Title: Sleep disturbance as a predictor of anxiety in children with Fetal Alcohol Spectrum Disorders and Typically Developing children.

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Abstract

Background: High levels of anxiety and sleep problems are common features of Fetal Alcohol Spectrum Disorders (FASD). The strong association between sleep and anxiety has been documented in typically developing (TD) populations and is thought to be bidirectional. The association between sleep and anxiety in children with FASD has not yet been examined.

Methods: Caregivers of children with FASD (*n*=91) and TD children (*n*=103) aged 6-16 completed the Children's Sleep Habits Questionnaire (CSHQ), Spence Children's Anxiety Scale (SCAS), and a background questionnaire. Hierarchical multiple regression analyses, group comparisons and ANCOVA interaction models were used to test the associations between sleep and anxiety within and between the two groups.

Results: Scores on sleep disturbances and anxiety were at clinical levels for the majority of the FASD group, and significantly higher in the FASD group than the TD group. After controlling for age and sex, 27% of the variance in anxiety scores in TD children was attributable to sleep problems, and 33% in children with FASD.

Conclusion: This study highlights associations between parent-reported sleep and anxiety in FASD. Sleep disturbances were significant predictors of anxiety in both children with FASD and in TD children. Given the importance of sleep to healthy neurodevelopment, there is a pressing need for sleep intervention studies in children with FASD. Early identification and intervention for sleep problems in this condition should be a therapeutic priority.

Keywords: Sleep, Anxiety, Fetal Alcohol Spectrum Disorders, Social Anxiety, Phobia, Separation Anxiety, Panic disorders, Generalised Anxiety, Sleep disorders, Insomnia.

Introduction

The term Fetal Alcohol Spectrum Disorders (FASD) describes the neurodevelopmental and physical consequences of prenatal alcohol exposure. FASD is characterised by difficulties in executive functioning, social functioning, sensory perception, learning and sleep. Syndromic physical features may also be present (See Table 1).

Prenatal alcohol consumption is considered by the World Health Organization to be a major public health concern and it may be the case that many children and adults with FASD remain undiagnosed (World Health Organization, 2014). In the UK, up to 79% of pregnant women consume alcohol (McQuire et al., 2018), while meconium sampling studies identify prenatal alcohol exposure in up to 44% of newborns (Gareri, Lynn, Handley, Rao, & Koren, 2008; Hutson, Magri, Gareri, & Koren, 2010). Prevalence estimates of FASD in the UK and USA vary between 1 and 9% in the school age population (May et al., 2018; McQuire et al., 2018).

Anxiety is common in children with FASD. Prenatal alcohol exposure results in disorganised neural circuitry and abnormal cortical gene expression, which can manifest in deficits in sensorimotor function and a propensity towards anxiety behaviours (Kozanian et al., 2018). This may be compounded by environmental stresses. Up to 80% of children with FASD are raised in foster care, where clinical anxiety, particularly separation anxiety, is prevalent (Popova, Lange, Burd, & Rehm, 2016; A. P. Streissguth et al., 2004). Furthermore, many children have multiple prenatal drug exposures which independently increase susceptibility to anxiety (Pei, Denys, Hughes, & Rasmussen, 2011; Rasmussen, Andrew, Zwaigenbaum, & Tough, 2008; Steinhausen & Spohr, 1998; Streissguth, Bookstein, Barr, Press, & Sampson, 1998).

To add to this, children with FASD often have difficulties with memory, mood regulation, aggression, understanding social concepts, attention, mathematical concepts, shifting, or understanding a series of instructions (Rasmussen et al., 2008). Many of these fall under the umbrella of executive functioning difficulties, which become more apparent when the child starts school and finds social situations and academic instructions difficult to attend to. Children with FASD can find themselves feeling misunderstood, while navigating seemingly complicated social rituals and distressing home and school environments. A lack of educational guidelines or awareness means that children with FASD are often labelled as disruptive and removed from their learning environment, while many teachers in the UK currently do not receive training around teaching a child with FASD (Price, Cook, Norgate, & Mukherjee, 2017; Williams, Catterick, & Calder, 2012). Early life environmental and neurodevelopmental traumas create complex difficulties and negative experiences in childhood, resulting in the chronic, intense ruminations of perceived negative experiences and realistic fears of

environmental threats. These are likely to contribute to the anxiety often observed in children with FASD.

