anemia may go unnoticed. Early detection of CKD is imperative in being able to diagnose and treat these comorbidities as well as mediate the progression of CKD (Assadi, 2012; VanDeVoorde et al., 2016).

Making diagnosing pediatric CKD even more difficult is that the definition of pediatric CKD has historically varied within the medical community. However, there is now an accepted definition provided by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI). CKD is defined by abnormalities of the kidney structure or function for ≥ 3 months and/or a glomerular filtration rate (GFR) that has remained below 60 ml/min/1.73 m^2 for the same amount of time (Hogg et al., 2003; KDOQI, 2006). However, children born with congenital kidney abnormalities may be diagnosed prior to this criteria being met. Though this definition has been widely accepted, there is still room for improvement as accurately estimating GFR remains difficult in the early stages of kidney malfunctioning and in children younger than 2-years-old (Eckardt, Berns, Rocco, & Kasiske, 2009; Hogg et al., 2003; Schwartz et al., 2009).

Causes of Pediatric CKD

The cause of CKD in children can be credited to both glomerular and nonglomerular causes with nonglomerular, causes such as genetic disorders and congenital anomalies of the kidney and urinary tract (CAKUT) comprising the bulk of pediatric cases. CKD can also stem from hereditary causes as well as prematurity, being small for gestational age or having a family history of CKD. Common hereditary causes include polycystic kidney disease and medullary cystic disease (Assadi, 2012).

Data from studies such as the National American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) has aided practitioners and researchers in better understanding the causes of pediatric CKD. NAPRTCS compiles data from pediatric nephrology centers, and contains a

database comprised of 7,000 children aged 21 and under. Reports from NAPRTCS show that roughly 48% of pediatric CKD cases are due to CAKUT while 10% of the cases are hereditary nephropathies and 14% are glomerulonephritis. Together, these make up the most common causes of CKD in children (Fathallah-Shaykh et al., 2015; Harambat, van Stralen, Kim, et al., 2012; NAPRTCS, 2008; VanDeVoorde et al., 2016). Within the Chronic Kidney Disease in Children (CKiD) cohort comprised of 586 patients, nonglomerular CKD was 78% of the total study population while glomerular CKD comprised 22%. Common diagnoses of CAKUT make up 53% of the population within the CKiD study including obstructive uropathy and reflux nephropathy along with aplastic, hypoplatstic, and dysplastic kidneys (Furth et al., 2011; VanDeVoorde et al., 2016). Prevalence of congenital abnormalities within the CKiD study is comparable to similar studies conducted internationally (Ardissino et al., 2003; Staples et al., 2010; Wuhl, Mehls, Schaefer, & Group, 2004).

Pediatric CKD presentation and type can vary by age, gender, and race. Children diagnosed at a younger age are more likely to have CAKUT, and children diagnosed with CKD past 12-years-old are more likely to have glomerulonephritis. The United States Renal Data System (URDS) demonstrated that with children who eventually progress to ESRD, a similar pattern of etiologies was found in that CAKUT and hereditary nephropathies were seen most in the youngest ESRD cohort. The likelihood of having an acquired type of CKD increased with age (Harambat, van Stralen, Kim, et al., 2012; NAPRTCS, 2008; USRDS, 2010). In regards to gender, boys tend to present with congenital causes, and the incidences of pediatric CKD is more common in boys. Similar findings been demonstrated in the CKiD study (Furth et al., 2006). Concerning race, international studies have found that indigenous children are at a much higher risk for ESRD (Hoy, 1996). While in North America, African American children have incidence

rates two to three times higher than Caucasian children. African American children also have rates of focal segmental glomerulosclerosis, which is the main cause of glomerular disease, that are three times higher than Caucasians. The rate of focal segmental glomeruloclerosis among African Americans is 19%; whereas the rate in Caucasians is 6%. The rate is even higher among African American adolescents at 35% (NAPRTCS, 2008).

Severity Classification

Severity of CKD is currently classified through measurements of glomerular filtration rate (GFR) and albuminuria. In 2002, K/DOQI proposed clinical guidelines for adult and pediatric CKD with the goal of detailing a classification system for CKD in both populations as well as recommending the protocols used for detecting CKD (Hogg et al., 2003). K/DOQI classified severity of CKD into 5 stages, and proposed action points for each stage. Stage 1 is defined by kidney damage but no loss of GFR or an increase in GFR. In the stage, the aim is to treat the comorbidities to slow the progress of CKD. Stage 2 represents a mild loss of CKD, and suggests that clinicians begin to estimate the rate of CKD progression for patients within this stage. Within stage 3, patients demonstrate moderate reduction of GFR, and the action plan for this stage is to evaluate and treat complications. Stage 4 is classified by severe loss of GFR. During this stage, a patient's care team may begin formulating and preparing the patient for renal replacement therapy. Kidney failure represents stage 5 with the action plan to initiate kidney replacement therapies such as dialysis or transplantation (K/DOQI, 2002).

The most recently proposed model for the classification of pediatric CKD was by the Kidney Disease Improving Global Outcomes (KDIGO) in 2012 after the previous model presented by K/DOQI in 2002 had such a positive global reception. The model aims to provide more in depth details related to mortality and kidney outcomes than KDOQI's model. Within

KDIGO's model, severity is measured through estimated GFR and albuminuria levels. Specific causes of CKD have also been incorporated into the model to better understand how CKD cause contributes to complications, management, and prognosis (2012a).

Within KDIGO's classification, progression is classified as G1 to G5 denoting the specifics risks for comorbidities and long-term effects associated within each category. Recent research has suggested a myriad of outcomes and risks within stage 3; therefore, the current model separates category G3 into G3a and G3b. Similarly, albuminuria levels have been classified into A1-A3 to denote mild, moderate, or severely increased levels of albuminuria (<30mg/g – >300 mg/g creatinine) (Coulthard, 1985; Nitsch et al., 2013; Schwartz, Brion, & Spitzer, 1987).

Controversy has surrounded the KDIGO classification system due to its limitations, and as a result, many researchers and clinicians still rely heavily on K/DOQI's classification. One of the main limitations to the new model is that the system is intended to be applied to the pediatric CKD population. However, the data used in deriving the system are largely based on the adult CKD population, and no studies have been done to validate the use of KDIGO's system in the pediatric population. There are several large research cohorts, such as the CKiD project that are capable of studying the effects of GFR and proteinuria, a measurement more commonly used than albuminuria levels in the pediatric population, on progression of CKD within this population, and it would be beneficial if the KDIGO model was validated using these cohorts (Furth et al., 2006; Hogg et al., 2003; Hogg et al., 2000; KDIGO, 2012a). Moreover, data are available to support the idea that high levels of proteinuria acts as an independent risk factor for the progressive decline in kidney functioning in both children and adults with CKD as well as an

initial indicator of kidney damage serving a two-fold purpose and suggesting this measurement

may be more precise than albuminuria in children (Fathallah-Shykh, 2015).

<p style="text-align:center">Comorbidities of CKD</p>

Cardiovascular Disease

CKD acts as a risk factor for cardiovascular disease (CVD) in both adults and children.

Many shared common comorbidities in adult and pediatric CKD including hypertension,

dyslipidemia, anemia, hyperparathyroidism, hyperhomocysteinemia, hypoalbuminemia, and

increased C-Reactive protein increase the rates of developing CVD in pediatric patients (M. M.

Mitsnefes, 2008). Due to the increased rate of CVD within Adult and pediatric CKD, patients are

susceptible to cardiovascular comorbidities such as stroke, heart failure, and cardiovascular

disease, and the rates of CVD in children with CKD are significantly higher than the national

averages for non CKD children of similar age groups (Greenbaum, Warady, & Furth, 2009).

Causes of death in pediatric patients with CKD are more commonly attributed to cardiovascular

comorbidities such as arrhythmia, valvular disease, and cardiomyopathy rather than primary

complications of CKD such as renal failure (Anavekar & Pfeffer, 2004; Assadi, 2012; Chavers,

Li, Collins, & Herzog, 2002). Rates of mortality due to CVD complications in pediatric CKD

have been on the rise, and are now reported to be closer to 23.4 per 1,000 patient-years. Among

those representing the pediatric CKD population, African Americans and young adults receiving

dialysis are at the highest risk for CVD related mortality (USRDS, 2007).

Elevated Blood Pressure/Hypertension

Elevated blood pressure (BP) or hypertension is common among adults and children with

CKD, and is a risk factor that develops earlier in the course of the disease (VanDeVoorde et al.,

2016). Research with adults has demonstrated that hypertension independently predicts the

progression of both non glomerular and glomerular renal disease. With children, research findings within the CKiD cohort demonstrated both diastolic and systolic hypertension upon study entry. A diagnosis of hypertension was classified as being at or above the 95th percentile in terms of age, height, and sex. Children who had a history of hypertension currently on antihypertensive medications were also classified within the hypertensive group. Rates of diastolic hypertension were 53% while rates of systolic hypertension were 54%. Rate of hypertension found within the CKiD cohort are similar to other study findings, which is approximately 50%. Additionally, 48% of children continued to have high BP despite being prescribed antihypertensive medications (Becherucci, Roperto, Materassi, & Romagnani, 2016; Fathallah-Shaykh et al., 2015; M. M. Mitsnefes, 2008; VanDeVoorde et al., 2016). Using the CKiD cohort, research has denoted multiple risk factors associated with elevated BP including glomerular cause of CKD, obesity, black race, and shorter duration of CKD (Flynn et al., 2008). Shorter duration of CKD diagnosis suggests that elevated BP is often present early on in disease progression but may go undetected (VanDeVoorde et al., 2016). Because there is mounting evidence that hypertension is going undetected within the pediatric population, ambulatory blood pressure monitoring has been recommended by KDOQI to detect variability in blood pressure that would otherwise go unnoticed using only casual blood pressure monitoring (Eckardt et al., 2009).

Children with CKD who also have high BP are at an increased risk of experiencing blood pressure variability (BPV). BPV in adults has been associated with decreased performance on neuropsychological tests. Previous studies have shown that increased in both short and long term BPV is associated with increased progression of CKD, damage to organs via hypertension, cardiovascular events, and possibly worse neurocognitive functioning. Not much is known about

the relationship between poorer cognitive functioning and BPV at this time. However, possible mechanisms for cognitive dysfunction in BPV include decreased hippocampal volumes and white matter hyperintensities, as well as cortical infarcts and cerebral microbleeds (Crichton, Elias, Dore, Torres, & Robbins, 2014; Diaz et al., 2014; McMullan et al., 2014; Ryu et al., 2014).

Anemia

Within pediatric CKD, anemia is a common comorbidity. Patient with more advanced CKD almost all have anemia, which has spurred global research efforts specific to evaluation and treatment of this comorbidity (KDIGO, 2012b; KDOQI, 2006). The development of anemia can be attributed to a multitude of factors. However, iron dysregulation and a diminishing production of erythropoietin, produced by the kidneys, are the main two contributory factors (Becherucci et al., 2016; Fraenkel, 2015). Multiple factors combine together to increase the risk of anemia within CKD patients. These interrelated factors disrupt the homeostasis of products in the blood leading to anemia.

Anemia has been associated with lower health-related quality of life (HQOL) as well as poorer neurocognitive outcomes and lower capacity for exercise. Additionally, anemia increases the risk of cardiovascular disease progressing (Becherucci et al., 2016; Kaspar, Bholah, & Bunchman, 2016). Along with other comorbidities, anemia has been associated with morbidity and mortality and an increase in poor cardiovascular functioning (Wong, Moxey-Mims, Jerry-Fluker, Warady, & Furth, 2012).

Within the CKiD study, 45% of patients were found to be anemic, and anemia became worse within these patients as their GFR levels decreased falling below 43 ml/min/1.73m^2. Studies have examined the prevalence of anemia within the CKiD data set using the definition of anemia

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proposed by 2006 KDOQI anemia guideline, which qualifies anemia as having a hemoglobin level at or below the 5th percentile after adjusting for sex and age (KDOQI, 2006).

Progression of anemia within the pediatric CKD population is associated with decreasing levels of GFR as measured by the iohexol method, which computes the iGFR. Within the CKiD cohort, 45% of the study population, which was comprised of 586 children at the time, were diagnosed with anemia, and 60% of those diagnosed with anemia were not prescribed erythropoiesis stimulating agents (ESAs), the common treatment for anemia. Of those receiving treatment with ESAs, 14% still had hemoglobin levels below the threshold for anemia. This finding suggests that detection and treatment of anemia with ESAs is imperative (Fadrowski et al., 2008). However, more research is needed to ensure that the current target hemoglobin levels set by KDOQI are adequate for allowing optimal growth and development as well as continuing to evaluate how current treatment standards effect kidney functioning and further cardiovascular risk (Filler, Mylrea, Feber, & Wong, 2007).

Treating anemia is commonly done with recombinant human erythropoietin therapy (rHuEPO), which has been associated with improvement in a variety of domains including appetite, quality of life, intelligence quotient (IQ) scores, and cardiovascular functioning. Specifically, reduction in left ventricular hypertrophy mass index has been found after a year of therapy (VanDeVoorde et al., 2016). In addition to rHuEPO therapy, iron supplements are frequently prescribed and are considered a necessary means of treatment for anemia within the pediatric population (Akizawa et al., 2011; Montini et al., 1990).

Growth Impairment

Growth impairment is a common, visible comorbidity of CKD. A risk factor for poor growth within the CKD population is irregular growth hormone insulin-like growth factor 1

(IGF1). Other risk factors for poor growth include malnutrition, acidosis, and renal osteodystrophy. Growth impairment and GFR have an inverse relationship, in that growth impairment worsens with decreases in GFR. However, significant decreases in growth are present at every stage of CKD (Mahesh & Kaskel, 2008; Rees, Rigden, Ward, & Preece, 1990; Rodig et al., 2014; Seikaly, Salhab, Gipson, Yiu, & Stablein, 2006).

Growth impairment in children with CKD is impacted by age of onset in that children who present at a younger age with CKD showed greater height deficits (Seikaly, Ho, Emmett, Fine, & Tejani, 2003). Children with poor growth are also at risk for increased morbidity and mortality rates (Furth, Stablein, Fine, Powe, & Fivush, 2002). More specifically, Wong et al. (2012) found that in a group of children receiving dialysis that mortality rates increased 14% for every one standard deviation decrease in height. Additionally, poor growth in childhood has been associated with poor psychosocial development and functioning along with poorer quality of life (Rosenkranz et al., 2005).

Children on dialysis tend to have more severe growth retardation as opposed to those whose CKD is managed with more conservative treatment methods or those who have undergone transplant (Mehls, Ritz, Hunziker, Tonshoff, & Heinrich, 1988). However, it should be noted that although growth in children does improve after receiving a transplant, these children do not tend to catch up to their peers; therefore, their height standard deviations do not show improvement (Hokken-Koelega et al., 1994).

Poor growth history in the pediatric population has been further explored within the CKiD cohort. Greenbaum et al. (2011) examined the relationship between abnormal birth history and growth outcomes in 426 children from the CKiD cohort. Findings revealed that the low birth weight (LBW) prevalence within the CKiD cohort was about 14%. National prevalence rates for

LBW is about 7.4% to 8.2%, which is significantly lower than the prevalence rate for LBW within this chorot. In addition, about 14% of the CKiD cohort was small for gestational age (SGA). Analyses performed showed that children with LBW or SGA had negative z-scores in relation to heights and weight. This suggests that children who have CKD and were classified as LBW or SGA may be at risk for poor growth for factors related to and independent of CKD (Greenbaum et al., 2011).

Impact on Cognitive Functioning and Development

Evidence for impaired cognitive functioning in adults with CKD has been well documented though not much is known about the cause or mechanism of cognitive impairment in adult CKD. It is has been thought cognitive impairment may be attributable at least in part to cardiovascular disease associated with CKD. However, even when controlling for comorbidities such as cardiovascular disease and other cardiac risk factors, cognitive impairment within the adult population persists. For example, Kurella-Tamura and colleagues (2008) conducted a study using a large national sample consisting of 23,405 African American and Caucasian adults from the Reasons for Geographic and Racial Difference in Stroke study (REGARDS). Findings from this study showed that adults with lower levels of kidney functioning were more likely to display cognitive impairment than adults with normal kidney functioning. Cognitive impairment was found to be present independent of cardiovascular disease and associated risk factors. However, cardiovascular disease has been well recognized as a potential risk factor for increased cognitive impairment within adult CKD (Kurella Tamura et al., 2011). Not only did results find that cognitive impairment is more prevalent in CKD than the general population, but also results indicate that cognitive impairment can occur in the early stages of CKD within adults. These results align with findings from other studies with adult populations conducted with smaller

sample sizes (Kurella, Chertow, et al., 2005; Kurella, Yaffe, Shlipak, Wenger, & Chertow, 2005; Seliger et al., 2004).

Due to evidence of cognitive dysfunction adult CKD populations, research within pediatric CKD has not only focused on the physical comorbidities of the disease, but also disease impact on neurocognitive development. Findings from this research shows that pediatric patients with CKD show higher risk of developing mild cognitive impairment, and CKD is considered an independent risk factors for such impairment (Martinez-Sanchis et al., 2011; VanDeVoorde et al., 2016). For example, previous research has consistently demonstrated lower performance on measures of IQ, academic achievement, and executive functioning (Gerson et al., 2006). Though etiology of cognitive impairment in pediatric CKD has yet to be determined, it has been hypothesized that these deficits may be the result of uremia or other metabolites interacting with the ever-developing brain. Other possibilities include secondary effects of kidney disease such as school absences, environmental factors, or CKD related comorbidities (VanDeVoorde et al., 2016).

Historically, neurocognitive and developmental deficits found in children with CKD have been attributed to poor disease control, poor nutrition, and the use of aluminum-containing phosphate binder, which led to aluminum toxicity in some patients. While aluminum-containing phosphate binders are typically prescribed only to patients on dialysis, K/DOQI and KDIGO guidelines have suggested using non-aluminum based phosphate binders to avoid potential for aluminum toxicity and its possible effects on cognition (Mudge et al., 2011). Infants and toddlers with ESRD show a rate of global developmental delays between 20-25%. Factors noted to be associated with severity of delays include age of CKD onset as well as duration of disease. Comorbid medical disorders were also associated with severity of developmental delays

(Polinsky, 1987; Warady, 1999b, Madden et al., 2003). High rates of mental retardation, microcephaly, and progressive encephalopathy were common, and seizure disorders were often associated with CKD (Gerson et al., 2006; VanDeVoorde et al., 2016). Presently, these major complications of neurodevelopmental functioning in CKD are less common likely due to increase in nutritional interventions as well as surgery on the bladder and kidneys to clear obstructions and the removal of aluminum based medications (Gerson et al., 2006).

A study conducted by Warady, Belden, and Kohaut (1999) showed that combining early initiation of dialysis, supplemental nutrition, and avoidance of the aluminum containing phosphate binders increases neurodevelopmental outcomes. Overall, CKD has a myriad of comorbidities, and as these have been identified and treated, physical functioning has improved. However, neurocognitive deficits continue to be present in the pediatric population, and these deficits can have a long-term impact. In particular, memory and concentration deficits continue to persist into adulthood, and neurocognitive deficits can also impact educational attainment within this population (Slickers, Duquette, Hooper, & Gipson, 2007).

A neurobiological approach to understanding the interaction between cognitive functioning and poor kidney filtration has been suggested by Icard, Hooper, Gipson, and Ferris (2010). As kidney filtration is improved, there will be a decreased level of neurotoxins in the brain, which should promote healthier brain development and performance. It may also lead to improved neuronal myelination and synaptic development during the childhood and adolescence. Findings from their study, further discussed in the Intelligence Quotient section of this paper, support previous research on the benefits of transplantation on neurocognitive functioning, and support the idea of a neurobiological approach to neurocognitive functioning in CKD. Further research on a neurobiological approach is warranted, however, due to the small sample size

within this study, and contradictory findings as compared to previous research. Previous research has suggested that improvement after transplant could result from multiple factors (Icard et al., 2010; Mendley & Zelko, 1999; Warady et al., 1999).

