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## The Prevalence Rate and Neurocognitive Morbidity Associated with Obstructive Sleep Apnea in Children with Sickle Cell Disease

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The Prevalence Rate and Neurocognitive Morbidity Associated with Obstructive Sleep  
Apnea in Children with Sickle Cell Disease

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## Abstract

Sickle-cell disease (SCD) refers to a group of genetic blood disorders resulting from the inheritance of genes for S-type hemoglobin. The disease is life-long and is associated with multiple complications including pain episodes, organ damage, and neurological morbidities such as stroke, and silent cerebral infarcts which often lead to cognitive dysfunction. Obstructive sleep apnea (OSA) is a serious medical condition characterized by intermittent hypoxemia (reduction in blood oxygen levels), hypoxia, and fragmented sleep that can lead patients to suffer from daytime behavioral and cognitive dysfunction and reduced quality of life. Children with SCD are at high risk for developing OSA, which can increase the likelihood for developing cognitive deficits. The prevalence of OSA in SCD is currently not well-documented; moreover, the relationship between the two conditions and its combined effect of neurocognitive functioning has received little attention to date. The purpose of this study is to describe the prevalence rate of OSA in children with SCD in a large clinic-wide sample and examine the relationship between OSA and neurocognitive morbidity in children with SCD.

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## Chapter 1: Introduction

Obstructive sleep apnea (OSA) is a serious medical condition characterized by intermittent hypoxemia (reduction in blood oxygen levels), hypoxia, and fragmented sleep. As a result, patients often suffer from daytime behavioral and cognitive dysfunction and reduced quality of life (Jackson, Howard, & Barnes, 2011). Untreated individuals with OSA have reported higher levels of depression, anxiety, fatigue, and irritability, as well as problems with memory, attention, and executive functions. Children with sickle-cell disease (SCD) often suffer from OSA (Rogers, Lewin, Winnie, & Geiger-Brown, 2010), however little information exists on the relationship between the two conditions. The prevalence of OSA in SCD is currently not well-documented and there is a need for studies describing the frequency, and severity of OSA in children with SCD. OSA may impart an additional risk for developing neurological morbidity and cognitive dysfunction.

Additionally, there is a complicated relationship between the pathophysiology of SCD and OSA, putting children suffering from both conditions at high risk for developing serious neurological complications and cognitive deficits. However, this relationship has received little attention to date. The purpose of this study is to describe the prevalence rate of OSA and examine the relationship between OSA and neurocognitive morbidity in children with SCD.

## *Epidemiology and Pathophysiology of Obstructive Sleep Apnea*

Obstructive sleep apnea is a severe form of sleep-related breathing disorders (SBD) and is a common condition in both adults and children. The full spectrum of SBD includes habitual snoring with minor or minimal disruption of sleep and no sleep-associated hypoxemia on the mild end, and OSA syndrome (OSAS) at the higher end. There is also an intermediate condition termed Upper Airway Resistance Syndrome (UARS), in which increased respiratory effort associated with the heightened upper airway resistance during sleep leads to sleep fragmentation in the absence of obvious hypoxemia (Kheirandish & Gozal, 2006). OSAS is usually characterized by obstruction of the upper airway and continuous respiratory effort with a normal central-nervous system respiratory drive; central sleep apnea (CSA), a variant of the condition, is characterized by unstable respiratory control with periods of reduced or absent breathing activity (Jackson et al., 2011). Mixed apnea is a condition in which OSA and CSA occur in the same individual.

OSA is a relatively common condition based on lifetime prevalence with approximately 24% of adult males and 9% of adult females suffering from the condition. Age is considered a risk factor with a 2- to-3-fold prevalence increase in older individuals (65 years and above)(Young, Skatrud, & Peppard, 2004). The spectrum of SBD also occurs in children of all ages, from neonates to adolescents. Snoring is considered the hallmark indicator of increased upper airway resistance during sleep and is a frequent symptom during childhood. Up to 27% of children are affected by snoring occasionally, and 7-12% reporting habitual snoring (defined as loud snoring recognized by parents three times or more per week). The prevalence of OSAS, at the higher end of the SBD

spectrum, is estimated at 2-3% of all children and African-American children are considered to be at higher risk for developing this condition (Gottlieb et al., 2003; Tauman & Gozal, 2011).

OSAS in children is characterized by recurrent events of partial or complete upper airway obstruction during sleep, resulting in intermittent hypoxia (complete oxygen deprivation), hypercapnia (excessive levels of carbon dioxide), and sleep fragmentation (Tauman & Gozal, 2011). Nighttime symptoms of OSAS in children generally include snoring, noisy breathing, snorting episodes, labored breathing, sweating, and restless sleep. Daytime symptoms can include mouth breathing, difficulty in waking up, moodiness, morning headaches, nasal obstruction, and daytime sleepiness. More severe cases of OSAS may be associated with behavioral disturbances including hyperactivity and cognitive deficits leading to problems in learning and school functioning (Kheirandish & Gozal, 2006). Additionally, these children may also suffer from cardiovascular complications, compromised somatic growth, as well as depression, enuresis, and increased health-related costs.

The most significant anatomic risk factor for OSAS in non-obese healthy children is adenotonsillar hypertrophy (enlarged tonsils). However, OSAS is not a result of this structural abnormality alone. Inflammation in the nasopharyngeal area is also involved in the pathophysiology of OSAS in children (Tauman & Gozal, 2011). Studies of adenotonsillar tissues from children with OSAS have revealed significant increases in inflammatory cell production (Dayyat et al., 2009; Goldbart et al., 2007; Kheirandish-Gozal et al., 2009) as well as pro-inflammatory cytokines (Kim et al., 2009). It has been suggested that among the multitude of potential factors accounting for inflammation of

the adenotonsillar tissues in OSAS, respiratory viruses and recurrent vibration of the upper airway may promote localized inflammation followed by swelling and over-expression of inflammatory cytokines.

#### *Neurological Complications Associated with OSA*

OSA is associated with two important complications thought to underlie neurocognitive morbidity: hypoxemia and sleep fragmentation (Sforza & Roche, 2012). The primary diagnostic criterion for OSA is frequent periods where the individual stops breathing for ten seconds or more during sleep. In severe patients, respiration may stop for periods of over three minutes or occur hundreds of times per night (Jackson et al., 2011). These episodes terminate when the patient wakes up to breathe and result in fragmented sleep. Additionally, hypoxemia occurs during apneic events, causing a disruption in the biochemical and hemodynamic state of the central nervous system with blood oxygen levels reported to be at 50% below normal.

In addition, OSA is associated with increased risk of stroke and silent cerebral infarction (Lal, Strange, & Bachman, 2012). These complications are thought to be related to inflammatory processes which cause endothelial dysfunction leading to constriction of blood vessels in the brain. Specifically, OSAS suppresses the vasodilator molecule nitric oxide (NO) thereby causing blood vessel constriction and increased risk of brain injury (Ip et al., 2000). Studies have suggested these complications are associated with a decrease in gray matter in the hippocampus, anterior cingulate, cerebellum, and the frontal, parietal, and temporal lobes (Canessa et al., 2011; Gale & Hopkins, 2004; Macey et al., 2002; Morrell et al., 2003; Torelli et al., 2011) as well as decrease in white matter in the frontal cortex (Algin et al., 2012).

Not surprisingly, the long-term consequences of OSAS in children include behavioral and neurocognitive deficits. Behavioral problems are the most commonly encountered complication of OSAS, and the vast majority of studies consistently report some association between OSAS and hyperactivity, attention deficits, impulsivity and attention deficit hyperactivity disorder-like symptoms. For example, one study (Rosen et al., 2004) reported children ranging from mild to severe symptoms on the SBD spectrum had a higher prevalence of problem behaviors with the strongest and most consistent associations for hyperactive and aggressive behaviors. Similarly, symptoms of hyperactivity, inattention, and aggressiveness were significantly higher than controls in a large sample of 5-year-old children (Gottlieb et al., 2003).

In addition to the behavioral comorbidities of OSAS, there are many reports of children with OSAS demonstrating cognitive impairments (Lal et al., 2012; Sforza & Roche, 2012). Problems in school performance have been reported in children with OSAS, and are associated with more extensive behavioral disturbances such as restlessness, aggressive behavior, excessive daytime sleepiness and poor test performance (Gozal, 1998). Impairments in executive functioning have been commonly reported in adults with SBD and also in children (Gozal, Kheirandish-Gozal, Bhattacharjee, & Spruyt, 2010; Naismith, Winter, Gotsopoulos, Hickie, & Cistulli, 2004). For example, preschoolers with SBD have shown lower general intelligence, poorer executive functioning, and poorer memory skills than unaffected peers (Beebe et al., 2004; Gottlieb et al., 2004).

Interestingly, treatments for OSA have resulted in improvements in learning and behavior problems (Friedman et al., 2003; Gozal & Pope, 2001; Lal et al., 2012;

Montgomery-Downs, Crabtree, & Gozal, 2005), suggesting these neurocognitive and behavioral deficits may be at least partially reversible in this clinical population. The most common treatment involves the use of continuous positive airway pressure (CPAP). This treatment has been shown to help reverse some neurological symptoms (Bedard, Montplaisir, Malo, Richer, & Rouleau, 1993; Ferini-Strambi et al., 2003; Gale & Hopkins, 2004) and evidence also suggests brain regions with decreased grey matter may regain some volume following treatment (Canessa et al., 2011).

#### *Epidemiology and Pathophysiology of Sickle-Cell Disease*

SCD refers to a group of genetic disorders that are characterized by the production of abnormal “S-type” hemoglobin (Hb-S) (Rees, Williams, & Gladwin, 2010). Production of this type of hemoglobin occurs when a person inherits a gene for the S-type hemoglobin from one biological parent along with another abnormal hemoglobin gene from the other biological parent. The disease occurs most frequently in people of African descent with about 1:400 African American newborns having the disease. Overall, close to 100,000 persons are affected by the disease in the United States (Hassell, 2010). The most common form of SCD is the homozygous variant called sickle cell anemia (HbSS), found in approximately 65% of patients. The second most common form is the heterozygous variant (HbSC), found in approximately 25% of patients. Two other common forms of the disease include sickle  $\beta$  plus thalassemia (HbS $\beta^+$  - 8%) and sickle  $\beta$  zero thalassemia (HbS $\beta^0$  - 2%) (Gold, Johnson, Treadwell, Hans, & Vichinsky, 2008). Patients with the HbSS and HbS $\beta^0$  genetic sub-types tend to suffer from the most severe complications (termed here “high risk genotypes”), while those with the HbSC and HbS $\beta^+$  variants tend to experience milder symptoms (Kirkham, 2007). The main

symptoms associated with SCD include episodes of pain, acute chest syndrome, pulmonary hypertension, neurological complications (including stroke and silent cerebral infarcts), hemolytic anemia, priapism, and organ damage such as osteonecrosis, and renal failure (Kato, Gladwin, & Steinberg, 2007).

Despite these severe complications, life expectancy for individuals with SCD has improved over the last several decades from only about 50% of all patients with SCD surviving beyond the age of twenty (Prabhakar, Haywood, & Molokie, 2010) to median ages at death of 42 and 48 for men and women (respectively) with sickle cell anemia, and 60 and 68 for men and women with hemoglobin SC disease (Platt et al., 1994). As life expectancy continues to improve, more attention needs to be paid to the serious neurocognitive complications associated with SCD, which have a significant negative impact on quality of life (McClellan, Schatz, Sanchez, & Roberts, 2008; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005).

The pathophysiology of SCD primarily results from the production of sickle hemoglobin (Hb-S). This type of hemoglobin, under low oxygen conditions (as found in distal arteries in the body), causes red blood cells (RBCs) to take on an abnormal crescent shape, become more viscous, lose oxygen carrying capacity, and break down prematurely (Rodgers, 1997; Steinberg, 2008). When Hb-S molecules in RBCs are deoxygenated, the cell wall polymerizes, deforming the cell's shape and weakening its structure. Multiple cycles of oxygenation and deoxygenation ultimately lead RBCs to become permanently sickled and breakdown prematurely. The cells' abnormal shape and early breakdown result in a cascade of chemical events leading to multiple complications including the

occlusion and constriction of blood vessels, as well as lower oxygen carrying capacity, hemolytic anemia, and organ damage.

Occlusion will likely first occur in smaller blood vessels when sickle cells adhere to vascular endothelium, causing further obstruction as platelets and white blood cells (WBC) also become entrapped (Steinberg, 2008). Larger vessels leading to the lungs and brain can also become occluded, likely due to injury of the endothelial wall, which causes an inflammatory reaction. Increased levels of cytokines due to inflammation also play an important role in vaso-occlusion by enabling RBCs to stick to vascular endothelium (Pathare, Kindi, Daar, & Dennison, 2003). Evidence suggests that a multitude of other factors related to elements in the sickle cell, on the cell, the endothelial cells, and other elements in the vascular walls and plasma are related to vaso-occlusion pathophysiology; however, the exact mechanisms are not yet fully understood (Steinberg, 2008).

Hemolytic anemia is another important disease mechanism that mainly results from the breakdown of RBCs within blood vessels (hemolysis) (Abboud & Musallam, 2009). Increased amounts of free hemoglobin that is released into the blood stream rapidly react with the nitric oxide (NO) molecules and convert them to nitrite. Normally, NO plays a crucial role in vaso-dilation and its decreased bioavailability results in further constriction of blood vessels.