Childhood anxiety is currently understood as a product of strengthened neural pathways in the emotion-generating and prefrontal/ regulatory areas of the brain, although traumatic stress, panic, and specific phobias are thought to be located amongst different regions (Duval, Javanbakht, & Liberzon, 2015). Whilst children as young as six can show symptoms of anxiety, a fully formed anxiety disorder requires a sophisticated neural pathway that is not usually apparent until a later age. Therefore the median onset of anxiety is 11 years old, with a lifetime prevalence of 28% (Cox & Olatunji, 2016). Elevated anxiety types are among the most common types of psychopathology found in both typically developing (TD) and FASD populations, with prevalence of around 13% and 60% respectively (Brown et al., 2018; Popova, Lange, Shield, et al., 2016). According to the DSM-V, anxiety disorders (Panic Disorder, Specific Phobia, Social Anxiety Disorder, Post Traumatic Stress Disorder and Generalised Anxiety Disorder) are characterised by chronic, intense ruminations that interfere with functioning or cause significant distress, but do not violate social norms (American Psychiatric Association, 2013).

Table 1

The Importance of Sleep

Sleep is fundamental to the developmental process and plays a role in cognition, neuroplasticity, brain maturation and optimal daytime functioning. It is not a period of quiescence, but one where the brain is highly active and engaged in organisational tasks and processes (e.g. Carskadon & Dement, 2011; Espie & Morin, 2012; Frank & Heller, 2003; Hill, Hogan, & Karmiloff-Smith, 2007; Meltzer & Mindell, 2006). Optimal sleep is associated with higher cognitive and behavioural functioning (Touchette et al., 2007).

One Magnetic Resonance Imaging (MRI) study shows that children with parentally reported sleep disturbances at a young age have neuroanatomical differences in later childhood, including smaller grey matter area volumes (Kocevska et al., 2017), and longitudinal data show that children whose parents reported significant sleep problems at 5, 7 and 9 years old were more likely to meet the diagnostic criteria of anxiety disorders at aged 21 and 26 (Gregory et al., 2005).

Neural stress-response mechanisms overlap with sleep-arousal mechanisms (Staner, 2010) and maybe be a factor in the significant correlations between sleep and anxiety. Around half of adolescents with a diagnosed anxiety disorder meet the criteria for chronic insomnia, whilst a diagnosis of insomnia is associated with an increased risk of mood disorders in later life. This suggests there is a complex and reciprocal association between anxiety and sleep (Brown et al., 2018). Furthermore, sleep problems (not restricted to insomnia) are present in up to 91% of children with anxiety disorders (Chase & Pincus, 2011).

FASD and Sleep

Sleep problems are widely reported amongst individuals with FASD, but there is a paucity of clinical published research in this area. The current estimates of sleep problems in this population are high and in line with many other developmental disorders. Chen and colleagues (2012) reported that 85% of their sample of children aged between 4 and 12 years with a diagnosis of FASD (*n*=33), scored above the clinical range on the Children's Sleep Habits Questionnaire (CSHQ). In the same study, five of the sample scoring above the CSHQ clinical cut off were assessed by polysomnography (PSG). All five were found to have fragmented sleep and an elevated Apnea- Hypopnea Index ((AHI), used to indicate the severity of sleep apnea – pauses in breathing lasting longer than two breaths, and hypopnea - associated with desaturation of oxygen or arousal) (M. L. Chen, Olson, Picciano, Starr, & Owens, 2012). Goril and Colleagues (2016) performed PSG and assessed dim-light melatonin onset (DLMO) in 6-18-year olds with FASD (*n*=36). Increased sleep fragmentation and low sleep efficiency was found in 78% of their sample, and a 58% prevalence of sleep disorders was found, with the most common being parasomnias and insomnia. An abnormal melatonin secretion curve was found in 79% of participants (Goril, Zalai, Scott, & Shapiro, 2016).

Ipsiroglu and colleagues (2011) used clinical records and qualitative methods to diagnose sleep problems, assess their impact on children with FASD (*n*=27) and understand sleep problems as reported by healthcare professionals and parents (*n*=13). Sleep problems were seen as being the underlying cause of many daytime problems, but pharmacological interventions treated sleep problems and daytime behavioural problems as separate symptoms of FASD rather than bidirectional features intrinsic to the FASD profile (Ipsiroglu, McKellin, Carey, & Loock, 2013). Similarly in another qualitative study analysing the number of times certain words were spoken during semi structured interviews with caregivers, 'night' and 'sleep' were associated with challenging behaviours and problems with sleep and waking (Spruyt, Ipsiroglu, Stockler, & Reynolds, 2018). Health professionals who are unfamiliar with sleep in this population may often suggest intervention strategies that are

useful for typically developing children, such as sleep hygiene management, but these are not always helpful for the sensory and perceptual profiles of children with FASD (Jan et al., 2010).