Impact on cognitive functioning has been found using functional techniques and imaging (CT and MRI) and electrophysiological investigations. Imaging studies have not focused on all diseases of the kidneys categorized under the term CKD, but rather have focused on diseases with CKD that have greater potential for central nervous system (CNS) deficits. These diseases include congenital nephrotic syndrome, cystinosis, and Lowe Syndrome (Gipson, Duquette, Icard, & Hooper, 2007). Valanne, Qvist, Jalanko, Holmberg, and Pihko (2004) used a 33 member cohort composed of kidney transplanted (prior to age 5) children diagnosed with congenital nephrotic syndrome ages 6-11 years old. Findings suggest chronic infarct lesions in the brain in 54% of the cohort. These infarcts were found largely in the periventricular white matter. Lesions in periventricular white matter have been linked to cognitive deficits in domains such as attention, processing speed, and visual spatial abilities (Schmahmann, Smith, Eichler, & Filley, 2008). The rates of cerebral atrophy in children with ESRD are widely variable. Gipson et al. (2007) suggests the rates lie between 12-23% based on previous research while Valanne et al. (2004) presents rates between 23-60%. Previous research has used cohorts of pre- and post-dialysis patients as well as post transplantation patients to derive these rates. Valanne et al.'s study found severe dilation in 9% of the cohort, which normalized after transplantation so this does not represent permanent cerebral atrophy. However, remaining cerebral atrophy was found in 15% of the cohort after transplantation suggesting that irreversible cerebral atrophy does occur in this population even after treatment.

Differences in electrophysiology have also been assessed in the pediatric CKD population. Unspecified abnormalities as measured by EEGs have been demonstrated in the pediatric CKD populations even after renal transplantation (Elzouki, Carroll, Butinar, & Moosa, 1994; Qvist et al., 2002). Though there is evidence for abnormal EEGs, which has the potential to lead to seizure disorders, the rates of seizure disorders within CKD is still unknown (Gipson et al., 2007).

Further examining structural impacts of CKD, Hurkx et al. (1995) and Elzouki et al. (1994) found no evidence of brain stem abnormalities in regards to auditory evoked potentials. However, evidence has been found suggesting delayed myelination and synaptogenesis specifically within the somatosensory pathway in children with CKD (Hurkx et al., 1995). This finding was seen through deficits in the cortical conductions through the thalamus, which was evidenced by significantly increased interpeak somatosensory evoked potential latencies. Gipson et al. (2007) hypothesizes that this finding suggests that earlier onset of CKD could inhibit development of the myelin sheath within the somatosensory cortex. Research by Icard et al. (2010) would suggest that treating CKD itself could mitigate this inhibition of myelination. Although there are many studies detailing the structural abnormalities found within both adult and pediatric CKD, the exact etiology of these neuroanatomical deficits are yet to be discovered.

CKD Comorbidities and Their Impact on Neurocognitive Functioning

Research has also focused on specific comorbidities of CKD and their potential influence on neurocognitive functioning within pediatric CKD. For instance, a study conducted by Lande et al. (2016) using between 279-622 (depending on the neurocognitive measure) participants from the CKiD cohort examined the difference in neurocognitive performance between those with an increased BP as compared to those with lower BP, and examined the impact of increased

BPV. Findings showed a negative association between systolic visit-to-visit BPV and cognitive performance within the domain of category switching on the DKEFS Verbal Fluency task in that as BPV increased, performance was worse on this task. No other significant associations were found on any other task for systolic visit-to-visit BPV. Additionally, there were no associations found between ambulatory blood pressure monitoring and neurocognitive performance. The authors explain this may be due to ambulatory blood pressure monitoring taking place 6-12 month prior to neurocognitive testing per study design. Additionally, association between visit-to-visit BPV and neurocognitive functioning within category switching domain cannot be generalized to ambulatory blood pressure monitoring, because of a weak correlation between the two forms of BP monitoring. The author suggest that these findings may indicate a particular difficulty for set shifting within executive functioning in children with CKD who experience long-term BVP.

Slickers et al. (2007) also examined the relationship between hypertension and neurocognitive functioning in pediatric CKD patients. Twenty children between the ages of 7-19 years old were recruited from a university-based pediatric nephrology practice and administered selected measure of neuropsychological functioning including the Wechsler Abbreviated Scale of Intelligence (WASI), Gordon Diagnostic System, which is similar to the Continuous Performance Test, and the Wide Range Assessment of Memory and Learning (WRAML). Hypertension was measured as a single and time-averaged measure neither of which showed an association with performance on neurocognitive measures. This finding is in contrast to a study conducted by Lande, Kaczorowski, Auinger, Schwartz, and Weitzman (2003), which examined the relationship between neurocognitive functioning and hypertension in a group of school-aged children. Lande et al. (2003) found lower neurocognitive performance on measures of short-term

memory as well as measures of attention and concentration. However, in Slickers et al.'s (2007) cohort, a majority of the children were currently on an antihypertensive treatment, which could account for the differences in findings. The authors also note that certain antihypertensive mediations can have varying effects in children such having a sedative effect in certain children while aiding in concentration in other children. The sample size within this study was too small to further explore this area.

Using the same cohort, Slickers and colleagues (2007) also investigated the relationship between neurocognitive functioning and blood hemoglobin levels given the high incidence rates of anemia within the pediatric CKD population. Findings revealed no association between neurocognitive functioning and hemoglobin levels taken at the time of testing. There was an association between time averaged hemoglobin levels below 10.5 mg/dl and lower performance on memory tasks. However, given the small sample of children with hemoglobin levels within their study (n=2), results are not generalizable the pediatric CKD population as a whole. However, evidence of the impact anemia on neurocognitive functioning in adult CKD patient populations, suggests that more research should be done on the impact of anemia on neurocognitive functioning in the pediatric population.

Within the adult ESRD population, results on the impact of anemia on neurocognitive functioning have been mixed. Kurella Tamura et al. (2011) explored the impact of anemia on cognitive functioning within the Chronic Renal Insufficiency Cohort (CRIC) consisting of 3,591participants. Low hemoglobin levels were associated with cognitive impairment and mitigated the relationship between lower eGFR and cognitive impairment suggesting anemia may be a mediating factor. However, this is only based on one measure of cognitive functioning, the Modified Mini-Mental State Exam.

In a follow up study conducted by Kurella Tamura et al. (2016) using 825 participants from the CRIC ancillary cohort (CRIC COG Study), patients underwent cognitive testing using the Modified Mini-Mental State Exam, Trails A and B, Category Fluency, Boston Naming, and Buschke Selective Reminding Test. Findings did not find an association between anemia and baseline cognitive functioning or decline in functioning after a 3 year follow up. Moreover, anemia was not indicated as an independent risk factor for cognitive impairment or rate of cognitive decline in adults with CKD. This study is unique from previous studies in that it focuses on moderate CKD compared to patient with more severe CKD or ESRD, which may account for differences in findings from the author's previous study as well as other previous studies. The authors also asserted that the follow-up period may have been too short to assess the relationship between anemia and cognitive decline over time.

Relationship Between CKD and the Domains of Neurocognitive Functioning

Intelligence Quotient (IQ)

Previous research on the impact of CKD on the intelligent quotient (IQ) has focused on patients with ESRD typically receiving dialysis or having undergone transplantation, and results have been varied. IQ scores are presented as standard scores with an average score being 100. Standard scores have a standard deviation (SD) of 15, with scores two or more SD denoting significant cognitive impairment. IQ scores within the pediatric CKD population tend to be lower than the typically developing population with a majority of the IQs in the low average (scores between 80-89) to average range (scores between 90-109) (Hulstijn-Dirkmaat, Damhuis, Jetten, Koster, & Schroder, 1995; Lawry, Brouhard, & Cunningham, 1994; Mendley & Zelko, 1999; Qvist et al., 2002; Warady et al., 1999).

Multiple studies have compared the effects of different renal replacement modalities namely dialysis and transplantation on general cognitive functioning. Lawry et al. (1994) compared a matched sample of 24 total patients comprised of transplants recipients (13) and dialysis dependent patients (11). Participants were matched on demographic factors, including age, sex, race, and socioeconomic status. Using the Wechsler Intelligence Scale for Children, Revised (WISC-R) and the Wechsler Adult Intelligence Scale (WAIS-R), the authors found no statistically significant difference between groups. Although there was a higher mean IQ score in the transplant group (mean IQ = 103.0; SD = 11.97) as opposed to the dialysis group (mean IQ = 92.9; SD = 16.86), both groups fell within the average range.

 Icard et al. (2010) conducted a study comparing neurocognitive data from a cohort of 49 patients including: 20 healthy controls, 23 CKD patients (receiving treatment but no transplant), and 6 CKD patients who had received a transplant. Findings from this study demonstrated a statistically significant difference of 12 points in IQ in children receiving transplants. Comparatively, children with CKD receiving alternative treatments suffered a 3 point decrease in IQ. For those receiving a transplant, their cognitive functioning was increased from the borderline range to the low average range.

Hooper and colleagues (2011) analyzed data from 368 children enrolled the CKiD study to examine neurocognitive functioning in children with mild to moderate CKD. Using the Wechsler Abbreviated Scale of Intelligence (WASI), the authors found a mean FSIQ in the average range (mean = 96.4; SD = 16.5). Twenty-five percent of the cohort was one SD below the mean. Similarly, verbal IQ (VIQ) and performance IQ (PIQ) also fell within the average range (mean VIQ = 98.0; VIQ SD = 17; mean PIQ = 95.4; PIQ SD = 16.3). Although IQ mainly fell within the average range, individual examination of the patients showed a significant number

of patients to be at risk for neurocognitive dysfunction. The authors found low birth weight to be related to lower IQ even after controlling for other variables. The sample used in this study had an 18% frequency of low birth rate, which is more than double the frequency of low birth rate in the general population of the United States, and suggests that children who have a history of low birth weight and comorbid CKD should be observed more carefully for potential neurocognitive deficits. Additionally, children who had higher levels of proteinuria tended to have both lowered FSIQ and VIQ. It should be noted that children with higher levels of proteinuria showed a particular pattern of variables, which included higher rates of glomerular causes of CKD, hypertension, and use of immunosuppressive medications.

Academic Achievement

In regards to academic achievement, children with CKD are at risk of struggling academically due to high frequency of school absenteeism. When compared to children without a chronic illness, children with CKD miss school more often for hospitalizations, outpatient clinic visits, temporarily illness, and medical treatments for CKD such as dialysis (Brouhard et al., 2000; Gerson et al., 2006; Gipson & Ferris, 2004; Warady, 2002). Lawry (1994) conducted a study using pediatric patients diagnosed with CKD (currently on dialysis or having undergone a transplant) or Chronic Renal Insufficiency (CRI). The authors found that children who received kidney transplants do better than the combined CRI and dialysis group in the academic domains of reading, math, and language using the Woodcock Johnson Tests of Achievement.

Duquette, Hooper, Wetherington, Icard, and Gipson (2007) reviewed academic achievement in 30 children between the ages of 6-18-years-old experiencing kidney dysfunction for 3 months or greater as measured by a decreased glomerular filtration rate or being dialysis dependent for 3 months or greater. The CKD cohort was compared to a group of health controls

providing findings on the intellectual and academic achievement of children with CKD using the Wechsler Abbreviated Scale of Intelligence (WASI) and Wechsler Individual Achievement Test (WIAT-II) as the main study instruments. Children with CKD performed worse than health controls on word reading and math reasoning. However, spelling scores were not significantly different between the two groups. Lower renal functioning did correlate with lower scores on spelling as well as math reasoning. Renal functioning was an overall significant predictor of academic achievement accounting for 47% of the variance.

Other studies such as the one conducted by Brouhard et al. (2000) found no difference between transplant and dialysis patients on measures of academic achievement. However, a significant difference was found when the dialysis group and transplant group were combined and compared against their siblings. When analyzing the data in this manner, lower achievement was found within the transplant and dialysis patient in math, reading, and spelling as compared to the control group. No group differences were found in a study by Bawden et al. (2004) comparing ESRD patients to their sibling controls. The academic domains reviewed in this study included basic math skills, reading as well as reading comprehension, spelling, and phonological processing.

It is possible that even though lower neurocognitive performance has been exhibited in children with CKD, they are not getting enough academic supports in the classroom. Studies have showed that 79-94% of children with CKD are placed into regular classroom setting and may or may not receive tutoring services. About 13-15% of the studies' population was receiving some sort of special educational services (Qvist et al., 2002; Warady et al., 1999). Duquette et al. (2007) reported that the rate of children with CKD receiving special educational services, approximately 13%, is roughly equal to the national rates of children with any disability

receiving special education services (Education, 2004). Effects of childhood CKD and ESRD on neurocognitive functioning persist into adulthood, and lower educational attainment is seen in this population when compared to healthy adult controls (Groothoff et al., 2002). Further exploration is needed to better understand why children with ESRD have lower rates of academic achievement and what type of academic remediation is best for this populations (e.g., hospital-based, home-based, or school-based intervention).

Language

The work of Fennell and colleagues (1990a) longitudinally examined multiple neuropsychological functions of 45 children with renal failure matched to a control group. Participants were matched on demographic factors. The pediatric cohort was actively receiving medical management of their disease, undergoing dialysis, or had already received a transplant. Findings from this study showed significant evidence decreasing scores on verbal measures as duration of disease increases in the 6-11 age group.

In a subsequent study conducted by Fennell et al. (1990b) subjects were children undergoing treatment for renal failure and a group of matched controls based on age, sex, and race. The children were between the ages of 6 and 18-years-old. Children undergoing treatment for renal failure had a successful transplantation, receiving hemodialysis, or other medical management of renal failure. Results from this study showed that patients in renal failure scored significantly lower in tests of verbal abstract abilities using the similarities subtest from the WSIC-R. Although levels are significantly lower than the control group, participants are not showing functional or clinical deficits.

However, Qvist et al. (2002) examined 33 children who received a renal transplant before age five on a number of neuropsychological domains finding no significant difference between

the transplant group and control on measures of verbal functioning. The mean verbal IQ for the group was 87.6; whereas, the non-verbal IQ was also 87.6. Only 6% of the study sample showed generalized language deficits.

A more recently published study by Molnar-Varga et al. (2016) examined differences between transplanted and non-transplanted children. Transplanted children with common CKD comorbidities (e.g., hypertension, diabetes, and bone density issues) performed significantly below children who had transplants but were not diagnosed with common CKD comorbidities on tasks of verbal abilities. Additionally, when comparing time on dialysis, children who had been on dialysis longer performed poorer on tasks of verbal abilities. Taken together, these findings suggest that there are potential risk factors for deficits within the domain of verbal abilities including increased disease duration, experiencing comorbidities and remaining on dialysis for an extended period of time. As results within the domain of language are mixed, more research should be conducted to better understand the preservation and decline of language abilities within the mild to moderate CKD population.

Visuospatial Skills

As with other areas of neurocognitive functioning, there has been little research on visuospatial abilities within mild to moderate CKD. However, research from ESRD and transplant patient has shown mixed results. Fennell et al. (1990a) measured visuomotor and visuospatial skills using the Raven's Progressive Matrices and the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery VMI) in a cohort of 56 children reported mild to moderate deficits in both visual motor and visuospatial skills. In a later study conducted by (Fennell et al., 1990b) the renal failure group performed below the matched control both in terms of clinical and statistical significance on the Beery VMI. This finding was consistent

across the renal failure subjects. The authors also found statistically significant lower

performance on measures of visuospatial skills, but these findings did not indicated a clinical

deficit. Qvist et al. (2002) did not find any significant difference in visuospatial in transplanted

children as compared to their matched control group. As with the domain of language, more

research is needed to better understand the visuospatial abilities of those with mild to moderate

CKD.

Executive Functioning

The executive functions (EF) are a group of neurocognitive functions that are top-down

mental processes, which have significant implications for day-to-day functioning. The ability to

employ the use of EF has implications for overall success in academic and career settings and are

important in general cognitive development along with social and psychological development.

Generally, EF are important in situations in which one should not or cannot rely on automatic

responses or instincts. This may require inhibiting automatic responses or switching to a new

way of responding. Because of this, employing EF is effortful (Burgess & Simons, 2005; Espy,

2004; Miller & Cohen, 2001).

Although there has been debate as to what functions qualify to be called EF, there are

three accepted as core EF including inhibition, working memory, and cognitive flexibility. Each

EF core function has a subset of functions. For example, inhibition includes inhibitory control,

self-control or behavioral inhibition, interference control, selective attention, and cognitive

inhibition. Cognitive flexibility encompasses set shifting and mental flexibility also known as

mental set shifting, which is associated with processes such as creativity. Extending from these

core EFs are abilities such as problem-solving, planning, and reasoning (Collins & Koechlin,

2012; Lehto, Juujarvi, Kooistra, & Pulkkinen, 2003; Lunt et al., 2012; Miyake et al., 2000).

Memory, particularly working memory (WM), is necessary for multiple day-to-day functions. WM involves the ability to hold a set of information in one's mind and mentally manipulate it (Baddeley & Hitch, 1994; Smith & Jonides, 1999). WM can be classified into two types: visual and verbal. Both types of WM are necessary in contexts where one must relate future information to information that came earlier. This type of skills is implicated in reading, writing, mathematics, and understanding language. Additionally, WM aids in one's ability to make connections between two things that are seemingly unrelated as well as pull out relevant pieces from an integrated whole. As such, WM also has implications in the creative process. WM also allows individuals to use both conceptual and perceptual knowledge in decision making while also using memories of one's past and desires for the future in decision making and planning (Diamond, 2013).

Working memory and short-term memory are distinguished from each by the difference in functions. Working memory requires that someone not only hold the information but also work with that information; whereas short-term memory only requires someone to hold that information in their mind (Diamond, 2013). Research has also shown that the two cluster differently on factor analyses, and imaging revealed that WM and short-term memory use different areas of the brain. Working memory has been shown to employ the dorsolateral prefrontal cortex, and short-term memory shows activation in the ventrolateral prefrontal cortex (Alloway, Gathercole, Willis, & Adams, 2004; D'Esposito, Postle, Ballard, & Lease, 1999; Eldreth et al., 2006; Gathercole, Pickering, Ambridge, & Wearing, 2004; Smith & Jonides, 1999).

Inhibitory control involves counteracting impulsive, automatic responses and instead changing or choosing how we react to internal or external stimuli. Inhibitory control can be

described as controlling one's attention, or selectively attending to a certain set of stimuli while suppressing or ignoring another set of stimuli. It also includes the ability to control one's thoughts (cognitive inhibition), behaviors (self-control), and emotions in favor of choosing responses more appropriate or needed for the given situation.

Self-control is an aspect of inhibition that concerns controlling one's behaviors and emotional response in order to aid in controlling behavioral responses. Self-control involved resisting temptation and is the opposite of impulsive responding. Additionally, self-control is having the ability to resist impulses and stay on task even when distracting stimuli are present. This is especially needed when a tasks are uninteresting yet needs to be completed; self-control aids you in completing the boring task when you desire to be doing something more interesting. Similarly, self-control involves delaying gratification. This is deferring immediate pleasure in order to gain a greater reward later on. Inhibition is difficult for children and adolescents and as a result, errors of impulsivity are frequent. Errors of impulsivity happen when a child is unable to wait when responding to stimuli. Being quick to respond, children often do not inhibit their automatic responses or inhibit responding to an immediately gratifying stimulus instead of waiting (Diamond, 2013).

