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Sleep and Neurobehavioral Outcomes in Children with Fetal Alcohol Spectrum Disorders

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of

Philosophy

in

Clinical Psychology

by

Sarah M. Inkelis

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2021

The Dissertation of Sarah M. Inkelis is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California San Diego

San Diego State University

2021

DEDICATION

To my parents: Thank you for your unwavering support and unconditional love. Your confidence

in me has allowed me to grow in more ways than I could have ever imagined.

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ACKNOWLEDGEMENTS

Chapters I, II, III, and IV, in part, are currently being prepared for submission for publication of the material. Inkelis, S. M.; Chambers, C.; Mattson, S. N.; Bhattacharjee, R.; Thomas, J. D. The dissertation author was the primary investigator and author of this material.

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ABSTRACT OF THE DISSERTATION

Sleep and Neurobehavioral Outcomes in Children with Fetal Alcohol Spectrum Disorders

by

Sarah M. Inkelis

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2021
San Diego State University, 2021

Professor Jennifer D. Thomas, Chair

The effects of prenatal alcohol exposure on sleep quality have been understudied, and the possibility that sleep disturbances contribute to deficits in other domains has not been explored. The current study aimed to characterize sleep quality in children with fetal alcohol spectrum disorders (FASD) and understand relationships with neurobehavioral functioning.

Participants aged 6-10 years with (alcohol-exposed [AE] = 27) and without (control [CON] = 27) prenatal alcohol exposure were included in the study. Objective sleep was measured via 24-hour actigraphy for two weeks. Parents completed sleep diaries and sleep

questionnaires (Children's Sleep Habits Questionnaire, Pediatric Sleep Questionnaire). Children completed neuropsychological testing (NIH Toolbox Cognition Battery) and parents completed the Child Behavior Checklist (CBCL) and Behavior Rating Inventory of Executive Functioning – Second Edition (BRIEF-2) as measures of problem behaviors and executive functioning skills. For a subset of participants (n = 31), neuropsychological assessment was modified and conducted remotely due to COVID-19. Multivariate analysis of variance was used to characterize the sleep profile (objective, subjective) and examine group differences. Multiple regression examined the relationships between sleep quality and neurobehavioral performance.

There were no group differences on actigraphy metrics averaged across two weeks; however, AE showed significantly greater intraindividual variability on most actigraphy measures, particularly total sleep time. Parents reported significantly more sleep problems in AE than CON, primarily driven by sleep onset delay, night wakings, and daytime sleepiness. AE performed significantly lower than CON on the subset of cognitive measures administered to the full sample. CBCL and BRIEF-2 scores were significantly higher for AE compared to CON, reflecting more behavioral and executive functioning problems. Greater sleep time variability was significantly correlated with poorer memory performance and more behavior problems, but did not moderate effects of group. There were no significant differences between the pre-COVID and COVID samples.

Despite similar two-week average sleep outcomes, children with FASD showed greater intraindividual sleep variability and parents reported more sleep problems. Across the sample, greater sleep time variability was associated with poorer episodic memory and more behavior problems. Interventions targeting variability in sleep, particularly sleep duration variability, may improve sleep quality and some aspects of cognition and behavior in children with FASD.

I.   INTRODUCTION

Background and Literature Review

Alcohol use during pregnancy is one of the leading preventable causes of neurodevelopmental disorders (American Academy of Pediatrics, 2000). Children with prenatal alcohol exposure suffer from a multitude of problems, including maladaptive behavioral characteristics, cognitive impairments, and physical abnormalities (Mattson, Crocker, & Nguyen, 2011) that impact quality of life and often persist into adulthood (Spohr, Willms, & Steinhausen, 2007). Fetal alcohol spectrum disorders (FASD) is a non-diagnostic term that encompasses the full range of the effects of prenatal alcohol exposure, and is conservatively estimated to affect 11.3 to 50.0 per 1000 children in the United States, although the prevalence may be as high as 98.5 per 1000 children (May et al., 2018). Fetal alcohol syndrome (FAS), one of the most severe outcomes of prenatal alcohol exposure, is characterized by prenatal-onset growth deficiency, craniofacial dysmorphology, and central nervous system dysfunction (Jones & Smith, 1975). Approximately 6.7 per 1000 individuals meet criteria for FAS (Roozen et al., 2016); however, the majority of persons affected by developmental exposure to alcohol do not have the facial abnormalities required for this diagnosis. Nonetheless, exposure to alcohol *in utero* profoundly affects neurodevelopment and, subsequently, cognitive and behavioral outcomes (Donald et al., 2015). These impairments are associated with adaptive dysfunction, academic difficulties, and psychopathology, which have significant repercussions across the lifespan for the individual, their caregivers, and society at large.

Despite these potential consequences, a considerable percentage of women in the U.S. report consuming alcohol during pregnancy, with 10.2% reporting any alcohol use and 3.1% reporting binge drinking in the past 30 days (Tan, Denny, Cheal, Sniezek, & Kanny, 2015),

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making prenatal alcohol exposure an important public health concern. To this end, research efforts have focused on characterizing the neurobehavioral profile of FASD to aid in understanding the consequences of prenatal alcohol exposure, increase the potential to identify these individuals, and develop targeted interventions.

Neurobehavioral Impact of Prenatal Alcohol Exposure

The potential outcomes of prenatal alcohol exposure are wide-ranging, and are affected by a multitude of factors, including amount, timing, and pattern (e.g., binge drinking, versus chronic) of alcohol use during pregnancy, as well as genetic vulnerability (Ungerer, Knezovich, & Ramsay, 2013). Most notably, alcohol exposure in utero affects growth and differentiation of the fetal brain (Ungerer et al., 2013), resulting in both global and specific structural and functional neurological abnormalities. Neuroimaging studies consistently report that individuals with FASD have smaller brain volumes overall, compared to typically developing controls (Lebel, Roussotte, & Sowell, 2011; Moore, Migliorini, Infante, & Riley, 2014). Furthermore, the cerebral cortex, cerebellum, corpus callosum, basal ganglia, and hippocampus tend to be smaller and/or exhibit structural abnormalities, relative to controls with no exposure history (Bookstein, Sampson, Connor, & Streissguth, 2002; Lebel et al., 2011; Mattson, Riley, Sowell, et al., 1996; Moore et al., 2014; Norman, Crocker, Mattson, & Riley, 2009). Atypical white matter microstructure is another common finding, particularly in the corpus callosum, major anterior-posterior fiber bundles, corticospinal tracts, and cerebellum (Moore et al., 2014; Wozniak & Muetzel, 2011). These brain abnormalities underlie both global and specific cognitive and behavioral deficits, and functional neuroimaging studies consistently show that individuals with prenatal alcohol exposure demonstrate differential activation of the frontal regions, relative to controls (Coles & Li, 2011; Moore et al., 2014). In particular, prenatal alcohol exposure is

associated with different levels of activation on tasks involving response inhibition (Fryer, Tapert, et al., 2007; O'Brien et al., 2013), working memory (Astley et al., 2009; Malisza et al., 2005; Malisza et al., 2012; Norman et al., 2013; O'Hare et al., 2009; Spadoni et al., 2009), arithmetic and number processing (Meintjes et al., 2010; Santhanam, Li, Hu, Lynch, & Coles, 2009), and verbal learning (Sowell et al., 2007).

Diminished general intelligence is commonly found in individuals with FASD, although even among those with FAS, most children affected by prenatal alcohol exposure are not intellectually disabled (i.e., IQ score <70, plus adaptive disability) (Mattson et al., 2011). More specifically, individuals with FASD tend to have deficits in learning and memory, executive function, attention, visuospatial skills, and delayed development of motor and language skills (Mattson et al., 2011).

Prenatal alcohol exposure is associated with deficits in learning and recall of both verbal and nonverbal information. Children with FASD demonstrate a consistent pattern of difficulty learning new verbal information, but have spared retention rates for the material that they do encode (Crocker, Vaurio, Riley, & Mattson, 2011; Mattson, Riley, Delis, Stern, & Jones, 1996; Mattson & Roebuck, 2002). Importantly, these verbal learning deficits persist even after controlling for IQ (Coles et al., 2010), and when compared to IQ-matched controls (Mattson, Riley, Delis, et al., 1996). However, for tasks assessing learning and memory of nonverbal information, children with heavy prenatal alcohol exposure do not retain as much nonverbal information as controls, even when accounting for initial level of encoding (Mattson & Roebuck, 2002). After controlling for IQ, visual learning and recall deficits also persist (Coles et al., 2010). Furthermore, children with FASD demonstrate deficits in auditory and spatial memory, as well as memory for designs and stories (Mattson et al., 2011). Learning and memory impairments

such as these can have a considerable impact on academic performance, and affected children are often diagnosed with specific learning disability (Coles et al., 1991).

Research regarding visual-spatial abilities in FASD has been more limited, but multiple studies have found that exposed children are impaired on tasks of simple visual-spatial construction (Aronson & Hagberg, 1998; Chiodo et al., 2009; Conry, 1990; Janzen, Nanson, & Block, 1995; Jirikowic, Olson, & Kartin, 2008; Mattson & Riley, 1998). Affected children also have difficulty processing local features (i.e., small details of a design) relative to global features (i.e., gestalt of design) (Mattson, Gramling, Delis, Jones, & Riley, 1996), suggesting that they may process visual information in a different manner, compared to controls.

Executive functioning difficulties are also common in children affected by prenatal alcohol exposure. Executive functioning encompasses many cognitive processes, including planning, organization, inhibition, working memory, set shifting, cognitive flexibility, and fluency, and deficits in these areas have been demonstrated in multiple studies of children with FASD (Kodituwakku & Kodituwakku, 2014; Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Mattson et al., 2011; Mattson, Goodman, Caine, Delis, & Riley, 1999). These abilities are associated with the frontal-subcortical circuits connecting the frontal lobes to the basal ganglia and thalamic nuclei (Cummings, 1993). The basal ganglia and frontal cortex are structurally vulnerable to prenatal alcohol exposure (Mattson, Riley, Sowell, et al., 1996; Sowell et al., 2002), and functionally, these circuits demonstrate altered activation during tasks of executive functioning in children with FASD (Fryer, Tapert, et al., 2007). On traditional neuropsychological measures, children with prenatal alcohol exposure demonstrate impairment on measures of response inhibition, problem solving, planning, fluency, cognitive flexibility, and working memory (Mattson et al., 2011; Nguyen et al., 2014). Parents of children with FASD also

endorse behavior problems related to executive functioning, and their ratings can distinguish alcohol-exposed children from non-exposed children with attention-deficit/hyperactivity disorder (ADHD) (Nguyen et al., 2014). In the day-to-day lives of these individuals, impairment in executive functioning may present as poor judgment, planning, and problem solving, as well as failure to anticipate consequences, and a disinhibited, disruptive behavioral profile (Fryer, Tapert, et al., 2007).

Attention deficits are considered a hallmark feature of the neurobehavioral profile of prenatal alcohol exposure (Mattson et al., 2011), and affected children have particular difficulty on tasks of vigilance, reaction time, and information processing (Burden, Jacobson, & Jacobson, 2005; Jacobson, Jacobson, & Sokol, 1994; Jacobson, Jacobson, Sokol, Martier, & Ager, 1993; Nanson & Hiscock, 1990; Streissguth et al., 1986; Streissguth et al., 1994). On objective measures of attention, such as continuous performance tasks, children with FASD demonstrate less accurate responding, more omission errors, greater variability in response time, and longer response latencies (Infante et al., 2015; Streissguth et al., 1994). However, alcohol-exposed individuals have an auditory attention span within normal limits at shorter time intervals, whereas visual attention is impaired regardless of interval length (Mattson, Calarco, & Lang, 2006). Clinically, these impairments may present as trouble with inhibiting impulsive responses, and difficulty organizing and maintaining attention for an extended period of time (Nanson & Hiscock, 1990). Furthermore, children with FASD exhibit many symptoms that overlap with ADHD, and an estimated 60% of alcohol-exposed children have a comorbid diagnosis of ADHD (Bhatara, Loudenberg, & Ellis, 2006; Burd, Klug, Martsolf, & Kerbeshian, 2003; D'Onofrio et al., 2007; Fryer, McGee, Matt, Riley, & Mattson, 2007). However, research suggests that the pattern of attention deficits seen in individuals with prenatal alcohol exposure may be unique,

characterized by greater difficulties shifting attention, encoding information, and flexibility in problem solving (Coles et al., 1997; Mattson et al., 2011).

Difficulties on tasks of motor function were described in the early reports of fetal alcohol syndrome, particularly poor hand-eye coordination, tremors, weak grasp, and balance and gait abnormalities (Jones & Smith, 1973). Considering that the cerebellum and basal ganglia are especially sensitive to the teratogenic effects of alcohol, it is not surprising that individuals with FASD have also been found to have deficits in fine and gross motor abilities, such as postural instability (Roebuck, Simmons, Richardson, Mattson, & Riley, 1998), delayed reaction time (Green et al., 2009; Simmons, Thomas, Levy, & Riley, 2010; Wass, Simmons, Thomas, & Riley, 2002), and sensory processing (Jirikowic et al., 2008).

Language skills are another area in which children with FASD demonstrate impairment (Mattson et al., 2011). Studies of language functioning have shown that affected children have difficulty with word comprehension (Conry, 1990; Mattson, Riley, Gramling, Delis, & Jones, 1998), naming (Mattson et al., 1998), articulation (Becker, Warr-Leeper, & Leeper, 1990), grammar and semantics (M. Becker et al., 1990), pragmatics (Abkarian, 1992), and receptive and expressive language skills (Aragon et al., 2008; Carney & Chermak, 1991; Janzen et al., 1995; McGee, Bjorkquist, Riley, & Mattson, 2009). These impairments likely underlie the struggles children with FASD demonstrate in using language to communicate effectively and navigate social situations (Coggins, Olswang, Carmichael Olson, & Timler, 2003), and contribute to deficits in adaptive functioning in the domains of communication and social skills (Crocker, Vaurio, Riley, & Mattson, 2009).

In addition, children with prenatal alcohol exposure also have higher rates of behavioral problems and emotional disturbance. These problems include difficulty with mood regulation,

which can manifest as increased internalizing and externalizing symptoms, negative affect, and conduct problems. Ultimately, alcohol-exposed children are at a greater risk of developing psychiatric disorders, particularly ADHD, major depressive disorder, oppositional defiant disorder, and conduct disorder (Burd et al., 2003; D'Onofrio et al., 2007; Disney, Iacono, McGue, Tully, & Legrand, 2008; Fryer, McGee, et al., 2007; O'Connor & Paley, 2006; Steinhausen & Spohr, 1998; Ware et al., 2013). Trouble with behavioral and emotional regulation often has secondary consequences, creating difficulties in academic, employment, and independent living situations, as well as increased incidence of substance abuse, trouble with the law, inappropriate sexual behavior, and confinement (Streissguth et al., 2004).

In the United States, the Centers for Disease Control and Prevention estimated the cost of one individual with FAS to be $2 million in 2002 (Lupton, Burd, & Harwood, 2004). More recently, these costs have been estimated in Canada: losses in productivity due to disability and premature mortality, law enforcement/corrections, and healthcare services comprise the majority of FASD-attributable costs, with the financial burden of individuals with FASD conservatively estimated to be $1.8 billion in 2013 (Popova, Lange, Burd, & Rehm, 2016). These estimates point to the need for continued research efforts to support and improve the lives of individuals with FASD and their caregivers.

Introduction to the Current Study

Caregivers of children with FASD commonly report that their child has sleep problems (Wengel, Hanlon-Dearman, & Fjeldsted, 2011), though little research has been done to characterize these sleep disturbances and their consequences (Ipsiroglu, McKellin, Carey, & Loock, 2013). Prevalence rates for pediatric sleep disorders in the general population are estimated to be between 28 and 36% (Meltzer, Plaufcan, Thomas, & Mindell, 2014), though the rate of this problem in children with prenatal alcohol exposure is unknown. Sleep is important to early neurodevelopment, and on average, children spend more time asleep during the first five years of life than in all other waking activities combined (Dahl, 1996). Similar to adults, children exhibit two types of sleep that cycle multiple times throughout the night: rapid eye movement (REM) sleep, and non-REM (NREM) sleep. NREM sleep is further divided into three different stages (i.e., N1, N2, N3). These stages are defined by measures of brain activity, eye movements, and muscle tone, and are obtained via polysomnography (see Table 1) (Iber, Ancoli-Israel, Chessonn, & Quan, 2007; Inkelis & Thomas, 2018).

Table 1. Electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), and respiratory characteristics of each sleep stage, as defined by the American Academy of Sleep Medicine (Iber et al., 2007; Inkelis & Thomas, 2018).

Stage	Brain Activity	Eye Movements (EOG)	Muscle Tone (EMG)	Breathing
Wakefulness	Alpha rhythm (8-13 Hz)	Eye blinks Reading/rapid eye movements	Normal or high chin muscle tone	
NREM				
N1	Low amplitude (4-7 Hz) Vertex sharp waves Hypnagogic hypersynchrony (bursts of 3-4.5 Hz)	Slow, conjugate, regular, sinusoidal eye movements	Normal chin muscle tone Few body movements	Regular, rhythmic
N2	Low amplitude, mixed frequency EEG K-complexes (well-delineated negative sharp wave) Sleep spindles (bursts of 11-16 Hz waves)	No or slow eye movements	Variable, can be very low	Regular, rhythmic
N3	Slow wave (0.5-2 Hz), large amplitude	Typically none	Variable, can be very low	Regular, rhythmic
REM	Low amplitude, mixed frequency EEG Triangular, serrated, "sawtooth" waves (2-6 Hz)	Rapid eye movements: conjugate, irregular, sharply peaked, <500 msec	Lowest of any sleep stage Short, irregular bursts of muscle activity <0.25 sec	Irregular

Maternal alcohol intake disrupts fetal sleep-wake cycles and breathing movements as early as week 37 of gestation (Mulder, Morssink, van der Schee, & Visser, 1998), and is also associated with sleep fragmentation (i.e., brief awakenings that occur during sleep) in infants (Troese et al., 2008). Most published studies have described sleep and circadian disturbances in infants with FASD, demonstrating that those exposed to alcohol prenatally exhibit more sleep problems, disrupted sleep state cycle length, and abnormal EEG patterns (Inkelis & Thomas, 2018; Scher, Richardson, & Day, 2000). Although data are limited, caregivers of children with FASD continue to report sleep problems beyond infancy (Wengel et al., 2011), including

problems with falling asleep, sleep duration, night wakings, bedtime resistance, sleep anxiety, and parasomnias (i.e., bedwetting, sleep talking, and night terrors) (Rzepecka, McKenzie, McClure, & Murphy, 2011), compared to controls (Chen et al., 2012; Wengel et al., 2011). Objective data obtained from limited ($n = 5$, $n = 19$, and $n = 36$, respectively; Chen et al., 2012; Dylag et al., 2021; Goril et al., 2016). Polysomnography studies indicate children with FASD have increased sleep fragmentation, mild sleep disordered breathing and greater frequency of central apneic events, and abnormal melatonin secretion (Chen et al., 2012; Dylag et al., 2021; Goril, Zalai, Scott, & Shapiro, 2016). Prenatal alcohol exposure is also associated with significantly longer sleep onset latency and shorter sleep duration, as measured by actigraphy (Pesonen et al., 2009; Wengel et al., 2011). Moreover, animal models show that alcohol exposure *in utero* disrupts sleep-wake behavior and negatively affects circadian rhythm (Earnest, Chen, & West, 2001; Hilakivi, 1986; Sakata-Haga et al., 2006; Wengel et al., 2011), suggesting that altered circadian rhythmicity and sleep disruption are a primary consequence of developmental alcohol exposure.

Sleep and Neurobehavioral Function

Sleep disturbance is related to poorer performance in domains that reflect functioning of the prefrontal cortex, and is also associated with hyperactive behaviors and mood disturbances. These cognitive and behavioral problems mirror many of the neurobehavioral characteristics associated with prenatal alcohol exposure, such as poor executive functioning, inattention, and behavioral and mood dysregulation. Sleep fragmentation in particular, which reduces time spent in the deeper, restorative stages of sleep (Sadeh, Gruber, & Raviv, 2002), is associated with increased daytime sleepiness and a pattern of cognitive deficits consistent with dysfunction of the prefrontal cortex (Beebe, 2006; Gozal, O'Brien, & Row, 2004; Kheirandish & Gozal, 2006).

In adults, psychomotor performance and cognitive function, particularly domains related to executive functioning (e.g., planning, monitoring, and self-regulation) (O'Brien et al., 2004), show impairment following sleep fragmentation (Stepanski, 2002). Studies of children with sleep fragmented by disordered breathing consistently demonstrate emotional dysregulation, hyperactivity, rebelliousness, aggression, and poor performance on tests of attention (Ali, Pitson, & Stradling, 1994; Ali, Pitson, & Stradling, 1993; Beebe, 2006; Beebe et al., 2004; Chervin et al., 2002; Ferreira et al., 2000; Melendres, Lutz, Rubin, & Marcus, 2004; Rosen et al., 2004; Smedje, Broman, & Hetta, 1999; Urschitz et al., 2003; Weissbluth, Davis, Poncher, & Reiff, 1983). Compared to controls, children with sleep disordered breathing also demonstrate significantly lower scores on measures of overall cognitive ability and non-verbal ability, as well as measures of executive function. Phonological awareness, a skill that is key to learning how to read, is also negatively impacted (O'Brien et al., 2004). Chronic moderate sleep deprivation in adults results in impaired working memory performance (Van Dongen, Maislin, Mullington, & Dinges, 2003), though findings in children are mixed (Beebe, 2006). Thus, the extant literature supports that sleep disruptions are related to alterations in cognitive performance.