To our knowledge, only one study has examined the association between sleep and daytime characteristics of children with FASD. Wengel, Fjeldsted & Hanlon Dearman (2011) used actigraphy, CSHQ and Sensory Profiles™ to assess sleep and sensory processing in children aged 3 to 6 years with FASD (*n*=19) and age matched TD controls (*n*=12). Results demonstrated significant positive (Spearman) correlations between sleep disturbances and sensory processing. In particular, sleep duration was correlated with sensory sensitivity, sensory processing affecting endurance/ tone, and behavioural outcomes of sensory processing (Wengel, Hanlon-dearman, Fjeldsted, Ot, & Mb, 2011). Whilst sleep and sensory issues are among the more commonly cited problems in children with FASD, it is clear that much further research is needed in evaluating the range of sleep problems in children and their impact on everyday life.

The purpose of the present study was to examine, for the first time, a predictive association between anxiety and sleep in a large group of children with FASD, and to compare this to a cohort of TD children. We hypothesised that levels of anxiety and sleep disturbances would be higher in children with FASD compared to TD, and that sleep disturbances would predict anxiety problems in both groups.

Methods

Ethical approval for this study was granted by the University College London Ethics Committee. All caregivers provided consent.

Participants

Participants were caregivers of children aged between 6 and 15 years (from the 6th birthday until the 16th) with a diagnosis of FASD made by a paediatrician (see Table 2). Recruitment was by nationwide advertising with the FASD UK Alliance. The study was advertised as an online questionnaire examining children's sleep and anxiety levels. Background data including child placement (whether the child was in foster, adoptive or biological care), age, and gender were collected. Control TD participants were recruited through three primary schools (expression of interest letters were sent to all parents of three schools and parents were directed to an online survey). Caregivers (*n*=229) completed the questionnaire. Nine were excluded as they did not meet the age criteria. 17 were excluded as they did not have a formal FASD diagnosis. An additional 9 participants were excluded as the child had an alternative diagnosis that was not FASD (e.g. Cerebral Palsy, Reactive Attachment Disorder), and therefore would not be eligible for either the FASD or TD group. The final sample included 91 FASD

and 103 TD participants (See Table 2). Participants were not excluded on the basis of co-occurring conditions or medication use.

Table 2

Procedure

Parents were directed to an online form where they completed the following questionnaires on sleep and anxiety.

Children's Sleep Habits Questionnaire (CSHQ)(Owens, Spirito, & McGuinn, 2000): A 33 item retrospective parent report, based on a Likert Scale with three options: 'rarely' for an event that occurs 0-1 times per week; 'sometimes' for an event that occurs 2-4 times per week; 'usually' for an event that that occurs between 5-7 times per week. Items are grouped into eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Waking, Parasomnia, Sleep Disordered Breathing, Daytime Sleepiness. The CSHQ is a widely used assessment tool in paediatric sleep, with high internal validity and Cronbach Alpha score of 0.83. Higher scores indicate increased sleep problems and total scores of 40 or above are clinically significant.

Spence Children's Anxiety Scale (SCAS) (S H Spence, 1997; 1998)*:* A 38-item questionnaire measuring anxiety symptoms in children aged between 6-16, used in the measurement of symptoms of DSM-V anxiety disorders, in both mainstream and non-mainstream settings. It includes subscales for Separation Anxiety, Social Phobia, Obsessive-Compulsive Disorder, Panic, Physical Injury Fears and Generalised Anxiety Disorder. Each item is rated for frequency of occurrence on a 4-point Likert Scale: Never (0), Sometimes (1) Often (2) Always (3). The SCAS has high internal validity with a Cronbach's Alpha score of 0.92 (Essau, Muris, & Ederer, 2002). Higher scores indicate increased anxiety and total scores of 33 and above are clinically significant. Subscale clinical cut off scores are: Separation Anxiety (8), Social Phobia (8), Obsessive-Compulsive Disorder (3), Panic (3), Physical Injury Fears (5) and Generalised Anxiety Disorder (7).

Background questionnaire: To ascertain diagnosis and background, caregivers were asked to name their child's diagnosis, where and at what age the child was diagnosed, the child's age, sex and living arrangement (lives with birth mother, biological relative, special guardianship order, foster parent, adoptive parent or other), household income, and highest level of education in the child's household. Socioeconomic Status (SES) was determined as either 1,2, or 3 based on the UK Office of National

Statistics Socio-economic Classification (ONS, 2019).