Cognitive flexibility is another core EF, which may build off of both working memory and inhibitory control. Cognitive flexibility is an EF that occurs later in development. It encompasses abilities such as changing perspective both spatially and interpersonally, which involves both inhibiting previous responses and activating a different response using WM. It also includes the ability to change the way one might think about something or approach a situation as we change problem-solving strategies. Cognitive flexibility also aids in switching from one task to another or changing plans from plan A to plan B when needed. In neuropsychological

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testing, cognitive flexibility is often measured through tasks which require set shifting or switching between sets of rules to accurately complete the task. Cognitive flexibility also represents aspects of creativity and problem solving (Diamond, 2013).

Within the literature on EF, there has been ongoing efforts to better understand the developmental trajectory of EF. Given that EF develops rapidly in toddler and preschool aged children, research on the developmental trajectory of EF has been limited in that many researchers use mainly young children, usually restricting their age range to the toddler and preschool years (2-5 years-old). However, a few studies do exist with larger age ranges. Best and Miller (2010) conducted a meta-analysis using the studies on EF that included these larger age ranges in order to better understand the developmental trajectory. The authors focused on the core EF including inhibition, working memory, and shifting.

In regards to inhibition, the authors found evidence for the initial formation of inhibitory control abilities during the preschool years (around 4 years-old). During this time, inhibition showed rapid improvement, and children are able to start successfully inhibiting responses on both simple and complex inhibition tasks. Best and Miller (2010) also found that as children age, they continue to improve on tasks of inhibition, particularly tasks that involve both inhibition and working memory. As children age, they showed better inhibition on computerized tasks. It is thought that as children age, they refine their inhibition skills and become more accurate and efficient in responding.

The ability to use working memory (WM) starts to emergence during the preschool years, and improves enough by age 6 that children are able to do more complex WM tasks. WM has both simple and complex components. Within simple working memory, one is only holding the information within the brain; whereas more complex WM skills require the information not only

be held by the brain but also be manipulated for use (Best & Miller, 2010; Gathercole et al., 2004). Gathercole et al. (2004) also compared the trajectories of simple and complex WM finding a similar pattern of development. Children typically show a linear increase in simple and complex WM skills from ages 4-14 years-old, and then improvements in WM skills begin to plateau thereafter. Luciana, Conklin, Hooper, and Yarger (2005) and Conklin, Luciana, Hooper, and Yarger (2007) using both verbal and visual measures of WM found that simple WM tasks tend to be mastered by age 9, showing little improvement in simple WM abilities past this age. However, children continued to show improvement on more complex WM tasks until age 16. Findings from their research led Conklin et al. (2007) to suggest that the age of mastery of WM skills may depend more on the degree of processing needed for the task rather than whether the task has verbally or visually based content.

From their review, Best and Miller (2010) determined that the ability to shift improves with age. Research conducted by Hughes (1998) showed that children ages 3-4 are able to shift between simple response sets if the rules for responding are placed within the context of a story. Garon, Bryson, and Smith (2008) suggested that the development of shifting abilities may come later as the ability to shift response sets is dependent upon the ability of the child to hold onto a response set in WM. As children age, they are able to complete increasingly more difficult switching tasks. During early adolescence, there is evidence that children are able to monitor their errors during switching tasks, and by mid-adolescence improvement in shifting abilities levels off (Davidson, Amso, Anderson, & Diamond, 2006; Huizinga, Dolan, & van der Molen, 2006).

Memory and CKD

Deficits within the domain of memory have been documented in children with CKD. A study conducted by Fennell et al. (1990b) found that children receiving treatment for renal failure did significantly worse than controls on immediate recall memory and learning tasks. Fennell and colleagues also demonstrated an interaction between renal disease and time of follow-up. Children with renal disease did not improve in performance at the same rate as the control group and they performed worse at 6 months and 12 months follow-up. Based on literature from adult patients with CKD, the authors hypothesized that pediatric chronic renal disease may have a progressive deteriorative effect on memory.

In a more recent study by Gipson et al. (2006), findings supported significantly lower short-term visual and verbal memory as well as some impairment in working memory in a population of 20 children and adolescents with CKD when compared to 18 typically developing children. Further review of the findings revealed that on subtests of the Wide Range Assessment of Memory and Learning (WRAML) that employed multiple repetitions and feedback on performance, children with CKD performed similarly to the typically developing comparison group. This finding was seen in both the visual and verbal tasks. The findings from this study are consistent with previous findings suggesting that children with CKD struggle with cognitive functioning and especially within the domain of memory. The study has implications for everyday life and schoolwork that can be applied to children with CKD such as a need for multiple repetitions of material presented for learning within the home, school, or medical settings.

A few studies suggest that memory functioning can improve after transplantation. Qvist et al. (2002) found no group effects in memory after transplant when compared to the NEPSY

normative sample, but general memory deficits were present in 20% of the study population of 33 children. Mendley and Zelko (1999) also found improvements in working memory one year after transplant when comparing pre/post-transplant scores.

Attention, Inhibitory Control, & Initiation and CKD

Within executive functioning (EF), attention regulation has been highlighted as an area of risk for poor performance among those with pediatric CKD. Attentional deficits are detrimental in that they can cause difficulties with acquisition of new information and skills as well as difficulties with exhibiting previously acquired information and skills (Gerson et al., 2006). Mendley et al. (2015) conducted a study examining the attentional regulation aspect of EF using a sample population from the CKiD data set. The study population consisted of 340 subjects aged 6-21 years old from the CKiD cohort. The median age of the group was 13-years-old, and the average length of disease was 10 years. The median estimated GFR was 43 ml/min/1.73m^2. Similarly with the cohort as a whole, the study sample had IQs in the lower range of normal with 22% of the sample having IQs falling below a standard score of 85. Additionally, 119 participants (35%) performed poorly on at least one test of EF. Thirty participants performed poorly on two tests while 10 participants showed poor performance on 3 or more tests. All participants within the study sample attended school (median grade = 6th), and 40% of these subjects were performing below grade level. Review of absences from school revealed a median of 4 days missed for medical related reasons, and 11% of the cohort missed more than 18 days of school in previous school year.

The authors also thought it important to account for cofounding variables such as fatigue, given that fatigue is related to poorer performance attention regulation and EF tasks. Mendley et al. (2015) accounted for fatigue in two ways. First, the authors accounted for fatigue related to

order effects for which they blocked testing administrated into two blocks and counterbalanced these blocks across subjects. Secondly, the authors accounted for physical fatigue using questions related to fatigue from the Pediatric Quality of Life Inventory (PedsQL). Seventeen percent of child or parent reports for participants endorsed having low energy often or almost always.

Using errors of commission on the Connors' CPT-II to measure inhibitory control and visual vigilance, the authors found an association with duration of disease. As duration of CKD increases, inhibitory control and visual vigilance decreases suggesting possible deficits with attention regulation. Cross-sectional findings of this study showed that duration of CKD is more pertinent than the GFR levels, which lead the authors to hypothesize that duration of disease may have a consistent, progressive effect on neurodevelopmental processes. An important limitation to consider within this research is that as CKD progresses, there is a higher likelihood of comorbidities, which could underlie at least some of the poor performance on measures of EF. No association was found between duration of CKD or levels of GFR with other aspects of EF. Similar findings were observed by Fennell et al. (1990b). Using a visual continuous performance task, the results showed children with CKD showed more errors of commission suggesting deficits in sustained attention than matched controls.

Some evidence suggests that attentional deficits show improvement after transplantation but evidence is mixed. Attention measured in children with CKD one-year post transplantation showed improvement in sustained attention and overall processing speed. However, no improvements were seen in focal attention (Mendley & Zelko, 1999). When compared to the NEPSY normative data, Qvist et al. (2002) cohort showed no significant deficits in attention, but 24% of the group did exhibit decreased attention spans. Mixed results in attention post

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transplantation could be due to disease onset, severity or duration of disease as well as factors like treatments initiated prior to transplantation or rate of deterioration. It is important to consider cognitive functioning prior to disease onset when considering rates of improvement as well (Gerson et al., 2006).

Using a cohort of 20 children with CKD and 18 typically developing children, Gipson et al. (2006) found significant differences between groups in selected EF such as task initiation behaviors and sustaining attention. However, there were no group differences found in regards to set-shifting and inhibition even after covarying with chronological age and IQ. The authors note that set-shifting tasks are the only tasks within their battery of EF that do not contain a time limit. Had a time limit been place on participants, it is suspected deficits would have appeared within this domain. On the surface, their findings regarding inhibition appear to be contrary to those found by Mendley et al. (2015) using a similar task. However, Mendley and colleagues covaried their data with duration of disease, which may account for the differences in findings.

Psychosocial Functioning

Psychosocial functioning is an all-encompassing term that incorporates multiple domains of a person's functioning including behavioral, social, and psychological. Broadly, previous research within the domain of psychosocial functioning demonstrates that psychosocial functioning can be impacted in children with various chronic illnesses. However, research on psychosocial functioning with pediatric CKD is sparse and the results have been largely mixed. There is some evidence to suggest that one mechanism by which CKD impacts psychosocial functioning is by prohibiting participation in developmentally typical activities such as peer interaction outside of school, sports, and other extracurricular activities. This can be attributed, at least in part, to medical appointments, including dialysis, and medication therapy (Assadi, 2013).

It has been hypothesized that physiological changes in CKD can affect psychosocial functioning of children and adolescents with CKD. Specifically focusing on adolescents, Fadrowski et al. (2006) conducted a study to examine the relationship between physical and psychosocial functioning with GFR decline, linear growth, hemoglobin levels, and albumin levels. The Child Health Questionnaire-Parent Form was utilized to assess physical and psychosocial functioning via the physical and psychosocial summary scales. The study used participants from the Functional Outcomes in Adolescent CKD study, a prospective cohort aimed specifically at examining physical and psychosocial functioning in adolescents with CKD. One hundred and eight participants, ages 11-18, were enrolled within the study between July 1999 and May 2004. Data from 78 participants were utilized within the study. Results suggested that age was the only significant association with psychosocial functioning, in that the psychosocial score decrease by 0.9 point for each 1-year increase in age. Therefore, older age was associated with poorer psychosocial functioning.

There are multiple measures with which to assess psychosocial functioning in pediatric populations, but the present study focused on the use of the Behavioral Assessment Systems for Children, Second Edition (BASC-2); therefore, the rest of the studies reviewed here were limited to those using this particular measure. To the best of the author's knowledge, only two studies (Hooper et al., 2009; Hooper et al., 2016) exist using the BASC-2 to measure psychosocial functioning in children with CKD.

Hooper et al. (2009) conducted a study to compare behavioral and social functioning in children with CKD to typically developing children. In order to do so, the researchers examined reports of behavioral and social functioning completed by both children and their parents. Researchers gathered 26 pediatric CKD patients from an academic medical center, specifically

patients came from a pediatric nephrology clinic within the medical center. The patient group was compared to a group of 33 children typically developing children. Children with a historical diagnosis of any chronic or psychiatric illness were excluded as well as any children with a historical neurodevelopmental disorder diagnosis. Children on a medication regimen were also excluded from the typically developing group as well as children with a history of seizures or head trauma. All study participants were administered the Behavioral Assessment Systems for Children (BASC) and the BASC Self-Report of Personality to better understand their social and behavioral functioning and the Wechsler Abbreviated Scale of Intelligence to acquire an abbreviated IQ estimate (Reynolds & Kamphaus, 2004; Wechsler, 1999). Parents of the study participants were administered the BASC Parent Rating Scale, which allows parents to rate their child's social and behavioral functioning.

Hooper et al (2009) found significant differences between the CKD and typically developing groups as reported by the parents on the internalizing problems scales. Specifically, these differences were uncovered in 3 scales: somatization, anxiety, and depression. However, it should be noted that further analysis did not show these differences to be clinically meaningful. While parents did rate children within the CKD as having more problems in relation to psychosocial functioning, the parental ratings were not elevated to a clinical level or indicative of psychopathology. Researchers accounted for disease severity in further analyses finding that those with chronic renal insufficiency (CRI) and end stage renal disease (ESRD) had more social and behavioral problems as reported by the parents, but even with the higher reporting, scores still remained in the average range. Even though findings from this study were not clinically significant, it does suggest that children with CKD may be at a higher risk for psychosocial difficulties or symptomology than typically developing children.

Another study conducted by Hooper et al. (2016) aimed to evaluate the neurocognitive, psychosocial, and adaptive functioning of preschool aged children with mild to moderate CKD. Participants (n=124) for this study were between 12 months and approximately 5.5 years old, and were gathered through the CKiD cohort. In order to assess psychosocial functioning within this group, parents were administered the BASC-2 parent rating form.

Results from this study showed psychosocial functioning to be in the average range. Across internalizing and externalizing symptoms along with general concerns for behaviors, few concerns were noted by parents for young children. Moreover, not many young children were ranked within the at-risk range either. Approximately 20% of children received scores that placed them at-risk for internalizing problems, and 14% of participants received scores placing them at-risk for behavioral problems. However, the authors noted that rates of those within the at-risk range are still considered within "normal curve expectations (Hooper et al., 2016, p. 7)." Results from this study suggested that preschool aged children are more at-risk for adaptive deficits rather than psychosocial deficits, which is likely a results of the developmental level of preschool aged children.

Medication Management of Pediatric CKD

Due to the complex nature of progressive CKD, multiple medical treatments are used to manage symptoms of CKD and its comorbidities as well as delay progression of the disease. Medication is often used in the early stages of CKD to delay progression, while dialysis and transplantation are used more frequently when the disease has progressed to ESRD. Medications used in CKD treat the specific comorbidities of CKD such as cardiovascular disease, hypertension, anemia, and poor growth among other comorbidities. Other medications commonly prescribed in pediatric CKD treat underlying kidney disease and include bladder

medication, noncorticosteroid immunosuppressants, corticosteroids and other medications meant to specifically treat the kidney disease itself. Symptom control medications are frequently prescribed with laxatives and antacids being the most common (Massengill & Ferris, 2014).

Types of Medications

ACE Inhibitors/ARBs

To treat one of the most prevalent comorbidities of both adult and pediatric CKD, hypertension, antihypertensive medications are considered to be the first-line treatment method. Most frequently a physician will prescribe an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blockers (ARBs). There are several ACE inhibitors/ARBs approved for use in children, examples of such include Benazepril, Fosinopril, Lisinopril, and Losartan (Doshi, 2014). ACE inhibitors act on an enzyme that causes blood vessels to narrow and blocks such an action from happening. Blood vessel are then able to relax and widen. Similarly, ARBs block the angiotensin II hormone, which again allows the blood vessels to relax and widen instead of narrowing. Specifically within CKD, ACE inhibitors and ARBs have been found to decrease levels proteinuria; therefore, aiding in slowing the progression of CKD. Additionally, ACE inhibitors and ARBs have possible positive side effects of preventing cardiac restructuring that leads to diagnoses such as left ventricular hypertrophy (LVH), which can occur when hypertension or elevated blood pressure goes untreated (KDIGO, 2012c; VanDeVoorde et al., 2016). Studies of ACE inhibitor and ARB usage within pediatric CKD have supported these hypotheses as children prescribed these medications are less likely to have LVH and more likely to have normal ambulatory blood pressure readings (M. Mitsnefes et al., 2010; Samuels et al., 2012).

Hypertension has an association with decreased cognitive functioning and thus, treatment with antihypertensive medications has raised the question of how these class of drugs effect neurocognitive functioning. Much of the research has been conducted on older adult populations, and has found that using ACE inhibitors can aid in improving cognitive functioning (Tedesco et al., 1999). Sink et al. (2009) conducted a study with 1,054 participants (404 exposed to ACE inhibitors; 640 not exposed to ACE inhibitors) examining if ACE inhibitors led to cognitive decline or dementia in an older population. Findings suggested that ACE inhibitors are not independently associated with neurocognitive decline or risk of developing dementia. ACE inhibitors that cross the blood-brain barrier may offer protective effects on cognition and against dementia. Moreover, ACE inhibitors that cross the blood-brain barrier may have a protective effect against cognitive decline. However, the authors suggest that more research should be conducted to better understand how ACE inhibitors impact cognitive functioning.

Tedesco et al. (1999) compared the use of losartan, an ACE inhibitor, and hydrocholorothiazide, a diuretic, on cognitive functioning and quality of life in patients with hypertension. Their study was conducted with 69 patients with ages ranging from 30-73 years old. Results showed that both medications were able to lower blood pressure and improve selected aspects of quality of life. Additionally, significant improvement in cognitive functioning was found in the losartan group. This improvement was seen after 26 months of treatment. The group showed improvement in memory, attention, concentration, and comprehension. They also showed improvement in psychosocial functioning domains such as depression, anxiety, and interpersonal relationships.

Erythropoiesis-Stimulating Agents

Erythropoiesis-Stimulating Agents (ESA) such as recombinant human erythropoietin (rHuEPO; trade names: Epogen, NeoRecormon, Procrit) along with iron supplements is the first-line treatment for anemia in children with CKD, and have shown treatment efficacy for over 20 years. The use of ESAs has transformed treatment for anemia in pediatric ESRD. Frequent blood transfusions for nearly all pediatric CKD patient was required prior to the development and use of ESAs. The risks of such frequent blood transfusions include infection and the possibility of iron overload. Blood transfusions are now only used in cases of symptomatic anemia in which ESAs treatment has been ineffective or there is continual hemolysis (VanDeVoorde et al., 2016).

The use of ESAs in children requires frequent dosing changes. Children who are under the age of 5 tend to need weekly or more frequent dosing compared to adults because there are more non-hematopoietic binding sites. Conversely, adults are more able to maintain target hemoglobin levels with less frequent dosing (Port, Kiepe, Van Guilder, Jelliffe, & Mehls, 2004; Provenzano, Bhaduri, Singh, & Group, 2005). Additionally when children are placed on ESA therapies, hemoglobin, mean corpuscular volume (MCV), and iron stores must be frequently monitored as well. These levels should be checked monthly when treatment is initiated and quarterly when hemoglobin levels stabilize. Too rapid of an increase in hemoglobin levels can lead to temporary hypertension or increased MCVs (VanDeVoorde et al., 2016).

Previous research has shown that treating anemia improves neurocognitive functioning and quality of life. Studies have mainly focused on adult patient populations and those receiving dialysis or in ESRD. No studies have been done within the pediatric mild to moderate CKD population. However, research conducted with dialysis and ESRD patients shows that treating anemia by increasing hematocrit levels via rHuEPO leads to continual improvement in

neurocognitive functioning, especially within the realm of attention (Pickett, Theberge, Brown, Schweitzer, & Nissenson, 1999). Additional research has suggest that although neurocognitive functioning can improve with the use of rHuEPO, neurocognitive abilities does not completely normalize after treatment of anemia suggesting multiple factors associated with poor neurocognitive functioning within ESRD (Grimm et al., 1990; Nissenson, 1992).

Research conducted by Lee et al. (2004) found that using rHuEPO to increase hematocrit levels shows an association with improved cognitive functioning. However, it does not show a significant association with improved quality of life. In contrast to previous ideas, findings from this study suggest that anemic patient should not be indiscriminately treated with rHuEPO, because quality of life is not significantly improved. The authors note that further research should continue to examine the effects of rHuEPO on both neurocognitive functioning and quality of life.

Recombinant Human Growth Hormone

To manage growth impairment and nutritional deficits frequently observed in pediatric CKD, KDOQI guidelines suggest using nutritional management strategies prior to the use of the recombinant human growth hormone (rhGH; trade names: Norditropin, Saizen, Nutropin) (KDOQI, 2009). Such nutritional management strategies may include caloric supplementation through nutrient dense formulas as well as the use of feeding tubes and scheduled feedings. Using such approaches to nutritional management has shown increases in both height and weight standard deviations (Claris-Appiani, Ardissino, Dacco, Funari, & Terzi, 1995; VanDeVoorde et al., 2016). Treating growth and nutritional deficiencies with nutritional management requires careful consideration and monitoring as this population is already at-risk for obesity (KDOQI, 2006).