It has also been suggested that sleep disturbances diminish an individual's ability to regulate emotion and behavior (Dahl, 1996; Wolfson & Carskadon, 1998). In children, sleep-related impairment is often acted out rather than expressed verbally, and can take the form of hyperactivity, impulsivity, or increased aggression (Owens, 2009b). Not surprisingly, poor sleepers have a greater prevalence of behavior problems, as measured by the Child Behavior Checklist (CBCL) (Achenbach & Ruffle, 2000; Sadeh et al., 2002). Children who snore (and thus, are more likely to have sleep disordered breathing and fragmented sleep) are more likely to be hyperactive and inattentive; conversely, sleep disordered breathing is more likely in children

with hyperactive behaviors (Kheirandish & Gozal, 2006). However, following adenotonsillectomy surgery for sleep disordered breathing, these behaviors tend to improve (Ali, Pitson, & Stradling, 1996). Furthermore, insomnia is a core symptom of depression, and sleep fragmentation is also associated with changes in mood, particularly increased negative mood and feeling more depressed (Stepanski, 2002). Additionally, sleep problems in early childhood are predictive of early onset alcohol, marijuana, and other drug use (Wong, Brower, Fitzgerald, & Zucker, 2004).

Clinical Impact of Sleep Disorders in Neurodevelopmental Populations

Sleep disturbance has been reported to be as high as 86% in children with neurodevelopmental disorders, such as autism spectrum disorder (ASD), Down syndrome, and ADHD (Robinson-Shelton & Malow, 2016). The most common sleep problem in children with ASD is insomnia, characterized by increased sleep onset latency, sleep fragmentation, shorter sleep duration, and low sleep efficiency (Robinson-Shelton & Malow, 2016). Children with ASD and sleep disruption demonstrate more affective problems, stereotypic behaviors, and social skills deficits, compared to children with ASD who sleep well (Malow et al., 2006; Richdale & Schreck, 2009). Children with Down Syndrome and obstructive sleep apnea perform worse on cognitive flexibility tasks (Breslin et al., 2014), have reduced visuo-perceptual skills (Andreou, Galanopoulou, Gourgoulianis, Karapetsas, & Molyvdas, 2002), and greater likelihood of disruptive school behavior, compared to children with Down Syndrome who do not snore (Carskadon, Pueschel, & Millman, 1993). There is often frequent overlap between sleep disorder symptoms and ADHD symptoms (e.g., inattention, impulsivity, hyperactivity), though children with ADHD have highly variable sleep/wake patterns (Owens, 2009a). Clinicians agree that children with ADHD should be regularly evaluated for sleep problems to best tailor treatment

planning (Konofal, Lecendreux, & Cortese, 2010; Owens, 2009a), as successful treatment of sleep disordered breathing in children can greatly improve attention (Konstantinopoulou & Tapia, 2016).

It is possible that sleep problems may also contribute to or exacerbate the effects of prenatal alcohol exposure on cognition, behavior, and health. Sleep difficulties are related to neurobehavioral deficits that are consistent with dysfunction of the prefrontal cortex, as well as hyperactive behaviors and mood disturbances (Gozal et al., 2004; Kheirandish & Gozal, 2006), all of which are also prevalent in children with FASD. Moreover, lack of sleep is also associated with obesity, cardiovascular disease, stress, and inflammation (Mullington et al., 2009). As noted, in children with neurodevelopmental disabilities, the effects of sleep disruption are more severe (Ingrassia & Turk, 2005), suggesting that sleep disturbance may exacerbate behavioral problems. Furthermore, the effectiveness of interventions delivered to individuals with FASD may be markedly reduced when sleep disturbance is present (Jan et al., 2010). The prevalence of sleep disturbance in the FASD population is still unknown, but its effects have the potential to be wide-ranging. Therefore, elucidating the characteristics of sleep problems in these individuals may be critically important to further understanding factors that influence executive dysfunction, inattention, and other behavioral problems in FASD.

Many of the symptoms of sleep deprivation manifest in behavioral patterns seen in those of FASD, particularly inattention and mood disturbance (Chervin, Hedger, Dillon, & Pituch, 2000; Mattson et al., 2011). Furthermore, the effects of sleep disturbance are more severe in children with neurodevelopmental disorders (Ingrassia & Turk, 2005), and sleep disturbances may exacerbate existing behavioral and cognitive impairments associated with prenatal alcohol exposure (Kheirandish & Gozal, 2006; Pesonen et al., 2009; Volgin & Kubin, 2012). For

example, one study of sleep and anxiety in children with FASD found that sleep problems were associated with greater levels of anxiety, based on parent-report measures (Mughal, Joyce, Hill, & Dimitriou, 2020). Unfortunately, sleep disorders often go undiagnosed and untreated in children with FASD (Ipsiroglu et al., 2013). This has resulted in an over-reliance on pharmaceutical interventions in patients with FASD, particularly for treatment of ADHD, without formal assessment of sleep disorder as a potential alternative etiology (Ipsiroglu et al., 2013). This study aims to identify patterns of sleep disturbance in children with FASD, and investigate how such disturbances relate to cognitive and behavioral deficits. Findings from this study will characterize sleep quality in children with FASD and elucidate its potential relationship to neurobehavioral deficits. This clinically valuable information will lay the groundwork for future interventions to improve sleep in this population, which has the potential to improve quality of life in affected individuals. Moreover, if primary disturbances in sleep contribute to or exacerbate deficits in other domains, then interventions that target sleep problems may impact performance in other domains as well.

Purpose and Specific Aims

A small number of studies indicate that individuals with prenatal alcohol exposure have fragmented sleep, increased levels of arousal during sleep, mild sleep disordered breathing, and melatonin secretion abnormalities (Chen et al., 2012; Goril et al., 2016; Wengel et al., 2011). In typically developing children and children with other neurodevelopmental disorders, such sleep disturbance is associated with neurocognitive deficits and increased behavior problems. However, the relationship between sleep quality and neurobehavioral functioning in FASD has yet to be investigated. Children with FASD may exhibit a pattern of neurobehavioral deficits that are related to sleep quality; consequently, this information could point to alternative avenues of intervention, specifically those targeted at improving sleep. This study aims to characterize the FASD profile of sleep and elucidate potential relationships between sleep quality and neurobehavioral measures. Ultimately, the knowledge gained from this study will help to identify additional targets for treatment in children with FASD.

Aim 1: Characterize sleep quality in children with FASD and compare the sleep profile to that of typically developing controls.

Sleep was objectively evaluated for a two-week period in children aged 6-10 years using actigraphy (Philips Respironics Actiwatch-2). Parents/caregivers completed a sleep diary to corroborate these data, as well as subjective caregiver-report questionnaires about their child's sleep (Children's Sleep Habits Questionnaire [CSHQ](Owens, Spirito, & McGuinn, 2000); Pediatric Sleep Questionnaire [PSQ] (Chervin et al., 2000)).

Hypothesis 1a. Children with FASD will demonstrate greater objective sleep disturbance (less total sleep time, more sleep fragmentation), compared to controls.

Hypothesis 1b. Subjective parent-reported data will show elevations on measures of bedtime resistance, sleep duration, sleep anxiety, night awakenings, parasomnias, sleepiness, and behavior in the FASD group compared to controls.

Aim 2: Determine the relationship between sleep quality and neurobehavioral outcome.

Subjects were administered the NIH Toolbox Cognition Battery (Gershon et al., 2013) and Quotient™ ADHD System (Teicher, Ito, Glod, & Barber, 1996) to determine how sleep is related to cognitive function in the domains of executive functioning, memory, attention, language, and processing speed. To assess behavior, parents/caregivers completed the Child Behavior Checklist (CBCL) (Achenbach & Ruffle, 2000). Parents/caregivers also completed the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) (Gioia, Isquith, Guy, & Kenworthy, 2000) as a measure of their child's executive functioning.

Hypothesis 2a. Children with FASD will perform worse on objective measures of executive functioning, memory, attention, language, and processing speed. On parent report measures, the FASD group will demonstrate greater executive functioning problems and behavior problems, compared to controls.

Hypothesis 2b. There will be a significant relationship between Sleep Quality (operationalized as total sleep time) and objective measures of executive functioning, attention, and memory, as well as caregiver-report measures of executive functioning (i.e., BRIEF Global Executive Composite) and problem behaviors (i.e., CBCL Internalizing Problems, Externalizing Problems). There will be no association between Sleep Quality and receptive language ability. Furthermore, there will be a significant Group x Sleep Quality interaction, in which FASD individuals will demonstrate a stronger relationship between Sleep Quality and performance on

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objective measures of executive functioning, attention, and memory, as well as caregiver-report measures of executive functioning and problem behaviors.

Hypothesis 2c. Sleep Quality will mediate the relationship between Group and objective measures of executive functioning, attention, and memory, and caregiver-report measures of executive functioning and problem behaviors. This is a strictly exploratory hypothesis, support for which would not be used to define a causal relationship among variables.

Chapter I, in part, is currently being prepared for submission for publication of the material. Inkelis, S. M.; Chambers, C.; Mattson, S. N.; Bhattacharjee, R.; Thomas, J. D. The dissertation author was the primary investigator and author of this material.

II.   METHODS

Preliminary Studies

Previous studies through the Center for Behavioral Teratology and Collaborative Initiative on FASD (CIFASD) have gathered a variety of neurobehavioral data, though few measures have examined sleep. In a small survey ($n = 22$) using a simple sleep screening tool (BEARS) (Owens & Dalzell, 2005) at the Rady Children's Hospital-San Diego Dysmorphology Clinic, 77% of prenatally alcohol-exposed children ages 2 to 12 screened positive for a sleep problem (**Table 2**). Examination of the Sleep Problems subscale of the Child Behavior Checklist (CBCL) in the current CIFASD-III cohort indicates that sleep disturbances are more commonly ($p < .001$) reported among 5-year-olds with FASD ($n = 26$) compared to controls ($n = 44$). Elevations in Sleep Problems scores were also significantly correlated with increased internalizing, externalizing, attention, and executive function problems (measured by CBCL (Achenbach & Ruffle, 2000), Conners 3 (Conners, 2008), BRIEF-2 (Gioia et al., 2000), but were not predictive of general cognitive ability, as measured by DAS-II (Elliott, 2007; Inkelis et al., 2017). Although the CBCL is limited (only 7 sleep items concerning sleep), these data provide evidence of greater likelihood of sleep problems among individuals with FASD.

Table 2. Percentage of children with FASD who screened positive in each Sleep Problem domain of the BEARS survey.

BEARS Domain	Percentage ($n = 22$)
Bedtime Problems	63
Excessive Daytime Sleepiness	40
Awakenings During the Night	63
Regularity and Duration of Sleep	23
Snoring	18

General Methods for Current Study

The proposed study had two primary goals: (1) characterize sleep disturbance in children with FASD; and (2) examine the relationships between sleep parameters and various cognitive and behavioral measures to determine how sleep is associated with neurobehavioral functioning. Subjects ($N = 54$) completed two visits, two weeks apart. The second visit consisted of one, 1-hour testing session. Parents or caregivers completed questionnaires during the subject's testing appointment. Informed consent was obtained from parents or caregivers, and subjects aged 7 and older provided informed assent.

Modifications due to COVID-19. Due to the COVID-19 pandemic, study procedures were converted to a virtual format, such that study materials were mailed to the subject's home, and both visits were conducted via Zoom. Modifications to procedures are detailed below.

Participants

Subjects. Two groups of children were recruited and assessed: children with histories of heavy prenatal alcohol exposure (AE; $n = 27$) and typically developing children (CON; $n = 27$). Children of all sexes, races, and ethnicities between 6:0-10:11 years of age were selected based on the inclusion and exclusion criteria listed below. To the extent possible, groups were matched based on age, sex, race, ethnicity, and socioeconomic status.

Inclusion Criteria. All children were primary English speakers and met criteria for a group below:

AE group. Children in the AE group had a history of heavy prenatal alcohol exposure (≥ 4 drinks per occasion at least once per week, or ≥ 14 drinks per week). Information regarding prenatal alcohol exposure was obtained from medical, legal, or social service records, or maternal report, if available. Children in this group received a dysmorphology exam by Dr.

Kenneth Lyons Jones to determine alcohol-related diagnoses using standard criteria (Jones et al., 2006). In order to meet criteria for FAS, individuals must have two of three facial dysmorphology markers (i.e., short palpebral fissures [$\leq 10^{th}$ centile], smooth philtrum, thin vermilion) as well as either growth deficiency (height $\leq 10^{th}$ centile) or microcephaly (head circumference $\leq 10^{th}$ centile) or both. Children in this group were identified retrospectively; thus, information concerning the exact amounts and timing of prenatal alcohol exposure was unavailable. Subjects for the AE group were recruited from the FASD Research Registry and the SDSU Center for Behavioral Teratology.

CON group. Children in the CON group were typically developing controls with minimal (<1 drink per week and never >2 drinks per occasion) or no history of prenatal alcohol exposure. Subjects for the CON group were recruited from the UCSD MotherToBaby research study and the SDSU Center for Behavioral Teratology.

Exclusion Criteria. Children were excluded if they had had a serious head injury with loss of consciousness for more than 30 minutes; significant physical (e.g., uncorrected vision impairment, hemiparesis) or psychiatric (e.g., active psychosis) disability that would preclude participation in the study; or other known cause of mental deficiency (e.g., chromosomal abnormalities, congenital hypothyroidism, neurofibromatosis). Children were excluded from the CON group if greater than minimal prenatal alcohol exposure was suspected or unconfirmed, or if they had a history of seizure disorder.

Recruitment. Subjects were recruited concurrently with other studies at the Genetics and Dysmorphology Clinic at Rady Children's Hospital-San Diego (RCHSD), the UCSD Center for Better Beginnings and FASD Research Registry, and the SDSU Center for Behavioral Teratology. Control subjects were recruited from the UCSD MotherToBaby Research Study and

SDSU Center for Behavioral Teratology, and included typically developing children, as well as children with ADHD, learning disorders, developmental disabilities, and behavioral problems without histories of prenatal alcohol exposure.

Sleep Assessment

Sleep was assessed using both objective and subjective measures. Actigraphy is a recommended method for detecting sleep quantity and circadian patterns in children, and is a less expensive, non-invasive alternative to the gold-standard of polysomnography (Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). This technology uses a small accelerometer, generally in the form of a wristband, to detect movement. Subjects were given an actigraph to wear for a two-week period, and parents/caregivers filled out a sleep diary to corroborate those data. Actigraphy measures included total sleep time, percent of time spent asleep, total wake time, percent of time spent awake, number of awakenings, and night-to-night variability in sleep, while daily sleep diaries were used to document bedtime, minutes to fall asleep, nocturnal awakenings, morning wake time, daytime naps, school attendance, and child health status. To augment objective measures, parents/caregivers completed questionnaires regarding their child's sleep, which assessed bedtime behavior, sleep-disordered breathing, sleep behaviors during the night, parasomnias (e.g., sleeptalking, sleepwalking), and daytime sleepiness.

Neuropsychological and Behavioral Assessment

Subjects completed one, 1-hour neuropsychological assessment battery to measure cognitive functioning in domains known to be impaired in FASD, some of which were also expected to be sensitive to sleep disturbance. Prior to COVID, all children were tested in person ($n = 23$) with a trained psychometrist in a quiet testing room, and were given breaks to minimize fatigue and maintain motivation. For participants who enrolled during the COVID-19 pandemic

($n = 31$), an abbreviated testing battery was conducted via Zoom. To assess behavior, parents/caregivers completed questionnaires regarding their child's behavior problems and executive functioning.

      Domains of Assessment. Prenatal exposure to alcohol is related to deficits in multiple cognitive domains (Mattson et al., 2011), including learning and memory (Mattson & Roebuck, 2002), executive function (McGee, Fryer, Bjorkquist, Mattson, & Riley, 2008; Vaurio, Riley, & Mattson, 2008), processing speed (Burden et al., 2005), language development (McGee et al., 2009), and attention (Burden et al., 2005; Glass et al., 2014). Within the domain of executive function, children with FASD demonstrate impairment in planning, response inhibition, abstract thinking, and cognitive flexibility (Mattson et al., 1999). Learning and recall of both verbal and nonverbal information is also impaired, as is the ability to hold and manipulate information in working memory (Green et al., 2009; Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998). Deficits in attention are common in prenatally alcohol-exposed children, particularly on tasks of vigilance, reaction time, and information processing (Burden et al., 2005; Jacobson et al., 1994; Jacobson et al., 1993; Streissguth et al., 1986). These cognitive domains are dependent on the integrity of the prefrontal cortex, an area of the brain known to be adversely affected by prenatal alcohol exposure (Fryer, Tapert, et al., 2007; Sowell et al., 2002) as well as sleep disturbance (Beebe, 2006; Gozal et al., 2004; Kheirandish & Gozal, 2006; O'Brien et al., 2003). Indeed, in typically developing children, there is strong evidence to suggest that sleep disturbance is associated with deficits in attention and executive function (Beebe, 2006). Receptive language skills were not expected to be sensitive to sleep disturbance (Beebe, 2006), and thus this measure served as a negative control.

General Statistical Analyses

SPSS statistical software version 27 was used for the primary analyses. Data were inspected for violations of assumptions of normality, homogeneity of variance, and linearity prior to analysis. To determine statistical significance, an alpha level of $p < .05$ (two-tailed) was used; practical significance was determined based on effect sizes. Benjamini-Hochberg correction was used to control for false discovery rate on all follow up tests. Dependent variables were expected to be correlated; therefore, multivariate analysis of variance (MANOVA) was used to address the central hypotheses. Wilk's Λ was used as the omnibus test statistic. Significant group differences were followed up using univariate ANOVAs to determine group differences on individual measures of cognition and behavior. If a demographic variable was significantly correlated with an individual dependent variable that significantly differed by group in the univariate ANOVA, the demographic variable was subsequently included as a covariate in a confirmatory ANCOVA. For analyses that involved continuous predictor variables, multiple regression was used.

Demographic Data and Sample Characteristics. Demographic data were analyzed using ANOVA (for continuous variables) or chi-square (for categorical variables) to examine group differences in age, sex, race, SES, or handedness. If a demographic variable was significantly correlated with a dependent variable, and did not interact with either the dependent or independent variables, it was included in the analysis as a covariate.

Potential Confounding Factors

Data regarding parental socioeconomic status (SES), including income and highest level of education, participant medication use, caffeine use, physical activity (as measured by average activity counts per day during waking periods), psychiatric comorbidity, pubertal stage of development, and testing time of day were also collected.

Aim 1: To use a combination of subjective and objective measures to characterize sleep quality in children with FASD.

Subjects wore a Philips Respironics Actiwatch-2 over a two-week period to obtain objective sleep measures. Parents and caregivers completed a sleep diary to corroborate objective data, as well as two questionnaires: the Children's Sleep Habits Questionnaire (CSHQ) and Pediatric Sleep Questionnaire (PSQ) (Chervin et al., 2000).

Actigraphy. Actigraphy provides objective measures of sleep and is a validated tool to detect sleep and wake states for extended periods of time in a child's natural environment (Meltzer et al., 2012; Van de Water, Holmes, & Hurley, 2011). Compared to polysomnography, actigraphy has high sensitivity (ability to detect sleep), but low specificity (ability to detect wakefulness) (de Souza et al., 2003; Martin & Hakim, 2011; Van de Water et al., 2011). Variables obtained from actigraphy included total sleep time, percent of time spent asleep, wake after sleep onset (WASO), number of nocturnal awakenings (wake bouts), and fragmentation index. Measures were averaged across nights, and differences between weekdays and weekends were also examined. Metrics on night-to-night variability were calculated by obtaining the standard deviation of each variable across two-weeks within each subject. Naps were defined as a period of inactivity during the day greater than 5 minutes that was also coded in the sleep diary or by an event marker. Total sleep time was used as the primary outcome for sleep quality. Standard deviation in total sleep time was used as the primary outcome for night-to-night variability.

Children's Sleep Habits Questionnaire (CSHQ). The CSHQ is a validated, retrospective, 45-item caregiver-report questionnaire that assesses sleep behaviors (i.e., bedtime resistance, sleep onset, sleep duration, anxiety around sleep, behaviors during sleep and night

wakings, sleep-disordered breathing, parasomnias, morning waking/daytime sleepiness) in children aged 4 to 10 (Owens et al., 2000). A Total Score ≥ 41 was considered a positive screen for sleep problems.

