Comorbid ADHD and Pediatric Sickle Cell Disease: Prevalence and Risk Factors

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ACKNOWLEDGMENTS

I would like to thank all of the youth and caregivers that participated in my research study, as well as all the committed staff, physicians, and nurses at the Center for Cancer and Blood Disorders at Prisma Health Children’s Hospital. I would also like to thank my mentor, Dr. Jeffrey Schatz, who has provided invaluable support and guidance not only in the completion of my dissertation but throughout my time in graduate school. In addition, I would like to thank Julia Johnston, Sreya Varanasi, and Mary Quattlebaum for their support and assistance with the completion of my study. Finally, I would like to thank my family, Elizabeth, Steven, and Joseph Bills, and my partner Ben Onnink, for their constant support and encouragement throughout the years.
ABSTRACT

Objective: Sickle cell disease (SCD) is a genetic blood condition that places youth at increased risk for deficits in attention and executive functioning suggestive of increased rates of Attention Deficit/Hyperactivity Disorder (ADHD). There is pronounced inconsistency in reported prevalence rates for attention deficits and ADHD diagnoses among youth with SCD, which is due in part to variability in methodology of previous studies. The primary aim of the present study is to use systematic screening to identify the prevalence of inattentive ADHD symptoms and ADHD diagnoses in a pediatric SCD population seen at a large hematology clinic. A secondary aim is to explore medical and social-environmental predictors of inattentive ADHD symptoms and ADHD diagnoses. Methods: One hundred and seven children with SCD (ages 7-11 years) completed a psychosocial screening at the Center for Cancer and Blood Disorders (CCBD) at Prisma Health Children’s Hospital in Columbia, South Carolina during a routine clinic appointment. Inattentive symptoms were assessed using the Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviors (SWAN) rating scale, a parent report scale of symptoms of inattention typically associated with ADHD. Follow up diagnostic procedures were completed for participants with positive screenings on the SWAN rating scale to determine if full inclusion and exclusion criteria for Predominantly Inattentive and Combined subtypes of ADHD (ADHD-I/C) were met.
Information on indicators of disease severity (i.e., genotype, history of cerebrovascular
disease) and social-environmental factors were collected through parent report and
medical chart review.

Results: The prevalence rate of clinically elevated inattentive symptoms in the current
sample (26%) was significantly greater than that observed in a large sample of school age
youth (5.3%; $X^2 = 92.86, p < .001, w = .93$). Additionally, the prevalence rate of ADHD-I/C diagnoses in the current sample (13.1%) was significantly greater than that reported
in the general population of Black youth in the United States (5.5%; $X^2 = 11.82, p = .001,
w = .33$). Indicators of disease severity (i.e., genotype, history of cerebrovascular
disease) did not predict inattentive symptoms or formal ADHD diagnoses. However,
elevated family distress/dysfunction did significantly predict SWAN inattentive
symptoms, $B = .23, t(104) = 2.39, p = .019, R^2 = .052$.

Conclusions: Children with SCD evidenced elevated rates of inattentive symptoms and
formal ADHD diagnoses, indicating increased risk for neurodevelopmental concerns.
These findings highlight the importance of systematic screening and subsequent
interventions for neurodevelopmental difficulties within the pediatric SCD population.
Indicators of disease severity did not predict inattentive symptoms or formal ADHD-I/C
diagnoses, suggesting that established medical predictors of neurocognitive deficits in
pediatric SCD may not translate to symptoms of neurodevelopmental disorders such as
ADHD. Family distress and dysfunction did significantly predict elevated inattentive
symptoms, indicating that parent and family factors may have a greater impact on the
presentation of ADHD in pediatric SCD. Future studies are needed to further examine
biopsychosocial predictors of neurodevelopmental conditions such as ADHD in pediatric SCD.
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CHAPTER 1

INTRODUCTION

Sickle cell disease (SCD) is a genetic blood condition that in the United States predominantly affects those with African ancestry (Barbarin & Christian, 1999; Edwards et al., 2005). Children born with SCD have biomedical and psychosocial risk factors that increase the risk for deficits in attentional abilities and executive functions. Decades of research exploring the impact of SCD on cognitive functions in youth have consistently found that attentional abilities and executive functions are particularly vulnerable to SCD-related disease mechanisms (Berg et al., 2012; Berkelhammer et al., 2007; Hjimans et al., 2010). The increased risk for deficits in these cognitive domains is suggestive of increased rates of Attention Deficit/Hyperactivity Disorder (ADHD) in this population, for which impairments in attention and executive functioning are hallmark features. However, despite suggestions in the literature of an increased prevalence of ADHD in youth with SCD there is minimal research substantiating this association.

Differences in methods and methodological quality have led to reported prevalence rates for attention deficits that vary from 8 to 40 percent, often with inferences that these attention deficits signify high rates of ADHD (Acquazzino et al., 2017; Benton et al., 2011; Boulet et al., 2010; Hood et al., 2020; Jerrell et al., 2011; Lance et al., 2015). Current diagnostic criteria for ADHD not only require behavioral symptoms of inattention and/or hyperactive-impulsive behavior, but also exclusion criteria related to
ruling out other potential causes of these symptoms (American Psychiatric Association, 2013). Research using formal diagnostic criteria, to date, has largely relied on pre-existing ADHD diagnoses without consideration of the lack of systematic screening or assessment for neurodevelopmental conditions in SCD in most clinic settings (Boulet et al., 2010; Jerrell et al., 2011; Lance et al., 2015). In addition, due to historic inequities, many children with SCD attend under-resourced schools that are more likely to fail to identify neurodevelopmental conditions and allocate special education services among minority students (Burchinal et al., 2021; Morgan et al., 2017). This literature has also focused almost exclusively on biomedical risks from SCD and has neglected the examination of social-environmental predictors of ADHD symptomatology in this population (Prussien et al., 2020; Yarboi et al., 2017). The overall goal of this dissertation is to use systematic screening to identify the prevalence of inattentive ADHD symptoms and ADHD diagnoses that include inattentive diagnostic criteria (i.e., ADHD-I, ADHD-C) among children and adolescents with SCD and to provide greater insight into medical and social-environmental risk factors for youth with SCD through systematic screening. The current study will directly assess for ADHD criteria, rather than relying on pre-existing diagnoses, and will integrate biological and social-environmental risk factors into predictive models.

**Sickle Cell Disease and Attention Deficit/Hyperactivity Disorder in Youth**

Sickle cell disease (SCD) is a complex genetic disorder associated with the potential for multiple medical complications that affects approximately 1 of every 365 children of African descent born in the United States (Barbarin & Christian, 1999; Edwards et al., 2005). The high-risk genotypes of SCD (e.g., HbSS, HbSβ0) account for
approximately 65% of patients and are associated with more severe complications, while lower risk genotypes (e.g., HbSC, HbSβ+) typically experience milder symptoms. SCD is marked by the production of abnormal hemoglobin, which causes the red blood cells to assume a sickled shape that reduces their ability to efficiently distribute oxygen throughout the body (National Heart, Lung and Blood Institute, 2014). Children with SCD are at increased risk for neurologic injury due to restricted oxygen delivery to the brain from an overall deficiency in red blood cells (i.e., anemia) and the occlusion of arteries delivering blood and oxygen to the brain (i.e., vaso-occlusion; Verduzco & Nathan, 2009). The occlusion of blood vessels in the brain, otherwise known as cerebral infarction, represents the largest risk to neurologic functioning among children with SCD. However, co-occurring medical conditions that exacerbate the pathophysiologcal underpinnings of vasculopathy in SCD can also elevate risk for early brain injury. Collectively, the various routes by which vasculopathy impacts the brain in individuals with SCD leads to a high rate of mild-to-moderate behavioral, cognitive, and academic deficits that impact everyday behavior (Berkelhammer et al., 2007; Debaun et al., 2012).

The impact of SCD on development, specifically cognitive and behavioral functioning, shares many characteristics associated with the broader category of neurodevelopmental disorders; however, the most notable overlaps in symptomatology are with a specific neurodevelopmental disorder, Attention Deficit/Hyperactivity Disorder (ADHD). The commonly observed deficits in attention and executive functions in pediatric SCD resulting from both acute (i.e., cerebral infarction) and diffuse neurologic injury mirror the core inattentive symptoms of ADHD. ADHD is a common neurodevelopmental condition that is typically first identified in early to middle
childhood, with symptoms most commonly presenting in preschool (Wilms Floet et al., 2010). The median age of ADHD diagnosis has been reported as seven years old, with approximately three out of four children diagnosed before the age of nine (Visser et al., 2015). ADHD is characterized by disruptions in brain development that manifest as impairments in attentional abilities and behavioral control and is estimated to impact 5% of children in the general population worldwide (American Psychiatric Association, 2013; Boulet et al., 2010; Collins & Cleary, 2016; Fairman et al., 2020; Wilms Floet et al., 2010). The most recent United States population-based estimate of ADHD among youth 3 to 17 years old from the National Health Interview Survey found an overall prevalence rate of 6.0% (Zablotsky & Alford, 2020), with an upward trend in ADHD diagnosis rates for White and minority youth over the last decade (Collins & Cleary, 2016; Fairman et al., 2020; Xu et al., 2018). However, there are concerns that this increase in prevalence rates may reflect methodological characteristics of studies rather than an increased rate of the disorder (Polancyzk et al., 2014).

There are three major subtypes of ADHD which include predominantly inattentive presentation (ADHD-I), predominantly hyperactive/impulsive presentation (ADHD-HI), and combined inattentive and hyperactive/impulsive presentation (ADHD-C) in which criteria are met for both the inattentive and hyperactive/impulsive presentations (American Psychiatric Association, 2013). ADHD-I is estimated to be the most common subtype and accounts for the largest proportion of school age youth when compared to ADHD-HI and ADHD-C subtypes (Willcutt, 2012). There is continued debate regarding subtype classifications. For instance, ADHD-HI subtype has been shown to be less consistent over time, leading researchers to postulate that the ADHD-HI
subtype may be best conceptualized as a milder form of the combined subtype (Lahey et al., 2005). Additionally, there is research suggesting less pronounced subtype differences among younger youth (e.g., 6-10yo) in comparison to youth ages 11-17, suggesting that the presentation of ADHD may differ based on developmental stage (Nikolas & Nigg, 2013).

Furthermore, there are pronounced sex differences in prevalence rates of ADHD subtypes. Among youth, ADHD is more commonly diagnosed in males, with estimates suggesting a male to female ratio of 3:1 in the general population (Wilcutt, 2012). However, as females are more likely to present with predominantly inattentive symptoms which are often less disruptive in structured environments such as school, there are concerns that these sex differences may partially reflect the underdiagnosis of ADHD-I in females (Mowlem et al., 2019).

Symptoms of ADHD include age-inappropriate behaviors in the domains of inattention, impulsivity, overactivity, and disorganization, which reflect deficits in higher order cognitive functions, or executive functions, that are important for goal-directed behavior and planning. Although these deficits in executive functions are characterized as behavioral level phenomena and are typically assessed at the behavioral level, they are thought to be mediated by brain abnormalities. Imaging studies have identified both structural and functional brain alterations in youth with ADHD that are thought to underly dysfunctional behaviors (Friedman & Rapoport, 2015; Rubia et al., 2014; Vaidya, 2011). Structural brain changes include decreased gray and white matter volumes in the frontal lobe and associated brain regions, altered growth trajectories of brain regions across time, and cortical thinning (Rubia et al., 2014). Disruptions are also
observed using functional imaging techniques that examine the activation of brain regions involved in executive functions, attention, and reward processing (Friedman & Rapoport, 2015; Vaidya, 2011).

These findings suggest that alterations in brain development are central to symptom presentation in ADHD. However, the precise causes of such alterations are unknown. Research on prenatal risk factors for ADHD has highlighted the dynamic interplay between biological (e.g., genetic determinants) and environmental factors (e.g., prenatal exposures) and their subsequent impact on brain development. Indeed, much of the research on risk factors for ADHD has focused on these prenatal influences. However, there are a number of salient postnatal biological and social-environmental risk factors for the development of ADHD symptoms that warrant discussion. Within the SCD population specifically, postnatal cerebrovascular complications represent a particularly relevant biological risk factor for the development of symptoms of ADHD, namely attention deficits. Cerebrovascular complications in youth with SCD that may potentially contribute to attention deficits include cerebral infarction, diffuse pathophysiological complications, and medical comorbidities.

Cerebrovascular Complications in Pediatric SCD

Cerebral Infarction

Cerebral infarction, often referred to as stroke, is one of the most concerning cerebrovascular complications of SCD. There are two primary presentations of cerebral infarction in the SCD population which include overt stroke and silent cerebral infarction (SCI). Overt strokes are most commonly identified by accompanying physical symptoms (e.g., hemiparesis) and typically affect larger blood vessels in the brain (Sundd et al.,
Risk for overt stroke peaks between two and ten years of age and is most common among high risk-genotypes (Ohene-Frempong et al., 1998). Children with SCD are at significantly increased risk for overt stroke when compared to the general population, with approximately 10% of youth with more severe SCD genotypes experiencing an overt stroke before the age of 20 if no preventative treatment is available (Bernaudin et al., 2011; Powars et al., 1978). In comparison, stroke risk in the general population is estimated to fall between 1.2 to 13 cases per 100,000 children (Tsze & Valente, 2011). This represents approximately a 100-fold risk of developing stroke when compared to children without SCD (Earley, et al., 1998).

Silent cerebral infarction lacks observable behavioral symptoms and is the most common form of neurologic complication for children with SCD. SCI is typically the result of occlusion in smaller blood vessels in areas of the brain with decreased blood flow (Bernaudin et al., 2011; Pegelow et al., 2001). In many cases the occurrence of SCI may go undetected given the lack of the outward symptoms typically associated with stroke (e.g., seizure, hemiparesis). As such, the detection of SCI is largely contingent on brain imaging techniques such as magnetic resonance imaging (MRI). Risk for SCI is present early in development and, similar to overt stroke, is highest for children diagnosed with more severe sickle cell genotypes (i.e., HbSS; Miller et al., 2001). Indeed, one study that implemented MRI screenings in infants and toddlers with high-risk genotypes found evidence of SCI in 13% of participants by 13.7 months of age (Wang et al., 2008). Risk for SCI continues throughout childhood, and it is estimated that SCI occurs in 37% of children with SCD before the age of 14 years (Bernaudin et al., 2011). Furthermore, SCIs are a risk factor for the occurrence of later overt strokes, with studies
finding a 14-fold increase in risk for overt stroke among children with a prior SCI (Kugler et al., 1993; Miller et al., 2001).