#### *Neurological Complications Associated with SCD*

Together, hemolytic anemia and vaso-occlusion put patients with SCD at high risk for developing cerebro-vascular disease (Schatz & Puffer, 2006). Direct effects of SCD on the brain include strokes and silent cerebral infarcts, as well as localized metabolic and perfusion deficits and diffuse effects on neurons. Cerebral vascular disease



is rare in childhood, but cerebral lesions from stroke and silent cerebral infarcts occur in approximately 20% of children with HbSS (Pegelow et al., 2002). In SCD, hemolysis can lead to insufficient oxygen and glucose delivery to the brain, resulting in deficits in brain function without structural tissue death (Powars et al., 1999; Reed, Jagust, Al-Mateen, & Vichinsky, 1999), and is also linked to higher rates of stroke (Abboud & Musallam, 2009; Kato et al., 2007; Kwiatkowski et al., 2009). Imaging studies in children with SCD have found considerable variability in the location of neurological damage (Grueneich et al., 2004; Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006; Kwiatkowski et al., 2009; Pegelow et al., 2002; Wang et al., 2008). The majority of patients appear to have lesions involving the frontal lobe, followed by the parietal lobe, the basal ganglia, thalamus, and the temporal lobe. Many children have more than one lesion that often spans more than one lobe or region. Lesions tend to encompass both cortex and white matter and frequently occur in border zones between middle and anterior cerebral arteries (Kirkham, 2007). More diffuse brain effects are also seen in this population across different regions of gray matter, which may represent neuronal changes caused by chronic oxygen deprivation induced by hemolytic anemia (Steen et al., 2003).

In addition to overt stroke or silent cerebral infarcts, there appears to be additional sources of cognitive deficits in children with sickle cell disease with a number of mechanisms that have been put forth as potential etiological sources such as pre-term birth, and/or low birth-weight (particularly if the mother has SCD), brain perfusion deficits without cerebral infarction, and other more speculative mechanisms (Schatz & Puffer, 2006). For example, pre-term birth can result in white matter injury and decreased volume of cortical tissue and cognitive deficits later in childhood. Children with SCD

also show nutritional deficiencies compared to controls. This may be due to increased metabolic demands related to their disease that are not met, and acute periods of illness and hospitalizations (Schatz & Puffer, 2006). Nutritional deficits may also be associated with cognitive deficits in these children (Puffer, Schatz, & Roberts, 2009).

Taken together, disease processes related to hemolytic anemia, vaso-occlusion, and other factors put children with SCD at high risk for neurocognitive impairments. Studies have suggested that children with SCD who have suffered from overt stroke have experienced an average of a 10-15 point decline in IQ scores compared with normative age groups as well as significant educational attainment deficits (Schatz & McClellan, 2006). Cognitive deficits that impact academic performance are also common in approximately 75% of children suffering from silent cerebral infarcts (Schatz, Brown, Pascual, Hsu, & DeBaun, 2001). Children with SCD and no known brain insults have been found to have specific deficits in attention and executive functions, which include inhibition, planning, organization, sequential processing, response monitoring, decision making, judgment, reasoning, mental flexibility and working memory (Berkelhammer et al., 2007). Deficits in working memory are especially important as they can limit performance in other areas such as problem solving and language comprehension, ultimately leading to lower academic attainment (Schatz, 2004). For example, in one study children with high-risk genetic subtypes have been found to have deficits in several language domains (Schatz, Puffer, Sanchez, Stancil, & Roberts, 2009). Cognitive deficits can be shown early in the pre-school period in high-risk subtypes of SCD (Schatz & Roberts, 2007). Although cognitive deficits in low-risk genotypes have not been well

studied to date, if these occur, they are most likely to happen later in the middle-childhood period (Schatz et al., 2009).

#### *Epidemiology of Co-occurring SCD and OSA*

The population prevalence of SBD, including OSA, in children with SCD is not well-documented, though several studies have examined base rates in relatively small samples of convenience. There is a high occurrence of SBD, ranging from 44% to 79%, among children with SCD referred due to concerns about sleep. Studies examining children that were not selected based on clinical concerns have suggested prevalence rates of approximately 20%, which appears much greater than the prevalence of 1-4% in children without SCD (Strauss et al., 2012). Additionally, there is a reported high prevalence (55%) of obstructive adenotonsillar hypertrophy in children and adolescents with SCD, a primary cause of OSA that is also linked with an increased risk of cerebrovascular morbidity (Abou-Elhamd, 2012). One study by Brooks and colleagues (1996) reported 44% of children with SCD referred for evaluation of OSA were diagnosed with the condition as measured by over-night polysomnography. In another study with a small sample of children (n=19), Kaleyias and colleagues (2008) reported 63% of patients with SCD referred for evaluation were found to have OSA as measured by polysomnography. The highest prevalence rate in children referred for OSA evaluation was 69% (Rogers et al., 2010). A more conservative prevalence rate of 19.4% was reported by Strauss and colleagues (2012). This study measured rates of OSA from a sample of children with SCD who were not pre-screened for OSA-related symptoms, which is a better estimate of prevalence rate than prior studies examining children referred for sleep studies. Another recent study also reported a prevalence rate of 23.7%

(Goldstein et al., 2011) in a sample of only high-risk genetic subtypes of SCD (HbSS and HbS $\beta^0$ ). Results from these studies suggest SBD are common in SCD, though better studies of prevalence rates are needed as well as an understanding of the screening procedures that lead physicians to recommend an evaluation for OSA diagnosis.

Research to-date suggests that OSAS affects children across the spectrum of SCD severity, but it is unclear whether there are differences in severity between genetic subtypes. Brooks and colleagues (1996) reported no statistically significant differences in OSA severity between mild and severe SCD genetic subtypes. However, this study had a small sample size (n=28) and therefore, conclusions are difficult to make. Similarly, Daniel and colleagues (2010) reported no statistically significant differences in SBD between mild and severe SCD patients in a larger sample of children (n=54); differences in severity of OSA were meaningful when the SCD group in its entirety was compared to healthy controls. Countering these results, others have found that patients with more severe SCD genetic subtypes (HbSS) had more OSA symptoms than those with lower-risk subtypes (HbSC) (Rogers et al., 2010). The reported lack of differences in OSA symptoms between mild and severe genetic subtypes of SCD in some studies is surprising since patients with more severe disease tend to suffer from more complications. Results from these studies may suggest that OSA could serve as a useful predictor of other complications such as neurocognitive morbidity over and above one's genetic subtype. However, the conflicting conclusions emerging from the literature do not lend themselves to making strong statements about sleep apnea across SCD genetic subtypes.

The methods of screening and selection criteria across studies of SBD differ, which may help account for some of the discrepant findings. Notably, several studies reported prevalence rate of OSA in groups of children who were referred for OSA evaluation. However, initial screening methods to determine those children that should be evaluated varied among studies. Studies recruited participants who had suspicious symptoms of OSA as evaluated by their primary care physician (Brooks et al., 1996), used established questionnaires (Kaleyias et al., 2008), established clinical guidelines (Maddern, Reed, Ohene-Frempong, & Beckerman, 1989; Rogers et al., 2010) or did not use or report the screening procedure (Goldstein et al., 2011; Strauss et al., 2012). This variability reflects different screening methodologies as well as sampling decisions (pre-screening vs. no screening) which likely account for some of the observed variability in prevalence rates and could confound the examination of morbidity associated with SBD.

Surprisingly, although considered clinically important (Kemp, 1996), studies did not report prevalence rates of OSA by age in children with SCD. In one report that focused only on OSA (Jackson et al., 2011), the authors mentioned that age can be considered a risk factor for OSA, but no studies to date have addressed this potentially significant relationship in the SCD population. Given that OSA has been reported to occur in children across a wide range of age, there is a need for studies to better characterize how the prevalence of OSA varies by age.

#### *Common Pathophysiological Mechanisms of SCD and OSA*

Hypoxia and hypoxemia are thought to be important drivers of red blood cell (RBC) polymerization and sickling in SCD. OSA is associated with hypoxia, but other chemical processes related to the condition also provide an environment favorable to

polymerization of sickle RBCs (Okoli, Irani, & Horvath, 2009). Additionally, sickle cells tend to adhere to vascular endothelium, causing vaso-occlusion, and hypoxia may induce adhesion of these cells to vascular walls, thereby exacerbating symptoms further (Sultana, Shen, Rattan, Johnson, & Kalra, 1998). Recently, it has also been suggested that neurocognitive deficits tend to coexist with endothelial dysfunction in children with OSAS, and that both of these consequences may share similar pathophysiological mechanisms (Gozal et al., 2010). Changes in brain metabolic function and systemic inflammatory responses have been identified as potential factors in these complications (Gozal, Crabtree, Sans Capdevila, Witcher, & Kheirandish-Gozal, 2007).

Hypoxia induced by OSA may also lower the bioavailability of nitric oxide (NO) in the blood, thereby increasing vasoconstriction and the risk for developing neurological complications such as stroke and silent cerebral infarcts (Kaleyias et al., 2008; Kirkham et al., 2001; Prengler, Pavlakis, Prohovnik, & Adams, 2002). The combined pathological effects of OSA and SCD on NO bioavailability make this sub-population particularly at risk for developing neurological complications.

Another important common factor in the pathophysiology of SCD and OSA, pro-inflammatory cytokines can be activated as a response to infection and cause inflammatory responses. Persons with SCD suffer from many infections due to factors such as tissue ischemia and spleen dysfunction (Rees et al., 2010) potentially making them more vulnerable to the pathophysiologic effects of cytokines. Inflammatory processes related to SCD and OSA may be exacerbated by cytokines and put patients at risk for further complications (Conran, Franco-Penteado, & Costa, 2009). Cytokines have also been associated with increased risk of stroke (Tuttolomondo, Di Raimondo, di

Sciacca, Pinto, & Licata, 2008; Tuttolomondo et al., 2009). Specifically, cytokines are found in the central nervous system and are activated after cerebro-vascular injury has occurred. They in turn produce pro-inflammatory and pro-coagulant effects on endothelium. It may be that hemolytic anemia that is associated with increased stroke risk (Abboud & Musallam, 2009), leads to cerebro-vascular injury that in turn produces more inflammation. Interestingly, a recent study (Ameringer & Smith, 2011) has also suggested that fatigue, a common symptom in SCD, may be related to the action of cytokines that are activated in response to vascular injury and can interrupt sleeping patterns. It may be that interrupted sleeping patterns related to hypoxia and OSA also induce further cytokine activity and exacerbate sickle cell adhesion, vaso-occlusion, vaso-constriction, and risk for neurological complications and associated cognitive dysfunction.

Blood flow velocity in the middle cerebral artery as measured by transcranial Doppler (TCD), which provides an indication of the adequacy of brain blood flow velocity, has emerged as an important predictor of cognitive outcomes for children with OSAS (Hogan, Hill, Harrison, & Kirkham, 2008) and for children with SCD (Hogan, Kirkham, et al., 2006; Hogan, Pit-ten Cate, Vargha-Khadem, Prengler, & Kirkham, 2006; Sanchez, Schatz, & Roberts, 2010; Schatz, McClellan, Puffer, Johnson, & Roberts, 2008). TCD is a screening tool commonly used to identify children with high risk of stroke in SCD (Adams, 2005; Quinn & Sargent, 2008) and can detect large-vessel cerebrovasculopathy. Abnormally high blood-flow velocities in these vessels are related to stroke, stenosis, severe anemia, and tissue hypoxia and therefore could be an indicator of chronic hypoxia and/or brain perfusion deficits (Bernaudin et al., 2005). To date,

however, the relationship between brain blood flow velocity and cognitive deficits in children with SCD suffering from OSA has only been examined in one investigation (Kirkham et al., 2001). These authors reported that elevated brain blood flow velocities as measured by TCD and OSA severity were associated with higher rates of neurocognitive morbidity. Given the overlap in underlying disease mechanisms of SCD and OSA, there is a further need to investigate the use of TCD as an indicator of cognitive risk in children who suffer from co-occurring SCD and OSA.

Surprisingly, few investigations to date have attempted to address the link between SCD and OSA in studying neurocognitive morbidity associated with these conditions. Robertson and colleagues (1988) reported on one six-year-old child with SCD and OSA who suffered from stroke. The authors suggested that severe OSA and related hypoxemia played a major role in precipitating the stroke and therefore the presence of OSA should be considered an important indicator of stroke risk. The most comprehensive study in this area was conducted by Kirkham and colleagues (2001) who prospectively followed 95 children with SCD, measuring cerebral blood flow velocity and night-time oxygen saturation. Of this sample, nineteen children who later suffered from strokes had significantly higher cerebral blood flow velocities and lower oxygen saturation. A more recent investigation (Hollocks et al., 2012) was the first to utilize magnetic resonance imaging (MRI), as well as neuropsychological measures to examine the relationship between SCD, OSA and neurocognitive dysfunction. Although only reporting from a small sample (n=10), this study found that higher OSA severity was associated with lower cognitive functioning, particularly on measures of executive function. From the paucity of research reports it is clear that further attention is warranted to this area of



investigation. Studies are needed to elucidate the relationship between OSA and SCD and their potential interactive effects on cognitive functioning in children. Given the evidence that some children with SCD have been found to suffer from cognitive deficits in the absence of cerebral infarcts (Berkelhammer et al., 2007; Schatz & McClellan, 2006), OSA may be an important additional factor that accounts for cognitive deficits. This may be especially relevant in light of evidence suggesting that treating OSA can reverse some of its negative effects on cognitive functioning (Friedman et al., 2003; Gozal & Pope, 2001; Montgomery-Downs et al., 2005).

### *Summary*

Review of the literature on SCD and OSA has revealed significant variability in prevalence rates of OSA occurring in children with SCD. Studies to date have not adequately clarified the exact screening procedures used to decide which children should be referred for evaluation of OSA. Variability in these procedures has likely contributed to the large range (5-79%) of prevalence rates reported in the literature. Moreover, studies have not yet established prevalence rates by age and there is a need for further research to describe the potential relationship between age and prevalence of OSA in children with SCD.

Additionally, multiple studies have reported neurocognitive complications in children with OSA, or SCD but the literature linking these two conditions is severely lacking. Only a handful of reports (Hollocks et al., 2012; Kirkham et al., 2001; Robertson et al., 1988) have attempted to investigate the extent of neurocognitive morbidity in children located at the intersection of these two debilitating conditions. Given the evidence of common underlying biological mechanisms of OSA and SCD, it is likely that

children suffering from the two conditions are at a particularly high risk for developing neurocognitive complications, highlighting the importance of further research in this area.