Although nutritional management is the first-line treatment for growth and nutritional deficiencies, only about 12% of children show catch-up growth and a height of less than 1 standard deviation below what would be expected with this therapy alone (Seikaly et al., 2006). Recombinant human growth hormone treatment is an approved treatment for children with CKD who are also experiencing growth failure. Use of rhGH in children with CKD has shown to be both safe and effective with few adverse side effects (Fine, Ho, Tejani, & Blethen, 2003; Vimalachandra et al., 2006). Some side effects that have occurred with the use of rhGH include increased insulin and parathyroid levels. These side effects appear to dissipate back to normal levels over the course of treatment, but in more extreme cases of hyperparathyroidism, medication may need to be temporarily suspended (Darendeliler, Karagiannis, & Wilton, 2007; Fine et al., 2003; Picca et al., 2004).

To the author's knowledge, no research on the neurocognitive effects of growth impairment or failure in children or adolescents with CKD has been conducted as research within this domain in general has been limited. Relevant research has mainly been conducted with patients who have growth hormone deficiency as a result of a primary pituitary or hypothalamic disorders and has tended to exclude patients with more complex medical histories including diagnoses like CKD (van Dam et al., 2005).

Results from previous studies have mixed findings, but may indicate some cognitive impairment in children and adults with growth hormone deficiencies. Most notably, studies have found deficits within memory, attention, and EF (Arwert, Deijen, Witlox, & Drent, 2005; Falleti, Maruff, Burman, & Harris, 2006). These results have also been mixed as to whether or not treatment with rhGH improves cognitive functioning, but generally shows treatment increases neurocognitive functioning especially as treatment duration increases (Falleti et al., 2006; van

Dam, 2005). Overall, more research should be conducted within this realm to better understand growth hormone deficiencies impact on neurocognitive functioning and medications effect on improving cognitive functioning.

Adherence to Medication

Treatment planning is difficult for physicians treating pediatric CKD patients, and the number of treatments can place a large burden on the patient and family. In order to better understand how to anticipate potential treatment efficacy in complex diseases such as CKD, Blydt-Hansen et al. (2014) suggested a better understanding of the variability of comorbidities within pediatric CKD as well as comorbidity onset. Having a more thorough understanding of comorbidities were thought to be beneficial to practitioners to aid them in predicting what medications and treatments would be necessary and appropriate given the stage of CKD. In their research, Blydt-Hansen and colleagues constructed a study to better understand the relationship between increasing numbers of comorbidities, specific medications, and medication adherence rates.

The authors used a subset of the CKiD cohort (n = 558) who were currently prescribed medications. They characterized the medications prescribed to participants by disease type and stage of progression and examined this with sociodemographic variables. The study grouped like medications together and the resulting groups were then assigned into four treatment categories including CKD-specific comorbidities, treatment for underlying kidney disease, therapies for control of symptoms, and non-CKD medications. During the study visits, patients or their guardians reported medication use in the past 30 days including supplements and medications that were prescribe and over-the-counter. Non-adherence was characterized by missing one or

more dose in the past seven days. The study relied on self-report in order to calculate non-adherence rates, which is a potential limitation of the methodology.

Results from the study showed that ACE/ARB treatment was most common medication group being utilized by over 50% of the study population. Children with more advanced CKD staging were prescribed medications for CKD associated comorbidities more often. Even though findings suggest that medication use increases with more advanced staging of CKD, there were no findings to suggest that certain medications or treatments are consistently prescribed at a particular stage of CKD. However, when applying a greater than 50% threshold, patients in stage IV of CKD are commonly prescribed both active vitamin D supplements and ACE inhibitors/ARBs. Prevalence rates of other medications commonly thought to be prescribed in advanced CKD staging (e.g., growth hormone, ESAs, and phosphate binders) ranges from 20%-44%. Stage II has a myriad of medications (e.g., antihypertensive, phosphate binders, vitamin, mineral, and other supplements) used with prevalence rates between 9-10% for these medications. The variation and non-specificity seen from these results suggests that CKD staging may not be enough to screen for comorbidities or base medications use (Blydt-Hansen et al., 2014).

Additionally, adherence rates may be related to degree of importance that a patient places on a particular medication. For instance, a study conducted by (Terebelo & Markell, 2010) showed that there is preferential adherence in transplant patients to immunosuppressant medications. Higher rates of non-adherence in this population were found among Caucasians even after controlling for several factors including age, sex, socioeconomic status, etiology (i.e., glomerular versus non-glomerular), and duration of CKD. This finding does contrast other studies in which non-adherence rates were higher in African Americans (Oliva et al., 2013;

Rolnick, Pawloski, Hedblom, Asche, & Bruzek, 2013; Zhu, Tu, Marrero, Rosenman, & Overhage, 2011).

Within the population of pediatric transplant patients, adolescents have the highest rates of medication non-adherence (Kaspar et al., 2016). During adolescence, teenagers are physically growing and maturing. However, the development of EF such as planning, organization, insight and judgment, logical reasoning, and risk planning are developing at a slower rate compared to physical development. Slower development of these functions may be a contributing factor to the higher rates of medication non-adherence. Additionally, decrease in parental supervision over medication use or poor communications between patients, parents, and physicians may also be a contributing factor. Depression and anxiety symptoms have also been thought to contribute to non-adherence within this population. Strategies to improve adherence rates within this population include health education for patients and integrating parents into their health care as well as teaching self-monitoring skills and problem-solving (Blydt-Hansen et al., 2014).

A factor thought to influence medication adherence is medication burden (number of medications prescribed to one patient). Given that CKD has many accompanying comorbidities, multiple medications are frequently required and prescribed, which can be burdensome to the patient. However, in the study conducted by Blydt-Hansen et al. (2014) non-adherence was independently associated with dosing frequency suggesting that what matters more than number of medications (medication burden) is how frequently a pediatric patient is required to take a medication (dosing frequency). These results are supported with other research reviewing medications management within hypertension, CVD, and HIV (Boyle et al., 2008; Buscher, Hartman, Kallen, & Giordano, 2012; Frishman, 2007; Gianotti et al., 2013; O'Connor et al., 2013; Robertson, Cooke, Wang, Shaya, & Lee, 2008). However, in a study conducted by Fraser

et al. (2015), results suggested that mild CKD is associated with high disease burden (i.e., disease severity, complexity, and associated comorbidities), decreased kidney functioning (low eGFR), high medication burden (taking 5 or more medications), and a decreased capacity to cope with all the treatment entails, which may affect adherence to medications.

Medication Burden

CKD treatment can be burdensome on pediatric patients and their families, even at the mild to moderate stages of CKD. Management of CKD may require daily self-catheterizations, blood pressure monitoring, fluid and dietary restrictions and monitoring. CKD is often paired with multiple medications, insulin injections (daily), and ESA injections (one to three times a week). One area of burden with increasing attention in adult CKD literature is medication burden, which is defined as the number of unique medications administered on a daily basis (Massengill & Ferris, 2014; Zalai, Szeifert, & Novak, 2012). Much of the research thus far has focused on the impact of medication burden on medication adherence. However, medication burden is also thought to impact several areas of functioning in CKD patients, including adjustment to illness, psychosocial functioning, and quality of life (Blydt-Hansen et al., 2014; Massengill & Ferris, 2014; Mohammed, Moles, & Chen, 2016).

To better understand the impact of medication burden on patients' experiences, Mohammed et al. (2016) conducted a metasynthesis of qualitative studies exploring medication burden, medication related beliefs, and medication taking practices on adult patients' experiences with medicine. Thirty-four studies were included within their review with 1,144 total participants. The researchers found 5 medication-related burden themes, including "(1) burden of medication routine, (2) burden of medication characteristics, (3) burden of medication adverse events (AEs), (4) healthcare and associated medication burden, and (5) mediation-related social

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burden (Mohammed et al., 2016, p. 7). Of note, the burden of medication routines (managing medications on a daily basis), was found to be a prominent theme throughout the review. While some patients were able to discuss strategies and adapt to managing medication routines on a daily basis, other patients reported a lack of adaptation to their medication routine, intensifying the burden of the routine. Patients also reported medication routine burden to have a negative impact on their day-to-day life and well-being. The authors found that those who did not adapt or cope with medication routine burden engaged in missing medication doses or modifying dosing schedules without informing their healthcare provider. Overall, medication burden was found to have an impact on patients' lived experiences with medicine, impacting psychosocial functioning, well-being, day-to-day functioning, and medication related beliefs and behaviors.

Studying a similar concept, Chiu et al. (2009) conducted a study to examine health-related quality of life and pill burden in adult patients undergoing maintenance dialysis. The study utilized the SF 36 to measure quality of life. The Short Form Survey 36 (SF 36) contains two component scores: physical and mental. The mental component score was comprised of general health, vitality, social functioning, mental health, and role emotional. Both component scores were included within the analysis. Pill burden was defined as the total numbers of pills taken on a daily basis. The study was multi-site, enrolling a total of 233 participants across three clinical sites. The mean age of participants was 53-years-old (SD = 15). Findings from the study demonstrated a significant correlation between total daily pill burden and the physical component score; however, no significant correlation was found between pill burden and the mental component score.

Current Study

The purpose of the current study was to better understand the role of medication adherence, medication burden and medication effectiveness on parent-reported executive functioning (EF) and psychosocial functioning in adolescents with chronic kidney disease (CKD). A diagnosis of pediatric CKD comes with a set of complex medical regimens including multiple medications to manage comorbidities. Recent research has shown that comorbidities such as hypertension and anemia can have a negative impact on neurocognitive functioning especially EF and psychosocial functioning. However, medication management of these comorbidities has been seen to improve neurocognitive and psychosocial functioning in some studies. The present study aimed to investigate the association between medication adherence and parent-reported neurocognitive and psychosocial functioning within specified comorbidities: hypertension, anemia, and growth hormone deficit. The association between medication burden and parent-reported EF and psychosocial functioning was also examined among adolescents with CKD prescribed medications.

The following hypotheses were proposed for the current study:

1) Research on the impact of medication burden and EF and psychosocial functioning is largely mixed (Chiu et al., 2009; Mohammed et al., 2016). For the present study, it was expected that participants with higher medication burden at Time 1 would be predictive of poorer performance on measures of EF (BRIEF Parent-Report t-scores [GEC and Plan/Organization]) and psychosocial functioning (BASC-2 t-score [Internalizing Problems]) at Time 2.

2) Previous studies have shown hypertension to be associated with decreased cognitive functioning. While studies specifically on aspects of executive functioning have been

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mixed, there is some evidence for decreased set shifting within children with CKD and hypertension (Lande et al., 2003; Lande et al., 2016; Slickers et al., 2007). Additionally, previous research has demonstrated that antihypertensives can aid in increasing neurocognitive and psychosocial functioning (Sink et al., 2009; Tedesco et al., 1999). Therefore, it was hypothesized that participants prescribed antihypertensive medication (i.e., ACE inhibitors/ARBs) who had lower adherence at Time 1 would be predictive of poorer performance on measures of EF (BRIEF Parent-Report t-scores [GEC and Shift]) and psychosocial functioning (BASC-2 Parent-Report t-score [Internalizing Problems]) at Time 2.

3) Research on the relationship between neurocognitive functioning and anemia in CKD populations has been mixed. However, some evidence for lowered neurocognitive functioning, particularly within the domain of memory has been demonstrated (Kruella Tamura et al., 2011; Slickers et al., 2007). Moreover, previous studies have found treating anemia with ESAs to be associated with improved neurocognitive functioning (Grimm et al., 1990; Lee et al., 2004); Nissenson, 1992; Pickett et al., 1999). While preliminary findings did not associate the use of ESAs with improved psychosocial functioning, further research was deemed important by Lee et al. (2004). In an effort to expand on previous research, it was hypothesized that participants prescribed medications for anemia (i.e., ESAs) who had lower levels of adherence at Time 1 were expected to have poorer performance on measures of EF (BRIEF Parent-Report t-score [Working Memory]) as well as poorer psychosocial functioning (BASC-2 Parent-Report t-score [Internalizing Problems]) at Time 2.

4) A study conducted by Slicker et al. (2007) demonstrated an association between hemoglobin below 10.5 mg/dl and decreased performance on tasks of memory. As such, it was hypothesized that adherence to ESAs that were ineffective in correcting anemia, hemoglobin levels remaining below 10.5 mg/dl, at Time 1 would be predictive of poorer performance on measure of EF (BRIEF Parent-Report t-score [Working Memory]) and psychosocial functioning (BASC-2 Parent-Report t-score [Internalizing Problems]) at Time 2.

5) While no studies on the effect of growth hormone on improving neurocognitive and psychosocial functioning within the pediatric CKiD population have been conducted, studies with children and adults whom have growth hormone deficiency and are treated with growth hormone have been mixed (Falleti et al., 2006; van Dam, 2005). Therefore, in an effort to expand on previous research, it was hypothesized that participants prescribed growth hormone who had lower levels of adherence at Time 1 would be predictive of poorer performance on measure of EF (BRIEF Parent-Report t-scores [Inhibition and Working Memory]) and psychosocial functioning (BASC-2 Parent-Report t-score [Internalizing Problems]) at Time 2.

6) Research on demographic variables association with neurocognitive functioning has been largely mixed, but has shown some evidence for neurocognitive functioning to be lower in females (Hooper et al., 2011). It is expected that there will be poorer EF in females in the present study. While Hooper et al., 2011 found poorer neurocognitive performance in African American participants, Terebelo & Markell (2010) found poorer adherence amongst Caucasians within the study. Given that the focus of this study is to examine the relationship between adherence and EF, it was

hypothesized that Caucasians will demonstrate poorer EF due to suspected poorer adherence.

The definition of medication adherence was based on the mediation adherence question asked by the clinician at any given CKiD study visit. The exact question asked was as follows: "How many times did (name of child) take prescribed (DRUG) in the last 30 days?" When examining the association between medication burden and EF and psychosocial functioning, medication burden will be defined the number of unique medications prescribed to the participant at Time 1. This definition is based on a previous study conducted by Robertson et al. (2008) and will allow for analysis of this predictor as a continuous variable. Additionally, when examining the impact of lowered kidney functioning, this will be defined as those children with eGFR below the median eGFR, which is 43 ml/min/1.73m^2.

The present study consisted of adolescents between the ages of 12-21, given that this age range is generally accepted as adolescence. However, there is no single definition of adolescence (APA, 2002). To be included in analysis for the first hypothesis, adolescents must have been prescribed at least one medication. For the second hypothesis, adolescents included must have been prescribed antihypertensive medications. Similarly, adolescents were included within the third and fourth hypotheses if they were prescribed ESAs. Lastly, adolescents were included within the analyses for the fifth hypothesis if they were prescribed rhGH. For each hypothesis, only adolescents with complete data for each predictor variable were included. Adolescents with missing data (e.g., missing BRIEF t-scores, bedside GFR, BASC-2, etc.) were excluded from the analysis.

CHAPTER II

METHODS

Participants

Participants were garnered from the Chronic Kidney Disease in Children (CKiD) cohort. The CKiD cohort was comprised of two cohorts, the first has 586 children enrolled, and the second cohort was projected to have 280 participants. No data on the second CKiD cohort such as descriptive statistics are currently available in the literature or on the CKiD website, and data from the second cohort were not included within the public data set utilized for the present study. All participants enrolled in the study were between the ages of 1-16 years-old, diagnosed with chronic kidney disease (CKD), and have estimated glomerular filtration rates (eGFR) between 30 and 90ml/min/per $1.73m^2$. Participants for the CKiD cohort were gathered from 57 clinical sites across the United States (Furth et al., 2006).

Inclusion criteria for the study was based on age, GFR, and ability to obtain informed consent for the participant. The age of the participants was strategically chosen by the investigators based on factors such as being able to obtain proper measurements to track progression of CKD from a young age, especially within the domains of cardiovascular and neurocognitive functioning. Participants must have been able to attended follow-up study visits. CKiD participants must have an estimated GFR of 30 to 75 ml/min per $1.73 m^2$ at study entry. Estimated GFR was calculated using the Schwartz Formula (Furth et al., 2006; Schwartz, Haycock, Edelmann, & Spitzer, 1976; Schwartz et al., 2009).

Exclusion criteria for the study included having had a renal, solid-organ, bone marrow, or stem-cell transplantation as well as being on dialysis within the past 3 months. Other factors considered as exclusionary criteria were pregnancy within the past 12 months, diagnosis of

cancer, leukemia, or HIV or treatment of these disorders within the past 12 months. Individuals

identified as having known structural heart diseases were excluded as well as those with genetic

syndromes (i.e., Down's Syndrome). Severe to profound intellectual disability, classified as an

IQ <40, inability to perform self-care acts, and severely impacted adaptive functioning skills,

were excluded. Patients were also excluded if they would be unable to attend all follow-up visits,

had intention of moving away from CKiD sites, or unable to partake in important aspects of data

collection (Furth et al., 2006).

In order to test each hypothesis, the present study utilized different groups of participants

from the CKiD study. Groups of participants were employed to evaluate a specific hypothesis,

and the groups were not compared to each other. Each group of participants was restricted to

adolescents, which was defined between the ages of 12-21 (APA, 2002). For hypothesis 1, CKiD

study participants were included if they were prescribed any medication at Time 1 (year 3 visit)

and Time 2 (year 5 visit). Medications at Time 1 were summed together to created the

medication burden variable. To conduct hypothesis 2, the study utilized CKiD participants

prescribed antihypertensive medications at Time 1 and Time 2 and must have answered the

medication adherence question ("How many times did [name of child] take prescribed (DRUG)

in the last 30 days?"). Participants included within hypothesis 3 were prescribed ESAs at Time 1

and Time 2 and answered the medication adherence question at Time 1. Similarly, those included

within the analysis for hypothesis 4 were adolescents prescribed ESAs at Time 1 and Time 2,

whom were medication non-responders, and had answered the medication adherence question at

Time 1. Medication non-responding for those prescribed ESAs was defined as hemoglobin levels

remaining below 10.5 mg/dl (KDOQI, 2006). Participants included within the analysis for

hypothesis 5 were adolescents prescribed rhGH and had answered the medication adherence

question. Descriptive statistics for each group of participants utilized are presented in the results section (beginning on page 61).

Procedures

Organization

In regards to data collection, the CKiD study consisted of two main clinical coordinating centers, which were located in Baltimore, MD and Kansas City, MO. In total, the study had 57 clinical sites across the country, a data coordination center (Baltimore, MD) and a central laboratory. There were also specialized sites such as the laboratory for cystatin C, central repositories for biological and genetic data, and central reading centers for echocardiograms, intima-media thickness, ambulatory BP monitoring, and magnetic resonance imagining. Chapel Hill, NC was designated as the site for neurocognitive data (Furth et al., 2006).

To ensure standardization of data collection across the clinical sites, trainings were held yearly, training DVDs were distributed to the clinical sites, and interactive web-based visits detailed the questionnaires and data needed for collection at any given study visit. Additionally, study progression was monitored through an External Advisory Committee, which meets annually, and a Steering Committee, which involved conference calls semimonthly to review progress and procedures within the study (Furth et al., 2006).

Study Visits

Participants engaged in a study enrollment visit (V0), a 3-6-month follow-up (V1a), a one year follow-up (V1b), and then had follow-up visits annually thereafter (V2, V3, V4, etc…). Children were followed until they reach 21 years of age or when a participant's CKD advanced enough to require renal replacement therapy (RRT). Phone follow-ups were used after the initiation of RRT to capture clinical events and mortality. If a child was deemed high risk for developing end stage renal disease, ESRD, (as defined by GFR measuring <15 ml/min per 1.73^2

or moving into stage 5 CKD) within a year after a given study visit, their next visit was to be scheduled within three months of the documentation of stage 5 CKD or GFR <15 ml/min per 1.73^2. The purpose of this was to collect data before the onset of ESRD giving the researchers a better view of physiological and neuropsychological data prior to the onset of ESRD. Phone follow-ups were conducted thereafter in order to document the date of RRT initiation (Furth et al., 2006).