Statistical methods

Data were analysed using IBM SPSS Version 22. Group differences between the FASD and TD raw scores in SCAS, CSHQ and subscales were examined with T-Tests. Raw scores were used for the SCAS since T-scores were capped at 70, which most of the FASD sample exceeded.

To determine whether sex was a confounding factor, independent samples t-tests were used to compare males and females within each group (FASD, TD) on the SCAS and CSHQ (See Table 3). Since sleep is known to change with age (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004), Pearsons correlations were used to investigate age-related changes in sleep and anxiety. Due to evident age and sex differences on some variables, and for consistency throughout, we controlled for both age and sex in all further analyses.

Pearson correlations were carried out on the subscales of both CSHQ and SCAS to check for multicollinearity. No correlations were above 0.8 (*range*=0.039 $\pm$ 0.787). Hierarchical multiple linear regression using the Enter model was used to assess whether sleep was able to predict anxiety in both the TD and FASD groups. Block one always controlled for age and sex. CSHQ subscale scores were taken together as a representation of sleep disturbance, and were entered in Block two. Seven separate models were run for each subscale of the SCAS. Cooks distances were used to inspect for outliers: six were found. Data were analysed with and without outliers, to see whether the removal of outliers changed the significance of any results. Any significant changes are reported below. Adjusted R^2 values are reported as the percentage of variance, in order to control for the number of predictors in the model.

ANCOVA interaction models were used to assess whether the strength of association between sleep and anxiety was significantly different between groups. Age, sex, and CSHQ subscales were entered as covariates with group (FASD, TD) as the fixed factor and each SCAS subscale as the dependent variable.

Results

CSHQ

As predicted, children with FASD scored significantly higher than TD children in overall CSHQ score (*p*=0.02). Children with FASD had significantly higher levels of bedtime resistance, sleep onset delay, sleep duration, sleep anxiety and night wakings than their TD peers. Parasomnias and sleep disordered breathing (SDB) were elevated in the FASD sample but not to a statistically significant degree. The total mean CSHQ score for the FASD sample was 41.93 (*SE* = 10.46), which is above the clinical cut off point of 40 (Mindell & Owens, 2009). The total mean CSHQ score for the TD group was 38.70 (*SE* = 9.48).

In the FASD group, 56 out of 91 (61%) children scored above the CSHQ clinical cut off for sleep problems. Children in this population had significantly higher total CSHQ scores than TD children, with the mean total score (41.93) above the clinical cut off. This is consistent with the prevalence from previous findings (M. Chen, Olson, Picciano, Starr, & Owens, 2012; Goril et al., 2016; Jan et al., 2010; Wengel et al., 2011).

Unexpectedly, 46 out of 103 TD children (45%) also scored above the CSHQ clinical cut off (*range*=29-66), however the mean score was 38.7 (*range*= 36-78), lower than the clinical cut off.

Figure 1

Sex Related Differences in Sleep

In the TD group females had better sleep, whilst in the FASD group males had better sleep. On the CSHQ, TD boys scored significantly higher in Sleep Anxiety (male *m*= 6.28, SD= 2.39; female *m*=5.93, SD=2.01; p=<0.05), Sleep Disordered Breathing (male *m*= 3.64, SD= 1.27; female *m*=3.35, SD=0.68; p=<0.05), and CSHQ Total (male *m*= 39.88, SD=10.72; female *m*=37.35, SD=8.29; p=<0.01). On the CSHQ, FASD girls scored higher on some subscale and total scores. FASD girls scored significantly higher on Bedtime Resistance (male *m*= 7.88, SD=2.39; female *m*=9.04, SD=3.38; p=<0.01), Sleep Disordered Breathing (male *m*= 3.26, SD=0.65; female *m*=3.95, SD=1.68; p=<0.05), Daytime Sleepiness (male *m*= 4.91, SD=4.13; female *m*=6.35, SD=4.97; p=<0.01).FASD girls scored higher on total CSHQ than boys (male *m*= 41.06, SD=8.963; female *m*=46.12, SD=11.16; p=<0.01).

Sleep variables in relation to Chronological Age

Our cross -sectional data suggest that sleep scores generally improved with increased chronological age in the TD group but not in the FASD group. Significant Pearson correlations were found between sleep subsets and chronological age in the TD group in: Bedtime Resistance (-0.28; *p*=0.04); Sleep Duration (-0.30; *p*=<0.001); Night Wakings (-0.21; *p*=0.04); Parasomnias (-0.44; *p*=<0.001); Daytime Sleepiness (-0.50; *p*=<0.001) and CSHQ Total (-0.48; *p*=<0.001). There were no significant changes for children with FASD.