Both overt strokes and SCIs are most common in the frontal areas of the brain, with the second most common region being the parietal lobe (Ford et al., 2018; Moser et al., 1996; Pegelow et al., 2002). In one study of 55 children with SCD with one or more cerebral infarction, 78% had a frontal infarct and 51% had a parietal lobe infarct (Moser et al., 1996). Overt strokes commonly involve both cortex and deep white matter tissue and are caused by the occlusion of major vessels responsible for blood delivery in the brain, with the anterior and middle cerebral arteries most often involved (Pegelow et al., 2002). In comparison, SCIs are typically confined to deep white matter regions, are smaller in size than overt strokes, and occur in brain regions at the terminal ends of the vascular supply (Ford et al., 2018; Pegelow et al., 2002).

Although prevalence rates of cerebral infarction among youth with SCD are markedly higher than the general population, these numbers represent a notable improvement from previous decades (Adams et al., 1998; Fullerton et al., 2004). This has been largely attributed to the implementation of routine screenings for neurologic risk for pediatric SCD patients and developments in preventative medical treatments for cerebrovascular disease in SCD. Current screening guidelines recommend that SCD patients receive transcranial doppler (TCD) screenings annually to monitor for changes in cerebral blood flow velocity, which is a precursor of later stroke (Adams et al., 1998). TCD is able to predict approximately 90% of children who would have a stroke in the next three years (Adams et al., 1992). Although TCD screenings are useful for identifying children at increased risk for acute stroke, research indicates TCD is less
reliable as a predictor of SCI when compared to its ability to predict overt stroke (Bernaudin et al., 2011; Pegelow et al., 2001; Wang et al., 2000). Chronic transfusion therapy and hydroxyurea are the current standards of care for primary and secondary stroke prevention (i.e., prevention of initial and subsequent strokes, respectively) and work by reducing the number of sickled blood cells (Verduzco & Nathan, 2009). Chronic transfusion therapy can prevent approximately 90% of strokes from occurring in those with positive TCD exams (Adams et al., 1998). Although hydroxyurea has been less studied, it is also effective for primary stroke prevention and is particularly useful in cases when chronic transfusion therapy is contraindicated or unavailable (Gulbis et al., 2005). Nonetheless, an increased risk for later strokes is present even for children receiving chronic blood transfusion therapy or hydroxyurea (Hulbert et al., 2011).

**Diffuse Pathophysiological Mechanisms**

Although overt stroke and SCI are the most commonly researched cerebrovascular complications in pediatric SCD, vasculopathy can be present in the absence of cerebral infarction. Children with SCD evidence abnormalities in brain imaging suggestive of more diffuse injury to the brain (Baldeweg et al., 2006). For instance, volumetric changes have been observed in the absence of visible infarcts, providing evidence that the presence of brain insults alone may not reflect total brain injury (Baldeweg et al., 2006; Schatz & Buzan, 2006; Steen et al., 2005). These volumetric changes have been attributed to generalized atrophy in both grey and white matter that increases with age, suggesting the presence of ongoing neuronal and axonal loss (Baldweg et al., 2006; Moser et al., 1996). White matter appears to be particularly susceptible, with decreased white matter volume identified in SCD patients independent
of lesions associated with silent cerebral infarction (Choi et al., 2017). However, similar to cerebral infarction, these decreases in white matter primarily occur in watershed areas in the frontal, parietal, and temporal lobes, which are the terminal areas of the large vessel supply (Choi et al., 2017). Pathophysiological mechanisms linked to these volumetric changes include chronic processes such as inflammation and hypoxemia that begin early in infancy and are thought to be precursors of later cerebral infarction (Baldweg et al., 2006). Although some of these more subtle presentations of vasculopathy can be difficult to detect using imaging techniques, they can be detected on tests of neurocognitive functioning (Chen et al., 2009; Schatz & Buzan, 2006).

**Comorbid Medical Conditions**

Youth with SCD are also at increased risk for comorbid medical conditions that can contribute to early brain injury, including obstructive sleep apnea, moyamoya syndrome, and preterm birth. Obstructive sleep apnea (OSA) is a severe form of sleep disordered breathing associated with decreased nocturnal oxygenation levels and poor sleep quality due to repeated airway obstruction during sleep (Marcus, 2001). Obstructive sleep apnea is estimated to affect 2-3% of children in the general population but has a much higher prevalence among youth with SCD (Gottlieb et al., 2003; Tauman & Gozal, 2011). Recent estimates place the prevalence rate of OSA at 41% among children with severe SCD genotypes and approximately 10-15% in children with less severe genotypes (Katz et al., 2018; Rosen et al., 2014). The high rate of comorbidity of OSA and SCD is cause for concern, particularly in light of a common pathophysiological mechanism (i.e., hypoxia). Indeed, children with both SCD and OSA are at increased
risk for impaired blood flow to the brain which is associated with poorer neurologic outcomes (Kirkham et al., 2001; Robertson et al., 1988).

Moyamoya syndrome, a relatively rare condition associated with the narrowing of blood vessels supplying blood to the brain, is estimated to occur in 20-35% of SCD patients (Moritani et al., 2004). Narrowing occurs primarily in the main branches of the internal carotid arteries, which results in the development of abnormal collateral vascular networks. The combination of SCD and moyamoya syndrome is linked to significantly increased risk for cerebrovascular injury despite compliance with treatments for stroke prevention such as chronic transfusion therapy (Dobson et al., 2002; Fullerton et al., 2003; Yang et al., 2017). Indeed, studies have identified a 5-fold increased risk for recurrent stroke among SCD patients with moyamoya syndrome as compared to those without (Dobson et al., 2002).

Preterm birth, broadly defined as birth before 37 weeks of gestation, occurs in approximately 10% of births in the general population and is the leading cause of neonatal death worldwide (Blencowe et al., 2013). In the United States, there are significant racial disparities in the incidence of preterm birth, with a twofold increased risk for preterm birth among Black women compared to White women (Dongarwar et al., 2021). Infants with SCD are at increased risk for prematurity compared to demographically matched controls (i.e., race, marital status, age, education, etc) with a 29% elevated risk for low birthweight and a 79-92% elevated risk for very low birthweight and very preterm birth (Whiteman et al., 2013). This suggests a double burden of race and disease status for infants with SCD. Preterm birth predominantly occurs during the third trimester, a critical period for brain development, which can
increase susceptibility to brain insults during infancy and childhood (Vandewouw et al., 2019). Broadly, preterm birth is associated with maturational delays in brain development during childhood and adolescence. Although many brain structures are implicated, disruptions in white matter development are most common. Longitudinal brain imaging studies have found that preterm children evidence decreased total brain volume, as well as slower maturation of specific brain regions beginning in early childhood (Batalle et al., 2017; Vandewouw et al., 2019). Despite the potential for added neurologic injury, to date there have been few studies examining the additive effect of a history of preterm birth on neurologic functioning in youth with SCD (Bills et al., 2021).

**Comorbid Medical Conditions and ADHD.**

Similar to SCD, there are related medical comorbidities associated with elevated neurologic risk that contribute to increased rates of ADHD. Medical conditions associated with alterations in brain development, such as preterm birth, pediatric traumatic brain injury (TBI), and pediatric brain tumors, are linked to increased risk for the development of ADHD symptoms. ADHD is one of most prevalent psychiatric diagnosis for children born preterm, with children born preterm more than twice as likely to meet diagnostic criteria for ADHD than the general population (Bhatta et al., 2002; Linnet et al., 2006). Attention problems are the most prevalent concern among children born preterm, with studies identifying the inattentive ADHD subtype as more common than the hyperactive/impulsive or combined subtypes (Arpino et al., 2010). Furthermore, the prevalence of ADHD appears to vary by the degree of prematurity, with higher rates of ADHD among extremely preterm children (i.e., < 28 weeks) compared to very preterm
children (i.e., 28 – 32 weeks), suggesting that the degree of medical risk plays a salient role (Taylor et al., 2000).

Symptoms of ADHD are also a frequent complication following pediatric TBI and pediatric brain tumors. The emergence of ADHD following a discrete event, such as traumatic brain injury or a brain tumor, is referred to as “secondary ADHD” to differentiate from neurodevelopmental ADHD. Attention difficulties associated with ADHD are estimated to affect 15-20% of children that have experienced a moderate or severe TBI (Levin et al., 2007) and 23-27% of survivors of pediatric brain tumors (Hardy et al., 2018). Of note, pediatric brain tumor research has primarily focused on inattentive symptoms, rather than hyperactive/impulsive symptoms, given the lack of evidence for hyperactive/impulsive symptoms among pediatric brain tumor survivors (Hardy et al., 2018). The inattentive subtype similarly predominates secondary ADHD diagnoses following pediatric TBI (Levin et al., 2007). These findings suggest that discrete brain injury may be uniquely associated with inattentive, rather than hyperactive/impulsive, symptomatology. The prevalence of ADHD varies by brain injury severity, with higher rates of ADHD among individuals with moderate to severe brain injury (Max et al., 2004; Max et al., 2005; Taylor et al., 2000). This pattern of findings suggests that the presence of medical conditions that impact brain development can lead to increased prevalence of ADHD symptoms.

**Neurocognitive and Neurodevelopmental Considerations**

Both SCD and ADHD are linked to neurologic changes that deviate from typical brain development, which can have significant implications for neurocognitive and neurodevelopmental functioning. While ADHD has been firmly categorized as a
neurodevelopmental disorder, there is less clarity regarding the categorization of cognitive and developmental impairments associated with SCD. The high rate of acute and diffuse central nervous system effects in SCD (e.g., cerebral infarction, hypoxia) early in development highlights the need for an approach that takes into account developmental factors (Armstrong, 2006; Schatz & McClellan, 2006). However, notably less attention has been given to neurodevelopmental concerns within the SCD literature, with an overall paucity of research using a neurodevelopmental lens. This can be attributed, in part, to a lack of clarity in terminology. Indeed, the terms “neurocognitive” and “neurodevelopment” are often used to describe similar phenomenon, making it difficult to differentiate their roles in the broader literature on pediatric SCD.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides the most concrete definitions of these two terms. Within the DSM-5, neurodevelopmental disorders are defined as a group of conditions manifesting early in development that are characterized by impairments across a range of functions to include personal, social, academic, or occupational domains. The DSM-5 further notes that these developmental deficits can include deficits in specific cognitive domains or more global deficits in intellectual or social functioning (American Psychiatric Association, 2013). In contrast, the DSM-5 defines neurocognitive disorders as a range of acquired, rather than developmental, conditions in which cognitive functions are the primary deficit. It notes that cognitive deficits are the core features of neurocognitive disorders and that such deficits must represent a decline from a prior level of functioning. Furthermore, the DSM-5 describes neurocognitive disorders as a unique category given that the etiology of such cognitive declines is often known and attributable to underlying pathology. For
instance, the neurocognitive disorders category is often used to diagnose cognitive
decline following diseases such as Alzheimers and was primarily developed for

Although the DSM-5 frames neurodevelopmental and neurocognitive disorders as
categorical diagnostic classes with clear separation, there is a spectrum of presentations
that fall between the two categories. This is particularly apparent within complex disease
populations, such as pediatric SCD. For example, youth with SCD can evidence
significant decrements in cognitive functions following a discrete event such as cerebral
infarction, which mirrors the core features of neurocognitive disorders. However, SCD is
also a genetic condition present from birth. Diffuse pathophysiological disease-related
mechanisms present early in development can impact cognitive processes beginning at a
young age, thereby altering developmental trajectories. Such characteristics align with
the neurodevelopmental class of disorders within the DSM-5 framework. The presence
of features of both diagnostic classes highlights the need for frameworks that
acknowledge the complexity of brain-behavior relationships in SCD and the importance
of considering the larger developmental context.

**Neurocognitive Functioning and Academic/Learning Related Challenges in
Pediatric SCD**

Elevated risk for early neurologic injury is suggestive of increased rates of
neurodevelopmental and neurocognitive disorders in pediatric SCD. However, the
majority of studies examining cognitive, behavioral, and academic functioning in
pediatric SCD have used a dimensional approach to examine abilities and skills focused
on examining the severity of symptoms rather than the presence/absence of diagnostic
criteria. This paucity of research on the diagnostic categorization of deficits further contributes to challenges differentiating between neurocognitive and neurodevelopmental disorders with this population. As such, the limited research explicitly examining ADHD symptoms and diagnoses among youth with SCD represents a recurrent omission with the pediatric SCD literature. However, the abundance of research over the past three decades on cognitive functioning in relation to history of neurologic risk in pediatric SCD provides strong evidence for increased rates of neurocognitive disorders. Furthermore, research on academic and learning challenges secondary to cognitive deficits is suggestive of increased rates of learning disabilities, another common neurodevelopmental condition, among youth with SCD.

**Neurocognitive Functioning**

Youth with SCD are at elevated risk for neurologic complications due to cerebral infarction, diffuse disease-related mechanisms of SCD, and medical co-morbidities. One of the most concerning consequences of these neurologic complications among children with SCD are neurocognitive deficits. The areas of cognition that are impacted are widespread. Children with SCD may score lower on tests of general intellectual functioning than same age peers, though the level of impairment varies by neurologic history (Berkelhammer et al., 2007). Overt strokes are associated with the most pronounced deficits, with intellectual quotient (IQ) scores generally falling in the very low (i.e., FSIQ = 70-79) range of cognitive ability (DeBaun et al., 2012; Kawadler et al., 2016). Children with a history of SCI also evidence deficits in general intellectual functioning, with IQ scores typically falling in the very low to low average range (DeBaun et al., 2012; Kawadler et al., 2016). Cognitive performance on tests of general
intellectual functioning when compared to same age peers decreases over time, with declines in function first detectable between 12 and 24 months of age (Armstrong et al., 2013; Thompson et al., 2002).