### *Aims and Hypotheses*

The first aim of this study is to describe the prevalence rate of OSA in children with SCD and examine factors that impact the prevalence rate. We examine prevalence rates as measured in a large, representative sample of children with SCD as well as in the sub-sample referred for OSA evaluation after screening.

*Hypothesis 1A:* Based on previous reports (Strauss et al., 2012), we hypothesize that the prevalence rates of OSA in the total sample should be approximately one in five (20%). In the sub-sample of children who were referred for OSA evaluation due to concerns about snoring, we hypothesize prevalence rates to be higher; for the purposes of this study we will describe the proportion of true positives (children correctly identified as having SBD) for this procedure.

*Hypothesis 1B:* The research to date has presented conflicting evidence as to the prevalence of OSA across SCD genetic subtypes. Since patients with the HbSS and HbS $\beta^0$  genetic sub-types tend to suffer from the most severe complications, while those with the HbSC and HbS $\beta^+$  variants tend to experience milder symptoms (Kirkham, 2007), we hypothesize that rates of OSA will differ between low risk (HbSC and HbS $\beta^+$ ) and high risk (HbSS and HbS $\beta^0$ ) subtypes with the high risk group showing higher rates.

*Additional Goal:* We aim to describe the relationship between age and OSA in children with SCD. The paucity of research addressing the relationship between age and prevalence rates of OSA in children with SCD compels this goal to be less specific focusing on the extent of this relationship or the best shape to describe the age curve.

The second aim of this study is to examine the relationship between OSA and neurocognitive morbidity in children with SCD.

*Hypothesis 2:* Based on the demonstrated relationship between OSA and cognitive dysfunction (Gottlieb et al., 2004; Gottlieb et al., 2003; Jackson et al., 2011; Kheirandish & Gozal, 2006; Rosen, 2004; Rosen et al., 2004), we hypothesize that children with OSA will exhibit more neurocognitive morbidity than those without OSA. Children with SCD and OSA will be compared to children with SCD but no OSA, statistically controlling for low vs. high risk genotype. We will examine functioning in areas of language, processing speed, visual-motor abilities, and academic skills.

*Additional goal (1):* Based on previous research, symptoms of hyperactivity, inattention, and aggressiveness have been found to be higher in children with OSA (Gottlieb et al., 2003; Gozal, 1998). We will describe differences between groups on these variables using the Strengths and Difficulties Questionnaire (SDQ). We will additionally explore group differences on other dimensions of the SDQ including peer and emotional problems.

*Additional Goal (2):* we aim to explore other areas of morbidity such as cerebral blood flow, pain, stroke, and hospitalizations for infections. We hypothesize that OSA will be associated with greater morbidity. Additionally, children with OSA are hypothesized to exhibit higher brain blood velocities as measured by TCD (Kirkham et al., 2001) than unaffected peers.

*Additional Goal (3):* we aim to describe sleep study variables for the OSA group and examine differences in OSA severity between low and high risk genetic subtypes. The high risk SCD group is hypothesized to exhibit higher severity of OSA.

## Chapter 2: Methods

### **Participants**

Participants were children with SCD receiving routine medical care at a pediatric hematology/oncology outpatient clinic in the southeastern USA. Approximately 450 families attend the clinic annually for their children's medical care. Medical chart reviews were conducted for a total of 300 children with SCD who were screened for OSA as part of their routine care between April 2002 and April 2013. A search of the medical record system using specific diagnostic codes for snoring, and OSA as defined by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization., 2004) identified 171 children. Chart reviews were then conducted for a sample of 129 children with SCD with negative screenings for OSA that served as a control group. A case-control matching system was used for matching the two groups according to age (within 4 months for children less than six years; within 6 months for children 6 -12 years; within 12 months for children 13 years and older), genotype, gender, and the control closest in hemoglobin level from the most recent routine blood lab, though minor deviations from this matching criteria occurred as described below.

Additional record reviews were later conducted, as described below, that allowed us to identify children who had overnight polysomnography exams, but who had not been assigned one of the diagnostic codes above. Data were collected from electronic and paper records using a standardized coding form and included insurance status, SCD

genetic subtype based on electrophoresis, routine blood lab results, height, weight, and body mass index (BMI). In addition, information was collected pertaining to history of preterm birth, and history of major disease complications including hospitalizations, pain, acute chest syndrome, pneumonia, transfusions, splenic sequestration, infection, leg ulcers, pulmonary hypertension, hydroxyurea treatment, and neurological complications, as well as TCD results.

Inter-rater reliability for the medical record reviews was assessed. 25% of the records ( $n = 68$ ) were selected at random and reviewed by a secondary coder blinded to the first coder's data. Inter-rater reliability was very good to excellent. Kappa values ranged from .87 to 1.0 for variables with narrow response ranges. Two variables, episodes of pneumonia and pain requiring hospital care, had large enough ranges to be considered ordinal rather than nominal. In such cases the kappa statistic is problematic as it is used generally used with nominal variables. Rank-order correlation were used for these variables and yielded values of  $r = .98$  and  $.97$ , respectively.

For the sub-sample receiving overnight polysomnography exams, additional variables related to sleep apnea were collected for descriptive purposes. These included general sleep variables such as total sleep time, sleep onset latency, sleep efficiency, REM sleep latency, and % REM sleep. Information on respiratory functions was collected including the apnea/hypopnea index (AHI) and/or respiratory disturbance index (RDI) as well as oxygen saturation (mean saturation and lowest saturation during sleep). OSA diagnosis was made based on results of overnight polysomnography. Of note, children who received a diagnostic code for OSA or snoring but did not have a sleep study done or did not have one available in the electronic or paper medical record ( $n =$

28) were excluded from the OSA group even if their chart indicated an OSA diagnostic code. Medical record reviews were conducted on these cases for descriptive purposes.

All children seen at the clinic were also offered routine cognitive screening exams at the beginning of middle childhood (approximately 5-7 years of age) since September of 2004 with over 90% of children participating in this routine screening. Because some children attend visits only every six months and there are occasional missed appointments, children as early as 4 years, 9 months or as late as 8 years, 3 months were also included to ensure that every child had the opportunity to participate in the screening.

Children who took part in the screening completed a battery of cognitive tests administered in a single, 60- to 90-minute session. Assessments were completed in the clinic during routine appointments by licensed psychologists or graduate students trained in administration of the measures according to the standardized testing procedures provided in the test manuals. Children who were experiencing fatigue or pain on the day of testing were rescheduled for their next clinic visit. Caregivers received letters with results and a phone call to discuss recommendations, such as further psycho-educational testing, if results suggested possible cognitive difficulties.

## **OSA Screening and Diagnosis**

### *Screening Procedure*

All patients are screened for symptoms of OSA at routine appointments. The hematologist asked parents whether the child is snoring. If they answered in the affirmative, follow-up questions include information on whether the snoring is loud and whether it is a concern for the parents. An answer in the affirmative to both these

questions prompted a referral for a sleep study to evaluate OSA symptoms. Additionally, the hematologist asked parents whether the child experiences early morning headaches and/or pain. The presence of these symptoms along with snoring also prompted and a referral to evaluate OSA symptoms. A diagnostic code for snoring is usually assigned in the medical record at this time.

### *Polysomnography*

Polysomnography is the electrographic recording of simultaneous physiologic variables during sleep and is currently considered the gold standard for objectively assessing sleep disorders (Roland et al., 2011). The polysomnography procedure and diagnosis of OSA are based on the current recommended guidelines for the evaluation of sleep disorders (Loughlin et al., 1996). Children who were referred for a diagnostic evaluation of sleep disorders underwent overnight polysomnography using the Cadwell Sleep System (Cadwell Laboratories, Inc. Kennewick, WA). A total of 16 channels were monitored including four electroencephalography (EEG) channels measuring electrical activity along the scalp, two electrooculography (EOG) channels measuring electrical activity associated with eye movements, and two leg electromyography (EMG) channels measuring electrical activity from skeletal muscles. Together these channels are used to determine wake/sleep state and arousals. Additionally, channels for electrocardiography (EKG) measuring heart rate changes and potential arrhythmias, as well as a snoring microphone, oxygen saturation, oronasal flow thermistor, abdominal respiratory movement, chest respiratory movement, chin EMG, and plethysmography used to measure chest and abdominal respiratory effort and discriminate between nasal and oral air flow were employed.

## Measures

The neuropsychological measures used in the screening procedure assessed language abilities, processing resources, visual-motor ability, and academic skills. Each of these measures were recently found to have robust effect sizes for differences between children with SCD at high risk for cognitive deficits and those with low risk or controls (Schatz et al., 2009). Therefore, they are likely to be sensitive in detecting deficits in this clinical population.

*Test of Language Development-Primary: Third Edition (TOLD-P:3).*

In the screening procedure, children's language abilities were assessed with three subtests taken from the Spoken Language Quotient of the TOLD-P:3 (Newcomer & Hammil, 1997) with one subtest from each of three language domains assessing syntactic, phonemic, and semantic processing abilities. Alpha coefficients for all TOLD subtests administered range from .80 to .91, and test-retest reliability coefficients range from .81 to .91, indicating high reliability across subtests. In addition, for African-Americans specifically, internal consistency reliability data reflects alpha values of .86 to .96 for subtests chosen for this study. Adequate validity of the TOLD has also been supported by analyses of item discrimination, item difficulty, and concurrent validity with similar language measures. In addition, item response theory analysis has shown very low cultural and gender bias on the TOLD. The syntactic domain was assessed using the Grammatical Understanding subtest requiring the child to select a picture that best demonstrates the meaning of sentences with increasingly complex syntax. Phonological processing was assessed using the Word Discrimination subtest, which requires the child to decide whether two similarly sounding words are the same word or two different



words. Lastly, the semantic domain was measured via the Oral Vocabulary subtest, which requires children to provide definition for orally presented words.

#### *Tests of other cognitive abilities*

The Decision Speed subtest from the Woodcock-Johnson test of Cognitive Abilities, 3<sup>rd</sup> edition (Woodcock, McGrew, & Mather, 2001b) was used to assess processing speed. High reliability coefficients have been reported for this subtest in five to seven year olds (range = .78 to .90). Psychometric data also suggest adequate construct validity, as well as low cultural bias. The Letter-Word Identification and the Applied Problems subtests from the Woodcock-Johnson test of Achievement, 3<sup>rd</sup> edition (Woodcock, McGrew, & Mather, 2001a) were used to assess academic/pre-academic skills. High reliability coefficients have been reported for these subtests as well (range = .92 to .99). Validity data from the WJ-III Tests of Achievement has shown adequate construct validity, as well as low cultural bias. Lastly, the Beery-Buktenica Developmental Test of Visual-Motor Integration (DTVMI), 5<sup>th</sup> edition (Beery & Beery, 2004) was used to assess visual-motor capabilities. Reliability coefficients for the Beery VMI are all above .80, and validity data show evidence of construct and concurrent validity.

#### *Strengths and Difficulties Questionnaire*

Parents completed the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001) as part of the screening procedure. The SDQ is a brief behavioral screening questionnaire designed for children aged 3-16 years. It is comprised 25 items intended to measure five scales including emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior. Each scale

yields a score for the specific dimension being assessed; additionally, the scores can be summed to yield a total score for the measure. The SDQ is commonly used for clinical assessment and screening for psychological disorders in normal child populations (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000) and also in children with chronic illness (Glazebrook, Hollis, Heussler, Goodman, & Coates, 2003). Internal consistency reliability for the SDQ is considered satisfactory (mean Cronbach's  $\alpha = .73$ ), as well as reliability measured by cross-informant correlation (mean  $r = 0.34$ ), or retest stability after 4 to 6 months (mean  $r = 0.62$ ) (Goodman, 2001). The SDQ has demonstrated construct validity with scores above the 90th percentile predicting a substantially raised probability of independently diagnosed psychiatric disorders (mean odds ratio: 15.7 for parent scales, 15.2 for teacher scales, 6.2 for youth scales) (Goodman, 2001). In another study, multi-informant (parents, teachers, older children) SDQ scores have identified individuals with a psychiatric diagnosis with a specificity of 94.6% (95% CI 94.1-95.1%) and a sensitivity of 63.3% (59.7-66.9%) (Goodman et al., 2000).

### **Data Analysis**

*Hypotheses 1A and 1B:* To address the first aim of this study, analyses will be conducted to examine the prevalence rate of OSA in a clinic-wide sample across ages and genetic sub-types. Prevalence rates will be calculated along with a 95% confidence interval. Binomial proportion confidence intervals were calculated with the Wilson score interval (Newcombe, 1998). The rates of OSA in children referred for evaluation in this sample will also be described. Differences in prevalence of OSA between genetic subtypes (low risk vs. high risk genotypes) will be described with a 95% confidence interval. These

analyses will also be reported for cases in which an OSA diagnostic code was provided without a sleep study.

*Additional goal:* Histograms and descriptive statistics will be used to describe prevalence rate of OSA by age and the relationship between the variables.

*Hypothesis 2:* To examine the differences in cognitive functioning, multivariate analysis of covariance (MANCOVA) procedures will be used with group (SCD and SCD/OSA) as the independent variable and cognitive measures as the dependent variables. SCD risk (“high risk” vs. “low risk” genotype) will be used as a covariate in the analysis. Two MANCOVAs will be used to examine group differences in language functioning (TOLD subtests), and academic skills (WJ-III Letter-Word Identification and Applied Problems). Two ANCOVAs will be used to examine differences in processing speed (WJ-III Decision Speed) and visual spatial ability (Beery VMI). Alpha of 0.05 will be used for statistical significance. Additional exploratory analyses were conducted to examine if severity of sleep apnea was related to cognitive functioning. Sleep study clinical categorization (mild vs. severe sleep apnea) was examined with similar MANCOVA and ANCOVA models as described above. Correlations between cognitive test performance and the sleep study variables of mean nocturnal oxygen saturation and minimum nocturnal oxygen saturation were examined based on their previous association with SCD morbidity (Hargrave, Wade, Evans, Hewes, & Kirkham, 2003; Kirkham et al., 2001).