Table 3

Table 4

SCAS

As predicted, children with FASD scored significantly higher than TD children in both the total and all subscales of the SCAS. The mean total score for the FASD sample was 41.84 (*SE*= 18.16), above the clinical cut off of 33. The mean total score for the TD sample was 24.24 (*SE* = 16.35). Anxiety levels were above clinical levels for 74% of children with FASD compared to 27% of TD children.

Figure 2

Sex Related Differences in Anxiety

On the SCAS, TD girls scored significantly higher in Physical Injury Fears (male *m*= 4.00, SD= 2.59; female *m*=4.85, SD=3.44; p=<0.05). There were no significant differences between sex in the FASD group on the SCAS.

Anxiety variables in relation to chronological age

Anxiety scores generally worsened with increased chronological age for children with FASD in the subsets of Panic (0.27; p=0.01), Separation Anxiety (0.25; p=0.017) and Social Phobia (0.327; p=<0.001) whilst there were no significant changes in the TD group.

SES related differences

SES was not a predictor of CSHQ or SCAS variables in either group. SES was therefore not included as a covariate in the regression analysis.

Associations between sleep and anxiety

Multiple regression showed that in both groups, sleep disturbances significantly predicted scores for every SCAS subscale and total score, except Generalised Anxiety and Obsessive Compulsive in the FASD group.

Panic: In both the TD and FASD groups, sleep disturbances were found to be predictors of panic symptoms (TD: ΔR^2 = 0.16, $\Delta F_{10,91}$ =2.25, p = 0.03; FASD:, ΔR^2 = 0.20, $\Delta F_{10,80}$ =2.71, p = 0.01). Sleep disturbances explained 9.6% of the variance in panic symptoms in the TD group, and 18.3% in the FASD group, after controlling for age and sex (See Table 4).

Separation Anxiety: In both the TD and FASD groups, sleep disturbances were found to be predictors of separation anxiety (TD: ΔR^2 = 0.29, $\Delta F_{10,91}$ =5.01, p = <0.001; FASD: ΔR^2 = 0.31, $\Delta F_{10,80}$ =5.23, p = <0.001). Sleep disturbances explained 27.1% of the variance in separation anxiety in the TD group, and 33.2% in the FASD group, after controlling for age and sex (See Table 5).

Physical Injury Fears: In both the TD and FASD groups, sleep disturbances were found to be predictors of physical injury fears (TD: ΔR^2 = 0.24, $\Delta F_{10,91}$ =3.67, p = 0.001; FASD:, ΔR^2 = 0.30, $\Delta F_{10,80}$ =4.35, p = <0.001). Sleep disturbances explained 19% of the variance in physical injury fears in the TD group, and 22.8 in the FASD group, after controlling for age and sex (See Table 6).

Social Phobia: In both the TD and FASD groups, sleep disturbances were found to be predictors of physical injury fears (TD: ΔR^2 = 0.19, $\Delta F_{10,91}$ =2.64, p = 0.01; FASD: ΔR^2 = 0.27, $\Delta F_{10,80}$ =4.43, p = <0.001). Sleep disturbances explained 11.2% of the variance in social phobia in the TD group, and 31.7% in the FASD group, after controlling for age and sex (See Table 7).

Obsessive Compulsive: In the TD group only, sleep disturbances were found to be predictors of obsessive- compulsive symptoms (ΔR^2 = 0.20, $\Delta F_{10,91}$ =2.80, p = 0.008). Sleep disturbances explained 11.5% of the variance in Obsessive- Compulsive symptoms in the TD group. No significant results were seen in the FASD group (See Table 8).

Generalised anxiety: In the TD group only, sleep disturbances were found to be predictors of obsessive- compulsive symptoms (ΔR^2 = 0.24, $\Delta F_{10,91}$ =3.68, p = 0.001). Sleep disturbances explained 16.2% of the variance in generalised anxiety in the TD group. No significant results were seen in the FASD group (See Table 9).

Total SCAS: As predicted, in both the TD and FASD groups, higher total anxiety levels were associated with sleep disturbances. After controlling for age and sex, sleep problems accounted for 27% of the variation in total TD SCAS scores (ΔR^2 = 0.28, $\Delta F_{10,91}$ =4.38, p = <0.001), and 30% of the variation in total FASD SCAS scores (ΔR^2 = 0.31, $\Delta F_{10,80}$ =4.58, p = <0.001). (See Table 10).