Pediatric Sleep Questionnaire (PSQ). The PSQ is a validated 22-item caregiver-report questionnaire used to investigate the presence of sleep-related breathing disorders in children aged 2 to 18, including symptoms such as snoring, daytime sleepiness, and behavioral disturbances (Chervin et al., 2000). A Total Score of ≥ 8 was considered a positive screen for a sleep-related breathing disorder.

Sleep Diary. Sleep diaries are a well-established tool for collecting information regarding sleep schedules and to aid in the scoring of actigraphy (Morgenthaler et al., 2007). Parents completed a sleep diary for their child each morning and evening. Variables collected from the sleep diary included time the child got into bed, lights out time, sleep onset latency (minutes to fall asleep), number of awakenings after first falling asleep, morning wake-up time, and time the child got out of bed. Additional information collected from the sleep diary included number of daytime naps, medications taken, whether the child experienced any illness, and whether the actigraph was taken off at any point.

Hypothesis 1a. Children in the AE group will demonstrate greater objective sleep disturbance (less total sleep time, more sleep fragmentation) compared to controls.

Hypothesis 1b. Subjective parent/caregiver-report data will show elevations on measures of bedtime resistance, sleep duration, sleep anxiety, night awakenings, parasomnias, sleepiness, and behavior for children in the AE group compared to controls.

Data Analysis. MANOVAs were performed separately for objective (actigraphy) and subjective (questionnaire) sleep measures as the dependent variables, and with group (AE, CON)

and sex (male, female) as the between-subjects factors (see **Table 3**). Homogeneity assumptions

were evaluated at an alpha level of .001 using Box's M test of homogeneity of covariance and

Levene's homogeneity test. Wilk's criterion (Λ) was used as the omnibus test statistic. A

significant omnibus multivariate effect was followed-up by using univariate ANOVAs to

examine the main effect for each dependent variable. Results from these analyses were used to

examine the extent to which there were group differences on each sleep variable.

Table 3. Measures for Sleep MANOVAs.

Objective (Actigraphy)	Subjective (Questionnaires)
Average	**CSHQ**
WASO (minutes)	Bedtime Resistance
# Wake Bouts	Sleep Onset Delay
Sleep Time (minutes)	Sleep Duration
% Sleep	Sleep Anxiety
Fragmentation Index	Night Wakings
Variability (Within-person SD)	Parasomnias
WASO (minutes)	Sleep Disordered Breathing
# Wake Bouts	**PSQ**
Sleep Time (minutes)	Snoring
% Sleep	Sleepiness
Fragmentation Index	Behavior

WASO = Wake after sleep onset

<u>Aim 2</u>: To determine the relationship between sleep quality and neurobehavioral outcome.

     NIH Toolbox Cognition Battery. Subjects were administered the computerized NIH

Toolbox Cognition Battery (Gershon et al., 2013) to obtain a general measure of cognitive

functioning, as well as specific indices of executive function, episodic memory, working

memory, language, and processing speed, assessed as follows: Executive function was evaluated

by the Flanker Inhibitory Control and Attention Test, in which participants focus on a given

stimulus while inhibiting attention to stimuli flanking it. The Dimensional Change Card Sort Test provided an additional measure of executive function, specifically cognitive flexibility and attention. For this task, pictures are presented that vary along two dimensions (e.g., shape, color), and the dimension for sorting is indicated by a cue on the screen. The Picture Sequence Memory Test is a measure of episodic memory, in which participants are asked to reproduce a sequence of pictures shown on the screen. The List Sorting Working Memory Test requires that participants recall and sequence different visually and orally presented stimuli. The Oral Reading Recognition Test is a measure of language skills that asks participants to read and pronounce words, letters, or other "prereading" items as accurately as possible. The Picture Vocabulary Test is a measure of receptive vocabulary, in which participants select a picture that most closely matches the meaning of a word. The Pattern Comparison Processing Speed Test asks participants to discern whether two side-by-side pictures are the same or not, measuring their response time. All subtests generated age-corrected standard scores (SS; $M = 100$, SD = 15), with higher scores reflecting better performance. Summary scores included a Cognitive Function Composite Score, Fluid Cognition Composite Score, and Crystallized Cognition Composite Score.

Modifications due to COVID-19. Due to restrictions on in-person testing during the COVID-19 pandemic, select subtests of the NIH Toolbox were administered remotely via Zoom following guidelines released by NIH Toolbox. Participants were instructed to complete testing in a quiet environment with limited noise and distractions. If possible, children were tested while alone in the room. For some children, it was necessary for parents to stay in the room to help their child remain at the computer. In these cases, parents were instructed not to assist the child in any way during testing procedures.

The List Sorting Working Memory Test and Oral Reading Recognition Test were administered without modification via screen sharing. The Picture Vocabulary Test and Picture Sequence Memory were revised to allow for remote assessment as follows: for Picture Vocabulary, numbers were added to the edge of images so that participants were able to answer by selecting the number corresponding to an image, rather than touching the image on the screen. For Picture Sequence Memory, numbers were added so that participants could tell the examiner orally how to sequence the pictures; the examiner then moved the pictures via touch screen as directed by the participant.

The Flanker Inhibitory Control and Attention Test, Dimensional Change Card Sorting Test, and Pattern Comparison Processing Speed Test were not adapted for remote administration due to the need to record reaction time accurately. Therefore, these subtests were only administered to the participants who completed the study prior to the COVID-19 pandemic ($n = 31$).

Quotient™ ADHD System. The Quotient™ ADHD System (Teicher et al., 1996) utilizes a computerized continuous performance task (CPT) to provide detailed measures of hyperactivity, inattention, and impulsivity. The task uses a Go/No-Go paradigm, presenting children with one of two geometric shapes in random spatial positions, and asking them to respond when the target shape appears, and withhold response when the non-target shape appears. An infrared motion analysis system simultaneously tracks and records the two-dimensional location of a reflective marker placed on a headband worn by the child. The following variables were collected and calculated: (1) movement variables (e.g., immobility duration, displacement), (2) traditional CPT variables (e.g., omission and commission errors, response latency), and (3) attentional state variables during CPT task performance, which are

derived by dividing the task into 30-second epochs and analyzing attentional state (e.g., distracted, impulsive, randomly responding) during each epoch. This type of task is one of the few that has been used across multiple studies of sleep and neurobehavioral functioning in children, and poor performance has consistently been related to sleep disturbance (Beebe, 2006).

Unfortunately, the manufacturer discontinued this system in the middle of the study. Therefore, these variables were only collected on a subset of participants ($n = 16$).

Child Behavior Checklist (CBCL). Parents or caregivers completed the CBCL (Achenbach & Ruffle, 2000) as a measure of their child's behavioral functioning. The CBCL is a parent-report form that is widely used to assess behavioral, emotional, and social problems in children ages 6-18. Questions correspond to problems in the following categories: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. All subscales and composite scores generate T-scores ($M = 50$, SD $= 10$), with higher scores reflecting more problem behaviors.

Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2). To complement scores from objective measures of executive functioning, parent/caregiver-report of these skills was collected using the BRIEF-2 (Gioia et al., 2000), which includes nine clinical scales (Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials) and four index/composite scores (Behavior Regulation Index, Emotion Regulation Index, Cognitive Regulation, and Global Executive Composite) used to assess critical executive functioning skills in children ages 5-18. All subscales and indexes generate T-scores ($M = 50$, SD $= 10$), with higher scores reflecting more executive functioning problems.

Hypothesis 2a. The AE group will perform worse on objective measures of executive functioning, memory, attention, language, and processing speed. On parent report measures, the AE group will demonstrate greater executive functioning problems and behavior problems, compared to CON.

Hypothesis 2b. Based on the associations between sleep and neurobehavioral outcomes in other neurodevelopmental disorders (Breslin et al., 2014; Malow et al., 2006), there will be a significant relationship between Sleep Quality (operationalized as total sleep time) and objective measures of executive functioning, attention, and memory, as well as parent/caregiver-report measures of executive functioning (i.e., BRIEF Global Executive Composite) and problem behaviors (i.e., CBCL Internalizing Problems, Externalizing Problems). There will be no association between sleep quality and receptive language ability. Furthermore, there will be a significant Group x Sleep Quality interaction, in which AE individuals will demonstrate a stronger relationship between Sleep Quality and performance on objective measures of executive functioning, attention, and memory, as well as caregiver-report measures of executive functioning and problem behaviors.

Data Analysis. Zero-order correlation was conducted to examine the relationship between total sleep time and cognitive and behavioral variables. Outcomes that were significantly correlated with Sleep Quality (i.e., total sleep time) at the $p < .05$ level were further explored using hierarchical multiple regression to examine the contribution of Group (AE, CON) and Sleep Quality to neurobehavioral performance. Regression models were analyzed in a stepwise fashion: the main effect of Group was entered on Step 1 (Model 1); the main effect of Sleep Quality was examined by entering total sleep time as a predictor on Step 2 (Model 2); finally, the Group x Sleep Quality interaction term was be entered on Step 3 (Model 3).

Hypothesis 2c. Sleep Quality will mediate the relationship between Group and objective

measures of executive functioning, attention, and memory, and caregiver-report measures of

executive functioning and problem behaviors.
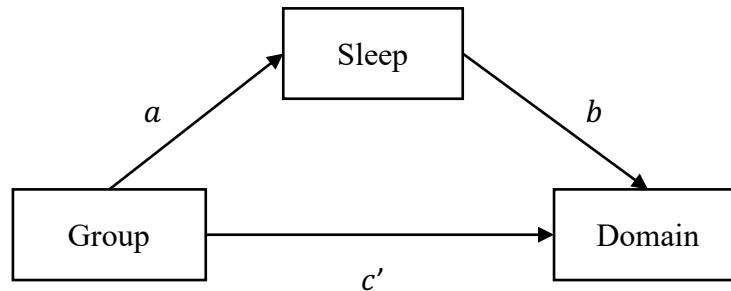
Figure 1. A potential mediation model.

Data Analysis. Path analysis was used to further explore the relations between group,

sleep quality, and neurobehavioral outcomes. Neurobehavioral outcomes were selected for path

analysis based on whether they demonstrated a significant relationship with sleep quality or sleep

quality variability in Analysis 2b. Sleep Quality was operationalized as total sleep time, and

sleep quality variability was operationalized as the night-to-night variability (SD) in total sleep

time. The target model specified indirect relations from group to neurobehavioral outcome via

sleep quality as the mediating variable. Moreover, a direct path from group to neurobehavioral

outcome was specified. Path coefficients were obtained from the lavaan package in R version

4.1.0. No known studies have investigated indirect relationships between sleep, cognitive, and

behavioral outcome in children with FASD, and path analysis is an excellent method to do so.

However, this model was strictly exploratory, and because these data were cross-sectional, the

model was not used to define a causal relationship among variables. Rather, these analyses were

conducted to provide preliminary data for future studies.

Sample Size

Power analyses were calculated using G*Power statistical software (Faul, Erdfelder, Lang, & Buchner, 2007) using an alpha level of .05 and 80% power to detect a significant omnibus effect to estimate the total required sample size. The few studies utilizing actigraphy and/or polysomnography to study sleep in children with FASD have found large effect sizes for outcome variables (Chen et al., 2012; Wengel et al., 2011). Studies of children with autism spectrum disorder and ADHD using actigraphy and the CSHQ as sleep measures and the CBCL to measure behavioral outcome demonstrate medium to large effects (Cohen, Conduit, Lockley, Rajaratnam, & Cornish, 2014; O'Brien et al., 2003; O'Brien et al., 2004). For Aim 2c, Thoemmes et al. (2010) suggest that in order to detect a mediated effect in a single mediator model with dichotomous treatment (i.e., Group) assignment, 76 subjects ($n = 38$ per group) are needed to detect a large effect for path a, and a medium effect for path b (see Figure 2). Based on these findings and recommendations, the proposed sample size was 76 subjects. Given the sample size of 54 subjects, power analyses indicated that in order to detect a significant omnibus effect, large effect sizes (partial $\eta^2 > .270$) would be needed. Please see the Limitations and Future Directions section for further discussion of sample size attainment.

Chapter II, in part, is currently being prepared for submission for publication of the material. Inkelis, S. M.; Chambers, C.; Mattson, S. N.; Bhattacharjee, R.; Thomas, J. D. The dissertation author was the primary investigator and author of this material.

Demographic Data

Groups did not significantly differ on age ($p = .058$), handedness ($p = .715$), sex ($p = 1.0$), or ethnicity ($p = .261$). However, groups differed on race ($p = .024$). The CON group had a significantly higher proportion of White subjects ($n = 21$; 77.8%) than the AE group ($n = 13$; 48.1%). See **Table 4** for demographic characteristics by group. Group differences on all sleep and neurobehavioral variables were tested using independent samples t-tests. Group differences on all sleep variables are presented in **Table 5**, and differences on all neurobehavioral variables are presented in **Table 11**. Correlations for measures used in MANOVA analyses are presented in **Figure 3** and **Figure 4**.

Potential confounding factors. Groups differed significantly on parental education ($p = .001$) such that the CON group had higher parental education level than the AE group. Significantly more children in the AE group used stimulant medications on the day of testing ($p = .011$). Children in the AE group were also more likely to have a sleep disorder diagnosis ($p = .031$) and use melatonin ($p = .013$). More children in the AE group were tested in the morning, compared to the CON group ($p = .032$). These variables were examined as potential covariates.

Significantly more children in the AE group had an ADHD diagnosis ($p = .001$). However, given the high level of co-occurring ADHD and FASD, covarying for ADHD-status could limit the ability to detect significant effects of both group and sleep disturbance on neurobehavioral outcomes by reducing the variance accounted for by these variables, and further limiting power. Due to these limitations, ADHD was not included as a covariate in our analyses.

Sample sizes. A total of 54 subjects enrolled in the study; however, some children did not complete certain aspects of the project. Deviations from the total sample size are noted in the

respective outcome tables. Specifically, two children (1 AE and 1 CON) refused to wear the Actiwatch-2. For parent sleep questionnaires (CSHQ, PSQ), data were missing for two children (1 AE and 1 CON); 4 children in the CON group did not have PSQ data. For the NIH Toolbox, four children in the AE group did not complete any neuropsychological testing; one child in the AE group refused to complete the Picture Sequence Memory and List Sorting Working Memory subtests due to frustration. Three parents of children in the AE group did not complete parent-report behavior questionnaires (CBCL, BRIEF-2).

Table 4. Demographic information by group. Groups included children with heavy prenatal alcohol exposure (AE) and non-exposed controls (CON).

Demographic Variable	AE (*n* = 27)	CON (*n* = 27)	*p*
Age in Years [M (SD)]	8.8 (1.65)	8.0 (1.57)	.058
Sex [*n* (% Female)]	14 (51.9)	14 (51.9)	1.0
Race [*n* (% White)]	13 (48.1)	21 (77.8)	.024
Ethnicity [*n* (% Hispanic)]	10 (37.0)	7 (25.9)	.261
Handedness [*n* (% Right)]	22 (81.5)	23 (85.2)	.715
FAS Diagnosis [*n* (% FAS)]	3 (11.1)	--	
Parent Education [*n* (%)]	--	--	.001
Partial High School	0 (0.0)	1 (3.7)	
High School Graduate	8 (29.6)	1 (3.7)	
Partial College	7 (25.9)	1 (3.7)	
Standard College/University	7 (25.9)	7 (25.9)	
Graduate/Professional Training	4 (14.8)	17 (63.0)	
Family Income [*n* (%)]	--	--	.243
$10,001-20,000	1 (3.7)	1 (3.7)	
$20,001-30,000	3 (11.1)	1 (3.7)	
$30,001-50,000	3 (11.1)	1 (3.7)	
$50,001-75,000	4 (14.8)	3 (11.1)	
$75,001-100,000	6 (22.2)	2 (7.4)	
$100,000+	9 (33.3)	18 (66.7)	
Parent-Reported Psychiatric Diagnoses [*n* (%)]	--	--	
Depression	1 (3.7)	1 (3.7)	.956
Anxiety	7 (25.9)	1 (3.7)	.123
ADHD	14 (51.9)	3 (11.1)	.001
Sleep Disorder Diagnosis [*n* (%)]	4 (14.8)	0 (0.0)	.031
Testing Day Stimulant Medication Use [*n* (%)]	5 (18.5)	0 (0.0)	.011
Melatonin Use [*n* (%)]	5 (18.5)	0 (0.0)	.013
Pubertal Status [M (SD)]	1.3 (.53)	1.5 (.57)	.569
Testing Time of Day [*n* (%)]	--	--	.032
Before 12pm	11 (40.7)	7 (25.9)	
After 12pm	12 (44.4)	20 (74.1)	
Participated during COVID [*n* (%)]	16 (59.3)	15 (55.6)	.783

Aim 1. To use a combination of subjective and objective measures to characterize sleep quality in children with AE.

       Hypothesis 1a. The alcohol-exposed group demonstrated significantly greater levels of

night-to-night variability in WASO, number of wake bouts, sleep time, and percent sleep,

relative to controls. There were no significant group differences observed on mean-based sleep

actigraphy metrics, averaged across two weeks (**Figure 2, Table 5**). Intraclass correlation

coefficients (ICC) for actigraphy metrics ranged from .313 to .478. Thus, 31.3% to 47.8% of the

variance in sleep measures is between-person, and 52.2% to 68.7% of the variance in sleep

measures is within-person. **Table 6** shows actigraphy metrics within each group, stratified by

participation prior to or during the pandemic (Pre-COVID and COVID). There were no

differences between pre-COVID and COVID outcomes and no group x COVID interactions, so

these data were combined for all analyses.

Table 5. Group differences on objective (actigraphy) and subjective (parent-questionnaire) sleep variables. Groups included children with prenatal alcohol exposure (AE) and non-exposed controls (CON). WASO = wake after sleep onset, SD = standard deviation, CSHQ = Children's Sleep Habits Questionnaire, PSQ = Pediatric Sleep Questionnaire. Note: * $p < .05$, ** $p < .01$, *** $p < .001$.

	AE (*n* = 26)	CON (*n* = 26)	*p*	Cohen's *d*
Actigraphy Measures				
2-Week Average				
WASO	74.6 (20.99)	72.2 (21.93)	.689	0.112
# Wake Bouts	32.1 (5.97)	33.0 (5.98)	.584	0.153
Sleep Time	488.2 (45.69)	479.2 (33.07)	.418	0.227
% Sleep	86.8 (3.92)	86.9 (3.89)	.899	0.035
Fragmentation Index	32.5 (7.31)	30.8 (7.27)	.394	0.238
Variability (Within-person SD)				
WASO**	25.0 (14.39)	16.5 (6.25)	**.008**	0.77
# Wake Bouts*	7.1 (2.46)	5.6 (1.30)	**.01**	0.747
Sleep Time**	56.6 (25.39)	38.7 (11.84)	**.002**	0.907
% Sleep*	3.9 (2.24)	2.7 (1.00)	**.024**	0.645
Fragmentation Index	8.5 (3.56)	7.1 (2.18)	.096	0.47
Sleep Questionnaires				
CSHQ				
Total Score*	48.8 (9.77)	43.4 (7.08)	**.027**	0.631
Bedtime Resistance	8.5 (2.92)	8.4 (2.96)	.925	0.026
Sleep Onset Delay**	1.8 (0.69)	1.3 (0.60)	**.004**	0.828
Sleep Duration	4.2 (1.95)	3.9 (1.29)	.505	0.186
Sleep Anxiety	6.4 (2.50)	5.4 (1.63)	.121	0.438
Night Wakings*	4.8 (1.55)	3.9 (1.18)	**.019**	0.671
Parasomnias	9.7 (2.86)	8.5 (1.61)	.069	0.515
Sleep Disordered Breathing	3.0 (0.72)	3.2 (0.61)	.537	0.173
Daytime Sleepiness	13.4 (3.09)	11.8 (2.99)	.061	0.531
PSQ[a]				
Total Score***	7.2 (2.63)	2.9 (2.78)	**<.001**	1.599
Snoring	0.5 (0.90)	0.1 (0.29)	.072	0.551
Sleepiness*	1.1 (1.34)	0.4 (0.59)	**.026**	0.684
Behavior***	4.5 (1.61)	1.9 (2.14)	**<.001**	1.412