Children with SCD also evidence deficits across more specific domains of functioning. Higher order processes such as executive functioning as well as attentional processes appear to be particularly vulnerable to sickle cell related disease mechanisms (Berg et al., 2012; Berkelhammer et al., 2007; Hijmans et al., 2010). Youth with SCD evidence impairments on both verbal and nonverbal tasks of executive functioning, with the largest deficits on tasks that require greater executive control (Arfè et al., 2018). These deficits have been most commonly identified using neurocognitive testing batteries. However, more recent studies have examined attention and executive function in youth with SCD using other approaches. For instance, Downes and colleagues (2018) examined attention modulation in youth with SCD through the use of auditory event-related potentials and found deficits suggestive of poorly attuned attentional control. Youth with SCD also evidenced increased difficulties compared to matched controls on a performance-based measure of executive functioning in which children were observed performing everyday activities that task executive systems (Berg et al., 2012). These attention and executive functioning deficits have been specifically linked to the increased prevalence of cerebral infarction in the frontal regions of the brain that are responsible for higher order cognitive processes (Berkelhammer et al., 2007; Watkins et al., 1998).

Findings on impairments in other domains of cognitive functioning such as long-term memory, visuomotor functions, and language are more mixed (Brandling-Bennett et al., 2003; Hijmans et al., 2011).
While neurological insults are related to cognitive deficits, the relationship between cognitive functioning and SCD is more nuanced, as many children with SCD and no history of infarction also evidence impairments in cognitive functioning (Debaun et al., 2012; Prussien et al., 2019; Schatz et al., 2002). A recent meta-analysis by Prussien and colleagues (2019) identified moderate deficits across cognitive functions among children with SCD with no prior history of cerebral infarction, suggesting the presence of other moderators of cognitive functioning. There is evidence that more diffuse pathophysiological effects of SCD, such as volumetric changes and low hematocrit secondary to brain hypoxia, are linked to poorer performance on measures of cognitive ability (Steen et al., 1999; Steen et al., 2003). However, these indirect pathophysiological mechanisms associated with SCD do not fully account for the magnitude of observed impairments, suggesting that social-environmental factors play a contributing role (Brown et al., 1993; Prussien et al., 2020).

There is more limited research exploring the impact of medical comorbidities (i.e., OSA, preterm birth, moyamoya syndrome) on cognitive functioning. Research on comorbid OSA suggests that children with severe OSA and SCD may be at increased risk for deficits in fluid reasoning abilities; however, further studies are needed to confirm such findings (Bills et al., 2019; Hollocks et al., 2012). There is a similar paucity of research on the impact of a history of preterm birth on cognitive functioning in pediatric SCD. Schatz and colleagues (2009) found that preterm birth was associated with lower scores on tests of early child development in a sample of children with SCD. Preterm birth has been similarly identified as a risk factor for deficits in cognitive abilities in young children with SCD (Bills et al., 2021). Research on the impact of comorbid
moyamoya and SCD on neurocognitive functioning is more robust. Youth with both conditions score lower on tests of general intelligence as well as on more specific domains of functioning such as processing speed, verbal comprehension, and executive functions (Hogan et al., 2005; Williams et al., 2012).

**Academic and Learning Related Challenges**

In addition to cognitive difficulties, youth with SCD face increased academic challenges. The etiology of such difficulties is multifactorial; however, the impairments in attention and executive functioning that are common among school-age children with SCD place them at increased risk for school-related difficulties (Schatz et al., 2001). Indeed, executive functions such as sustained attention, working memory, and inhibitory control play a central role in the development of cognitive control and behavioral self-regulation, both of which facilitate learning in the classroom environment (Liew, 2012; Visu-Petra et al., 2011). To date, academic functioning among youth with SCD has been most commonly measured through the metrics of academic achievement and grade retention.

Youth with SCD frequently evidence poorer performance on tests of academic achievement in the areas of reading and mathematics compared to demographically matched peers without SCD (Schatz, 2004; Schatz et al., 2001). Although there is limited longitudinal data on academic achievement in SCD, some findings suggest that academic achievement in mathematics decreases over time in school-aged children with SCD (Wang et al., 2001). The degree of impairment in academic functioning may be correlated with the presence, severity, and location of neurologic injury; however, children without a history of infarction also experience academic difficulties (Schatz et
Indeed, one study found that 27% of youth without silent infarcts demonstrated academic challenges in reading and math (Schatz et al., 2001). Furthermore, over a 3-year period, nearly three-fourths of youth with silent infarcts experienced some degree of school difficulty compared to demographically matched peers without SCD (Schatz et al., 2001). Although these school difficulties are suggestive of specific learning disorders, diagnostic criteria have rarely been examined.

Children with SCD are also at increased risk for grade retention, with estimates indicating one-fourth and as many as one-half of youth with SCD will be retained during their time in the educational system (Epping et al., 2013; King et al., 2006). This is similar to or greater than the overall grade retention rate for Black youth in a nationally representative sample (Giano et al., 2022). Of concern, the majority of children with SCD that are retained do not receive special education services, indicating a lack of educational support for children with SCD within school systems (Epping et al., 2013; Schatz et al., 2004). Those with a history of silent cerebral infarcts are estimated to be two times more likely to be retained students compared with SCD without silent cerebral infarction (Schatz et al., 2001). Beyond cerebral infarction, age, higher rates of school absenteeism, and lower family cohesion are associated with increased risk for grade retention (Ladd et al., 2014).

**Social-Environmental Risk Factors in SCD and ADHD**

The causal link between neurologic injury and neurocognitive and academic functioning underscores the substantial role of disease-related mechanisms in children with SCD. However, children with SCD without a history of neurologic injury evidence consistent decrements in cognitive and academic functioning in comparison to peers
without a chronic health condition. Indirect pathophysiological mechanisms associated with SCD do not fully account for the magnitude of observed impairments, suggesting the etiology of cognitive impairment is multifactorial (Brown et al., 1993; Prussien et al., 2020; Schatz et al., 2002). ADHD is similarly recognized as a multi-factorial disorder that is associated with myriad pathways for risk and resilience, highlighting the importance of considering the role of larger contextual factors (Deault, 2010). The historic focus on biomedical and genetic risk factors for SCD and ADHD has often disregarded the influence of systems that extend beyond individual, disease-related characteristics. These spheres of influence include the home environment as well as broader social and economic factors. As such, it is important to consider the impact of non-medical factors, such as social and environmental influences on neurocognitive functioning.

The influence of such factors, henceforth referred to as social-environmental factors, are particularly relevant for families of youth with SCD given the prevalence of SCD within historically disadvantaged populations. Families of children with SCD in the United States are disproportionately affected by social challenges and the impacts of historical and structural racism across multiple sectors of society (e.g., housing, education, healthcare, criminal justice). This results in multiple disadvantages and social inequalities such as financial hardship, stigmatization, and discrimination, which present multiple challenges to managing their chronic disease (Hankins & Wang, 2008; Jenerett & Valrie, 2010; Robinson et al., 2014). The cumulative impact of these risk factors can be seen in increased financial insecurity, resulting from institutionalized discrimination as
well as the loss of employment opportunities due to the added burden of caring for a child with a chronic illness (Brandow et al., 2009; Smith et al., 2002).

Measures of socioeconomic status (SES) represent one of the most frequently included indicators of social-environmental risk and typically include metrics such as parental education level and household income. Socioeconomic status has been found to impact cognitive functioning of youth with SCD, with lower SES associated with poorer outcomes across a range of cognitive domains (King et al., 2014; Prussien et al., 2020). SES has also been linked to cognitive abilities such as executive functioning in the general population (Lawson et al., 2016). Indeed, studies have found a higher prevalence rate of ADHD among socially disadvantaged groups (Russell et al., 2016). A variety of variables are hypothesized to mediate this relationship between SES and ADHD including parental health, health behaviors, and parenting practices. Furthermore, for children with ADHD SES has been identified as a potential moderator of ADHD symptoms and related impairments (Cheung et al., 2015; Liu et al., 2019). These findings indicate that environmental influences related to SES have the potential to influence cognitive and behavioral outcomes in both SCD and ADHD. There are a number of benefits of employing SES metrics as proxies for social-environmental risk, such as ease of data collection and the use of more simple statistical models for social-environmental risk. However, there are also significant limitations to using such a broad and static measure of social-environmental risk, including the minimization of the multidimensional nature of social-environmental risk and difficulty translating research findings into interventions.
More recent research has included additional dimensions of social-environmental risk representative of a range of relevant psychological and social factors that can impact functioning. The literature on parent and family factors in typically developing children has clearly shown that factors such as parenting and home environment impact cognitive functioning, particularly early in development (Fay-Stammbach et al., 2014). Although limited, research within the SCD population has found that factors such as home environment, parenting style, and parent stress significantly impact cognitive functioning (Bills et al., 2020; Drazen et al., 2016; King et al., 2014; Yarboi et al., 2017). These studies note that these modifiable parent and family factors represent key targets for future intervention efforts.

The literature on parent and family factors for families of children with ADHD is more robust and has increasingly acknowledged the influence of parent and family factors, namely parenting styles and parental stress, on ADHD symptomatology. Higher levels of authoritarian parenting styles, characterized by high parental demands and low responsiveness, and low parenting satisfaction are predictors of poor outcomes among children with ADHD (Kaiser et al., 2011; Lange et al., 2005). This relationship between parenting and ADHD outcomes is bidirectional, with child ADHD symptom severity associated with ineffective and dysfunctional parenting, which is then predictive of decreased social skills and increased aggressive symptoms among children (Kaiser et al., 2011; Lange et al., 2005). Parenting can also serve as a protective factor, with positive parenting practices conveying warmth and responsiveness associated with greater peer acceptance and decreased social problems among youth with ADHD, particularly during early development (Chronis et al., 2007; Dvorsky & Langberg, 2016; Masten, 2001).
Indeed, longitudinal studies have found that this protective influence of positive parenting practices on healthy adjustment of children with ADHD exists even after controlling for numerous demographic characteristics such as socioeconomic status (Chronis et al., 2007). These findings highlight the importance of social behaviors, namely the parent-child relationship, in predicting child functioning.

Parental stress, defined as aversive psychological reactions to parent demands, is broadly elevated for parents of children with neurodevelopmental disorders (Deater-Deckard, 1998). However, parents of children with ADHD demonstrate higher elevations of stress in comparison to parents of children with other neurodevelopmental disorders (i.e., specific learning disabilities), suggesting that having a child with ADHD confers additional parental stress (Craig et al., 2016). There is an abundance of research demonstrating the association between child ADHD symptom severity and parental stress (Graziano et al., 2011; Harrison & Sofronoff, 2002; Rogers et al., 2009). Additionally, lower SES along with physical health status of children and parents are significant predictors of parental stress for parents of children with ADHD (Anastopoulos et al., 1992; Baldwin et al., 1995). As such, it is important to consider the multidimensional nature of parental stress within families of children with ADHD.

**Comorbid ADHD and Pediatric SCD**

The neurologic features resulting in increased risk for neurocognitive deficits, namely impairments in attentional abilities and executive functions, in pediatric SCD are suggestive of increased risk for the development of ADHD subtypes that include inattentive symptomatology (i.e., ADHD-I, ADHD-C). Furthermore, the documented emergence of inattentive symptoms of ADHD due to medical events such as preterm
birth and discrete brain injury indicates that ADHD risk can be modified by prenatal and postnatal events. The shared neurocognitive features, notably attentional difficulties, between ADHD and SCD have been acknowledged in prior research and have led researchers to explore the use of stimulant medication, the most common pharmacological treatment for symptoms of ADHD, to address attentional deficits in SCD (Nicholls et al., 2012). Although research is limited, early findings support the efficacy of stimulant medication for treating inattentive symptoms in children with SCD, suggesting the presence of shared neurologic features between SCD and ADHD. Despite this acknowledgement of clinical overlaps between ADHD and SCD, there is limited research establishing rates of comorbidity between these two conditions.

**Prevalence Estimates of Comorbid ADHD and Pediatric SCD**

The few studies that have investigated ADHD in pediatric SCD have reported mixed findings, with prevalence rates ranging from 8.6% to as high as 40.0% (Acquazzino et al., 2017; Benton et al., 2011; Boulet et al., 2010; Hood et al., 2020; Jerrell et al., 2011; Lance et al., 2015). The disparity in prevalence estimates is likely attributable, in part, to methodological variability between studies as well as a number of significant methodological limitations. First, the screening procedures used by three of these studies did not directly assess for ADHD symptoms, but rather recorded whether participants had received a previous diagnosis of ADHD through parent report or medical chart review (Boulet et al., 2010; Jerrell et al., 2011; Lance et al., 2015). This is methodologically concerning given research showing ADHD continues to go undiagnosed in medical settings, as providers are often not informed of parental concerns related to ADHD and are therefore unable to connect families to assessment and
treatment services for ADHD (Hood et al., 2020; Sayal et al., 2006). Indeed, a study by Hood and colleagues (2020) found a notable discrepancy in prevalence rates of elevated ADHD symptoms between medical chart review (6%) and parent-report questionnaires of ADHD symptoms (22%). Furthermore, there were differences in the scope of the samples of these studies, which included a national sample (Boulet et al., 2010), state sample (Jerrell et al., 2011), and clinic-based sample (Lance et al., 2015).

Second, the two studies that did directly measure diagnostic criteria of ADHD had relatively small sample sizes (i.e., n=51, n=40) which limits the generalizability of findings (Benton et al., 2011; Hood et al., 2020). Other limitations of these two studies include the use of a convenience sample (Benton et al., 2011) and solely including children receiving chronic transfusion therapy or hydroxyurea (Hood et al., 2020). The former further limits the generalizability of findings while the latter overrepresents children with more severe SCD complications. Limitations of the remaining studies include not providing information on clinical cutoff scores for categorizing cases and solely reporting on subgroups of children with SCD referred for full neuropsychological evaluations (Acquazzino et al., 2017; Ekinci et al., 2012). As such, although comorbidity between SCD and ADHD has been the focus of prior studies, methodological limitations highlight the need for further research.

Additionally, little is known about the medical and social-environmental risk factors for ADHD among youth with SCD. There is some evidence for medical factors, such as the receipt of chronic transfusion therapy and specific genotypes of SCD, as risk factors for ADHD symptoms (Hood et al., 2020; Lance et al., 2015). No studies to date have examined social-environmental risk factors for ADHD symptomatology within
pediatric SCD. This is concerning as both medical and social-environmental risk factors have been identified as significant predictors of cognitive functioning and neurodevelopmental delay in prior research on children with SCD. Both factors should be considered to have a more accurate view of the degree of potential influence of these factors on ADHD.