Interaction between models

ANCOVA interaction models showed no significant between-group differences for the strength of association between sleep and anxiety (all p values >.05) indicating that, whilst both CSHQ and SCAS scores were elevated in the FASD group, the strength of the association did not significantly differ from TD.

Discussion

This is the first study to report the significant association between sleep and anxiety in children with FASD. As predicted, children with FASD had significantly more sleep and anxiety problems than TD children. Children with FASD had significantly shorter sleep duration, higher levels of bedtime resistance, sleep onset delay, sleep anxiety and night wakings than typically developing children. Children with FASD also had significantly higher levels of anxiety, in both total and subscores of the SCAS (Panic, Separation Anxiety, Physical Injury Fears, Social Phobia, Obsessive Compulsive, Generalised Anxiety). There were also sex differences in both the TD and FASD groups, which have not previously been reported. Girls with FASD scored significantly higher on a number of CSHQ variables (Bedtime Resistance, Sleep Disordered Breathing, Daytime Sleepiness, and CSHQ Total).

Regression analysis revealed that a significant proportion of anxiety problems in both groups was associated with sleep problems.

Unexpectedly, a high number of TD children showed sleep problems, which may be attributable to selection bias. There were significant differences between TD and FASD on both the Generalised Anxiety and Obsessive Compulsive scales, and in both scales the mean scores for the FASD group exceeded the clinical cutoff points

Previous studies on sleep and anxiety have noted Generalised Anxiety symptoms as being the most associated with sleep disturbances (e.g. Alfano, Zakem, Costa, Taylor, & Weems, 2009; Fletcher et al., 2018; Gregory & Eley, 2005); however, sleep did not significantly predict Generalised Anxiety or Obsessive Compulsive symptoms in the FASD group.

There were no significant differences in the correlation coefficients between TD and FASD CSHQ and SCAS subscales/ composite scores. Whilst it was predicted that the FASD group would show significantly higher levels of sleep disturbances and anxiety, it was not (and cannot be) predicted whether the correlation coefficient would differ between groups. This is because the neural mechanisms of anxiety behaviours and sleep are still only theorised in typically developing individuals, and yet unknown in FASD. A greater understanding of the underlying neural mechanisms involved in sleep and anxiety in prenatally alcohol exposed individuals would inform us of whether such associations would be expected to be stronger within atypical groups. Further research in this area would benefit the current understanding of these mechanisms.

The complex interaction between environmental stresses, neurophysiological processes and sleep disturbances should also be acknowledged. Failure to fall asleep and stay asleep, when driven by persistent anxious ruminations, are likely to have several neurobiological as well as environmental causes. Sleep-wake regulation results from circadian and homeostatic processes. These include sleep inducing inhibitors (such as the neurotransmitter GABA) and wake and arousal mechanisms including (among many others) the neurotransmitter CRH (Corticotropin Releasing Hormone), the LC-AN (Locus Cereleus- autonomic nervous) System, and the HPA (Hypothalamic Pituitary Adrenal) Axis. These mechanisms are involved in a feed-forward system which responds to environmental and physiological stresses, but are vulnerable to dysfunction. Therefore, neurochemical reactions to environmental and physiological arousals can proceed even when the stressful situation is removed. Acute stress, mediated by CRH and HPA Axis mechanisms, can manifest in changes in both NREM and REM sleep, and contribute to spontaneous waking even without stressors (Staner, 2010). This may be a reason for the spontaneous waking experienced by individuals with anxiety symptoms, in particular with Panic Disorder, Separation Anxiety and Social Phobia.

In the present study, significant associations were found between symptoms of Panic and sleep disturbances in both the TD and FASD groups. Panic Disorder symptoms include autonomic occurrences including palpitations, sweating, shortness of breath, paresthesia, or chest pains. Individuals with a diagnosed Panic Disorder are more likely to experience nocturnal panic attacks, sleep paralysis, apnea, night terrors, or nightmares, with or without environmental cues. The SCAS measures panic symptoms from questions such as "My child suddenly starts to tremble or shake when there is no reason for this", "All of a sudden my child feels really scared for no reason at all" or "My child worries that (s)he will suddenly get a scared feeling when there is nothing to be afraid of", which both fits the neurobehavioural profile of a dysfunctional HPA axis (Wieczorek, Fish, O'Leary-Moore, Parnell, & Sulik, 2015) and may explain elevated scores in items such as sleep latency and night waking. Prenatal alcohol exposure, mediated by negative early life experiences, alters the developmental programming of the HPA axis in children with FASD (McLachlan et al., 2016). Concomitantly around 91% of children with FASD have a co-occurring mental health condition, and 20% of children with FASD will experience panic symptoms at a clinical level (Pei et al., 2011).