*Additional goals (1) and (2):* Between-group t-tests will be used to describe differences in hyperactivity, inattention, and aggressiveness (conduct problems) as well as emotional symptoms and peer relationship problems as indicated by the Strengths and Difficulties Questionnaire (SDQ). We will also tabulate the total number of complications from the

medical record reviews to assess the hypothesis of higher SCD morbidity in children with OSA. Morbidities will be organized into groupings to capture a profile of morbidity types for descriptive purposes. There was significant positive skew in these variables. Therefore, Mann Whitney U tests were used to avoid the influence of outliers on results. Z-scores from the Mann Whitney U were used as the test statistic given the sample size. An alpha level of 0.05 was used to evaluate each hypothesis.

*Additional goal (3):* Statistics for sleep study variables will be examined for descriptive purposes. Between-group t-tests will be used to describe differences in OSA severity for the low and high risk genetic subtypes. All group comparisons will have an alpha level of 0.05. All analyses are performed using SPSS version 21.

## Chapter 3: Results

### Sample Description

The clinic-wide sample consisted of 641 individuals (46.33% female) ranging in age between 4 months and 32 years at the time of medical record reviews who carry a diagnosis of SCD (M = 11.5; SD = 6.9). The major genetic subtypes identified were HbSS (58.2%), HbSC (25.7%), HbSβ<sup>+</sup> (12.2%), and HbSβ<sup>0</sup> (2.2%). 1.1% of cases were identified as “other” genetic subtypes. The chart review identified 171 cases (26.68%; 95% CI 23.4% - 30.24%) as positive screenings for OSA based on diagnostic codes provided in their medical record or sleep study results indicating an OSA diagnosis. Of the positive screenings, 143 cases (83.63%; 95% CI 77.36% - 88.43%) had sleep studies conducted. The 28 remaining cases had no sleep study data available because it could not be obtained or was not done. Therefore a positive OSA diagnosis could not be made or confirmed from sleep study results. These cases were not used in computing the overall proportion of OSA cases in the total sample. Of the 143 positive screenings, 7 cases (5%; 95% CI 1.43% - 8.57%) did not receive an OSA diagnosis in the medical record following a sleep study. Figure 3.1 presents a flow chart for OSA screening and sleep study results.

The matched control group consisted of 129 individuals matched by age (within 4 months for children less than six years; within 6 months for children 6 -12 years; within 12 months for children 13 years and older), genotype, gender, and the control closest in hemoglobin level from a routine blood lab. We located 111 cases with a precise match

(81.62%). In cases where a precise match was not possible, we attempted to first match by genotype followed by age, closest hemoglobin level, and gender. In 4 cases (2.94%) where an exact match by genotype was not possible, we matched participants by similar genotype (“milder” vs. “more severe”). Due to an uneven distribution of cases by age, 13 cases (9.56%) were matched outside of the desired age range. In these cases, the mean number of months outside the specified age range was  $M = 16.1$ ;  $SD = 8.98$  and ranged from 7 to 38 months. The median number of months was 13. One case (.75%) was not matched by gender. Lastly, we were unable to locate an appropriate match for 7 of the 136 OSA cases (5.15%) among children with negative screenings. The 7 cases with positive screenings, but negative sleep study exams were used to complete the matching process with an equal number of cases and controls.

### ***Hypothesis 1A***

Based on previous prevalence estimates (Strauss et al., 2012), we hypothesized that the prevalence rates of OSA in the total sample should be approximately one in five (20%). This hypothesis was supported. In the clinic-wide sample, 136 cases (21.22%; 95% CI 18.23% – 24.55%) of individuals were diagnosed with some form of OSA based on sleep study data. The screening procedure employed at the clinic correctly identified 136 of 143 cases referred for a sleep study (hit rate = 95.1%; 95% CI 90.23% - 97.61%). The hit rate was determined by dividing the number of confirmed OSA cases based on a sleep study ( $n = 136$ ) divided by the number of positive screenings ( $n = 143$ ).

### ***Hypothesis 1B***

We hypothesized that rates of OSA will differ between “low risk” (HbSC and HbS $\beta^+$ ) and “high risk” (HbSS and HbS $\beta^0$ ) genetic subtypes with the high risk group

showing higher rates. Of note, we identified three relatively rare variants of the disease as part of the chart review. Three cases of HbS/o Arab and two cases of HbS/D were also included in the analysis as part of the “high risk” group; two cases of HbS/HPFH-1 were included in the “low risk” group (Rees et al., 2010). Of the 396 cases (61.78%) included in the “high risk” group, 108 cases were diagnosed with OSA (27.27%; 95% CI 23.12% - 31.86%). In the “low risk” group, of 245 cases, only 28 cases (11.43%; 95% CI 8.03% - 16.02%) received an OSA diagnosis. Therefore, our hypothesis was supported.

Individuals with genetic subtypes that are associated with more severe complications also suffered higher rates of OSA. Individuals with more severe genetic subtypes were approximately 2.5 times more likely to have OSA.

We conducted separate analyses for the group of cases ( $n = 28$ ) who received a positive screening for OSA but for whom a sleep study could not be found. Eighteen cases had a “high risk” genetic subtype (64.29%; 95% CI 45.83% - 79.3%) while 10 cases had a “low risk” variant (35.71%; 95% CI 20.7% - 54.17%). It is unclear whether individuals who were positively identified during the screening procedure actually had OSA.

***Additional Goal: the relationship between age and OSA***

Figure 3.2 displays a histogram of age (in years) at time of sleep study for the OSA group. One case did not have the sleep study date and therefore age at time of sleep study could not be computed. The mean age of OSA diagnosis for the remaining 135 cases was  $M = 9.27$ ;  $SD = 4.73$  ranging from 1.39 to 19.26 years of age. The median and modal ages were 9 and 5 respectively suggesting a positively skewed shape. The obtained skewness and kurtosis values were approximately 2 standard deviations from zero and

therefore the curve may be considered as significantly deviating from a normal shape. The results indicate that in our sample most children reported symptoms and were diagnosed around 5 years of age followed by a decline between ages 6-8 and a sharp rise in diagnoses around age 9. Most patients (64.4%) were diagnosed on or before their 10<sup>th</sup> birthday; it is clear, however, that OSA diagnoses frequently occurred during the second decade of life as well.

Our second aim was to examine the relationship between OSA and neurocognitive morbidity in children with SCD. We first examined the time lag between cognitive testing and OSA diagnosis. On average, children received an OSA diagnosis approximately 0.85 years after cognitive testing ( $SD = 2.5$ ), with a median time to diagnosis of 0.46 years after testing, ranging between 3.5 years prior to testing to 7.9 years after testing. We further examined the time lag by OSA severity (mild vs. severe). The mild OSA group received an OSA diagnosis 1.2 years after testing on average ( $SD = 2.6$ ) with a median time of .72 years, ranging between 3.5 years before testing to 7.9 years after testing. The severe OSA group received a diagnosis on average .22 years after testing ( $SD = 2.2$ ) with a median time of .2 years, ranging from 3.4 years before testing to 3.9 years after testing. The mean time lag difference between the mild and severe OSA groups was not statistically significant,  $t(39) = -1.2$ ,  $p = .22$ . We found 16 cases (10 mild, 6 severe) received an OSA diagnosis within one year before or after cognitive testing; 8 cases (4 mild, 4 severe) were diagnosed more than one year prior to cognitive testing; and 17 cases (12 mild, 5 severe) were diagnosed more than one year after testing.

For our primary analysis of neurocognitive morbidity we examined group differences (SCD/OSA vs. SCD) in four cognitive domains: language functioning,



processing speed, visual-motor abilities, and academic skills. We also examined differences in emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior for descriptive purposes. Lastly, we described other areas of morbidity including stroke, pain, priapism, lung and other types of infection.

### ***Hypothesis 2***

We hypothesized that children with OSA will exhibit more neurocognitive morbidity than those without OSA. To follow-up on our primary hypothesis, we also conducted post-hoc analyses to examine group differences within the OSA group between mild OSA and severe OSA. We hypothesized that mild OSA group would show better performance on cognitive tasks than the severe OSA group. Because the comparison within the OSA group (mild vs. severe) was added post-hoc, we applied a more conservative alpha level of .025 in an attempt to better balance Type I and Type II errors. This was equivalent to applying a Bonferonni correction where there are two comparisons made (alpha level divided by number of comparisons). As an additional exploratory set of analyses we assessed the correlation between cognitive variables and two key sleep study variables linked previously to SCD morbidity: average nighttime oxygen saturation and lowest nighttime oxygen saturation.

Cognitive data were available for a sub-sample of 90 children. Within this group 41 children had OSA. Within the OSA group 26 children had mild OSA and 15 had severe OSA. OSA severity level was determined based on participants' AHI or RDI scores. These indices are generally used to determine a diagnosis of OSA and a severity level. Since the measurement of these indices was not consistent across participants (most

cases had either AHI or RDI), we used either score to assign a severity level based on established guidelines for children (Marcus & Katz, 2005): mild = 1-10 apnea, hypopnea, or other respiratory events per hour of sleep, severe = more than 10. Table 3.2 presents descriptive information for the sample. None of the groups differed significantly on age, gender, SCD risk, or genotype.

Two MANCOVAs for language functioning (TOLD Grammatical Understanding, Word Discrimination, and Oral Vocabulary subtests) and academic skills (WJ-III Applied Problems and WJ-III Letter-Word identification) and two ANCOVA procedures for processing speed (WJ-III Decision Speed) and visual-motor ability (DTVMI) were used in these analyses. The factor was OSA status (SCD only, mild OSA, and severe OSA) and the covariate was SCD risk (high/low) for all analyses.

#### *Assumptions of ANCOVA and MANCOVA*

Normality of the sampling distribution was assumed for all dependent variables. Generally when  $df > 20$ , the sampling distribution will be normal. Additionally, if the variable distribution is normal in shape, the sampling distribution will also be normal. An examination of histograms as well as skewness and kurtosis values for all dependent variables revealed no significant deviations from normality (see table 3.3).

ANCOVA also assumes independence of the covariate (SCD risk) and the factor (OSA status). Logistic regression with SCD risk as the outcome variable and OSA as the predictor indicated that OSA status did not differentiate between high and low risk genotypes,  $\chi^2(1) = 1.6, p = .205$ .

Finally, ANOCOVA assumes homogeneity of regression slopes: the DV in each group should have the same relationship with the covariate (SCD risk). This assumption

can be checked by adding the interaction term (OSA status X SCD risk) to the ANCOVA. A non-significant interaction term suggests the relationship between the covariate and the DV does not change depending on group. The analysis indicated that for the DTVMI the interaction term was not significant,  $F(2, 82) = 0.125$ ,  $p = 0.883$ . Similarly, for the WJ-III DS, the interaction term was also not significant,  $F(2,81) = 2.15$ ,  $p = 0.123$ . Therefore, this assumption was likely met for both dependent variables.

The MANCOVA procedure assumes multivariate normality. If every DV is univariate-normal, multivariate normality can be assumed. Since univariate normality for each DV is assumed (see above), this assumption of MANCOVA is likely met.

MANCOVA also assumes homogeneity of covariance matrices. For this assumption to hold, the univariate tests for equality of variances between groups should be met. Levene's test for equality of variance was non-significant for all dependent variables. Box's test for equality of the covariance matrices was also not significant for both MANCOVAs. Therefore this assumption is likely met.

Lastly, MANCOVA assumes the correlation between dependent variables must be equal across all levels of the factor. Similar to ANCOVA, including the interaction term in the analysis can help determine whether the assumption is likely to be met. A non-significant interaction term indicates that correlation among dependent variables does not vary across levels of the factor. For the language functioning MANCOVA, the TOLD-OV interaction term was not significant,  $F(2,75) = .231$ ,  $p = .795$ ; similarly for the TOLD-GU,  $F(2,75) = .043$ ,  $p = .958$ ; and for the TOLD-WD,  $F(2,75) = .302$ ,  $p = .74$ . For the academic skills MANCOVA, the WJ-III AP interaction term was not significant,  $F(2,82)$

= 1.37,  $p = .26$ ; and for the WJ-III LW,  $F(2,82) = 1.36$ ,  $p = .261$ . As none of the interaction terms was significant, the assumption was likely met.

### *Analyses of Cognitive Test Performance*

Table 3.3 presents means and standard deviations for all cognitive dependent variables. Tables 3.4 and 3.5 present results of the MANCOVA and ANCOVA analyses. In the Language Functioning domain, our primary hypothesis was not supported. The SCD group did not differ significantly from SCD/OSA group. An examination of the specific dependent variables indicated a statistically significant effect of OSA status only for the TOLD-OV, controlling for the effects of SCD genotype (high vs. low risk), though the direction of the effect was not as predicted. However, the post hoc comparison of the Mild OSA and Severe OSA groups did differ significantly,  $t(34) = 2.47$ ,  $p = .016$ , Cohen's  $d = .85$ , with the severe OSA group exhibiting worse performance.

The overall MANCOVA for academic skills was statistically significant. Controlling for SCD genotype (high vs. low risk), significant group differences were found for the WJ-III LW and the WJ-III AP subtests; however, the direction of these effects was not as hypothesized. Therefore, our primary hypothesis was not supported. The difference between those and without OSA was not significant for WJ-III LW,  $t(86) = 1.8$ ,  $p = .074$ , Cohen's  $d = .39$ ; and for WJ-III AP,  $t(86) = -.28$ ,  $p = .78$ , Cohen's  $d = -.06$ . The post-hoc comparisons within the OSA group revealed a difference for the WJ-III LW,  $t(39) = 2.12$ ,  $p = .037$ , Cohen's  $d = .74$  with the severe group performing worse; however, this was not considered statistically significant with an alpha of .025. The comparison between mild and severe OSA groups revealed a statistically significant difference for the WJ-III AP,  $t(39) = 4.02$ ,  $p < .001$ , Cohen's  $d = 1.15$ .

