The Relationship Between Sleep-Disordered Breathing and Memory in Early Childhood

by

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Abstract

This dissertation consists of two related studies that examine children's sleep in the first three years of life. The literature pointed to a need for more objective data concerning sleep in young children (Gokdemir & Ersu, 2016). However, it was not feasible to conduct lab polysomnography (PSG) on all participants. Therefore, the first study was developed to examine the reliability and validity of a home sleep recording device to diagnose sleep-disordered breathing (SDB) in 25 children with typical development. Results showed that the T3 home sleep device is a valid tool when compared to the in-hospital lab PSG. The T3 machine's performance was comparable to PSG for several indexes but less effective for moderate apnea-hypopnea index (AHI) and oxygen desaturation index (ODI).

For the second study, participants were recruited through the Canadian Healthy Infant Longitudinal Development (CHILD) Study in Edmonton. In this study I examined the relationships between sleep duration, SDB and several variables that influence the development of memory in 501 children at three years of age. CHILD cohort study participants were administered the Developmental NEuroPSYchological Assessment – Second Edition (NEPSY–II). Sleep was only associated with memory at age three in univariate analysis. The final model that best explained the primary outcome measure (NEPSY–II sentence repetition) included the following predictors: female, screen time, maternal fruit intake and neighbourhood crime index. These studies contribute to the pertinent literature in the area under study and emphasize the need for further research into the specificities of sleep disorders and the most important factors that affect early cognitive development.

Keywords: sleep, sleep-disordered breathing (SDB), memory, apnea-hypopnea index (AHI), oxygen desaturation index (ODI), home sleep device, sleep disruption

PREFACE

The first research study in this dissertation received research ethics approval from the University of Alberta Research Ethics Board, "Validation of a home sleep study device in children", Study REB ID: MS4_Pro00014603, 08/11/2010. The study also received operational approval by Alberta Health Services, "Validation of a Level 3 Polysomnography using the T3 compared to Level 1 Polysomnography in Hospital", O/A #12266, 02/17/2011. The study investigator for this project is Dr. Piush Mandhane. I was responsible for the recruitment of participants as well as the data collection for this study. The staff from the Northern Paediatric Sleep (NAPS) Lab was instrumental to this study. The NAPS administrative staff assisted with the recruitment of prospective participants and coordination of bookings for sleep studies performed in the lab. Additionally, the NAPS sleep technicians performed the hookup and overnight monitoring of the polysomnography studies for all participants. I coordinated and performed the home T3 sleep study hookups.

The second research study in this dissertation relied on data belonging to the Canadian Healthy Infant Longitudinal Development (CHILD) study, a national longitudinal birth cohort that focuses primarily on the environment and gene-environment interactions underlying the development of allergies and asthma in childhood. I used data collected from participants belonging to the Edmonton site of the CHILD cohort study. The CHILD study was approved independently by each of the recruitment centres' respective HREBs (Health Research Ethics Board; Edmonton HREB approval # PRO00002099). Dr. Piush Mandhane is the Principal Investigator for the Edmonton site of the CHILD study and is running a concurrent sub-study whose primary objective is to determine the relationship between infant SDB and neurodevelopment in early childhood. Dr. Jacqueline Pei is a Co-Investigator on this study in the

area of neurodevelopment and behaviour. I also used the sleep and neurodevelopment variables from CHILD Edmonton for the second study. The CHILD study received base funding from the Canadian Institutes of Health Research (CIHR) and from the Allergy, Genes and Environment Network of Centres of Excellence (AllerGEN) starting in December 2007, for a period of six years. My role in CHILD Edmonton was in the coordination, collection and analysis of the level 3 home sleep studies that were performed on CHILD participants at one year of age using the T3 sleep monitor.

DEDICATION

This project is dedicated to my grandparents, *Fafa* and *Ditti*, who always taught me to "reach for the stars and heaven will come closer". Your unwavering support and guidance during my formative years has led me to this moment and for that I will be eternally grateful.

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GLOSSARY OF TERMS

Actigraphy: A non-invasive technique used to collect data on cycles of activity and rest over several days to several weeks. Actigraphy data is captured by wearing an actigraph (watch-like device) on the wrist of the non-dominant hand to measure activity through light and movement.

Apnea: Discrete pauses in breathing with complete or almost complete (≥ 90% drop) cessation of airflow at the nose and mouth, with a duration ≥ 10 seconds (or in children at least 2 baseline breaths).

AHI: Apnea-hypopnea index. AHI is calculated by totaling the number of apneas and hypopneas and dividing this number by the total sleep time in hours.

Arousal: An abrupt shift in EEG frequency lasting at least three seconds, following at least 10 seconds of sleep.

Behavioural insomnia of childhood: Difficulties with sleep onset (e.g., bedtime resistance or refusal) or sleep maintenance (e.g., prolonged night-time awakenings).

Biomarker: A measurable indicator of the severity or presence of some disease state.

Desaturation: Reduction in blood oxygen levels which are recorded during polysomnography or other sleep monitoring.

Event-related potential: the measured brain response through voltage changes in the ongoing EEG activity that are a direct result of a specific sensory, motor. or cognitive event.

IL–23: Interleukin-23 is a member of the IL-12 family of cytokines with pro-inflammatory properties.

HS–CRP: High-sensitivity C-reactive protein level that is thought to be elevated in patients with both sleep disordered breathing (SDB) and metabolic syndrome.

Hypercarbia : An increase in carbon dioxide in the bloodstream.

Hypopnea: Partial closing of the airway or reduced airflow. In particular a ≥ 30% reduction in airflow for a duration of 10 seconds or at least two breaths and associated with an arousal or awakening or ≥ 3% oxygen desaturation.

Hypoxemia: An abnormally low level of oxygen in the blood. It has many causes and often causes hypoxia since the blood is not supplying enough oxygen to the tissues of the body.

Hypoxia: When tissues are starved of oxygen.

Intermittent hypoxia: A desaturation-reoxygenation sequence which is a typical pattern of the majority of respiratory events.

Intrinsic dyssomnia: A sleep disorder (dyssomnia) that is intrinsic (e.g., arising from within the body), such as obstructive sleep apnea.

MD: Mean diffusivity, which is used to described microstructural properties in diffusion tensor imaging in cortical gray matter.

Nocturnal ventilation: The use of ventilatory assistance via a non-invasive interface mainly during sleep.

Sleep efficiency: The ratio of the total time spent asleep (total sleep time) in a night compared to the total amount of time spent in bed.

Sleep fragmentation: Repeated, short sleep interruptions during the night. These interruptions lead to excessive tiredness during the day.

Tonsillar and adenoid hypertrophy: Enlarged tonsils and adenoids. A child with enlarged tonsils and adenoids is a risk for developing sleep apnea.

ODI: Oxygen desaturation index, the number of times per hour of sleep that the blood's oxygen level drop by a certain degree from baseline.

OAHI: Obstructive apnea hypopnea index. Clinical categories are commonly defined as OAHI ≤ 1 hour of total sleep time (TST) as normal, 1 < OAHI ≤ 5 mild OSA, 5 < OAHI ≤ 10 moderate OSA, and an OAHI > 10/hour of TST as severe OSA.

OSA: Obstructive sleep apnea. It is a sleep related breathing disorder characterized by repeated episodes of prolonged upper airway obstruction during sleep in the face of continued or increased respiratory effort, resulting in complete or partial cessation of airflow at the nose and/or mouth.

Phenotype: Set of observable characteristics or traits of an individual resulting from the interaction of its genotype with the environment. Influenced by epigenetic modifications, environmental and lifestyle factors.

Primary snoring: Snoring in the absence of gas exchange abnormalities during sleep.

Pulse oximetry: A non-invasive method for monitoring a person's oxygen level of the blood.

Sleep spindle: **:** Bursts of neuronal oscillatory activity that are generated by interplay of the thalamic reticular nucleus and other thalamic nuclei during stage 2 NREM sleep in a frequency range of ~11 to 16 Hz with a duration of 0.5 seconds or greater.

CHAPTER I

Introduction

"To die, to sleep; To sleep: perchance to dream: ay, there's the rub; For in that sleep of death what dreams may come / When we have shuffled off this mortal coil, must give us pause." – William Shakespeare, *Hamlet*

Background of Topic

Sleep is a basic requirement for cognitive function and health in human beings (Nunn et al., 2016) and adequate sleep is biologically necessary to sustain life (Zhao et al., 2017). Sleep is an active, highly organized sequence of events and physiological conditions. During sleep, the body rests, yet the brain remains active while continuing to control many bodily functions, including breathing. Furthermore, sleeping is considered a regulator of toxins accumulating in the brain throughout the day (Cordone et al., 2019). When we sleep, brain channels expand, allowing the cerebrospinal fluid to flush out toxins, a system referred to as the glymphatic system (Nedergaard et al., 2015). Recent studies on the glymphatic system point to a possible new role of sleeping in health and disease (Nedergaard et al., 2015).

Optimal sleep in children is challenging to define. Blunden and Galland (2014) outline the interacting factors that impact the definition of optimal sleep as the following: individual differences (sleep-wake traits, subjective sleepiness, temperament, culture, race, sex); performance markers (task type, health, well-being); physiology (sleep quality, sleep quantity, sleep architecture, circadian fit, sleepiness) and psychosocial factors (sleep hygiene choices, cost-benefit advantage, cultural factors, day-night schedule). Inadequate sleep quality and quantity is associated with deleterious physiological (Chaput & Dutil, 2016), psychological (Ragni et al., 2019) and neurocognitive deficits (Vriend et al., 2015; Wajszilber et al., 2018).

The cognitive growth seen in early childhood parallels the rapid changes that sleep undergoes during early development. Optimal sleep in childhood plays an important role in cognitive development (Tham et al., 2017) and in future learning and development (Miller, 2015). There is substantive evidence to support the association between sleep characteristics and cognitive development (Blackham et al., 2019; Carpenter et al., 2015). Researchers have demonstrated that slow wave sleep (SWS) and rapid eye movement (REM) sleep play an important role in memory consolidation (Cortese et al., 2014; El Shakankiry, 2011). Moreover, researchers have recently identified the thalamic nucleus reuniens as an area of the brain responsible for coordinating synchronous slow waves between the prefrontal cortex and the hippocampus (Hauer et al., 2019). According to researchers, the thalamic nucleus reuniens is an area of the brain that has an important role in the formation of long-term memories during sleep (Hauer et al., 2019). Examining sleep and memory during early childhood is important as it is a time when the brain develops at a rapid pace and where the foundations for healthy development are formed (Wang & Gulgoz, 2019).

Several sleep disorders are common in children. Sleep disorders can be divided into pathophysiological sleep disorders, such as obstructive sleep apnea, and behavioural sleep disorders which include symptoms such as trouble falling asleep, delayed sleep, frequent waking at night and excessive daytime sleepiness (Gupta, 2017). Approximately 30% of parents report that sleep is a problem for their child during the first few years of life (Hiscock & Davey, 2018). Bedtime resistance during preschool age may delay sleep, resulting in daytime sleepiness (Blackham et al., 2019). Children who are not getting optimal or sufficient amounts of total sleep may demonstrate problems with attention, irritability and hyperactivity (Chattu et al., 2018). Additionally, insufficient sleep has been linked to the onset of obesity, both in adults and in the

pediatric population, and can lead to weight gain while reciprocally, weight gain and obesity can lead to sleep disorders forming a “vicious circle” (Chaput & Dutil, 2016). Parental sleep interventions including a consistent bedtime routine and limit setting are very important in developing healthy sleep habits among children (Hiscock & Davey, 2018). Addressing child sleep problems early in development can avoid the risk that they become chronic.

Sleep disordered breathing (SDB) is a common sleep disorder in childhood. SDB affects 1–5% of children and has been linked to developmental and behavioural deficits (Gipson et al., 2019). As a general clinical term (Mindell & Owens, 2015), SDB represents a spectrum of upper airway conditions ranging from mild (snoring) to severe (obstructive sleep apnea). Risk factors for pediatric SDB include adenotonsillar hypertrophy, obesity, male sex, snoring and breastfeeding (Xu et al., 2020). The consequences of untreated SDB in childhood can include a number of negative cardiovascular, metabolic and neurocognitive sequalae (Mindell & Owens, 2015).

Introduction of Current Research

Most of the scientific knowledge about sleep and cognitive development has been based on research involving older children and adults (see Walker, 2008, for a review). Studies where sleep duration and cognition were objectively measured in children aged 5 to 13 years old found that longer sleep duration was associated with better cognitive functioning (Short et al., 2018). Additionally, studies among school-aged children have found evidence that SDB and primary snoring are associated with cognitive deficits (Biggs et al., 2014). These cognitive impairments can be attributed to periods of intermittent hypoxia in children with SDB but not among those with primary snoring (Biggs et al., 2014). Recent research among adolescents supports the importance of sleep in both cognitive function and mental health (Tarokh et al., 2016). The literature among adults concluded that experimentally manipulated sleep restriction impaired

sustained attention, executive functioning and long-term memory (Lowe et al., 2017). However, there were null-effects found among other areas of cognitive functioning, such as intelligence, impulsive decision making and problem solving (Lowe et al., 2017). The authors concluded that this result may indicate that sleep restriction is better tolerated in younger versus older children and adults (Lowe et al., 2017).

In recent years, studies aiming to replicate sleep's beneficial role on memory consolidation during slow-wave sleep among adults has yielded mixed results (Cordi & Rasch, 2021). For example, recent research showed that sleep following exposure to a task did not increase the likelihood of correctly solving the problem. On the contrary, it was time spent away from the task that had an impact on the ability to solve the problem (Brodt et al., 2018). The authors of this review suggest that sleep's effect on memory may be less robust, more task-dependent and less long-lasting than previously thought (Cordi & Rasch, 2021).

Few studies have investigated the relationship between sleep and neurocognitive outcomes in preschool-aged children (Paavonen et al., 2010; Waters et al., 2020). A birth cohort study determined that short sleep duration and SDB were correlated with adverse neurodevelopment at age two (Smithson et al., 2018). Another study indicated that retention of new words was more successful among children who had a short nap after learning the new word-object pair (Axelsson et al., 2016). In an Edmonton-based birth cohort study, Tamana and colleagues (2018) examined age of onset and duration of parent-reported symptoms of SDB and behavioural problems at age two. The study showed that persistent SDB predicted the greatest effect on total behaviour problems, but also that children with either early onset SDB or late-onset SDB had a higher overall level of behavioural problems compared to children without SDB at age two. The cognitive dysfunction seen among children with SDB presents a

neurodevelopmental concern. These deficits can impact a child's successful achievement of academic goals and the development of appropriate adaptive skills that foster independence over time.

Memory difficulties in the preschool years can lead to learning challenges during the school-age period. Researchers have not found consistent evidence to draw definitive conclusions between SDB and memory functioning in children (O'Brien, 2015). Systematic reviews and meta analyses (da Silva Gusmao Cardoso et al., 2018; Konstantinopoulou, & Tapia, 2016; Spruyt, 2019) suggest that more research is required to better understand the impact of SDB on cognition. Gaining a better understanding of the pathophysiology of SDB among preschool-aged children may be critical in reversing their neurocognitive deficits (Konstantinopoulou & Tapia, 2016). Moreover, further research into the mechanisms underlying SDB can prevent specific end-organ dysfunction in different systems leading to important cardiovascular, metabolic or neurocognitive outcomes (Gokdemir & Ersu, 2016). Therefore, identifying SDB early in life can ensure prompt treatment, which may prevent morbidity associated with SDB.

Reliable and valid sleep tools in children are important for elucidating the associations between sleep, SDB and memory. The pediatric sleep literature tends to utilize subjective tools to collect sleep information (Spruyt, 2019). In-lab polysomnography (PSG) remains the gold standard in diagnosing SDB among children (Cortese et al., 2014). However, the high cost, long waiting lists, burden placed on parents and limited availability of sleep specialists remain barriers for access to in-lab PSG for children. A variety of home sleep devices may be used as alternatives to in-lab PSG; however, these objective sleep devices may not always be sensitive or

reliable enough to detect important effects. The lack of studies validating home sleep devices among children (Tan et al., 2015) points to a research gap that this dissertation hopes to address.

Research Questions

Based on the review of the literature on SDB, this thesis hopes to address some of the gaps in the literature by asking the following questions:

Study 1: What is the diagnostic accuracy of a home sleep recording device, NOX T3™ (T3), compared to in-hospital PSG in children.

Study 2: What is the relationship between SDB and memory during the first three years of life?

This thesis examines the role that sleep and SDB in a population-based birth cohort has on early memory development. I was fortunate to be part of a longitudinal study, which enabled me to view the development of memory across the first few years of life in a large sample of children. Since participants of the Canadian Healthy Infant Longitudinal Development (CHILD) Edmonton study were from a healthy birth cohort, this study enabled us to see how natural development occurs in this group of children. A recent review found only a limited number of studies of SDB in preschool children (Gokdemir & Ersu, 2016), pointing to the need for more objective sleep data in young children. For practical reasons, an in-laboratory polysomnography study could not be conducted on all 1,000 CHILD study participants at 1,3 and 5 years of age. Therefore, the researchers proposed to assess sleep with a portable sleep monitor as an alternative to the gold-standard PSG.

Organization of the Dissertation

This dissertation contributes to an increase in the understanding of childhood sleep and memory through two related studies. First, I will provide a narrative review of the literature on

SDB and cognitive development in children (Chapter II). Chapter III presents the data from a study where I employed multiple measures of sleep (parent and child questionnaires, T3 home sleep recording device and PSG) to evaluate the diagnostic accuracy of a home sleep recording device to diagnose SDB and to assess its clinical use and feasibility. I was responsible for recruiting participants for this study, as well as administering home sleep studies, analyzing sleep data and writing up the results.

In Chapter IV, I examine the relationships between several variables that influence the development of memory in young children. Scaled scores (adjusted for age) from the Memory and Learning domain of the Developmental NEuroPSYchological Assessment – Second Edition (NEPSY–II) from 501 participants (245 males, 256 females) were employed to assess children's memory at three years of age. Few studies have used objective measures to examine sleep and memory functioning in non-clinical populations. My role in this study was to administer and coordinate the home sleep studies for the CHILD Edmonton participants, perform statistical analyses and write up the results.

Chapter V integrates the results from the two studies comprising this thesis. In addition, the chapter outlines the limitations of these studies, their implications for future research and some related clinical implications.

CHAPTER II

Background and Literature Review

The purpose of this narrative review is to provide background information on Sleep-Disordered Breathing (SDB) and to review the current pediatric literature examining SDB and cognition. This section will conclude by outlining how the current thesis addresses gaps in the field and will also identify future directions.

SDB is common among children of preschool age (3–5 years old). SDB pertains to a group of sleep disorders that occur due to pathophysiological disorders and are referred to as intrinsic dyssomnias. Obstructive sleep apnea (OSA) is one of the most common causes of SDB in children. Sleep fragmentation, intermittent hypoxia, hypercarbia and apneas make up the sequelae of SDB symptoms. The pathophysiology of SDB is upper airway obstruction due to lymphoid tissue growth (palatine and pharyngeal tonsils; Francis & Lam, 2020), obesity (Kohler et al., 2018) and sex (Inoshita et al., 2018).

The most common cause of SDB is enlarged tonsils and adenoids, which result in obstruction of the upper airway during sleep (Tsubomatsu et al., 2016). The age when tonsils and adenoids tend to enlarge, and when SDB develops, is preschool (Francis & Lam, 2020). The most common treatment of SDB in children is adenotonsillectomy (AT, Marcus et al., 2012). Among preschoolers, SDB may persist or reoccur several years after treatment. A study by Walter and colleagues (2015) found that 39% of children still met the diagnosis of SDB even three years following treatment. This study also indicated that the treatment of children with moderate to severe SDB had better treatment outcomes compared to those with less severe SDB (Walter et al., 2015).

Several studies have examined risk factors for SDB in childhood. Kamal and colleagues (2018) identified certain unique predictors for each SDB phenotype to two years of age, including the maternal gestational diet as mediated by some family, maternal, child and environmental covariates previously correlated with SDB. Sex differences were found in a retrospective study of 63 Japanese children (3–15 years old) with OSA (Inoshita et al., 2018). Results indicated that adolescent girls with OSA had a greater upper airway space, less severe SDB and better sleep efficiency compared to adolescent boys with OSA. No differences were found between pre-adolescent boys and girls (Inoshita et al., 2018). Other significant risk factors of OSA identified among a group of 1009 Chinese children included snoring at 3 months of age or later, male sex, obesity, breastfeeding and tonsillar and adenoid hypertrophy (Xu et al., 2020).

Identifying Children With SDB

A variety of subjective and objective techniques and methods are employed to measure SDB, including PSG, videosomnography, nap studies, actigraphy, nocturnal oximetry, direct observation and parent report questionnaires (Crabtree & Williams, 2009). These methods vary in cost, ease of use, level of intrusiveness and the quality of data they provide. Both the American Academy of Sleep Medicine (AASM) and the American Academy of Pediatrics (AAP) recommend PSG to evaluate the presence and severity of SDB in children (Chang & Chae, 2010; Gruber et al., 2014; Marcus et al., 2012; Sateia, 2014).

Traditionally, sleep devices have been classified in four levels (level 1, level 2, level 3 and level 4). Attended in-laboratory nighttime PSG, or level 1, conducted within an AASM-accredited sleep facility, has become the gold standard for the diagnosis of pediatric OSA and SDB (Aurora et al., 2011; Cortese et al., 2014; El Shakankiry, 2011). A level 1 sleep monitoring device typically records respiratory, cardiovascular and neurological data (El Shayeb et al.,

2014). Level 2 through level 4 represent unattended sleep studies. According to the AASM, a level 2 sleep study refers to a full unattended portable PSG (≥ 7 channels), a level 3 device records between four and 7 channels (e.g., oximetry, airflow, hear rate, respiratory effort) and level 4 sleep monitors have one or two channels (Kapur et al., 2017).

In-laboratory and at-home PSG studies can be used to diagnose SDB and determine SDB severity by identifying apneas, hypopneas and arousals during sleep (Gupta et al., 2019). AHI is calculated by the sum of all apneas and hypopneas divided by the total sleep time in hours. The AASM manual defines the scoring rules of sleep and respiratory events in PSG studies (Iber et al., 2007). A systematic review of SDB in children indicated that the most frequently reported polysomnographic criterion for SDB severity was AHI (Kaditis et al., 2016b). An AHI > 1 event/hour indicates the presence of obstructive SDB (Kaditis et al., 2016b). However, there is no consensus in the literature on this criterion, and research groups use different cut-off values to define pediatric SDB (Mindell & Owens, 2015).

Most research on the validation of level 3 portable devices has been conducted within the adult population. Studies have compared the diagnostic accuracy of level 3 portable sleep devices with in-lab PSGs. The portable device's sensitivity and specificity for diagnosing OSA ranged from 77% to 100% and 71% to 100%, respectively, with correlations for AHI ranging between .85 and .98 (Cairns et al., 2014). The validity of software-based algorithms for scoring portable sleep studies versus the manually scored approach used in the scoring of in-hospital PSGs is a concern (Hoffman & Barnes, 2012). Researchers have found poor inter-rater agreement between scorers (Gudnadottir et al., 2019; Park et al., 2015).