Separation anxiety is a common feature of FASD and studies within this area are now well established (e.g: Alberry & Singh, 2016; Hellemans et al., 2010). Infants with negative caregiver experiences can develop insecure attachments and develop a view of the world as unreliable, frightening and unpredictable, which manifests as fearfulness (Bowlby, 1973). In the present study, the strongest predictors of sleep on a SCAS subscale were on separation anxiety. Bedtime resistance and parasomnias were significant predictors of separation anxiety in the FASD group. Bedtime resistance includes stalling the bedtime routine, multiple 'curtain calls' once bedtime has passed, repeated requests for attention, or meltdowns in which the child becomes distressed when a parent leaves the room. Such behaviours fit the profile of a child who is apprehensive about being separated from a caregiver, and have previously been noted about children in the care of foster or adoptive parents (Trejos-Castillo, Bedore, Davis, & Hipps, 2015). Separation anxiety also encompasses the fear of something happening to the caregiver, alongside frequent nightmares with themes of separation (Schlarb, Jaeger, Schneider, In-Albon, & Hautzinger, 2016). A strong association between bedtime resistance and parasomnia in separation anxiety profiles can therefore expected. In young children, parasomnias tend to begin at the development of an active imagination, where the ability to decipher reality from fiction has not yet been established. This results in the common fears young children will experience of monsters, witches, imaginary creatures, etc. and are often the cause of bedtime resistance in this age category. Older children and adolescents tend to display more sophisticated fears around school or social anxiety, or negative events in the news (Meltzer & Mindell, 2006). Similarly, Social Phobia, which is measured on the SCAS through questions such as "My child is scared

when s(he) has to take a test", "My child feels afraid that (s)he will make a fool of him/herself in front of people ", and "My child worries what other people think of him/her" fit the profile of a child with more sophisticated fears.

Social Anxiety was also significantly associated with sleep disturbances. Anxiety is theorised as a twofold interaction between a primary fear and a failure of self-efficacy (Wenar & Kerig, 2000). In FASD, this is often compounded with previous negative experiences of social or academic instructions, caregiver separation, and early life trauma. Additionally, children with FASD can have a sophisticated imagination but not reach all neurodevelopmental milestones (Williams et al., 2012). Issues with memory processing can result in confabulations, inaccurate recollections, or the inability to decipher whether or not a story happened in real life. Put together, it can be expected these outcomes turn into negative and nocturnal ruminations and can be associated with poor sleep.

Somatic and sensory complaints are common in children with FASD. Wengel et al. (2013) reported that somatic complaints (low endurance and tone, and sensory seeking behaviour) were significantly associated with sleep problems in their population of 3-6 year olds with FASD (Wengel et al., 2011). The present study complements these previous findings; overall sleep disturbances in both TD and FASD groups were significant predictors of Physical Injury Fears, which encompass somatic and sensory complaints.

The present study assessed the predictive association of sleep on anxiety. Sleep disturbances are commonly associated with anxiety symptoms, although causative or bidirectional associations here are less well established (Alvaro, Roberts, & Harris, 2013). Heightened and dysfunctional emotional reactivity mediates the interaction between cognitive and autonomic hyperarousal, as well as the occurrence and maintenance of sleep problems. At the same time, emotional disturbances can be reinforced by dysfunctional sleep-wake regulating neural circuitry (Baglioni, Spiegelhalder, Lombardo, & Riemann, 2010). This probably due to neural stress-response mechanisms overlapping with sleep-arousal mechanisms (Staner, 2010). Since sleep interventions can improve cognitive, behavioural, affect related and higher order processing, causal associations between sleep and neuropsychological functioning have been inferred (e.g: Baglioni, Spiegelhalder, Nissen, & Riemann, 2011; Martin, Hiscock, Hardy, Davey, & Wake, 2007; Sharma & Mazmanian, 2003). The cross-sectional nature of the present data means that any inference about direction of the associations between sleep and anxiety can only be hypothetical. Therefore, it must also be acknowledged that associations between sleep and anxiety are part of a complex interplay combining multiple psychological and sensory domains. To give an example, it is not clear whether insomnia is a diagnosis with depression as an outcome, or

whether depression is a diagnosis with insomnia as an outcome, and neither have definitive conclusions been made regarding these seemingly bidirectional occurrences (Alvaro et al., 2013; Litwiller, Snyder, Taylor, & Steele, 2017). Further analysis would be warranted of the potential bidirectionality of sleep and anxiety in individuals with FASD.