The overall ANCOVA for visual-motor ability (DTVMI) was statistically significant. The comparison between SCD/OSA and SCD again was not statistically significant,  $t(86) = 1.77$ ,  $p = .08$ , Cohen's  $d = .38$ . Therefore, our primary hypothesis was not supported. The post-hoc comparison between mild and severe OSA also failed to reach statistical significance,  $t(39) = 1.91$ ,  $p = .059$ , Cohen's  $d = .62$ . The overall MANCOVA was significant due to group differences between the mild OSA and no OSA group,  $t(39) = 2.93$ ,  $p = .005$ ; however, this was in the opposite of the expected direction.

Lastly, the ANCOVA for processing speed was not statistically significant. Contrasts revealed no significant group differences between SCD/OSA and SCD groups,  $t(85) = .65$ ,  $p = .514$ , Cohen's  $d = .14$ . The mild and severe OSA differed with the severe OSA group showing poorer performance; however, this comparison fell short of the required statistical significance threshold,  $t(37) = 2.15$ ,  $p = .034$ , Cohen's  $d = .66$ .

Correlations between cognitive testing and key sleep study variables are shown in Table 3.10. Based on previous research (Hargrave et al., 2003; Kirkham et al., 2001) showing an association between SCD morbidity (pain, CNS events) and nighttime oxygen saturation, we examined whether cognitive functioning data will be similarly associated. Overall, the pattern of correlations suggested a weak association between mean oxygen or lowest oxygen saturation and cognitive functioning. Only one cognitive test (WJ-III AP) had a statistically significant negative association with mean oxygen saturation, which was in the opposite of the expected direction.

Finally, we repeated the analyses of cognitive functioning (Mild vs. Severe OSA; correlations with sleep study variables) while also statistically controlling for the time lag

between cognitive testing and the sleep study. This statistical control did not change the inference (reject the null hypothesis, do not reject the null hypothesis) for any of the above analyses.

Together these results suggest that while cognitive functioning did not vary between individuals with OSA and without, the severity of OSA symptoms appears to be important in predicting some cognitive abilities. Within the OSA group, those classified as having more severe OSA symptoms tended to exhibit poorer cognitive functioning compared with those with milder symptoms.

***Additional goal (1)***

We aimed to describe group differences in symptoms of hyperactivity, inattention, emotional problems, peer relationship problems, and conduct problems from the SDQ. Table 3.6 presents these results. No group differences were found on these variables comparing SCD/OSA vs. SCD. Post-hoc examination of mild vs. severe OSA also did not reveal significant group differences.

***Additional goal (2)***

We aimed to explore other areas of morbidity including cerebral blood flow, pain, stroke, and hospitalizations for infections. These comparisons were made using data from the full sample. We tabulated the total number of complications from the medical record reviews to assess the hypothesis of higher SCD morbidity in children with OSA. Morbidities were organized into groupings to capture a profile of morbidity types for descriptive purposes. There was significant positive skew in these variables. Therefore, Mann Whitney U tests were used to avoid the influence of outliers on results. Z-scores from the Mann Whitney U were used as the test statistic given the sample size. Table 3.7

presents the results of group comparisons. The primary test of our hypothesis showed higher rates of SCD complications for children with SCD and OSA as compared to the control group with SCD ( $p < .001$ ). Children with SCD and OSA had approximately 47% higher rates of complications than the control group with SCD, though in statistical effect size terms the magnitude of this effect was relatively small ( $r = .24$ ). This overall higher rate of complications appeared to be related primarily to higher rates of lung morbidity and infections requiring health care use. For variables that were not statistically significant, however, the direction of the effect was consistently toward higher morbidity in the group with OSA.

***Additional goal (3)***

We aimed to describe sleep study data for the OSA group. Table 3.8 presents descriptive information on the collected sleep study variables for the OSA group. These included total sleep time (minutes), sleep latency (minutes), sleep efficiency (%), rapid eye movement (REM) sleep (%), REM latency (minutes), arousal index (AI), apnea/hypopnea index (AHI), respiratory disturbance index (RDI), mean oxygen saturation, and lowest oxygen saturation. Only 11 cases had data for all the variables included. This is due to the variability in data reporting procedures between sleep laboratories. While all laboratories adhere to appropriate clinical standards, there was considerable variability between studies from different laboratories in which sleep variables were reported. As a result, some variables have a large number of missing cases. All cases had data on the AHI or RDI that are used in determining an OSA diagnosis.

We examined differences in OSA severity between high and low risk genetic subtypes. The more severe genotypes were hypothesized to exhibit higher OSA severity. This hypothesis was partially supported. Table 3.9 presents the results of these group comparisons. While groups did not differ significantly in the indices used to determine the diagnosis of OSA (AHI or RDI), they did vary on three sleep variables including total sleep time, sleep efficiency, and mean oxygen saturation. These differences suggest overall worse sleep in quantity and quality for patients with severe genotypes which ultimately can result in more daytime behavioral disturbances and neurocognitive deficits.



Table 3.1. Descriptive Information for the SCD Sample and Matched Controls

<b>Sample</b>	<b>SCD+OSA group</b>	<b>SCD Only group</b>	<b>Statistic</b>
<i>N</i>	136	136	
<i>Age at time of review (SD)</i>	13.6 (5.3)	14.2 (5.2)	$t(263) = .8$
<i>Gender (% Female)</i>	49.3	48.8	$\chi^2(1) = .005$
<i>SCD Risk (% Severe)</i>	79.4	78.3	$\chi^2(1) = .05$
<i>Genotype</i>			$\chi^2(4) = 10.3^*$
% <i>HbSS</i>	69.9	77.5	
% <i>HbSC</i>	14.7	15.5	
% <i>HbSβ<sup>+</sup></i>	5.9	6.2	
% <i>HbSβ<sup>0</sup></i>	8.1	0.8	
% <i>Other</i>	1.5	0	
<i>Mean Hematocrit</i>	26.8 ( 4.6)	26.9 (4.8)	$t(263) = .2$
<i>Mean WBC</i>	12.7 (14.7)	10.8 (4.1)	$t(263) = -1.4$
<i>Mean BMI</i>	20.3 (6.4)	19.4 (5.1)	$t(263) = -1.5$
<i>% Pre-term birth</i>	6.6	10.1	$\chi^2(1) = 1.0$
<i>% Hydroxyurea</i>	44.1	28.1	$\chi^2(1) = 7.3^{**}$
<i>% Transfusion</i>	18.4	15.5	$\chi^2(1) = .4$

\*  $p < .05$ . \*\*  $p < .01$ . WBC = White blood cells; BMI = Body mass index

Table 3.2. Descriptive Information for the Cognitive Dataset by Group

Sample	SCD/OSA group		SCD group	Statistic
	Mild OSA	Severe OSA		
<i>N</i>	26	15	49	
<i>Mean Age at time of review (SD)</i>	9.8 (2.0)	9.8 (1.6)	10.9 (2.4)	F(2,87) =3.0
<i>Mean Age at OSA diagnosis (SD)</i>	6.8 (2.3)	6.0 (2.1)	--	F(1,39) =1.1
<i>Mean Age at Testing (SD)</i>	5.6 (0.6)	5.8 (0.9)	6.0 (0.8)	F(2,87) =2.9
<i>Gender (% Female)</i>	50.0	66.7	44.9	$\chi^2(2) =2.2$
<i>SCD Risk (% high)</i>	73.1	80.0	63.3	$\chi^2(2) =1.8$
<i>Genotype</i>				$\chi^2(8) =10.1$
% HbSS	65.4	60.0	61.2	
% HbSC	23.1	13.3	24.5	
% HbS $\beta^+$	3.8	6.7	12.2	
% HbS $\beta^0$	7.7	13.3	2.0	
% Other	0.0	6.7	0	
<i>Mean Hematocrit (SD)</i>	25.9 (4.6)	26.4 (4.5)	27.3 (4.5)	F(2,83) =.8
<i>Mean WBC (SD)</i>	11.2 (3.8)	11.3 (3.4)	10.9 (4.0)	F(2,83) =.1
<i>Mean BMI (SD)</i>	17.4 (4.0)	16.9 (5.5)	18.1 (4.9)	F(2,86) =.8
<i>% Pre-term birth</i>	3.8	20.0	12.2	$\chi^2(2) =2.7$
<i>% Hydroxyurea</i>	34.6	33.3	27.1	$\chi^2(2) =.5$
<i>% Transfusion</i>	15.4	33.3	16.7	$\chi^2(2) =2.4$

\* p < .05. \*\* p < .01. WBC = White blood cells; BMI = Body mass index

Table 3.3. Descriptive Statistics for Cognitive Variables.

<b>Cognitive variables</b>	<b>N Valid</b>	<b>N Missing</b>	<b>Mean (SD)</b>	<b>Median</b>	<b>Mode</b>	<b>Skweness (std. err)</b>	<b>Kurtosis (std. err)</b>	<b>Min.</b>	<b>Max.</b>
<i>TOLD-OV</i>	90	0	8.9 (2.4)	9.5	11	-.45 (.25)	-.53 (.50)	3	14
<i>TOLD-GU</i>	89	1	8.6 (2.8)	9	8	-.08 (.26)	.22 (.50)	1	15
<i>TOLD-WD</i>	82	8	8.2 (3.1)	8	7	-.27 (.27)	-.75 (.53)	2	14
<i>WJ-III DS</i>	87	3	91.3 (13.6)	91	88	-.06 (.26)	-.76 (.51)	62	114
<i>WJ-III LW</i>	90	0	97.7 (12.1)	100	100	-.14 (.25)	-.81 (.50)	73	123
<i>WJ-III AP</i>	88	2	95.2 (12.0)	95	99	.32 (.26)	.32 (.51)	71	131
<i>DTVMI</i>	88	2	88.0 (12.9)	87.5	91	.07 (.26)	.003 (.51)	59	117

Table 3.4. Means and Standard Deviations for cognitive variables by OSA Status

	<b>Mild OSA</b>	<b>Severe OSA</b>	<b>No OSA</b>
TOLD-OV	M = 9.9 <sub>a</sub> (SD = 1.9)*	M = 7.7 <sub>a</sub> (SD = 2.2)*	M = 8.7 (SD = 2.7)
<i>TOLD-GU</i>	M = 9.7 <sub>a</sub> (SD = 2.8)	M = 8.4 (SD = 2.7)	M = 8.3 <sub>a</sub> (SD = 2.7)
TOLD-WD	M = 8.8 (SD = 3.1)	M = 8.4 (SD = 2.8)	M = 8.0 (SD = 3.1)
WJ-III DS	M = 96.6 <sub>ab</sub> (SD = 12.5)	M = 87.0 <sub>a</sub> (SD = 16.5)	M = 89.8 <sub>b</sub> (SD = 12.7)
<i>WJ-III LW</i>	M = 103.8 <sub>ab</sub> (SD = 11.7)	M = 95.7 <sub>b</sub> (SD = 10.1)	M = 95.0 <sub>a</sub> (SD = 11.8)
<i>WJ-III AP</i>	M = 101.2 <sub>a</sub> (SD = 13.5)*	M = 86.7 <sub>a</sub> (SD = 11.6)*	M = 94.6 <sub>a</sub> (SD = 9.4)
<i>DTVMI</i>	M = 93.8 <sub>a</sub> (SD = 9.9)	M = 85.9 (SD = 15.1)	M = 85.4 <sub>a</sub> (SD = 12.7)

Shared subscripts indicate mean differences are statistically significant,  $p < .05$ . \*  $p < .025$ ; TOLD-OV = TOLD Oral Vocabulary; TOLD-GU = TOLD Grammatical Understanding; TOLD-WD = TOLD Word Discrimination; WJ-III AP = WJ-III Applied Problems; WJ-III LW = WJ-III Letter-Word identification; WJ-III DS = WJ-III Decision Speed; DTVMI = Developmental Test of Visual-Motor Integration.

Table 3.5. MANCOVAs for Language Functioning and Academic Skills

		SS	df	MS	F	p	Partial $\eta^2$	
<b>Language Functioning</b>								
<i>MANCOVA</i>								
	Genotype		(3, 75)		.72	.55	.03	
	OSA		(3, 76)		2.65	.05	.10	
<i>Between-subjects effects</i>								
	Genotype	<i>TOLD-OV</i>	2.26	1	2.26	.39	.54	.005
		<i>TOLD-GU</i>	5.72	1	5.72	.74	.39	.010
		<i>TOLD-WD</i>	5.20	1	5.20	.53	.47	.007
	OSA	<i>TOLD-OV</i>	40.66	2	20.33	3.46	.036	.083
		<i>TOLD-GU</i>	33.43	2	16.71	2.16	.12	.053
		<i>TOLD-WD</i>	7.21	2	3.60	.37	.69	.009
	Error	<i>TOLD-OV</i>	452.13	77	5.87			
		<i>TOLD-GU</i>	595.80	77	7.74			
		<i>TOLD-WD</i>	753.19	77	9.78			

		SS	df	MS	F	p	Partial $\eta^2$	
<b>Academic Skills</b>								
<i>MANCOVA</i>								
	Genotype		(2, 83)		.56	.57	.01	
	OSA		(2, 84)		8.85	<.001	.17	
<i>Between-subjects effects</i>								
	Genotype	<i>WJ-III AP</i>	98.65	1	98.65	.74	.393	.009
		<i>WJ-III LW</i>	8.44	1	8.44	.07	.795	.001
	OSA	<i>WJ-III AP</i>	1307.59	2	653.80	4.88	.010	.104
		<i>WJ-III LW</i>	2044.75	2	1022.37	8.23	.001	.164
	Error	<i>WJ-III AP</i>	11247.83	84	133.90			
		<i>WJ-III LW</i>	10438.43	84	124.27			

TOLD-OV = TOLD Oral Vocabulary; TOLD-GU = TOLD Grammatical Understanding; TOLD-WD = TOLD Word Discrimination; WJ-III AP = WJ-III Applied Problems; WJ-III LW = WJ-III Letter-Word identification.