Nocturnal pulse oximetry and actigraphy are other types of non-intrusive, easy to use, objective sleep measures. Oximetry studies have been used to screen children with suspected

SDB. The McGill oximetry scoring system describes levels of severity of nocturnal hypoxemia that range from 1 (normal or inconclusive), 2 (mildly abnormal), 3 (moderately abnormal) and 4 (severely abnormal; Nixon et al., 2004). The McGill criteria classify a nocturnal oximetry recording as abnormal (McGill oximetry score > 1) when three or more clusters of desaturation events ≥ 4% and at least three desaturations drop below 90% (Kaditis et al., 2016b). Studies indicate that a positive oximetry result is likely to confirm a diagnosis of severe SDB (high specificity). Still, a negative result does not necessarily rule out SDB (low sensitivity; Tan et al., 2015).

Actigraphy studies employ a watch-like device called an actigraph that measures sleep-wake patterns based on activity monitoring algorithms (Sadeh, 2011). The American Academy of Sleep Medicine (AASM) conducted a systematic review of the clinical use and guidelines of actigraphy relative to sleep logs and PSG across a range of clinical populations (Smith et al., 2018). The review did not suggest that clinicians use actigraphy in the assessment of SDB. Recent research has employed the Hidden Markov Model machine learning classification to identify hidden sleep states of accelerometer-assessed sleep duration in three- and five-year-old CHILD study participants (Hammam et al., 2020). This novel approach can contribute to the future role of actigraphy in diagnosing and managing children with SDB.

Parent report questionnaires represent a valuable subjective tool in assessing the sleep of children. With young children, parents or caregivers are very familiar with their child's sleep patterns simply because they are often awake when their child is having difficulty sleeping. The use of a validated sleep questionnaire is a non-invasive, quick, low-cost and easy alternative to the PSG. The Pediatric Sleep Questionnaire (PSQ) is a valid and reliable tool for children (two to eight years of age) to identify SDB (Chervin et al., 2000). When compared to PSG, the PSQ has

a 78% sensitivity and 72% specificity in identifying SDB in clinical research (Chervin et al., 2000). A meta-analysis compared the sensitivity and specificity of the PSQ with AHI (≥ 1 = mild, ≥ 5 = moderate, and ≥ 10 = severe) measured through in-laboratory PSG or home PSG (Wu et al., 2020). Results from pooled analyses indicated 0.73% sensitivity and 0.48% for specificity for mild SDB. Moderate SDB showed 0.80% sensitivity and 0.46% specificity, whereas severe SDB indicated 0.89% sensitivity and 0.26% specificity (Wu et al., 2020).

One limitation when relying on questionnaires alone to collect sleep data is that their validity is subject to response bias. Parents may not be as aware of the sleep habits of their older children, which is why a sleep log or diary would be helpful and useful in conjunction with a questionnaire. Another issue is the fact that questionnaires are "retrospective." When parents look back on the past sleep behaviours and habits of their children, their memory and accuracy of the events may be skewed by *recall bias*. Using sleep logs or diaries to corroborate a child's typical sleep-wake cycle with a parent's memory of events helps to correct for recall bias.

Imprecise measurement of SDB can lead to type 1 or 2 errors in determining associations between SDB and neurodevelopment. Recent systematic reviews (da Silva Gusmao Cardoso et al., 2018; Spruyt, 2019) identified a need for more studies that employ objective criteria (e.g., PSG) to diagnose SDB. In a literature review, Spruyt (2019) reported that sleep information in studies was primarily measured via subjective reports (30.2%). Additionally, da Silva Gusmao Cardoso and colleagues (2018) found inconsistencies in the criteria used to categorize SDB severity, as each research team has tended to set their own arbitrary cut-offs.

Associations between SDB and Neurocognitive Development

Recent systematic reviews and meta-analyses have found no consistent evidence that SDB in children negatively affects cognition (da Silva Gusmao Cardoso et al., 2018; Spruyt,

2019). However, SDB could have lasting and possibly irreversible effects when it occurs early during the vulnerable period of brain development (Song et al., 2016). The following section provides a review of the recent literature on SDB and cognition in typically developing children. The following narrative literature review was conducted by means of searches on PubMed, PsycINFO and Web of Science, employing key terms and MeSH terms for "sleep" or "sleep-disordered breathing" and "memory" and "cognitive outcomes" and "cognition". The search was initially limited to preschool children (two to five years old). However, this approach produced few results. I then expanded the search to include children from birth to 12 years of age. The searches were limited to studies published in peer-reviewed journals over the last five years (2015–2020). I also looked for reviews on the subject of "SDB in childhood" and "SDB and cognition". Studies were excluded if (1) research was performed in a specialized medical patient population (e.g., Down syndrome or cleft lip or palate), (2) children were diagnosed with attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) or (3) children were diagnosed with chronic conditions. Further studies were identified by examining the reference lists of all articles included in the review. Other articles were included when they were relevant to the topic and supported themes that came out of the literature review. The full list of sources are included in the reference list at the end of this chapter.

Children with SDB present with daytime deficits that are age-related: school-age children tend to have more severe neurocognitive deficits and worse cardiovascular functioning compared to preschoolers. However, preschool children present with negative behaviour similar to that of school-age children (Tamanyan et al., 2018). Researchers studied cognition in a group of 59 Chinese children (4–12 years old) diagnosed with mild or moderate obstructive sleep apnea-hypopnea syndrome (OSAH) by PSG compared to 60 age- and sex-matched controls and

cognition (Zhao et al., 2018). The study found that younger children (4–6 years old) had significantly lower scores on full-scale IQ (FSIQ), verbal IQ, comprehension tests and visual analysis compared to healthy controls. In contrast, the study found that the verbal IQ but not FSIQ was associated with OSA in the subgroup of older children (6–12 years old; Zhao et al., 2018).

A study of toddler and preschool-aged children (1–5 years old) referred for clinical evaluation of SDB or behavioural insomnia of childhood (n = 20) along with a comparative sample of non-snoring healthy sleepers (n = 77) found that SDB was associated with cognitive deficits in children's visual reception and receptive language use (Spooner et al., 2016). In a study of slightly older children with SDB (6–8 years old) significant deficits in inhibition, attention and conflict monitoring were found as measured via event-related potentials; the same study found that boys with SDB exhibited more behaviour problems, compared to girls (Kaihua et al., 2019). These findings demonstrate that even in young children, SDB can negatively affect a range of developing neurocognitive abilities. Consistent with previous studies (Tamana et al., 2018), current research suggests that boys with SDB may be more vulnerable to externalizing behaviour problems compared to girls (Kaihua et al., 2019).

Results from a community sample of 631 children between four and ten years of age indicated that cognitive function may decline with greater snoring severity. Participants had not been previously identified or clinically referred for sleep-related pathologies. Researchers found that more frequent snoring was associated with poorer cognitive outcomes, independent of AHI (Smith et al., 2017a). Another study among preschool children (two and a half to six years old) demonstrated different results. A clinical sample of preschool children with primary snoring (n = 41, mild OSA), children with moderate–severe OSA (n = 36) and 83 controls (n = 83) underwent

a PSG-validated questionnaire PSG and a neurocognitive assessment (Pietropaoli et al., 2015), and the study found no differences between groups in cognitive scores. This indicates that SDB of all severities is not associated with cognitive impairment in preschoolers, compared to a control group (Pietropaoli et al., 2015). One possible explanation for these contradictory findings could be that the studies differed in their sample populations. Smith and colleagues (2017a) examined sleep and cognition in a large cohort study in the United States, whereas Pietropaoli and colleagues (2015) utilized a clinical sample in Italy for their case control study.

The existence and severity of cognitive impairments seen in children with SDB may be dependent on the assessment methods used (Biggs et al., 2011). Parent-reported measures used to assess children with mild SDB overestimated the children's working memory deficits (Biggs et al., 2011). Recent reviews and meta-analyses have concluded that children with SDB have a higher risk of developing cognitive deficits (Biggs et al., 2014); however, the underlying studies include varying sample sizes and employ different outcome measures, so the conclusions are inconsistent across these studies.

Reversing Neurocognitive Deficits Associated With SDB

A meta-analysis compared the efficacy of AT for children with OSAS and cognitive functioning. Analysis of the literature between children with OSAS and healthy controls 6 to 12 months after AT showed worse scores in general intelligence, memory, attention, executive function and verbal ability (Yu et al., 2017). The mixed results on the cognitive benefits of AT may indicate the need for more extended follow-up for any reversal of cognitive deficits to become apparent (Taylor et al., 2016).

Researchers have studied whether interventions for SDB have long-lasting impacts (Biggs et al., 2014; Kohler et al., 2018). A systematic review of prospective studies of children

from 2.5 to 14 years of age who were treated with AT showed improvements in neurocognitive functioning and IQ, especially among preschoolers (Song et al., 2016). The authors note that these results should be interpreted with caution since there were only three studies conducted with the preschool children; the effectiveness of AT on neurocognitive outcomes was stronger among younger children, which may suggest a threshold age when cognitive deficits become irreversible even with treatment (Song et al., 2016). It should be noted that this systematic review was conducted prior to the Preschool Obstructive Sleep Apnea Tonsillectomy and Adenoidectomy study (POSTA).

To date, only two randomized controlled studies have evaluated the effect of AT for children with SDB on neurocognitive function: the Childhood Adenotonsillectomy Trial (CHAT; (Marcus et al., 2013) and the POSTA study (Waters et al., 2020). The POSTA's aim was to determine whether treatment with AT for OSA in preschoolers improved cognitive function. Researchers randomly assigned children to early AT (within two months) or to routine wait lists (12-month wait, no AT). The results from sleep studies, measured via PSG and parent-reported behaviour questionnaires, indicated sustained improvements in sleep and behaviour for the AT group at 12-month follow-up. Although cognitive ability improved over time in both groups, none of the improvement in intellectual ability could be attributed to treatment 12 months post AT (Waters et al., 2020).

Unlike the POSTA, primary results from the CHAT study did not show improved neurocognitive functioning for the early AT group compared to the watchful waiting group at seven-month follow-up (Marcus et al., 2013). Differences found between these two RCT could be due to the age of participants. Marcus and colleagues (2013) suggested that there could be an age threshold related to the effectiveness of AT on SDB. Further exploratory analyses, which

modified the initial CHAT protocol, randomly assigned children five to nine years of age with OSA without prolonged oxyhemoglobin desaturation to either early AT (n = 226) or watchful waiting with supportive care (n = 227). Neuropsychological measures obtained at baseline and seven months following the intervention were included in the analyses. Cognitive scores improved on measures of nonverbal reasoning, fine motor skills and selective attention (Taylor et al., 2016). Despite these results, the differences had small effect sizes (Cohen's *d,* 0.20–0.24). Surprisingly, decreased sleep efficiency was associated with improved scores on the Wide Range Assessment of Memory and Learning, Second Edition Verbal Learning Recognition subtest (Taylor et al., 2016). These results should be interpreted with caution since the exploratory analyses did not correct for multiple comparisons, which could lead to Type 1 error (Taylor et al., 2016).

The efficacy of AT in children may be modified by the presence of comorbidities, such as obesity. Kohler and colleagues (2018) compared cognitive performance, sleep, ventilation and body mass before and at four years post-adenotonsillectomy (AT) in younger children (3–12 years old) with SDB and healthy controls at the same time points. Improved sleep and nocturnal ventilation was found at four-years post-AT; however, only limited neurocognitive gains were found among normal weight or overweight/obese children with SDB. Kohler and colleagues (2018) note that obese children with SDB presented with significantly lower neurocognitive scores than normal-weight controls with SDB at baseline. Therefore, body mass index (BMI) should be assessed as a potential important confounder in studies of AT for the treatment of SDB. Contrasting results were found in a study of slightly older children and adolescents (8–16 years old) where no differences in cognitive outcomes were found between overweight children

and adolescents with SDB versus healthy-weight children and adolescents with SDB or age-matched healthy weight, non-snoring control subjects (Biggs et al., 2017).

Another study followed preschool children (3–6 years old) diagnosed with SDB and an age-matched, non-snoring control group three years after baseline (Weichard et al., 2016). At follow-up, children were categorized into the following groups: control (n = 13), resolved SDB (n = 15) or unresolved SDB (n = 14). Despite the small sample sizes, this study indicated that children diagnosed with SDB in early childhood continued to exhibit reduced cognitive performance and behaviour compared to control children three years following complete resolution of disease (Weichard et al., 2016). Improvements in cognitive functioning following treatment have only been seen in non-verbal aspects of cognition (Biggs et al., 2014; Taylor et al., 2016).

The small effect sizes of AT on cognitive outcomes (Taylor et al., 2016) indicate the need for additional research in this area. Konstantinopoulou and Tapia's (2016) review indicated that more research is needed to elucidate which specific cognitive areas can be improved with the treatment of SDB, including multimodal assessment of sleep and cognitive functioning such as self-report, parent report, teacher or daycare worker report and objective testing. They also indicated that future longitudinal studies are needed to assess the reversibility of neurocognitive deficits associated with SDB (Konstantinopoulou & Tapia, 2016).

How does SDB impair cognition?

Episodes of hypoxemia or sleep fragmentation may also mediate the relationship between SDB and cognition (Poets, 2020). Frequent parent-reported snoring (questionnaire) has been associated with poor school performance (Urschitz et al., 2003). The Canadian Oxygen Trial, using data from 997 pre-term infants (< 28 week gestation) and older infants, found that those

with intermittent hypoxemia (percentage of time with Spo2 < 80%) lasting for a minimum of one minute were three times more likely to develop cognitive or language delays or sleep fragmentation (Poets, 2020).

A four year longitudinal study among children originally diagnosed with SDB at 7 to 12 years of age and a healthy, non-snoring control group examined treatment of SDB on neurocognition, academic ability and behaviour (Biggs et al., 2014). Results indicated that a decrease in obstructive apnea hypopnea index (OAHI) was predictive of improvement in Performance IQ but not Verbal IQ, academic measures or behaviour (Biggs et al., 2014). However, other researchers have shown that an AHI value may not be the only factor in evaluating the severity of SDB among children (da Silva Gusmao Cardoso et al., 2018). Some studies fail to demonstrate a dose-response relationship (for a review, see Galland et al., 2015). However, a large pediatric cohort of 1,010 children 5 and 7 years old found a SDB severity-dependent relationship with cognitive outcomes (Hunter et al., 2016). Participants were divided into four severity groups based on questionnaires and AHI: (a) non snoring, AHI < 1 events/hour; (b) habitual snoring, AHI < 1 events/hour; (c) habitual snoring, AHI 1 to < 5 events/hour and (d) habitual snoring and AHI > 5 events/hour (Hunter et al., 2016).

Research into the identification of sleep spindles activity may help in better understanding the complex mechanisms involved in the influence of SDB on neurocognition. A sleep spindle is a burst of neuronal oscillatory activity generated by the interplay of the thalamic reticular nucleus and other thalamic nuclei during stage 2 NREM sleep, in a frequency range of ~11 to 16 Hz and with a duration of 0.5 seconds or greater. A pilot study of 19 children (6–11 years old) with mild OSA compared to 14 healthy control subjects showed a different pattern of sleep spindle activity during NREM sleep. These sleep spindles were significantly correlated

with neurocognitive performance, especially with working memory (Brockmann et al., 2018). The authors of this study hypothesized that sleep spindles may be markers for the cerebral mechanisms damaged in mild cases of OSA (Brockmann et al., 2018). Future studies that compare children with mild SDB with and without cognitive deficits could be beneficial in identifying a pattern of sleep microstructure that is predictive of cognitive performance (Brockmann et al., 2018).

Disruptions to the microstructure of the brain as a result of SDB may help explain some of the neurocognitive deficits described in children. Evidence of gray matter atrophy is a normal part of the aging process (Ramanoël et al., 2018) but should not be seen among young children. Findings from imaging studies on the effects of SDB on learning and memory in children indicate that those with SDB suffer from the neurodegeneration of the dentate gyrus. In particular, lower mean diffusivity of the dentate gyrus in children with OSAS is correlated with a lower verbal learning and memory score (Cha et al., 2017). In a similar study, children with OSA demonstrated significant grey matter volume reductions in areas that control cognition compared to controls (Philby et al., 2017). Direct brain changes were measured via mean diffusivity (MD) among a group of 12 year old children with SDB (n = 18) compared to non-snoring controls (n = 20). Acute (reduced MD values) brain changes were seen in the hippocampus, insula, thalamus, temporal and occipital cortices and cerebellum, whereas chronic changes were seen in the front and prefrontal cortices in the SDB group compared to the control group (Horne et al., 2018). Acute changes are seen in areas that regulate autonomic, cognitive and mood function versus chronic (increased MD values) changes that are related to behavioural control (Biggs et al., 2011).

Gaps in the Research Literature and Future Directions

The first gap in the literature that this thesis addresses is the lack of objective measures employed to measure sleep among children (Chapter 3). Therefore, this study examined the reliability and validity of respiratory indices of a portable type 3 device. Additionally, there is a consensus among review articles that the literature addressing SDB and cognition among children is limited (da Silva Gusmao Cardoso et al., 2018; Konstantinopoulou & Tapia, 2016; Krysta et al., 2017; Spruyt, 2019). A review (Krysta et al., 2017) has identified the need for studies on cognition and SDB in children of specific age groups. The second study (Chapter 4) hopes to address this gap by examining SDB and cognition among preschool children. Furthermore, the current thesis (Chapter 4) collected objective sleep (Chapter 3) and neurodevelopment data, which has been noted as a methodological limitation in the literature.

Research in the area of cognition and SDB has been inadequate due to the heterogeneous methodologies used (e.g., different sample sizes and varying recruitment strategies) and the various subtypes of cognition investigated. Therefore, it has been difficult to determine any pattern concerning the effect of SDB on specific cognitive domains (da Silva Gusmao Cardoso et al., 2018).

Although studies to date have shown that children with SDB demonstrate impaired cognitive abilities, they remain within the normal range and therefore are not clinically significant. Systematic reviews and meta-analyses in this area of research have identified the lack of homogeneity among methodologies used and the need for more research in this area to elucidate the relationship between cognition and SDB among young children (da Silva Gusmao Cardoso et al., 2018; Konstantinopoulou & Tapia, 2016; Spruyt, 2019). Therefore, the field calls for more prospective, randomized, controlled studies using standardized neurocognitive

assessment tools to better evaluate the impact of SDB on memory functioning in preschool children.

The relationship between SDB and cognition may be mediated by other factors, such as behavioural problems (Smith et al., 2017b). A study of 1,115 school-aged children (5–10 years old) found no direct effects of SDB on cognitive functioning (Smith et al., 2017b). The study's authors suggested that common behaviour problems associated with SDB (e.g., inattention, emotional pathology or conduct problems) may disrupt a child's learning process and affect their overall cognitive functioning during their formative years. Furthermore, excessive body mass appears to be an important factor in the risk of neurocognitive performance deficits among children with SDB (Kohler et al., 2018). These results suggest that future studies should look at other possible confounding factors that may impact the relationship between SDB and cognition.

Identifying a particular biomarker for the prediction of cognitive deficits in children with SDB may help with early detection and diagnosis (Hunter et al., 2016). Children may be diagnosed younger and more accurately by focusing on hypoxemic events and episodes of nighttime arousals rather than respiratory events (e.g., apneas) or low heart rate (bradycardia; Poets, 2020). Researchers have found that children with OSA can continue to have negative inflammatory effects following treatment (Huang et al., 2020). Results from this study of 79 children (4–12 years old) with OSA and 32 healthy control subjects suggests that IL–23 and HS–CRP may serve as blood markers for the persistence of SDB following AT (Huang et al., 2020).

Given that the limited number of studies in this field have used differing cognitive measures, it remains challenging to draw definite conclusions concerning preschoolers with SDB. To date, only one randomized study has been performed among preschool children

(Waters et al., 2020). Most of the studies in this area are limited by their nonrandomized design, which could lead to an overestimation of effects. Additionally, the varying definitions of SDB have contributed to heterogeneity among the published studies. The relevant studies reviewed in the narrative literature review have employed different assessment tools to measure memory and have also measured different aspects of memory, which makes any comparison of their results quite challenging.

Overall, research in the area of cognition and SDB has been inadequate due to the heterogeneous methodologies used (e.g., different sample sizes and varying recruitment strategies) and the various subtypes of cognition investigated. Therefore, it has been difficult to determine any pattern concerning the effect of SDB on specific cognitive domains (da Silva Gusmao Cardoso et al., 2018). This thesis hopes to add to the literature by examining a diagnostic tool to assess SDB in children (Chapter 3) and the association between SDB and memory among preschoolers in a large prospective longitudinal birth cohort study (Chapter 4).

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CHAPTER III

Study 1: Reliability and Validation of Respiratory Indices of the Nox T3 in Children

Abstract

BACKGROUND: Home sleep monitoring is currently not recommended for children. We evaluated the reliability and validity of a portable sleep monitor in-laboratory and at home in children.

METHODS: Participants (n = 25) 4–15 years old underwent a simultaneous in-laboratory polysomnography (PSG) study and NOX T3^{TM} portable sleep monitoring in addition to two consecutive nights of unattended T3 sleep studies at home. Each T3 sleep study was scored twice by two independent scorers. The reliability and validity of the T3-measured respiratory indices were examined using a nested-design multilevel analysis.

RESULTS: Of the 20 children who completed both the T3 and PSG, 75% preferred the home study. We found that 46% of children had an apnea-hypopnea index (AHI) < 1.5 on the T3 studies while 30% of studies had an AHI between 1.5 and 5. The AHI from the lab PSG studies yielded similar results. The T3 automated scoring was the biggest source of variability in the home T3 studies. When the automated scoring algorithm was excluded, the individual who scored the T3 home studies provided the most AHI variability. The in-laboratory completed T3 AHI had an area-under-curve (AUC) of 0.73; (SE = 0.10: $p < 0.05$) for a threshold of AHI ≥ 1.5 events/hour compared to PSG. A threshold AHI ≥ 10 events/hour yielded an AUC = 0.98 (SE = 0.19, $p < 0.05$). The home T3 AHI was significantly associated with the PSG (β = 0.66, p = 0.001).

CONCLUSION: The T3 was able to identify children with severe SDB (AHI ≥ 10). A significant correlation was found between home and lab AHI. Larger prospective studies are required before the widespread use of the T3 at home in children.

Introduction

Sleep disordered breathing (SDB) affects 12–15% of children (Lumeng & Chervin, 2008), with symptoms ranging from primary snoring to obstructive sleep apnea (OSA). OSA affects approximately 1–4% of children (Ferini-Strambi, 2012). The sequelae associated with untreated OSA and SDB include cognitive deficits (Bourke et al., 2011), hyperactivity (Touchette et al., 2007) and cardiovascular consequences (Halbower et al., 2008). The gold standard method for diagnosing of SDB (Chang & Chae, 2010; Hoffman & Barnes, 2012) is an in-laboratory polysomnography (PSG) sleep study (Kheirandish-Gozal, 2010).

Limitations associated with completing an in-hospital PSG include long waitlists, high cost and the patient burden associated with having to sleep in a hospital for the night (Collop, 2009). Home or unattended portable sleep studies are alternatives to the in-hospital laboratory PSG studies in adult patients (Blackman et al., 2010; Collop et al., 2007). The advantages of using a home sleep device include increased accessibility, which may result in earlier treatment initiation, greater patient comfort and healthcare cost savings (Bruyneel & Ninane, 2014). Few studies have examined the clinical utility of portable home PSGs in young children (Tan et al., 2015).