Annual visits for each child involved a physical examination, collection of biological samples, and parents and children completed a set of clinical questionnaires. The physical examination included measurements of height, weight, head and mid-upper arm circumferences. The physical exam also included clinical blood pressure and resting pulse among other measurements. The annual questionnaires distributed to the parents and child asked for information regarding medical history, medication use/adherence, current symptomology, quality of life, and information about nutrition and diet. Reports on medication use captured information regarding prescription and over-the-counter medication as well as dietary supplements or nutritional aids and any alternative medicines. The study utilized the 2005 Youth Risk Behavior Survey (CDC, 2005; Grunbaum et al., 2004) to gather information on physical activity and substance use. Further data were collected on diet including a three-day diet record and the Willett food frequency questionnaire (Rockett et al., 1997). The study coordinators completed training on the standardized instructions for the three-day, 24 hour food recall diary, and these coordinators provided parents with the standardized instructions to complete this measure (Furth et al., 2006).

Blood pressure (BP) measurements were collected in two ways for the CKiD study: clinical BP and ambulatory blood pressure monitoring. Clinical BP measurements were taken at

each study appointment. During each study visit, clinical BP was measured three times and the average of those three systolic and diastolic readings were documented. ABPM measures BP over a 24-hour period, and ABPM were completed as part of odd year visits (Furth et al., 2006).

Neurocognitive Testing

Neurocognitive functioning was also assessed in the CKiD study. Broadly, the neurocognitive battery included intellectual and EF measures (i.e, Wechsler Abbreviated Scale of Intelligence, Delis-Kaplan Executive Function System) as well as parent- and self-reports regarding quality of life, behavioral and emotional functioning. Neurocognitive testing took place at the 3-6 month follow-up appointment and even-year appointments thereafter (Furth et al., 2006). Testing was conducted by a licensed psychologist, trained examiner, or graduate student (supervised by a licensed psychologist). It was projected that the neurocognitive battery would take an hour and a half to administer. Because all tests used in the neurocognitive battery are standardized measures, the psychologists were provided with scripts for standardized administration and asked to provide instructions verbatim (CKiD Website, 2014).

In order to achieve a valid assessment on the participants, it was requested that neurocognitive testing not be completed on a day when a child had undergone a non-routine invasive procedure, a procedure that caused significant distress, or any medical procedure that required the use of sedatives. Additionally, children with CKD are likely to become easily fatigued. With this in mind, the researchers attempted to correct for potential order effects in the core battery through creating two testing blocks and counterbalancing the blocks across all participants (CKiD Website, 2014).

For each participant, clinicians completed a behavioral coding form for each task administered aimed at providing the clinician with information on the reliability of the

neurocognitive data collected. Each rating was completed immediately following the completion of a task and was recorded on the CKiD reliability coding worksheet. The reliability coding system was comprised of a primary and secondary code, and was used to help the CKiD researchers better understand any irregularities that may have occurred during administration. The reliability coding system was also used in determining whether or not the neurocognitive data for a given participant were added to the database. Data with low reliability scores were excluded from the study (CKiD Website, 2014).

In order to ensure quality control of the data collected, the regional psychologists reviewed the first two completed cases from each clinical site and then 20% of the cases from then on. Any errors in administration or record keeping were communicated to clinicians administering the neurocognitive battery. The regional psychologist continued to review 25% of the neurocognitive data across all the clinical sites that was collected at baseline and at the even year appointments that followed. During data review, the regional psychologists checked for errors in administration as well as rescored the data to ensure no errors were made in scoring. This includes transforming raw scores into standardized scores to ensure accuracy. More information regarding quality control, reliability coding, or general data collection procedures for the neurocognitive data can be found on the CKiD Website (2014).

Medication Burden and Adherence Variables

Medication burden and medication adherence variables were created for each study participant at Time 1 and Time 2. As previously stated, medication burden was defined as the number of the unique medications prescribed to an adolescent at each visit. To create this continuous variable, medications prescribed for each adolescent were summed in order to determine the total number of unique medications prescribed to an adolescent at Time 1 and

Time 2. The medication adherence variable was created for each participant by computing the percentage of antihypertensive, ESAs, and growth hormone medications an adolescent took in the past month. For example, if an adolescent reported taking 45 doses of medication that was prescribed for twice daily use (60 times total over 30 days), their adherence percentage over the past 30 days would be .75 or 75%. If participants were taking more than one antihypertensive, ESA, or growth hormone medication during the past 30 days, their adherence percentage for each prescribed medication was averaged together to create one adherence percentage. A similar methods of computing medication adherence was utilized by Chiu et al. (2009).

Measures

Demographics

Specific demographic variables of participants meeting inclusion criteria for the present study were reported within the results section. Although there are no data present in the literature on the demographics of cohort two, demographic data do exist for the first cohort (n= 586). The median age of children enrolled in the first cohort is 11 years-old, and males comprise 62% (n=364) of the cohort. The cohort was both racially and ethnically diverse. Caucasians made up 66% of the cohort (n=384) while African Americans comprised 23% of the cohort (n=137). Eleven percent (n=65) were multi-racial or other, and 15% (n=84) were of Hispanic ethnicity (Furth et al., 2006; Wong et al., 2012).

Executive Functioning

Behavior Rating Inventory of Executive Functioning. The BRIEF (Gioia, Isquith, Guy, & Kenworthy, 2000) is a parent- and teacher-report measure, which assesses EF in everyday environments such as the home and school giving a real life picture of EF in children and adolescents. The BRIEF measures EF in children and adolescents ages 5-18 years-old. The

BRIEF contains 86 questions from which 8 clinical scales have been derived: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. From the clinical scales come two broader indexes, Behavioral Regulation and Metacognition, and an overarching composite score, Global Executive Composite (GEC). The BRIEF contains two validity scales to measure inconsistent and unusually negative responding. The BRIEF has high internal consistency (range = .80 -.98) and test-retest reliability (range = .76-.86). In contrast, the BRIEF shows lower levels of interrater reliability for parent and teacher ratings of the same child with coefficient between .30-.50. The BRIEF was designed with high content validity in mind, and a majority of the items in the scales have high interrater agreement. The BRIEF manual can be referenced for further information on reliability and validity (Gioia et al., 2000).

Psychosocial Functioning

Behavior Assessment Scales for Children, Second Edition. Psychosocial functioning was assessed using the BASC-2 (Reynolds & Kamphaus, 2004). The BASC-2, a norm-referenced diagnostic measure assessing behavioral and emotional functioning, was completed by parents at the 3-6 month follow-up and with neurocognitive assessments thereafter. The BASC-2 contains 11-16 scales with 4-5 composite scales depending on the form used (parent vs. teacher) and age of the child (e.g., adolescents do not have a Activities of Daily Living scale). The composite scales included on the parent-report form are Adaptive Skills, Behavioral Symptoms Index, Externalizing Problems, and Internalizing Problems. The BASC-2 was shown to have high internal consistency for composite scales, greater than or equal to .90. Similarly, individual scales also had high internal consistency for individual scales, greater than or equal to .80. Test-retest reliability for parent-report measures had a mean of .80. Interrater reliability for

the parent-report from was acceptable (.57-.74). The BASC-2 was compared to other measures of behavior, emotional, and executive functioning. The BASC-2 correlated between .70-.80 with the following measures, the ASEBA Child Behavior Checklist, BRIEF, and Conners' Parent Rating Scale-Revised. When compared to the BASC, correlations fell within the .90s (Community-University Partnership for the Study of Children, 2011; Reynolds & Kamphaus, 2004, 2010).

Statistical Analyses

Hierarchical multiple regressions were utilized to investigate the predictive ability of medication burden and adherence on measures of EF (BRIEF GEC, Inhibition, Planning/Organization, Shift, Working Memory; BASC-2 Internalizing Scale). These EF measures served as the dependent variables. In total, 9 multiple regressions were conducted, one for each dependent variable within each hypothesis. Hierarchical multiple regressions were unable to be performed for hypothesis 4 and 5 due to small sample size (n = <9). For a majority of the regression models, demographic information, including age, sex, and race, were entered into the first step of the regression, with the exception of hypothesis 2, specifically the analysis utilizing parent-reported BRIEF Shift t-scores, and hypothesis 3 (all analyses). Demographic variables were left out of these analyses due to small sample size. Within the second step for hypothesis 1 and 2, parent-reported BRIEF and BASC-2 t-scores were entered for Time 1 to better understand the predictive ability of Time 1 on Time 2. Executive and psychosocial functioning measures were entered as step 1 for hypothesis 2 utilizing BRIEF Shift t-score and hypothesis 3 (all analyses). Medication burden (hypothesis 1) or medication adherence (hypotheses 2 and 3) were entered into step 3, and entered as the second step for hypothesis 2 using the BRIEF Shift t-score and hypothesis 3 (all analyses). The final step for each of the

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regressions was to enter the estimated glomerular filtration rate (eGFR) to better understand its predictive ability in the current study as previous evidence has shown lower levels of eGFR to be associated with poorer scores on measures of EF.

CHAPTER III

RESULTS

Hypothesis 1: Prediction of Executive and Psychosocial Functioning by Medication Burden

Three hierarchical multiple regressions were performed to test the first hypothesis. One analysis was conducted for each measure of EF and psychosocial functioning. Overall, the analysis revealed the hypothesis was partially supported. Medication burden was not predictive of poorer EF over and above demographic variables and Time 1 EF measures. However, higher medication burden was predictive of poorer psychosocial functioning at Time 2, even when accounting for demographic variables and psychosocial functioning at Time 1.

Prior to the interpretation of each regression model, the assumptions of the hierarchical multiple regression were reviewed to ensure none of the assumptions were violated. All models displayed linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. Each model demonstrated independence of residuals, as assessed by a Durbin-Watson statistics of 1.72, 1.79, and 2.46, respectively. There was homoscedasticity for each model, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. There were no studentized deleted residuals greater than ±3.5 standard deviations, no leverage values greater than 0.2, and values for Cook's distance above 1 for each regression. There assumption of normality was met, as assessed by a Q-Q Plot created for each regression.

A hierarchical multiple regression was conducted to determine if the addition of Time 1 GEC, medication burden, and then bedside GFR improved the prediction of Time 2 GEC over and above age, gender, and race alone. One hundred and two participants were included in this

analysis. Participants were included within this analysis if they were prescribed medication at Time 1. There were 58 males and 44 females included in the analysis. The mean age of participants was 14.47 with a standard deviation of .81. Sixty-nine participants were Caucasian and 33 participants were racial minorities, including African American, Asian, "other," and participants who identify as more than one race. The mean BRIEF GEC t-score was 54.38, with a standard deviation of 10.89. Participants were prescribed a mean of 3.94 medications (SD = 2.50). The mean bedside GFR rate was 46.29 with a standard deviation of 15.73. See Table 1 for full details on each regression model.

The results of model 1, including demographic variables (age, gender, and race), were statistically significant, $R2$ = .10, $F(3, 98)$ = 3.56, $p < .05$; adjusted $R2$ = .07. Age and race were not statistically significant; whereas, gender was statistically significant predictor of Time 2 GEC, β = .29, $p<.01$. That is, males were more likely to be rated higher by parents on Time 2 GEC scores than females. The addition of Time 1 GEC to the model led to statistically significant increase in R2 of .42, ($F_{(4, 97)}$=26.37, $p<.001$, adjusted R^2 = .50, β = .27, $p>.001$), meaning participants were rated higher by parents on Time 1 GEC continued to be rated higher than other participants on Time 2 GEC. The addition of medication burden revealed no statistically significant change in the variance accounted for with R2 = .002 ($F_{(5, 96)}$ = 21.04, $p<.001$, adjusted R^2 = .50, β = .05, $p>.001$). Additionally, the addition of bedside GFR in model 4 did not result in a statistically significant increase in R2 of .00 ($F_{(6, 95)}$ = 17.46, $p<.001$, adjusted R^2 = .49, β = -.02, $p>.001$). See Table 2 for full details.

Table 1

Means, Standard Deviations, and Intercorrelations for GEC From Medication Burden

Variable	*M*	*SD*	1	2	3	4	5	6
Time 2 GEC	52.86	11.61	-0.13	**0.27***	0.03	**0.69***	**0.18***	-0.10
Predictor Variables								
1. Age	14.47	1.81		0.06	-0.11	-0.09	-0.14	-0.09
2. Gender	0.57	0.50			-0.12	0.11	0.05	-0.26***
3. Race	1.32	0.47				-0.00	0.25	0.10
4. Time 1 GEC	54.38	10.89					0.15	-0.01
5. Medication Burden	3.94	2.50						**-0.28***
6. Bedside GFR	46.29	15.73						

Note. N = 102 *p<.05 **p< .01 ***<.001

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Table 2

Hierarchical Multiple Regression Predicting Time 2 GEC From Medication Burden

	Time 2 GEC							
	Model 1		Model 2		Model 3		Model 4	
Variable	B	β	B	β	B	β	B	β
Constant	61.17		18.29		17.77		19.82	
Age	-0.93	-0.15	-0.54	-0.084	-0.51	-0.08	-0.54	-0.08
Gender	6.66	**0.29***	4.97	**0.21***	4.89	**0.21***	4.66	**0.20**
Race	1.04	0.04	1.08	0.04	0.80	0.03	0.96	0.04
Time 1 GEC			0.70	**0.66***	0.69	**0.65***	0.70	**0.65***
Medication Burden					0.21	0.05	0.14	0.03
Bedside GFR							-0.03	-0.05
R^2	0.10		0.52		0.52		0.52	
F	**3.56***		**26.37***		**21.04***		**17.46***	
ΔR^2	0.10		0.42		0.00		0.00	
ΔF	**3.56***		**85.58***		0.37		0.34	

Note. N= 102 *p<.05 **p< .01 ***<.001

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Similarly, a hierarchical multiple regression was conducted to determine if the addition of Time 1 Plan/Organization, medication burden, and then bedside GFR improved the prediction of Time 2 Plan/Organization over and above age, gender, and race alone. Eighty-one participants were included in this analysis. All participants included within the analysis were prescribed at least one medication at Time 1. There were 48 males and 33 females included in the analysis. The mean age of participants was 14.52 with a standard deviation of 1.69. Fifty-six participants were Caucasian and 25 participants were racial minorities, including African American, Asian, "other," and participants who identify as more than one race. The mean BRIEF Plan/Organization t-score was 54.59 with a standard deviation of 10.59. Participants were prescribed a mean of 4.11 medications ($SD = 2.608$). The mean bedside GFR was 45.14 ($SD = 15.29$). See Table 3 for further details on descriptive statistics and intercorrelations of predictor variables.

The results of model 1, including demographic variables (age, gender, and race), were not statistically significant, $R2 = .04$, $F(3, 77) = 1.17$, $p > .05$; adjusted $R2 = .01$. The addition of Time 1 Plan/Organization to the model led to statistically significant increase in R2 of .42, ($F_{(4, 76)} = 16.71$, $p<.001$, adjusted $R^2 = .44$, $\beta = .65$, $p<.001$). The addition of medication burden in model 3 revealed no statistically significant change in the variance accounted for with R2 = .01 ($F_{(5, 75)} = 13.19$, $p<.001$, adjusted $R^2 = .43$, $\beta = .01$, $p>.05$). Lastly, the addition of bedside GFR in model 4 did not result in a statistically significant increase in R2 of .00 ($F_{(6, 74)} = 10.98$, $p<.001$, adjusted $R^2 = .43$, $\beta = -.06$, $p>.05$). See Table 4 for full details.

Table 3

Means, Standard Deviations, and Intercorrelations for Plan/Organization From Medication Burden

Variable	*M*	*SD*	1	2	3	4	5	6
Time 2 Plan/Organization	54.89	11.28	-0.10	0.16	0.07	**0.66***	0.14	-0.07
Predictor Variables								
1. Age	14.52	1.69		-0.02	-0.04	-0.00	-0.09	-0.05
2. Gender	0.59	0.49			-0.10	0.03	0.10	**-0.29***
3. Race	1.31	0.46				0.02	0.21*	0.10
4. Time 1 Plan/Organization	54.59	10.59					0.15	0.03
5. Medication Burden	4.11	2.61						**-0.29***
6. Bedside GFR	45.14	15.29						

Note. N = 81 *p<.05 **p< .01 ***<.001

Table 4

Hierarchical Multiple Regression Predicting Time 2 Plan/Organization From Medication Burden

Variable	Model 1		Model 2		Model 3		Model 4	
	B	β	B	β	B	β	B	β
Constant	59.24		21.95		21.88		24.35	
Age	-0.64	-0.10	-0.64	-0.10	-0.63	-0.09	-0.66	-0.10
Gender	3.90	0.17	3.50	0.15	3.48	0.15	3.14	0.14
Race	2.00	0.08	1.66	0.70	1.62	0.07	1.83	0.08
Time 1 Plan/Organization			0.69	**0.65*****	0.69	**0.65*****	0.70	**0.66*****
Medication Burden					0.04	0.01	-0.05	-0.01
Bedside GFR							-0.04	-0.06
R^2	0.04		0.47		0.47		0.47	
F	1.17		**16.71*****		**13.19*****		**10.98*****	
ΔR^2	0.04		0.42		0.00		0.00	

	ΔF	1.17	**60.62*****	0.01	0.41

Note. N= 81 *p<.05 **p< .01 ***<.001

Lastly, a third hierarchical multiple regression was conducted to determine if the addition of Time 1 Internalizing Problems Scale, medication burden, and then bedside GFR improved the prediction of Time 2 Internalizing Problems Scale over and above age, gender, and race alone. One hundred thirty-four participants were included in this analysis with each participant being prescribed at least one medication at time 1. The sample consisted of 76 males and 58 females. The mean age of participants was 15.30 with a standard deviation of 2.20. In regards to race, 89 participants were Caucasian and 45 participants were racial minorities, including African American, Asian, American Indian, "other," and participants who identify as more than one race. The mean BASC-2 Internalizing Problems t-scores was 47.99 ($SD = 8.29$). Participants were prescribed a mean of 4.04 medications ($SD = 2.48$). The mean bedside GFR rate was 45.67 with a standard deviation of 15.86. See Table 5 for further details on descriptive statistics and intercorrelations of predictor variables.

The results of model 1, including demographic variables (age, gender, and race), were not statistically significant, $R2 = .01$, $F(3, 130 = .35$, $p > .05$; adjusted $R2 = -.02$. The addition of Time 1 Internalizing Problems to the model led to statistically significant increase in R2 of .26, ($F_{(4, 139)} = 11.73$, $p<.001$, adjusted $R^2 = .24$, $\beta = .51$, $p<.001$). Similarly, the addition of medication burden in model 3 revealed a statistically significant change in the variance accounted for with R2 = .03 ($F_{(5, 128)} = 11.02$, $p<.001$, adjusted $R^2 = .27$, $\beta = .19$, $p<.05$). Conversely, the addition of bedside GFR in model 4 did not result in a statistically significant increase in R2 of .00 ($F_{(6, 127)} = 9.26$, $p<.001$, adjusted $R^2 = .27$, $\beta = -.07$, $p>.05$). See Table 6 for full details.