Table 3.6. ANCOVAs for Processing Speed and Visual Motor Abilities

	<b>SS</b>	<b>df</b>	<b>MS</b>	<b>F</b>	<b>p</b>	<b>Partial <math>\eta^2</math></b>
<b>processing Speed</b>						
<i>WJ-III DS</i>						
Genotype	1.25	1	1.25	.007	.93	.000
OSA	1065.44	2	532.72	2.97	.057	.067
Error	14868.06	83	179.13			
<b>Visual-Motor Ability</b>						
<i>DTVMI</i>						
Genotype	146.52	1	146.52	.95	.333	.011
OSA	1318.88	2	659.44	4.27	.017	.092
Error	12965.42	84	154.35			

WJ-III DS = WJ-III Decision Speed; DTVMI = Developmental Test of Visual-Motor Integration

Table 3.7. Group Differences on the SDQ

<b>Domain</b>	<b>SCD + OSA (<i>n</i> = 40)</b>	<b>SCD only (<i>n</i> = 48)</b>	<b>Statistic</b>	<b>Effect size (<i>d</i>)</b>
Emotional symptoms	M = 2.4 (SD = 1.7)	M = 2.2 (SD = 1.7)	<i>t</i> (86) = -.45	-.10
Inattention/hyperactivity	M = 4.2 (SD = 2.3)	M = 4.1 (SD = 2.2)	<i>t</i> (86) = -.01	-.01
Conduct problems	M = 1.8 (SD = 1.7)	M = 1.9 (SD = 1.8)	<i>t</i> (86) = .30	.07
Peer problems	M = 1.7 (SD = 1.3)	M = 1.8 (SD = 1.7)	<i>t</i> (86) = .20	.04
	<b>Mild OSA (<i>n</i> = 25)</b>	<b>Severe OSA (<i>n</i> = 15)</b>		
Emotional symptoms	M = 2.1 (SD = 2.0)	M = 2.9 (SD = 1.0)	<i>t</i> (38) = -1.50	-.49
Inattention/hyperactivity	M = 4.1 (SD = 2.4)	M = 4.2 (SD = 2.3)	<i>t</i> (38) = -.10	-.03
Conduct problems	M = 1.8 (SD = 1.6)	M = 1.9 (SD = 1.8)	<i>t</i> (38) = -.20	-.07
Peer problems	M = 1.6 (SD = 1.4)	M = 1.9 (SD = 1.3)	<i>t</i> (38) = -.74	-.24



Table 3.8. History of SCD morbidity for children with OSA and controls

<b>Morbidity type</b>	<b>SCD + OSA (n = 136)</b>	<b>SCD only (n = 136)</b>	<b>Statistic</b>	<b>Effect size (r)</b>
<b>Neurologic</b>				
<i>Total neurologic findings (M (SD))</i>	0.42 (0.84)	0.26 (0.63)	z = 1.60	.10
-Overt stroke (cases)	10	7	$\chi^2$ (1) = .056	
-Transient ischemic attack (cases)	4	3	$\chi^2$ (1) = 0.15	
-Elevated stroke risk (cases)	7	5	$\chi^2$ (1) = 0.35	
TCD Conditional				
TCD Conditional + stenosis on MRA	4	3	$\chi^2$ (1) = 0.15	
TCD Abnormal	15	9	$\chi^2$ (1) = 1.64	
-Silent cerebral infarcts (cases)	17	8	$\chi^2$ (1) = 3.57	
<b>Pain</b>				
<i>Total hospitalizations (M (SD))</i>	5.03 (9.20)	3.68 (6.99)	z = 1.76	.11
<b>Lung</b>				
<i>Total hospitalizations (M (SD))</i>	1.99 (2.37)	1.14 (1.93)	z = 4.08***	.25
-Acute chest syndrome	0.84 (1.44)	0.40 (1.16)	z = 3.18**	
-Pneumonia	1.15 (1.45)	0.74 (1.45)	z = 3.47**	
<b>Priapism</b>				
<i>Total episodes (M (SD))</i>	0.32 (2.34)	0.19 (1.16)	z = 0.62	.04
<b>Other infection</b>				
<i>Total episodes (Mean (SD))</i>	1.50 (1.85)	1.05 (1.91)	z = 2.67**	.16
-Hospitalized for fever	1.17 (1.72)	0.82 (1.60)	z = 1.99*	
-Aplastic episode	0.18 (0.39)	0.11 (0.50)	z = 2.47*	
-Sepsis	0.02 (0.15)	0.00 (0.00)	z = 1.74	
-Osteomyelitis	0.01 (0.12)	0.04 (0.22)	z = 0.83	
-Urinary tract infection	0.11 (0.34)	0.09 (0.31)	z = 0.62	
<b>Total complications (M (SD))</b>	9.26 (10.28)	6.32 (8.81)	z = 3.92***	.24

Variables in italics were used as primary follow-up measures of morbidity types; TCD = transcranial Doppler ultrasound; MRA = magnetic resonance angiography; statistical comparisons were based on the Mann Whitney U test due to skewed distributions, except within specific neurologic conditions, for which Chi-square tests are reported; \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ ; two-tailed p-values are indicated, though the primary hypothesis for total complications was directional.

Table 3.9. Sleep Study Variables Descriptive Statistics

<b>Sleep variables</b>	<b>N Valid</b>	<b>N Missing</b>	<b>Mean (SD)</b>	<b>Median</b>	<b>Mode</b>	<b>Skweness (std. err)</b>	<b>Kurtosis (std. err)</b>	<b>Min.</b>	<b>Max.</b>
<i>Age at study</i>	135	1	9.27 (4.73)	8.78	5.64	0.42 (0.21)	-0.85 (0.41)	1.39	19.26
<i>TST</i>	123	13	378.02 (58.42)	385	408	-0.98 (0.22)	1.79 (0.43)	140	500
<i>SL</i>	128	8	21.64 (27.18)	11	0	2.39 (0.21)	7.86 (0.43)	0	168
<i>SE</i>	128	8	90.3 (8.15)	92	99	-1.30 (0.21)	1.54 (0.43)	61	100
<i>REM</i>	111	25	16.85 (5.70)	17	12	-0.11 (0.23)*	-0.03 (0.46)*	0	32.7
<i>REM L</i>	122	14	114.93 (60.61)	111.75	156	0.82 (0.22)	1.23 (0.44)	0	350.5
<i>AHI</i>	91	45	8.51 (7.00)	7	4	1.38 (0.25)	2.22 (0.50)	0	35
<i>RDI</i>	70	66	11.54 (9.78)	8	7	1.53 (0.29)	2.33 (0.57)	0	43
<i>Mean O2</i>	111	25	95.63 (2.98)	96	98	-1.26 (0.23)	1.89 (0.46)	84	100
<i>Nadir</i>	131	5	86.67 (8.31)	88	91	-2.80 (0.21)	15.03 (0.42)	31	98

\* Skewness and kurtosis values within limits

TST = total sleep time (minutes); SL = sleep latency (minutes); SE = sleep efficiency (%); rapid eye movement (REM) sleep (%); REM L = REM latency (minutes); AI = arousal index; AHI = apnea/hypopnea index; RDI = respiratory disturbance index; Mean O2 = mean oxygen saturation (%); Nadir = lowest oxygen saturation recorded (%).

Table 3.10. Group Differences in Sleep Study Variables Based on SCD Genotype

Variable	Mild Risk Genotype		Severe Risk Genotype		Statistic	Effect size ( <i>d</i> )
	N	M (SD)	N	M (SD)		
TST	27	398.89 (54.54)	96	372.15 (58.39)	$t(121) = 2.13^*$	.47
SL	28	15.55 (18.44)	100	23.34 (29.01)	$t(126) = -1.34$	-.32
SE	26	93.35 (4.78)	102	89.52 (8.65)	$t(126) = 2.17^{**}$	.55
REM	26	18.05 (4.96)	85	16.47 (5.88)	$t(109) = 1.24$	.29
REML	26	128.06 (55.76)	96	111.37 (61.65)	$t(120) = 1.25$	.28
AI	12	14.25 (9.1)	60	14.13 (9.98)	$t(70) = .04$	.01
AHI	20	8.92 (9.63)	71	8.40 (6.10)	$t(89) = .30$	.08
RDI	13	11.22 (10.66)	57	11.61 (9.66)	$t(68) = -.13$	-.04
Mean O2	25	97.84 (1.07)	86	94.99 (3.05)	$t(109) = 4.58^{**}$	1.05
NADIR	28	88.61 (7.78)	103	86.14 (8.40)	$t(129) = 1.4$	.30

\*  $p < .05$

\*\*  $p < .01$

TST = total sleep time (minutes); SL = sleep latency (minutes); SE = sleep efficiency (%); rapid eye movement (REM) sleep (%); REM L = REM latency (minutes); AI = arousal index; AHI = apnea/hypopnea index; RDI = respiratory disturbance index; Mean O2 = mean oxygen saturation (%); Nadir = lowest oxygen saturation recorded (%).

Table 3.11. Correlations between Oxygen Saturation and Cognitive Variables

	<b>Mean O<sub>2</sub></b> <b>(n = 38)</b>	<b>NADIR</b> <b>(n = 41)</b>
<b>TOLD-OV</b>	.035	.079
<b>TOLD-GU</b>	-.203	-.172
<b>TOLD-WD</b>	-.123	.090
<b>WJ-III DS</b>	-.265	-.302
<b>WJ-III LW</b>	-.137	.055
<b>WJ-III AP</b>	-.347*	-.096
<b>DTVMI</b>	-.122	-.157
<b>Mean O<sub>2</sub></b>	1	.455**

\* p < .05. \*\* p < .01. TOLD-OV = TOLD Oral Vocabulary; TOLD-GU = TOLD Grammatical Understanding; TOLD-WD = TOLD Word Discrimination; WJ-III AP = WJ-III Applied Problems; WJ-III LW = WJ-III Letter-Word identification; WJ-III DS = WJ-III Decision Speed; DTVMI = Developmental Test of Visual-Motor Integration; NADIR = Lowest oxygen saturation recorded.