Research Questions

The main purpose of this study is to evaluate the reliability and validity of a home sleep recording device, NOX T3^{TM} (T3), compared to in-hospital PSG, for children. Additionally, we examined the validity of the automated scoring of the Noxturnal software program. Finally, we

used a nested study design to examine the different sources of variation (e.g., scorer, location, night effects and scoring algorithm) that may impact the reliability of a home sleep study.

Hypotheses

1**.** Home sleep studies using the NOX T3^{TM} (T3) will demonstrate a Receiver Operating Characteristic (ROC) curve of 0.8 or higher when compared to an in-hospital polysomnography.

2. The automated Noxturnal scoring algorithm with sleep and wake times entered manually will be significantly associated with manually scored sleep studies.

3. The most significant source of variability among T3 sleep studies will be the location the study was performed (lab versus home).

Method

Study Sample

Children from 4–16 years old were recruited from the Northern Alberta Pediatric Sleep (NAPS) Lab in Edmonton, Alberta. A pediatric sleep questionnaire (PSQ) was administered as part of the screening process and subjects were recruited in three groups: (1) children with a history suggestive of SDB (a PSQ or a prior overnight oximetry study suggestive of SDB), (2) children with an intermediate risk for SDB (a prior negative or inconclusive overnight oximetry) or (3) children at low risk for SDB (a negative PSQ and negative overnight oximetry study). Children with no indication of SDB were recruited from the community. This study received local ethics board approval (PRO00014603); the study inclusion and exclusion criteria are presented in Table 3.1.

When the study was conceived, the intended sample size was a total of 90 participants. This sample size was based on a null hypothesis Area Under the Curve (AUC) of 0.7, and alternative hypothesis AUC of 0.85, which indicated that we would require 45 children with

sleep disordered breathing (SDB) and 45 children without SDB (alpha level 0.05, power of 0.80). However, the study's achieved sample size was a total of 25 participants. During the recruitment phase of this study, changes occurred at the Stollery Hospital's Pediatric Sleep Lab where the lab was only conducting up to 12 sleep studies per month. For this research project, I recruited participants from the waitlist at the Pediatric Sleep lab. Due to the limited number of PSG studies being conducted in the lab, participants who met the criteria for this study were not prioritized. This presented a barrier to the current study as it prevented the recruitment of participants who were intended to be part of the moderate (n = 30) to high-risk group (n = 30).

Table 3.1

Inclusion and Exclusion Criteria of T3 Validation Study

Inclusion criteria:

- Children 4–16 years old
- Parents capable of communicating in English
- Residence in Edmonton

Exclusion criteria:

- Children with acute infection (defined as fever > 38.0° C) or a history of fever chills in last 72 hours
- Children with known immunodeficiency (AIDS, chronic oral steroid use, proven malignancy, present or recent chemotherapy, suspected or proven tuberculosis)
- Children with Down syndrome
- Children with Pierre Robin syndrome
- Children with Cleft palate (cleft palate "repair" was not an exclusion)
- Children with Cerebral palsy
- Children with Craniofacial synostosis syndromes (Apert, Crouzon)
- Children with neuromuscular disease
- Children with congenital heart disease
- Children with Achondroplasia
- Children undergoing a Split Night sleep study
- Children undergoing a Mask fitting
- Children with Oppositional Defiant Disorder
- Children with Fetal Alcohol Spectrum Disorder (FASD)
- Children with Autism

Measures

Each parent or caregiver and child participant (age 6 and older) separately completed the Patient Preference Questionnaire (PPQ), the Children's Sleep Habits Questionnaire (CSHQ) and the Pediatric Sleep Questionnaire (PSQ). Parents or caregivers completed the questionnaires for their children. Finally, each parent or caregiver was asked to complete a brief home environment questionnaire.

The Patient Preference Questionnaire (PPQ). The PPQ is a brief questionnaire that asks each parent or caregiver and child participant (age 6 and older) separately – the morning after each sleep study – to describe how the child's sleep was for the previous night on a scale from 0 (very bad) to 10 (very good). The second question asked on this questionnaire was for each parent or caregiver and child participant (age 6 and older) separately to choose which recording device they preferred: home sleep device or in-hospital sleep study (see Appendix A).

The Child Sleep Habits Questionnaire (CSHQ). The CSHQ is a multidimensional, well-established 45-item, retrospective, parent-report measure designed to examine sleep behaviours in children from 4–12 years old. The CSHQ is not intended as a means of diagnosing specific sleep disorders, but rather to identify the need for possible further evaluation to a sleep specialist (Owens et al., 2000). The self-report CSHQ focuses on sleep disorders common to this age group in three domains: dyssomnias (difficulty getting to sleep or staying asleep), parasomnias (e.g., sleepwalking/talking, night terrors, bedwetting or restless leg syndrome) and SDB. The CSHQ is easy to administer and to complete; parents are asked to recall sleep behaviours occurring over a typical recent week.

The CSHQ has been studied and validated for clinical use for screening sleep disturbances in toddler and preschool children (two and a half to five years of age) as well as in

older children from four to ten years old (Goodlin-Jones et al., 2008; Owens et al., 2000). The internal consistency of the CSHQ was 0.68 for the community sample and 0.78 for the clinical sample. The test–retest reliability for the subscales ranged from 0.62 to 0.79, which is an acceptable level (Owens et al., 2000). Comparing the clinical sample to the community sample for each item and subscale of the questionnaire established the instrument's validity. Owens and colleagues (2000) wanted to examine whether the CSHQ was able to correctly identify children who had sleep problems and those who did not warrant any additional investigation into possible sleep problems. The results generated using the Receiver Operator Characteristic (ROC) curve found a sensitivity rate of 0.80 and specificity at 0.72. Using a cut-off score of 41 on the CSHQ, 80% of subjects were correctly identified in the clinical group.

The Pediatric Sleep Questionnaire (PSQ). The PSQ is a multidimensional, well-established, 69 item parent/self-report questionnaire containing 8 subscales ("When sleeping your child…"). The PSQ has been validated in children from 2–18 years old (Chervin et al., 2000). The questions are asked in a simple format where possible responses are "YES" = 1, "NO" = 0 or "Don't Know" (DK) = missing. This questionnaire measures the presence of sleep-related breathing disorders, daytime sleepiness, snoring and inattention.

Each of the 22 symptom items assessed have been shown to correlate with PSG-confirmed OSA (Chervin et al., 2007). Test–retest reliability ranges from .66–.92 for each subscale (Lewandowski et al., 2011). The PSQ is a widely used pediatric SDB screening tool for high- and low-risk groups with a sensitivity of 0.85 and specificity of 0.87 in correctly identifying children with SDB (Chervin et al., 2000). The validity of the PSQ has been established in several clinical settings by comparing items to objective criteria (PSG) and by the fact that the questionnaire scales were able to predict diagnostic classifications of sleep disorders

(Chervin et al., 2000). A score of greater than 0.33 has been shown to predict a 3-fold increased risk of developing SDB as measured by PSG (Chervin et al., 2000).

Home Environment Questionnaire. This questionnaire is an abbreviated version of the home environment questionnaire that is used in the Canadian Healthy Infant Longitudinal Development (CHILD) study. The CHILD study began in 2008 and is an ongoing national longitudinal birth cohort study that recruits pregnant women in centres in Vancouver, Edmonton, Winnipeg and Toronto. The Home Environment questionnaire contains 49 questions, including some that have the "YES" or "NO" format as well as others asking the respondent to circle the best answers from a list. It asks the parent or caregiver to provide information regarding the age of the home; the function, condition and maintenance history of their home; renovations; the source and extent of dampness indicators; mould growth; new furnishings; appliance emissions; the presence and type of air conditioning and conditions of use; smoke exposure and a description of all rooms in which their child may sleep.

Data Collection

Each participant spent one night in NAPS and two consecutive nights at home with the NOX T3™ (T3) portable sleep device. Participants were randomly allocated to begin with either the home PSG or in-hospital PSG using a random number generator (www.random.org). The home studies and in-lab PSG study were scheduled within one week of each other. Parents completed the PSQ (Chervin et al., 2000) at enrollment.

In-laboratory Testing

The PSG studies were completed by NAPS clinical sleep technicians in accordance with American Academy of Sleep Medicine (AASM) standards of practice. PSG monitoring included electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (ECG), O_2 saturation

pulse oximetry (Nellcor), pulse wave monitoring, respiratory inductance plethysmography (respiratory, abdominal and sum channels; Respitrace, Sensormedics, CA, USA) and transcutaneous PCO_2. Children were also monitored and recorded on videotape, using an infrared video camera, and were continuously observed by a PSG technician. Oronasal airflow (three-pronged thermistor), nasal pressure and measured end-tidal PCO_2 were also completed. The T3 sensors were applied by trained staff from the CHILD Edmonton research team after the PSG set-up was completed. Each participant wore four respiratory inductance plethysmography (RIP) belts (two abdominal and two thoracic) and a dual nasal cannula that allowed for simultaneous T3 and PSG pressure sampling via a y-connector. The technologists in the lab were instructed to adjust the T3 sensors only if the patient was uncomfortable or if they noticed that a wire had fallen off.

Home Testing

The home sleep study utilized the T3 machine with wireless pulse oximetry, real-time audio, chest/abdominal (RIP) and nasal thermistor. Two EMG electrodes above and below a rib and one electrode on the chest were used to measure muscle activity to determine REM and Non-REM sleep. Trained staff installed the sleep equipment for the first home study night. The parent or caregiver installed the sleep equipment on their child during the second night of the study, and CHILD Edmonton staff did not spend the night at the participant's home. A member of the study team was on-call to help parents and caregivers if they had any questions or concerns during the night. Each parent or caregiver was given the option of using a video "baby monitor" for the study night to monitor their child, but parents were not expected to stay up all night monitoring.

Sleep Study Scoring

The full-night laboratory PSG studies were scored according to the AASM Pediatric Guidelines, while the T3 study data were scored using adapted AASM Pediatric Guidelines (see Appendix B). Each T3 study was manually evaluated two times, once each by two NAPS staff people trained in scoring PSG studies. Once a study was scored, the scorer deleted all the scored markers and only kept the start and stop times. Scorers ran an analyzer that automatically scored position, desaturation, activity module, snoring and pulse artifacts. All other events were scored manually. We also scored the T3 studies using the Noxturnal software version 3.2 autoscoring module (NOX Medical, Iceland): the first autoscoring module ran the *Pediatric Respiratory RIP Flow* algorithm (Table 3.2), and a second autoscoring module was run where only the start and stop times were kept.

Table 3.2

Pediatric Respiratory RIP Flow Auto-Scoring Algorithm

Desaturation drop	3%
Shortest apnea/hypopnea (no. of breaths)	2
Longest apnea/hypopnea (sec.)	120
Apnea drop (%)	90
Hypopnea drop (%)	50
Minimum duration of central apneas (sec.)	20

Statistical Analyses

A T3 study was considered successful if at least five hours of continuous data were recorded (Hoffman & Barnes, 2012) from the pulse oximeter and both abdominal and thoracic effort belts. Studies that did not meet this criterion were excluded from the analysis. The primary outcome for all analyses was the apnea hypopnea index (AHI), with secondary outcomes

including the oxygen desaturation index (ODI), mean $sp0_2$, lowest $sp0_2$ and estimated sleep efficiency. The sources of variation of the T3 results were examined using a nested-design multilevel mixed analysis where the levels included: location, night, scoring algorithm, human, individual and replicate (Figure 3.1). A sensitivity analysis was completed removing the T3 sleep studies that were machine-scored (using the auto-scoring algorithm). A linear regression was completed to compare the manually scored home T3 sleep studies to the lab T3 sleep study and between the T3 night 1 and night 2 results. We used AHI cut-off values of 1.5, 5 and 10 per hour to determine true and false positive results for the AHI and ODI of the T3 study done in the lab compared to the AHI and ODI from the in-hospital PSG (see Appendix C). The same sensitivity and specificity analyses were conducted comparing the AHI and ODI of the in-hospital PSG to the second night of the T3 sleep study (see Appendix D). A nonparametric estimate was used, and we bootstrapped to obtain standard error. Data were analyzed using Stata 14 (STATA Corp.).

Figure 3.1

Nested Design Using Xtmixed Analysis

Note. Location has 2 levels (Lab or Home); Night has 3 levels (First night, Second Night, PSG); Scoring algorithm has 5 levels (Scorer1, Scorer2, Autoclean, Autodirty, Lab); Human has 2 levels (Machine or Human); Individual has 2 levels (Scorer1 or Scorer2); and Replicate has 2 levels (First or Second time).

Results

There were 25 participants recruited and consented for the study (Table 3.3): 14 female and 11 male. Among the 23 parents who completed the PSQ, 15 (65%) reported children meeting the criteria for sleep-related breathing disorder (SRBD). A total of 25 PSG lab sleep studies were included in the analyses. Almost 15% (11/75) of the T3 sleep studies were excluded from the analysis due to poor signal quality or malfunctioning equipment (Figure 3.2). Of the dropped studies, 11% (8/75) were T3 home studies, whereas 4% (3/75) were T3 lab studies.

Following the first home sleep study, 15 children (75%) preferred the home study compared to 2 children (10%) who preferred the lab study; 3 children (15%) did not have a preference between the lab or home sleep study. No significant difference was found ($p > 0.05$) between parent-reported sleep quality for the lab study night ($M = 6$, $SD = 2.25$) compared to the sleep quality for the home study night ($M = 7.6$, $SD = 1.90$).

Table 3.3

Characteristics of Participants

	n	*M (SD)*
Age	25	7.84 (2.72)
Sex (Female)	14 (44%)	
BMI, kg/m^2	23	19.33 (4.83)
PSG AHI	25	3.37 (3.35)
Yes SRBD	15 (65.22%)	
PPQ		
Preferred lab study	2 (9%)	
Preferred home study	17 (77%)	
No Preference	3 (14%)	
Lab night Sleep Quality	16	6 (2.25)
Home night Sleep Quality	21	7.6 (1.90)

Note. PSG = polysomnography; AHI = apnea hypopnea index; SRBD = sleep related breathing disordered scale on PSQ; PSQ = Pediatric Sleep Questionnaire; PPQ = Patient Preference Questionnaire.

A total of 25 full-polysomnography lab sleep studies were included in the analyses with 21 T3 studies from the lab night, 21 T3 studies completed at home on night one and 21 T3 studies from the second home night (Table 3.4). A total of 11/75 T3 sleep studies from both home and lab T3 study nights were dropped from the analysis due to poor signal quality or malfunctioning equipment (Figure 3.2).

Table 3.4

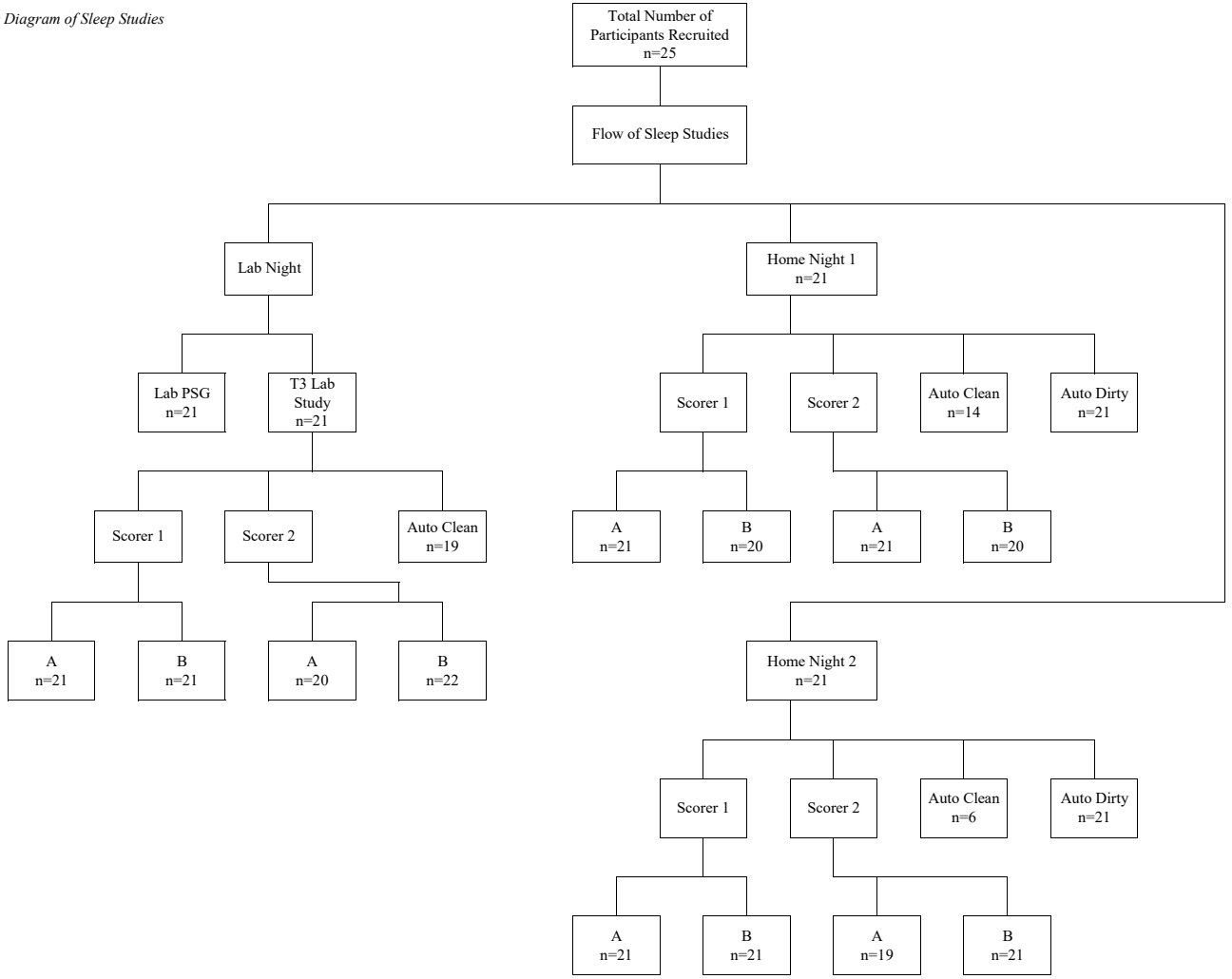
Home T3 Studies

	T3 in lab	T3 Home 1	T3 Home 2
Scorer 1a	21	21	21
Scorer 1b	21	20	21
Scorer 2a	20	21	19
Scorer 2b	22	20	21
Auto Clean	19	14	6
Auto Dirty	22	21	21

Note. a = the first time the Scorer manually scored the T3 home sleep study; b = the second time the Scorer scored the T3 home sleep study.

Figure 3.2

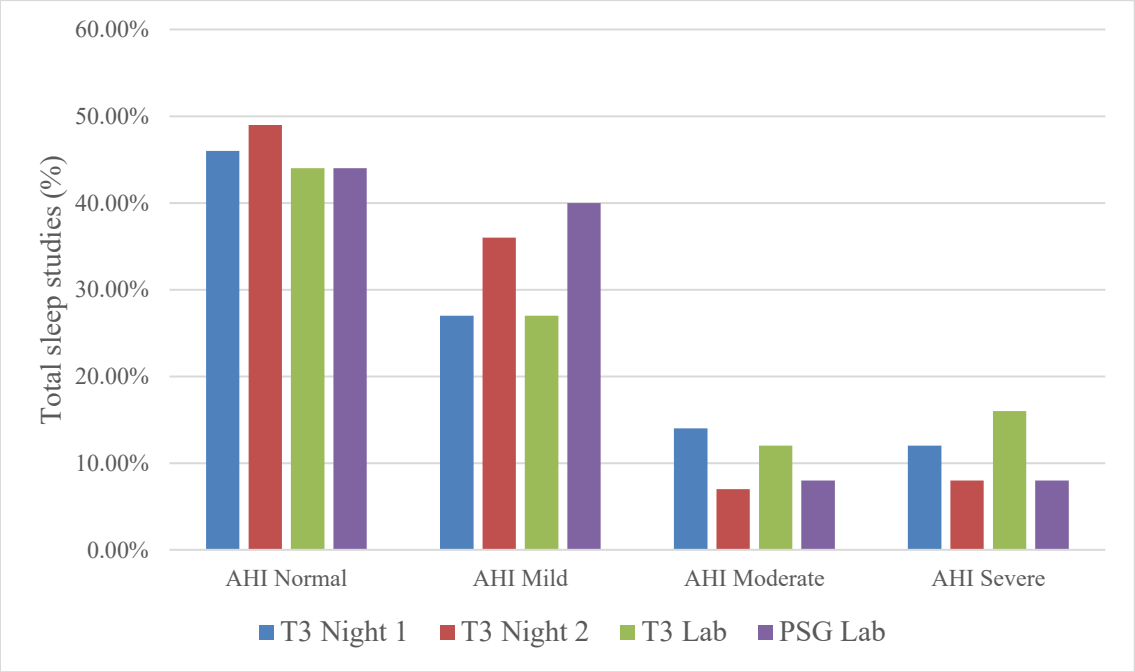
Flow Diagram of Sleep Studies



We found that 46% of children had an AHI < 1.5 (normal) on their T3 study while 30% of children had an AHI between 1.5 and 5 (mild; Figure 3.3). The AHI from the lab PSG studies yielded similar results to the T3 studies: 44% of children had PSG studies classified as normal and 40% of children had PSG AHI that were in the mild range. The respiratory data for the sleep lab and at home studies are presented in Table 3.6a and Table 3.6b.

Figure 3.3

Classification of AHI Severity in T3 and PSG Lab Sleep Studies



Note. Apnea Hypopnea Index (AHI) Classification of all T3 sleep studies and all PSG lab studies; AHI Normal = 0 ≥ AHI < 1.5; AHI Mild = 1.5 ≤ AHI < 5; AHI Moderate = 5 ≥ AHI < 10; AHI Severe = AHI ≥ 10 (El Shayeb et al., 2014).

Sources of Variation in Scoring the T3 Studies

Differences between the automated and human scorers accounted for most of the variability for AHI, ODI and sleep efficiency within the T3 results (Table 3.5a). When the automated scoring was removed from the nested design, differences between the individual

human scorers accounted for the greatest variability in scoring the T3 studies (Table 3.5b). Little variability in AHI, ODI and sleep efficiency was explained by (1) where the study was conducted, (2) whether a PSG technician or parent placed the T3 equipment or (3) variability within individual scorers. There was no significant amount of variability captured by these random effect parameters for mean $sp0_2$ and lowest $sp0_2$.