**Current Study**

Given the overlap in symptomatology between SCD and ADHD, the negative ramifications of children going undiagnosed, and mixed findings in studies conducted to date, further research is needed on the prevalence of ADHD in the pediatric SCD population. Furthermore, little is known about risk factors that might be associated with neurodevelopmental concerns in children with comorbid SCD and ADHD. This dissertation project aims to examine the rates of ADHD-I/C (i.e., ADHD-I and ADHD-C) and associated inattentive symptomatology in a clinic-based pediatric SCD population served at a single large hematology clinic through the use of a multi-tiered screening and diagnostic process. As such, the aims of the current study are to (1) determine the prevalence of clinically elevated inattentive symptoms of ADHD in a pediatric SCD population seen at a large hematology clinic, (2) examine the base rate of ADHD-I/C in a pediatric SCD population seen at a large hematology clinic, and (3) examine medical and social-environmental risk factors as predictors of clinically elevated inattentive symptoms and formal ADHD diagnoses. This study will take place in the context of a psychosocial screening program implemented at a hematology clinic in South Carolina developed to improve access to screening, evaluation, and intervention services for social and behavioral health risks.
Objectives and Hypothesis

The first objective of the proposed study is to investigate the prevalence of clinically elevated inattentive symptoms of ADHD in a clinic-based sample of pediatric SCD patients. Caregivers of children ages 7-11 years completed the inattentive scale of the Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviors (SWAN) rating scale during routine hematological visits. The SWAN is a reliable and validated screening measure assessing inattentive symptoms. *Hypothesis 1a:* Children with SCD will evidence higher rates of elevated ADHD inattentive symptoms than that observed in a large sample of school age youth as measured by total mean scores on the SWAN inattentive scale.

The second objective is to examine the base rates of ADHD-I/C in a clinic-based sample of pediatric SCD patients. Additional diagnostic assessment procedures (e.g., structured diagnostic parent interview, psychological evaluations) will be conducted for children with elevated scores on the inattentive scale of the SWAN rating scale to determine if DSM-5 inclusion and exclusion criteria for a full diagnosis of ADHD-I/C are met. *Hypothesis 2a:* Children with SCD will evidence higher prevalence rates of ADHD-I/C diagnoses than the general population of Black youth in the United States.

The third objective is to examine medical and psychosocial risk factors as predictors of clinically elevated inattentive symptoms and formal ADHD diagnoses. Medical risk factors of interest include SCD genotype (severe versus mild or moderate) and history of cerebrovascular disease as indicated by factors such as abnormal TCD results and history of stroke. Available measures of psychosocial factors such as family distress/dysfunction, family material needs, and neighborhood socioeconomic status will
also be explored. *Hypothesis 3a:* Higher risk SCD genotypes and history of cerebrovascular disease (from abnormal TCD results or history of overt stroke) will predict increased ADHD inattentive symptoms and formal ADHD-I/C diagnoses compared to those with lower risk genotypes and normal TCD results. *Hypothesis 3b:* Social-environmental factors will be associated with increased ADHD inattentive symptoms and formal ADHD-I/C diagnoses
CHAPTER 2
METHODS

Participant Selection

Data were collected from 107 youth ages 7-11 years with SCD from the Center for Cancer and Blood Disorders at Prisma Health Children’s Hospital in Columbia, SC who participated in the psychosocial screening program. Inclusion in the screening program is considered part of routine clinical care and screenings take place as part of routine hematological preventative care visits at the pediatric hematology/oncology outpatient clinic at Prisma Health Children’s Hospital. The clinic provides medical care to approximately 450 SCD patients (birth to 21 years of age) each year representing approximately 90% of all known SCD cases in the catchment area. Children with SCD at this site are scheduled for routine visits every 4 to 12 months depending on the severity of their disease.

Study Inclusion and Exclusion Criteria

Inclusion criteria for children included youth diagnosed with SCD (any genotype) between the ages of 7 years 0 months and 11 years 11 months, which is the age range when the ADHD-I/C screening questionnaire (i.e., SWAN rating scale) is included in the annual screening. This age group was selected as ADHD symptoms typically present in school-age youth and monitoring for these symptoms at routine visits is recommended by the American Academy of Pediatrics (Subcommittee on Attention-Deficit/Hyperactivity
Disorder, Steering Committee on Quality Improvement and Management, 2011).

Inclusion criteria for adults included caregivers (i.e., parents or other adult caregivers) that live in the same home as the youth. Inclusion criteria for adults also included English competency; caregivers do not complete the SWAN rating scale if they do not possess the necessary English language skills to complete the screener.

**Procedures**

Caregivers of children with SCD being seen for routine hematological visits were administered a psychosocial screening annually. The screenings are designed to implement age-specific screening and surveillance procedures recommended to address social and behavioral health (Council on Community Pediatrics, 2016; Council on Community Pediatrics & Committee on Nutrition, 2015; Lipkin et al., 2020; Siu & US Preventative Task Force, 2016; Weitzman et al., 2015; Wolraich et al., 2019). The program provides annual screening for social and behavioral health risks, with the risk factors examined dependent on the age of the child. There are distinct foci of the screening program for early childhood (2–6 years of age), middle childhood (7–11 years) and adolescence (12–17 years) based on American Academy of Pediatrics recommendations and age-specific risk factors within SCD. I was part of the team who developed the 7–11 year old screening battery and served as the primary coordinator of the program from July 2020 to April 2022. Members of the pediatric psychology team at the sickle cell clinic identified which youth scheduled for routine visits were eligible for the annual screening. The full screener is approximately five minutes in length and is administered electronically on a tablet computer through Alchemer, an online survey platform. The screener includes items to address child-specific factors (e.g., concerns or
symptoms of academic, behavioral, or emotional difficulties) and family risk factors (e.g., family functioning, social needs, social support). Scores for ADHD inattentive symptomatology and other screening measures were calculated immediately following completion of the screener to determine if scores fell above the predetermined cutoff for a positive screening. For the SWAN items, endorsement of four or more inattentive symptoms by caregivers is considered a positive screening in need of follow-up. There were specific follow-up procedures for each screening measure. Below I will focus on the follow-up procedures for inattentive symptoms of ADHD.

Participants with elevated scores on the SWAN rating scale were reviewed to determine appropriate diagnostic follow-up procedures. These procedures were intended to determine if diagnostic criteria for ADHD-I/C or other psychological conditions (e.g., specific learning disability, internalizing disorders) that might account for inattentive symptoms were met. Follow-up diagnostic procedures included: (1) a structured parent interview for ADHD symptoms (both inattentive and hyperactive/impulsive) and a structured interview to screen for academic and internalizing concerns, (2) a brief psychoeducational evaluation, or (3) a full neuropsychological evaluation. Decisions regarding appropriate follow up procedures were based on available information from participants’ medical charts and included prior psychological screenings or assessments and risk for other psychological conditions as documented in the medical record. As such, the decision of which diagnostic procedure to use as well as the total amount of testing included in brief psychoeducational or full neuropsychological testing varied based on clinical decision making. In general, semi-structured interviewing to assess parent concerns and a structured clinical interview for ADHD, depressive episode, and
anxiety disorder symptoms occurred first. If ADHD was ruled out with these procedures and the remaining clinical concerns did not warrant additional evaluation, then the assessment part of the follow-up ended. Otherwise, additional psychoeducational or neuropsychological assessment was used to clarify the diagnosis and provide recommendations for intervention. Structured parent interviews were conducted either in person or over the phone and psychoeducational and neuropsychological evaluations were conducted in-person at the clinic. When possible, in-person appointments were scheduled to coincide with routine medical visits.

**COVID-19 Precautions**

Precautions were taken to minimize risk of COVID-19 exposure for study investigators and participants. Prisma Health’s hospital wide precautions for employees and patients mandated the wearing of masks on hospital premises and social distancing when possible in waiting areas. The tablets used for the screening were sanitized before and after usage by participants. Follow-up procedures were conducted over the phone when possible (e.g., parent interviews). Multiple layers of precautions were taken for all in-person psychoeducational and neuropsychological testing. The examiner and participants wore masks at all times during testing. A plexiglass barrier was placed between the examiner and participant during testing and the assessment room was fully sanitized before and after testing sessions. Furthermore, frequent breaks were taken during testing and a HEPA air filter was run throughout testing to allow for room air circulation. If participants reported any COVID-19 symptoms, sessions were rescheduled for a later date.
Data Management

Results from annual psychosocial screenings and follow-up procedures were entered into participants’ medical records as part of their routine clinical care. Data collection through medical chart review was approved by the joint University of South Carolina/Prisma Health Institutional Review Board. Trained coders extracted relevant data from psychosocial screenings and follow-up procedures as well as relevant information on medical risk factors (e.g., genotype, history of abnormal TCD), social-environmental risk factors (e.g., neighborhood SES, insurance status), and prior diagnoses of neurodevelopmental disorders from participants’ electronic medical charts using a structured medical chart review template. Data were used from the first screening conducted if multiple annual psychosocial screenings were identified through medical chart review. The primary coder completed structured medical chart reviews for all participants. A second coder completed medical chart reviews for approximately 25% of participants (n = 31), selected at random, as a reliability check for the chart review process. There was 95.3% agreement between raters. Any discrepancies in ratings were resolved through discussion between raters and reexamining the medical chart.

Unique study identifiers were used to track participants’ data in statistical software. The study investigator had access to a confidential document linking participant numbers with identifying information. This document as well as all other data were stored on computers that are password and firewall protected. Data analysis was conducted on a password protected personal computer owned by the principal investigator.

Measures
Screening Measures

**ADHD Screening.** A 9-item version of The Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviors (SWAN) Rating Scale for ADHD was used to assess symptoms of inattention typically associated with ADHD (Swanson et al., 2012). The SWAN rating scale is unique in its dimensional approach to ADHD symptomatology and measurement of positive attentional skills in addition to attention problems. To reduce rater burden a four-point Likert scale version of the SWAN was used (i.e., “Not at all,” “Just a little,” “Quite a bit,” “Very much”) which has been shown to yield a similar distribution of scores as other validated screening tools (Swanson et al., 2012). The four-point Likert scale also typically improves inter-rater reliability for parent proxy reports of child behavior (Achenbach, 1985). Caregivers were instructed to compare their child’s behavior to peers across various settings over the past month. The SWAN rating scale has demonstrated good internal consistency and validity across samples (Brites et al., 2015; Young et al., 2009). A previous study using the SWAN rating scale identified the prevalence rate of ADHD-I as 5.3% using a large sample of youth in Australia and found high consistency for items measuring inattentive symptomatology (Young et al., 2009). This study was conducted in Australia; as such, the demographic characteristics of the sample may not be representative of the United States. Scores were calculated by summing the number of items on which caregivers endorsed a rating of “Quite a bit” or “Very much,” with total scores ranging from zero to nine. Prior studies have used a clinical cutoff score of six; however, the present study used a more liberal cutoff score of four to identify participants potentially in need of
follow-up, which would correspond to approximately the top 10% of the distribution reported from larger, non-clinical samples (Swanson et al., 2012).

**Social-Environmental Measures.** Five domains of social-environmental factors were measured, which included family functioning, family resiliency, social support, health related social needs, and proxy measures of SES. Family functioning was measured using the Brief Assessment of Family Functioning Scale (BAFFS; Mansfield et al., 2019), which is the three-item version of the General Functioning Scale of the Family Assessment Device (FAD; Byles et al., 1988). The FAD is a caregiver-report measure of structural, organizational, and transactional characteristics of families. Caregivers rate statements regarding family functioning on a four-point Likert scale ranging from “Strongly Agree” to “Strongly Disagree.” (Epstein et al., 1983). A total score for the BAFFS was calculated by summing responses on the three items. The BAFFS has demonstrated strong concurrent validity with the full 12-item version of the General Functioning Scale of the FAD and good correlations with an objective, interview-based measure of family functioning (Mansfield et al., 2019). Within the current sample, Cronbach’s alpha for the BAFFS was .54, although internal consistency scores for measures with three items are often low due to the statistical properties of Cronbach’s alpha. The General Functioning Scale of the FAD has previously been shown to be a reliable and valid scale among youth with SCD.

Family resiliency was measured with several items modified from a resiliency scale designed to measure protective factors for adverse childhood experiences (ACES). The following items were included: (1) We talk in our family about how to make our lives better; (2) We have family rules in our house and are expected to keep them; (3) We
talk in our family about the importance of doing well in school; (4) We talk in our family about the importance of being involved in our community (e.g., church, neighborhood, etc). Responses were on a 4-point Likert scale ranging from “Strongly Agree” to “Strongly Disagree.” A total family resiliency score was calculated by summing responses across the four items. Within the current sample, Cronbach’s alpha for the family resiliency items was .77, indicating acceptable internal consistency.

Social support and health-related needs were measured using the 13-item Social Support and Needs Questionnaire. Ten of the items are from the Health Leads Social Needs Screening Toolkit, which provides single item screening questions for different domains of social support (Health Leads, 2016). These 10 items measure domains such as education/health literacy, childcare, housing stability, utilities, violence exposure, financial need, and transportation. Caregivers were asked to rate the presence of social needs in these domains with either “Yes” or “No” responses. The remaining three items of the Social Support and Needs Questionnaire are from the Patient-Reported Outcomes Measurement Information System (PROMIS) and measure three domains of social support: emotional, informational, and instrumental (Hahn et al., 2010). Responses were on a five-point Likert scale ranging from “Never” to “Always.” A total social support score was calculated by summing responses across the three items. Within the current sample, Cronbach’s alpha for the three social support items was .83, indicating good internal consistency. Clinical follow-up procedures were conducted for positive screenings for concerns related to family functioning, social support, and social needs. Follow-up procedures included a referral to the medical social worker integrated into the medical clinic or connecting families to community services such as counseling.
Proxy measures of SES were collected through chart review and the annual psychosocial screening. Information on insurance status (e.g., private insurance in addition to Medicaid versus only Medicaid) and neighborhood level SES was collected through medical chart review. Data on neighborhood-level socioeconomic status was extracted by noting the census tract for each participant based on their address. This census tract was then matched to the Center for Disease Control’s Social Vulnerabilities Index (SVI). The SVI is used to classify individuals based on social vulnerabilities at the neighborhood level (e.g., poverty, education, housing data); a higher percentile score indicates higher social vulnerability (Cutter et al., 2003; Flanagan et al., 2018). Total number of phones and cars in the household was collected as part of the psychosocial screener to assess for family health communication and transportation resources. These specific measures were included as proxies for SES in the current study (Currie et al., 1997). Studies have found these single item indicators to be reliable and valid measures of family SES when used in combination with other SES indicators (Currie et al., 2008). Additionally, the total number of adults and children in the household was collected as part of the psychosocial screener.