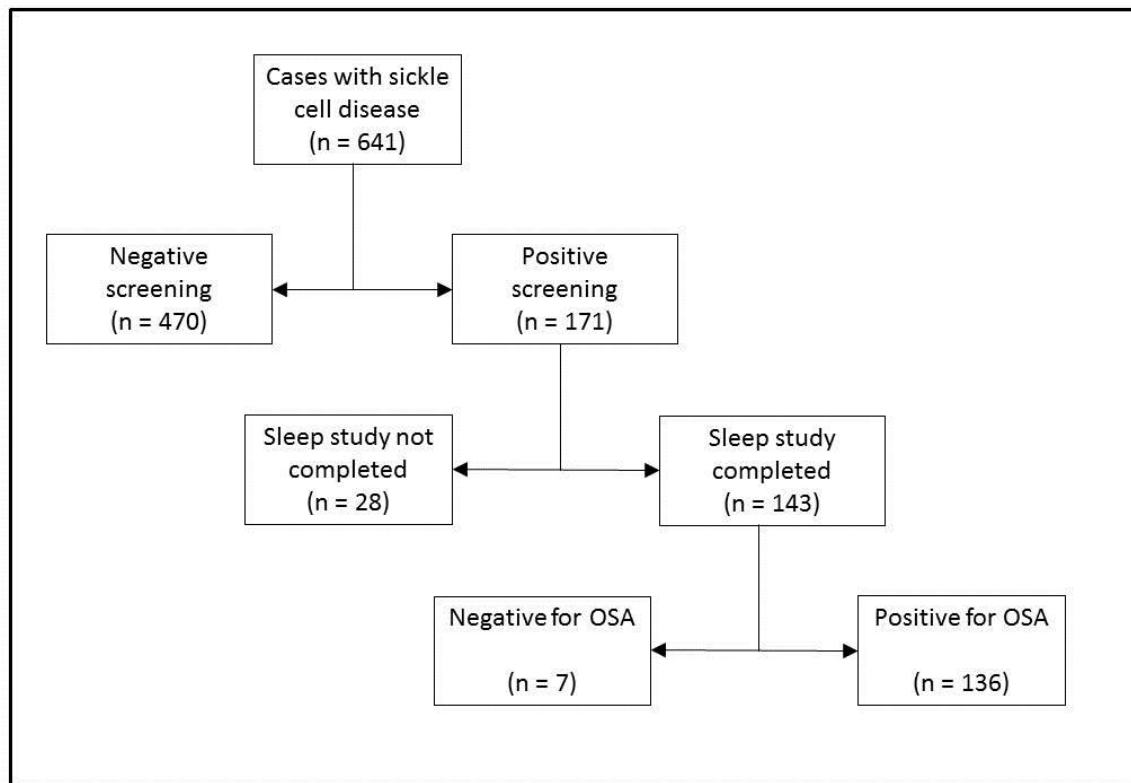


Figure 3.1. Flow Chart for OSA Screening and Sleep Study Results

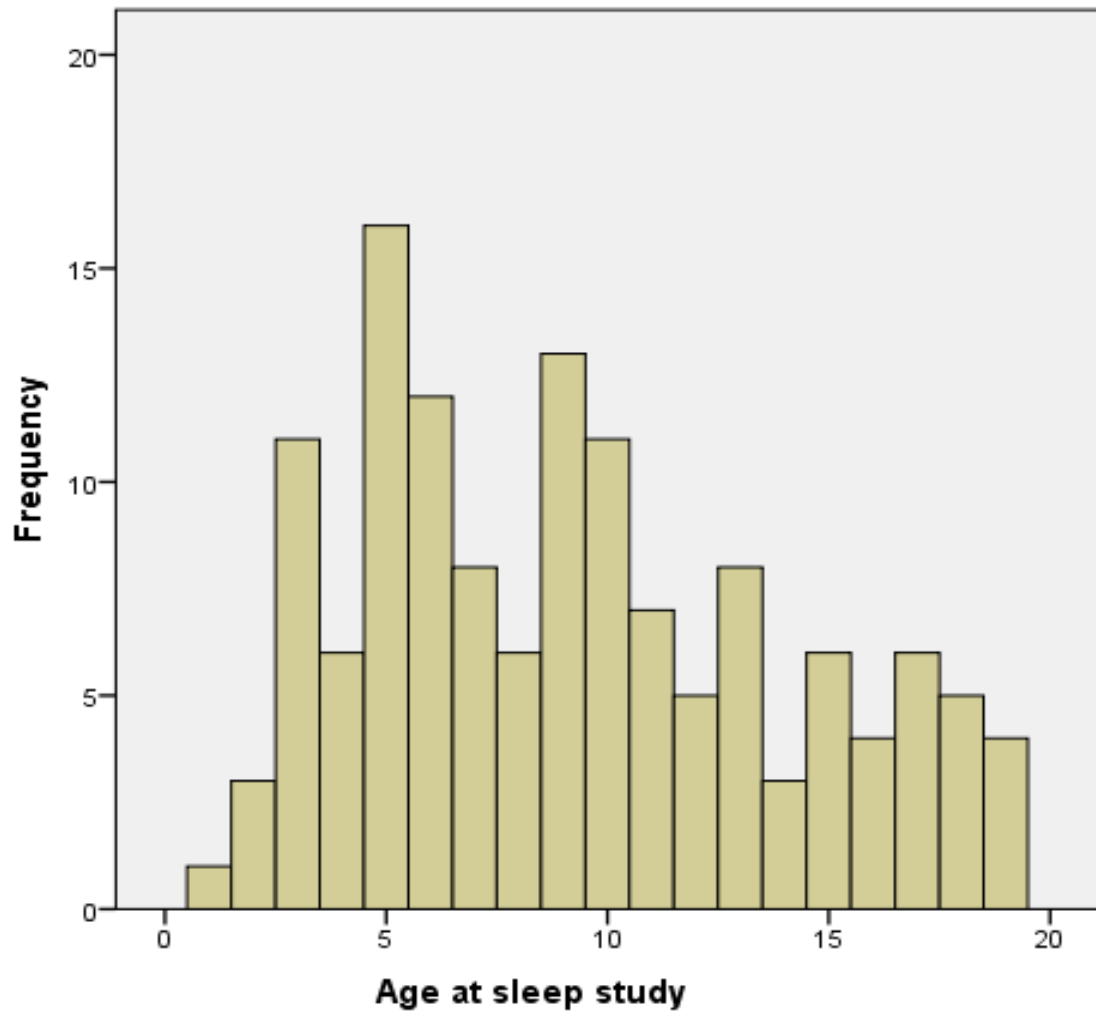


Figure 3.2. Age (in years) at Time of Sleep Study for the SCD/OSA Group

## Chapter 4: Discussion

This work describes the prevalence rate of OSA in pediatric SCD and examines factors that impact the prevalence rate in a large clinic-wide sample as well as in the subsample referred for OSA evaluation after screening. The first aim of this study was to examine the prevalence rate of OSA in children with SCD. We also examined the OSA screening procedure and its sensitivity in detecting OSA in children with SCD. We made two a-priori hypotheses about the prevalence rate of OSA in the overall sample as well as the specific differences in prevalence based on SCD genotype (high vs. low risk). Lastly, we described the prevalence of OSA by age.

Based on previous estimations of OSA prevalence (Strauss et al., 2012), we hypothesized that approximately 20% of individuals will have a diagnosis of OSA. Our hypothesis was supported. In the clinic-wide sample, 136 cases (21.22%) received an OSA diagnosis. It should be noted that this may be an underestimate of the prevalence rate as children with negative screenings for OSA did not receive overnight polysomnography. Thus, these data indicate a prevalence rate of greater than or equal to 21%. This finding lends further support to previous research indicating a relatively high prevalence of OSA in children with SCD and appears to be higher in prevalence than other notable morbidity in SCD, such as stroke and silent cerebral infarction. In comparison, the prevalence of OSA in children in the general population is estimated at 2-3% (Gottlieb et al., 2003). African-American children are already considered to be at a

particularly higher risk for developing OSA. At least one study estimated that African American children were 1.88 times more likely to have increased apneic activity compared to Caucasians (Redline et al., 1997). It is unclear if sickle cell status was controlled for in estimating this increased risk. SCD may be a factor contributing to the higher rate of OSA in African-American children compared with the general population. Specifically, obstructive adenotonsillar hypertrophy is prevalent in children and adolescents with SCD and is considered a primary cause of OSA. At least one study reported the prevalence of this complication to be as high as 55% (Abou-Elhamd, 2012). Other factors in SCD that may increase the risk for developing OSA include hypoxia and hypoxemia that are thought to be important drivers of red blood cell (RBC) polymerization and sickling in SCD (Okoli et al., 2009). Pro-inflammatory cytokines also play an important role in SCD and OSA pathophysiology (Kim et al., 2009; Sultana et al., 1998). Given the common underlying pathophysiological mechanisms, it is not surprising that children with SCD exhibit such a high prevalence rate of OSA. While further research is needed, our prevalence estimates in a large clinic-wide sample indicate that OSA should be considered a major complication in SCD.

From these prevalence rates, it is clear that children with SCD should be screened for OSA symptoms. Our study found that the screening procedure used in the clinic correctly identified 95% of cases with OSA. The literature discussing OSA screening procedures for children with SCD is scarce and studies have reported wide ranging prevalence estimates. One study (Brooks et al., 1996) reported 44% of children with SCD referred for evaluation of OSA were diagnosed with the condition as measured by overnight polysomnography. They did not report the screening procedure itself but only noted



that children were referred for a sleep study due to suspicion of OSA by their primary care physician. Another study (Rogers et al., 2010) reported 69% of patients with SCD referred for evaluation were diagnosed with OSA as measured by polysomnography. However, they also did not report the initial screening procedure. Lastly, in a small sample of children (n=19), one study (Kalevayas et al., 2008) found 63% received an OSA diagnosis. This study used the Children's Sleep Habit Questionnaire (Owens, Spirito, & McGuinn, 2000) to identify children that are at high risk for developing OSA. Clinicians reviewed 4 symptoms including snoring, pauses in breathing, snorting, and waking gasping from sleep). However, from 100 families participating in the study, 48 children were found to have symptoms but only 19 agreed to undergo polysomnography. Therefore this prevalence estimate may not be accurate.

The screening procedure used in our clinic appeared to have identified the highest rate to date of positive OSA cases. The screening itself includes questions about snoring, its loudness, and whether it is a concern for the parents. Additionally, parents are asked whether the child experiences early morning headaches and/or pain. This screening procedure seems to be simple to administer and extremely effective at identifying children who have OSA. The high true positive rate may be due to the fact that all patients are screened for symptoms of OSA at each routine appointment; thus, serial screenings over time may perform better than measures of screening effectiveness based on screenings at a single point in time. Such an approach may be more effective in a clinical setting than using self-report measures such as the Children's Sleep Habit Questionnaire, which may be cumbersome with 53 items. In addition, screenings in our

clinic are performed by a single hematologist and it is unclear how clinician variables may impact the realized effectiveness of such screenings.

We also hypothesized that rates of OSA will differ between “low risk” (HbSC and HbS $\beta^+$ ) and “high risk” (HbSS and HbS $\beta^0$ ) genetic subtypes with the high risk group showing higher rates. Our hypothesis was supported. In the clinic-wide sample, individuals with more severe genetic subtypes (27%) were approximately 2.5 times more likely to have OSA than those with the mild subtypes (11%). These results do not agree with some previous findings. For example, Rogers and colleagues (2010) reported 65.8% of patients with HbSS had OSA compared with 78.5% with HbSC. However, the study had a small sample size (N=55) with only 41 individuals having HbSS and 14 having HbSC. The small sample may be less representative than our clinic-wide sample in which we identified 396 cases with high risk genetic subtypes and 245 cases with low risk subtypes. Nonetheless, the discrepant findings indicate the need for further research in this area. With respect to the overall distribution of SCD genotypes, examining the clinic-wide sample as well as the SCD/OSA and SCD matched control group, we found similar proportions with HbSS being most prevalent followed by HbSC, HbS $\beta^+$ , and HbS $\beta^0$ . This finding is consistent with other studies of SCD prevalence rates (Gold et al., 2008).

Finally, we examined the prevalence of OSA by age. To our knowledge, this study is the first to report the shape of the age curve. Our results suggested that the distribution of age at time of OSA diagnosis took on a positively skewed shape with the modal age of 5.64 years, median age of 8.78 years and a mean of 9.27 years. Most patients (64.4%) were diagnosed on or before their 10<sup>th</sup> birthday but OSA diagnoses also frequently occurred during the second decade of life. These results join previous findings

regarding the mean age at time of OSA diagnosis. For example, Rogers and colleagues (2010) reported a mean age of 9.65 years; Kaleyias et al. (2008) found a mean age of 10.7 years in their sample; another study (Mullin et al., 2012) found a mean age of 12.4 years. Based on our results, it may be that while the average OSA diagnosis is given around 9-10 years of age, most children have significant symptoms much earlier around age 5. This finding highlights the need for early screening and identification of OSA symptoms. If left untreated, OSA has been found to increase the risk for neurological complications such as stroke and silent cerebral infarcts (Lal et al., 2012) as well as other serious consequences such as decreases in grey matter in the hippocampus, anterior cingulate, cerebellum, and the frontal, parietal, and temporal lobes (Canessa et al., 2011; Gale & Hopkins, 2004; Macey et al., 2002; Morrell et al., 2003; Torelli et al., 2011) and a decrease in white matter in the frontal cortex (Algin et al., 2012).

The second aim of this study was to examine the relationship between OSA and neurocognitive morbidity in children with SCD. We examined available cognitive data for a sub-sample of 90 children ages 5-7. Our primary hypothesis was that children with OSA would show more neurocognitive morbidity than those without OSA. The main analyses included measures of cognitive functioning in four domains that served as dependent variables: language functioning, academic skills, processing speed, and visual-motor ability. The key independent variable in all analyses was OSA status. We statistically controlled for SCD severity by including SCD risk (high risk vs. low risk genotypes) as a covariate in the analyses. In these primary analyses our hypothesis was not supported as children with OSA as a group did not perform more poorly on cognitive testing than those without OSA. Post hoc exploratory analyses suggested differences

within the OSA group: children with severe OSA exhibited worse cognitive functioning than children with mild OSA symptoms.

Correlations between key sleep variables and cognitive functioning revealed an overall weak degree of association. Previous studies (Hargrave et al., 2003; Kirkham et al., 2001) have indicated a relationship between oxygen saturation levels and SCD morbidity (pain, CNS events). In our study, only one cognitive test had a significant negative association with mean oxygen saturation. A major weakness of this facet of our study was the high degree of variability across children in the timing of cognitive testing in relation to the onset and diagnosis of sleep apnea. It is also possible that because of the limited age range of our sample (5-7 years) we were unable to detect stronger associations. More severe cognitive deficits may emerge with time as the cumulative effects of the disease impact the central nervous system. Future studies should include a wider age range to examine the relationship between sleep study data and cognitive functioning over time.

The content of the cognitive testing battery may also have contributed to the null effects. Overall, analyses of the cognitive data suggest that in the domains of language functioning, academic skills, processing speed, and visual-motor ability, children with SCD and OSA overall performed no worse than those with SCD alone. Previous studies have found that children with OSA only exhibited poor attention and executive functioning abilities such as working memory, planning, and problem solving (Antonelli Incalzi et al., 2004; Beebe et al., 2004; Gottlieb et al., 2004; Naismith et al., 2004; Tauman & Gozal, 2011). At least one study has also found executive functioning differences between SCD controls and SCD patients with a sleep-related breathing

disorder (Hill et al., 2006). Our study did not include measures specifically designed to assess executive functioning and therefore we were unable to assess group differences on this important cognitive domain. The data in this study were obtained through a medical record review of children with SCD who underwent a routine cognitive screening between the ages of 5 and 7. The measures for the screening were chosen because they have been shown to be sensitive to differences in the degree of neurologic risk across SCD genotypes (Schatz et al., 2009). It may be beneficial to include measures of executive functioning in a future prospective study designed to examine differences between children with SCD/OSA and SCD alone.

Another potential explanation for the null findings may be the limited age range of our sample. We only had data for children tested at ages 5-7 years. It may be that differences in cognitive functioning are more apparent later in life if OSA is left untreated. At an early age there may not have been enough time for OSA-related neurological complications to develop. The repeated insult of OSA on the brain together with the effects of SCD could take time to manifest and only become detectable with neuropsychological testing several years after they have begun. Studies of OSA have mentioned increasing age to be an important risk factor for cognitive decline (Lal et al., 2012). Findings from the SCD literature may also suggest the age plays a role in the onset or the detection of cognitive deficits. For example, Schatz and colleagues (2009) noted that children with lower risk genetic subtypes may show cognitive deficits in middle childhood or adolescence while those with high risk subtypes will likely show deficits as early as the pre-school period. In our study, 17 cases received an OSA diagnosis more than a year after testing and up to over 7 years after testing. It is possible that children

who did not show cognitive deficits at a young age, developed complications later in life as indicated by their OSA diagnosis. Our analysis of OSA prevalence by age indicated a mean and median age of diagnosis of 9 years suggesting many children may have developed OSA symptoms and associated cognitive deficits several years after testing. Future studies should examine cognitive abilities in a large sample with a wider age range of children with SCD and OSA.