Table 3.5a

Proportion of Variation Within T3 Scored Studies (With Automated Scoring Highlighted in Red)

Source	AHI	ODI	Sleep Eff	Mean $Sp0_2$	Lowest $Sp0_2$
	Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
Location	6.78e-17 (3.05e-13)	2.64e-22 (1.06e-20)	4.31e-16 (1.77e-12)	0.04 (0.05)	0.04 (0.05)
Night	2.18e-16 (5.85e-15)	1.48e-22 (5.83e-21)	5.63e-16 (1.71e-14)	9.07e-15 (2.33e-13)	9.07e-15 (2.33e-13)
Scoring algorithm	17.45 (7.37)	0.71 (0.46)	6.96 (2.99)	1.52e-18 (2.17e-17)	1.52e-18 (2.17e-17)
Human vs. machine	7.19e-17 (1.01e-15)	2.57e-20 (3.28e-19)	1.34e-18 (1.46e-17)	2.17e-19 (2.79e-18)	2.17e-19 (2.79e-18)
Individual scorer	7.20e-17 (9.88e-16)	2.29e-20 (3.00e-19)	1.38e-18 (1.51e-17)	4.66e-19 (5.71e-18)	4.66e-19 (5.71e-18)
Replicate	2.11e-17 (2.15e-16)	1.94e-22 (1.76e-21)	4.20e-20 (5.21e-19)	4.01e-20 (1.73e-16)	4.01e-20 (1.73e-16)
Error (Residual)	14.17 (1.14)	5.95 (0.67)	7.85 (0.63)	1.68 (0.13)	1.68 (0.13)
Constant *(b)* *(SE)*	5.35 (1.23)	2.16 (0.29)	96.92 (0.78)	96.11 (0.16)	89.88 (1.00)
N	337	331	337	332	332
chi^2	<0.001	0.03	<0.001	0.70	0.70

Note. AHI = apnea hypopnea index; ODI = oxygen desaturation index;

SE = standard error; Sleep Eff = sleep efficiency.

Table 3.5b

Proportion of Variation Within T3 Scored Studies (Without Automated Scoring)

Source	AHI	ODI	Mean $Sp0_2$	Lowest $Sp0_2$	Sleep Eff
	Estimate (SE)	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*	*Estimate (SE)*
Location	1.45e-09 (2.30e-08)	1.12e-13 (5.38e-12)	0.04 (0.05)	1.65 (2.01)	6.45e-12 (2.17e-10)
Night	1.77e-09 (2.44e-08)	5.38e-12 (2.61e-12)	3.26e-19 (.)	5.85e-12 (1.89e-10)	5.12e-12 (7.67e-09)
Individual scorer	3.76 (0.92)	0.58 (0.60)	1.34e-22 (2.09e-21)	6.57e-15 (1.17e-13)	4.59 (2.30)
Replicate	2.28e-09 (1.36e-08)	5.71e-13 (7.12e-12)	1.50e-23 (1.73e-22)	5.71e-16 (6.85e-15)	6.55e-13 (7.47e-12)
Error (Residual)	3.99 (0.16)	6.01 (0.59)	1.68 (0.13)	53.36 (4.77)	9.47 (0.76)
Constant *(b)* *(SE)*	4.30 (1.27)	1.99 (0.29)	96.11 (0.16)	89.88 (1)	97.46 (0.73)
N	337	331	332	332	337
chi^2	<0.001	0.01	0.43	0.23	<0.001

Note. AHI = apnea hypopnea index; ODI = oxygen desaturation index; SE = standard error; Sleep Eff = sleep efficiency.

Table 3.6a

Means and SD of Respiratory Indices of Nox T3 Polygraphic Findings for the Lab Night

Scorer	n	AHI	ODI	Mean $Sp0_2$	Lowest $Sp0_2$	SE
		M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Nox T3						
Scorer 1a	21	1.46 (1.64)	1.26 (1.99)	96.34 (1.17)	92.40 (1.99)	99.00 (1.95)
Scorer 1b	21	1.61 (1.87)	1.27 (2.07)	96.34 (1.17)	92.41 (2.00)	99.18 (1.80)
Scorer 2a	20	1.9 (2.09)	1.31 (2.08)	96.36 (1.17)	90.70 (7.51)	98.03 (3.88)
Scorer 2b	22	2.07 (2.06)	1.24 (2.05)	96.38 (1.15)	90.80 (7.33)	98.15 (3.74)
Human scored		1.85 (1.84) N =22	1.22 (1.99) N = 21	96.38 (1.15) N = 21	91.62 (4.17) N = 21	98.66 (2.39) N = 22
Auto Clean	19	7.06 (7.47)	1.53 (1.85)	96.27 (1.19)	92.55 (1.96)	97.68 (2.33)
Auto Dirty	22	13.35 (7.05)	3.54 (3.98)	96.43 (1.14)	89.80 (4.91)	91.74 (3.13)
PSG lab	25	3.37 (3.35)	2.48 (3.58)	96.48 (1.34)	90.04 (2.64)	87.05 (7.30)

Note. SD = standard deviation; S1 = Scorer 1; S2 = Scorer 2; T3 = the Nox T3 portable sleep monitor; a = 1st time study was manually scored; b = 2nd time study was manually scored; AHI = apnea-hypopnea index (events/hour); ODI = oxygen saturation index (events/hour); SE = estimated sleep efficiency (%); Sp02 = blood oxygen saturation; Auto Clean = automated scoring module that was manually cleaned; Auto Dirty = automated scoring module in Noxturnal software without any manipulation of data.

Table 3.6b

Means and SD of Respiratory Indices of Nox T3 Polygraphic Findings for Home Nights

Scorer	n	AHI	ODI	Mean $Sp0_2$	Lowest $Sp0_2$	SE
		M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Scorer 1a Home 1	21	1.46 (1.37)	1.56 (2.63)	95.92 (1.41)	89 (5.96)	99.89 (0.49)
Scorer 1b Home1	20	1.46 (1.28)	1.59 (2.65)	95.87 (1.39)	88.95 (5.95)	99.89 (0.49)
Scorer 1a Home2	21	1.25 (1.27)	1.54 (2.00)	95.91 (1.43)	88.85 (9.27)	99.75 (0.59)
Scorer 1b Home2	21	1.22 (1.13)	1.79 (2.22)	95.89 (1.34)	88.80 (9.29)	99.75 (0.57)
Scorer 2a Home1	21	2.12 (2.39)	1.71 (2.84)	95.93 (1.38)	88.90 (5.95)	98.5 (3.42)
Scorer 2b Home1	20	1.72 (1.46)	1.19 (2.42)	95.92 (1.50)	89.03 (5.49)	99.51 (1.55)
Scorer 2a Home2	19	1.31 (1.05)	1.06 (1.83)	95.88 (1.40)	89.05 (9.76)	99.16 (2.25)
Scorer 2b Home2	21	1.54 (1.12)	1.55 (2.15)	95.99 (1.36)	89.18 (9.25)	97.97 (3.27)
Human scored Home1	21	2.23 (2.68) N=21	1.55 (2.61) N=20	95.90 (1.37) N=21	89.13 (5.69) N=21	98.35 (5.08) N=21
Human scored Home 2	21	1.36 (1.06)	1.54 (2)	95.94 (1.36)	89.03 (9.25)	99.13 (1.27)
Auto Clean Home1	14	6.85 (5.76)	3.02 (2.83)	96 (1.34)	90.42 (2.57)	97.89 (1.96)
Auto Clean Home2	6	5.98 (4.86)	3 (2.97)	95.95 (1.36)	85.83 (17.14)	95.83 (3.51)
Auto Dirty Home1	20	12.25 (6.58)	4.15 (2.76)	95.91 (1.40)	86.65 (8.75)	92.72 (3.74)
Auto Dirty Home2	21	9.61 (5.61)	3.65 (2.41)	96 (1.34)	86.14 (10.53)	93.12 (2.29)

Note. SD = standard deviation; S1 = Scorer 1; S2 = Scorer 2; T3 = the Nox T3 portable sleep monitor; a =

1st time study was manually scored; b = 2nd time study was manually scored; AHI = apnea-hypopnea index (events/hour); ODI = oxygen saturation index (events/hour); SE = estimated sleep efficiency (%); Sp02 = blood oxygen saturation; Auto Clean = automated scoring module that was manually cleaned; Auto Dirty = automated scoring module in Noxturnal software without any manipulation of data.

Predictive Validity of PSQ and CSHQ

A linear regression analysis was used to test whether parent reported questionnaire data from the PSQ and CSHQ was related or able to predict the AHI of all the T3 studies and the laboratory PSG study (Table 3.7). The results of the regression analysis indicated that the SRBD scale of the PSQ did not predict AHI on any of the T3 studies ($R^2 = 0$, $F(1,318) = 0.49$, $p = 0.48$) or the lab PSG study ($R^2 = 0.08$, $F(1,21) = 1.76$, $p = 0.2$). Similarly, the linear regression results comparing the CSHQ SD Index with AHI with the T3 studies ($R^2 = 0.01$, $F(1,318) = 2.41$, $p = 0.12$) or the lab PSG study ($R^2 = 0$, $F(1,21) = 0.04$, $p = 0.85$).

Table 3.7

Summary of Simple Regression Analyses for Variables Predicting T3 AHI and PSG AHI

	T3 AHI				PSG AHI			
Variable	*B*	*SE B*	*β*	*N*	*B*	*SE B*	*β*	*N*
srbd (PSQ)	-0.45	0.64	-0.04	320	1.97	1.49	0.28	23
R^2		0.00				0.08		
F		0.49				1.76		
CSHQ SD Index	1.43	0.92	0.09	320	0.43	2019	0.04	23
R^2		0.01				0.00		
F		2.41				0.04		

Note. SRBD = sleep related breathing disordered scale on PSQ; CSHQ = Child Sleep Habit Questionnaire; SD = sleep disturbance; SE = standard error.

*$p < .05$. **$p < .01$

Validity of T3

Lab PSG and T3 Lab Analyses

The T3 AHI explained 41% of the variance in PSG AHI ($\beta = 0.66$, $p = 0.001$). Receiver operating characteristic (ROC) curves were created to compare AHI from lab PSG (cut-off values of 1.5, 5 and 10) to the T3 lab study results (see Appendix C). The ROC curve for detecting severe AHI (≥ 10 events/hour) for the PSG had an area under the curve (AUC) of 0.98 (*SE* = 0.19, $p < 0.05$; 95% CI [0.91, 1]; Appendix C, Figure C1c). Using a threshold of AHI ≥ 10 events/hour, a cut point of 4.8 or greater on the T3 correctly classified 91% of cases with a 50% sensitivity, 95% specificity, likelihood ratio (LR) for a positive test of 10 and LR of a negative test of 0.5 (see Appendix C, Table C3). The AUC = 0.73 (*SE* = 0.10, $p < 0.05$; 95% CI [0.51, 0.94]; Appendix C, Figure C1a) for mild AHI (≥ 1.5 events/hour). The AUC = 0.68 for moderate AHI (*SE* = 0.19, $p < 0.05$; 95% CI [0.31, 1]; Appendix C, Figure C1b).

Results from ROC analysis comparing ODI from the lab PSG and the T3 lab study for severe ODI had an AUC = 0.95 (Appendix C, Figure C2c). Using a threshold of AHI ≥ 10 events/hour for the lab PSG, a T3 cut point of ≥ 5.4 correctly classified 95% of cases with a 100% sensitivity, 95% specificity, positive LR of 20 and negative LR of 0 (Appendix C, Table C6). The AUC = 0.75 (*SE* = 0.11, $p < 0.05$; 95% CI [0.54, 0.96];) for mild ODI (≥ 1.5 events/hour; Appendix C, Figure C2a). ROC analysis comparing ODI from the lab PSG and the T3 lab sleep study showed an AUC = 0.66 (SE = 0.18, $p < 0.05$; 95% CI [0.32, 1]) for moderate ODI (≥ 5 events/hour; Appendix C. Figure C2b).

Bland-Altman (B-A) analysis was performed comparing AHI (cut-off values of 1.5, 5 and 10) from the lab PSG and the T3 lab (Appendix C, Figure C3). A threshold of AHI ≥ 1.5

events/hour (Appendix C, Figure C3a), resulted in a M = -1.07, 95% CI = [-4.53, 2.38]. A threshold of AHI ≥ 5 events/hour (Appendix C, Figure C3b) and a threshold of AHI ≥ 10 events/hour resulted (Appendix C, Figure C3c) resulted in a M = -2.81, 95% CI = [-8.88, 3.26]. The B-A plot with a threshold of AHI ≥ 1.5 had one participant score that fell out of range of the confidence intervals.

B-A analysis was performed comparing ODI (cut-off values of 1.5, 5 and 10) from the lab PSG and the T3 lab (Appendix C, Figure C4). A threshold of ODI ≥ 1.5 events/hour (Appendix C, Figure C4a) resulted in a M = -0.83, 95% CI = [-4.29, 2.63]. A threshold of ODI ≥ 5 events/hour (Appendix C, Figure C4b) produced a M = -0.55, 95% CI = [-4.05, 2.96]. A threshold of ODI ≥ 10 events/hour (Appendix C, Figure C4c) resulted in a M = -0.99, 95% CI = [-4.55, 2.57]. A threshold of ODI ≥ 1.5 resulted in two participant scores that fell out of range and one that fell on the lower confidence interval line. A threshold of ODI ≥ 5 resulted in three participant scores that fell out of range, whereas a threshold of ODI ≥ 10 had one participant that fell out of range and one participant that fell at the lower confidence interval line.

Lab PSG and Second Night (Home 2) of the T3 Home Sleep Study Analyses

Receiver operating characteristic curve (ROC) analysis compared AHI (cut-off values of 1.5, 5 and 10) from the lab PSG and the T3 Home 2 sleep study (Appendix D, Figure D1). The area under the curve (AUC) for detecting severe AHI (≥ 10 events/hour) was 0.74 (SE = 0.27, p < 0.05; 95% CI [0.21, 1]; Appendix D, Figure D1c). Using a threshold of AHI ≥ 10 events/hour, a cut point of 3.23 or greater on the T3 correctly classified 90% of cases with a 50% sensitivity, 95% specificity, likelihood ratio (LR) for a positive test of 9.5 and LR of a negative test of 0.53 (Appendix D, Table D3). The AUC = 0.65 (SE = 0.16, p < 0.05; 95% CI [0.38, 0.96]; Appendix D, Figure D1b) for moderate AHI (≥ 5 events/hour). Using a threshold of AHI ≥ 5 events/hour, a

cut point of ≥ 3.23 on the T3 correctly classified 81% of cases with a 25% sensitivity, 94% specificity (positive LR of 4.25 and negative LR of 0.8 [Appendix D, Table D2]). The AUC = 0.57 for mild AHI (≥ 1.5 events/hour; *SE* = 0.14, $p < 0.05$; 95% CI [0.30, 0.85]; Appendix D, Figure D1a).

Results from ROC analysis comparing ODI from the lab PSG and the T3 Home 2 for severe ODI had an AUC = 0.95 (Appendix D, Figure D2c). Using a threshold of AHI ≥ 10 events/hour a T3 cut point of ≥ 7.18 correctly classified 90% of cases with a 0% sensitivity, 95% specificity, positive LR of 0 and negative LR of 1.05 (Appendix D, Table D6). The AUC = 0.65 (*SE* = 0.13, $p < 0.05$; 95% CI [0.39, 0.91];) for mild ODI (≥ 1.5 events/hour; Appendix D, Figure D2a). ROC analysis comparing ODI from the lab PSG and the T3 Home 2 sleep study showed an AUC = 0.41 (*SE* = 0.19, $p < 0.05$; 95% CI [0.03, 0.78]) for moderate ODI (≥ 5 events/hour; Appendix D, Figure D2b).

Discussion

Reliability and Validity

We examined the reliability and validity of the Nox T3 device among school-aged children. There was a significant correlation between the T3 sleep device and the lab PSG for AHI and ODI. Even with manual identification of sleep and wake times, the T3 autoscoring module did not provide adequate results compared to the manually scored studies. When all the autoscoring studies were removed from the analysis, the greatest source of variability was still attributed to the scorer. None of the variables tested were associated with variation in mean $sp0_2$ and lowest $sp0_2$, suggesting that these outcomes were robust to location and scorer. The T3 sleep device had a high positive and negative LR for identifying children with severe and mild OSA. Results from the ROC analyses indicated that the T3 lab study had a high diagnostic accuracy for

detecting children with severe AHI, versus low diagnostic accuracy for detecting moderate AHI. The T3 lab study achieved an acceptable level of diagnostic accuracy for detecting mild AHI. When comparing results from the second home night to the lab PSG, the T3 was more accurate in detecting severe AHI and ODI. Unlike the AHI results, the T3 from the second night was better at detecting mild ODI compared to moderate.

Gudnadottir and colleagues (2019) found similar results regarding variability between the scorers of home sleep studies. They identified poor data quality concerning nasal airflow as a common denominator among sleep studies in children four to ten years of age using the Nox T3 portable home sleep monitor. They examined the interrater reliability of nasal airflow by comparing studies with good nasal airflow signals to those relying on a calibrated RIP flow signal to determine respiratory events. Each study was scored by two independent scorers, which yielded moderate agreement with and without nasal airflow signals (ICC = 0.66 vs. ICC = 0.53). One scorer had good agreement in scoring the studies with and without nasal airflow (ICC = 0.81) while the other scorer demonstrated poorer agreement (ICC = 0.12). The authors attributed the difference in ICC between the scores to the experience of scorers. Those performing the T3 evaluation in the current study have more experience with in-laboratory sleep studies that rely on EEG and good quality nasal airflow for evaluating respiratory events. However, Scorer 1 and Scorer 2 differed in their level of training and experience in scoring sleep studies.

One of the advantages of a lab PSG is that trained technicians monitor the equipment in the event of device malfunction or failure. Level 3 portable devices tend to function better in a laboratory setting, versus at home (Bruyneel & Ninane, 2014; El Shayeb et al., 2014). Despite their relatively low cost and ease of administration, the use of home recording devices results in a greater need to repeat sleep studies, compared to in-lab PSG, due to lost data (Collop et al.,

2007). Cairns and colleagues (2014) reported that Type 3 sleep recording device failure and false negatives have been reported as frequently as 18% of observations. Additionally, data loss for Type 3 monitors has been shown to range from 3–18% (Collop et al., 2007). We reported a total loss of 11 T3 sleep studies (15%) due to poor data and malfunctioning equipment, which is congruent with research by Cairns and colleagues (2014). Of the 15% of studies dropped, 11% were T3 home studies and 4% were T3 lab studies.

The autoscoring module may be more appropriate for adults than for children. Cairns and colleagues (2014) found that the autoscored T3 AHI and manually scored PSG were strongly related ($r = 0.93$). When compared to in-lab PSG, the T3 device demonstrated a high degree of sensitivity for the presence of OSA (100%) and acceptable specificity for the exclusion of OSA (70%), when using an AHI threshold of ≥ 5 events per hour (Cairns et al., 2014). The T3 autoscore module reported a high degree of both sensitivity (92%) and specificity (85%) when OSA was defined with an AHI of > 15 events per hour. When OSA was defined with an AHI of ≥ 5, the T3 showed high degrees of both sensitivity (88%) and specificity (100%) (Cairns et al., 2014). A study by Xu and colleagues (2017) evaluating the performance of the Nox T3 sleep monitor to diagnose OSA in Chinese adults also showed close agreement between automatic and manual scoring of the Nox T3. They reported a mean difference of two events per hour between automatic and manual scoring on both home and in-laboratory portable monitor recordings. Despite the recent validation studies of home portable sleep devices in the adult population (Cairns et al., 2014; Chang et al., 2019; Xu et al., 2017), validation studies of level 3 devices for children have represented a research gap (Gudnadottir et al., 2019; Scalzitti et al., 2017).

Children may be more likely to present for SDB evaluation with mild to moderate OSA than for severe OSA. A review assessing the utility of portable sleep monitoring found that the

variability between manual and autoscoring may be greater for mild and moderate OSA compared to more severe OSA (Sunwoo & Kuna, 2010). Another study validating a portable sleep monitor against in-lab PSG in children (three to six years of age) found that the autoscore algorithm underestimated obstructive hypopneas and overestimate central apneas (Zucconi, Calori, Castronovo, & Ferini-Strambi, 2003). Our study also found significant differences between the autoscored and manually scored studies.

The strength of this study is that we collected data in the home on two consecutive nights. This enabled us to determine the device's reliability. Additionally, we were able to evaluate the validity of the T3 device, as we compared the in-hospital PSG results with the T3 sleep study results collected on the same night. We were able to determine inter-rater reliability and intra-rater reliability, as we had two different scorers who scored each study twice.

Limitations

There were several limitations identified in this study. The current study's small sample size (N = 25) limits the power of its results. Additionally, there were a limited number of participants in our study with moderate to severe OSA, which made it difficult to draw conclusions for these groups. The fact that there were no young children (under the age of four) among our sample represents another limitation in the generalizability of results among age groups. Another limitation is related to the assumption that the home T3 study is more preferred than typical in-hospital PSG. The hospital PSG was not a typical sleep study since it also included the T3 study, and as such this is not a typical PSG study. Although wearing both PSG and T3 sensors is more cumbersome for participants, we tried to secure all the leads and sensors in a way that was as comfortable for the child as possible. Most participants did prefer the home

sleep study compared to the in-lab PSG, and the extra sensors and leads may have contributed to their ratings.

The lack of EEG data among the home sleep study data represents a limitation with our study. As a result, home testing is likely to be appropriate for use as a diagnostic tool for high likelihood OSA or SDB among children with no other sleep disorders, respiratory or cardiac disease. There is no consensus around parameters that defined an acceptable and successful recording. Gudnadottir and colleagues (2019) used at total of 180 minutes of interpretable data from three leads as an acceptable study whereas Scalzitti and colleagues (2017) set their limit at 360 minutes.

Future Directions

Future studies could incorporate both subjective and objective sleep measures (e.g., AHI) to diagnose SDB. Most studies that compare Type 3 sleep monitors to in-lab PSG have been limited to otherwise healthy children (Tan et al., 2015). Therefore, future research in the use of Type 3 sleep monitoring among children with other health conditions may be warranted.

Researchers have previously identified the cost savings of using a portable sleep test among adults, versus in-lab PSG (Corlateanu et al., 2017; Kundel & Shaw, 2017). Analysis of the cost-effectiveness of home respiratory polygraphy among adults was performed in 12 tertiary hospitals in Spain, which demonstrated substantially lower costs compared to in-lab PSG. However, there is no evidence of any studies among pediatric sleep centres, comparing cost-effectiveness (Corlateanu et al., 2017). The current study concluded that the T3 sleep device can be used to screen children with suspected SDB. Those children with a T3 AHI result between 1.5 and 5 (intermediate OSA) can be referred for a laboratory PSG in order to confirm a diagnosis of SDB. Caregivers can install the T3 home sleep study equipment on their child without the

assistance of a trained technician, as we found no significant difference in AHI from lab to home, or from instances where technicians or parents were responsible for affixing of the equipment. Future economic evaluation studies conducted among pediatric centres would be beneficial in helping to evaluate the economic benefit of conducting home sleep studies.

Conclusion

This study showed that the T3 home sleep device is a valid tool, compared to the in-hospital lab PSG, for children with mild or severe SDB. Increased use of ambulatory monitoring allows for timely diagnosis and treatment of patients and more effective use of in-laboratory testing for children whose tests are inconclusive. We demonstrated that the T3 home sleep device had a significant correlation for AHI and ODI when compared to the in-hospital lab PSG. However, the automated scoring module for the portable T3 machine was not as good as manually scored sleep studies. Compared to in-lab PSG, the T3 machine was better able to predict severe and mild AHI and ODI. Larger prospective studies comparing children with and without symptoms of SDB and among children with other health conditions are needed prior to the widespread use of this device with children.