Table 5

Means, Standard Deviations, and Intercorrelations for Internalizing Problems From Medication Burden

Variable	M	SD	1	2	3	4	5	6
Time 2 Internalizing Problems	47.99	8.29	0.04	-0.07	0.04	**0.50*****	**0.24*****	-0.05
Predictor Variables								
1. Age	15.30	2.20		0.01	0.05	-0.09	0.03	**-0.17***
2. Gender	0.57	0.50			-0.08	-0.08	0.01	**-0.31*****
3. Race	1.34	0.47				-0.09	0.23	**0.16***
4. Time 1 Internalizing Problems	50.84	10.01					0.07	0.11
5. Medication Burden	4.04	2.47						**-0.26*****
6. Bedside GFR	45.67	15.86						

Note. N = 134 *p<.05 **p< .01 ***<.001

Table 6

Hierarchical Multiple Regression Predicting Time 2 Internalizing Problems From Medication Burden

| | Time 2 Internalizing Problems | | | | | | | |
| | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
Variable	B	β	B	β	B	β	B	β
Constant	45.52		19.95		19.61		21.58	
Age	0.16	0.04	0.32	0.08	0.30	0.08	0.26	0.07
Gender	-1.17	-0.07	-0.40	-0.02	-0.52	-0.03	-0.83	-0.05
Race	0.51	0.03	1.32	0.08	0.51	0.03	0.77	0.04
Time 1 Internalizing Problems			0.43	**0.51*****	0.41	**0.50*****	0.42	**0.50*****
Medication Burden					0.64	**0.19****	0.57	**0.17***
Bedside GFR							-0.04	-0.066
R^2	0.02		0.27		0.30		0.30	
F	0.35		**11.73*****		**11.02*****		**9.26*****	
ΔR^2	0.01		0.26		0.03		0.00	

| ΔF | 0.35 | 45.50*** | 6.29* | 0.61 |

Hypothesis 2: Prediction of Executive and Psychosocial Functioning by Adherence to

Antihypertensive Medication

To test the second hypothesis, three hierarchical multiple regressions were conducted, one analysis per measure of EF and psychosocial functioning. The analyses revealed the hypothesis was not supported. Lower medication adherence was not predictive of poorer EF over and above demographic variables and Time 1 EF measures. Similarly, lower medication adherence was not predictive of poorer psychosocial functioning at Time 2 after accounting for demographic variables and psychosocial functioning at Time 1.

All regression models conducted to test hypothesis 3 were reviewed to ensure the model did not violate the assumptions of the hierarchical regression. Each regression demonstrated linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. The Durbin-Watson statistic for each model were reviewed and independence of residuals was found for each regression (Durbin-Watson values: 2.01, 1.71, and 2.08). There was homoscedasticity for each model, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. Additionally, there was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. There were no studentized deleted residuals greater than ±3.5 standard deviations, high leverage points, and values for Cook's distance above 1 for any of the regressions conducted. The assumption of normality was met, as assessed by Q-Q Plot for each regression.

A hierarchical multiple regression was conducted to determine if the addition of Time 1 GEC, adherence to antihypertensive medications, and then bedside GFR improved the prediction of Time 2 GEC over and above age, gender, and race alone. Sixty-seven participants met inclusion criteria and were included within the analysis. Out of 67 participants, 35 participants

were male and 32 participants were female. The mean age of participants was 14.63 ($SD = 1.89$). There were 45 participants who identified as Caucasian, and 22 participants identified as a racial minority, including African American, "other," participants who identify as more than one race. The mean BRIEF GEC t-score for Time 2 was 51.42 ($SD = 11.20$). At Time 1, the mean parent-reported BRIEF GEC t-score was 53.88 ($SD = 10.86$). The mean adherence rate was .94 ($SD = .12$). That is, participants reported taking their medication as prescribed 93% of the past 30 days. Participants within this analysis had a mean bedside GFR of 45.99 with a standard deviation of 15.39. See Table 7 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

The results of model 1, including demographic variables (age, gender, and race), were not statistically significant, $R2 = .32$, $F_{(3, 63)} = 2.33$, $p > .05$; adjusted $R2 = .06$. Given that the model was not significant, individual demographic variables were not reviewed for significance. The addition of Time 1 GEC to the model led to statistically significant increase in R2 of .41, ($F_{(4, 66)} = 15.79$, $p<.001$, adjusted $R^2 = .47$, $\beta = .09$, $p<.001$). The addition of medication adherence within model 3 revealed no statistically significant change in the variance accounted for with R2 $= .00$ ($F_{(5, 66)} = 12.58$, $p<.001$, adjusted $R^2 = .47$). Lastly, the addition of bedside GFR in model 4 did not result in a statistically significant increase in R2 of .004 ($F_{(6, 66)} = 10.47$, $p<.001$, adjusted $R^2 = .46$). See table 8 for full details.

Table 7

Means, Standard Deviations, and Intercorrelations for GEC From Adherence to Antihypertensives

Variable	*M*	*SD*	1	2	3	4	5	6
Time 2 GEC	51.42	11.20	-0.11	**0.30****	0.05	**0.66***	-0.02	-0.09
Predictor Variables								
1. Age	14.63	1.89		-0.03	-0.15	**-0.03*****	0.07	-0.02
2. Gender	0.52	0.50			0.03	0.09	0.16	**-0.30****
3. Race	1.33	0.47				0.02	**-0.29****	0.08
4. Time 1 GEC	53.88	10.86					0.00	0.04
5. Adherence to Antihypertensives	0.94	0.12						-0.16
6. Bedside GFR	45.99	15.39						

Note. N = 67 *p<.05 **p< .01 ***<.001

Table 8

Hierarchical Multiple Regression Predicting Time 2 GEC From Adherence to Antihypertensives

	Time 2 GEC							
	Model 1		Model 2		Model 3		Model 4	
Variable	B	β	B	β	B	β	B	β
Constant	55.49		19.70		24.93		27.97	
Age	-0.57	-0.10	-0.48	-0.08	-0.47	-0.08	-0.50	-0.09
Gender	6.58	**0.30***	5.32	**0.24****	5.54	**0.25****	5.12	**0.23***
Race	0.58	0.03	0.38	0.02	-0.01	0.00	0.07	0.00
Time 1 GEC			0.66	**0.64*****	0.66	**0.64*****	0.66	**0.64*****
Adherence to Antihypertensives					-5.30	-0.06	-5.88	-0.06
Bedside GFR							-0.05	-0.07
R^2	0.10		0.51		0.51		0.51	
F	2.33		**15.79*****		**12.58*****		**10.47*****	
ΔR^2	0.10		0.41		0.00		0.00	
ΔF	2.33		**50.65*****		0.36		0.46	

Note. N= 67 *p<.05 **p< .01 ***<.001

Next, a second hierarchical multiple regression was conducted to determine if the addition of adherence to antihypertensive medications and then bedside GFR improved the prediction of Time 2 Shift over and above Time 1 Shift. Fifty-four participants met inclusion criteria and were included within the analysis. Of the 54 participants, 30 participants were males and 24 were female. There were 38 participants who identified as Caucasian, and 16 participants were identified as a racial minority, including African American, "other," participants who identify as more than one race. The mean BRIEF Shift t-score for Time 2 was 50.46, with a standard deviation of 11.35. At Time 1, the mean parent-reported BRIEF Shift t-score was 53.13 (SD = 13.11). The mean adherence rate was .9288 (SD = .13). That is, participants reported taking their medication as prescribed 93% during the past 30 days. Participants within this analysis had a mean bedside GFR of 44.37 (SD = 14.79). See Table 9 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

Given the smaller sample size, demographic variable were not included within this analysis. Time 1 Shift was added to model 1 and was found to be statistically significant, $R2$ = .42, $F_{(1, 53)}$ = 38.17, p<.001; adjusted $R2$ = .41. The addition of adherence to antihypertensive medications to model 2 did not lead to a statistically significant increase in R2 of .00, ($F_{(2, 53)}$ = 18.91, p<.001, adjusted R^2 = .43). Lastly, the addition of bedside GFR within model 3 revealed statistically significant change in the variance accounted for with R2 = .05 ($F_{(3, 53)}$ = 14.96, p<.001, adjusted R^2 = .47). See table 10 for full details.

Table 9

Means, Standard Deviations, and Intercorrelations for Shift From Adherence to Antihypertensives

Variable	*M*	*SD*	1	2	3
Time 2 Shift	50.46	11.35	**0.65*****	0.11	-0.09
Predictor Variables					
1. Time 1 Shift	53.13	13.11		0.65	0.11
2. Adherence to Antihypertensives	0.93	0.13			-0.24
3. Bedside GFR	44.37	14.79			

Note. N = 54 *p<.05 **p< .01 ***<.001

Table 10

Hierarchical Multiple Regression Predicting Time 2 Shift From Adherence to Antihypertensives

	Time 2 Shift					
	Model 1		Model 2		Model 3	
Variable	B	β	B	β	B	β
Constant	20.53		24.06		34.99	
Time 1 Shift	0.56	**0.65***	0.57	**0.66***	0.62	**0.71***
Adherence to Antihypertensives			-4.43	-0.05	-10.31	-0.12
Bedside GFR					-0.18	**-0.23***
R^2	0.42		0.43		**0.47***	
F	**38.17***		**18.91***		**14.96***	
ΔR^2	0.42		0.00		0.05	
ΔF	38.17		0.22		4.48*	

Note. N= 54 *p<.05 **p< .01 ***<.001

A third hierarchical multiple regression was conducted to determine if the addition of Time 1 Internalizing Problems, adherence to antihypertensive medications, and then bedside GFR improved the prediction of Time 2 Internalizing Problems over and above age, gender, and race alone. Fifty-four participants met inclusion criteria and were included within the analysis. Thirty participants were males and 24 were female. There were 38 participants who identified as Caucasian, and 16 participants were identified as a racial minority, including African American, "other," participants who identify as more than one race. The mean BRIEF Shift t-score for Time 2 was 50.46, with a standard deviation of 11.35. At time Time 1, the mean parent-reported BRIEF Shift t-score was 53.13 ($SD = 13.11$). The mean adherence rate was .93 ($SD = .13$). That is, participants reported taking their medication as prescribed 93% during the past 30 days. Participants within this analysis had a mean bedside GFR of 44.37 with a standard deviation of 14.79. See Table 11 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

The results of model 1, including demographic variables (age, gender, and race), were not statistically significant, $R2 = .01$, $F_{(3, 87)} = .34$ $p > .05$; adjusted $R2 = -.02$. Individual demographic variables were not reviewed for significance due to lack of statistical significance for the model. The addition of Time 1 Internalizing Problems to the model led to statistically significant increase in R2 of .21, ($F_{(4, 86)} = 6.02$, $p < .001$, adjusted $R^2 = .18$, $\beta = .46$, $p > .001$). The addition of medication adherence within model 3 revealed no statistically significant change in the variance accounted for with R2 $= .001$ ($F_{(5, 85)} = 4.78$, $p = .001$, adjusted $R^2 = .17$). Lastly, the addition of bedside GFR in model 4 did not result in a statistically significant increase in R2 of .03 ($F_{(6, 84)} = 4.73$, $p < .001$, adjusted $R^2 = .20$, $\beta = -.20$, $p = .06$). See table 12 for full details.

Table 11

Means, Standard Deviations, and Intercorrelations for Internalizing Problems From Adherence to Antihypertensives

Variable	M	SD	1	2	3	4	5	6
Time 2 Internalizing Problems	47.01	7.74	0.11	-0.01	-0.00	**0.45***	0.08	-0.13
Predictor Variables				-0.05	-0.01	-0.04	0.03	-0.14
1. Age	15.52	2.20			0.04	-0.06	-0.02	-**0.33***
2. Gender	0.54	0.50				-0.08	-**0.33***	0.16
3. Race	1.33	0.47					0.13	0.12
4. Time 1 Internalizing Problems	50.44	9.83						-0.04
5. Adherence to Antihypertensives	0.96	0.08						
6. Bedside GFR	44.97	16.07						

Note. N = 91 *p<.05 **p< .01 ***<.001

Table 12

Hierarchical Multiple Regression Predicting Time 2 Internalizing Problems From Adherence to Antihypertensives

	Time 2 Internalizing Problems							
	Model 1		Model 2		Model 3		Model 4	
Variable	B	β	B	β	B	β	B	β
Constant	41.22		21.10		18.36		23.29	
Age	0.38	0.10	0.45	0.13	0.44	0.13	0.34	0.10
Gender	-0.08	-0.00	0.30	0.02	0.31	0.02	-0.72	-0.05
Race	-0.04	-0.00	0.50	0.03	0.66	0.04	1.23	0.08
Time 1 Internalizing Problems			**0.36***	**0.46***	**0.36***	**0.45***	**0.38***	**0.48***
Adherence to Antihypertensives					2.82	0.031	2.75	0.03
Bedside GFR							-0.10	-0.20
R^2	0.01		0.22		0.22		0.25	
F	0.34		**6.02***		**4.78***		**4.73***	

ΔR^2	0.01	0.21	0.00	0.03
ΔF	0.34	**22.77*****	0.10	3.73

Note. N= 91 *p<.05 **p< .01 ***<.001

Hypothesis 3: Prediction of Executive and Psychosocial Functioning by Adherence to

Medications for Anemia

Three hierarchical multiple regressions were conducted to evaluate the third hypothesis. One regression analysis was conducted per EF and psychosocial functioning measure. The analyses revealed the hypothesis was not supported. Medication non-adherence to ESAs was not predictive of poorer EF over and above demographic variables and Time 1 EF measures. Similarly, medication adherence was not predictive of poorer psychosocial functioning at Time 2 after accounting for demographic variables and psychosocial functioning at Time 1. It is important to note that there was not strong model fit for each regression model conducted. Assumptions of the hierarchical regression were violated when conducting these analyses. It is likely that small sample size contributed to poor model fit.

The first hierarchical multiple regression to test hypothesis 3 was conducted to determine if the addition of adherence to medications for anemia (ESAs) and then bedside GFR improved the prediction of Time 2 GEC over and above Time 1 GEC. Twenty-eight participants met inclusion criteria and were included within the analysis. Of the 28 participants, 17 participants were males and 11 were female. There were 19 participants who identified as Caucasian, and 9 participants were identified as a racial minority, including African American, Asian, "other," and participants who identify as more than one race. The mean BRIEF GEC for Time 2 was 53.64, with a standard deviation of 12.93. At Time 1, the mean parent-reported BRIEF GEC t-score was 55.89 ($SD = 11.79$). The mean adherence rate was .90 ($SD = .22$). That is, participants reported taking their medication as prescribed 90% during the past 30 days. Participants within this analysis had a mean bedside GFR of 40.95 ($SD = 18.33$). See Table 13 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

The regression model was evaluated to determine if the data violated the assumptions of the model. There was independence of residuals as determined by the Durbin-Watson statistic (2.57). Linearity was demonstrated by visual assessment of the partial regression plots and a plot of studentized residuals against the predicted values. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by no tolerance values greater than 0.10. There were no studentized deleted residuals greater than ±3 standard deviations or values for Cook's distance above 1. Four high leverage points were present ranging from 0.26 - 0.43, and these were not removed from the analyses. It is likely high leverage points were due to the small sample size. The assumption of normality was met, as assessed by visual review of the Q-Q Plot.

Given the small sample size, demographic variable were not included within this analysis. Time 1 GEC t-score was added to model 1 and was found to be statistically significant, $R2 = .58$, $F_{(1, 27)} = 36.45$, $p<.001$; adjusted $R2 = .57$. The addition of adherence to medications for anemia to model 2 did not lead to a statistically significant increase in R2 of .01, $(F_{(2, 27)} = 18.05$, $p<.001$, adjusted $R^2 = .59)$. Lastly, the addition of bedside GFR within model 3 did not lead to a statistically significant change in the variance accounted for with R2 = .00 $(F_{(3, 27)} = 11.78$, $p<.001$, adjusted $R^2 = .55)$. See table 14 for full details.

Table 13

Means, Standard Deviations, and Intercorrelations for GEC From Adherence to ESAs

Variable	M	SD	1	2	3
Time 2 GEC	53.64	12.93	**0.76*****	-0.02	-0.18
Predictor Variables					
1. Time 1 GEC	55.89	11.79		0.09	-0.12
2. Adherence to ESAs	0.90	0.22			0.20
3. Bedside GFR	40.95	18.34			

Note. N = 28 *p<.05 **p< .01 ***<.001

Table 14

Hierarchical Multiple Regression Predicting Time 2 GEC from Adherence to ESAs

| | Time 2 GEC | | | | | |
| | Model 1 | | Model 2 | | Model 3 | |
Variable	B	β	B	β	B	β
Constant	6.84		10.98		12.81	
Time 1 GEC	**0.84***	**0.76***	**0.85***	**0.77***	**0.84***	**0.76***
Adherence to ESAs			-5.08	-0.09	-4.20	-0.07
Bedside GFR					-0.05	-0.07
R^2	0.58		0.59		0.60	
F	**36.45***		**18.05***		**11.78***	
ΔR^2	0.58		0.01		0.01	
ΔF	**36.45***		0.44		0.28	

Note. N= 28 *p<.05 **p< .01 ***<.001

Additionally, a second hierarchical multiple regression was conducted to determine if the addition of adherence to medications for anemia and then bedside GFR improved the prediction of Time 2 Working Memory over and above Time 1 Working Memory. Twenty-two participants met inclusion criteria and were included within the analysis. Of the 22 participants, 15 participants were males and 7 were female. There were 16 participants who identified as Caucasian, and 6 participants were identified as a racial minority, including African American, "other," and participants who identify as more than one race. The mean BASC-2 Working Memory for Time 2 was 56.36, with a standard deviation of 13.95. At Time 1, the mean parent-reported BASC-2 Working Memory t-score was 57.59 (SD = 11.46). The mean adherence rate was .93 (SD = .19). That is, participants reported taking their medication as prescribed 93% during the past 30 days. Participants within this analysis had a mean bedside GFR of 40.47 (SD = 19.12). See Table 15 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

The regression model was evaluated to determine if the data violated the assumptions of the model. There was independence of residuals as determined by the Durbin-Watson statistic (1.84). Linearity was demonstrated by visual assessment of the partial regression plots and a plot of studentized residuals against the predicted values. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by no tolerance values greater than 0.1. There were no studentized deleted residuals greater than ±3 standard deviations or values for Cook's distance above 1; however, there were 4 high leverage points ranging from 0.26 - 0.64. High leverage points are likely attributable to the small sample size, and were not removed from the analyses. The assumption of normality was met, as assessed by visual review of the Q-Q Plot.

Given the smaller sample size, demographic variable were not included within this analysis. Time 1 Working Memory t-score was added to model 1 and was found to be statistically significant, $R2 = .61$, $F_{(1, 21)} = 31.43$, $p<.001$; adjusted $R2 = .59$. The addition of adherence to medications for anemia to model 2 did not lead to a statistically significant increase in R2 of .00, ($F_{(2, 21)} = 14.99$, $p<.001$, adjusted $R^2 = .57$). Lastly, the addition of bedside GFR within model 3 did not lead to a statistically significant change in the variance accounted for with R2 = .64 ($F_{(3, 21)} = 10.60$, $p<.001$, adjusted $R^2 = .58$). See table 16 for full details.

Table 15

Means, Standard Deviations, and Intercorrelations for Working Memory From Adherence to ESAs

Variable	*M*	*SD*	1	2	3
Time 2 Working Memory	56.36	13.95	**0.78***	0.19	-0.11
Predictor Variables					
1. Time 1 Working Memory	57.59	11.46		0.28	0.07
2. Adherence to ESAs	0.93	0.19			0.14
3. Bedside GFR	40.47	19.12			

Note. N = 22 *p<.05 **p< .01 ***<.001

Table 16

Hierarchical Multiple Regression Predicting Time 2 Working Memory From Adherence to ESAs

| Variable | Time 2 Working Memory | | | | | |
| | Model 1 | | Model 2 | | Model 3 | |
	B	β	B	β	B	β
Constant	1.57		3.15		6.19	
Time 1 Working Memory	**0.95*****	**0.78*****	**0.96*****	**0.79*****	**0.97*****	**0.80*****
Adherence to ESAs			-2.39	-0.03	-0.84	-0.01
Bedside GFR					-0.12	-0.16
R^2	0.61		0.61		0.64	
F	**31.43*****		**14.99*****		**10.60*****	
ΔR^2	0.61		0.00		0.03	
ΔF	**31.43*****		0.05		1.31	

Note. N= 22 *p<.05 **p< .01 ***<.001

Lastly, a third hierarchical multiple regression was conducted to determine if the addition of adherence to medications for anemia and then bedside GFR improved the prediction of Time 2 Internalizing Problems over and above Time 1 Internalizing Problems. Thirty-four participants met inclusion criteria and were included within the analysis. Of the 34 participants, 18 participants were males and 16 were female. There were 24 participants who identified as Caucasian, and 10 participants were identified as a racial minority, including African American, Asian, "other," participants who identify as more than one race. The mean BASC-2 Internalizing Problems t-score for Time 2 was 48.21, with a standard deviation of 9.48. At Time 1, the mean parent-reported BASC-2 Internalizing Problems t-score was 50.76 ($SD = 9.18$). The mean adherence rate was .94 ($SD = .16$). That is, participants reported taking their medication as prescribed 94% during the past 30 days. Participants within this analysis had a mean bedside GFR of 41.66 ($SD = 17.41$). See Table 17 for full details on means, standard deviations, and intercorrelations between the constant and each predictor variable.