[a]PSQ scores were available for *n* = 22 in the CON group
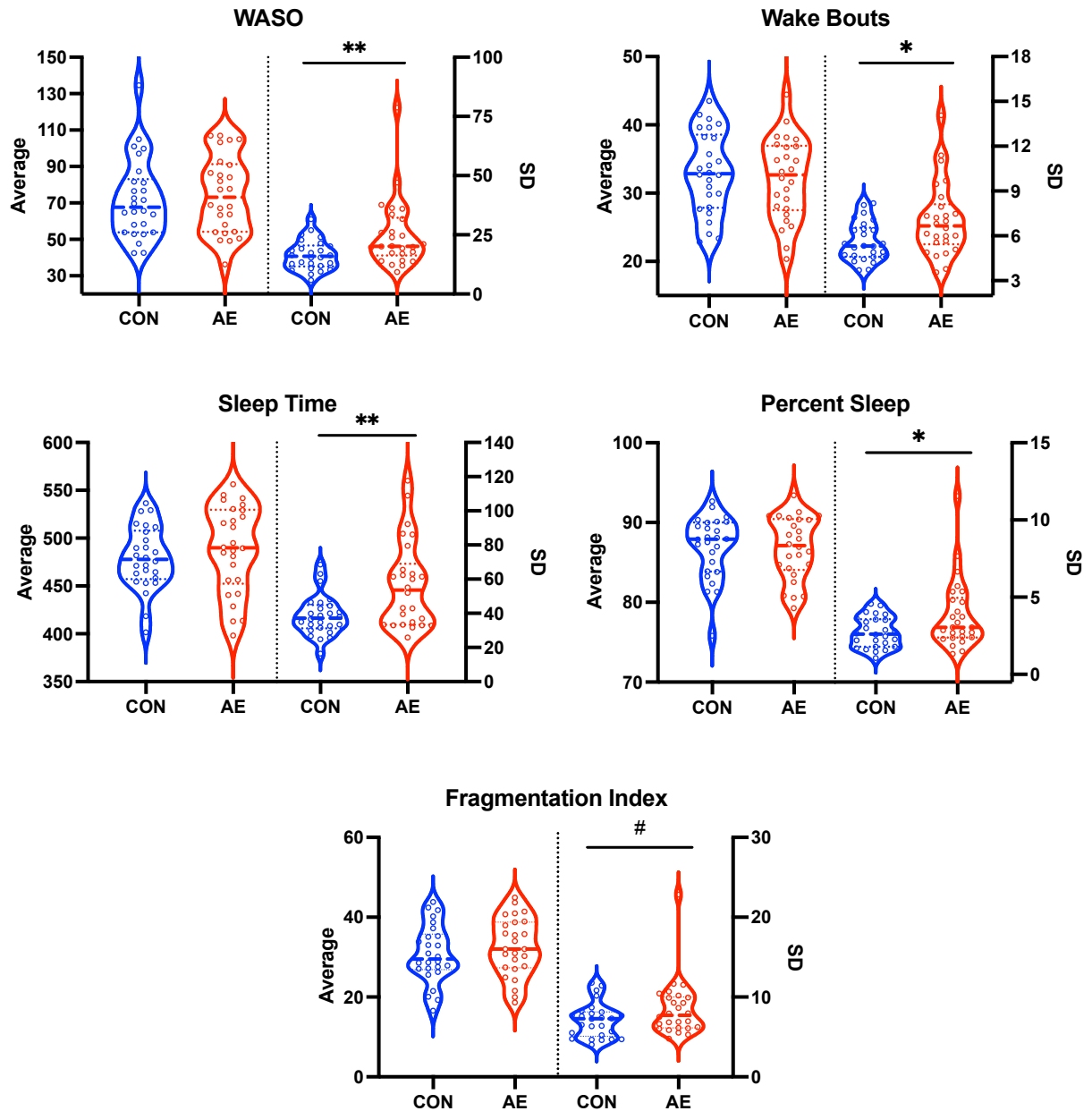
Figure 2. Distribution of sleep actigraphy measures (two-week average [left panel] and night-to-night variability [SD; right panel]) by group. Groups included children with prenatal alcohol exposure (AE) and non-exposed controls (CON). Data were collapsed across participants who completed the study prior to and during COVID. The groups did not differ on two-week average actigraphy measures. The AE group showed significantly greater intraindividual variability in WASO, number of wake bouts, sleep time, and percent sleep than the CON group. Night-to-night variability in the fragmentation index was higher in the AE group than the CON group at the trend-level. *Note:* ** $p < .01$, * $p < .05$, # $p < .10$. WASO = wake after sleep onset, SD = standard deviation.

Table 6. Group differences on objective (actigraphy) and subjective (parent-questionnaire) sleep variables, stratified by enrollment prior to (pre-COVID) or during the COVID-19 pandemic (COVID). Groups included children with prenatal alcohol exposure (AE) and non-exposed controls (CON). WASO = wake after sleep onset, SD = standard deviation, CSHQ = Children's Sleep Habits Questionnaire, PSQ = Pediatric Sleep Questionnaire. Note: * $p < .05$, ** $p < .01$, *** $p < .001$.

	Pre-COVID				COVID			
	AE (n = 11)	CON (n = 12)	p	Cohen's d	AE (n = 16)	CON (n = 15)	p	Cohen's d
Actigraphy Measures								
2-Week Average								
WASO	65.4 (22.14)	71.4 (24.83)	.547	0.256	81.4 (17.90)	72.9 (20.05)	.239	0.446
# Wake Bouts	31.0 (6.02)	32.4 (4.79)	.545	0.256	33.0 (6.00)	33.6 (6.96)	.790	0.1
Sleep Time	490.9 (48.71)	480.2 (28.38)	.523	0.268	486.3 (44.99)	478.4 (37.68)	.611	0.192
% Sleep	88.2 (4.40)	87.2 (4.27)	.570	0.241	85.8 (3.30)	86.7 (3.68)	.458	0.279
Fragmentation Index	30.0 (7.63)	29.5 (6.65)	.864	0.072	34.4 (6.74)	31.9 (7.84)	.369	0.339
Variability (Within-person SD)								
WASO	22.6 (11.64)	18.0 (6.87)	.262	0.476	26.8 (16.28)	15.1 (5.56)	.017	0.959
# Wake Bouts	7.3 (3.30)	5.8 (1.41)	.184	0.563	6.9 (1.73)	5.4 (1.22)	.011	1.023
Sleep Time**	62.9 (24.49)	36.3 (10.19)	.002	1.415	52.1 (25.88)	40.7 (13.13)	.151	0.555
% Sleep	3.7 (2.10)	2.9 (1.03)	.231	0.507	4.0 (2.40)	2.6 (1.00)	.064	0.727
Fragmentation Index*	8.1 (1.97)	6.3 (1.46)	.021	1.035	8.8 (4.42)	7.8 (2.48)	.470	0.275
Sleep Questionnaires								
CSHQ								
Total Score	46.7 (13.27)	43.9 (8.75)	.563	0.251	50.3 (6.23)	43.1 (5.89)	.003	1.199
Bedtime Resistance	7.8 (2.79)	8.7 (3.69)	.522	0.278	9.0 (3.00)	8.2 (2.40)	.426	0.295
Sleep Onset Delay	1.5 (0.69)	1.2 (0.60)	.334	0.422	2.1 (0.59)	1.3 (0.62)	.003	1.211
Sleep Duration	3.8 (2.18)	3.6 (1.03)	.805	0.107	4.5 (1.77)	4.1 (1.46)	.504	0.247
Sleep Anxiety	5.8 (2.48)	5.3 (1.68)	.553	0.257	6.7 (2.52)	5.5 (1.64)	.134	0.564
Night Wakings	5.2 (1.78)	4.1 (1.30)	.116	0.7	4.5 (1.36)	3.7 (1.10)	.087	0.648
Parasomnias	8.9 (3.42)	8.3 (1.62)	.583	0.238	10.2 (2.34)	8.6 (1.64)	.039	0.793
Sleep Disordered Breathing	2.9 (1.04)	3.3 (0.90)	.393	0.372	3.1 (0.35)	3.1 (0.26)	.559	0.216
Daytime Sleepiness	13.4 (3.88)	12.5 (3.17)	.554	0.256	13.5 (2.50)	11.3 (2.87)	.039	0.792

Table 6 (continued). Group differences on objective (actigraphy) and subjective (parent-questionnaire) sleep variables, stratified by enrollment prior to (pre-COVID) or during the COVID-19 pandemic (COVID). Groups included children with prenatal alcohol exposure (AE) and non-exposed controls (CON). WASO = wake after sleep onset, SD = standard deviation, CSHQ = Children's Sleep Habits Questionnaire, PSQ = Pediatric Sleep Questionnaire. Note: * $p < .05$, ** $p < .01$, *** $p < .001$.

	Pre-COVID				COVID			
	AE	CON	p	Cohen's d	AE	CON	p	Cohen's d
	($n = 11$)	($n = 12$)			($n = 16$)	($n = 15$)		
PSQ[a]								
Total Score***	7.4 (2.11)	2.0 (2.58)	<.001	2.275	7.1 (3.02)	3.3 (2.85)	.001	1.295
Snoring	0.73 (1.27)	0.14 (0.38)	.259	0.623	0.3 (0.46)	0.1 (0.26)	.152	0.538
Sleepiness	1.2 (1.54)	0.3 (0.49)	.158	0.786	1.1 (1.22)	0.5 (0.64)	.103	0.615
Behavior***	4.7 (1.10)	1.4 (2.15)	.001	1.931	4.4 (1.92)	2.1 (2.19)	.004	1.134

[a]PSQ scores were available for $n = 7$ in the Pre-COVID CON group.

A between-subjects MANOVA was performed on ten dependent sleep actigraphy variables. The ten dependent variables were average and night-to-night variability (SD) scores for five distinct sleep actigraphy metrics: wake after sleep onset (WASO), number of wake bouts, sleep time, percent sleep, and fragmentation index. See **Figure 3** for intercorrelations among MANOVA dependent variables. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance was statistically significant ($p < .001$), and Levene's homogeneity test was not statistically significant (all ps > .001). MANOVA results are presented in **Table 7**. Using Wilk's criterion (Λ) as the omnibus test statistic, the combined dependent variables resulted in a significant main effect for group [$F(10, 41) = 3.077$, $p = .005$, partial $\eta^2 = .43$]. There was no significant omnibus effect of COVID when included as a factor in the model.
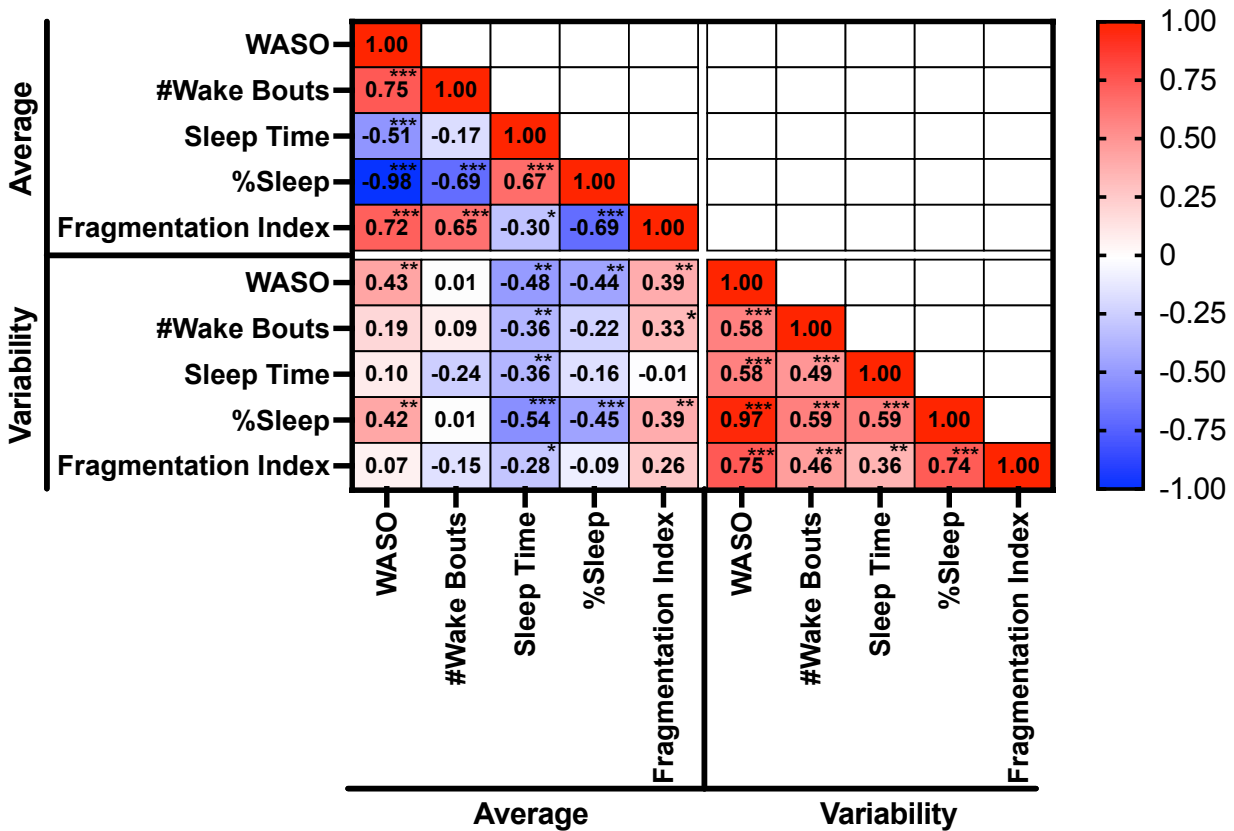
Figure 3. Correlations among MANOVA dependent variables for sleep actigraphy analyses. Note: * $p < .05$, ** $p < .01$, *** $p < .001$. WASO = wake after sleep onset.

To probe the statistically significant multivariate effects of group, univariate one-way ANOVAs were conducted on each individual dependent variable. There were statistically significant main effects of group on WASO variability (SD WASO; $F(1, 50) = 7.704$, $p = .008$, partial $\eta^2 = .134$) and number of wake bouts variability (SD # Wake Bouts; $F(1, 50) = 7.26$, $p = .01$, partial $\eta^2 = .127$) such that the AE group had more variability in WASO and number of wake bouts than CON. There were also statistically significant main effects of group on sleep time variability (SD Sleep Time; $F(1, 50) = 10.96$, $p = .002$, partial $\eta^2 = .176$) and percent sleep variability (SD % Sleep; $F(1, 50) = 5.41$, $p = .024$, partial $\eta^2 = .098$) such that the AE group exhibited greater sleep time variability and percent sleep variability than CON. There was a

trend-level main effect of group for fragmentation index variability (SD Fragmentation Index [$F(1, 50) = 2.87$, $p = .096$, partial $\eta^2 = .054$]).

There were no statistically significant main effects of group for the average sleep actigraphy metrics (WASO [$F(1, 50) = 0.162$, $p = .69$, partial $\eta^2 = .003$]; wake bouts [$F(1, 50) = 0.30$, $p = .584$, partial $\eta^2 = .006$]; sleep time [$F(1, 50) = 0.67$, $p = .418$, partial $\eta^2 = .013$]; percent sleep [$F(1, 50) = 0.016$, $p = .899$, partial $\eta^2 < .001$]; fragmentation index [$F(1, 50) = 0.739$, $p = .394$, partial $\eta^2 = .015$]).

To examine the effects of covariates on significant univariable outcomes (SD WASO, SD # Wake Bouts, SD Sleep Time, SD % Sleep), follow-up ANCOVAs were conducted individually. Prior diagnosis of a sleep disorder was related to greater SD WASO (b = 16.25, $p = .005$) and SD % Sleep (b = 2.73, $p = .002$). When this was added to the model, the effect of group on SD WASO was trend level (b = 5.114, $p = .094$). There were no statistically significant effects of race, parent education level, or melatonin use.

Table 7. MANOVA results for sleep profile by group. Groups included children with heavy prenatal alcohol exposure (AE) and non-exposed controls (CON). Note: * $p < .05$ level, # $p < .10$ level, df = degrees of freedom, WASO = wake after sleep onset. Average sleep metrics were calculated across total days of actigraphy. Variability sleep metrics were calculated from standard deviations for each metric, across total days of actigraphy.

Sleep Variable	Group [F (df)]	p	Partial η^2
Omnibus*	3.08 (10, 41)	.005	0.43
Average			
WASO	0.16 (1, 50)	.689	0.003
# Wake Bouts	0.304 (1, 50)	.584	0.006
Sleep Time	0.667 (1, 50)	.418	0.013
%Sleep	0.016 (1, 50)	.899	0.0
Fragmentation Index	0.739 (1, 50)	.394	0.015
Variability			
WASO*	7.704 (1, 50)	.008	0.134
# Wake Bouts*	7.26 (1, 50)	.010	0.127
Sleep Time*	10.691 (1, 50)	.002	0.176
%Sleep*	5.407 (1, 50)	.024	0.098
Fragmentation Index#	2.872 (1, 50)	.096	0.054

Weekdays vs. Weekends. For actigraphy values collected on weekdays compared to weekends, there were significant differences across the sample on average WASO, number of wake bouts, and sleep time (**Table 8**). WASO and number of wake bouts were significantly greater on weeknights than weekend nights. However, sleep time was 15 minutes longer on weeknights, significantly more than on weekend nights. There was also significantly less variability in sleep time on weeknights, relative to weekend nights. See **Figure 4** for average sleep time across day of the week, and **Table 9** for group differences in actigraphy metrics, stratified by weekdays and weekends.
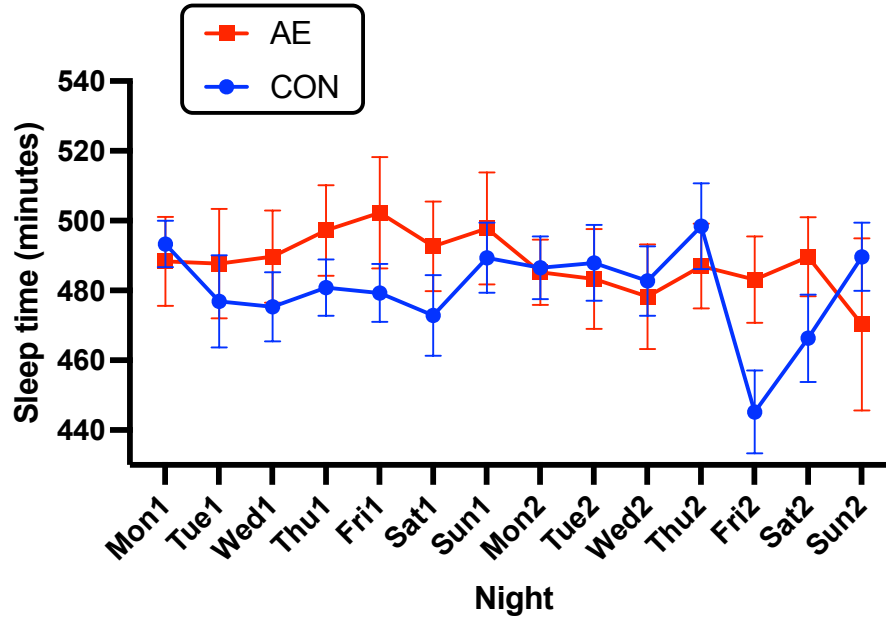
Figure 4. Nightly average total sleep time, stratified by group. AE = alcohol-exposed, CON = control.

Table 8. Comparison of actigraphy data collected on weekdays and weekends.

	Weekday	Weekend	*p*	*r*
Actigraphy Measures				
Average				
WASO (minutes)	75.0 (22.03)	70.6 (24.77)	.045	.81
# Wake Bouts	33.2 (6.01)	31.2 (6.83)	.003	.76
Sleep Time (minutes)	487.6 (38.27)	472.8 (53.2)	.006	.69
% Sleep	86.7 (3.97)	87.1 (4.56)	.315	.83
Fragmentation Index	32.1 (7.49)	31.2 (8.65)	.274	.77
Variability (Within-person SD)				
WASO (minutes)	20.7 (12.81)	19.2 (15.24)	.526	.32
# Wake Bouts	6.2 (1.68)	5.9 (3.71)	.574	.50
Sleep Time (minutes)	42.7 (19.10)	54.1 (34.89)	.018	.36
% Sleep	3.4 (1.95)	3.1 (2.82)	.519	.27
Fragmentation Index	7.6 (3.38)	8.2 (4.79)	.438	.08

Table 9. Group comparison of actigraphy measures collected on weekdays and weekends.

	Weekday			Weekend		
	AE	CON	*p*	AE	CON	*p*
Actigraphy Measures						
Average						
WASO (minutes)	77.1 (22.48)	72.9 (21.81)	.503	68.8 (22.28)	72.4 (27.36)	.605
# Wake Bouts	32.5 (6.26)	33.9 (5.78)	.392	31.5 (6.94)	30.9 (6.85)	.792
Sleep Time (minutes)	490.5 (42.68)	484.6 (33.89)	.587	482.6 (62.6)	463.0 (40.6)	.186
% Sleep	86.4 (4.14)	86.9 (3.85)	.653	87.7 (3.91)	86.5 (5.14)	.364
Fragmentation Index	32.8 (7.78)	31.3 (7.26)	.454	31.8 (7.98)	30.5 (9.36)	.603
Variability (Within-person SD)						
WASO (minutes)	25.2 (15.61)	16.2 (7.02)	.010	20.8 (16.82)	17.7 (13.71)	.467
# Wake Bouts	6.8 (1.75)	5.5 (1.35)	.004	7.1 (4.38)	4.8 (2.56)	.030
Sleep Time (minutes)	49.6 (22.34)	35.7 (12.06)	.008	64.2 (42.63)	44.4 (22.14)	.041
% Sleep	4.0 (2.38)	2.73 (1.11)	.019	3.0 (2.78)	3.2 (2.9)	.772
Fragmentation Index	8.6 (4.03)	6.65 (2.27)	.037	7.5 (3.94)	8.9 (5.47)	.303

Weekday MANOVA. A between-subjects MANOVA was performed on ten dependent weeknight sleep actigraphy variables. The ten dependent variables were average and night-to-night variability (SD) scores for five distinct sleep actigraphy metrics collected on weeknights only: wake after sleep onset (WASO), number of wake bouts, sleep time, percent sleep, and fragmentation index. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance was not statistically significant ($p = .014$), and Levene's homogeneity test was not statistically significant (all *p*s > .001). Using Wilk's criterion (Λ) as the

omnibus test statistic, the combined dependent variables resulted in a significant main effect for group [$F(10, 41) = 2.956$, $p = .007$, partial $\eta^2 = 0.419$].