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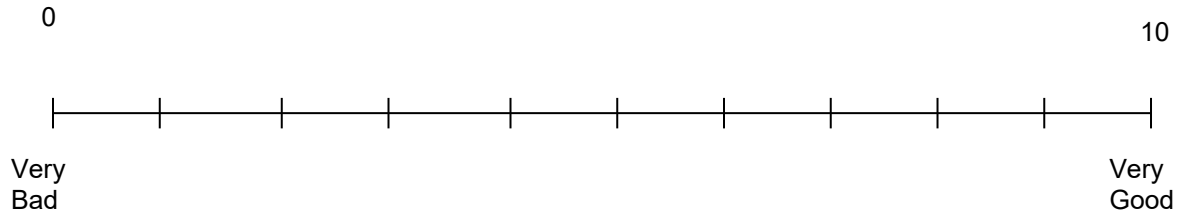
APPENDIX A: Patient Preference Questionnaire (PPQ)

1. How would you describe your child's sleep last night?



2. Which recording device do you prefer?

☐ Home Sleep Device

☐ In-Hospital Sleep study

APPENDIX B: T3 Scoring Rules

The study data from the NOX T3™ (T3) acquired through the use of the ambulatory device were scored using adapted AASM Pediatric Guidelines which fit the available parameters of the ambulatory device.

Visual Rules

Stage W (wake) Score wake when both criteria are met

A. Score stages as W when 50% of the epoch (30 seconds) has increased activity by, increased EMG by at least 3 mV and if available audio recording.

B. An increase from baseline sleep SpO2 by 2% and/or heart rate by 10-15 BPM.

Note: Wake is mostly based on activity and audio recording as EMG is not always clear. You do not need to hear talking to score wake. Additionally, there are no respiratory events that are scored in wake.

Stage N1 (accounting for stages N1, N2 and N3) Score N1 when all four criteria are met

A. Score N1 when EMG amplitude is decreased from Wake, but may remain variable, for more than 50% of the epoch and if available audio recording to distinguish snoring, or lack of noises (i.e. speech), which would indicate a state of wakefulness.

B. Score N1 when activity has decreased from Wake for more than 50% of the epoch.

C. Score N1 when regular respiration is seen over 50% of the epoch and a drop from baseline SpO2 of at least 2% (this is not always the case- do not need to meet this criteria for every instance).

A. Drop in base line heart rate by 5-15 BPM from wake baseline in a 5 minute epoch.

Stage REM (R) Score REM when all criteria are met (please note that REM is not always clear, use clinical judgment based on the quality of data available)

A. Score R with a reduction of EMG amplitude from baseline N1 accompanied by short irregular bursts of EMG activity usually with a duration of <0.25 seconds superimposed on low EMG tone.

B. Score R with respiratory instability from baseline seen in N1 sleep.

C. Increased heart rate from wake baseline by 5-15 BMP in a 5 minute period (please note as an alternative, you can trend the heart rate signal and use this information to score REM since heart rate and breathing instability are easier to use in order to score REM in these studies as baseline SpO_2 is not always as apparent.

D. Increased respiratory instability from base line N1 sleep is seen.

Arousal Rules

A. Arousal: Score an arousal during sleep stages N1 or R if there is an abrupt change in activity and increase in EMG lasting at least 3 seconds and has at least 10 seconds of stable sleep preceding the change. Arousal may or may not be accompanied by a position change.

B. Arousal: Events in sleep which include all three: a change in activity, position change and increased EMG associated with a preceding respiratory event should be scored as respiratory arousal. Arousals can be scored when there is snoring.

C. Spontaneous Arousal: Score a spontaneous arousal during sleep stages N1 or R when an increase in activity by at least 50% is accompanied by an increase in thorax, abdominal and nasal pressure signals for a duration of 3 seconds.

* An arousal out of R must also have a concurrent increase in EMG lasting at least 1 second.

Respiratory Rules for Children (ages <18 years)

Note: several studies have published data using pediatric criteria in children up to 18 years of age, but to date there has been no studies comparing adult and pediatric criteria in adolescents.

Apnea Rules

The duration of an apnea is measured from the end of the last normal breath to the first breath that matches the pre-event baseline inspiratory excursion.

A. Score a respiratory event as an **obstructive apnea** if it meets all the following criteria:

1) The event lasts for 2 missed breaths (based on baseline breathing)

2) The event is associated with a >90% fall in signal amplitude for at least 90% or longer of the entire respiratory event compared to pre-event baseline

3) The event is associated with increased inspiratory effort during the entire period of decreased airflow

B. Score **a mixed apnea** if:

1) The event lasts for 2 missed breaths (based on baseline breathing)

2) The event is associated with a >90% fall in signal amplitude for at least 90% or longer of the entire respiratory event compared to pre-event baseline

3) The event is associated with absent inspiratory effort at the beginning of the event with the resumption of inspiratory effort by the end

C. Score a **central apnea** if the event is associated with an absent inspiratory effort throughout the entire duration and one of the following is met:

1) The event lasts at least 20 seconds or longer

OR

2) The event lasts 2 missed breaths (based on baseline respiratory pattern) and is associated with either one of the following: an arousal, spontaneous arousal, awakening or a desaturation equal to or greater than 3%

Hypopnoea Rules

A. Score a respiratory event as a hypopnoea if it meets all the following criteria:

1) The event is associated with at least a 50% drop in the amplitude of the nasal pressure or alternative signal (thermal sensor) compared to baseline excursion

2) The event lasts at least 2 breaths as determined by baseline respiratory pattern from the end of the last normal breath (amplitude) measured off the chest and abdomen belts

3) The fall in nasal pressure signal amplitude must last for 90% of the entire event compared to the signal amplitude preceding the event

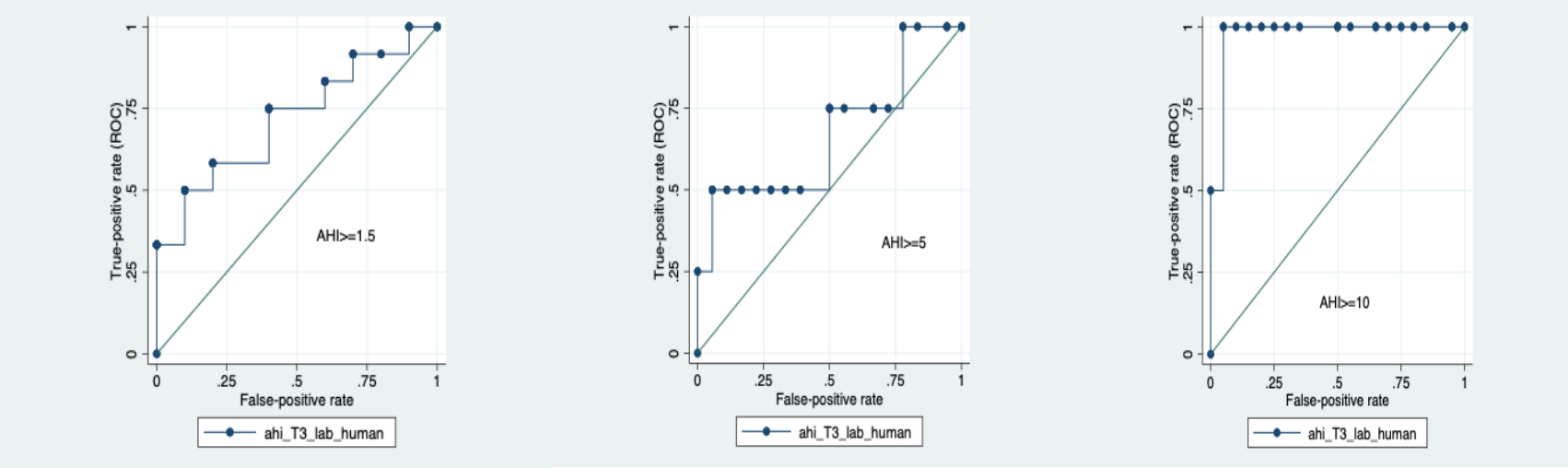
4) The event is associated with either an arousal, awakening or a 3% drop or greater in saturation

APPENDIX C: Lab PSG and T3 Lab Sleep Study Analyses

Figure C1

ROC for the AHI from Manually Scored T3 Lab Sleep Studies Compared to Gold Standard PSG Study

a b c



Note. At an AHII cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, the area under the curve was 0.73, 0.68 and 0.98 respectively.

Table C1

Sensitivity and Specificity of AHI Cut-off Value of 1.5 for T3 Lab Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	75.00%	40.00%	59.09%	1.2500	0.6250
(>=1.6)	50.00%	90.00%	68.18%	5.0000	0.5556
(>=2.225)	41.67%	90.00%	63.64%	4.1667	0.6481
(>=2.85)	33.33%	90.00%	59.09%	3.3333	0.7407
(>=3.325)	33.33%	100.00%	63.64%		0.6667
(>=4.6)	25.00%	100.00%	59.09%		0.7500
(>=4.8)	16.67%	100.00%	54.55%		0.8333
(>=7.85)	8.33%	100.00%	50.00%		0.9167
(>7.85)	0.00%	100.00%	45.45%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table C2

Sensitivity and Specificity of AHI Cut-off Value of 5 for T3 Lab Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	75.00%	33.33%	40.91%	1.1250	0.7500
(>=1.6)	50.00%	72.22%	68.18%	1.8000	0.6923
(>=2.225)	50.00%	77.78%	72.73%	2.2500	0.6429
(>=2.85)	50.00%	83.33%	77.27%	3.0000	0.6000
(>=3.325)	50.00%	88.89%	81.82%	4.5000	0.5625
(>=4.6)	50.00%	94.44%	86.36%	9.0000	0.5294
(>=4.8)	25.00%	94.44%	81.82%	4.5000	0.7941
(>=7.85)	25.00%	100.00%	86.36%		0.7500
(>7.85)	0.00%	100.00%	81.82%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table C3

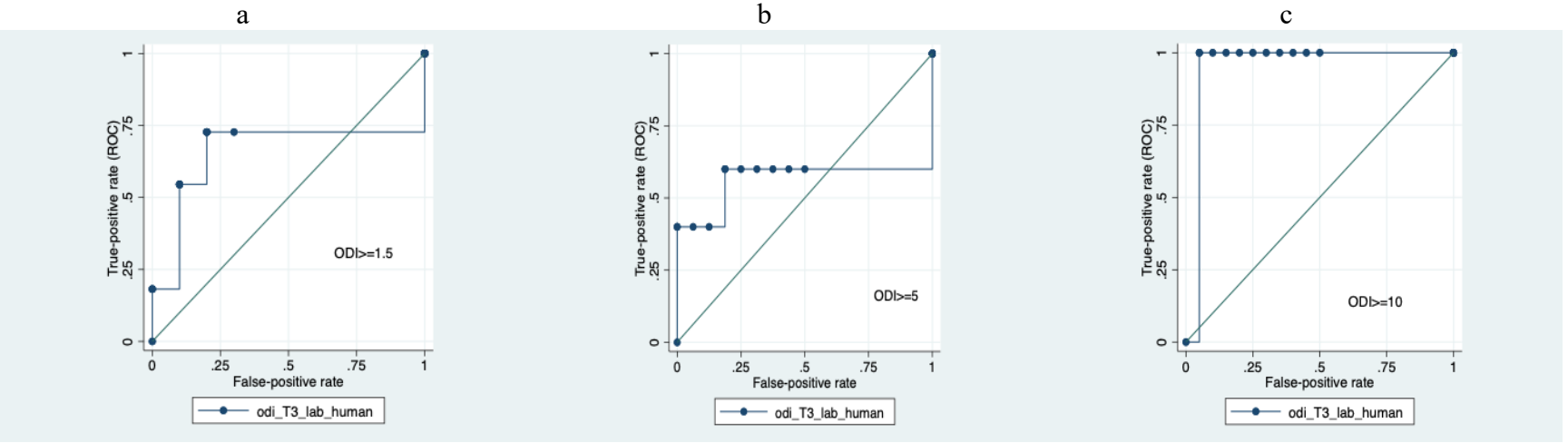
Sensitivity and Specificity of AHI Cut-off Value of 10 for T3 Lab Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	100.00%	35.00%	40.91%	1.5385	0.0000
(>=1.6)	100.00%	75.00%	77.27%	4.0000	0.0000
(>=2.225)	100.00%	80.00%	81.82%	5.0000	0.0000
(>=2.85)	100.00%	85.00%	86.36%	6.6667	0.0000
(>=3.325)	100.00%	90.00%	90.91%	10.0000	0.0000
(>=4.6)	100.00%	95.00%	95.45%	20.0000	0.0000
(>=4.8)	50.00%	95.00%	90.91%	10.0000	0.5263
(>=7.85)	50.00%	100.00%	95.45%		0.5000
(>7.85)	0.00%	100.00%	90.91%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Figure C2

ROC for the ODI from Manually Scored T3 Lab Sleep Studies Compared to Gold Standard PSG Study



Note. At an ODI cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, the area under the curve was 0.75, 0.66 and 0.95 respectively.

Table C4

Sensitivity and Specificity of ODI Cut-off Value of 1.5 for T3 Lab Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	52.38%	1.0000	
(>=1.575)	45.45%	90.00%	66.67%	4.5455	0.6061
(>=1.7)	36.36%	90.00%	61.98%	3.6364	0.7071
(>=3.925)	27.27%	90.00%	57.14%	2.7273	0.8081
(>=4.5)	18.18%	90.00%	52.38%	1.8182	0.9091
(>=5.4)	18.18%	100.00%	57.14%		0.8182
(>=6.2)	9.09%	100.00%	52.38%		0.9091
(>6.2)	0.00%	100.00%	47.62%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table C5

Sensitivity and Specificity of ODI Cut-off Value of 5 for T3 Lab Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	52.38%	1.0000	
(>=1.575)	45.45%	90.00%	66.67%	4.5455	0.6061
(>=1.7)	36.36%	90.00%	61.98%	3.6364	0.7071
(>=3.925)	27.27%	90.00%	57.14%	2.7273	0.8081
(>=4.5)	18.18%	90.00%	52.38%	1.8182	0.9091
(>=5.4)	18.18%	100.00%	57.14%		0.8182
(>=6.2)	9.09%	100.00%	52.38%		0.9091
(>6.2)	0.00%	100.00%	47.62%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table C6

Sensitivity and Specificity of ODI Cut-off Value of 10 for T3 Lab Study

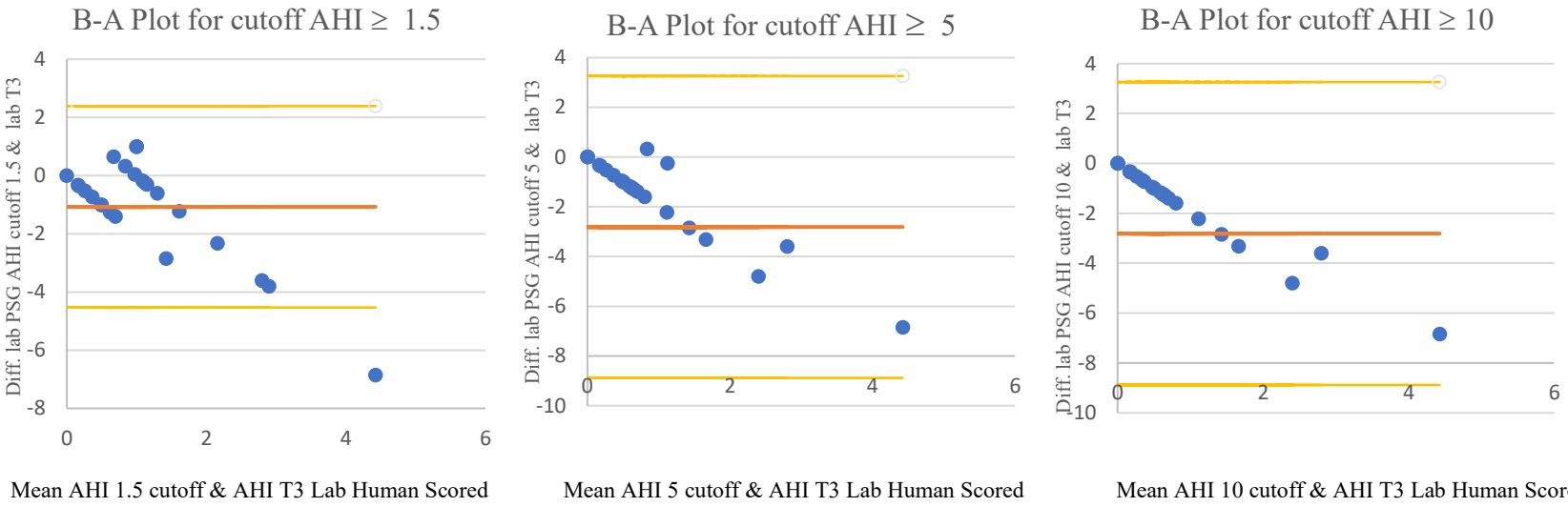
Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 0)	100.00%	0.00%	4.76%	1.0000	
(>=1.575)	100.00%	75.00%	76.19%	4.0000	0.0000
(>=1.7)	100.00%	80.00%	80.95%	5.0000	0.0000
(>=3.925)	100.00%	85.00%	85.71%	6.6667	0.0000
(>=4.5)	100.00%	90.00%	90.48%	10.0000	0.0000
(>=5.4)	100.00%	95.00%	95.24%	20.0000	0.0000
(>=6.2)	0.00%	95.00%	90.48%	0.0000	1.0526
(>6.2)	0.00%	100.00%	95.24%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Figure C3

Bland-Altman Plots Comparing AHI Cut-offs from the Lab PSG to the T3 Lab Study

a b c

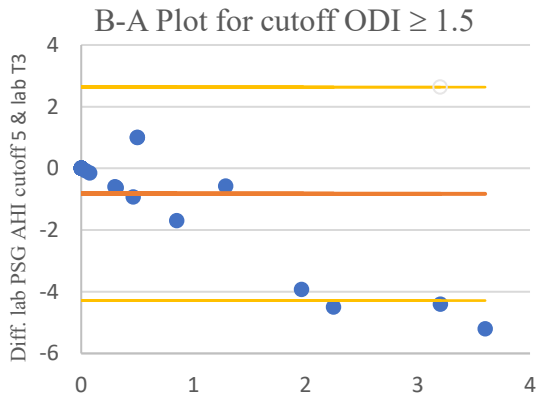


Note. Bland-Altman plots for AHI cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, Diff=difference.

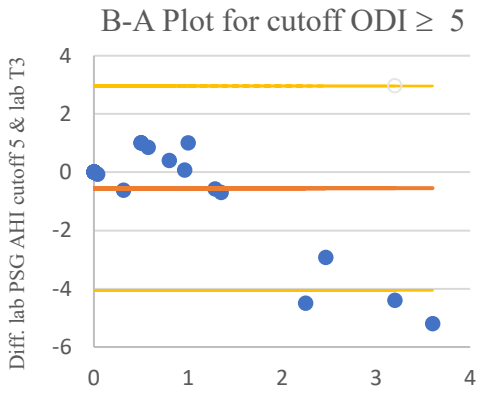
Figure C4

Bland-Altman Plots Comparing ODI Cut-offs from the Lab PSG to the T3 Lab Study

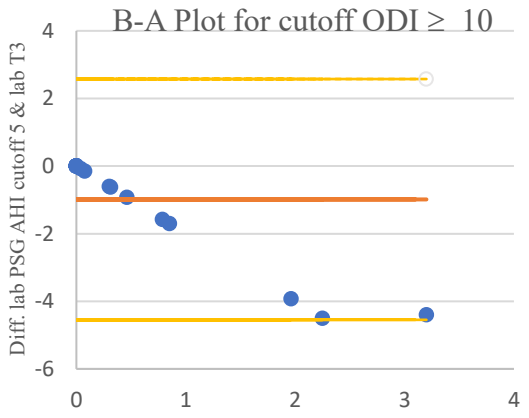
a



b



c

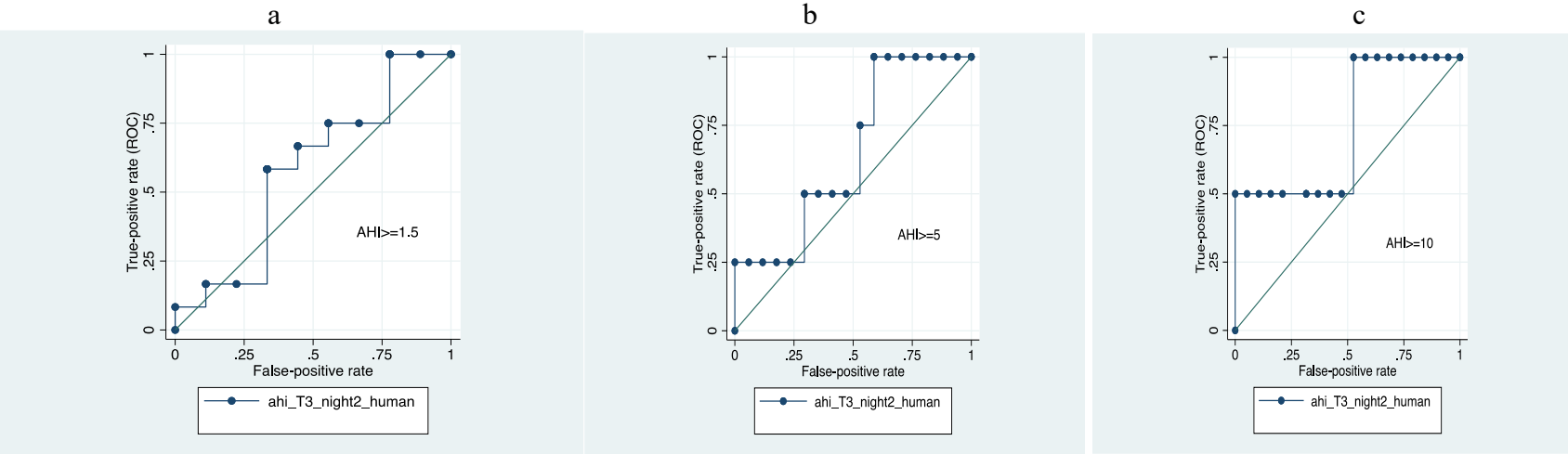


Note. Bland-Altman plots for ODI cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, Diff = difference.

APPENDIX D: Lab PSG and Second Night (Home 2) of the T3 Sleep Study Analyses

Figure D1

ROC for the AHI from Manually Scored T3 Home 2 Sleep Studies Compared to Gold Standard PSG Study



Note. At an AHI cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, the area under the curve was 0.57, 0.65 and 0.74 respectively.