The regression model was evaluated to determine if the data violated the assumptions of the model. There was independence of residuals as determined by the Durbin-Watson statistic (2.26). Linearity was demonstrated by visual assessment of the partial regression plots and a plot of studentized residuals against the predicted values. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by no tolerance values greater than 0.10. There were no studentized deleted residuals greater than ±3.5 standard deviations or values for Cook's distance above 1; however, there were 4 high leverage points ranging from 0.23 - 0.61. High leverage points are attributed to small sample size, and were not removed from the analyses. The assumption of normality was met, as assessed by visual review of the Q-Q Plot.

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Given the smaller sample size, demographic variable were not included within this analysis. Time 1 Internalizing Problems t-score was added to model 1 and was found to be statistically significant, $R2 = .54$, $F_{(1, 32)} = 37.16$, $p<.001$; adjusted $R2 = .52$. The addition of adherence to medications for anemia to model 2 did not lead to a statistically significant increase in R2 of .00, $(F_{(2, 33)} = 18.13$, $p<.001$, adjusted $R^2 = .51$). Lastly, the addition of bedside GFR within model 3 did not lead to a statistically significant change in the variance accounted for with R2 $= .05$ $(F_{(3, 33)} = 14.04$, $p<.001$, adjusted $R^2 = .54$). See table 18 for full details.

Table 17

Means, Standard Deviations, and Intercorrelations for Internalizing Problems From Adherence to ESAs

Variable	M	SD	1	2	3
Time 2 Internalizing Problems	48.21	9.48	**0.73***	0.05	-0.13
Predictor Variables					
1. Time 1 Internalizing Problems	50.76	9.18		0.12	0.12
2. Adherence to ESAs	0.94	0.16			0.15
3. Bedside GFR	41.66	17.41			

Note. N = 34 *p<.05 **p< .01 ***<.001

Table 18

Hierarchical Multiple Regression Predicting Time 2 Internalizing Problems From Adherence to ESAs

Variable	Time 2 Internalizing Problems					
	Model 1		Model 2		Model 3	
	B	β	B	β	B	β
Constant	9.75		11.90		13.99	
Time 1 Internalizing Problems	**0.76*****	**0.73*****	**0.76*****	**0.74*****	**0.79*****	**0.76*****
Adherence to ESAs			-2.59	-0.04	-0.87	-0.02
Bedside GFR					-0.12	-0.22
R^2	0.54		0.54		0.58	
F	**37.16*****		**18.13*****		**14.04*****	
ΔR^2	0.54		0.00		0.05	
ΔF	**37.16*****		0.12		3.24	

Note. N= 34 *p<.05 **p< .01 ***<.001

Hypothesis 4: Prediction of Executive and Psychosocial Functioning by Adherence to

Medications for Anemia in Medication Non-Responders

Hierarchical multiple regressions were unable to be conducted for this hypothesis due to sample size. For each measure of EF and psychosocial functioning, only 5 participants met inclusion criteria and had scores input into the dataset for the measures of EF and psychosocial functioning.

Hypothesis 5: Prediction of Executive and Psychosocial Functioning by Adherence to

Growth Hormone

Hierarchical multiple regressions were unable to be conducted for this hypothesis due to sample size. For each measure of EF and psychosocial functioning, only 9 participants met inclusion criteria and had scores input into the dataset for the measures of EF and psychosocial functioning.

CHAPTER IV

DISCUSSION

Pediatric CKD is associated with several comorbidities and requires a complex medical regimen to manage the disease process, even within the mild to moderate stages of CKD. While research has been conducted examining the pediatric ESRD population, less research has been conducted within the mild to moderate CKD pediatric population. As such the CKiD study was developed to research pediatric patients with mild to moderate CKD, examining physical, neurocognitive, and psychosocial functioning within this population. Previous research has shown that proper management of CKD and its comorbidities can improve neurocognitive and psychosocial functioning within this population. As such, the aim of the present study was to better understand the effects of medication burden and adherence on EF and psychosocial functioning in adolescents with CKD, whom were prescribed antihypertensives, ESAs, and growth hormone.

It was hypothesized that higher medication burden would be predictive of lowered psychosocial functioning. Results supported this, in that adding medication burden to the model was predictive of Time 2 psychosocial functioning over and above demographic variables. While adding medication burden to the hierarchical regression model only accounted for 3% of the change from Time 1 to Time 2, this was a significant finding. However, it is unlikely that this finding is of clinical significance given that the mean parent-reported BASC-2 Internalizing t-score was 47.99, which is below the at-risk range. Results from the present study differ from results from Chiu et al. (2009), which did not find a significant relationship between the mental component score from the SF 36, a quality of life measure, and medication burden. It is important to note that this study was conducted among an adult population in maintenance

dialysis to treat CKD. Differences in findings may be attributable to age, disease progression, and the specific constructs measured (e.g., health related quality of life versus psychosocial functioning).

When reviewing individual scores, 12% of the participants fell in the at-risk to clinically significant range on the BASC-2 Internalizing scale. Results from this analysis align with Hooper et al.'s (2009) study, which found that parents reported more symptoms of psychological distress, even if symptoms did not reach thresholds for a clinical diagnosis. More broadly, the current study supports previous research asserting that the burden of CKD treatment is related to poorer psychosocial functioning, even during the mild to moderate stages of CKD (Zalai et al., 2012). The present study highlights the relationship specifically between medication burden and psychosocial functioning. To the best of the author's knowledge, this is the first study to examine the impact of medication burden on psychosocial functioning within the pediatric CKD population. The findings emphasize the need for continued research on the impact of medication burden on psychosocial functioning.

Further, within the present study, the Internalizing scale from the BASC-2 was utilized as the psychosocial measure. The BASC-2 reports scores as t-scores with a mean of 50 and a standard deviation of 10. The BASC-2 is also age-normed. The Internalizing scale from the BASC-2 is comprised of three subscales: Anxiety, Depression, and Somatization (Reynolds & Kamphaus, 2004). In future studies, it may be beneficial to test the predictive ability of medication burden on each individual subscale comprising the internalizing problems score. By doing this, relationships between medication burden, anxiety, depression, and somatization will be better understood. Examining the relationship between medication burden and each individual

scale was outside the scope of the present study, but should be considered an area for future research.

The findings from the current study continue to support the need for routine screening for internalizing disorders, such as depression and anxiety, within the pediatric CKD population. Routine screenings will be beneficial in identifying adolescents at-risk for internalizing disorders, aid in early identification, and help link patients and their families with appropriate mental health services (Massengill & Ferris, 2014).

It was hypothesized that higher medication burden would be predictive of lower EF. Previous studies have suggested that medications for CKD comorbidities, such as hypertension and anemia, may improve cognitive functioning; while research on other comorbidities (e.g., growth hormone) is mixed (Falleti et al., 2006; Lee et al., 2004; Pickett et al., 1999; Sink et al., 2009; Tedesco et al., 1999; van Dam et al., 2005). However, it is unknown how medication burden impacts neurocognitive functioning, specifically EF, within the mild to moderate pediatric CKD population. For the present study, it was hypothesized that an increase in the number of unique medications prescribed (medication burden) to an adolescent with CKD would be predictive of poorer EF. Studies examining the impact of medication burden on neurocognitive functioning within adult and older adult populations is largely mixed (Gnjidic et al., 2012; Hilmer et al., 2007; Kashyap et al., 2014; Sanders et al., 2017).

Results from the present study indicated that medication burden was not predictive of poor EF at Time 2 over and above demographic variables and EF at Time 1. Both analyses utilizing measures of EF, GEC and Plan/Organize scales from the BRIEF, found a lack of effect with medication burden. A possible explanation for a lack of relationship between medication burden and EF is that participants within the present study exhibited EF generally within age

appropriate ranges. This is consistent with a study conducted by Hooper et al. (2011) within the CKiD cohort, which demonstrated generally age-appropriate parent-reported ratings of EF on the BRIEF.

The BRIEF measures executive functioning through t-scores, with a mean of 50 and a standard deviation of 10. The measures yields scores that are normed for several age ranges (e.g., 5-7, 8-10, 11-13, 14-18). According to the BRIEF manual, t-scores between 60 and 65 are considered mildly elevated, and t-scores above 65 are described as clinically elevated (Gioia et al., 2000; Roth, Isquith, & Gioia, 2014). The mean score for parent-reported EF fell between 52.86 and 54.89 on the GEC and Plan/Organize scales respectively. Generally, adolescents within this group are exhibiting EF skills within an age appropriate range. While these scores represents generally intact EF, further examination of individual scores revealed that some adolescents with CKD are at continued risk for EF. Twenty-four percent of participants scored above 60 on the GEC, and 35% of the study population scored above 60 on the Plan/Organize scale. These findings also are largely consistent with Hooper et al.'s (2011) study, which found 27-40% of the CKiD sample to be at-risk for EF deficits.

A lack of statistically significant relationship between medication burden and EF also may be due to the type of medications utilized within this population. While several different classes of medications (e.g., antihypertensives, ESAs, gastrointestinal, phosphate binders, immunosuppressants) where prescribed to participants within the present study, none of the medications had anticholinergic properties. Previous research examining the impact on medication burden in pediatric populations on neurocognitive functioning have centered on medications with anticholinergic properties, and demonstrated adverse effects, such as altered mental status or changes in cognition, which may be temporary (Madden, Tasker, & Hussain,

2018). Adolescents within the CKiD cohort were not prescribed anticholinergic medications, which may account for the lack of significant findings.

It is also important to note that it is unlikely central nervous system stimulants (CNS) are contributing to a lack of effect between medication burden and EF. CNS stimulants work by stimulating the dopamine and norepinephrine systems, which produce increased arousal and alertness. CNS stimulants also suppress functioning of the locus coeruleus in turn decreasing the stimulation of the thalamic reticular nucleus, which also increases cortical arousal. Use of CNS stimulants in children with Attention Deficit/Hyperactivity Disorder has been associated with better performance on measures of EF (Littleton et al., 2015). The study population utilized in examining the relationship between medication burden and EF had low rates of CNS stimulant usage. Specifically, only 9 prescriptions for CNS stimulants were reported over Time 1 and Time 2, making up only 1% of the total medications prescribed within the study sample. Given such minimal usage of CNS stimulants, it is unlikely that CNS stimulants increased EF within the study sample, masking a relationship between medication burden and EF.

Another possible explanation for a lack of relationship between EF and medication burden may be due to improvement in physical health functioning when taking medications. While higher medication burden is typically associated with greater disease burden and severity, adherence to medication regimens could improve EF. As medications begin to take action and decrease disease burden and severity, it is possible there is an improvement in neurocognitive functioning. This may be demonstrated in the current study.

Definitions of medication burden employed in previous studies quantifies medication burden as taking 5 or more medications. The definition of medication utilized within the current study was broader, as it was defined as the number of unique medications prescribed. The mean

number of medications prescribed to participants within the present study was 4. It is possible that another reason there is no relationship between medication burden and EF is that the sample used within the present study was prescribed a lower number of medications than previous studies. This allows for potentially less adverse effects of drugs and less interaction between different drugs.

Also, antihypertensive medications were the most frequently prescribed medication across both Time 1 and Time 2, with 191 total prescriptions of antihypertensive medications reported by participants across both time points. This is 24% of all medications prescribed across Time 1 and Time 2. Previous research has demonstrated antihypertensive medications can help to improve neurocognitive functioning, which may be another reason for a lack of relationship between medication burden and EF (Sink et al., 2009; Tedesco et al., 1999). The effects of antihypertensive medications on neurocognitive functioning will be discussed further later in this paper.

The present study also aimed to better understand the predictive ability of adherence to antihypertensive medications on EF and psychosocial functioning. Children and adolescents with CKD are frequently prescribed antihypertensive medications as first-line treatment for hypertension with the most frequently prescribed types being ACE inhibitor ARBs. ACE inhibitors block enzymes from causing blood vessels to narrow, allowing blood vessels to relax and widen. ARBs work by blocking the angiotensin II hormone, which similarly allows the blood vessels to relax and widen instead of narrowing. Additionally, within CKD, ACE inhibitors and ARBs have been found to decrease levels proteinuria; therefore, aiding in slowing the progression of CKD (KDIGO, 2012c; VanDeVoorde et al., 2016).

Hypertension has been associated with decreased cognitive functioning, and previous studies have sought to understand if ACE inhibitors and ARBS have an impact on cognitive functioning. Previous research demonstrated mixed results on the association between the use of antihypertensive medications and improved neurocognitive functioning within adult populations with some studies demonstrating improvement with adherence to antihypertensive medications. Specifically, improvements were found in memory, attention, concentration, and comprehension (Sink et al., 2009; Tedesco et al., 1999). Therefore, it was hypothesized that non-adherence to antihypertensive medications would be associated with lower EF. It was thought to be particularly important to examine this relationship within the adolescent population, given that previous research demonstrated poorest adherence within the adolescent population (Kaspar et al., 2016). Results from the present study yielded a lack of effect between adherence to antihypertensive medications and EF.

It is possible that there was a lack of relationship between adherence to antihypertensive medications and EF due to high adherence to antihypertensive medications within the study sample. Participants within the present study reported taking their medications as prescribed 93%-96% over the past 30 days at Time 1. Therefore, participants were largely adherent to their antihypertensive medication regimens. This is contrary to other reports of adolescent medication adherence, which demonstrates adherence that is highly variable between 10% and 89% (Taddeo, Egedy, & Frappier, 2008). However, there was little variability in adherence among the study population.

Additionally, just as with the medication burden group, parent-reported EF within the adherence to antihypertensive group were generally within an age-appropriate range. The mean t-score for the GEC scale was 51.42, and the mean t-score for the Shift scale was 50.46. Thus

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participants had relatively intact EF abilities. Further examination of individual scores revealed 18%-20% of participants score one standard deviation above the mean on the GEC and Shift scales respectively, which means less participants within this sample are at-risk for executive dysfunction than reports from previous studies (Hooper et al., 2011). A lack of EF deficits within the study sample could have contributed to the lack of effect between adherence to antihypertensive medication and EF.

As discussed previously, some medications have properties that stimulate the CNS, and usage of CNS stimulants has been associated with better performance on measures of EF (Littleton et al., 2015). Few antihypertensive medications have centrally-acting properties, and are infrequently prescribed. One participant within the adherence to antihypertensive medications group was prescribed a centrally-acting antihypertensive medication. Parent-report of EF skills placed this participant in the clinically significant range, suggesting this participant has difficulty with EF despite taking a centrally-acting antihypertensive. The use of centrally-acting antihypertensive likely did not positively influence the EF t-scores.

In regards to psychosocial functioning, a previous study within the adult population demonstrated some improvement in psychosocial functioning after initiation of antihypertensive medications, specifically within the domains of depression, anxiety, and interpersonal relationships (Tedesco et al., 1999). It was hypothesized within the present study that non-adherence to antihypertensive medications would be related to lower psychosocial functioning. However, the present did not demonstrate an association between adherence to antihypertensive medication and psychosocial functioning, which is likely related to the high adherence rates within the study population.

Participants prescribed antihypertensive medication and included within the analysis regarding psychosocial function reported having taken their medication as prescribed 96% of the time of the past month. Again, this is generally higher adherence than found in the general adolescent population (Dean, Walters, & Hall, 2010). It is very likely that high adherence to mediation within this group contributed to the lack of relationship between adherence to antihypertensive medication and psychosocial functioning.

Additionally, just as with EF, the mean score on the BACS-2 were within age expectation. The mean score on the BASC-2 internalizing scale was 47.01. Only 8% of participants had scores that placed them within the at-risk category and no participants had scores placing them within the clinically significant range. This is generally consistent with Hooper et al. (2009), which demonstrated no clinically significant different in psychosocial functioning in CKD and typically developing children. It is possible that the combination of high adherence to antihypertensive medication and low psychosocial deficits contributed to lack of effects in this study.

The third hypothesis evaluated the predictive ability of adherence to ESAs on EF and psychosocial functioning. As a class of medications, ESAs stimulate the bone marrow to make more red blood, as those who are anemic have an inadequate amount of red blood cells (VanDeVoorde et al., 2016). Previous research in ESRD and dialysis population has demonstrated improvement in EF after treating anemia with ESAs (Pickett et al., 1999). While adult research has demonstrated such improvement, there have been no studies conducted within the pediatric CKD population to examine the relationship between ESAs and EF and psychosocial functioning.

The present study extended previous research by specifically examining the predictive ability of adherence to ESAs on EF within the pediatric mild to moderate CKD population. The results of the present study did not demonstrate a relationship between medication adherence to ESAs and parent-reported EF. As with those in the adherence to antihypertensive group, participants within this group demonstrated high adherence and little variability in adherence with a mean adherence of 90-93% over the past month. This differs slightly from adherence reported in a previous study by Akchurin et al. (2014), which found non-adherence to ESAs was approximately 4% across all study visits, meaning there is more non-adherence within the CKD sample utilized. Even still, adherence reported within the adherence to ESA group is higher than previous research on pediatric adherence rates as a whole (Dean et al., 2010). High adherence to ESAs may be due to the perceived importance of the medication. Patients and families may deem the consequence of non-adherence to ESAs to be too dangerous (e.g., drop in hemoglobin levels) to miss a dose; whereas, the consequences for missing doses of other medications (e.g., Vitamin D or growth hormone) may not be as noticeable in the short-term contributing to higher non-adherence (Akchurin et al., 2014).

Again, parent-reported EF skills fell largely within an age-appropriate range. The mean GEC scale score was 53.64 at Time 2, and the mean Working Memory scale score was 56.36. Across both scales, 21-32% of participants fell one standard deviation or above as compared to the normative population. This is generally consistent with the medication burden group and the study conducted by Hooper et al. (2011). While a majority of participants remained within an age appropriate range for EF skills, some adolescents with CKD still remain at-risk for EF deficits. Within the present study, there was no predictive relationship between adherence to

ESAs and EF abilities, which was likely not observed given that a majority of participants were adherence to their medications and fell within the age-appropriate range on measures of EF.

Previous research is mixed regarding the relationship between ESA use and increased quality of life or psychosocial functioning (Lee et al., 2004; Wolcott, Marsh, La Rue, Carr, & Nissenson, 1989). However, studies have suggested further research within this domain given that anemia has been associated with lower health-related quality of life and psychosocial functioning (Becherucci et al., 2016; Kaspar et al., 2016). The present study examined the relationship between adherence to ESAs and psychosocial functioning. There was no significant predictive relationship between these two variables.

Participants taking medication for ESAs had a mean internalizing t-score of 48.21, which demonstrated generally age-appropriate psychosocial functioning within this sample. Additionally, only 18% of the group had t-scores placing them in the at-risk or clinically significant range for an internalizing disorder. This could account for a lack of a relationship between adherence to ESAs and psychosocial functioning.