**Emotional Functioning.** The Strengths and Difficulties Questionnaire (SDQ) is a behavioral screening questionnaire that assesses psychological adjustment of youth (Goodman et al., 1997). Three items from the parent-report version of the SDQ (i.e., “Has many fears, easily scared”; “Is often unhappy, depressed, or tearful”; “Has many worries or often seems worried”) were used to screen for internalizing concerns. Responses were on a three-point Likert scale ranging from “Not True” to “Certainly True.” The full five item version was not used because the remaining two items tap into
physical symptoms that conflate medical symptoms often found in SCD with internalizing problems.

**Follow-up Measures**

**Structured Parent Interview for ADHD and Other Disorders.** The ADHD module of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was used to conduct the ADHD follow-up interview (Sheehan et al., 1998). The MINI-KID is a parent-report structured interview consisting of diagnostic modules. The ADHD module assesses for all three ADHD subtypes and is comprised of a series of interview questions based on DSM-5 diagnostic criteria for ADHD, with a focus on severity, frequency, and duration of symptoms. A diagnosis of ADHD-I or ADHD-HI requires elevated symptoms in only one domain while a diagnosis of ADHD-C requires elevated symptoms in both domains. Screening items from the Major Depressive Episode, Social Anxiety Disorder, and Generalized Anxiety Disorder modules of the MINI-KID were used to screen for internalizing psychological disorders that may be responsible for elevated inattentive symptoms, with the full diagnostic interview completed when screening questions are endorsed. In previous studies, the MINI-KID has demonstrated satisfactory test-retest reliability ($\kappa = .66$) and validity ($\kappa = 0.42$; Duncan et al., 2018).

**School Functioning.** Surveillance questions were included in the psychosocial screening asking if the child has had any problems at school in the most recent school year and if they have accommodations at school for academic concerns. Follow-up questions were used to understand the nature of the reported school problems and to clarify if the child is receiving school accommodations through a 504 Plan or
Individualized Education Plan (IEP). In addition, for children with positive screenings for inattentive symptoms, open-ended questions on school functioning were used to screen for learning concerns and included the following items: (1) How does your child do in mathematics at school?; (2) How does your child do in reading at school?; (3) Is there a big difference between their performance in math compared to reading?; (4) Has your child ever received an evaluation or testing from the school?

**Psychological Evaluation.** Youth received a brief psychoeducational evaluation or a full neuropsychological evaluation if a recent evaluation (i.e., within 24 months of the screening) was not available and indicators of other neurodevelopmental or neurocognitive concerns beyond inattentive symptoms were present. Both psychoeducational and neuropsychological evaluations were designed to assess for non-ADHD conditions (e.g., specific learning disabilities, mild/moderate neurocognitive disorders) that may better account for inattentive symptoms. The decision as to which type of evaluation was conducted depended on the extent of indicators of other neurodevelopmental or neurocognitive concerns beyond inattentive symptoms and the presence of medical risk factors for cognitive, academic, or behavioral difficulties. Brief psychoeducational evaluations consisted of the structured parent interview for ADHD and other disorders and school functioning screening items as well as abbreviated measures of core domains of cognitive functioning (4-5 measures to assess neurocognitive functioning) and academic achievement (4 measures to assess reading and math skills). Full neuropsychological evaluations included the structured parent interview for ADHD as well as a comprehensive battery of cognitive functioning (typically 7-12 measures) and academic achievement (typically 5-6 measures). This
battery included additional measures of specific cognitive domains to include, but not limited to, memory and learning, executive functioning, and working memory. See Appendix A for sample psychoeducational and neuropsychological assessment batteries. Additional information on school functioning and academic services (e.g., current IEP) was collected when available from a participant’s school following authorization from the parent/guardian.

**Disease-Related Measures and Other Diagnoses.** Medical records were systematically reviewed to gather information on disease-related risk factors using a structured medical chart coding sheet. Information was collected on medical factors known to be associated with poor neurodevelopmental outcomes in children with SCD including genotype, preterm birth status, history of cerebral infarction, and history of abnormal TCD. Furthermore, any prior diagnoses of a neurodevelopmental disorder (e.g., ADHD, Specific Learning Disorder, Autism Spectrum Disorder) and the source of the diagnosis was recorded.

**Data Analysis**

All analyses were performed in IBM SPSS. Preliminary descriptive analyses were conducted to provide information regarding demographic and other descriptive characteristics of the sample. Bivariate correlations were run to examine the relationship between possible demographic modifiers (e.g., sex, age) and inattentive symptoms and ADHD diagnoses.

*Hypothesis 1a: Children with SCD will evidence higher rates of elevated ADHD inattentive symptoms than that observed in a large sample of school age youth as measured by total mean scores on the SWAN inattentive scale.* Chi squared goodness of
fit tests were used to compare the prevalence of elevated ADHD inattentive symptoms on the SWAN rating scale in our sample to that of the best available estimate of prevalence rates using the SWAN rating scale from a large sample of school age youth. Separate chi squared goodness of fit tests were run with the full sample and then excluding participants born preterm to examine if preterm birth status impacts findings. For purposes of this analysis, elevated ADHD inattentive symptoms was defined as scores ≥ 5 on the SWAN rating scale. A prevalence rate of 5.3% was used for this analysis, which reflects the prevalence of elevated ADHD inattentive symptoms on the SWAN rating scale in a large study of school age youth in Australia (Young et al., 2009).

Approximately 51% of the sample in this population-based study was male. As this study was conducted in Australia where indicators of race/ethnicity are frequently not collected, the precise demographic breakdown of the sample is unclear. However, given the significantly smaller percentage of Black individuals in Australia compared to the United States, there are likely notable differences in race/ethnicity. As population-based prevalence rates of ADHD inattentive symptoms using the SWAN rating scale in the United States are unavailable, this is a limitation of this analysis.

Hypothesis 2a: Children with SCD will evidence higher prevalence rates of ADHD-I/C diagnoses than the general population of Black youth in the United States.

Chi-squared goodness of fit tests were used to compare the prevalence of ADHD-I/C diagnoses to that of Black youth in the United States. Separate chi squared goodness of fit tests were run with the full sample and then excluding participants born preterm to examine if preterm birth status impacts findings. A prevalence rate of 5.5% was used for this analysis (Boulet et al., 2010; Froehlich et al., 2007). This reflects the prevalence rate
of ADHD Predominantly Inattentive and Combined subtypes among Black youth ages 8 to 15 years as measured by the National Health and Nutrition Examination Survey (Froehlich et al., 2007). This sample consisted of 3,907 children, with an oversample of minority populations. Approximately 51% of the sample was male. Data were collected through a structured diagnostic interview for ADHD symptoms administered to caregivers via phone (Froehlich et al., 2007). A prevalence rate of 5.5% also reflects the prevalence rate of all ADHD subtypes among Black youth ages two to seven in the United States as measured by the National Health Interview Survey (Boulet et al., 2010). This sample consisted of 19,335 children whose race was reported as Black or African American, with data collected through phone interviews in which a caregiver was asked: “Has a doctor or health professional ever told you that your child had ADHD.” Approximately 51% of the sample was male and approximately 47% of the sample had private insurance (Boulet et al., 2010).

Hypothesis 3a: Higher risk SCD genotypes and a history of cerebrovascular disease will predict increased ADHD inattentive symptoms and formal diagnoses compared to those with lower risk genotypes and no history of cerebrovascular disease.

Regression models were run to examine medical risk factors as predictors of ADHD inattentive symptoms and diagnoses with preterm birth and potential demographic (e.g., sex) confounders included as covariates in regression analyses. History of cerebrovascular disease included both a history of abnormal TCD results and/or a history of overt stroke. Linear regression was used to examine genotype and history of cerebrovascular disease as predictors of increased scores on the SWAN rating scale as a continuous dependent variable. Logistic regression was used to examine genotype and
history of cerebrovascular disease as predictors of ADHD-I/C diagnoses as a categorical dependent variable.

**Hypothesis 3b: Social-environmental functioning will be associated with increased ADHD inattentive symptoms and formal ADHD diagnoses.** Regression models were run to examine domains of social-environmental functioning (family distress/dysfunction, family structure/material resources, neighborhood socioeconomic status) as predictors of ADHD inattentive symptoms and diagnoses with preterm birth and potential demographic (e.g., sex) confounders included as covariates in regression analyses. Linear regression was used to examine domains of social-environmental functioning as predictors of increased scores on the SWAN rating scale as a continuous dependent variable. Logistic regression was used to examine domains of social-environmental functioning as predictors of ADHD-I/C diagnoses as a categorical dependent variable.

**Statistical Power**

Statistical power is dependent on the reliability of the measures used and the sample size. Prior studies with similar aims of exploring prevalence rates of ADHD diagnoses or clinically elevated symptoms in youth with SCD have collected sample sizes ranging from 40 to 51 participants. These studies have identified statistically elevated prevalence rates of clinically significant symptoms of ADHD. Given the variability in the prior estimates of ADHD prevalence and inattentive symptoms among youth with SCD, it is difficult to determine a specific effect size estimate. As such, a priori power analyses were run to determine the sample size needed to observe a medium effect.
Power analyses revealed a sample size of 107 is needed to detect the desired medium effect size of $f^2 = .15$ for multiple regression analyses (Cohen, 1988). For the purposes of this dissertation project, a desired effect size of $w = .35$ was selected for chi squared goodness of fit analyses. Power analyses revealed a sample size of 107 is needed to detect an effect size of $w = .35$. This translates to an ADHD prevalence rate of 13.1% required for statistically significant results, which falls within the range of ADHD prevalence rates identified in prior studies. Although an effect size of $w = .30$ is often used as a benchmark for a medium effect, an effect size of $w = .35$ still falls in the medium effect size range based on general guidelines for the social and behavioral sciences (Cohen, 1988). It is estimated that an additional six months of data collection beyond the current time allotted for the project would be needed to achieve the sample size needed to detect an effect size of $w = .30$ (i.e., $n = 145$), which translates to an ADHD prevalence rate of 11.7% required for statistically significant results.
CHAPTER 3

RESULTS

Descriptive Statistics

A total of 107 participants completed a routine psychosocial screening between June 2020 and October 2021 (see Figure 3.1). This represents 84% of all eligible participants seen for routine medical visits at the SCD clinic within the study range (ages 7 - 11 years). A participation rate of 84% is generally consistent with participation rates found in prior studies implementing systematic psychosocial screenings for youth with SCD which have ranged from 80-90% (Karlson et al., 2012; Reader et al., 2020). Of note, data collection began shortly after the onset of the COVID-19 pandemic. Forty-four participants were female (41.4%), and the mean age of participants was 9.42 years (range = 7.1 - 11.8yo, SD = 1.44). Results from descriptive analyses of key demographic and medical characteristics are shown in Table 3.1. Sixty-six percent of the sample fell in the high or very high social vulnerability category of the Social Vulnerabilities Index. No caregivers were excluded on the basis of inadequate English language skills; however, two caregivers reported difficulty completing the screening on the electronic tablet due to visual impairments. For these caregivers, the screening was printed using large font and completed using paper and pencil.

A total of 14 participants (13.1%) met diagnostic criteria for ADHD- I/C based on the systematic screening and subsequent follow-up procedures for the SWAN rating scale outlined in the Methods section. There was notation in the medical chart of a possible
prior diagnosis of ADHD for an additional three participants that did not screen positive on the SWAN rating scale. As such, an alternative estimate of ADHD in the current sample based on more inclusive inclusion criteria yielded a total of 17 participants (15.9%). The more conservative estimate of 14 participants based on systematic screening procedures was used for all descriptive and planned analyses described in the following sections.

Notably, the sex distribution of ADHD-I/C among youth with SCD was 64% male. This is not statistically different than what would be expected in the general United States population, $X^2 = .318, p < .561, w = .02$, which is estimated to be 71% male in community samples aged 7-12 years, using just the ADHD-C and ADHD-I cases (Ramtekkar et al., 2011). The average age of youth with ADHD-I/C diagnoses was nine years old. Bivariate correlations examining the association between key demographic variables (i.e., age, sex) and SWAN inattentive symptoms and ADHD diagnoses were nonsignificant ($r < .13$, see Table 3.2).

**Follow-Up Procedures**

Of the 28 participants with a positive screening on the SWAN, 14 (50%) met diagnostic criteria for ADHD-I/C diagnoses. These diagnoses were established based on diagnostic procedures following the completion of the psychosocial screening ($n = 11$) or results from a psychological evaluation conducted within 24 months prior to the screening ($n=3$). Eight participants met criteria for ADHD-I and 6 participants met criteria for ADHD-C. These diagnoses were established through diagnostic interviewing ($n=4$), diagnostic interviewing plus psychoeducational evaluations ($n=4$), and diagnostic interviewing plus neuropsychological evaluations ($n = 6$). See Figure 3.1 for an overview
of follow-up procedures conducted. Of the 14 participants that met criteria for ADHD-I/C, eight were receiving school supports through an existing IEP and additional five participants were receiving school accommodations through a 504 plan.

Of the 14 participants with positive SWAN screenings that did not meet criteria for ADHD-I/C diagnoses, six participants (21%) were lost to follow-up due to caregivers not responding to follow-up contacts. The remaining eight participants did not meet diagnostic criteria for ADHD on testing procedures conducted following the positive SWAN screening (n = 7) or on an evaluation conducted within 24 months prior to the screening (n=1). Follow-up testing procedures included psychoeducational evaluations and structured parent interviews which included the MINI-ADHD module and screenings for emotional and academic concerns. Based on these follow-up procedures, one participant met criteria for a major neurocognitive disorder, three participants only displayed ADHD symptoms following the transition to virtual schooling with no impact on academic performance (i.e., symptoms only present in one context), and four participants failed to meet inclusion criteria for ADHD based on symptom counts. See Figure 3.2 for a detailed summary of follow-up procedures for youth with positive screenings on the SWAN. Results from structured diagnostic interviews and psychoeducational/neuropsychological evaluations were reviewed with caregivers of participants through a scheduled feedback session and a copy of the psychological evaluation report was provided to families. When requested by caregivers, results from evaluations were shared with schools to assist with connecting participants with school services.
**Sensitivity of SWAN Screener**

For descriptive purposes, the impact of different cut-off scores on the number of positive screenings and correspondence with ADHD diagnoses was evaluated. There was no difference in rates of positive screening when using a 4-symptom cutoff versus a 5-symptom cutoff on the SWAN rating scale, with both cutoffs yielding a positive screening rate of 26.2% (n = 28). When using a 6-symptom cutoff, the positive screening rate dropped to 23.4% (n = 27). There was no difference in ADHD-I/C diagnosis rates when using a 4-symptom versus a 5-symptom cutoff on the SWAN rating scale (see Figure 3.3).