To probe the statistically significant multivariate effects of group, univariate one-way ANOVAs were conducted on each individual dependent variable. There were statistically significant main effects of group on WASO variability (SD WASO; $F(1, 50) = 7.14$, $p = .01$, partial $\eta^2 = .125$) and number of wake bouts variability (SD # Wake Bouts; $F(1, 50) = 9.12$, $p = .004$, partial $\eta^2 = .154$) such that the AE group had more variability in WASO and number of wake bouts than CON. There were also statistically significant main effects of group on sleep time variability (SD Sleep Time; $F(1, 50) = 7.75$, $p = .008$, partial $\eta^2 = .134$), percent sleep variability (SD % Sleep; $F(1, 50) = 5.93$, $p = .018$, partial $\eta^2 = .106$), and fragmentation index variability (SD Fragmentation Index [$F(1, 50) = 4.6$, $p = .037$, partial $\eta^2 = .084$]), such that the AE group exhibited greater sleep time variability, percent sleep variability, and sleep fragmentation than CON on weeknights.

Weekend MANOVA. A between-subjects MANOVA was performed on ten dependent weekend sleep actigraphy variables. The ten dependent variables were average and night-to-night variability (SD) scores for five distinct sleep actigraphy metrics collected on weekend nights only: wake after sleep onset (WASO), number of wake bouts, sleep time, percent sleep, and fragmentation index. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance was statistically significant ($p < .001$), and Levene's homogeneity test was not statistically significant (all ps > .007). Using Wilk's criterion (Λ) as the omnibus test statistic, the combined dependent variables resulted in a trend-level main effect for group [$F(10, 40) = 2.052$, $p = .053$, partial $\eta^2 = 0.339$].

Sleep Diaries. Time in bed recorded by parents in the sleep diary was significantly correlated with time in bed as measured by actigraphy ($r = .73$, $p < .001$; see **Figure 5**). In the overall sample, average sleep diary time in bed was 47 minutes longer ($p < .001$) than the average time in bed measured by actigraphy (see **Table 10**). Within groups, sleep diary time in bed was 53 minutes longer for AE ($p < .001$) and 41 minutes longer for CON ($p < .001$) than actigraphy time in bed.

The average sleep diary bedtime (i.e., "lights out" time) was 29 minutes earlier ($p < .001$) than the average actigraphy bedtime (i.e., start time of the rest period) in the overall sample. Average sleep diary bedtime was 35 minutes earlier than actigraphy bedtime in the AE group ($p < .001$). Within the CON group, average sleep diary bedtime was 25 minutes earlier than actigraphy bedtime ($p < .001$). Average sleep diary wake time (i.e., time of final awakening) was also significantly later by 17 minutes ($p < .001$) than the average actigraphy wake time (i.e., end time of the rest period). Within the AE group, average sleep diary wake time was 19 minutes later than average actigraphy wake time ($p < .001$). The CON group also had an average sleep diary wake time that was 16 minutes later than average actigraphy wake time ($p < .001$).
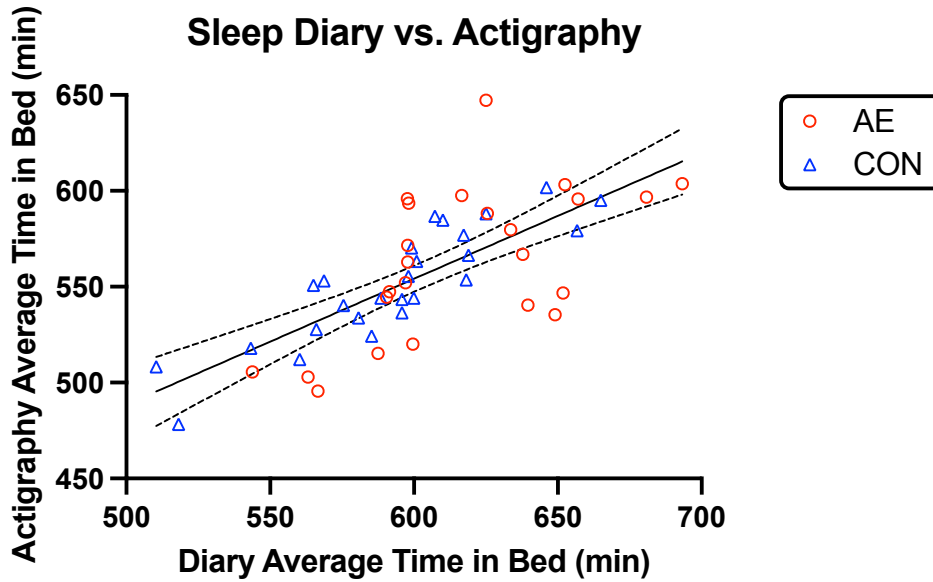
Figure 5. Association between average time in bed as measured by actigraphy and sleep diaries.

Table 10. Average bed time, wake time, and time in bed as measured by actigraphy and sleep diaries.

	AE		CON	
	Mean	SD (minutes)	Mean	SD (minutes)
Average Actigraphy Bed Time[a] (hh:mm:ss)	9:21:07 PM	47.63	9:17:46 PM	50.12
Average Actigraphy Wake Time[a] (hh:mm:ss)	6:45:42 AM	34.26	6:29:09 AM	57.74
Average Actigraphy Sleep Time[a] (min)	562.8	37.71	551.4	29.88
Average Sleep Diary Bed Time[b] (hh:mm:ss)	8:47:43 PM	40.10	8:52:20 PM	50.96
Average Sleep Diary Wake Time[b] (hh:mm:ss)	7:05:35 AM	42.21	6:45:17 AM	53.85
Average Sleep Diary Sleep Time[b] (min)	616.4	37.02	592.9	37.01

[a]AE: *n* = 26, CON: *n* = 26
[b]AE: *n* = 24; CON: *n* = 26

Aim 1a Summary. Overall, the AE group showed similar two-week average actigraphy metrics compared to the CON group. However, children in the AE group demonstrated

significantly more night-to-night variability than CON in WASO, number of wake bouts, sleep

time, and percent sleep.

Hypothesis 1b. The AE group had significantly higher scores than the CON group on the CSHQ Total Score, specifically the Sleep Onset Delay and Night Wakings subscales. PSQ Total Score was also significantly higher in the AE group than the CON group, specifically driven by higher scores on the PSQ Sleepiness and Behavior subscales. There were trend-level group differences on the CSHQ Parasomnias and Daytime Sleepiness subscales, such that the AE group had higher scores. See **Table 5** for sleep questionnaire outcomes by group.

A between-subjects MANOVA was performed on the 11 dependent parent-report sleep questionnaire variables: subscales from the Children's Sleep Habits Questionnaire (CSHQ; Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, Daytime Sleepiness) and the Pediatric Sleep Questionnaire (PSQ; Snoring, Sleepiness, Behavior). See **Figure 6** for intercorrelations among MANOVA dependent variables. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance ($p < .001$) was significant. Levene's homogeneity test was significant for PSQ Snoring ($p < .001$); all other variables were not statistically significant (all ps $> .001$). MANOVA results are presented in **Table 11**. Using Wilk's criterion (Λ) as the omnibus test statistic, there was a significant main effect for group using the combined dependent variables, [$F(11, 36) = 3.55$, $p = .002$, partial $\eta^2 = 0.520$]. There was no significant omnibus effect of COVID when included as a factor in the model.
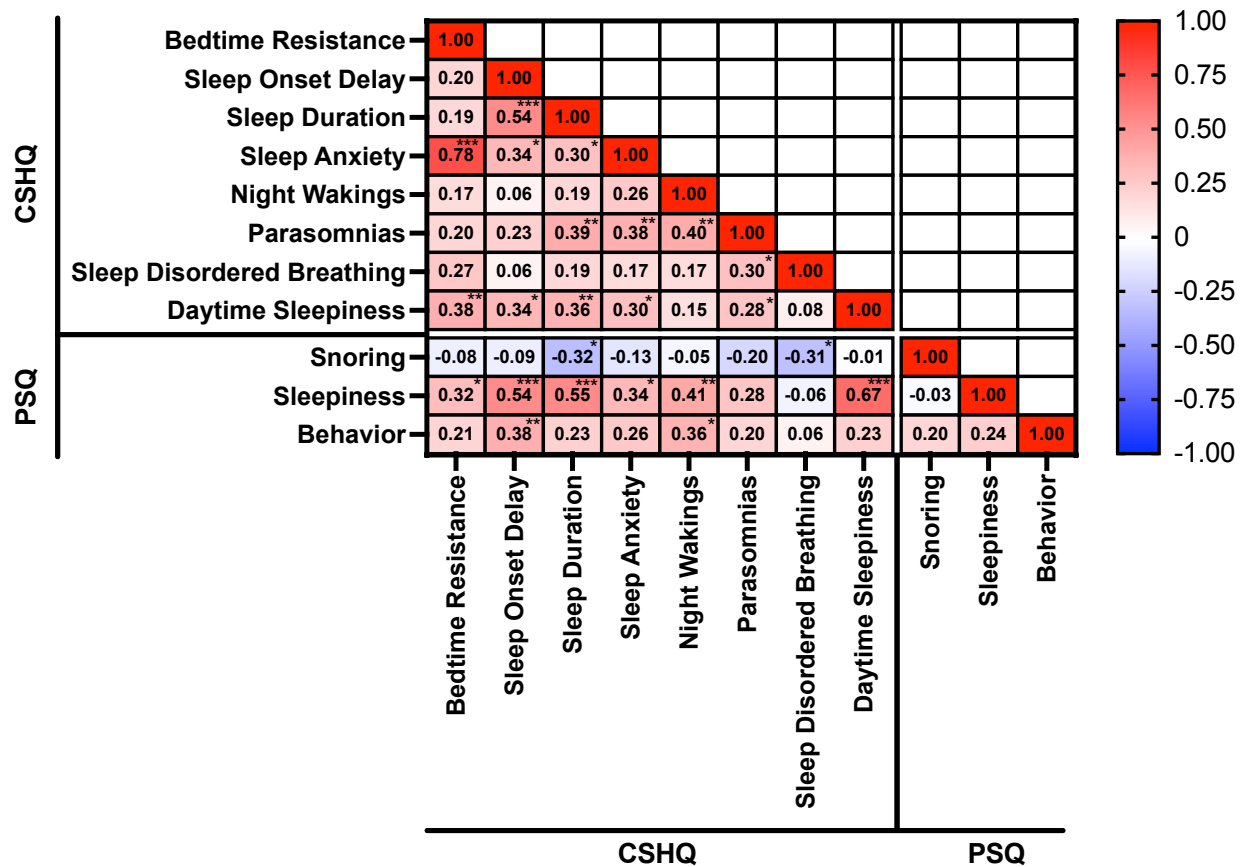
Figure 6. Correlations among MANOVA dependent variables for parent-report sleep questionnaire analyses. Note: * p < .05, ** p < .01, *** p < .001. CSHQ = Children's Sleep Habits Questionnaire, PSQ = Pediatric Sleep Questionnaire.

To probe the statistically significant multivariate effects of group, univariate one-way ANOVAs were conducted on each individual dependent variable. There was a statistically significant main effect of group on CSHQ Sleep Onset Delay [$F(1, 46) = 6.31$, $p = .016$, partial $\eta^2 = 0.12$], Night Wakings [$F(1, 46) = 10.23$, $p = .003$, partial $\eta^2 = 0.18$], and Daytime Sleepiness [$F(1, 46) = 4.28$, $p = .044$, partial $\eta^2 = 0.85$] subscales, as well as PSQ Sleepiness [$F(1, 46) = 5.26$, $p = .026$, partial $\eta^2 = 0.103$] and PSQ Behavior [$F(1, 46) = 24.35$, $p < .001$, partial $\eta^2 = 0.35$], such that the AE group had higher parent-reported scores than the CON group. There was

also a trend-level main effect of group on PSQ Snoring [$F(1, 46) = 3.38$, $p = .072$, partial $\eta^2 = .07$]; the AE group had higher parent-reported scores than the CON group.

To examine the effects of covariates on significant univariable outcomes (CSHQ Sleep Onset Delay, Night Wakings, Daytime Sleepiness; PSQ Sleepiness, Behavior), follow-up ANCOVAs were conducted individually. Parental education was related to CSHQ Night Wakings and PSQ Sleepiness. Sleep Disorder Diagnosis was also predictive of higher CSHQ Night Wakings scores. There were no statistically significant effects of race, ADHD diagnosis, or melatonin use.

Aim 1b Summary. Our hypotheses were partially supported, and the AE group had higher parent-reported problems on the CSHQ Total Score and PSQ Total Score than the CON group. These group differences were primarily related to more problems with sleep onset delay, night wakings, daytime sleepiness, and behavior.

Table 11. MANOVA results for parent-reported sleep questionnaire profile by group. Groups included children with prenatal alcohol exposure (AE) and non-exposed controls (CON). Note: * $p < .05$ level, # $p < .10$ level, df = degrees of freedom, CSHQ = Children's Sleep Habits Questionnaire, PSQ = Pediatric Sleep Questionnaire.

Questionnaire Variable	Group [F (df)]	p	Partial η^2
Omnibus*	3.55 (11, 36)	.002	0.52
CSHQ			
Bedtime Resistance	0.55 (1, 46)	.464	0.01
Sleep Onset Delay*	6.31 (1, 46)	.016	0.12
Sleep Duration	0.14 (1, 46)	.709	0.003
Sleep Anxiety	2.04 (1, 46)	.160	0.04
Night Wakings*	10.23 (1, 46)	.003	0.18
Parasomnias	2.77 (1, 46)	.103	0.06
Sleep Disordered Breathing	0.002 (1, 46)	.965	<0.001
Daytime Sleepiness*	4.28 (1, 46)	.044	0.09
PSQ			
Snoring#	3.38 (1, 46)	.072	0.068
Sleepiness*	5.26 (1, 46)	.026	0.103
Behavior*	24.35 (1, 46)	<.001	0.346

Aim 2. To determine the relationship between sleep quality and neurobehavioral outcome.

Hypothesis 2a. On the NIH Toolbox Cognition Battery, the AE group had significantly lower scores than the CON group on the Picture Vocabulary, Picture Sequence Memory, List Sorting Working Memory, and Oral Reading Recognition subtests (see **Table 12**). Group differences did not reach significance on subtests that were only administered in person (i.e., Dimensional Change Card Sorting, Flanker, Pattern Comparison Processing Speed subtests). There was no indication of significant differences when comparing face-to-face administration (pre-COVID) to virtual administration (COVID) of NIH Toolbox measures. Additionally, when

stratified by group, there were no differences between pre-COVID and COVID outcomes (see **Table 13**).

On the Child Behavior Checklist (CBCL), parents reported significantly more problems in the AE group, relative to the CON group on all subscales and composite scores (see **Table 12**). Similarly, parent-reported executive functioning problems, as measured by the BRIEF-2, were significantly higher across all subscales in the AE group compared to the CON group. There were no differences in scores when comparing the pre-COVID and COVID samples overall (see **Table 13**). When stratified by exposure group, there was a trend-level difference on CBCL Rule-Breaking scores only in the AE group; scores were higher in the pre-COVID sample relative to the COVID sample ($p = .05$). There were no COVID-related differences in the CON group.

Table 12. Group performance on neuropsychological (Toolbox) and behavioral variables (CBCL, BRIEF-2).

Neuropsychological Variable [*Mean* (SD)]	AE (*n* = 23)	CON (*n* = 27)	*p*	*Cohen's d*
NIH Toolbox (Age-Corrected SS)				
Picture Vocabulary	101.1 (11.17)	110.4 (18.87)	**.043**	0.60
Picture Sequence Memory^	91.2 (12.88)	102.4 (19.13)	**.023**	0.69
Dimensional Change Card Sorting+	94.9 (15.02)	94.7 (17.76)	.976	0.01
Flanker Executive Functioning & Inhibitory Control+	95.0 (15.69)	98.5 (12.83)	.58	0.24
List Sorting Working Memory^	91.2 (16.64)	102.3 (18.80)	**.037**	0.62
Oral Reading Recognition	93.7 (12.39)	103.0 (12.42)	**.012**	0.74
Pattern Comparison Processing Speed+	84.7 (15.91)	95.6 (16.56)	.145	0.67
Fluid Composite+	87.7 (13.67)	96.7 (20.50)	.269	0.52
Crystallized Composite+	94.9 (10.18)	106.3 (15.91)	.075	0.86
Total Composite+	89.2 (10.15)	101.7 (21.28)	.123	0.75
Early Childhood Composite+	93.7 (12.30)	101.8 (19.81)	.291	0.50

+*Conducted on a partial sample. CON: n = 12; AE: n = 9*

^*Conducted on a smaller AE sample: n = 22*

Child Behavior Checklist (CBCL; T-Score)	AE (*n* = 24)	CON (*n* = 27)	*p*	*Cohen's d*
Anxious/Depressed	60.3 (8.61)	55.2 (6.41)	**.018**	0.68
Withdrawn/Depressed	60.9 (9.12)	54.3 (6.33)	**.004**	0.84
Somatic Complaints	58.4 (7.82)	54.3 (6.09)	**.038**	0.59
Social Problems	61.0 (6.60)	55.3 (7.31)	**.005**	0.82
Thought Problems	66.5 (9.92)	56.1 (7.22)	**<.001**	1.20
Attention Problems	68.2 (8.66)	56.7 (8.69)	**<.001**	1.33
Rule Breaking Behavior	65.2 (7.49)	54.9 (5.98)	**<.001**	1.52
Aggressive Behavior	66.0 (7.45)	55.4 (7.91)	**<.001**	1.38
Sluggish Cognitive Tempo	60.1 (8.23)	54.0 (6.07)	**.004**	0.84
Obsessive Compulsive Problems	62.4 (11.88)	56.4 (7.75)	**.034**	0.60
Stress Problems	65.4 (9.02)	55.7 (7.05)	**<.001**	1.19
Internalizing Problems	60.2 (10.43)	51.4 (10.26)	**.004**	0.85
Externalizing Problems	66.1 (7.22)	50.8 (11.64)	**<.001**	1.58
Total Problems	66.8 (7.20)	51.4 (11.66)	**<.001**	1.58

Table 12 (continued). Group performance on neuropsychological (Toolbox) and behavioral variables (CBCL, BRIEF-2).

BRIEF-2 (T-Score)	AE (n = 24)	CON (n = 27)	p	Cohen's d
Behavior Regulation Index	69.0 (11.94)	53.6 (12.81)	**<.001**	1.25
Inhibit	66.7 (9.79)	53.5 (11.86)	**<.001**	1.21
Self-Monitor	70.0 (10.98)	53.9 (12.97)	**<.001**	1.34
Emotion Regulation Index	71.9 (11.86)	54.6 (11.33)	**<.001**	1.49
Shift	68.2 (10.04)	56.3 (11.64)	**<.001**	1.10
Emotional Control	71.7 (10.48)	55.9 (11.60)	**<.001**	1.43
Cognitive Regulation Index	64.4 (7.86)	53.1 (9.27)	**<.001**	1.32
Initiate	68.4 (7.11)	53.4 (11.86)	**<.001**	1.54
Working Memory	64.0 (9.53)	51.8 (9.42)	**<.001**	1.28
Plan/Organize	61.1 (11.51)	51.0 (10.68)	**.002**	0.91
Task-Monitor	64.1 (9.06)	49.9 (7.93)	**<.001**	1.66
Organization of Materials	66.8 (8.43)	52.4 (9.81)	**<.001**	1.57
Global Executive Composite	72.1 (8.41)	54.8 (11.32)	**<.001**	1.74

Table 13. Group performance on neuropsychological (Toolbox) and behavioral variables (CBCL, BRIEF-2), stratified by enrollment prior to (pre-COVID) or during the COVID-19 pandemic (COVID).