Table D1

Sensitivity and Specificity of AHI Cut-off Value of 1.5 for T3 Night 2 Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	66.67%	55.56%	61.90%	1.5000	0.6000
(>=1.425)	41.67%	66.67%	52.38%	1.2500	0.8750
(>=1.875)	33.33%	66.67%	47.62%	1.0000	1.0000
(>=2.225)	16.67%	66.67%	38.10%	0.5000	1.2500
(>=2.35)	16.67%	77.78%	42.86%	0.7500	1.0714
(>=2.7)	16.67%	88.89%	47.62%	1.5000	0.9375
(>=3.225)	8.33%	88.89%	42.86%	0.7500	1.0312
(>=3.966..)	8.33%	100.00%	47.62%		0.9167
(>3.966..)	0.00%	100.00%	42.86%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table D2

Sensitivity and Specificity of AHI Cut-off Value of 5 for T3 Night 2 Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	75.00%	47.06%	52.38%	1.4167	0.5313
(>=1.1)	50.00%	52.94%	52.38%	1.0625	0.9444
(>=1.35)	50.00%	58.82%	57.14%	1.2143	0.8500
(>=1.425)	50.00%	64.71%	61.90%	1.4167	0.7727
(>=1.875)	50.00%	70.59%	66.67%	1.7000	0.7083
(>=2.225)	25.00%	76.47%	66.67%	1.0625	0.9808
(>=2.35)	25.00%	82.35%	71.43%	1.4167	0.9107
(>=2.7)	25.00%	88.24%	76.19%	2.1250	0.8500
(>=3.225)	25.00%	94.12%	80.95%	4.2500	0.7969
(>=3.966..)	25.00%	100.00%	85.71%		0.7500
(>3.966..)	0.00%	100.00%	80.95%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table D3

Sensitivity and Specificity of AHI Cut-off Value of 10 for T3 Night 2

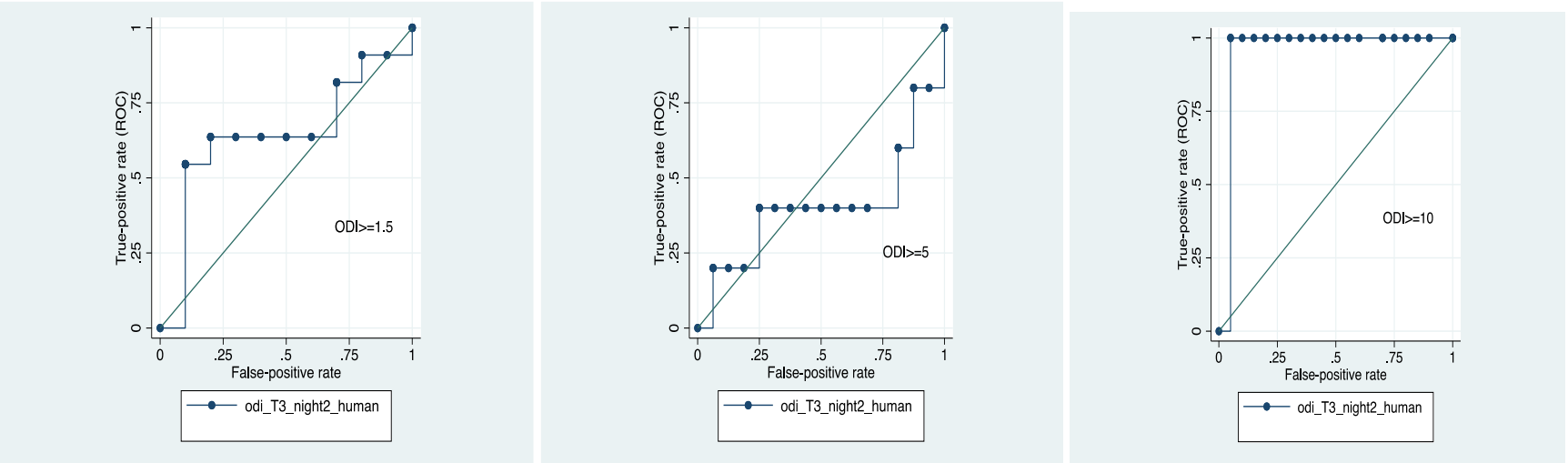
Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>=1)	100.00%	47.37%	52.38%	1.9000	0.0000
(>=1.1)	50.00%	52.63%	52.38%	1.0556	0.9500
(>=1.35)	50.00%	57.89%	57.14%	1.1875	0.8636
(>=1.425)	50.00%	63.16%	61.90%	1.3571	0.7917
(>=1.875)	50.00%	68.42%	66.67%	1.5833	0.7308
(>=2.225)	50.00%	78.95%	76.19%	2.3750	0.6333
(>=2.35)	50.00%	84.21%	80.95%	3.1667	0.5938
(>=2.7)	50.00%	89.47%	85.71%	4.7500	0.5588
(>=3.225)	50.00%	94.74%	90.48%	9.5000	0.5278
(>=3.966..)	50.00%	100.00%	95.24%		0.5000
(>3.966..)	0.00%	100.00%	90.48%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Figure D2

ROC for the ODI from Manually Scored T3 Home 2 Sleep Studies Compared to Gold Standard PSG Study

a b c



Note. At an ODI cut-off value of 1.5 (a), 5 (b) and 10 (c) events per hours, the area under the curve was 0.65, 0.41 and 0.95 respectively.

Table D4

Sensitivity and Specificity of ODI Cut-off Value of 1.5 for T3 Night 2 Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 1)	63.64%	60.00%	61.90%	1.5909	0.6061
(>= 1.625)	54.55%	80.00%	66.67%	2.7273	0.5682
(>= 1.666..)	54.55%	90.00%	71.43%	5.4545	0.5051
(>= 2)	36.36%	90.00%	61.90%	3.6364	0.7071
(>= 5.2)	18.18%	90.00%	52.38%	1.8182	0.9091
(>= 5.3)	9.09%	90.00%	47.62%	0.9091	1.0101
(>= 7.175)	0.00%	90.00%	42.86%	0.0000	1.1111
(> 7.175)	0.00%	100.00%	47.62%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table D5

Sensitivity and Specificity of ODI Cut-off Value of 5 for T3 Night 2 Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 1)	40.00%	43.75%	42.86%	0.7111	1.3714
(>= 1.625)	40.00%	62.50%	57.14%	1.0667	0.9600
(>= 1.666..)	40.00%	68.75%	61.90%	1.2800	0.8727
(>= 2)	20.00%	75.00%	61.90%	0.8000	1.0667
(>= 5.2)	20.00%	87.50%	71.43%	1.6000	0.9143
(>= 5.3)	20.00%	93.75%	76.19%	3.2000	0.8533
(>= 7.175)	0.00%	93.75%	71.43%	0.0000	1.0667
(> 7.175)	0.00%	100.00%	76.19%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

Table D6

Sensitivity and Specificity of ODI Cut-off Value of 10 for T3 Night 2 Study

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 1)	100.00%	50.00%	52.38%	2.0000	0.0000
(>= 1.625)	100.00%	65.00%	66.67%	2.8571	0.0000
(>= 1.666..)	100.00%	70.00%	71.43%	3.3333	0.0000
(>= 2)	100.00%	80.00%	80.95%	5.0000	0.0000
(>= 5.2)	100.00%	90.00%	90.48%	10.0000	0.0000
(>= 5.3)	100.00%	95.00%	95.24%	20.0000	0.0000
(>= 7.175)	0.00%	95.00%	90.48%	0.0000	1.0526
(> 7.175)	0.00%	100.00%	95.24%		1.0000

Note. LR+ = likelihood ratio for a positive test result; LR- = likelihood ratio for a negative test result.

CHAPTER IV:

Study 3: The Relationship Between SDB and Memory in Early Childhood

Abstract

OBJECTIVE: The objective of this study was to elucidate the relationship between SDB and memory during the first three years of life.

METHODS: CHILD Edmonton participants (n = 501) had their memory assessed at three years of age, using the Sentence Repetition subtest of the Developmental NEuroPSYchological Assessment – Second Edition (NEPSY–II). Multivariate linear regression identified factors associated with memory performance on the NEPSY–II. Parents reported sleep duration and sleep-disordered breathing (SDB) by completing the Pediatric Sleep Questionnaire (PSQ). Total screen time was reported by parents, including time on gaming and mobile devices.

RESULTS: Children with SDB (M = 8.63, SD = 2.72) had significantly lower scores on the NEPSY–II sentence repetition subtest than those without SDB (M = 9.63, SD = 3.03, $p < 0.05$) in univariate analysis. There were no sleep variables that were significantly associated with memory in multivariate analysis. Both mean replacement and multiple imputation models had similar results. Sex and screen time were the variables that best explained scores on the NEPSY–II sentence repetition in multivariate regression analyses. Among the children studied, watching more than one hour of screen time each day was associated with a drop of almost 1 point on the NEPSY–II memory score (b = -0.99, 95% CI = [-1.88, -0.11], $t(500) = -2.20$, $p < 0.05$). Females (b = 0.83, 95% CI = [0.31, 1.36], $t(500) = 3.10$, $p = 0.002$) performed significantly higher on memory at age three compared to males. Maternal fruit intake and neighbourhood crime index were significant covariates that were included in the final multivariate regression model.

CONCLUSION: Neither sleep duration nor SDB were associated with memory in multivariate analyses. Screen time was associated with lower memory scores. Results of this study may help inform parenting practices around screen time use.

Keywords: sleep-disordered breathing, memory, sex, screen time

Introduction

Preschool age is a critical period for cognitive, social and brain development. A systematic review of sleep duration (objectively measured) and cognitive function in children 5–13 years old found that longer sleep durations were associated with better cognitive functioning (Lo et al., 2016). Sleep disordered breathing (SDB) refers to multiple conditions characterized by abnormal breathing during sleep, often relating to obstruction or narrowing of the pharynx. SDB can manifest as snoring or frequent apneas involving continuing hypoxemia and arousals resulting in daytime sleepiness and sleep disorders.

Findings from a recent systematic review of the relationship between SDB and children's cognition found 11 studies that evaluated various aspects of memory (short-term memory, working memory and long-term declarative memory). Only studies that measured sleep objectively by polysomnography (PSG) or clinical assessment were included in the analysis. No impairments were found in verbal short-term memory, but deficits were found with verbal memory tasks (e.g., sentence span) among children with SDB. Additionally, no deficits were found in visual-spatial working memory or verbal learning (da Silva Gusmao Cardoso et al., 2018). Overall, the authors emphasized that the small number of studies that met the eligibility criteria (n = 11), and the heterogeneity among these studies, made it difficult to draw definitive conclusions on the effect of SDB on memory (da Silva Gusmao Cardoso et al., 2018*).*

Results from the Childhood Adenotonsillectomy Trial (CHAT) randomized control trial did not show that adenotonsillectomy (AT) for SDB significantly improved neurocognitive functioning compared to the watchful waiting group among school-age children (Marcus et al., 2013). However, the study found improvement in secondary outcomes of behaviour, quality of life and sleep measures (Marcus et al., 2013). More recent findings from exploratory analyses of CHAT study neuropsychological measures found improved scores on nonverbal reasoning, fine motor skills and selective attention for the early AT group compared to the watchful waiting group (Taylor et al., 2016). Although these scores were statistically significant, the effect sizes were small (Taylor et al., 2016). Surprisingly, improved scores on verbal learning recognition tasks were associated with decreased sleep efficiency (Taylor et al., 2016).

Studies among younger children have shown contrasting results when evaluating SDB following AT. A prospective longitudinal study among three- to twelve-year olds (Kohler et al., 2018) did not show any effect on neurocognitive functioning following four years post-AT. However, results from a prospective randomized controlled trial (RCT) of children from the Preschool Obstructive Sleep Apnea Tonsillectomy and Adenoidectomy study (POSTA) did show improved scores in long-term retrieval (memory) scores among children in the AT group compared to the no-surgery group (Waters et al., 2020). The CHAT (Marcus et al., 2013) and the POSTA (Waters et al., 2020) are the only RCTs that evaluate the cognitive outcomes of SDB following treatment. The limited number of experimental studies and the inconclusive evidence from observational studies on the effect of SDB on cognitive outcomes in children speaks to the need for more research in this area, and especially among preschool-aged children.

Although previous research has shown that sleep plays an important role in memory (Mindell & Owens, 2015), studies among young children remain inconclusive (da Silva Gusmao

Cardoso et al., 2018). Moreover, no conclusive evidence has emerged on sex-related differences in memory skills and the differences in effects of sleep problems on memory development between boys and girls (Dewald et al., 2010).

The relationship between sleep quantity and neurocognitive development among healthy preschoolers has also received a paucity of research. A recent systematic review (Chaput et al., 2017) of the relationship between sleep duration and health indicators in children 0–4 years old found one RCT where the number of correct answers in an explicit recognition task was significantly higher in the nap (control) group compared to the wake (sleep-restricted) condition. However, implicit memory (a priming task) did not differ between the nap and sleep-restricted groups (Giganti et al., 2014). Sleep duration was mostly assessed by subjective measures (parental report) in 70% of studies (n = 48/69) included in the review (Chaput et al., 2017).

Although this is not an exhaustive list, there are other variables besides sleep which have shown to be important predictors of early childhood memory, including age (Dohmen et al., 2016; Wang & Gülgöz, 2019; Wang & Peterson, 2016), language ability (Allen & Kelly, 2015), sex (Amundsen et al., 2014; Haden et al., 2011), socio-economic status (SES; Agnihotri et al., 2019), prenatal and postnatal environment (Anjos et al., 2013; Carr et al., 2018; Subbarao et al., 2015; Wojtyla, 2011), attention (Kokkalia & Drigas, 2015; Luo, Zhang & Wang, 2017) and screen time (Hutton et al., 2019; Tamana et al., 2019).

CHILD Edmonton is the first birth cohort to use home cardio-respiratory monitoring to assess sleep disordered breathing (SDB) in children under five years of age. Additionally, there have been few cohort studies that objectively assess a child's sleep via home cardio-respiratory monitoring while also evaluating their neurodevelopment at the same age.

Research Question

The aim of this study is to elucidate the relationship between SDB and memory during the first three years of life. We hypothesized that children with SDB at age three have lower measures of memory at the same age as assessed by the NEPSY–II. Additionally, we hypothesize that there will be a significant interaction effect between sex and SDB on memory.

Methods

Study Participants

This analysis included CHILD Edmonton participants who consented to additional sleep questionnaires as well as in-clinic neurodevelopment testing and at-home sleep testing. Of the 822 CHILD Edmonton participants who originally consented to the study, 598 (72.7%) completed the three-year NEPSY–II assessment. A total of 501 participants had a scaled score on the sentence repetition subtest of the NEPSY–II.

CHILD is a multi-centre population-based longitudinal birth cohort study with the initial goal of investigating the correlation between genes and environment behind the development of atopy and asthma (Subbarao et al., 2015). The parent questionnaires included questions on the characteristics of the child and family (for example, sex of the child, ethnicity, socioeconomic status, and so on), nutrition (of mothers and infants) and the level of stress in mothers when recruited and annually across the study (see Appendix A). CHILD families in Edmonton were involved in a sub-study on the longitudinal relationship between neurodevelopment and sleep in children (Tamana et al., 2018). With the informed consent from the participants, the study also included questionnaires about the child's sleep and participation in a home PSG sleep study, parent-reported behavioural questionnaires and neurodevelopmental assessments (Tamana et al., 2018). The current study was included in the CHILD Edmonton study ethics application. Ethics

approval was obtained from the University of Alberta Health Ethics Research Office (Pro00002099).

Study Variables

Memory (primary outcome). Memory was measured by the NEPSY–II. The NEPSY–II includes 32 subtests and four delayed tasks that assess six theoretical functional domains: executive function & attention, language & communication, memory & learning, sensorimotor, visuospatial processing and social perception (Brooks et al., 2010). It is a standardized test designed for children and adolescents aged 3–16 years old (Brooks, Sherman & Strauss, 2010). Scaled scores (adjusted for age) from the Memory and Learning domain of the NEPSY–II were utilized to assess memory of children at age three. This subtest is administered to children 3–6 years old and is designed to assess the child's ability to repeat sentences of increasing complexity and length. The child is read a series of sentences and asked to recall each sentence immediately after it is presented. Sentence repetition represents immediate memory, as it refers to the recall of verbal information immediately after exposure to the material to be learned. Short-term memory has often been used to describe immediate recall. Since the sentences are said aloud to the child, sentence repetition refers in particular to the ability to recall auditory information.

The sentence repetition subtest was selected as the subtest to represent the Memory & Learning domain. Test-retest correlation for the Sentence Repetition total score is acceptable (r = 0.74) among children three to four years old. The NEPSY–II generates scaled scores that range between 1–19 that are normalized and corrected by age (M = 10, SD = 3). A score below seven is classified as below expected levels (clinical range), whereas scores from 8–12 are at expected levels (average range). The sentence repetition subtest was found to be strongly correlated with

the Differential Abilities Scales – Second Edition (DAS–II; Elliott, 2007) General Conceptual Ability composite score. Additionally, strong correlations were found between the Wechsler Individual Achievement Test – Second Edition (WIAT–II; Wechsler, 2001) composite scores and the sentence repetition subtest.

SDB (primary exposure variable). The presence of SDB was assessed quarterly using the parent-reported Pediatric Sleep Questionnaire (PSQ; Chervin et al., 2000) at three years of age. Children were classified as having SDB if they had a PSQ score ≥ 0.33.

Sleep duration (secondary exposure variable).

Subjective. Sleep duration was subjectively assessed via parent-reported SDB. The Brief Infant Sleep Questionnaire (BISQ; Sadeh, 2004) was completed by parents every three months from three months to two years of age. At three years of age, parents completed the Child Sleep Habits Questionnaire (CSHQ; Owens et al., 2000). The BISQ and CSHQ also provided information on the child's sleep: sleeping arrangement, sleep position, sleep latency, and method of falling asleep. The CSHQ included items related to anxiety around sleep, behavior occurring during sleep and night wakings, sleep-disordered breathing, parasomnias, and morning waking/daytime sleepiness. Nighttime sleep duration was calculated from the parent-reported bedtime and awake time and total sleep was calculated by summing day and night sleep times.

Objective. Sleep duration, sleep efficiency and AHI was objectively assessed for one night at one year of age, using a portable sleep device (T3) that measured respiratory inductance plethysmography (respiratory, abdominal and sum channels), movement (actigraphy), heart rate, EMG (intercostal region), snoring, O_2 saturation pulse oximetry and sleep/wake states. Trained research assistants went out to the participant's home to set up the T3 monitor on the child around a half hour prior to bedtime. Families were provided with an audio/video "baby monitor"

to monitor their child at night (if needed), and a CHILD Edmonton study team member was on-call for the night of the sleep study. The T3 scoring was completed by Sleep Strategies using a scoring rubric (see Appendix B) based on the American Academy of Sleep Medicine (AASM) pediatric scoring guidelines (Iber et al., 2007), modified to reflect the channels available. Measures of apneas, hypopneas, AHI, sleep duration and total time in bed were obtained from the PSG.

Sleep duration was objectively assessed at three years of age using a wrist-worn Actigraph GT3X-BT accelerometer (ActiGraph Corp, Pensacola, FL, USA). Parents were instructed to have their child wear the accelerometer on their non-dominant wrist for seven consecutive 24-hour periods. Data were collected in 60-second epochs using a 30 Hz sampling frequency. Sleep during the day (i.e., naps) and night for each 24-hour period was determined via visual inspection of sleep analysis graphs using Actilife® software with the support of the logbooks.

Covariates. The following covariates were assessed among CHILD Edmonton participants.

General demographics. Mothers reported on their ethnicity, family income, marital status and highest education achieved. Family incomes were categorized, using the highest reported annual family income, as below $60,000, equal or above $60,000 or prefer not to say. $68,000 is the median after-tax income for Canada (The Government of Canada, Employment and Social Development Canada).

Pregnancy history. Information on maternal age, birth weight (kg), gestational age (in weeks) and birth order was extracted from hospital birth charts.

Prenatal maternal smoking. Mothers reported how often they smoked during pregnancy. Mothers that responded "daily or occasionally" were categorized as having smoke prenatally; mothers that responded "not at all" were categorized as no smoking prenatally.

Maternal diet during pregnancy. A food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center was modified to reflect Canadian multi-ethnic food choices. The 175-item self-administered FFQ was completed at enrolment, asking pregnant mothers to report the frequency and portion size of food since becoming pregnant. The Healthy Eating Index (2010; Guenther et al., 2013) was calculated for each participant. The University of Minnesota Nutrition Data Systems for Research (Dennis et al., 1980) was "Canadianized" to include foods from multiple ethnic backgrounds and used to calculate the nutrient intake (e.g., caffeine, calcium, fruit) for each subject.

Fruit intake. Total fruit intake (the "5-a-day" method) was calculated from the FFQ and includes the sum of "servings of fruit, not including juices" plus "servings of juice" per day (Kristal et al., 2000). The FFQ defined a medium serving of fruit as either a ¾ cup of 100% fruit juice, ½ cup of fresh fruit or ¼ cup of dried fruit.

Season of birth. This variable was determined using the child's month of birth extracted from the child's hospital birth chart. Seasons were categorized as summer (June, July and August), fall (September, October and November), winter (December, January and February) or spring (March, April and May).

Duration of breastfeeding. Breastfeeding is associated with increased nighttime waking (Hysing et al., 2014). Mothers reported whether they were breastfeeding, formula feeding or providing solid food for their infants at three, six, 12 and 24 months of age.

Maternal depression. This variable was reported at three, six and twelve months using a self-administered questionnaire based on the Center for Epidemiological Studies–Depression (CES–D).

Maternal stress. This variable was measured using Cohen, Karmarck and Mermelstein's abbreviated ten-item version of the Perceived Stress Scale (PSS; Loyd & Abidin, 1985) questionnaire when their child was three, six and twelve months of age. The PSS has a maximum score of 40 with higher scores indicating higher levels of maternal stress. Mothers with a score greater than 13 were classified as having significant stress.

Child's ability to self-soothe. This variable was assessed from the BISQ questionnaire where parents were asked about how their child fell asleep most of the time (while feeding, being rocked, being held, in bed, or in bed near a parent) to identify the child's ability to self-soothe.

Wheeze. Wheeze was defined a whistling sound coming from the chest. Parent reported whether their child had a wheeze at 36 months of age. Parents were then asked to indicate the total number of wheezing episodes (e.g., an episode is defined as wheeze for more than 12 minutes at a time separated by at least 7 days or more than 20 minutes if separated by less than 7 days) at each assessment point if the child did wheeze.

Child atopy. Atopy was determined using skin prick allergy test (SPT) at 12 and 36 months of age. A positive SPT test was defined as an average wheal size > 2 mm than the negative control. A child was classified as atopic if they had at least one positive test result.

Parent–infant bonding. This variable assessed bonding via the Parent–Child Dysfunction Interaction Scale (P–CDI), a 12-item self-administered questionnaire. Scores range from 12–60, with higher scores indicating that parents perceive that their child does not meet expectations and that interactions with the child are not reinforcing.

Parental history of SDB. Mothers and fathers were assessed via the Global Sleep Assessment Questionnaire (GSAQ), which provided information on whether or not they experienced symptoms indicative of SDB or had sleep problems. Fathers completed the Global Sleep Assessment Questionnaire (GSAQ) during the prenatal visit, while mothers completed this questionnaire during the one year visit. The GSAQ is an 11-item ordinal scale validated sleep questionnaire that can aid in recognizing sleep disorders (Roth et al., 2002). Test-retest reliabilities ranged from 0.51 to 0.92. The GSAQ is able to discriminate between different diagnoses and has demonstrated acceptable levels of sensitivity and specificity.

Environmental factors. Parents reported information about the communities they live in, such as number of trees in their area, playground count, number of people living in the home and perceived crime index (average Crimecast). The average Crimecast score across most neighbourhoods is 100 (range: 0–2000; higher scores mean more crime in the neighbourhood).