**Planned Analyses**

*Hypothesis 1a: Children with SCD will evidence higher rates of elevated ADHD inattentive symptoms than that observed in a large sample of school age youth as measured by total mean scores on the SWAN inattentive scale.* Chi squared goodness of fit analyses were run to compare the prevalence of inattentive symptoms on the SWAN rating scale in the current sample to that of the best available estimate of prevalence rates from a large sample of school age youth using the SWAN rating scale. For the purposes of this analysis, elevated ADHD inattentive symptoms were defined as scores ≥ 5 on the SWAN rating scale. Consistent with my hypothesis, a chi squared goodness of fit test revealed a significant difference between the prevalence of elevated ADHD inattentive symptoms on the SWAN inattentive scale in the current sample (26.2%) compared to a large sample of school age youth (5.3%; $X^2 = 92.86, p < .001, \omega = .93$). A separate chi squared goodness of fit test excluding participants born preterm was also significant, indicating that a history of preterm birth did not significantly impact findings, $X^2 =$
77.47, \( p < .001, w = .94 \). This analysis excluded seven cases in which data on history of preterm data was missing. A separate chi squared goodness of fit test was run in which these seven cases were coded as “born at term” to determine if excluding missing data impacted findings. Results from this analysis were similarly significant, \( X^2 = 84.98, p < .001, w = .95 \). See Table 3.3 for a summary of analyses.

**Hypothesis 2a: Children with SCD will evidence higher prevalence rates of ADHD-I/C diagnoses than the general population of Black youth in the United States.** Chi squared goodness of fit analyses were run to compare the prevalence of formal ADHD-I/C diagnoses in the current sample to that of the general population of Black youth in the United States. Consistent with my hypothesis, a chi squared goodness of fit test revealed a significant difference between the prevalence of ADHD-I/C diagnoses in the current sample (13.1%) to that of the general population (5.5%; \( X^2 = 11.82, p = .001, w = .33 \)).

A separate chi squared goodness of fit test excluding participants born preterm was also significant, indicating that a history of preterm birth did not significantly impact findings, \( X^2 = 8.52, p = .004, w = .31 \). This analysis excluded seven cases in which data on history of preterm data was missing. A chi squared goodness of fit test was run in which these seven cases were coded as “born at term” to determine if excluding missing data impacted findings. Results from this analysis were similarly significant, \( X^2 = 6.96, p = .008, w = .27 \). See Table 3.4 for a summary of analyses.

**Hypothesis 3a: Higher risk SCD genotypes and a history of cerebrovascular disease will predict increased ADHD inattentive symptoms and formal ADHD-I/C diagnoses compared to those with lower risk genotypes and no history of cerebrovascular disease.** Regression analyses were run to examine indicators of disease severity as predictors of
inattentive symptoms on the SWAN rating scale and formal ADHD diagnoses. Contrary to my hypotheses, results from linear regression analyses found that higher risk SCD genotypes, $B = .03, t(105) = .344, p = .731, R^2 = .001$, and history of cerebrovascular disease, $B = .05, t(105) = .56, p = .576, R^2 = .003$, did not significantly predict SWAN inattentive symptoms. There was no significant change in results when sex and history of preterm birth were added as covariates. Logistic regression analyses were run to examine genotype and history of cerebrovascular disease as predictors of ADHD-I/C diagnoses as a categorical dependent variable. The overall logistic regression model was nonsignificant, $X^2 (2, n = 107) = 1.08, p = .583$, indicating that higher risk SCD genotypes and history of cerebrovascular disease did not significantly predict ADHD-I/C diagnoses. There was no change in results when sex and history of preterm birth were added as predictors to the model, $X^2(4, n = 107) = 3.12, p = .538$.

*Hypothesis 3b: Social-environmental functioning will be associated with increased ADHD inattentive symptoms and formal ADHD diagnoses.*

Principal component analysis was used to reduce the number of social-environmental variables to develop a parsimonious model for analysis and interpretation and to address the inter-correlation among measures. Private insurance was excluded from these analyses due to a lack of variability in this variable, with only 11% of participants having private insurance based on medical chart review. Bivariate correlations were first run examining the correlations among various social-environmental variables (see Table 3.5). A principal component analysis was run with Varimax rotation, which revealed three factors with eigenvalues greater than 1.00. The remaining factors had eigenvalues ranging from .798-.291. Visual inspection of the scree
plot also suggested a three-factor solution; as such, a three-factor solution explaining 64.17% of the variance was chosen. Factor 1 accounted for 34.08% of the variance and was comprised of measures assessing family functioning and instrumental and social support and included the BAFFS, items measuring family resiliency, and items measuring social support and unmet social needs (Childcare, Utilities) from the Social Support and Needs Questionnaire. This factor was labeled “Family Distress/Dysfunction.” Factor 2 accounted for 17.07% of the variance and included total number of adults in the household, information on material resources (i.e., number of cars and phones), as well as unmet social needs, specifically, Utilities. This factor was labeled “Family Structure and Material Resources.” Factor 3 accounted for 13.01% of the variance and included the social vulnerabilities index and unmet social needs, specifically Childcare. This factor was labeled “Neighborhood Socioeconomic Status.” A cutoff value of .300 was used to determine which variables were included in each factor. Factor weights for each variable loading .300 or higher were multiplied by the value of each variable for each participant and summed to create summary variables for the three factors for each participant (see Table 3.6).

Bivariate correlations were run to examine the relationship between the previously defined three factors and SWAN inattentive symptoms and ADHD-I/C diagnoses (see Table 3.7). There was a significant correlation between Factor 1 (Family Distress/Dysfunction) and SWAN inattentive symptoms, r = .228, p = .019. All other correlations were nonsignificant. Linear regression analyses were run to examine each factor as a predictor of SWAN inattentive symptoms (see Table 3.8). Factor 1 (Family Distress/Dysfunction) significantly predicted SWAN inattentive symptoms, B = .23,
\( t(104) = 2.39, p = .019, R^2 = .052 \), with higher Family Distress/Dysfunction predicting elevated SWAN Inattentive symptoms. Neither Factor 2, \( B = -13, t(92) = -1.27, p = .208, R^2 = .017 \), nor Factor 3, \( B = -1.58, t(96) = -1.27, p = .120, R^2 = .025 \), significantly predicted SWAN inattentive symptoms. As none of three social-environmental factors were significantly correlated with ADHD-I/C diagnoses (\( r < .14 \), see Table 3.7), subsequent logistic regression analyses were not conducted.

### Exploratory Analyses

There are a range of population-based prevalence estimates for ADHD that vary based on methodology and time span of data collection. Additional chi squared goodness of fit analyses were run comparing the prevalence of formal ADHD-I/C diagnoses in the current sample to these alternative estimates to examine how study outcomes might change based on the use of alternative prevalence estimates. These alternative prevalence rates were from the 2015-2016 National Health Interview Survey and included the ADHD prevalence rate for Black youth ages 4-17 years (12.8%) and the ADHD prevalence rate for youth of all race/ethnicities between the ages of 4 and 11 (7.7%) to better match the age range of the current sample (Xu et al., 2018). A chi squared goodness of fit test revealed no significant difference between the prevalence of ADHD-I/C diagnoses in the current sample (13.1%) to that of the ADHD prevalence rate for Black youth ages 4-17 years from the 2015-2016 National Health Interview Survey (12.8%; \( X^2 = .01, p = .930 \)). However, chi squared goodness of fit test did reveal a significant difference between the prevalence of ADHD-I/C diagnoses in the current sample (13.1%) and that of the ADHD prevalence rate for youth of all race/ethnicities between the ages of 4 and 11 (7.7%; \( X^2 = 4.36, p = .037 \)).
Multiple regression analyses were run examining Factor 1 and history of cerebrovascular disease as predictors of SWAN inattentive symptoms to examine the relative impact of medical and social-environmental variables. The overall model was not significant, $F(2,103) = 2.85, p = .062, R^2 = .05$. Although individual level variables cannot be interpreted as the overall model was not significant, results showed that Factor 1 predicted SWAN inattentive symptoms, $B = .23, t(103) = 2.33, p = .022$, while history of cerebrovascular disease did not significantly predict symptoms, $B = .05, t(103) = .55, p = .583$.

As planned analyses found that the hypothesized indicators of disease severity (i.e., genotype, history of cerebrovascular disease) were not significant predictors of inattentive symptoms or ADHD diagnoses, exploratory analyses were run examining additional indicators of disease impact. Correlation analyses were run examining the association between SWAN inattentive symptoms and ADHD diagnoses with hemoglobin lab values. Hemoglobin was not significantly associated with SWAN inattentive symptoms ($r = .03, p = .794$) or ADHD diagnoses ($r = .12, p = .234$).
Table 3.1. *Sample Demographics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (n = 107)</th>
<th>≥ 5 SWAN Symptoms (n=28)</th>
<th>≤ 5 SWAN Symptoms (n = 79)</th>
<th>Test statistic</th>
<th>No ADHD (n=93)</th>
<th>ADHD (n=14)</th>
<th>Test statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (M (SD))</td>
<td>9.42 (1.44)</td>
<td>9.36 (1.25)</td>
<td>9.47 (1.51)</td>
<td>t(105) = .62</td>
<td>9.48 (1.48)</td>
<td>9.04 (1.14)</td>
<td>t(105) = 1.01</td>
</tr>
<tr>
<td>Sex (n (% Female))</td>
<td>44 (41.1)</td>
<td>13 (46.4)</td>
<td>31 (39.2)</td>
<td>X² = .44</td>
<td>39 (41.9)</td>
<td>5 (35.7)</td>
<td>X² = .20</td>
</tr>
<tr>
<td>SCD Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbSS</td>
<td>71 (66.4)</td>
<td>19 (67.9)</td>
<td>52 (65.8)</td>
<td></td>
<td>64 (68.8)</td>
<td>7 (50.0)</td>
<td></td>
</tr>
<tr>
<td>HbSC</td>
<td>20 (18.7)</td>
<td>4 (14.3)</td>
<td>16 (20.3)</td>
<td></td>
<td>17 (18.3)</td>
<td>3 (21.4)</td>
<td></td>
</tr>
<tr>
<td>HbSBeta’tal</td>
<td>10 (9.4)</td>
<td>3 (7.7)</td>
<td>7 (8.9)</td>
<td></td>
<td>7 (7.6)</td>
<td>3 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (5.6)</td>
<td>2 (7.2)</td>
<td>4 (5.1)</td>
<td></td>
<td>4 (4.3)</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>History of preterm birth a,b</td>
<td>13 (13%)</td>
<td>3</td>
<td>10</td>
<td></td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (M (SD))</td>
<td>9.49 (1.69)</td>
<td>9.54 (1.72)</td>
<td>9.47 (1.70)</td>
<td>t(105) = -.17</td>
<td>9.41 (1.66)</td>
<td>9.93 (1.86)</td>
<td>t(105) = -1.20</td>
</tr>
<tr>
<td>Hematocrit (M (SD))</td>
<td>27.23 (5.01)</td>
<td>27.49 (4.86)</td>
<td>27.15 (5.09)</td>
<td>t(105) = -.31</td>
<td>26.98 (4.94)</td>
<td>28.96 (5.30)</td>
<td>t(105) = -1.38</td>
</tr>
<tr>
<td>WBC count (M (SD))</td>
<td>9.31 (3.37)</td>
<td>9.40 (3.57)</td>
<td>9.28 (3.32)</td>
<td>t(105) = -.16</td>
<td>9.31 (3.32)</td>
<td>9.31 (3.78)</td>
<td>t(105) = -.00</td>
</tr>
<tr>
<td>Platelet (M (SD))</td>
<td>367.25 (148.47)</td>
<td>356.59 (128.19)</td>
<td>370.90 (155.38)</td>
<td>t(105) = .43</td>
<td>376.56 (150.81)</td>
<td>300.69 (114.21)</td>
<td>t(105) = 1.74</td>
</tr>
<tr>
<td>History of abnormal TCD</td>
<td>10 (9.3)</td>
<td>4 (14.3)</td>
<td>6 (7.6)</td>
<td>X² = 1.09</td>
<td>9 (9.7)</td>
<td>1 (7.1)</td>
<td>X² = .09</td>
</tr>
<tr>
<td>Overt stroke</td>
<td>3 (2.8)</td>
<td>1 (3.6)</td>
<td>2 (2.5)</td>
<td>X² = .08</td>
<td>3 (3.2)</td>
<td>0</td>
<td>X² = .47</td>
</tr>
</tbody>
</table>

Note.

a Data missing on history of preterm birth for 7 participants
b Preterm birth defined as < 37 weeks.

*None of the values reached a typical alpha level for statistical significance
Table 3.2. *Bivariate Correlations Between Age, Sex, SWAN Inattentive Symptoms, and ADHD-I/C Diagnoses*

<table>
<thead>
<tr>
<th>ADHD-I/C Diagnosis</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SWAN Symptoms</td>
<td>.648**</td>
<td>-.10</td>
</tr>
<tr>
<td>ADHD-I/C Diagnosis</td>
<td>--</td>
<td>-.10</td>
</tr>
</tbody>
</table>

Note.