Neuropsychological Variable [*Mean* (SD)]	Pre-COVID				COVID			
	AE (*n* = 9)	CON (*n* = 12)	*p*	Cohen's *d*	AE (*n* = 14)	CON (*n* = 15)	*p*	Cohen's *d*
NIH Toolbox (Age-Corrected SS)								
Picture Vocabulary	101.4 (13.45)	110.1 (18.84)	.257	0.53	100.9 (9.98)	110.7 (19.55)	.104	0.63
Picture Sequence Memory	93.4 (6.84)	101.9 (21.05)	.262	0.54	89.62 (15.89)	102.7 (18.21)	.054	0.77
Dimensional Change Card Sorting	94.9 (15.02)	94.7 (17.76)	.976	0.01	--	--		
Flanker Executive Functioning & Inhibitory Control	95.0 (15.69)	98.5 (12.83)	.580	0.24	--	--		
List Sorting Working Memory	95.6 (14.93)	100.3 (22.52)	.588	0.25	88.2 (17.67)	103.8 (15.88)	.021	0.93
Oral Reading Recognition	90.0 (8.53)	101.0 (14.77)	.061	0.91	96.1 (14.11)	104.5 (10.45)	.079	0.68
Pattern Comparison Processing Speed	84.7 (15.91)	95.6 (16.56)	.145	0.67	--	--		
Fluid Composite	87.7 (13.67)	96.7 (20.50)	.269	0.52	--	--		
Crystallized Composite	94.9 (10.18)	106.3 (15.91)	.075	0.86	--	--		
Total Composite	89.2 (10.15)	101.7 (21.28)	.123	0.75	--	--		
Early Childhood Composite	93.7 (12.30)	101.8 (19.81)	.291	0.5	--	--		

Table 13 (continued). Group performance on neuropsychological (Toolbox) and behavioral variables (CBCL, BRIEF-2), stratified by enrollment prior to (pre-COVID) or during the COVID-19 pandemic (COVID).

Neuropsychological Variable [*Mean* (SD)]	Pre-COVID				COVID			
	AE (*n* = 9)	CON (*n* = 12)	*p*	*Cohen's d*	AE (*n* = 15)	CON (*n* = 15)	*p*	*Cohen's d*
Child Behavior Checklist (CBCL; T-Score)								
Anxious/Depressed	60.2 (10.53)	53.6 (6.10)	.084	0.77	60.4 (7.64)	56.4 (6.59)	.136	0.56
Withdrawn/Depressed	62.0 (11.66)	53.2 (4.55)	.026	1.00	60.3 (7.59)	55.3 (7.49)	.080	0.66
Somatic Complaints	59.1 (8.48)	53.6 (6.05)	.097	0.75	58.0 (7.67)	54.8 (6.28)	.222	0.46
Social Problems	60.7 (5.79)	54.1 (6.29)	.024	1.09	61.1 (7.24)	56.2 (8.13)	.090	0.64
Thought Problems	65.9 (9.44)	54.7 (5.66)	.003	1.44	66.9 (10.51)	57.2 (8.27)	.009	1.02
Attention Problems	69.3 (6.69)	56.5 (8.64)	.002	1.66	67.5 (9.81)	56.8 (9.03)	.004	1.13
Rule Breaking Behavior	69.0 (5.66)	54.9 (4.78)	<.001	2.69	62.9 (7.67)	54.9 (6.96)	.006	1.09
Aggressive Behavior	68.9 (9.05)	54.8 (5.29)	<.001	1.90	64.3 (6.01)	55.9 (9.68)	.008	1.04
Sluggish Cognitive Tempo	62.3 (8.70)	52.1 (4.14)	.002	1.50	58.8 (7.94)	55.6 (7.01)	.252	0.43
Obsessive Compulsive Problems	61.7 (13.94)	54.3 (4.91)	.105	0.70	62.9 (10.96)	58.0 (9.29)	.200	0.48
Stress Problems	66.3 (11.47)	54.8 (5.97)	.007	1.26	64.8 (7.58)	56.5 (7.95)	.007	1.07
Internalizing Problems	60.6 (11.94)	48.4 (10.53)	.023	1.08	60.0 (9.85)	53.8 (9.73)	.094	0.63
Externalizing Problems	69.2 (5.76)	51.0 (10.23)	<.001	2.19	64.2 (7.52)	50.6 (13.00)	.002	1.28
Total Problems	67.4 (7.13)	49.4 (11.43)	.001	1.89	66.4 (7.47)	53.1 (11.97)	.001	1.34

Table 13 (continued). Group performance on neuropsychological (Toolbox) and behavioral variables (CBCL, BRIEF-2), stratified by enrollment prior to (pre-COVID) or during the COVID-19 pandemic (COVID).

Neuropsychological Variable [*Mean* (SD)]	Pre-COVID				COVID			
	AE (*n* = 9)	CON (*n* = 12)	*p*	*Cohen's d*	AE (*n* = 15)	CON (*n* = 15)	*p*	*Cohen's d*
BRIEF-2 (T-Score)								
Behavior Regulation Index	72.7 (8.94)	56.7 (12.64)	.004	1.46	66.9 (13.23)	51.1 (12.82)	.003	1.21
Inhibit	63.7 (7.84)	53.6 (7.65)	.008	1.30	68.5 (10.64)	53.4 (14.67)	.003	1.18
Self-Monitor	71.1 (8.10)	56.1 (11.29)	.003	1.53	69.4 (12.63)	52.2 (14.33)	.002	1.27
Emotion Regulation Index	70.6 (10.39)	53.4 (9.92)	.001	1.69	72.7 (12.94)	55.5 (12.61)	.001	1.35
Shift	69.3 (10.42)	58.7 (10.03)	.028	1.04	67.5 (10.11)	54.4 (12.81)	.004	1.14
Emotional Control	71.8 (11.01)	56.6 (10.00)	.004	1.45	71.7 (10.54)	55.3 (13.06)	.001	1.38
Cognitive Regulation Index	62.3 (7.95)	54.2 (7.26)	.024	1.07	65.7 (7.80)	52.2 (10.78)	.001	1.43
Initiate	68.8 (6.76)	52.8 (9.10)	<.001	1.99	68.2 (7.54)	53.9 (13.98)	.002	1.28
Working Memory	62.9 (9.33)	53.3 (7.64)	.018	1.12	64.6 (9.92)	50.6 (10.74)	.001	1.35
Plan/Organize	61.6 (11.86)	53.3 (11.89)	.129	0.70	60.8 (11.71)	49.3 (9.65)	.006	1.08
Task-Monitor	64.4 (9.95)	49.7 (6.18)	<.001	1.78	63.9 (8.85)	50.1 (9.31)	<.001	1.51
Organization of Materials	66.7 (8.97)	52.9 (8.44)	.002	1.58	66.8 (8.41)	52.0 (11.06)	<.001	1.51
Global Executive Composite	71.9 (5.62)	56.2 (9.73)	<.001	1.98	72.3 (9.91)	53.7 (12.68)	<.001	1.63

A subset of the sample completed the Quotient ADHD System; no significant group differences were observed on any Quotient variable (see **Table 14**).

Table 14. Group performance on Quotient ADHD System variables.

Quotient ADHD System Variable Age Percentile (*Median* [IQR])	AE (*n* = 5)	CON (*n* = 11)	*p*
Movement			
Immobility Duration	61 [3, 76]	21 [7, 37]	.495
Movements	56 [3, 71]	9 [6, 36]	.363
Displacement	62 [4, 76]	8 [5, 30]	.255
Area	32 [4, 55]	6 [3, 17]	.306
Spatial Complexity	36 [4, 61]	11 [4, 24]	.569
Temporal Scaling	39 [4, 69]	26 [4, 31]	.307
Attention			
Accuracy	37 [8, 58]	30 [20, 61]	.777
Omission Errors	20 [3, 54]	14 [2, 35]	.82
Commission Errors	41 [25, 58]	58 [35, 90]	.212
Latency	80 [65, 87]	84 [48, 99]	.854
Variability	11 [7, 44]	11 [1, 29]	.460
C.O.V.	24 [7, 63]	25 [13, 57]	.910
Attentional State			
Number of Shifts	51 [34, 61]	40 [20, 68]	.734
Attentive Blocks	33 [10, 61]	32 [20, 64]	.821
Impulsive Blocks	58 [41, 70]	83 [54, 89]	.173
Distracted Blocks	24 [16, 52]	13 [6, 74]	.532
Random Blocks	29 [15, 99]	99 [28, 99]	.586
Minimal Blocks	99 [2, 99]	16 [3, 99]	.907
Contrary Blocks	99 [52, 99]	99 [99, 99]	.934

Aim 2a Summary. Hypotheses for this aim were partially supported, such that the AE group showed poorer performance than the CON group on measures of episodic memory, working memory, and language. In addition, the AE group had significantly higher scores than the CON group on all subscales of the CBCL and BRIEF-2, reflecting more problems.

Hypotheses 2b and 2c.

NIH Toolbox. Across groups, there were no significant correlations between average sleep time and NIH Toolbox Cognition variables (see **Figure 7**). Correlations stratified by group revealed that, within the CON group, greater average sleep time was significantly associated with better performance on the Pattern Completion Processing Speed subtest as well as higher scores on the Fluid Cognition Composite, Crystallized Composite, Total Composite, and Early Childhood Composite. In contrast, there were no significant associations within the AE group.

Night-to-night variability in sleep time was significantly associated with Picture Sequence Memory across the entire sample: greater sleep time variability was related to poorer performance on this subtest. When stratified by group, greater variability in sleep time was unexpectedly associated with better performance on the Pattern Completion Processing Speed subtest within the AE group. Within the CON group, there were no significant relationships between sleep time variability and NIH Toolbox Cognition variables.

Post-hoc analyses. Across groups, there was a significant correlation between CSHQ Total Score and List Sorting Working Memory and Early Childhood Composite, such that more parent-reported sleep problems were related to lower scores on these subscales (see **Figure 8**). When stratified by group, CSHQ Total Score was significantly negatively correlated with List Sorting Working Memory in the AE group; there were no significant associations within the CON group.

The PSQ Total Score showed significant relationships with the Picture Vocabulary, List Sorting Working Memory, Oral Reading Recognition subscales, as well as the Crystallized Composite and Total Composites; higher PSQ Total Score was related to lower scores on these subscales and composites. When stratified by group, PSQ Total Score showed a significant

negative correlation with Picture Vocabulary, List Sorting Working Memory, and Crystallized Composite in the AE group. In the CON group, higher PSQ Total Score was associated with lower scores on the Pattern Comparison Processing Speed subtest.

	Average Sleep Time			Sleep Time Variability		
	All	CON	AE	All	CON	AE
Picture Vocabulary	0.12	0.19	0.13	-0.17	-0.17	0.02
^Picture Sequence Memory	0.25	0.31	0.37	-0.35*	-0.24	-0.28
+Dimensional Change Card Sorting	0.07	0.53	-0.42	0.22	0.33	0.30
+Flanker	0.11	0.12	0.15	0.05	-0.12	0.41
^List Sorting Working Memory	0.07	0.13	0.09	-0.28	-0.14	-0.24
Oral Reading	0.02	0.07	0.06	-0.12	-0.31	0.26
+Pattern Completion Processing Speed	0.12	0.62*	-0.19	-0.02	-0.11	0.69*
+Fluid Composite	0.28	0.76**	-0.13	-0.09	-0.10	0.45
+Crystallized Composite	0.23	0.66*	-0.02	-0.30	-0.09	0.04
+Total Composite	0.29	0.74**	-0.10	-0.20	-0.10	0.38
+Early Childhood Composite	0.25	0.70*	-0.18	-0.06	0.08	0.30

Figure 7. Pearson r correlations between NIH Toolbox Cognition measures and two-week average Sleep Time and night-to-night variability in Sleep Time. Note: * $p < .05$, ** $p < .01$, ^AE group: $n = 22$, +CON group: $n = 12$; AE group: $n = 9$.

	CSHQ Total Score			PSQ Total Score		
	All	CON	AE	All	CON	AE
Picture Vocabulary	-0.24	-0.10	-0.29	-0.41**	-0.21	-0.50*
^Picture Sequence Memory	-0.16	-0.01	-0.09	-0.30	-0.21	0.02
+Dimensional Change Card Sorting	-0.37	-0.35	-0.46	-0.29	-0.46	-0.60
+Flanker	-0.39	-0.15	-0.54	-0.31*	-0.59	-0.03
^List Sorting Working Memory	-0.33*	-0.04	-0.49*	-0.36**	-0.09	-0.44*
Oral Reading	-0.21	-0.09	-0.11	-0.42	-0.42	-0.11
+Pattern Completion Processing Speed	0.01	0.07	0.08	-0.34	-0.88**	0.15
+Fluid Composite	-0.35	-0.21	-0.52	-0.41	-0.66	-0.18
+Crystallized Composite	-0.33	-0.32	-0.32	-0.59*	-0.46	-0.74*
+Total Composite	-0.37	-0.27	-0.61	-0.55*	-0.59	-0.57
+Early Childhood Composite	-0.45*	-0.37	-0.62	-0.47	-0.52	-0.51

Figure 8. Pearson r correlations between NIH Toolbox Cognition measures and CSHQ Total Score and PSQ Total Score. Note: * $p < .05$, ** $p < .01$, ^AE group: $n = 22$, +CON group: $n = 12$; AE group: $n = 9$.

CBCL. There were no significant correlations between average sleep time and CBCL variables across groups (see **Figure 9**). Correlations stratified by group revealed that, within the AE group, greater average sleep time was associated with lower scores (i.e., fewer problems) on the Attention Problems, Sluggish Cognitive Tempo, and Obsessive Compulsive subscales. There were no significant associations within the CON group.

Greater night-to-night variability in sleep time was significantly associated with higher scores (i.e., more problems) on the Attention Problems, Rule Breaking Behavior, and Sluggish Cognitive Tempo subscales across groups. In addition, greater sleep time variability was associated with higher scores on the Externalizing Problems and Total Problems composite scores. However, when stratified by group, there were no significant associations between sleep time variability and CBCL variables.

Figure 9. Spearman's rho correlations between Child Behavior Checklist subscales and two-week average Sleep Time and night-to-night variability in Sleep Time. *Note: * p < .05, ** p < .01.*

Post-hoc analyses. Across groups, CSHQ Total Score showed significant positive associations with most CBCL outcomes, with the exception of Social Problems, Rule Breaking, and Externalizing Problems (see **Figure 10**). When stratified by group, the AE group showed significant positive associations between CSHQ Total Score and the Anxious Depressed, Somatic Complaints, Thought Problems. Attention Problems, Obsessive Compulsive, and Stress subscales, as well as the Internalizing and Total Problems composite scores. In contrast, the CON group showed a single negative association between CSHQ Total Score and Rule Breaking Behavior.

Across the sample, higher PSQ Total Score was significantly associated with higher

scores on nearly all CBCL outcomes, with the exception of the Anxious Depressed subscale.

Within the AE group, there was a significant positive association between PSQ Total Score and

the Thought Problems subscale. The CON group showed a significant positive correlation

between PSQ Total Score and the Attention Problems, Sluggish Cognitive Tempo, and Stress

subscales, as well as Internalizing Problems composite score.
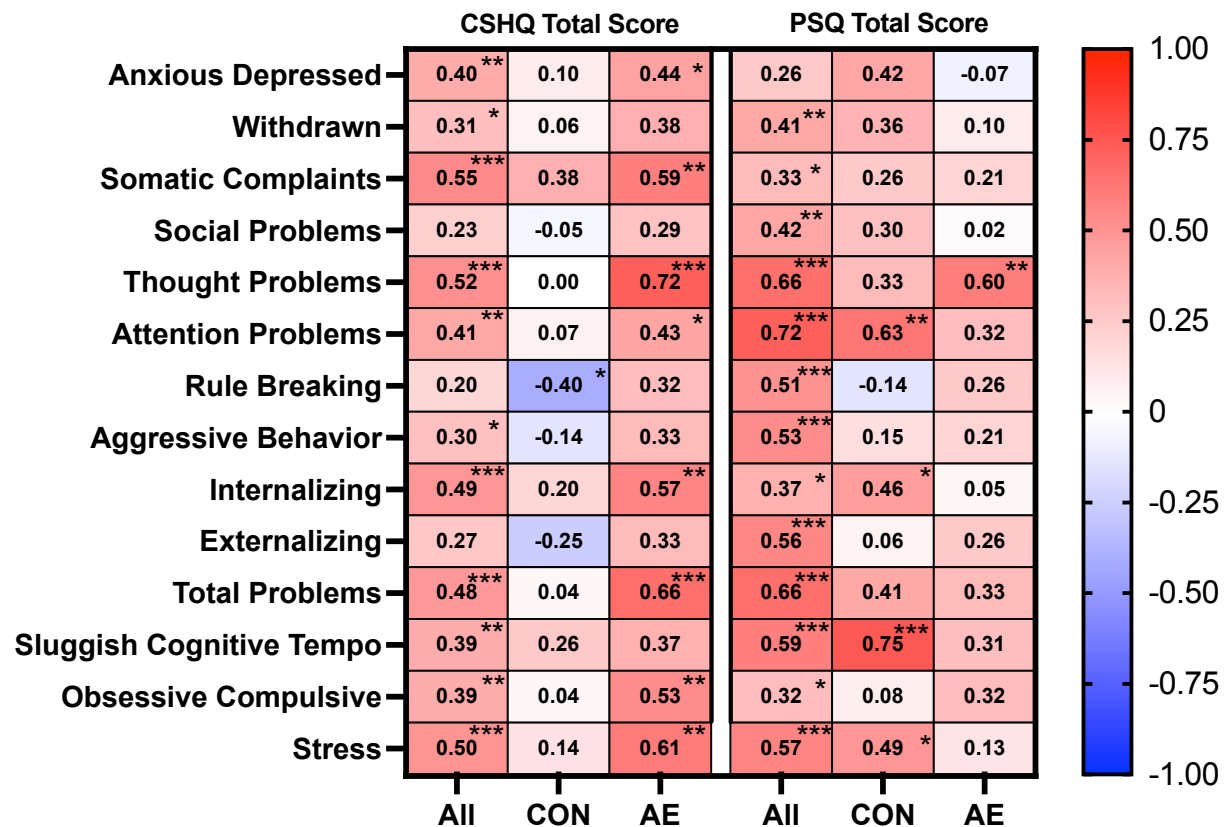
Figure 10. Spearman's rho correlations between Child Behavior Checklist subscales and CSHQ Total Score and PSQ Total Score. Note: * $p < .05$, ** $p < .01$, *** $p < .001$.

BRIEF-2. There were no significant relationships between average sleep time and BRIEF-2

variables across the sample or when stratified by group (see **Figure 11**). However, greater night-

to-night variability in sleep time was significantly associated with higher scores (i.e., more

problems) on the Working Memory subscale across groups. There were no significant

associations between sleep time variability and BRIEF-2 outcomes when stratified by group.

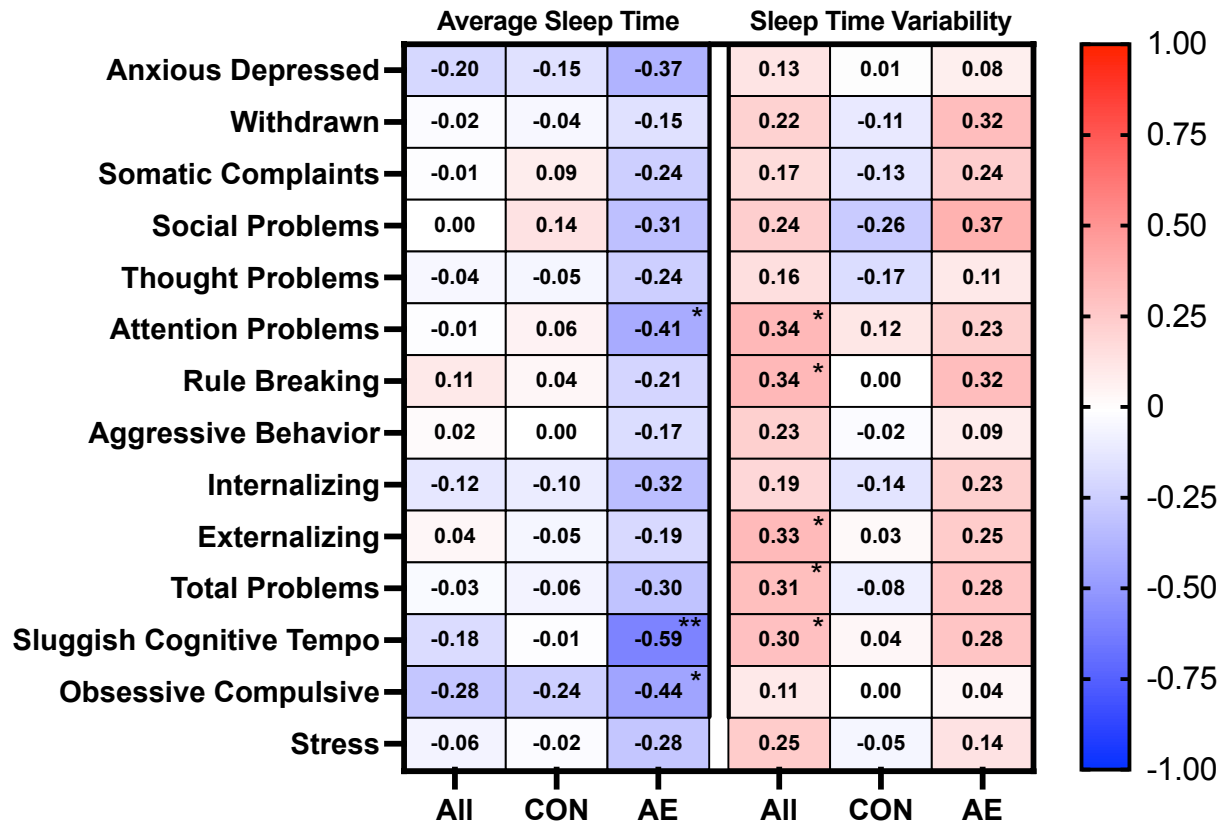|	Average Sleep Time			Sleep Time Variability		
Inhibit	0.08	-0.02	0.08	0.19	-0.07	-0.03
Self Monitor	-0.04	-0.08	-0.13	0.15	-0.14	0.12
Behavior Regulation Index	0.07	-0.04	0.13	0.18	-0.11	-0.05
Shift	-0.02	-0.01	-0.20	0.17	-0.26	0.14
Emotional Control	0.14	0.23	0.05	-0.04	-0.31	-0.30
Emotional Regulation Index	0.07	0.11	-0.01	0.07	-0.29	-0.16
Initiate	-0.05	0.05	-0.35	0.26	-0.09	0.36
Working Memory	0.09	0.21	-0.26	0.31 *	0.12	0.08
Plan/Organize	-0.07	-0.08	-0.30	0.16	-0.25	0.12
Task Monitor	0.01	-0.04	-0.14	0.10	0.02	-0.07
Organization Materials	-0.07	-0.21	-0.32	0.14	0.09	-0.11
Cognitive Regulation Index	0.00	0.01	-0.24	0.22	0.05	-0.02
Global Executive Composite	0.01	0.06	-0.27	0.20	-0.10	0.00
	All	CON	AE	All	CON	AE

Figure 11. Spearman's rho correlations between BRIEF-2 subscales and two-week average Sleep Time and night-to-night variability in Sleep Time. Note: * *p* < .05.