Behavior problems. Parents completed the Child Behavior Checklist (CBCL) 1½-preschool version (Achenbach & Ruffle, 2000) at two years. The CBCL is a standardized measure of childhood mental health and has good internal reliability and validity in a number of population settings (Achenbach, 1991; Achenbach et al., 1987). The CBCL yields a T-score (adjusted for age) for total problems, internalizing problems, and externalizing problems composite scales (Achenbach et al., 1987; Achenbach & Ruffle, 2000). The CBCL normative mean is 50 and higher scores indicate increased behavior problems. T-score greater than 65 suggest clinical behavioral problems.

Screen time. Screen time (hh:mm) was assessed at the age of three. Parents reported their child's total screen time/day, which included watching TV/DVD's, using a computer, tablet, mobile phone or gaming device. Screen time was separated into three categories based on the

recommended Canadian 24-hour Movement Guidelines for Young Children 0–4 years (Tremblay et al., 2017). The categories are (1) less than 30 minutes/day, (2) between 30 minutes and one hour per day and (3) more than one hour per day (Tremblay et al., 2017).

Statistical Analysis

Participants had to complete the sentence repetition subtest on the NEPSY–II to be included in the analysis. Chi-square tests (categorical predictors) and t-test (continuous predictors) were used to compare demographic variables between participants with and without NEPSY–II cognitive scores at three years of age. Univariate linear regression analyses identified factors associated with memory performance on the NEPSY–II at three years of age (primary outcome). Predictors significant in univariate analysis ($p < 0.05$) were included in multivariate analyses. Akaike information criterion and Bayesian information criterion (BIC) criteria were used to compare competing regression models to select the least complex model (a lower BIC). Significance was set at $p < 0.05$. For multivariate analyses, missing values on all variables were replaced with the mean or reference value (for continuous and categorical variables, respectively) and a dummy variable was included in the analysis to account for the replacement. Missing data was also treated using imputations for missing data. Stata 14 (STATA corp.) was used for all analyses.

Results

Descriptive Analyses

Of the 822 CHILD Edmonton participants originally consented, 598 (72.7%) completed the three-year NEPSY–II assessment. A total of 525 participants attempted the sentence repetition subtest of the NEPSY–II. Of the 24 participants who were excluded from the sentence repetition analysis, fifteen were removed from the dataset as they *did not manage* to complete the subtest, while nine participants were removed because they *refused* to complete the task, despite attempting some items. Children with NEPSY–II data at age three were more often Caucasian and had higher family income; their mothers were more likely to have attended post-secondary school, were less likely to smoke, were slightly older mothers and had breastfed them longer compared to individuals without NEPSY–II data at three years of age. Additionally, those with NEPSY–II data had slightly higher sleep efficiency and spent more time in bed during sleep assessment at one year of age compared to individuals without NEPSY–II data at three-years of age (Table 4.1a and Table 4.1b).

Of the 501 participants who completed the sentence repetition subtest on the NEPSY–II, 24% (N = 122) of participants scored below the clinical cut-off one standard deviation (SD) below the mean and 7% (N = 35) scored two SD below the mean. Screen time was available for 85% (427/501) of participants with NEPSY–II sentence repetition data at three years of age. Mean screen time was 1.69 hours/day (95% CI 1.58, 1.80). At three years of age, 51% of children (217/427) met the Canadian recommended screen-time guideline of less than one hour of screen time/day.

Table 4.1a

Demographic Characteristics for Children With and Without NEPSY–II Data at Age Three

	NEPSY–II data (3yr) absent	NEPSY–II data present	*p-Value*
Categorical Predictors	% (n/total)	% (n/total)	
Caucasian (child)	55.88% (171/526)	71.14% (355/526)	0.001
Males	53.92% (165/410)	49.10% (245/410)	0.18
Caucasian (mother)	66.34% (203/599)	79.36% (396/599)	0.001
Married or Common Law	84.64% (259/708)	89.98% (449/708)	0.06
Full-term birth	95.35% (287/756)	94.75% (469/756)	0.71
First-born child	44.59% (136/352)	43.29% (216/352)	0.72
Income $60,000 or more	70.92% (217/677)	92.18% (460/677)	<0.001
Mother attended post-secondary	79.08% (242/702)	92.18% (460/702)	<0.001
Maternal smoking	6.67% (19/34)	3.13% (15/34)	0.03
Attends daycare at 36 months	48.11% (51/244)	46.52% (193/244)	0.78
SDB at 36 months	11.21% (12/58)	11.44% (46/58)	0.95

Note: NEPSY–II *p*-value represents the statistical significance of chi-squared.

Table 4.1b

Demographic Characteristics for Children With and Without NEPSY–II Data at Age Three

	NEPSY–II data absent (3yr)	NEPSY–II data present	*p-Value*
Continuous Predictors	*M* 95% CI	*M* 95% CI	
Mother's age	30.53 [29.98, 31.07]	31.76 [31.39, 32.13]	<0.001
Child age when formula started	1.55 [1.21, 1.90]	2.54 [2.19, 2.89]	<0.001
Breast feeding duration (months)	7.50 [6.70, 8.29]	9.11 [8.58, 9.63]	0.001
Infant weight (kg)	3.41 [3.35, 3.47]	3.43 [3.38, 3.47]	0.69
Gestational age (weeks)	39.34 [39.19, 39.49]	39.51 [39.39, 39.63]	0.08
Sleep efficiency (min. asleep/min. in bed)	90.46 [89.51, 91.41]	91.72 [91.20, 92.24]	0.02
Apnea Hypopnea Index (AHI) at 1 year home sleep test	5.02 [4.36, 5.68]	5.37 [4.94, 5.81]	0.39
Time in bed (min.; assessed using PSG at 1 year)	530.19 [513.20, 547.17]	560.14 [551.03, 569.25]	0.002
Nighttime sleep at 36 months	11.94 [11.65, 12.24]	11.72 [11.59, 11.85]	0.14

Note: M = mean; CI = confidence interval; *p-value* = represents the statistical significance of a t-test.

Cognitive Development at Three Years of Age (Primary Outcome)

Univariate Analyses

Univariate analyses for categorical variables are presented in Table 4.2a and Table 4.2b. An independent-samples t-test indicated that children with SDB (M = 8.63, SD = 2.72) had significantly lower scores on the NEPSY–II sentence repetition subtest than those without SDB (M = 9.63, SD = 3.03, $t(401) = 2.13$, $p < 0.001$). Females (M = 9.84, SD = 3.17) had significantly higher sentence repetition scores than males (M = 9, SD = 2.92, $t(499) = -3.08$, $p < .001$).

Univariate analyses of continuous variables are presented in Table 4.3a and Table 4.3b. The continuous measure of screen time at three years of age was associated with lower scores on the memory measure (b = -0.43, 95% CI = [-0.69, -0.18], $t(426) = -3.34$, $p = 0.001$). Screen time was measured as the average number of hours per day that the child watches screens or plays videogames. Mother's calcium (b = 0, 95% CI = [0,0], $t(444) = 2.09$, $p < 0.05$) and daily fruit consumption ("5-a-day" method) during pregnancy (b = 0.17, 95% CI =[0.01, 0.33], $t(444) = 2.15$, $p < 0.05$) were prenatal nutrition variables that were significantly associated with lower scores on memory at age three. The neighbourhood's average crime index was significantly associated with the memory score for children at age three (b = 0.01, 95% CI = [0, 0.02], $t(311) = 2.66$, $p < 0.05$). Scores on both the Internalizing scale (b = -0.04, 95% CI = [-0.07, -0.01], $t(444) = -2.53$, $p < 0.05$) and the Externalizing scale (b = -0.04, 95% CI = [-0.07, -0.01], $t(444) = -2.52$, $p < 0.05$) of the CBCL were associated with lower memory scores at age three.

Table 4.2a

Univariate Analysis of Categorical Child Variables for Memory at 36 Months of Age

Categorical Variables	Categories	M (SD)	95% CI	p-value
Child variables				
Sex	Male Female	9 (2.92) 9.84 (3.17)	[8.63, 9.37] [9.45, 10.23]	**<0.001*****
Ethnicity	Caucasian Other	9.47 (3.16) 9.28 (2.88)	[9.14, 9.80] [8.79, 9.76]	0.54
Term	Late preterm	8.88 (2.80)	[7.75,10.0]	0.34
	Full term	9.47 (3.10)	[9.19, 9.75]	
Birth order	First born	9.47 (2.98)	[9.07, 9.87]	0.76
	Subsequent born	9.39 (3.16)	[9.02, 9.76]	
Child's ability to self-soothe at 3 months.	Self-soother Not self-soother	9.47 (3.07) 9.44 (3.15)	[8.90, 9.97] [9.12, 9.81]	0.92
Child's ability to self-soothe at 6 months.	Self-soother Not self-soother	9.35 (3.28) 9.34 (2.76)	[8.94, 9.98] [8.92, 9.75]	0.97
Atopy at 36 months	No Yes	9.42 (0.15) 9.55 (0.37)	[9.13, 9.71] [8.81,10.2]	0.75
Wheeze at 36 months	No Yes	9.44 (0.15) 9.64 (0.46)	[9.15, 9.74] [8.72,10.5]	0.69
Child slept more than 10 hours	No Yes	9.59 (0.39) 9.39 (0.16)	[8.81,10.3] [9.07, 9.70]	0.60
BISQ sleep position at 21 months	On belly On side On back	9.70 (3.13) 9.17 (2.94) 8.84 (2.92)	[9.27,10.1] [8.52, 9.82] [8.29, 9.38]	**0.04***
BISQ sleeping arrangement at 30 months	Crib in separate room Crib in parents' room In parents' bed Crib in room with sibling Other	9.58 (2.94) 11.8 (3.03) 8.21 (2.68) 11.22(4.47) 9.25 (3.05)	[9.08,10.0] [8.04,15.5] [7.26, 9.16] [7.78,14.6] [8.82, 9.68]	**0.02***
Co-sleep at 30 months	No Room sharing Bed sharing	9.43 (3.06) 11.8 (3.03) 8.21 (2.68)	[9.15, 9.71] [9.63,13.9] [7.49,8.93]	**0.02***
SDB at 36 months. (PSQ)	No Yes	9.63 (3.03) 8.63 (2.72)	[9.31 ,9.95] [7.82, 9.44]	**0.03***
Screen time at 36 months	Less than 30 min/day Between 30 min and 1 hour/day More than 1 hour per day	10 (3.71) 9.75 (3.08) 9 (2.77)	[9.04, 11] [9.27, 10.2] [8.63, 9.38]	0.02*
CSHQ sleep disturbance index at 36 months	Below diagnostic threshold Above diagnostic threshold	9.62 (0.19) 9.23 (0.23)	[9.24,10.0] [8.78,9.68]	0.18
CSHQ sleep onset delay scale at 36 months	Usually falls asleep in 20 min Sometimes falls asleep in 20 min. Rarely falls asleep in 20 min.	9.56 (3.02) 9.27 (3.36) 8.91 (2.72)	[9.22, 9.9] [8.57, 9.97] [8, 9.82]	0.42

Note. BISQ = Brief Infant Sleep Questionnaire; CSHQ = Child Sleep Habits Questionnaire; PSQ = Pediatric Sleep Questionnaire

*$p < .05$. **$p < .01$. ***$p < 0.001$.

Table 4.2b

Univariate Analysis of Categorical Family Variables for Memory at 36 Months of Age

Categorical Variables	Categories	M (SD)	95% CI	p-value
Family variables				
Marital status	Married/Common Law Divorced/Separated/Single	9.46 (3.09) 9.14 (3.01)	[9.17, 9.74] [7.99,10.28]	0.59
Mother's ethnicity	Caucasian Other	9.47 (3.15) 9.28 (2.88)	[9.16, 9.78] [8.65, 9.77]	0.45
Father's ethnicity	Caucasian Other	9.44 (3.11) 9.3 (2.98)	[9.14, 9.75] [8.71, 9.89]	0.68
Household income	<$60,000 >=$60,000	9.29 (2.67) 9.44 (3.12)	[8.31,10.27] [9.15, 9.72]	0.80
Mother's education	Mother did not attend post-secondary Mother attended post-secondary	9.4 (2.21) 9.42 (3.14)	[8.37,10.43] [9.13, 9.71]	0.98
Gestational diabetes	No Yes	9.48 (3.09) 8.71 (2.88)	[9.20, 9.76] [7.70, 9.71]	0.16
Prenatal smoking	No Yes	9.40 (3.10) 9.47 (2.47)	[9.12, 9.69] [8.10,10.84]	0.94
Mother employed at 1 month	No Yes	9.38 (3.12) 9.41 (3.15)	[8.63,10.14] [9.08, 9.74]	0.94
Mother employed at 12 months	No Yes	9.44 (2.91) 9.41 (3.17)	[8.89,10.05] [9.07, 9.76]	0.95
Job loss	No Yes	9.47 (3.12) 9.67 (3.89)	[9.12, 9.82] [7.52,11.82]	0.81
Mother SDB	No Yes	9.62 (3.05) 9.26 (3.11)	[9.18,10.06] [8.87, 9.65]	0.24
Father SDB	No Yes	9.41 (3.06) 9.48 (3.29)	[8.64,10.17] [9.04, 9.92]	0.87

Table 4.3a

Univariate Analyses for Continuous Variables Predicting Memory at 36 Months of Age

Continuous Variables	*β*	95% CI	p-value
Child variables			
Gestational age (weeks)	0.01	[-0.18, 0.22]	0.86
Infant weight (kg)	0.05	[-0.21, 0.89]	0.23
Age stopped co-sleeping	-0.05	[-0.11, 0.03]	0.27
Breast feeding duration (months)	0.07	[-0.01, 0.09]	0.14
Age formula start (months)	0.06	[-0.05, 0.17]	0.28
Colds at 36 months.	0.10	[0.05, 1.38]	0.04*
Age child was out of house	0.03	[-0.02, 0.03]	0.54
Child ever away from home	0.04	[-0.33, 0.79]	0.42
Screen time at age 36 months	-0.16	[-0.69, -0.18]	0.001***
CBCL internalizing problems at 36 months	-0.12	[-0.07, -0.01]	0.012*
CBCL externalizing problems at 36 months	-0.12	[-0.07, -0.01]	0.012*
Family variables			
Mother's age	0.02	[-0.05, 0.08]	0.63
Mother's prenatal calcium	0.10	[0,0]	0.04*
Fruit during pregnancy	0.10	[0.01, 0.33]	0.03*
P-CDI at 36 months	-0.09	[-0.12, 0.01]	0.08
PSS at 36 months	-0.03	[-0.06, 0.03]	0.54
CES-D at 36 months	0	[-0.04, 0.04]	0.93
Environment variables			
Trees per neighbourhood area at 36 months	0.10	[0, 0.02]	0.07
Playground count at 36 months	0.10	[-0.01, 0.36]	0.07
Household crowding index at 12 months	-0.02	[-0.88, 0.60]	0.71
Perceived neighbourhood crime index	0.15	[0, 0.02]	0.01*
Bedroom dust at 3 months	-0.07	[0,0]	0.16

Note. B = beta; P–CDI = Parent–Child Dysfunctional Interaction subscale; PSS = Perceived Stress Scale;

CES-D = Maternal Depression. *$p < .05$. **$p < .01$. ***$p < 0.001$

Table 4.3b

Univariate Analyses for Continuous Sleep Variables Predicting Memory at 36 Months of Age

Continuous Variables	*β*	95% CI	p-value
Sleep variables			
CSHQ subscales			
CSHQ night awakening scale at 36 months	-0.06	[-0.31, 0.07]	0.22
CSHQ SDB scale at 36 months	-0.01	[-0.40, 0.36]	0.91
CSHQ sleep duration problems scale at 36 months	-0.03	[-0.39, 0.22]	0.57
CSHQ sleep disturbance index at 36 months	-0.06	[-0.98, 0.19]	0.19
CSHQ bedtime resistance scale at 36 months	-0.08	[-0.19, 0.02]	0.10
CSHQ sleep anxiety scale at 36 months	-0.02	[-0.21, 0.15]	0.73
CSHQ parasomnia scale at 36 months	-0.02	[-0.21, 0.14]	0.71
CSHQ daytime sleepiness scale at 36 months	-0.05	[-0.22, 0.07]	0.33
CSHQ sleep variables			
Nighttime sleep at 36 months	0.05	[-0.13, 0.41]	0.32
Room sharing	-0.05	[-0.07, 0.02]	0.28
Bed sharing	-0.08	[-0.05, 0]	0.09
Age stopped co-sleeping	-0.05	[-0.11, 0.03]	0.27
T3 sleep study at 1 year			
T3 hypopnea index	-0.04	[-0.21, 0.08]	0.38
T3 apnea index	0.07	[-0.03, 0.16]	0.16
T3 ahi	0.03	[-0.04, 0.09]	0.51
T3 desaturation index	-0.01	[-0.05, 0.05]	0.90
T3 desaturation<92% index	0.01	[-0.10, 0.12]	0.84
T3 total time in bed (mins)	-0.08	[-0.01, 0]	0.11
T3 Rem sleep	-0.03	[-0.01, 0]	0.58
T3 non-rem sleep	-0.05	[-0.01, 0]	0.34
T3 sleep efficiency	0.01	[-0.05, 0.06]	0.85
Actigraphy at 3 years			
Average total sleep time	0.01	[0, 0]	0.87
Average sleep latency	-0.03	[-0.01, 0]	0.60
Average WASO	-0.03	[0, 0]	0.52
Average number of awakenings	-0.04	[-0.01, 0]	0.51
Average awakening length	-0.06	[-0.02, 0.01]	0.26
Average fragmentation index	-0.04	[-0.01, 0]	0.44
Average sleep frag index	-0.06	[0, 0]	0.27
Average sleep efficiency	-0.02	[0, 0]	0.74

Note. WASO = Wake After Sleep Onset.

*$p < .05$. **$p < .01$. ***$p < 0.001$.

Multivariate analyses

Tests for Multicollinearity. Multicollinearity occurs when independent variables in a regression model are correlated with one another. This correlation presents a concern in regression models, since independent variables should be independent (Wilcox, 2019). If the degree of correlation between independent variables is too high, it can cause issues with the statistical power and accuracy of the estimated coefficients in a regression model. Therefore, multicollinearity checks were conducted by running the following analyses: (1) a Pearson correlation (Table 4.4) among variables included in the model, to ensure that every variable in the model is unique (no duplicates) and (2) a variance inflation factor (VIF), to determine whether any of the variables in the model need to be investigated further (Table 4.5). The results from the preliminary analyses showed that the variables were not highly correlated with each other, and the range of correlation coefficients among the variables was low (r = -0.15 to 0.22). Additionally, the VIF values ranged from 1.00 to 1.02; thus, multicollinearity was not an issue.

Table 4.4

Correlation for Multivariate Analyses Before Mean or Reference Replacement (n = 501)

Variable	NEPSY–II SR	Sex	SDB	Screen time total	Fruit intake	Crime Index
NEPSY-II SR	1					
Sex	0.22	1				
SDB	-0.10	-0.12	1			
Screen time total	-0.15	-0.02	0.03	1		
Fruit intake	0.09	-0.02	-0.03	-0.04	1	
Crime index	0.13	0.07	0	0.03	-0.11	1

Note. SR = sentence repetition

Table 4.5

VIF Analysis for Multivariate Analyses

Variable	VIF	1/VIF
Sex	1.02	0.98
SDB	1.02	0.98
Crime index	1.02	0.98
Fruit intake	1.01	0.99
Screen time total	1.00	1.00
Mean VIF	1.01	

Note. VIF = variance inflation factor

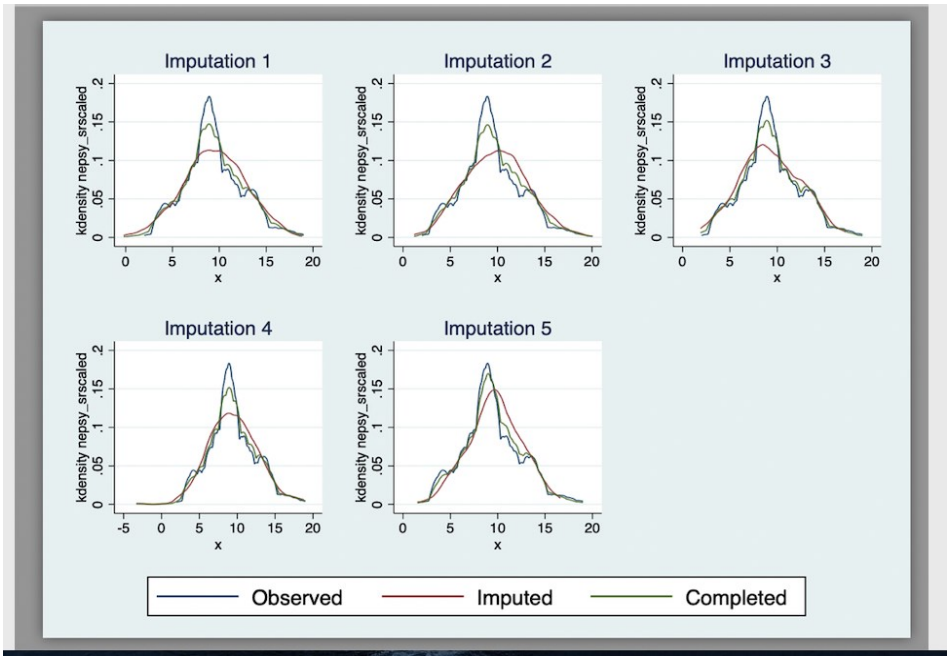
Power analysis. With a null hypothesis equal to zero versus an alternative hypothesis that does not equal zero, the estimated sample size to achieve an R^2 of 5%, with a power of 0.80 and alpha of 0.05, is 125. Therefore, the current sample size of 501 is sufficient to achieve a power of 0.80 (alpha = 0.05).

Multivariate Analyses. In this study, I made use of several different methods of dealing with missing values in large datasets. First, I addressed missing values for all covariates by replacing them with the mean for continuous variables and the reference for categorical variables. I also included a dummy variable in the analysis, to account for the mean replacement for continuous variables (see Table 4.6a and Table 4.6b). Second, I ran multivariate regression models using multiple imputation (MI) to address missing values. Multiple imputation was examined using chained equations (MICE) and the MVN method. Trace plots for both MICE and MVN showed that posterior distribution stabilized after iteration, and no trends were identified among variables. Both the MICE and MVN methods produced similar results to using the mean replacement method. The multivariate models shown in the tables are the ones that used mean replacement to treat missing data. Distributions of the imputed, completed and observed data for NEPSY-II sentence repetition were analyzed to determine whether they all

follow the same trajectory (Figure 4.1). The imputed, original and combined datasets yielded a similar distribution. The combined dataset did not appear to be very different from the original.

Figure 4.1

Imputed Graphs for NEPSY–II Sentence Repetition



The linear screen-time variable resulted in a superior model fit, compared to the model that used the screen-time cut-off variable, based on the lower BIC. Demographic variables such as SES and maternal education were not associated with memory at age three in univariate analyses and were thus excluded from the multivariate models. However, sex remained a constant significant variable in the multivariate models.