*p < .05, **p < .01
Table 3.3. *Chi Squared Goodness of Fit Analyses Comparing Rate of Elevated Inattentive Symptoms in the Current Sample to a Large Sample of School Age Youth*

<table>
<thead>
<tr>
<th>SWAN screening</th>
<th>Observed n</th>
<th>Expected n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample (n = 107)</td>
<td></td>
<td></td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Negative screen</td>
<td>79</td>
<td>101.3</td>
<td></td>
</tr>
<tr>
<td>Positive screen</td>
<td>28</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Excluding preterm (n = 94)</td>
<td></td>
<td></td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Negative screen</td>
<td>69</td>
<td>89.0</td>
<td></td>
</tr>
<tr>
<td>Positive screen</td>
<td>25</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Excluding preterm and missing data (n = 87)</td>
<td></td>
<td></td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Negative screen</td>
<td>62</td>
<td>82.4</td>
<td></td>
</tr>
<tr>
<td>Positive screen</td>
<td>23</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.4. Chi Squared Goodness of Fit Analyses Comparing Rate of ADHD-I/C Diagnoses in Current Sample to the General Population of Black Youth

<table>
<thead>
<tr>
<th>ADHD Diagnoses</th>
<th>Observed n</th>
<th>Expected n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample (n = 107)</td>
<td></td>
<td></td>
<td><em>p = .001</em></td>
</tr>
<tr>
<td>No, ADHD</td>
<td>93</td>
<td>101.1</td>
<td></td>
</tr>
<tr>
<td>Yes, ADHD</td>
<td>14</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Excluding preterm (n = 94)</td>
<td></td>
<td></td>
<td><em>p = .008</em></td>
</tr>
<tr>
<td>No, ADHD</td>
<td>83</td>
<td>88.8</td>
<td></td>
</tr>
<tr>
<td>Yes, ADHD</td>
<td>11</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Excluding preterm and missing data (n = 87)</td>
<td></td>
<td></td>
<td><em>p = .004</em></td>
</tr>
<tr>
<td>No, ADHD</td>
<td>76</td>
<td>82.2</td>
<td></td>
</tr>
<tr>
<td>Yes, ADHD</td>
<td>11</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.5. *Bivariate Correlations Between Social-Environmental Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td># of adults in household</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of telephones in household</td>
<td>.41**</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of cars in household</td>
<td>.48**</td>
<td>.45**</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childcare needs</td>
<td>-.10</td>
<td>-.30*</td>
<td>-.18</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utilities needs</td>
<td>-.21*</td>
<td>-.30**</td>
<td>-.35**</td>
<td>-.33**</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Functioning</td>
<td>.01</td>
<td>-.26*</td>
<td>-.24*</td>
<td>-.19*</td>
<td>-.37**</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Resiliency</td>
<td>-.05</td>
<td>.08</td>
<td>.08</td>
<td>-.17</td>
<td>-.39**</td>
<td>-.53**</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Practices</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social support</td>
<td>.22*</td>
<td>.37**</td>
<td>.26*</td>
<td>-.29**</td>
<td>-.47**</td>
<td>-.55**</td>
<td>.37**</td>
<td>-</td>
</tr>
<tr>
<td>Neighborhood SES</td>
<td>.03</td>
<td>-.18</td>
<td>-.16</td>
<td>-.01</td>
<td>.06</td>
<td>.15</td>
<td>-.06</td>
<td>.03</td>
</tr>
</tbody>
</table>

Note.

SES = Socioeconomic Status

*p < .05, **p < .01
Table 3.6. Factor Weightings of Social-Environmental Measures for Principal Components Analyses

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Factor 1 (Family Distress/Dysfunction)</th>
<th>Factor 2 (Family Structure and Material Resources)</th>
<th>Factor 3 (Neighborhood SES)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of adults in household</td>
<td>.159</td>
<td>.806*</td>
<td>.135</td>
</tr>
<tr>
<td># of telephones in household</td>
<td>-.282</td>
<td>.746*</td>
<td>-.042</td>
</tr>
<tr>
<td># of cars in household</td>
<td>-.205</td>
<td>.784*</td>
<td>.109</td>
</tr>
<tr>
<td>Childcare needs</td>
<td>.402*</td>
<td>-.249</td>
<td>-.494*</td>
</tr>
<tr>
<td>Utilities needs</td>
<td>.670*</td>
<td>-.320*</td>
<td>-.151</td>
</tr>
<tr>
<td>Family Functioning</td>
<td>.821*</td>
<td>-.029</td>
<td>.165</td>
</tr>
<tr>
<td>Family Resiliency Practices</td>
<td>-.785*</td>
<td>-.082</td>
<td>-.079</td>
</tr>
<tr>
<td>Social support</td>
<td>-.640*</td>
<td>.316*</td>
<td>.247</td>
</tr>
<tr>
<td>Neighborhood SES</td>
<td>.144</td>
<td>-.151</td>
<td>.889*</td>
</tr>
</tbody>
</table>

Note.

SES = Socioeconomic Status

*loaded onto factor
Table 3.7. *Bivariate Correlations of SWAN Screening, ADHD-I/C Diagnoses, and Social-Environmental Factors*

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Factor 1 (Family Distress/Dysfunction)</th>
<th>Factor 2 (Family Structure and Material Resources)</th>
<th>Factor 3 (Neighborhood SES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SWAN Symptoms</td>
<td>.23*</td>
<td>-.13</td>
<td>-.16</td>
</tr>
<tr>
<td>ADHD-I/C Diagnosis</td>
<td>.04</td>
<td>-.14</td>
<td>-.14</td>
</tr>
</tbody>
</table>

Note.

SES = Socioeconomic Status

*p < .05, **p < .01
Table 3.8. Univariate Linear Regression Analyses Examining Social-Environmental Factors as Predictors of SWAN Inattentive Symptoms.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>t</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor 1 (Family Distress/Dysfunction)</td>
<td>.18</td>
<td>2.39</td>
<td>.019*</td>
<td>.05</td>
</tr>
<tr>
<td>Factor 2 (Family Structure/Material Resources)</td>
<td>-.52</td>
<td>-1.27</td>
<td>.208</td>
<td>.02</td>
</tr>
<tr>
<td>Factor 3 (Neighborhood SES)</td>
<td>-1.71</td>
<td>-1.57</td>
<td>.120</td>
<td>.03</td>
</tr>
</tbody>
</table>

Note.  
SES = Socioeconomic Status  
*p < .05, **p < .01
Eligible Patients (n = 128)

Screened (n = 107)

Positive SWAN screen (n = 28)

ADHD-I/C diagnosis (n = 14)

ADHD-I (n = 8) ADHD-C (n = 6)

Lost to follow-up (n = 6)

Criteria not met for ADHD (n = 8)

ADHD from medical chart review (n = 3)

Criteria met for non-ADHD condition (n = 1)

Not screened (Missed, n = 20; Declined, n = 1)

Negative screen (n = 79)

ADHD from medical chart review (n = 3)

No diagnosis (n = 7)

Criteria met for non-ADHD condition (n = 1)

ADHD-I (n = 8) ADHD-C (n = 6)

Figure 3.1. Flow diagram of screening outcomes and follow-up procedures.
Figure 3.2. Flow diagram of follow procedures for participants with positive SWAN screenings
Figure 3.3. Frequency of SWAN inattentive symptoms by total number of SWAN symptoms endorsed. Numbers listed above columns represent the number of ADHD-I/C diagnoses within each category of SWAN symptoms.
CHAPTER 4
DISCUSSION

Sickle cell disease is linked to increased risk for deficits in attentional abilities and executive functions as a result of biomedical and psychosocial risk factors. However, despite suggestions in the literature of an increased prevalence of ADHD in youth with SCD, there is minimal research substantiating this association, with differences in methods and methodological quality leading to significant variability in reported prevalence rates for attention deficits and formal ADHD diagnoses. The rate of ADHD in SCD is important to understand to better plan for the clinical, educational, and family supports needed to detect and treat this condition. This study aimed to address this issue by examining prevalence rates of inattentive ADHD symptoms and formal ADHD-I/C diagnoses for youth with SCD within a large hematology clinic by directly assessing for symptoms, rather than relying on medical chart reviews or diagnoses/reports made by other health professionals. A secondary aim was to examine medical and social-environmental predictors of inattentive ADHD symptoms and formal ADHD-I/C diagnoses.

The current study found significantly elevated rates of inattentive symptoms (defined as ≥ 5 symptoms on the SWAN rating scale; Young et al., 2009), with more than one-fourth of youth screening positive for attention difficulties (26.2% vs 5.3%). This is generally consistent with findings from previous studies using parent-report
questionnaires of attention concerns for youth with SCD, which have found significantly elevated rates of attentional difficulties (Ekinci et al., 2012; Hood et al., 2020). Indeed, a prior study by Hood and colleagues (2020) found that 22% of youth with SCD in their sample had elevated or extremely elevated scores on a parent-report measure of ADHD symptoms. However, it is important to note that Hood and colleagues excluded participants with lower risk genotypes and participants that were not receiving chronic transfusion or hydroxyurea therapy. The current study was considerably broader in its inclusion criteria, including participants with less severe disease presentations (e.g., mild/moderate genotypes). As such, our finding of a prevalence rate of elevated inattentive symptoms that is similar to or higher than that found in a more severe disease sample suggests that attentional difficulties are not limited to individuals with SCD with higher disease burden.

There were also significantly elevated rates of formal ADHD-I/C diagnoses in the current sample compared to that of Black youth in the general population (13.1% vs 5.5%). The average age of youth with ADHD-I/C diagnoses was nine years old, which generally aligns with findings from prior studies examining the typical age of ADHD diagnosis (Visser et al., 2015). Exploratory analyses were also conducted comparing our prevalence estimate of ADHD-I/C to alternative population-based prevalence estimates. These exploratory analyses were conducted to address potential concerns that the use of older prevalence estimates might underestimate ADHD prevalence rates among Black youth given a general upward trend in ADHD diagnoses among Black youth in the United States reported by some studies. The prevalence rate of ADHD-I/C in the current study did not significantly differ from the prevalence rate of ADHD among Black youth 4
to 17 years of age from a population-based estimate collected in 2015-2016. The lack of significant findings using this alternative estimate may be attributable, in part, to the wider age range of youth in this population-based sample compared to the current study (i.e., 7-11 years). Prevalence estimates of ADHD are consistently higher among youth ages 12 to 17 when examining 20-year trends, with the gap widening in recent years (Xu et al., 2018). Indeed, in reports on the 2015-2016 data from the National Health Interview Survey there was a significant difference in the prevalence estimate of ADHD between youth ages 4-11 years (7.7%) and youth ages 12-17 years (13.5%; Xu et al., 2018). This is supported by findings from our exploratory analyses revealing a significantly elevated rate of ADHD-I/C in the current sample when compared to the ADHD prevalence estimate for youth of all races/ethnicities ages 4-11 years. Unfortunately, a prevalence estimate of ADHD for Black youth between the ages of 4 to 11 years was not available, prohibiting a more direct comparison with the prevalence rate from the current study.

Furthermore, it is important to note that all prevalence estimates from the National Health Interview Survey (Boulet et al., 2010; Xu et al., 2018) relied on caregiver report of a prior diagnosis of ADHD from a healthcare professional rather than directly assessing for ADHD symptomatology. This is a notable limitation of many available population-based estimates of ADHD given research showing stark differences in prevalence rates of ADHD in the general population when standardized diagnostic procedures are used compared to parent or physician report of a prior diagnosis (Polanczyk et al., 2014). This highlights the importance of the specific methodological approach of the current study. Ours is the first study to directly assess for ADHD-I/C
inclusion and exclusion criteria in a large sample of school age youth with SCD using a systematic screening approach. This addresses methodological limitations of many prior studies examining ADHD prevalence in pediatric SCD, which have historically relied on retrospective medical chart review or parent-report of a prior diagnosis of ADHD, rather than directly assessing for ADHD symptoms (Boulet et al., 2010; Jerrell et al., 2011; Lance et al., 2015). Our prevalence estimate of 13.1% is lower than the two prior studies within pediatric SCD that have directly assessed for ADHD diagnostic criteria using similar diagnostic procedures as the current study (i.e., clinical interviewing, formalized assessment procedures). Those studies identified prevalence estimates ranging from 25% to 40% (Acquazzino et al., 2017; Benton et al., 2011). However, it is difficult to directly compare the prevalence estimate from the current study to these prior studies due to notable methodological differences in sample selection. For instance, Benton and colleagues (2011) recruited their sample of 40 adolescents with SCD through random sampling, rather than systematic screening to identify youth at increased risk for attention difficulties while the sample in the study by Acquazzino and colleagues (2017) represented a subset youth with SCD that were already referred by providers for a neuropsychological evaluation for a variety of concerns related to school, behavior, or development. Furthermore, there are notable differences in the age range of these prior studies, which included youth with SCD up to 19 years of age. Given these methodological differences, additional studies directly assessing for ADHD diagnostic criteria through systematic screening are needed to confirm our findings.

Regardless of findings from statistical comparisons with population-based estimates, the ADHD-I/C prevalence rate of 13.1% in the current study underscores that a
significant number of youth with SCD are experiencing elevated neurodevelopmental concerns. The high rates of attentional concerns and formal ADHD diagnoses have important implications for efforts to detect, prevent, and treat this condition among youth with SCD. These high rates of neurodevelopmental concerns highlight the importance of systematic screening for attentional concerns for all youth with SCD, regardless of genotype, within specialty care settings to identify patients in need of more comprehensive assessment for ADHD. For many patients with SCD the hematology clinic serves as their primary medical home and the location where they receive the majority of their medical care. Although routine screenings for emotional and behavioral concerns are recommended by the American Academy of Pediatrics at primary care visits (Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, 2011), adherence to this recommendation appears to have been poor in our sample, as only one-fourth of youth with positive screenings for inattentive concerns had received a prior ADHD diagnosis. Additionally, as youth with SCD are at increased risk for other conditions that may account for inattentive symptoms, it is important that a thorough diagnostic assessment is completed to ensure that inattentive symptoms due to internalizing concerns or neurocognitive deficits are not misattributed to ADHD. Primary care providers often do not have the same access to psychology providers with training in the assessment of neurodevelopmental disorders as specialty care settings, further highlighting the importance of screening and assessment services through hematology clinics.

Our findings have important implications for educational systems. School represents a system with the potential to assist in the early identification and treatment of
ADHD concerns among youth with SCD. However, many high-risk students with SCD (e.g., those with histories of infarcts, intellectual deficits, or significant emotional or behavioral challenges) often go unidentified and/or unsupported at school (Connolly et al., 2021; Herron et al., 2003; Peterson et al., 2005). Indeed, as previously noted, only one-fourth of the participants in our sample that met diagnostic criteria for ADHD had received an ADHD diagnosis prior to participation in our screening program, suggesting behavioral concerns were undetected by the school system. This is concerning given research demonstrating poorer academic outcomes for youth with ADHD that do not receive school supports (Bussing et al., 2012).