Given the null results in our main analyses, we conducted post-hoc comparisons within the OSA group to examine differences in cognitive functioning between mild and severe OSA. We hypothesized that children with more severe OSA would exhibit worse cognitive functioning. Our hypothesis was partially supported. Children with severe OSA showed worse performance on the TOLD Oral Vocabulary sub-test, and the Woodcock-Johnson Applied Problems subtest. Scores for the Woodcock-Johnson Letter-Word identification and the Woodcock-Johnson Decision Speed sub-tests as well as the Beery VMI were in the same direction, but fell short of achieving statistical significance on these measures. Nonetheless, the effect sizes for these comparisons were all considered moderate to large and our null effects should be interpreted with caution due to the small size of the groups in these comparisons (Cohen, 1988).

Although few studies have examined differences in cognitive functioning based on OSA severity, findings have generally indicated that patients with more severe OSA symptoms showed poor performance in several cognitive domains. One study found differences in performance on tasks of verbal abilities between patients with mild and severe OSA (Lewin, Rosen, England, & Dahl, 2002). On the other hand, others have found that even patients with milder OSA symptoms also exhibit difficulties in language

functioning (O'Brien, Mervis, et al., 2004; O'Brien, Tauman, & Gozal, 2004). Children with severe OSA have shown deficits in memory functioning compared to those with mild OSA (Rhodes et al., 1995) although this effect was not detected in other cases (O'Brien, Mervis, et al., 2004). Lastly, difficulties with sustained attention were suggested to increase based on OSA severity (Owens-Stively et al., 1997). The OSA literature has not been consistent in finding group differences in cognitive functioning based on OSA symptom severity. These discrepancies may be due to the wide range of methodologies and measures employed, making conclusions more difficult (Jackson et al., 2011).

Studies examining neurocognitive functioning in children with SCD and OSA are few but findings have also suggested a dose-dependent response such that more severe OSA symptoms correlate with worse cognitive performance. For example, Hollocks and colleagues (2012) found that full-scale IQ scores, and performance on executive functions measures were inversely related to measures of OSA severity including lowest oxygen saturation recorded and average number of awakenings during overnight polysomnography. Our results suggest that differences in cognitive functioning between children with and without OSA are less likely to be detected with the measures used in this study and the limited age range; however, differences based on OSA severity were more readily identified. These results further strengthen the importance of early detection of OSA with children in SCD since severe OSA symptoms may lead to higher risk of developing neurocognitive deficits even at a young age. This issue is especially crucial since early detection and treatment may help reverse some of these adverse effects (Kheirandish & Gozal, 2006).

Of note, in our sample, we found that the mild OSA group performed better than the severe OSA group on several cognitive measures but also better than children without OSA. These results were unexpected and are difficult to explain. It is unclear why children with mild OSA out-performed children with no OSA. It is possible that there are demographic differences between these groups that have contributed to these results such as socio-economic status. However, due to the retrospective nature of the study, we were unable to collect more relevant demographic data. Future prospective studies can address this issue by collecting more comprehensive demographic information.

We explored differences in behavioral outcomes between children with SCD/OSA and SCD alone using the Strengths and Difficulties Questionnaire (SDQ). We did not find any statistically significant differences between children with OSA or without in the areas of emotional symptoms, peer problems, inattention/hyperactivity, and conduct problems. These results are in contrast to other studies that have indicated significant differences in these areas of functioning. For example, Gottlieb and colleagues (2003) reported that children with sleep-disordered breathing were more likely to have parent-reported problem behaviors including inattention, hyperactivity and aggressiveness than healthy controls. These researchers also reported differences in inattention based on cognitive testing (Gottlieb et al., 2004). Another study found parent-reported increases in externalizing behaviors, hyperactivity, emotional lability, oppositional behaviors, aggressive behaviors, internalizing behaviors, somatic complaints, and social problems for children with sleep-related breathing disorders compared with healthy controls (Rosen et al., 2004).



It may be that we were unable to detect differences in parent behavioral report of emotional-behavioral symptoms due to two reasons. First, other studies have used more comprehensive parent report measures including the Child Behavior Checklist, and the Conners Parent Rating Scale-Revised: Long. While the SDQ is a well-validated screening measure, it contains only five items per construct and may not be sensitive enough to detect differences in behavioral outcomes for children with SCD. Second, irrespective of OSA diagnosis, SCD is a serious chronic medical condition that may already increase one's risk for exhibiting behavioral problems (Schatz & Roberts, 2007) and poor social functioning (Noll, Reiter-Purtill, Vannatta, Gerhardt, & Short, 2007) due to chronic pain, missed school, multiple hospitalizations, and cognitive deficits. The addition of OSA may not necessarily increase behavioral problems to a degree that can be detected with parent-report measures.

We also examined differences in other areas of SCD morbidity in a larger sample of children with and without OSA. We did not find differences in rates of neurological complications including stroke, silent infarcts, and TCD exams. However, we did find the SCD/OSA group had significantly higher rate of total complications compared with the SCD only group. Specifically, we found a higher rate of hospitalizations for lung morbidities including pneumonia and acute chest syndrome as well as higher rate of each of these conditions regardless of hospitalization. Additionally, we found higher rates of infection in patients with OSA. Infections can increase pro-inflammatory cytokine activity (Conran et al., 2009) that in turn may increase the risk for developing OSA symptoms. OSA itself is associated with increased pro-inflammatory cytokines (Dayyat et al., 2009; Kim et al., 2009) that can in turn increase inflammation and pain in SCD.

These findings together highlight OSA as an additional complication incurred by individuals who are already at high risk for severe and complex medical morbidities.

Although we did not find a statistically significant difference in blood flow velocity in the brain as measured by TCD, in the SCD literature, TCD exams have been established as an important predictive tool for neurological morbidity in children (Hogan, Kirkham, et al., 2006; Hogan, Pit-ten Cate, et al., 2006; Sanchez et al., 2010; Schatz et al., 2008). Only one study to date had addressed the relationship between sleep-related breathing disorders and neurological morbidity in children with SCD and concluded that lower oxygen saturation was associated with higher risk of incurring a central nervous system (CNS) event as measured by increased brain blood flow velocities. Our study results suggest children with OSA were more than 1.5 times as likely to have an abnormal or conditional TCD exam as children without OSA, again highlighting the importance of early detection and treatment of OSA in this vulnerable population. They also had more than twice the incidence of silent infarcts compared with children without OSA. Further research is needed however to establish the relationship between higher brain blood flow velocities and OSA in children with SCD.

Finally, we examined differences in OSA severity between low and high risk genetic subtypes based on sleep study data. The high risk genotypes were hypothesized to exhibit higher OSA severity. This hypothesis was partially supported. Groups did not differ significantly in the indices used to determine the diagnosis of OSA (AHI or RDI), but did vary on three key sleep variables including total sleep time, sleep efficiency, and mean oxygen saturation. These differences suggest overall worse sleep in quantity and quality for patients with severe genotypes that ultimately can result in more daytime

behavioral disturbances and neurocognitive deficits. These results are similar to those of Kirkham and colleagues (2001) who also found mean oxygen saturation to be a significant predictor of having a CNS event. On the other hand, another study has reported no differences on these variables but did find significant group differences in sleep time spent with low oxygen saturation (Kaleyias et al., 2008). Also similar to our results, in a recent examination of polysomnographic characteristics of children with HbSS (high risk) vs. HbSC (low risk) genetic subtypes, Rogers et. al (2010) found mean oxygen saturation to be significantly lower in children with HbSS. They did not find differences in sleep efficiency and total sleep time. Overall, our results are consistent with the well-established difference between high and low risk genetic subtypes in SCD in terms of number and severity of complications (Schatz & McClellan, 2006).

### **Limitations**

This study has several limitations. First, it is a retrospective chart review. Such a design makes control over extraneous variables more difficult. When examining the data in a retrospective manner, it is difficult to account for effects of history (other external events occurring that may have an effect on SCD or OSA severity) or maturation (naturally-occurring changes over time that may affect the measured outcomes in the study). For this reason, we compared children with SCD/OSA to a matched control group. We used a careful matching procedure to reduce the impact of confounding factors of the relationship between OSA and neurocognitive morbidity including age, gender, hemoglobin level, and SCD genetic subtype. Additionally, we statistically controlled for the effects of SCD risk which was based on genetic subtype in our analyses. Our results indicating group differences between mild and severe OSA are therefore likely to be

independent from SCD risk. The lack of differences between SCD/OSA and SCD alone after statistically removing the effects of SCD risk may indicate that genetic subtype is still a primary predictor of neurocognitive morbidity.

Additionally, in a retrospective study there may be concerns regarding incomplete documentation of participants' clinical history in the medical record, which is less likely in prospectively followed cohorts. However, this type of problem is more likely to lead to type II errors than type I errors. Thus, it is unlikely this issue will have created an artificially high rate of OSA or over-estimated the size of the relationship between OSA and other morbidities.

It is important to note that cognitive testing was only available for a narrow age range in our sample (ages 5-7) which significantly limits the generalizability of our findings. On the other hand, the limited age range may have helped reduce the potential confounding influence of age on the results and allow greater confidence in generalizing the results to a wider population within the tested age range. Nonetheless, future studies should examine differences in cognitive functioning in children with co-occurring SCD and OSA in a wider age range. An examination of the age at time of testing compared with age at time of OSA diagnosis revealed that 17 of 41 patients with OSA who had cognitive testing (41.5%) received an OSA diagnosis more than a year after testing. As mentioned previously, it is possible that cognitive deficits appeared later in life closer to the time of diagnosis, partially explaining the lack of differences in cognitive functioning between patients with and without OSA.

Another important limitation was that cognitive testing data were collected retrospectively and therefore we were not able to choose the most ideal

neuropsychological measures for use in this study. For example, the OSA literature indicated that children with OSA tend to have deficits in executive functioning and sustained attention but we did not have measures to directly assess these domains. The cognitive measures included in this study were previously chosen for their ability to differentiate between mild and severe SCD genotypes. This distinction has great utility since genetic subtype has been shown to be associated with greater risk of neurocognitive morbidity (Schatz & Roberts, 2007); however, these measures may not be the best suited for examining differences based on OSA in children with SCD. Future studies should examine neurocognitive morbidity in children with SCD and OSA in a prospective manner which will allow for better planning and administration of appropriate neuropsychological measures. At least one study (Hollocks et al., 2012) has demonstrated differences in executive functioning depending on nocturnal hemoglobin oxygen desaturation and sleep fragmentation in children with SCD, underscoring the importance of continued research in this area.

### **Implications**

The results of this study may have important implications for future research. First, to date, there have not been any studies describing the prevalence rates of OSA in children with SCD in a large, clinic-wide sample. Studies have mainly reported prevalence in small samples. Because this is an understudied area, there is a need for more descriptive data. Results from this study will help future investigations in estimating power and inform the current literature in establishing expected base rates. Our results will also allow for a better computation of effect size for use in future studies

based on a more systematic examination of OSA prevalence rates and associated morbidity than in previous studies.

Results from the current study also carry important clinical implications. Outcomes from the current study will contribute to a better understanding of the relationship between OSA and neurocognitive morbidity in children with SCD. The overlap in underlying biological disease mechanisms suggests that OSA may be an additional important factor contributing to cognitive deficits in children with SCD. While we did not detect differences between children with SCD/OSA and SCD alone for cognitive functioning, our results suggested that for children with SCD that have been diagnosed with OSA, symptom severity may be an important predictor of cognitive functioning with children that have severe OSA at high risk for cognitive deficits. Evidence for the effectiveness of OSA treatment in reversing some cognitive consequences suggests patients with SCD may also potentially benefit from similar treatments.

Perhaps the most important clinical implication from this study is the need for routine screening for OSA in children with SCD. The high prevalence rate we have found suggests at least one of every five children with SCD will also have OSA. Given the literature on neurocognitive morbidity in children with OSA and SCD, early detection and treatment of OSA may help prevent further cognitive deficits over time. While most studies to date described the mean age of OSA diagnosis around age 9-12, our finding is that the modal age tends to be much earlier in life around age 5. The OSA screening procedure we have described in this study is simple and less time consuming than other lengthy parent-report measures. The screening procedure was administered by an

experienced hematologist and was able to correctly detect 95% of OSA cases. Because of its ease of administration, this procedure can be employed at every routine visit to ensure potential OSA symptoms are recognized early. This may be especially important given that most children with OSA in our sample showed symptoms relatively early in life. Of note, we were unable to compute the specificity for this screening procedure (percent of children correctly classified as not having OSA). A prospective study could examine the sensitivity and specificity of this screening procedure and will help in better understanding the procedure's utility in clinical settings.

In summary, this study examined the prevalence rate and neurocognitive morbidity associated with OSA in children with SCD. We found approximately one in five children with SCD had a diagnosis of OSA. Children with high risk SCD genotypes were much more likely to have OSA than the low genotypes. Children tended to receive the OSA diagnosis around age 9-10 on average but the modal age was 5. It was also clear that many children continued to be diagnosed during their teenage years. A retrospective examination of cognitive functioning data obtained during routine screenings at our clinic between the ages of 5 and 7 indicated no differences between children with or without OSA. However, for those diagnosed with OSA, severity played a role in predicting worse cognitive functioning in several domains. Our findings suggest that OSA is a serious complication of SCD that is highly prevalent and is associated with neurocognitive morbidity. A simple screening procedure employed in our clinic has been useful in detecting many children with OSA. It is recommended that OSA screening be done regularly during routine visits and that children undergo sleep studies to evaluate the

severity of OSA symptoms. Early detection and treatment can have important effects on cognitive functioning later in life.



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