Post-hoc analyses. Across groups, CSHQ Total Score showed significant positive

associations with nearly all BRIEF-2 outcomes, with the exception of Self Monitor, Emotional

Control, and Task Monitor Subscales (see **Figure 12**). When stratified by group, the AE group

showed significant associations between higher CSHQ Total Score and more problems on the

Shift and Initiate subscales, as well as the Emotion Regulation Index and Global Executive

Composite. There were no statistically significant associations between CSHQ Total Score and any BRIEF-2 outcomes within the CON group.

Across the sample, higher PSQ Total Score was significantly associated with higher scores on all BRIEF-2 outcomes. Within the AE group, PSQ Total Score showed a positive association with the Plan/Organize subscale, as well as the Global Executive Composite. In the CON group, PSQ Total Score was significantly positively correlated with the Inhibit, Working Memory, and Task-Monitor Subscales, as well as the Cognitive Regulation Index.

	CSHQ Total Score			PSQ Total Score		
	All	CON	AE	All	CON	AE
Inhibit	0.29 *	0.00	0.28	0.63 ***	0.45 *	0.33
Self Monitor	0.25	-0.19	0.13	0.48 ***	0.23	0.11
Behavior Regulation Index	0.28 *	-0.10	0.18	0.60 ***	0.37	0.21
Shift	0.51 ***	0.12	0.59 **	0.58 ***	0.19	0.35
Emotional Control	0.25	-0.01	0.14	0.44 **	0.21	0.00
Emotional Regulation Index	0.40 **	0.02	0.42 *	0.53 ***	0.18	0.18
Initiate	0.39 **	0.10	0.43 *	0.61 ***	0.40	0.38
Working Memory	0.29 *	0.09	-0.01	0.65 ***	0.44 *	0.24
Plan/Organize	0.35 *	-0.14	0.35	0.60 ***	0.28	0.41 *
Task Monitor	0.26	0.02	0.31	0.56 ***	0.47 *	0.36
Organization Materials	0.35 *	0.00	0.21	0.52 ***	0.13	0.25
Cognitive Regulation Index	0.38 **	0.01	0.30	0.67 ***	0.43 *	0.38
Global Executive Composite	0.41 **	-0.02	0.46 *	0.69 ***	0.42	0.46 *

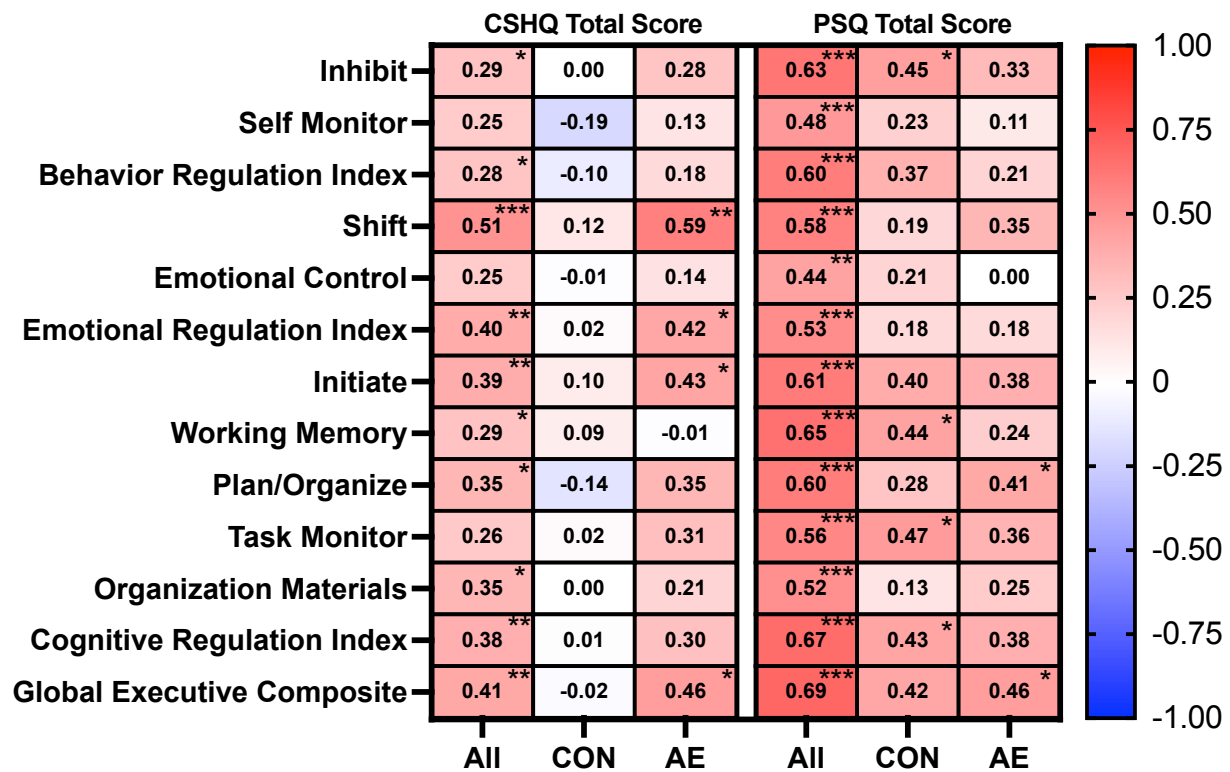**Figure 12**. Spearman's rho correlations between BRIEF-2 subscales and CSHQ Total Score and PSQ Total Score. Note: * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 15 reports results for the stepwise multivariable linear regression analysis predicting outcomes from the NIH Toolbox, CBCL, and BRIEF-2 that were significantly

associated with SD Sleep Time. Parental education, sleep disorder diagnosis, testing day

stimulant medication use, melatonin use, and testing time of day were examined as covariates.

Those that demonstrated a significant association with the dependent variable were included in

the regression model. Relationships between SD Sleep Time and outcome variables stratified by

group are shown in **Figure 13.**

Table 15. Stepwise multivariable linear regression models predicting neurobehavioral outcomes on the NIH Toolbox, Child Behavior Checklist (CBCL), and BRIEF-2.

Outcome	Step 1			Step 2			Step 3		
Picture Sequence Memory T-Score	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Group	-11.86	[-21.54, -2.17]	.018	-8.10	[-18.78, 2.57]	.133	-7.05	[-18.21, 4.12]	.21
SD Sleep Time				-0.22	[-0.49, 0.06]	.122	0.06	[-0.79, 0.91]	.883
Group x SD Sleep Time							-0.22	[-0.87, 0.42]	.489

Outcome	Step 1			Step 2			Step 3		
Attention Problems T-Score	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Group	11.51	[6.47, 16.55]	<.001	9.47	[3.99, 14.95]	.001	9.32	[3.52, 15.12]	.002
SD Sleep Time				0.12	[-0.02, 0.26]	.09	0.09	[-0.35, 0.52]	.694
Group x SD Sleep Time							0.03	[-0.31, 0.36]	.866

Outcome	Step 1			Step 2			Step 3		
Rule Breaking Behavior T-Score	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Group	10.18	[6.25, 14.12]	<.001	8.69	[4.4, 12.98]	<.001	8.87	[4.33, 13.41]	<.001
SD Sleep Time				0.09	[-0.02, 0.2]	.112	0.13	[-0.21, 0.48]	.437
Group x SD Sleep Time							-0.04	[-0.3, 0.23]	.781

Outcome	Step 1			Step 2			Step 3		
Sluggish Cognitive Tempo T-Score	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Group	6.60	[2.48, 10.72]	.002	4.71	[0.27, 9.14]	.038	4.94	[0.25, 9.63]	.039
SD Sleep Time				0.11	[0, 0.23]	.053	0.17	[-0.19, 0.52]	.341
Group x SD Sleep Time							-0.05	[-0.32, 0.23]	.733

Outcome	Step 1			Step 2			Step 3		
Externalizing Problems T-Score	b	95% CI	*p*	b	95% CI	*p*	b	95% CI	*p*
Group	14.62	[9.03, 20.21]	<.001	13.65	[7.42, 19.89]	<.001	13.76	[7.16, 20.36]	<.001
SD Sleep Time				0.06	[-0.1, 0.22]	.475	0.08	[-0.42, 0.58]	.738
Group x SD Sleep Time							-0.02	[-0.4, 0.36]	.912

Table 15 (continued). Stepwise multivariable linear regression models predicting neurobehavioral outcomes on the NIH Toolbox, Child Behavior Checklist (CBCL), and BRIEF-2.

Outcome	Step 1			Step 2			Step 3		
Total Problems T-Score	b	95% CI	p	b	95% CI	p	b	95% CI	p
Group	10.26	[3.76, 16.75]	.003	8.91	[2.04, 15.77]	.012	9.15	[2.05, 16.24]	.013
Parent Education Level	13.19	[-5.84, 32.22]	.169	15.18	[-4.08, 34.44]	.119	14.0	[-6.75, 34.73]	.181
SD Sleep Time				0.09	[-0.06, 0.25]	.244	0.11	[-0.07, 0.28]	.24
Group x SD Sleep Time							0.07	[-0.33, 0.47]	.737

Outcome	Step 1			Step 2			Step 3		
Working Memory T-Score	b	95% CI	p	b	95% CI	p	b	95% CI	p
Group	14.43	[8.73, 20.13]	<.001	12.98	[6.66, 19.29]	<.001	12.39	[5.73, 19.05]	.001
SD Sleep Time				0.09	[-0.08, 0.25]	.291	-0.06	[-0.56, 0.45]	.823
Group x SD Sleep Time							0.12	[-0.27, 0.5]	.55

NIH Toolbox Picture Sequence Memory. Step 1, which examined the independent effect of group, demonstrated significantly lower standard scores on the NIH Toolbox Picture Sequence Memory subtest in the AE group compared to the CON group (b=-11.85, *p*=.018). Step 2, which added SD Sleep Time as a predictor of Picture Sequence Memory standard scores, demonstrated no significant effect of sleep time variability on Picture Sequence Memory performance (b=-0.215, *p*=.122). Step 3, which examined whether SD Sleep Time moderated the effects of group on Picture Sequence Memory performance, showed no significant interaction of sleep time variability and group for Picture Sequence Memory performance (b=-0.223, *p*=.489).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on NIH Toolbox Picture Sequence Memory was not statistically significant (B = -3.76, SE = 2.54, *p* = .140).

CBCL Attention Problems. Step 1, which examined the independent effect of group, demonstrated significantly higher T-scores on the CBCL Attention Problems subscale in the AE

group compared to the CON group (b=11.51, $p<.001$). Step 2, which added SD Sleep Time as a predictor of Attention Problems T-scores, demonstrated a trend-level effect of sleep time variability on Attention Problems (b=0.12, $p=.09$). There was also still a significant effect of group (b=9.47, $p=.001$). Step 3, which examined whether SD Sleep Time moderated the effects of group on attention problems, showed no significant interaction of sleep time variability and group for Attention Problems T-scores (b=0.03, $p=.866$).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Attention Problems T-score was not statistically significant (B = 2.05, SE = 1.30, $p = .114$).

CBCL Rule Breaking Behavior. Step 1, which examined the independent effect of group, demonstrated significantly higher T-scores on the CBCL Rule Breaking Behavior subscale in the AE group compared to the CON group (b=10.18, $p<.001$). Step 2, which added SD Sleep Time as a predictor of Rule Breaking Behavior T-scores, demonstrated no significant effect of sleep time variability on Rule Breaking Behavior (b=.09, $p=.112$), although there was still a significant effect of group (b=8.69, $p<.001$). Step 3, which examined whether SD Sleep Time moderated the effects of group on rule breaking behavior, showed no significant interaction of sleep time variability and group for Rule Breaking Behavior T-scores (b=-0.04, $p=.781$).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Rule Breaking Behavior T-score was not statistically significant (B = 1.50, SE = 1.00, $p = .134$).

CBCL Sluggish Cognitive Tempo. Step 1, which examined the independent effect of group, demonstrated significantly higher T-scores on the CBCL Sluggish Cognitive Tempo subscale in the AE group compared to the CON group (b=6.6, $p=.002$). Step 2, which added SD

Sleep Time as a predictor of Sluggish Cognitive Tempo T-scores, demonstrated a trend-level effect of sleep time variability on Sluggish Cognitive Tempo (b=0.112, p=.053), as well as a significant effect of group (b=4.706, p=.038). Step 3, which examined whether SD Sleep Time moderated the effects of group on sluggish cognitive tempo, showed no significant interaction of sleep time variability and group for Sluggish Cognitive Tempo T-scores (b=-0.05, p=.733).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Sluggish Cognitive Tempo T-score was trend-level but did not reach statistical significance (B = 1.90, SE = 1.08, p = .080).

CBCL Externalizing Problems. Step 1, which examined the independent effect of group, demonstrated significantly higher T-scores on the CBCL Externalizing Problems composite score in the AE group compared to the CON group (b=14.62, p<.001). Step 2, which added SD Sleep Time as a predictor of Externalizing Problems T-scores, demonstrated no significant effect of sleep time variability on Externalizing Problems (b=0.06, p=.475), although group demonstrated a significant effect (b=13.65, p=.038). Step 3, which examined whether SD Sleep Time moderated the effects of group on externalizing problems, showed no significant interaction of sleep time variability and group for Externalizing Problems T-scores (b=-0.02, p=.912).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Externalizing Problems T-score was not statistically significant (B = 0.97, SE = 1.33, p = .468).

CBCL Total Problems. Step 1, which examined the independent effect of group controlling for parent education level, demonstrated significantly higher T-scores on the CBCL Total Problems composite score in the AE group compared to the CON group (b=10.26, p=.003).
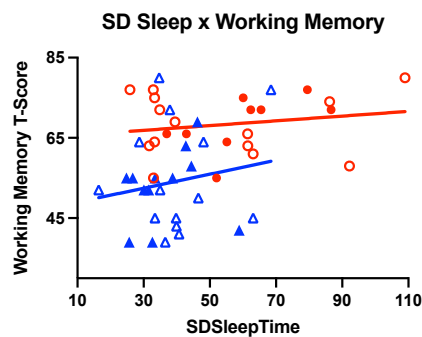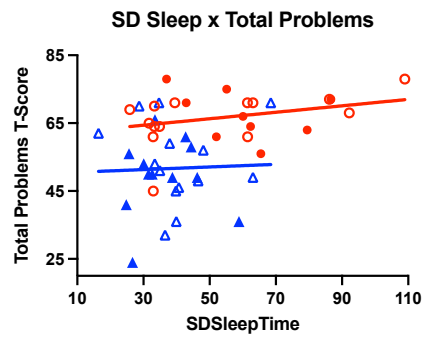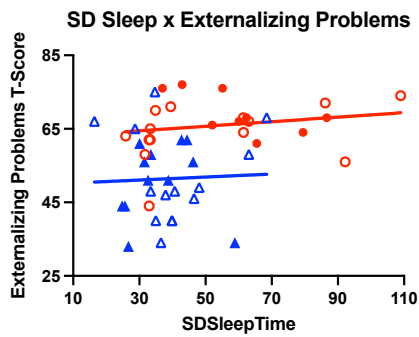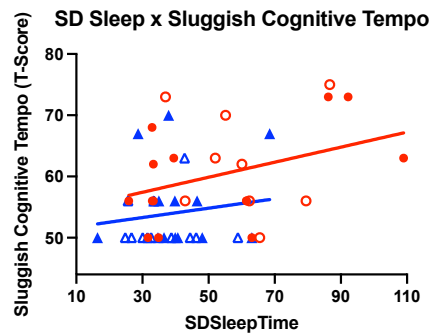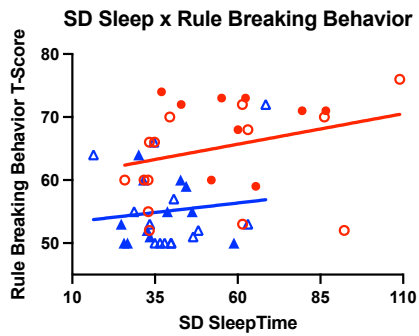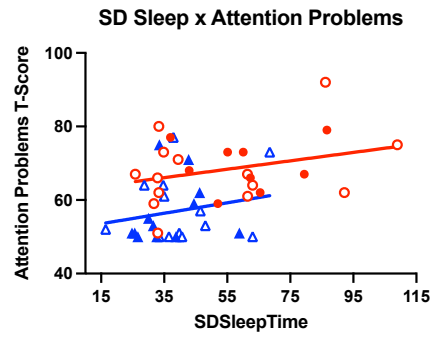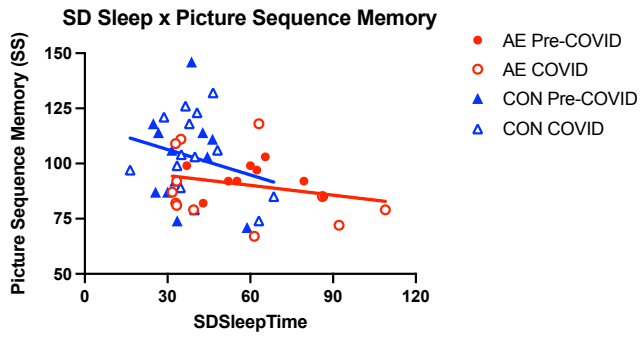
Step 2, which added SD Sleep Time as a predictor of Total Problems T-scores, demonstrated no significant effect of sleep time variability on Total Problems (b=0.09, *p*=.244). Step 3, which examined whether SD Sleep Time moderated the effects of group on total problems, showed no significant interaction of sleep time variability and group for Total Problems T-scores (b=0.07, *p*=.737).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Total Problems T-score was not statistically significant (B = 1.39, SE = 1.40, *p* = .319).

BRIEF-2 Working Memory. Step 1, which examined the independent effect of group, demonstrated significantly higher T-scores on the BRIEF-2 Working Memory subscale in the AE group compared to the CON group (b=14.43, *p*<.001). Step 2, which added SD Sleep Time as a predictor of Working Memory T-scores, demonstrated no significant effect of sleep time variability on working memory (b=0.09, *p*=.291),), although group demonstrated a significant effect (b=12.98, *p*<.001). Step 3, which examined whether SD Sleep Time moderated the effects of group on working memory, showed no significant interaction of sleep time variability and group for Working Memory T-scores (b=-0.06, *p*=.550).

When group and SD Sleep Time were entered simultaneously in the mediation model, the indirect effect of group via SD Sleep Time on Working Memory T-score was not statistically significant (B = 1.45, SE = 1.39, *p* = .294).

Figure 13. Scatter plots of sleep time variability (SD Sleep Time) with neurobehavioral outcomes that demonstrated a statistically significant correlation. Slope estimates are based on AE-status; pre-COVID and COVID data points are presented for descriptive purposes only. AE = alcohol-exposed, CON = control, SD = standard deviation, SS = standard score.

SD Sleep x Picture Sequence Memory

SD Sleep x Attention Problems

SD Sleep x Rule Breaking Behavior

SD Sleep x Sluggish Cognitive Tempo

SD Sleep x Externalizing Problems

SD Sleep x Total Problems

SD Sleep x Working Memory

AE Pre-COVID
AE COVID
CON Pre-COVID
CON COVID

Chapter III, in part, is currently being prepared for submission for publication of the material. Inkelis, S. M.; Chambers, C.; Mattson, S. N.; Bhattacharjee, R.; Thomas, J. D. The dissertation author was the primary investigator and author of this material.

IV. DISCUSSION

A small number of studies have demonstrated that children with prenatal alcohol exposure have sleep problems, including fragmented sleep, increased arousal during sleep, and melatonin secretion abnormalities. Typically developing children and children with neurodevelopmental disorders both show relationships between greater levels of sleep disturbance and more cognitive and behavioral difficulties. However, investigation of these relationships in children with FASD has been limited. Therefore, the aim of this study was to characterize the sleep profile in children with FASD and explore potential relationships between sleep quality and neurobehavioral measures.