It is important to acknowledge the historic inequities due to sociodemographic factors when discussing access to supports within school systems for youth with SCD. Families of children with SCD must contend with risk factors stemming from the cumulative disadvantage of social inequities (e.g., financial hardship, racial discrimination, and stigmatization) and chronic disease (Hankins & Wang, 2009; Jenerette & Valrie, 2010; Robinson et al., 2014). The detrimental impact of this cumulative burden is evidenced in marked financial insecurity, with approximately 60% of children with SCD receiving public insurance (King et al., 2014; McCavit et al., 2013), as well as decreased employment opportunities for caregivers due to the demands of caring for a child with a chronic illness (Brandow et al., 2009; Smith et al., 2002). Indeed, 89% of our sample was receiving public insurance and more than half of our sample fell in the high to very high percentile on the social vulnerabilities index, indicating that families served by our clinic live in neighborhoods with higher rates of poverty and unemployment and lower rates of receipt of high school diplomas. This
implies that youth with SCD are more likely to attend schools with fewer financial resources which may limit their ability to ensure students have access to educational supports. Additionally, low-income working parents may face unique challenges that restrict their ability to engage with school systems, such as limited paid leave or flexibility in their work schedule that would afford them opportunity to meet with teachers and school staff. There is a paucity of research focused on interventions designed to target these inequities within the educational system for youth with SCD (Miller et al., 2022). Although it was outside of the scope of the current study, there is a strong need for research efforts focused on developing systems-level interventions for families of youth with SCD to improve access to educational supports.

To our knowledge, ours is the first study to use the SWAN rating scale to screen for attention difficulties among youth with SCD. The SWAN rating scale is unique in its dimensional approach to ADHD symptomatology and measurement of positive attentional skills in addition to attention problems. Of the participants with a positive screen for attention concerns on the SWAN, only half met full diagnostic criteria for ADHD on follow-up testing procedures. However, many of the participants that did not ultimately receive an ADHD diagnosis did report attention difficulties related to other factors such as another diagnosis (e.g., neurocognitive disorder) or environmental factors (e.g., difficulties transitioning to virtual schooling). This suggests that the SWAN rating scale is sensitive to attention concerns within the pediatric SCD population but is not necessarily specific to the attention concerns resulting from ADHD. In summary, the SWAN rating scale demonstrated clinical utility as a screening tool for general attentional difficulties within the pediatric SCD population. However, future research is needed to
determine the specificity of the SWAN rating scale within the pediatric SCD population.

A secondary aim of the current study was to explore medical and psychosocial predictors of inattentive symptoms and formal ADHD diagnoses. Contrary to our hypotheses, commonly used indicators of disease severity within the SCD literature, specifically, genotype and history of cerebrovascular disease (i.e., stroke, abnormal TCD), did not predict inattentive symptoms or formal ADHD-I/C diagnoses. Genotype and indicators of cerebrovascular disease have consistently predicted attentional difficulties and other executive functioning deficits as measured by neurocognitive testing within the SCD population (Berkelhammer et al., 2007; Kral et al., 2003). The association between disease severity and cognitive deficits in domains such as attention and executive functions in pediatric SCD is driven by the increased likelihood of cerebrovascular injury to the frontal lobe, an area of the brain associated with higher order cognitive functions (Brown et al., 2000; Ford et al., 2018; Pegelow et al., 2002), and diffuse white matter changes in the brain which are thought to reflect axonal loss, demyelination, and cortical thinning (Choi et al., 2019; Kawadler et al., 2013, Schatz et al., 2002). However, it is notable that while many studies have examined genotype and history of cerebrovascular disease as indicators of cognitive deficits, these indicators of disease severity have not been examined as predictors of deficits associated with neurodevelopmental conditions such as ADHD. The few studies that have explored these indicators of disease severity in relation to neurodevelopmental conditions have found mixed results. For instance, a study by Lance and colleagues (2015) found a higher prevalence of attentional concerns in a subgroup of youth with a lower risk SCD genotype (HbS Beta thalassemia +) but not for participants with HbSS, the most common
high risk SCD genotype. Additionally, a study by Hood and colleagues (2020) found that a history of cerebral infarction was not a significant predictor of ADHD symptoms. However, this study did identify a different medical variable, number of days hospitalized, as a significant predictor. Overall, these findings suggest that the established medical predictors of neurocognitive deficits in pediatric SCD may not translate to symptoms of neurodevelopmental disorders such as ADHD.

There are a number of potential explanations for this discrepancy. Perhaps most notably, there is a distinction between neurocognitive deficits as measured by performance on cognitive testing, and symptoms of inattention associated with neurodevelopmental conditions such as ADHD which are assessed through behavioral indicators. This is evidenced in the DSM-5 diagnostic criteria for ADHD which does not require the presence of cognitive deficits on neurocognitive testing (American Psychiatric Association, 2013). Regardless, lower performance on cognitive testing, particularly on tests of executive functioning, is well documented for youth with ADHD compared to youth in the general population (Biederman et al., 2009). Discrepancies in performance between youth with ADHD and controls are present on general measures of intellectual functioning (i.e., IQ) as well as specific domains of executive functioning including sustained attention, inhibitory control, and working memory (Martinussen et al., 2005; Coghill et al., 2014). Specifically, a meta-analysis by Frazier and colleagues (2004) identified a 9-point difference in IQ between individuals with ADHD and controls. Although the reported effect sizes for the studies included in this meta-analysis typically fell in the medium range indicating robust findings, this does not necessarily translate to psychometric deficits on tests of cognitive ability. In contrast, within the pediatric SCD
population, psychometric deficits indicative of performance significantly below that of same age peers are well-documented (Berkelhammer et al., 2007; Kawadler et al., 2006). In summary, indicators of disease severity that have typically been used in pediatric SCD to identify youth at high risk for neurocognitive deficits may not be as sensitive to the profile of cognitive and behavioral difficulties associated with ADHD.

If indicators of disease severity linked to increased risk for neurocognitive deficits in pediatric SCD are not responsible for significantly elevated rates of ADHD diagnoses, what is? A potential contributing factor may be the more global impact of SCD as a chronic medical condition on youth and family functioning. National surveys have identified higher rates of ADHD among youth with fair or poor health status compared to those in excellent or very good health, with prevalence estimates closer to 21% (Bloom et al., 2009). Specifically, ADHD prevalence rates have been found to be higher among children with a variety of other chronic medical conditions such as asthma, headaches/migraines, and gastrointestinal problems (Jameson et al., 2016). The etiology of these comorbidities among youth with ADHD has not been clearly identified, largely due to the limited availability of longitudinal studies to establish temporal precedence. However, it has been hypothesized that both biological and psychosocial risk factors associated with these chronic medical conditions are responsible for elevated prevalence rates (Blackman & Gurka, 2007; Chen et al., 2013; Pan et al., 2022). As such, it may be that children with SCD evidence higher rates of ADHD due to the more general impacts of having a chronic medical condition which are not restricted to youth with higher risk genotypes or cerebrovascular injury. For youth with SCD, these may include the widespread effects of a chronic health condition such as SCD on physical/medical...
functioning (e.g., frequent medical visits/hospitalizations) as well as the impacts on various dimensions of social-environmental risk.

To that end, the current study also explored social-environmental predictors of inattentive symptoms and ADHD diagnoses. A strength of the current study was the ability to examine multiple dimensions of social-environmental risk including socioeconomic status, material and financial resources, and family functioning. Family structure/material resources and neighborhood level SES were not associated with inattentive symptoms. However, higher levels of family distress/dysfunction did significantly predict elevated attentional difficulties. This aligns with findings from a prior study conducted by our research group in which parent and family functioning, but not SES, emerged as a significant predictor of parent-report ADHD symptoms (Bills et al., 2020). This suggests that factors specific to the home environment, such as parent stress and family dynamics, may have a stronger impact on the development of inattentive symptoms than material or financial resources. This is further supported by robust findings on the importance of social-environmental factors for families of children with ADHD, which has increasingly acknowledged the bidirectional influence of parent and family functioning on ADHD symptomatology (Kaiser et al., 2011; Lange et al., 2005).

Our findings regarding the salience of the home environment coupled with the existing literature on role of parent and family functioning in the development of ADHD symptoms highlights the importance of routine screening for indicators of parent and family distress in the SCD population. The early identification of such concerns among families of youth with SCD can then be used to inform prevention and early intervention
efforts focused on connecting families with behavioral health and other psychosocial resources to support holistic family functioning. Findings from the ADHD literature have highlighted the importance of including parent and family factors in psychosocial interventions for ADHD. Specifically, parenting has been identified as a salient mechanism for change in ADHD interventions, as evidenced by the inclusion of parent skills training in the majority of evidence-based treatments for the attentional concerns and executive functioning difficulties associated with ADHD (Haack et al., 2017; Hinshaw et al., 2007). Families of youth with SCD with elevated attentional difficulties may benefit from similar skills-building interventions focused on improving parent-child interactions to mitigate the potential negative impacts of attentional difficulties on youth and family functioning.

Social-environmental factors were also examined in relation to formal ADHD diagnoses. None of the three social-environmental factors were significant predictors of formal ADHD diagnoses. These null findings may be attributable to insufficient power to detect the more nuanced effects of these factors on ADHD diagnoses. While our overall sample of 107 participants was larger than prior studies examining ADHD prevalence rates within pediatric SCD, the number of participants with ADHD diagnoses within our sample is much smaller (n= 14). Alternatively, null findings may reflect the nature of the social-environmental factors used in the current study. The social-environmental domains included in analyses were based on a relatively small number of items from the larger psychosocial screening, some of which have not been previously validated within the SCD population. Furthermore, the primary function of the selected items was to screen for concerns across a number of social-environmental domains,
rather than thoroughly assess for concerns within a specific domain. This approach reflects the primary function of the screening as a clinical service and was intended to minimize the burden placed on caregivers when completing the screening and to cover a wide variety of potential risk factors. Further research exploring social-environmental predictors of formal ADHD diagnoses is needed to determine specific risk and protective factors that may be targets for prevention and intervention efforts.

Despite several important findings in the current study, it is important to note potential limitations. First, the study took place during the initial onset of the COVID-19 pandemic. Although patient medical care and routine medical visits were largely uninterrupted by the pandemic, there was significant disruption to many facets of life for patients and their families. The onset of the pandemic introduced extraneous variables, such as shifts in education and financial security, that have the potential to impact the emotional and behavioral well-being of patients with SCD and their families (Green et al., 2020). Perhaps most notably for the current study, many of the participants that completed psychosocial screeners were enrolled in virtual schooling due to the COVID-19 pandemic making it challenging, at times, to collect reports from informants outside of the home regarding ADHD symptoms. However, study staff involved in the assessment process were aware of the potential impact of the transition to new educational environments and, if unable to determine the presence of ADHD symptoms across multiple environments, were conservative in making ADHD diagnoses. Second, it is important to note that as the current study did not screen for hyperactive/impulsive symptoms of ADHD in the initial psychosocial screening, we cannot speak to rates of ADHD-HI presentation within our sample. Prior research has found that ADHD-HI
comprises a smaller number of total ADHD cases compared to the ADHD-I subtype (Willcutt, 2012). Regardless, our prevalence estimate may represent an underestimate of ADHD diagnosis rates in our sample as some youth with ADHD-HI may have been missed.

Third, there were three participants that were identified through medical chart review as having a prior diagnosis of ADHD that did not screen positive on the SWAN. As we did not directly assess for ADHD or conduct ADHD-related follow up among participants that did not screen positive on the SWAN, it is possible that additional youth with ADHD in our sample could have missed using our screening method. False negative screenings on the SWAN could be attributable to a reduction in inattentive ADHD symptoms following the receipt of treatment or the presence of hyperactive/impulsive symptoms in the absence of inattentive concerns. However, it is important to note that we do not know if the three participants identified as having ADHD through medical chart review met full DSM diagnostic criteria. A fourth limitation pertains to the use of regression models when examining social-environmental factors as predictors of inattentive symptoms and ADHD diagnoses. We do not yet have longitudinal data to make causal inferences regarding the direction of the relationship between social-environmental factors and inattentive symptoms. As such, we are unable to explore bidirectional relationships between ADHD symptoms and social-environmental factors. Finally, the lack of a comparison group in the current study limits our ability to control for extraneous variables, such as race, SES, and geographical location, thereby limiting some conclusions regarding the implications of our findings.

In conclusion, this study expanded on prior research by establishing prevalence
rates of ADHD diagnoses through multi-tiered screening and assessment as well as exploring biopsychosocial predictors of ADHD. Our findings of elevated rates of inattentive symptoms and formal ADHD diagnoses indicate increased risk for neurodevelopmental concerns for youth with SCD, highlighting the importance of systematic screening in specialty care settings to support the early identification and treatment of ADHD. While none of the hypothesized medical or social-environmental factors emerged as significant predictors of elevated rates of ADHD diagnoses, higher family distress and dysfunction did predict total inattentive symptoms. These findings suggest that established medical predictors of neurocognitive deficits in pediatric SCD may not translate to symptoms of neurodevelopmental disorders such as ADHD and underscore the importance of parent and family functioning in the development of ADHD symptoms. Further investigation of medical and social-environmental risk factors for ADHD within pediatric SCD is needed to inform efforts to detect, treat, and prevent poor psychosocial outcomes for youth with SCD and their families.


https://doi.org/10.1007/BF00916812


https://doi.org/10.1542/peds.2012-0283


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*Neurodevelopmental outcomes in preterm children with sickle cell disease.*

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Hematology/Oncology, 43(5), e666–e676.

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APPENDIX A

SAMPLE PSYCHOEDUCATIONAL AND NEUROPSYCHOLOGICAL ASSESSMENT BATTERIES

<table>
<thead>
<tr>
<th></th>
<th>Sample Brief Psychoeducational Battery</th>
<th>Sample Neuropsychological Battery</th>
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</thead>
<tbody>
<tr>
<td><strong>WJ-IV Cognitive Subtests</strong></td>
<td>Oral Vocabulary, Number Series, Verbal Attention, Letter-Pattern Matching</td>
<td>Oral Vocabulary, Number Series, Verbal Attention, Letter-Pattern Matching, Phonological Processing, Story Recall, Visualization</td>
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<tr>
<td><strong>WJ-IV Achieve Subtests</strong></td>
<td>Letter Word Identification, Calculation, Math Facts Fluency, Sentence Reading Fluency</td>
<td>Letter Word Identification, Calculation, Math Facts Fluency, Sentence Reading Fluency, Passage Comprehension, Applied Problems</td>
</tr>
<tr>
<td><strong>Diagnostic Interviewing/Screening</strong></td>
<td>MINI ADHD Interview and Screening Questions</td>
<td>MINI ADHD Interview and Screening Questions</td>
</tr>
<tr>
<td><strong>Additional Tests of Executive Functioning</strong></td>
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<td>DKEFS (Color Word Interference, Verbal Fluency)</td>
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<tr>
<td><strong>Additional Tests of Memory</strong></td>
<td>--</td>
<td>WRAML (List Memory, Design Memory)</td>
</tr>
</tbody>
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