The final model using mean or reference replacement for missing values indicated that females (b = 0.83, 95% CI = [0.31, 1.36], $t(500) = 3.10$, $p = 0.002$) performed significantly higher on memory at age three compared to males. The presence of SDB was significant in univariate analysis (see Table 4.2a); with memory at age three, however, it was no longer significant in the multivariate models (Table 4.6a; b = - 0.04, 95% CI = [-0.33, 0.25], $t(477)$

= -0.26, p = 0.795). The linear predictor of screen time at three years of age was associated with lower scores on the memory measure (b = -0.41, 95% CI = [-0.67, -0.16], t(500) = -3.17, p = 0.002). Additionally, watching more than one hour of screen time each day was associated with a drop of almost 1 point on the NEPSY–II memory score (b = -0.91, 95% CI = [-1.80, -0.02], t(500) = -2.02, p = 0.044). None of the sleep variables were significantly associated with memory in the multivariate analysis. A correlation including variables from the final multivariate model (Table 4.6b, Model 2) following mean or reference replacement indicated that the variables were not highly correlated with each other (see Table 4.7); the range of correlation coefficients among the variables remained low (r = -0.15 to 0.14).

Table 4.6a

Multivariate Analysis Examining Predictors for Memory at Three Years of Age With Mean or Reference Replacement with SDB (n = 501)

	Model 1		**Model 2**	
Variables	BIC: 2577.11	r^2 0.07	BIC: 2565.76	r^2 0.08
	Coefficient (*SE*)	*p*-value	Coefficient (*SE)*	*p*-value
Female	0.77 (0.27)	0.005**	0.79 (0.27)	0.004**
Screen time total	-	-	-0.45 (0.13)	0.001**
Screen time total dummy	-	-	-0.07 (0.48)	0.889
Screen time 30 min-1 hour/day	-0.28 (0.46)	0.541	-	-
Screen time >1 hour/day	-0.96 (0.45)	0.033*	-	-
Screen time missing	-0.45 (0.61)	0.461	-	-
SDB	-0.66 (0.48)	0.163	-0.63 (0.47)	0.180
SDB missing	-0.63 (0.40)	0.116	-0.65 (0.40)	0.105
Fruit intake	0.17 (0.79)	0.029	0.18 (0.08)	0.022*
Fruit intake dummy	-0.78 (0.47)	0.097	-0.85 (0.47)	0.070
Crime index	0.01 (0)	0.007	0.01 (0)	0.006**
Crime index dummy	0.07 (0.28)	0.812	-0.07 (0.48)	0.889
Constant	9.16 (0.74)	0.000***	9.43 (0.68)	0.000***

Note. BIC = Bayesian information criterion; SE = standard error.

*p < .05. **p < .01. ***p < .001.

Table 4.6b

Final Multivariate Analysis Examining Predictors for Memory at Three Years of Age With Mean or Reference Replacement without SDB (n =501)

	Model 1		**Model 2**	
Variables	BIC: 2568.74	r^2 0.06	BIC: 2557.41	r^2 0.07
	Coefficient (*SE*)	*p*-value	Coefficient (*SE*)	*p*-value
Female	0.81 (0.27)	0.003**	0.83 (0.27)	0.002**
Screen time total	-	-	-0.46 (0.13)	0.000***
Screen time total dummy	-	-	0.29 (0.41)	0.483
Screen time 30 min-1 hour/day	-0.27 (0.46)	0.557	-	-
Screen time >1 hour/day	-0.99 (0.45)	0.028*	-	-
Screen time missing	-0.80 (0.55)	0.149	-	-
Fruit intake	0.18 (0.08)	0.025*	0.19 (0.08)	0.019*
Fruit intake dummy	-0.94 (0.46)	0.041*	-1.01 (0.46)	0.027*
Crime Index	0.01 (0)	0.009**	0.01 (0)	0.008*
Crime Index dummy	0.03 (0.28)	0.903	0.02 (0.28)	0.934
Constant	9.19 (0.73)	0.000***	9.43 (0.68)	0.000***

Note. BIC = Bayesian information criterion; SE = standard error.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 4.7

Correlation for Multivariate Analyses After Mean or Reference Replacement (n = 501)

Variable	NEPSY–II SR	Sex	Screen time total	Fruit intake	Crime Index
NEPSY–II SR	1				
Sex	0.14	1			
Screen time total	-0.15	0.03	1		
Fruit intake	0.09	0.02	-0.01	1	
Crime index	0.12	0.06	0.02	-0.07	1

Discussion

In this study, no association was found between sleep variables – either subjectively or objectively assessed – and memory at three years of age. SDB was associated with lower memory scores on the NEPSY–II in univariate analysis but not in the multivariate analyses. The linear measure of screen time was significantly associated with lower scores for memory at age three. Additionally, the categorical measure of screen time indicated that watching more than one hour of screen time per day was associated with a drop of almost 1 point on the NEPSY–II memory score. The final multivariate model also indicated that total fruit intake during pregnancy, and the neighbourhood crime index, were associated with memory at age three.

The current literature supports the finding that screen time has an effect on early memory development (Hutton et al., 2019). Recent studies have revealed that children between three and five years of age, who used screens beyond the recommended one hour a day, exhibited lower levels of development in the brain's white matter, crucial for literacy, language and cognitive development (Hutton et al., 2019; Stiglic & Viner, 2019). Excessive screen time has also been shown to negatively affect executive function skills (Carter et al., 2016; Tomopoulos et al., 2016) and to increase inattention problems among preschoolers (Tamana et al., 2019).

The results of this study indicated that screen time at three years of age was associated with lower scores on the memory measure, whereas children who watched more than one hour of screen time each day had a drop of almost one point in their NEPSY memory score. On the NEPSY–II sentence repetition scale, the scaled scores range from 1–19 (M = 10, SD = 3). A score of 7 or below on the sentence repetition subtest is considered to be in the clinically significant range. Although a one point decrease is not a large effect, a one point difference may be the difference between a normal (7–12), clinically significant (7 or below) or above average

(13–19) score.

In the current study, none of the sleep variables were associated with memory at age three. This finding is in contrast with the POSTA study, where improvement in long-term memory scores was found following AT (Waters, 2020). Mixed findings have been reported on the association between sleep patterns and cognitive development among children 0–4 years of age (Chaput et al., 2017). Systematic reviews of recent literature on the relationship between cognition and SDB among young children remains inconclusive (da Silva Gusmao Cardoso et al., 2018; Konstantinopoulou & Tapia, 2016; Spruyt, 2019). Given the important role that sleep plays in healthy cognitive development (Nunn et al., 2016; Uehara, 2015), it was surprising that our study did not find any of the sleep variables significant in the multivariate regression analyses. Perhaps our negative finding is a result of our small sample size. Another possible explanation for why objective and subjective measures of sleep did not affect memory could be due to the measure of memory used in our study (sentence repetition on NEPSY–II). It could be that a different measure of memory would yield different results.

Our study found that fruit during pregnancy improves early memory development. Although fruit intake was collected prospectively among pregnant women, it remained significant for children's memory at three years of age. These results corroborate studies in rats (Ward-Flanagan et al., 2020) and fruit flies (Bolduc et al., 2016), supporting biological coherence across model systems. Although the impact is small, the results from this study indicate sustained benefits from gestational fruit consumption on later cognitive development.

The neighbourhood crime index was among the environmental factors that remained significant in multivariate regression models. However, this result is hard to explain, as it is difficult to connect crime in a neighbourhood to an individual's cognitive score. When interpreting

the average crime index, interpretations of data risk being subject to ecological fallacy. It was surprising that other demographic variables such as maternal education, SES and attendance at an outside child-care centre were not associated with memory.

Sex differences were found in our study where girls performed better on the memory task, compared to boys. This finding is supported in other studies that have also found sex to be a significant predictor of memory performance, with girls scoring higher than boys (Haden et al., 2011). In contrast, other studies among slightly older children (six- to eight-year olds) have not found differences in working memory (Leon et al., 2014). Sex-related differences in memory among preschoolers could be attributed to the differences in maturation of certain cerebral structures.

Limitations of the Study

Despite the present study's contribution to advancing research in the area of sleep and memory development, this study has several limitations. The first of these is the fact that it was limited to participants from a healthy cohort of children. This lack of variation within the sample may have had an influence on whether sleep problems or disorders influence memory. Therefore, results from the current study might be applicable to the general population but not to a clinical sample. However, the generalizability of our data should be reconsidered, since the study population was not a representative sample. Observations from visiting the homes of all CHILD Edmonton participants to administer the sleep study at one year of age indicated that most of the mothers who participated in our study were highly educated and from families of high SES.

One major limitation of this study is the absence of objective SDB data at three years of age. Also, it is important to note that our model may not be culturally sensitive, since most of our sample was Caucasian. Therefore, our results may not reflect culturally and societally valued

norms and expectations. It should also be noted that many of the sleep variables were collected via parent-reported questionnaires. Social desirability biases among parents could lead to under- or over-reporting sleep symptoms and behaviours. In addition, children at age three did not provide more detailed information about types of screen time (e.g., tablet, television, videogames).

The CHILD Edmonton study conducted 41 T3 sleep studies at the age of three. Unfortunately, it was very difficult for the children at this age to keep all the leads and equipment on them at home, so the machines came back damaged and the data was very poor. We decided to stop the administration of the T3 sleep studies and move to an easier method of sleep data collection (actigraphy) due to the poor quality of the data collected by this method. Due to the difficulty in administering a home sleep study to three-year-old children, our one-year old T3 sleep data could not be compared to T3 data at age three.

It is difficult to discount completely the effect that sleep might have on memory, based on this one study. Although we did not find any sleep variables that were significant with memory, it is possible that these results could change in later childhood or adolescence. A longitudinal analysis examining the factors associated with early memory development from birth until adolescence might yield more robust results. However, this study does provide support for parents to follow the recommended guidelines on the use of screen time in preschoolers.

The selection of the NEPSY–II sentence repetition subtest as the only memory outcome measure might also be seen as a limitation of the current study. As part of a much larger study (CHILD Edmonton), the time and task demands of incorporating additional memory measures for this study would have been too burdensome for the participants. The strength of this study is that it utilizes a population birth cohort as its sample where we were able to collect objective

measurements of sleep and NEPSY–II data for 500 children. The CHILD study collects a myriad of variables; therefore, it is able to control for numerous potentially confounding variables that could influence the outcome variables. Spruyt (2012) reported that ethnicity or race, SES or such surrogate measures as parental education have been missing from several analyses, whereas CHILD provides insight into these data for all participants enrolled in the study.

Future studies examining screen time in greater depth could better aid in guiding parents and clinicians around their children's engagement with TVs, tablets or smartphones and their impact on sleep quality and memory development. Examining screen time and memory among five-year olds from the CHILD Edmonton cohort study could yield additional insights. Further research might focus on providing a deeper understanding of the effects of sleep on different types of memory, including emotional, procedural or visual memory, and on memory consolidation. In particular, research focused on the dynamics of memory formation through a systematic examination of the changes in memory representation across sleep-dependent consolidation may be warranted. Future studies could focus on elucidating the role of normal sleep on memory consolidation in young children. These results can help determine the outcomes of disrupted sleep in children with sleep disorders and aid in developing subsequent treatment strategies.

Conclusion

The results of this study indicate that SDB is associated with lower memory scores on the NEPSY–II in univariate analysis, albeit not in multivariate analyses. In addition, screen time was reported as a significant predictor of lower scores on memory at age three. The results of the present study are in line with previous studies, in that they support a crucial and positive role of sleep in toddlers in memory development. However, when sleep is examined along with other factors that may impact memory, its role is not as clear. Future research should focus on core

environmental and parental variables, use a combination of subjective measures (sleep diaries & questionnaires) and objective measures (i.e., actigraphy, type 3 sleep monitoring) and adopt a more longitudinal approach to sleep and memory development.

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APPENDIX A: CHILD Edmonton data collection in the first three years

Questionnaires/Samples Collection	During Pregnancy	Birth	Infant's age (months)									
			3	6	9	12	15	18	21	24	30	36
Mother												
Mother's Health	X					X						
Mother's Nutrition	X		X			X						
Mother's Stress	X			X				X		X	X	X
Mother's Psychosocial	X					X						X
SES	X					X						X
Parenting Questionnaire						X				X		X
Skin Prick Test						X						
Spirometry						X						
Global Sleep Assessment Questionnaire (GSAQ)						X						X
Home Environment												
Residential history	X		X			X				X		
Home Environment Questionnaire	X		X	X		X		X		X	X	X
Home Assessment												
Infant bedroom dust sample			X									
Outdoor pollutant exposure (TRAP)			X									
Child												
Hospital birth record		X										
Medication		X	X	X		X		X		X	X	X
Health			X	X	X			X		X	X	X
Nutrition and Diet			X	X		X		X		X	X	X
Skin Prick Test						X						X
Health and weight measurement			X			X						X
BISQ			X	X	X	X	X	X	X	X		
PSQ			X	X	X	X	X	X	X	X	X	X
CSHQ												X
NOX-T3 portable sleep monitor						X						
BSID-III						X				X		
BRIEF-P										X		X
CBCL						X				X		X
Father (if applicable)												
Health	X											
SPT	X											
Spirometry	X											
GSAQ	X											

CHAPTER V

General Discussion

Through the studies described in this dissertation, I have attempted to explore the relationship between SDB and memory function in early childhood. Memory is an integral component of cognition. Healthy brain development enables the maturation of memory functions and plays a critical role in a child's social, emotional and cognitive functioning. Memories form the basis for our sense of self; they influence our emotional responses and guide us as we learn. Early interventions targeting maternal and child health critically impact how children develop into healthy and productive adults (Black et al., 2017). Sleep is an important health factor for children. Healthy sleep will enhance a child's cognitive, behavioural and emotional functioning (Uehara, 2015). Conversely, disrupted sleep, as seen in children with SDB, is associated with cardiovascular, neurocognitive and metabolic morbidity (Gokdemir & Ersu, 2016; Gupta, 2017). Understanding the impact of SDB on cognition during a child's formative years can help in the development of timely interventions.

This thesis has several strengths in helping understand associations between SDB and memory. These strengths include: (1) use of home sleep monitoring device (T3) to provide objective sleep in an ecologically valid environment, (2) use of an objective measure (NEPSY-II) of cognitive performance to examine memory and (3) utilizing data from a large cohort of children, recruited from the general population, for whom repeated longitudinal observations were collected.

Despite the strengths identified above, there were also several limitations identified in this thesis. This research project was not able to determine whether sleep problems or SDB precede memory functioning. Despite objectively assessing both sleep and memory outcomes, the study was not sufficiently powered to examine the effect of persistent SDB on cognition.

Additionally, its findings may not be generalizable since children in this study were more likely to be Caucasian and had higher levels of SES and maternal education (Maghera et al., 2014).

The analysis provided in this dissertation did not find an association between SDB and memory among preschoolers from the CHILD Edmonton cohort. This result was surprising given that the pediatric literature has shown that SDB is related to poor cognitive outcomes (Biggs et al., 2014; Hunter et al., 2016). A possible explanation could be that current available neurocognitive measures (e.g., NEPSY-II) are not sensitive enough to detect memory deficits in preschool children. Another limitation is the fact that our study focused on one aspect of memory (e.g., short-term memory). Studies have shown that cognitive impairments in children with SDB may be dependent on the type of assessment method used (Biggs et al., 2011; Mietchen et al., 2016). Utilizing various memory tasks that differ in degree of difficulty may aid in better explaining how SDB impacts a child's developing memory skills (Allen & Kelly, 2015).

Another limitation was that the CHILD Edmonton study assessed SDB using predominantly subjective measures. The CHILD Edmonton study only assessed sleep via home PSG (T3 sleep monitor) at age one. At age three, participants had their sleep assessed by means of actigraphy and parent reported questionnaires. Although promising research is underway to explore the potential of machine learning to identify sleep states in actigraphy (Hammam et al., 2020), such techniques are not yet available as robust measures in the field. Therefore, the only SDB data the current thesis collected was from a validated subjective sleep questionnaire (PSQ). The use of parent-reported questionnaires to gather data on sleep is subject to recall bias. Subjective reports of sleep tend to indicate more sleep disturbances than objective measures, so parent-reported questionnaires may overestimate actual sleep problems.

The power of the present studies was constrained by limited participant recruitment, data loss in using a portable sleep monitor and lack of consistent criteria in defining SDB. Several challenges were encountered around recruitment for the T3 validation project. It was hard to recruit children that could commit to a three-night sleep study. The research team also encountered difficulties in access to sleep lab resources due to a reduction in the number of sleep studies permitted. As a result, participants who met the inclusion and exclusion criteria for this research project would not be triaged as a "number one" priority for time in the lab. Some studies were excluded from the analysis due to poor quality data. These results are similar to Gudnadottir and colleagues (2019), who also identified poor quality nasal airflow data quality as a common denominator among pediatric sleep studies. Data loss remains an issue among Type 3 monitors (Cairns et al., 2014) which can range from 3–18%.

Another issue in portable sleep monitoring is that the automated scoring module has not been validated for use with children. Most home sleep monitors come equipped with an automated scoring module. Although some researchers have found autoscoring to be valid and reliable (Xu et al., 2017), our research found that autoscoring was not as accurate as manually scored studies. Most studies use different criteria for scoring respiratory events and defining disease severity in children (Tan et al., 2015). We chose to have all the home sleep studies manually scored by experienced sleep technicians. Unfortunately, we had to adapt the AASM Pediatric Guidelines to the available parameters of the portable sleep device to score sleep studies manually.

Clinical Implications

Sleep, whether assessed subjectively or objectively, was not associated with cognitive functioning in the study population. That there was no link between sleep and cognition may

have occurred because the study did not use PSG to assess sleep in children at three years of age. Pietropaoli and colleagues (2015) did not find any severity of SDB to be associated with cognitive impairment among a clinical sample of preschoolers, compared to a control group. These researchers (Pietropaoli et al., 2015) hypothesized that short term exposure to the negative sequelae of SDB in preschool age may not be enough to impair cognitive functioning. These results may be pointing to the need for a study design that does not look at memory at one specific (young) age but rather over time, in a longitudinal approach. Focusing more on sleep architecture as opposed to the total amount of night sleep may help us identify patterns in sleep and memory across a developmental trajectory.

Another aspect that should be considered is “timing of the assessments”. Hunter and colleagues assessed cognitive functioning the morning after sleep was assessed and found cognitive deficits in children with more moderate to severe SDB (Hunter et al., 2016). The size of the CHILD study precluded the temporal assessment of sleep and neurodevelopment. If the timing of the objective sleep studies were set in tandem with neurocognitive testing, perhaps researchers could assess whether fatigue and other sleep factors were responsible for memory results.

My findings indicated that the T3 sleep device is able to identify children with severe and mild SDB. Meanwhile, a full lab-PSG remains the gold standard (Aurora et al., 2011; Cortese et al., 2014; El Shakankiry, 2011) in the field for diagnosing SDB. These results are congruent with previous studies, which showed that a laboratory PSG is likely still required to diagnose children experiencing intermediate or moderate SDB. The T3 sleep monitor can be an alternative for children with suspected SDB to use, instead of an in-lab PSG.

Focusing on reducing screen-time, rather than trying to change children's sleep behaviour, may be more effective in improving cognitive development. Sleep disorders, language delays, impaired executive function and lower levels of parent-child engagement correlated with excessive screen use (Carter et al., 2016; Tomopoulos et al., 2010). Children who used smartphones for more than one hour a day had reduced total sleep, increased problems with bedtime resistance, sleep anxiety, nocturnal awakening and sleep latency compared to controls (Kim et al., 2019). Furthermore, researchers from the CHILD birth cohort study found that increased screen time (more than two hours per day) among preschoolers was associated with more inattention problems compared to children with less than two hours of screen time per day (Tamana et al., 2019). Future research could include longitudinal studies of early screen-time exposure and later mental health outcomes.

Clinicians can utilize this evidence-based research to support and guide parents in setting appropriate boundaries around daily screen use. It will be important for clinicians to know what types of screen time (e.g., tablet, TV, phone, games, educational programming, virtual learning) have the most significant impact on sleep outcomes and memory. More detailed, focused interventions vis-à-vis screen use may be conducted. Implementation of appropriate boundaries around screen time at an early age can help to reduce future behavioural concerns. Providing young children with alternative activity choices can, I hope, lead to improvement in cognitive development and quality of life. Given the widespread use of screens in the classroom environment (e.g., tablets, Chromebooks, smart boards), screen use in that setting also needs to be considered. Teachers and educators will benefit from knowing whether the use of screens in a classroom setting or virtual learning environment is always associated with effective learning.

Children's ongoing and still unresolved sleep problems have a compounding effect on the functioning of the child within the family. Night waking sometimes leads to exhaustion, parental depression, marital issues and the overall deterioration of parent-child relationships (Blackham et al., 2019). Having a better understanding of sleep difficulty will aid psychologists and mental health professionals in the development and implementation of better behavioural sleep interventions. A structural equation model that investigates the relationship between factors related to sleep and memory may contribute to deeper understanding in this area of research.

Future Directions

Further investigation on the impact of screen time and sex on memory outcomes among preschool children is needed. Future research on the association between sex and memory among young children can help elucidate this relationship. Males tend to lag behind females in cognitive developmental at early ages, however these differences may not be as significant later in life. Research on interventions that target sex differences in the memory functioning of preschoolers may help to enhance the future development of these skills. Future research on parents' media use is warranted, as it is a strong predictor of children's media habits. Therefore, reducing parent media use and enhancing parent-child interactions can be an important area to focus on that can ultimately affect cognitive development.

Additionally, researchers have investigated alternative forms of SDB diagnosis. A systematic review and meta-analysis indicated that the identification of four urinary proteins can be used as a biomarker to diagnose SDB in children (De Luca Canto et al., 2015). Future research employing machine learning classification to identify sleep states of accelerometer-assessed sleep duration can also be used to diagnose and manage children with SDB (Hammam et al., 2020).

Future studies measuring other aspects of memory (e.g., long-term, working, visual and verbal memory), along with short-term memory, could yield a more comprehensive assessment of preschoolers' memory functioning. SDB was negatively related to academic performance for academic domains related to language arts and science but not to general school performance (Galland et al., 2015). Given these results, children who present with learning difficulties may benefit from being screened for SDB. The earlier SDB and learning issues are identified, the earlier interventions can be put in place to avoid or mitigate long term consequences.

Conclusion

This dissertation makes a significant contribution to the literature examining memory and sleep in young children. The overall investigation has a number of strengths, including (1) the use of a home sleep monitoring device (T3) to provide objective sleep measures in an ecologically valid environment, (2) the use of an objective measure of cognitive performance (NEPSY–II) to examine memory and (3) being one of the few studies to examine objectively the role of memory and sleep in a large birth cohort of children with typical development.

Through this body of research, the research team was able to demonstrate the validity and reliability of a home sleep monitoring device among children. However, replicating our study with a larger sample could help to support the widespread use of this device for assessing and diagnosing SDB. Our findings also demonstrated that female sex, screen time, maternal fruit intake and neighbourhood crime index were the predictors that best explained the primary outcome measure (NEPSY–II sentence repetition). The CHILD Edmonton study collected observational data; replicating these results in other model systems is needed to better understanding their association. This dissertation highlights the importance of a large sample size and generalizability of data in research. I hope these findings will contribute to advancing the

field by identifying important future directions for continued exploration of SDB and memory in early childhood.

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