Similar to the adherence to antihypertensive group, those prescribed ESAs reported high adherence to their medication. Participants reported taking their mediations as prescribed 94% over the past month before the study. This is generally consistent with adherence reported by Akchurin et al. (2014) and adherence reported within the current study.

It should be noted that there was a small sample size employed in each of the analyses for the adherence to ESAs group. In addition to high adherence and age appropriate EF abilities, this is another potential reason for lack of effects within this hypothesis. It is likely that the sample size was not large enough and did not vary enough in adherence, EF, and psychosocial functioning to yield significant results. However, despite the small sample size, the data on

adherence, EF, and psychosocial functioning are largely consistent with data reported in the adherence to antihypertensive group.

Lastly, the present study was unable to examine the relationship between adherence in non-responders to ESAs and its impact on EF and psychosocial functioning due to small sample size. Similarly, the researcher was unable to examine the impact of adherence to growth hormone on EF and psychosocial functioning for the same reason. As the CKiD study continues to enroll participants and collect data, it will be important for researchers to examine the effects of medication non-responders on neurocognitive and psychosocial functioning. Given that research on the impact of growth hormone on neurocognitive and psychosocial functioning is mixed, it would likely be beneficial to continue research efforts within this domain.

To the best of the author's knowledge, this is the first study conducted within the pediatric CKD population to examine the relationship between medication burden and adherence with EF and psychosocial functioning. The samples from the CKiD cohort utilized within the present study appear to be largely consistent with previous research in regards to mean scores on the BRIEF and BASC-2. The study samples demonstrated generally within age-appropriate range EF and psychosocial functioning, which is consistent with previous studies (Fadrowski et al., 2006; Hooper et al., 2009; Hooper et al., 2011). Generally, the CKiD participants within the present study reported higher adherence than is generally found within the adolescent population (Dean et al., 2010). Additionally, they demonstrated higher adherence than is typically found in CKD patients (Mechta Nielsen, Frojk Juhl, Feldt-Rasmussen, & Thomsen, 2018). While a number of factors likely contributed to a lack of predictive relationship between medication burden and adherence and EF and psychosocial functioning, lack of EF and psychosocial deficits

as well as high adherence and little variability among adherence is likely highly contributing to the lack of effects observed within the present study.

Several ancillary analyses were conducted in order to better understand the study population and examine whether other factors, such as race, SES, and being amongst the lowest adherers or highest medication burden had an impact on EF and psychosocial functioning. It was deemed important to explore the impact of medication burden and adherence on EF and psychosocial functioning specifically with African American participants as they are are not only at a higher risk for kidney disease, but also demonstrate a quicker progression of kidney disease. African American children have incidence rates of CKD that are two to three times higher than that of Caucasian children (NAPRTCS, 2008). Additionally, African Americans have been found to be at greater risk of CKD comorbidities, such as cardiovascular disease and anemia. Within the pediatric CKD population, African American children receiving dialysis are amongst those at the highest risk for CVD related mortality (USRDS, 2007). Moreover, the CKiD study found that African American children had lower hemoglobin levels. Lastly, while research remains mixed on rates of adherence, some studies have found African Americans to have lower rates of adherence to medication (Oliva et al., 2013; Rolnick et al., 2013; Zhu et al., 2011).

Hierarchical multiple regressions were conducted to examine the predictive ability of medication burden on EF (BRIEF GEC, Plan/Organization) and psychosocial functioning (BASC-2 Internalizing Problems Scale). For the three analyses conducted, there were 11-22 participants included. Participants had mean EF scores falling between 52.44 to 57.36, and mean psychosocial functioning scores of 45.23 to 45.32. Participants were prescribed a mean of 4.75 to 5.18 medications and had GFRs falling between 42.28 and 48.34.

Hierarchical multiple regressions were also conducted evaluating the predictive ability of medication adherence on EF (BRIEF GEC, Shift) and psychosocial functioning (BASC-2 Internalizing Problems Scale). Nine to 18 participants were included within these analyses. Participants had mean EF scores falling between 50.89 and 54.23. The mean psychosocial functioning scores were 45.06 to 46.17. Participants across analyses of EF and psychosocial functioning reporting taking their medication as prescribed 85%-91% of the time over the past month. GFR ranged from 38.12 to 47.76. Regression models were unable to be conducted for adherence to anemia as the sample size for such regression was between 3 to 5 participants.

Overall, there was a lack of significant relationship between medication burden and adherence and EF and psychosocial functioning across all analyses. While African Americans with CKD are quicker to progress in their disease course, the participants within this particular sample had GFR ranging from 38.12 to 48.34, which is generally consistent with the study sample as a whole. Similarly, African Americans within the present study demonstrated EF and psychosocial functioning within an age appropriate range, consistent with the study sample. Additionally, they demonstrated high rates of adherence to their mediation regimen and were prescribed a similar number of mean medications as the general study population. Taken together, this likely explains the lack of significant relationship between medication burden and adherence and EF and psychosocial functioning within African American participants in the present study.

Additionally, socioeconomic status (SES) was thought to be a potential contributing factor to age-appropriate scores on measure of executive functioning as well as high adherence, contributing to a lack of relationship between medication adherence and EF. SES factors, such as income and maternal education level, have been associated with higher cognitive and

executive functioning. Indeed, a study conducted by Hackman, Gallop, Evans, and Farah (2015) found that lower income predicted worse performance on measures of working memory and planning in early childhood. Similarly, lower maternal education also predicted worse performance on measures of planning and working memory. The study also demonstrated that these disparities in EF remain stable over time. In regards to medication adherence, low SES is associated with poorer adherence; whereas, higher SES is associated with greater adherence. Therefore, it was thought that the current study population may have had higher maternal education and higher SES as compared to the country as a whole, which may explain, at least in part, high medication adherence and age-appropriate ratings on measures of EF.

Maternal education was unable to be reviewed at both Time 1 and Time 2, as this information was not collected at these visits. Income data was available for review at Time 2. The median household income bracket for the study population was $36,001 and $75,000. This was compared against the median household income across the United States (U.S.) between the years 2009 and 2013, as this was the general timeframe of when data for Time 2 was collected for participants. During the years 2009-2013, the median household income in the U.S. ranged from $50,221 - $52,250 (Noss, 2010, 2014). It is somewhat difficult to compare the median income bracket against the median income of the U.S. during the years of data collection for Time 2 given that it is unknown where a majority of participants fall (high or low end of income bracket). There is a potential that income could have contributed to high adherence and age-appropriate EF, but further research is needed to determine if income is truly having an impact in this sample. More detailed information regarding family income would likely be beneficial.

Additionally, was thought there may be potential differences in EF and psychosocial functioning between participants with the highest and lowest medication burden as well as

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between those with the highest and lowest adherence rates. As such, several t-tests were conducted to compare EF and psychosocial functioning scores of participants in the first and third quartiles of the medication burden, adherence to antihypertensives, and adherence to ESAs. Results revealed no significant differences between those in the first and third quartiles in regards to parent-reported EF and psychosocial functioning. This further suggests that EF and psychosocial across the study population fell within the age-appropriate range.

Lastly, medication burden is thought to be a factor that influences medication adherence (Fraser et al., 2015). Therefore, it was thought beneficial to understand whether or not medication burden had a relationship with medication adherence in the present study. As such, correlations were conducted to better understand if there was a significant relationship existed between medication burden and adherence to antihypertensive medication and ESAs. Correlation coefficients ranged between -2.26 to .22. Thus, the present study demonstrated a lack of relationship between medication burden and medication adherence. Future studies using the CKiD cohort may find it beneficial to instead examine the relationship between medication dosing frequency and medication adherence, as dosing frequency was found to have a significant impact on medication adherence in previous research (Blydt-Hansen et al., 2014).

Limitations

This study had several limitations. Most notably, medication adherence was assessed through self- and/or parent-report measures, and data were unavailable regarding who (i.e., caregiver/parent, adolescent, or both) was providing a response to this question. Overall, research is mixed on the accuracy of self-reported and/or parent-reported medication adherence. There are studies conducted within the adult population that support self-report as an accurate measure when compared to other methods of assessing adherence (e.g., pill counts, cap trackers, etc.).

Additionally, meta-analyses support criterion validity, comparing medication adherence to clinical outcomes, in HIV/AID when assessed in pediatric patients (children and adolescents) and caregivers. However, other studies have found that self-reported adherence can evoke social desirability, leading to a large proportion of patient reporting high to perfect adherence. Similarly, medication taking behaviors, such as being more consistent in taking medication, can occur when patients and parents know medication adherence is being monitored within a study (Stirratt et al., 2015).

Further, adherence research within the pediatric population raises concern for parents over reporting or inflating adherence to medication; therefore, parent report of medication adherence should likely not be the only means of measuring adherence within pediatric studies (Dean et al., 2010). It is possible that in cases where parents were the reporters of medication adherence, reports may have been inaccurate depending on the level of independence the adolescent had in taking medications as prescribed. That is, when answering medication adherence questions during study visits, parents may have inflated, over-estimated, or provided inaccurate adherence if they were not involved in medication taking behaviors on a daily basis (Dean et al., 2010; Matsui, 2007). In the present study, it is difficult to determine if this occurred or how frequently this occurred across medication adherence reports. This is because no data were available on parental involvement in medication taking behaviors (e.g., relying on parental reminders, parental support for taking medication as prescribed). Generally, research supports more accurate information on adherence when it is gathered from multiple informants within the pediatric population, including reports from the child or adolescent and parents (Taddeo et al., 2008). In future studies, it would be beneficial to gather information regarding medication

adherence from multiple sources, including the adolescent, parent, and objective measures of medication adherence.

It should be noted that medication adherence was only assessed at Time 1. However, literature on medication adherence within the adult population has found that adherence does not increase overtime; nor does adherence increase with age (Stirratt et al., 2015). It is unlikely that adherence within study population changed from Time 1 to Time 2. Pediatric adherence research tends to show that adherence levels are lowest during adolescence, especially for adolescents who are assuming full responsibility for medication taking behaviors (Matsui, 2007).

Reported adherence to medication was higher than what is typically reported within research on medication adherence and there was little variability in reported adherence, which likely contributed to the lack of effect within the present study. Participants within the current study reported adhering to their medication regimen 90% to 96% percent of the time. It is estimated that medication adherence within the adolescent population is highly variable with rates between 10% and 89% (Taddeo et al., 2008). Moreover, medication non-adherence rates within the CKD population are also variable with reports of non-adherence between 17% and 74% (Mechta Nielsen et al., 2018). As previously stated, the rate of adherence to ESAs found within this study is generally consistent with rate of adherence to ESAs within the CKiD cohort as reported by Blydt-Hansen et al. (2014). While high rates of adherence may be related to inflated parental reporting of medication adherence, it is also important to consider that high adherence within the current study could be related to the type of research participants that choose to enroll and maintain participation in medication adherence studies. Dean et al. (2010) reported that those who are non-adherent to medication are unlikely to participate and/or continue to participate within medication adherence research. Therefore, studies on medication

adherence tend to not be generalizable to those who are non-adherent to medication. In a prospective cohort, such as the CKiD cohort, requiring several follow-up visits over multiple years, it is possible that those with high adherence to treatment and medical regimens are the participants that continuously completed study visits.

The relationship between medication burden and adherence and EF and psychosocial functioning has the potential to be bidirectional. It is possible that poorer adherence can influence poorer EF, but it is also possible that poorer EF results in poorer adherence. It was outside the scope of the present study to examine whether or not a bidirectional relationship exists between medication burden/adherence and EF and psychosocial functioning. Additionally, a third factor, such as daily pill burden may be impacting this relationship as well, and again, was not accounted for within the present study. However, this is an important area for future research as dosing and daily pill burden have been found to be associated with medication adherence and burden (Blydt-Hansen et al., 2014; Chiu et al., 2009).

Similarly, measuring medication burden within the present study did not account for different dosing schedules; therefore assuming burden of each medication to be equal. However, dosing is not equal as some medication were taken more frequently (e.g., phosphate binders) and some less frequently (e.g., ESAs). The burden of medications may vary based on dosing (Blydt-Hansen et al. (2014). Again, this calls for future research to take into account dosing frequencies and daily pill burden as a potential variables influencing EF and psychosocial functioning. This is further discussed in the future research section.

The present study utilized parent-report measures for EF and psychosocial functioning as well. Performance-based measures of EF (e.g., DKEFS) were unable to be incorporated into analyses due to missing data. As such, EF was only assessed through parent-report measures.

While it is typically preferred to use an objective measure or a combination of objective and parent-report measures, the clinical utility of the DKEFS, the only objective measure of EF included in the CKiD study, has been questioned. Given that the DKEFS is a newer measure of EF, continued research is needed to ensure sound psychometric properties and that it is a superior measure to older, more well-established measures of EF (Crawford, Sutherland, & Garthwaite, 2008; Keifer & Tranel, 2013; Lezak, Howieson, Bigler, & Tranel, 2012; Strauss, Sherman, & Spreen, 2006). It is also important to note that parent-report measures of EF may be influenced by parental frustration, and are likely a better measurement of day-to-day EF. Day-to-day EF represents applying EF skills into real life scenarios rather than simply a measurement of individual EF abilities (Gross, Deling, Wozniak, & Boys, 2015).

In addition to utilizing a parent-report measure to examine EF, a parent-report measure (BASC-2) was also used to assess psychosocial functioning. It should be noted that research on the accuracy of parent-report measures is generally mixed. As stated above, parent-report measures can be influenced by parental frustration with a child's behavior; therefore, portraying a child as more impaired than they are. Contrary to this, parent-reports can also positively bias results, making a child appear to have less EF or psychosocial deficits than they do (Gross et al., 2015; Hooper et al., 2011). Within the present study, it is possible parental biased influenced results on both EF and psychosocial measures.

Data were not available on how long adolescents had been prescribed medication. Therefore, the present study was unable to account for length of time on medication as a possible interaction between predictor variables (e.g., medication burden, medication adherence) and outcome variables (i.e., EF, psychosocial functioning). While the present study was unable to examine the possible interaction, previous research within the adult population has found that

length of time on medication is not associated with better adherence to medication so it is unlikely that length of time on medication would lead to a significant change in adherence over time (Stirratt et al., 2015). However, the present study is not able to account for the impact of length of time on medication on neurocognitive and psychosocial functioning.

The present study had a narrow focus, particularly within the medication adherence. These hypotheses were aimed at examining the relationship between medication adherence to antihypertensive medications and ESAs. The aim was to examine the impact of medication adherence specifically with adolescents with CKD being treated for common comorbidities within CKD: hypertension and anemia. The present study did not find an association between medication adherence to antihypertensives and ESAs with EF and psychosocial functioning, likely attributable to relatively age-appropriate EF and psychosocial skills as well as high adherence to medication among the study participants. However, it remains beneficial in future research to broaden the investigation to examining the relationship between adherence to any medication used to treat CKD and EF and psychosocial functioning.

Future Research

As previously stated, future research should begin to parse out the different aspects of psychosocial functioning (e.g., anxiety, depression, social support, etc.) to better understand the relationship between medication burden and differing aspects of psychosocial functioning. This will provide richer information on the internalizing problems for which children and adolescents with CKD are at-risk. This will likely have an impact on clinical practice and routine screenings performed within pediatric CKD population.

Further, the present study focused on the relationship between medication burden and adherence on psychosocial functioning, specifically internalizing symptoms (i.e., anxiety,

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depression, and somatization) utilizing the BASC-2. Future research may be beneficial on examining the relationship between medication burden and adherence on health-related quality of life (HRQOL) using a measure such as the PEDsQL 4.0 (Varni, Seid, & Kurtin, 2001). Whereas psychosocial functioning is a measure of emotional, behavioral, and social functioning, HRQOL is a measure of the impact of a disease on a child's functioning physically, mentally, and socially. This can include factors such as health and activities as well as school and work functioning, which are not accounted for by the BASC-2. Research has demonstrated lower HRQOL within the pediatric CKD population across physical, social, emotional, and school domains, warranting a need for further investigation into what may impact HRQOL of life within this population (Gerson et al., 2010). Examining the relationship between HRQOL and medication burden and adherence, may provide researchers and clinicians not only with information regarding the impact of medication burden and adherence on emotional and social functioning, but provide a broader their impact on physical and school functioning as well.

The current study focused the ability of medication burden to predict EF and psychosocial functioning, while other recent studies have also begun to examine the relationship between pill burden and psychosocial functioning. There is an important distinction between medication and pill burden, in that medication burden is typically defined as the number of unique medications prescribed on a daily basis. Whereas, pill burden is often defined as the total number of pills taken per day and this begins to account for dosing burden (Chiu et al., 2009). It is possible that pill burden may have an impact on psychosocial functioning, given the findings of the present study in combination with findings from Blydt-Hansen et al. (2014) research asserting that pill burden and dosing frequency has an impact on medication adherence. Future research within the pediatric CKD population should explore the relationship between pill

burden and psychosocial functioning, while taking into account different classes of medications as a possible interaction within the relationship. Moreover, it would likely be beneficial for future studies to examine both medication and pill burden within the same study, especially within the pediatric CKD population.

It would be beneficial for future research to utilize multiple methods of assessing medication adherence, given the potential bias and inflation when relying on self- and parent-reported medication adherence alone. It is important to highlight that previous research suggests there is no "gold standard" for measuring medication adherence (Stirratt et al., 2015; Taddeo et al., 2008). Medication adherence can be assessed through direct and/or indirect methods. Self- and parent-report measures fall into the category of indirect methods. Other forms of indirect measurement include utilizing open-ended questions to gather information about medication taking behaviors, history of adherence, and barriers to adherence. There are several self-report questionnaires that can used to measure adherence in addition to verbal self-report. However, self-report questionnaires carry similar propensity of overestimating adherence as verbal self-reports, and validity and reliability of these such measures has not been well established (Stirratt et al., 2015; Taddeo et al., 2008).

Direct methods of assessing adherence should be considered as well. Such methods include pill counts and electronic monitoring devices. However, such measurements are thought to add limited value. Direct methods of assessing adherence can also include using blood levels or other clinical data for disease control. For example, within pediatric patient with CKD, iron and hemoglobin levels can be utilized in assessing adherence. Similarly, blood pressure monitoring can be used to assess adherence to antihypertensive medications. Pitfalls with assessing medication through only direct measures remain. Direct measure such as assessing

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disease control may reflect only recent medication adherence or may be reflective of non-response to therapy. Taddeo et al. (2008) also cautions that direct measures of medication adherence can rupture rapport between medical care providers and adolescents that is critical for compliance. Taken together, it may be beneficial for future research to use a combination of indirect and direct methods for assessing medication adherence. While there is no gold standard for assessing medication adherence, studies generally support utilizing multiple methods and multiple informants (Dean et al., 2010; Taddeo et al., 2008).

Conclusion

The aim of the present study was to better understand the effects of medication burden and adherence on EF and psychosocial functioning in adolescents with CKD, whom were prescribed antihypertensives, ESAs, and growth hormone. Results suggest that higher medication burden is predictive of poorer psychosocial functioning. However, increasing medication burden explained only 3% of the change in psychosocial functioning, which is likely not clinically significant. Nonetheless, this finding highlights the need for routine screening for internalizing disorders within the pediatric CKD population. Conversely, medication burden was not predictive of EF. This is likely attributable to parent-reported EF abilities falling within age-appropriate ranges. Similarly, adherence to antihypertensives and ESAs did not demonstrate a significant effect with EF and psychosocial functioning. This lack of effect is likely due to a combination of high adherence to medication with little variability among reported adherence and parent-reported EF falling within age-appropriate ranges. It is possible there was too little variability in adherence to truly examine the impact of medication adherence on EF and psychosocial functioning within the present study. Future research should continue to examine the relationship between medication burden and psychosocial functioning, specifically

investigating the relationship between medication burden and the internalizing scales on the

BASC-2. It would likely also be beneficial for future research to investigate the relationship

between pill burden and dosing frequencies on psychosocial functioning as well.

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