Specific Aim 1

Actigraphy. Overall, there were no group differences on average actigraphy sleep metrics. Both groups slept approximately 8 hours on average, with nearly identical percent sleep (86.8% vs. 86.9%), which is similar to values observed in a large polysomnography study of FASD (Dylag et al., 2021). Despite similar two-week averages on actigraphy variables, the AE group had significantly greater levels of intraindividual (night-to-night) variability in WASO, number of wake bouts, sleep time, and percent sleep, relative to controls. There were no COVID-related differences in sleep metrics across the sample or in either group.

Average weekday and weekend actigraphy measures were highly correlated. Across the sample, average sleep time was 15 minutes lower on weekends, and there was greater variability in sleep time, compared to weekdays. On weekdays, average WASO and number of wake bouts were also higher. Separate MANOVAs examining the sleep profile on weekdays and weekends revealed similar patterns relative to the two-week actigraphy analysis: the omnibus effect of

group was driven by differences in sleep variability, with no differences in average actigraphy values.

Although the use of actigraphy to study sleep in children with FASD has been very limited, these findings are similar to those observed by Wengel and colleagues (2011), who found no significant differences between children with FASD and controls ages 3 to 6 on one-week average actigraphy measures of sleep efficiency, sleep percent, sleep time, or number of wake bouts. In contrast, another week-long actigraphy study of children ages 6 to 12 showed that the FASD group had lower average sleep time, sleep efficiency, and more fragmentation than typically developing controls (Mughal, Hill, Joyce, & Dimitriou, 2020). Examining the means reported in the study by Mughal et al. (2020), their alcohol-exposed group had 6 hours 58 minutes of actual sleep time on average, whereas our AE group had 8 hours 8 minutes. The sleep efficiency and fragmentation index were also higher in their alcohol-exposed group compared to controls. In contrast, our AE and CON groups were very similar on these metrics. Intraindividual variability metrics were not reported, but the standard deviation of actual sleep time was more than 1 hour (FASD: 1 hour 11 minutes, Control: 1 hour 4 minutes), suggesting high variability in this measure across both groups.

Importantly, actigraphy is not the gold-standard of sleep measurement and has a low specificity (i.e., accuracy) in detecting wakefulness during periods of sleep (Sadeh, 2011). The lack of observed group differences on average actigraphy metrics may also be a reflection of unmeasured characteristics of the AE group (e.g., level of family/home environment stability, parenting style, stress level) that fostered overall sleep variables that were relatively similar to the CON group. Although the CON group showed average sleep time similar to that observed in the Mughal et al. (2020) control sample, it should be noted that our sample included typically

developing children who had behavioral concerns and diagnoses (e.g., ADHD, anxiety, depression) that are also related to sleep disturbance. In addition, there may have been selection bias such that typically developing children may have been more likely to participate in the study if they had concerns about sleep and/or pre-existing sleep problems.

Overall, the profile of objectively measured sleep in this sample is characterized by similar average sleep metrics, but much greater intraindividual variability in number of awakenings, time spent awake (WASO), sleep time, and percent sleep. Few studies have examined the implications of daily variations in sleep, although research has increasingly demonstrated that intraindividual variability in sleep patterns is related to a variety of physical and mental health outcomes (Becker et al., 2017). For example, frequent changes in sleep timing can disrupt the sleep-wake cycle, which can then affect sleep structure, sleep consolidation, and sleep-related biological functions (e.g., hormone expression) (Bangerter et al., 2020; Konen, Dirk, & Schmiedek, 2015; Phillips et al., 2017). Indeed, on polysomnography, children with FASD show altered sleep structure, with a higher number of stage shifts and arousals than controls (Dylag et al., 2021), as well as melatonin secretion abnormalities (Goril et al., 2016). In children and adolescents, sleep variability is also associated with more behavioral problems (e.g., externalizing behavior, aggression, inattention, risky behavior; Becker, Sidol, Van Dyk, Epstein, & Beebe, 2017). Sleep research has traditionally focused on mean sleep variables (e.g., average sleep duration); however, mean sleep/wake variables and intraindividual variability in sleep may have distinct etiologies (Becker et al., 2017; Bei et al., 2016). Bei and colleagues (2016) explain that the biological bases of overall sleep/wake patterns, which are driven by homeostatic drive and circadian rhythm, tend to be relatively stable across days; in contrast, many other factors, such as physical health, stress, home environment, and sleep deprivation/disruption have the

potential to affect sleep/wake cycles on a day-to-day basis (Bei, Wiley, Trinder, & Manber, 2016). Children with FASD are often exposed to adverse environmental circumstances and stressors in the home environment (Streissguth et al., 2004); although these variables were not measured as part of this study, these psychosocial factors may contribute to the elevated sleep variability metrics in our sample. Additionally, preclinical evidence suggests that developmental alcohol exposure affects the expression of clock genes, which play an important role in generating biological rhythms, including the circadian rhythm (Chen, Kuhn, Advis, & Sarkar, 2006). Sarkar et al. (2019) found that children with FASD had increased methylation of two genes that are critical to stress and circadian regulation: period 2 (*PER2*) and proopiomelanocortin (*POMC*). Although further study in humans is needed, these alterations in gene expression may disrupt circadian rhythmicity, and as a result, destabilize the sleep/wake cycle. Differential expression of stress and clock genes could therefore point to specific biological mechanisms that underlie the elevated sleep time variability observed in the AE group.

Sleep Questionnaires. On parent-report questionnaires measuring children's sleep problems, the AE group had significantly higher scores than the CON group. Notably, the AE and CON groups each had average CSHQ total scores above the clinically significant cutoff score of 41, reflecting a high level of reported sleep problems in both groups. Even still, the AE group had significantly higher total scores on the CSHQ, specifically driven by elevated problems with sleep onset delay, night awakenings, and daytime sleepiness. Although we hypothesized there would be group differences on more CSHQ subscales, this profile is similar to findings from Dylag et al. (2021), who found higher scores for FASD on the sleep onset delay, night wakings, and daytime sleepiness subscales, as well as the parasomnias and sleep disordered breathing subscales. In addition, the elevated CSHQ total score is consistent with results from

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prior studies showing that children with FASD had CSHQ total scores above the clinical cutoff (Chen et al., 2012; Wengel et al., 2011). The AE group also had significantly higher PSQ total scores, primarily driven by the sleepiness and behavior subscales. It is important to note that the PSQ behavior subscale contains items that assess inattentive/hyperactive behavior, which are hallmark symptoms of FASD. Although there were three children in the CON group with parent-reported diagnoses of ADHD, half of the AE group (14 children) had ADHD, which likely inflated the high PSQ Total Score in the AE group. However, the group difference on the Sleepiness subscale, coupled with higher daytime sleepiness scores on the CSHQ, suggests that regardless of behavior, the AE group had more problems with sleepiness during the day.

Parent/caregiver-reported sleep problems in children with FASD have been associated with poorer caregiver quality of life, decreased daily family activities, and higher levels of anxiety and worry (Hayes, Moritz, & Reid, 2020). Although measuring caregiver functioning was outside the scope of the current study, these prior studies (Hayes et al., 2020; Ipsiroglu et al., 2013) suggest that sleep problems affect not only the functioning of the child, but also the functioning and well-being of caregivers and the family unit. In one qualitative study, it was noted that the pattern that child sleep problems contributed to caregiver exhaustion and the need for respite care, sometimes even leading to breakdown in the child's placement (Ipsiroglu et al., 2013). When caregivers feel supported to manage the behavior and complex needs of their child with FASD, they are better able to provide a positive, stable home environment, which is a major factor in improving outcomes for individuals affected by prenatal alcohol exposure (Hayes et al., 2020; Petrenko, Tahir, Mahoney, & Chin, 2014; Streissguth et al., 2004). Our findings of clinically significant parent-reported sleep problems further emphasize the need to identify sleep difficulties, not only for the direct benefit of the affected child, but also the well-being of the

caregiver and family. In turn, enhancing the functioning of the family as a whole will promote optimal outcomes for the child's quality of life.

Specific Aim 2

Objective Neuropsychological Performance. Lower performance on measures of neuropsychological functioning is a well-established finding in the FASD literature (Mattson et al., 2011). We therefore hypothesized that the AE group would have lower scores than controls on measures of executive functioning, memory, attention, language, and processing speed. Our hypothesis regarding these differences was partially supported. For assessments that were administered to the entire sample, which included measures of receptive vocabulary, episodic memory, working memory, and reading, the AE group performed significantly worse than the CON group, as expected. For measures that were only administered to the pre-COVID sample (due to in-person testing restrictions during the pandemic), including measures of executive functioning, attention, and processing speed, no significant group differences were observed. The AE group showed a general pattern of lower scores than the CON group, consistent with our hypothesis, and Cohen's *d* effect sizes ranged from 0.24 to 0.86. However, post-hoc power analyses indicated that our pre-COVID subsample was underpowered. Importantly, there were no significant differences in performance on neuropsychological measures that were administered in person or virtually via Zoom.

Subjective Behavior Questionnaires. Parent-reported outcomes on measures of behavioral and executive functioning were consistent with our hypotheses and the literature (Nguyen et al., 2014; Tsang et al., 2016). Parents of children with AE reported more behavioral problems across all subscales, relative to the CON group. Similarly, parent-report measures of

executive functioning showed that the AE group had significantly more problems than the CON group regarding executive functioning skills in everyday life.

      Sleep Quality and Cognition. Contrary to our hypothesis, average sleep quality (operationalized as average total sleep time) was not significantly associated with any cognitive outcome. On the other hand, greater intraindividual variability in sleep time was significantly correlated with poorer performance on a measure of episodic memory (Picture Sequence Memory Test). To our knowledge, only one study has examined the relationship between sleep variability (operationalized as time in bed variability) and memory in typically developing children with obstructive sleep disordered breathing (Suratt et al., 2007), although there was no significant association. Other studies of sleep intraindividual variability and cognition in children have had mixed outcomes, with some showing relationships between greater sleep duration intraindividual variability and poorer performance on complex tasks of sustained attention and working memory (Gruber & Sadeh, 2004; Konen et al., 2015), and others finding no relationship (Suratt et al., 2007). No significant correlation between sleep time intraindividual variability and working memory (List Sorting Working Memory) was observed in our sample, although higher levels of parent-reported sleep problems were associated with lower working memory scores, as well as lower performance on measures of receptive vocabulary and reading. Given our limited sample sizes for more complex measures of attention and executive functioning (e.g., Dimensional Change Card Sort, Flanker), we were not able to fully characterize the associations with sleep time intraindividual variability or other sleep measures due to limited power.

      In terms of group differences, we did not observe differential associations between sleep time intraindividual variability and memory performance based on group membership. Although both group and sleep time intraindividual variability were predictive of memory performance

individually, when they were included in the same model, neither were significant predictors. The failure to detect significant, independent effects of group and sleep variability on memory performance in the multivariable model may be influenced by the small study sample size, thereby limiting power, as well as the intercorrelation between group and sleep, thereby modestly reducing the effect size of each term. Therefore, the significant associations identified in the univariable analysis warrant further exploration of these effects in larger sized samples.

   Relationships between Sleep Quality and Behavior. Our hypothesis that average sleep time would relate to parent-report measures of problem behaviors and executive functioning was not supported. However, intraindividual variability in sleep time was significantly associated with more externalizing problems and total problems, as well as higher scores on subscales examining attention problems, rule breaking behavior, and sluggish cognitive tempo. This is consistent with findings from a study of healthy pre-school children (age 3 to 6), which showed that intraindividual variability in wake times was associated with parent-reported externalizing behavior problems (Yokomaku et al., 2008). In addition, greater parent-reported sleep problems were associated with most measures of parent-reported behavior and executive functioning problems. Further examination of these relationships within each group showed that this finding was primarily driven by the AE group, as nearly all behavioral subscales were significantly positively associated with the level of sleep problems. In contrast, there was only one significant association within the CON group. This discrepancy may reflect a stronger relationship between sleep and behavior problems in the AE group. This could also be related to generally elevated parent-reported problems in the AE group. However, the CSHQ and PSQ demonstrated some selectivity: only a handful of subscales showed elevations in the AE group relative to controls, suggesting that parents reported specific problems related to sleep. In addition, the limited

associations within the CON group may also be related to a floor effect for the T-scores derived from the CBCL and BRIEF-2, resulting in a lack of variability at the lower end of problem behaviors in the CON group, and making it difficult to detect potential associations with measures of sleep problems.

In our sample, group membership accounted for most of the variance in problem behavior scores, and no interaction effects between sleep time intraindividual variability and group were observed. However, for sluggish cognitive tempo, there was an independent trend-level effect of sleep time intraindividual variability, such that greater variability was related to more problems with sluggish cognitive tempo. In addition, there was a trend-level indirect effect of group on sluggish cognitive tempo via sleep time intraindividual variability. Although this exploratory finding did not reach statistical significance, these results suggest that the relationships between sleep and sluggish cognitive tempo should be investigated further in individuals with prenatal alcohol exposure. Sluggish cognitive tempo is characterized by a unique cluster of behavioral symptoms, including decreased alertness, sluggishness, daydreaming, mental fogginess/confusion, and slowed thinking (Kofler et al., 2019; Rondon, Hilton, Jarrett, & Ollendick, 2020). Several studies have found associations between sluggish cognitive tempo and parent-reported sleep problems and daytime sleepiness (Becker, Garner, & Byars, 2016; Becker, Pfiffner, Stein, Burns, & McBurnett, 2016; Koriakin, Mahone, & Jacobson, 2015). In addition, children with prenatal alcohol exposure show elevated scores on measures of sluggish cognitive tempo (Graham et al., 2013). Given its overlapping relationships with sleep and prenatal alcohol exposure, sluggish cognitive tempo is an important outcome to examine in larger studies investigating sleep in individuals with FASD.

Implications for Intervention

Although the present study did not show group differences with respect to average sleep outcomes on objective measures, both the AE and CON groups had clinically relevant sleep problems, as reported on parent sleep questionnaires, which were correlated with objective neuropsychological performance. It is critical to identify sleep problems when they exist and provide adequate treatment, regardless of whether an individual has had prenatal exposure to alcohol. The goal of this study was to elucidate the FASD sleep profile, and our most robust finding was that sleep patterns in children with FASD are characterized by intraindividual variability across objectively measured sleep outcomes, including nighttime awakenings and time spent awake, total sleep time, and percent sleep. The majority of sleep research has focused on average sleep metrics, and as a consequence, recommendations for intervention and public policy changes have targeted overall nightly sleep duration as the metric for optimal sleep health. However, the present findings add to a growing body of literature demonstrating disruptions in night-to-night sleep consistency in clinical populations, independent of mean-based sleep metrics (Becker et al., 2017). The few intervention studies examining sleep intraindividual variability have shown mixed results and are limited by small sample sizes and lack of randomized design and active control groups (Becker et al., 2017), but brief sleep hygiene interventions (i.e., setting a consistent bed/wake-time, discontinuing naps and caffeine use) show some promise in stabilizing sleep. In a systematic review of intraindividual variability of sleep patterns children, less optimal sleep environment, such as watching TV or falling asleep with the lights on, and less structured environmental schedules, such as during weekends and vacations, were related to greater sleep intraindividual variability (Becker et al., 2017). Another observational study found that adaptive bedtime routine activities, such as putting on pajamas, brushing teeth, bedtime hugs, and being tucked in were associated with lower variability in sleep duration and sleep

quality (Spruyt, Raubuck, Grogan, Gozal, & Stein, 2012). Importantly, sleep is a modifiable

behavior, and problems with sleep variability present a significant area for intervention, with the

potential to impact quality of life in children with FASD and their families (Hayes et al., 2020).

Specific interventions for sleep in the FASD population have not been examined and represent

an important future direction for research.

Limitations and Future Directions

The current study is limited by several factors. First, analyses were conducted on a partial sample ($N = 54$) due to recruitment limitations in the midst of the COVID-19 pandemic. In addition, some neuropsychological measures could not be administered in a virtual format, further reducing the number of subjects for those analyses ($n = 21$). Given these restrictions in sample size, many analyses were likely underpowered to detect group differences and relationships with smaller effect sizes (e.g., interactions). In spite of analyses being conducted on a partial sample, there were several statistically significant results, and effect sizes from some analyses point to other relationships between sleep variability and episodic memory and sluggish cognitive tempo that may reach statistical significance with a larger sample.

In addition, a portion of the study data was collected in the midst of a global pandemic, during which stay-at-home orders were implemented and children were typically attending school online. Actigraphy data were collected throughout the year, and for data collected prior to the pandemic, we did not account for deviations from the typical school schedule, such as school holidays and vacations. Although there were no significant group differences between subjects who participated prior to the pandemic and during the pandemic, it is possible that this unique situation affected sleep and behavior in ways that were not directly measured by our study, and scheduling differences between school, vacation, and pandemic periods, as well as stress, could be another source of variability in our sample (Suratt et al., 2007). Additionally, analyses may have been underpowered to detect COVID-related differences within each group, given small sample sizes when stratifying by prenatal alcohol exposure. The administration of neuropsychological tests via Zoom also deviated from the standardized administration procedures that were used for test validation and normative data. It should be noted that the NIH

Toolbox manufacturers advise caution in interpreting the normative data obtained from tests administered remotely (https://nihtoolbox.force.com/s/article/Coronavirus-Covid-19).

As noted above, the inclusion of a heterogeneous control group may have further limited our ability to detect group differences in average sleep parameters. The study was advertised as an investigation of sleep, and thus, there may have been selection bias for typically developing controls who had sleep problems. However, the heterogeneity of the control group also represents a strength of the study: by including controls with sleep issues, ADHD, and other behavioral problems, but with no history of prenatal alcohol exposure, our findings suggest that the observed group differences may be unique to FASD. To better understand the specificity of these relationships, future studies would benefit from including a separate behavioral contrast group (e.g., children with ADHD or other behavioral concerns). Studies that include a contrast group with behavior problems similar to those of the AE group can parse apart whether relationships between sleep and behavior problems are specific to FASD, or rather due to features that are shared across FASD and other neurodevelopmental and behavioral disorders (e.g., attention deficits, impulsivity).

The data for this study were collected cross-sectionally, and thus, do not meet the temporal requirements to determine causality of relationships observed between sleep and neurobehavioral outcomes. Rather, the relationships described should be used to inform future research projects and interventions that collect data across multiple time points and can further delineate directionality of these associations. For example, time-series or lag-based analysis of serially collected data measuring both sleep and behavioral factors would facilitate the examination of temporal relationships across these constructs. In addition, given the group differences in sleep time intraindividual variability, it will be important for future studies to

examine potential contributions of altered circadian rhythmicity. Preclinical and clinical data indicate that prenatal alcohol exposure is associated with differential expression of clock genes, which are instrumental in generating biological rhythms at the cellular level (Chen et al., 2006; Farnell et al., 2008; Sarkar et al., 2019). Disruptions in circadian rhythm and clock gene expression could be a biological mechanism that contributes to sleep variability, but further study of these relationships is needed.

Conclusions

Sleep problems are commonly reported in individuals with FASD, yet this topic has been understudied, and examination of the relationships between sleep and neurobehavioral functioning has been limited. The current study demonstrated that while children with FASD and typically developing controls had similar sleep characteristics on average, there was substantial intraindividual variability in the sleep quality of the alcohol-exposed children. In addition, parents of children with FASD reported clinically significant levels of sleep problems, particularly related to delayed sleep onset, night wakings, and daytime sleepiness. Greater intraindividual variability in sleep was correlated with poorer episodic memory and working memory, as well as more problem behaviors, such as attention problems, rule breaking, and sluggish cognitive tempo. Although many of our analyses were underpowered to detect significant effects, based on the observed effect sizes, these domains warrant further study with larger samples. As a future direction, these areas also represent outcomes that should be examined in studies that investigate sleep interventions tailored to the FASD population.

Given the high rate of parent-reported sleep problems and objectively measured sleep variability in alcohol-exposed individuals, our findings indicate that sleep intervention trials are a critical area for research that has not yet been explored in FASD. The limited literature suggests that sleep hygiene strategies can help to stabilize sleep, such as setting a consistent bedtime and wake time (including weekends), implementing bedtime routines, and optimizing the environment for sleep (e.g., turning off the TV, limiting screen time before bed). These interventions hold promise, as they have been efficacious in reducing sleep problems in children with ADHD and autism spectrum disorders (Corkum et al., 2016; Weiskop, Richdale, & Matthews, 2005).

Overall, sleep disturbance is a significant, clinically relevant issue that warrants further exploration in individuals with FASD. Identifying and treating sleep disorders is essential to the health and well-being of alcohol-exposed children. Furthermore, understanding the relationships between sleep problems and neurobehavioral functioning will help to target interventions and maximize the quality of life of affected children and their families.

Chapter IV, in part, is currently being prepared for submission for publication of the material. Inkelis, S. M.; Chambers, C.; Mattson, S. N.; Bhattacharjee, R.; Thomas, J. D. The dissertation author was the primary investigator and author of this material.

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