We predicted that children with FASD would exhibit significantly higher anxiety and sleep problems than TD children, and that both groups would have significant associations with anxiety scores. Significant proportions of the TD and FASD scores were attributable to disordered sleep after controlling for age and sex. Due to the large sample size we can confidently assume a significant association between anxiety and sleep in children with FASD.

Limitations

Several limitations are of importance are evident, notably parental reports are subjective views of children's behaviours and further analysis can benefit from objective sleep measures such as actigraphy or polysomnography; data may be attributed to a selection bias in that parents of children with sleep problems were more likely to want to take part and the sample may not have the heterogeneity of a population-based sample. Many participants had to be excluded because of the lack of a formal diagnosis of FASD due to a general lack of diagnostic services available in the UK. Furthermore, predictions within this study are statistical descriptions. Without an experimental design and with the limits of cross-sectional data, causation cannot be implied. However, this study has provided a platform for the need for further examination using objective sleep and cognitive measures in this clinical population.

This is the first study to show how sleep disturbance predicts anxiety in children with FASD. Given the importance of sleep to healthy neurodevelopment, supported by our data, there is a pressing need for sleep intervention studies in children with FASD. Too often sleep disturbances are overlooked or assumed to be intrinsic to the FASD rather than amenable to treatment. Early identification and intervention for sleep problems in this condition should be a therapeutic priority, supported by research to assess whether improvements in sleep are associated with improved cognitive and behavioural outcomes, including reduced anxiety.

Table 1: FASD Diagnostic Criteria

	Institute of Medicine Diagnostic Criteria
FAS (Fetal Alcohol Syndrome)	(Requires all 4 criteria) 1. Confirmed or unconfirmed maternal alcohol exposure 2. Facial features - evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and anomalies in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface). 3. Growth retardation - at least one of the following: - Low birth weight for gestational age - Decelerating weight over time not due to nutrition - Disproportional low weight to height. 4. CNS neurodevelopmental abnormalities. At least one of the following: - Decreased cranial size at birth - Structural brain anomalies - Neurological hard or soft signs (age appropriate).
Partial FAS (pFAS)	(diagnosis requires sections 1 and 2, and one other): 1. Confirmed maternal alcohol exposure. 2. Facial features - evidence of some components of the pattern of characteristic facial anomalies. 3. Growth retardation. At least one of the following: - Low birth weight for gestational age - Decelerating weight over time, not due to nutrition - Disproportional low weight to height 4. CNS Neurodevelopmental abnormalities. At least one of the following: - Decreased cranial size at birth; Structural brain anomalies; Neurological hard or soft signs (age appropriate): - Evidence of a complex pattern of behaviour or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties; deficits in higher-level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgement.
Alcohol Related Neurodevelopmental Disorder (ARND)	(Diagnosis requires Section 1 and one other) 1. Confirmed maternal alcohol exposure. 2. CNS neurodevelopmental abnormalities - any of the following: - Decreased cranial size at birth - Structural brain anomalies - Neurological hard or soft signs (age appropriate) 3. Evidence of a complex pattern of behaviour or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties; deficits in higher-level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgement.
Alcohol Related Birth Defects (ARBD)	(Diagnosis requires Section 1 and one other) 1. Confirmed maternal alcohol exposure, and one or more birth defects: - Cardiac anomalies - Skeletal anomalies - Renal anomalies - Ocular anomalies - Auditory anomalies

Table 2: Participant Details

	TD (n=102)	FASD (n=91)
Male/Female	50/52	54/37
Age in Years (M (SE))	9.58 (2.52)	9.69(2.86)
Living with adoptive parent (*n*)	0	15
Living with foster parent (*n*)	2	51
Living with relative (*n*)	0	21
Living with biological parent (*n*)	100	4
SES (1/2/3)	(11/76/15)	(9/62/20)

Table 3: Sex Differences

	TD (n=102)			FASD (n=91)		
	Male (M/SD)	**Female (M/SD)**	***p***	**Male (M/SD)**	**Female (M/SD)**	***p***
CSHQ						
Sleep Anxiety	6.28 (2.39)	5.93(2.01)	0.04			
Sleep Disordered Breathing	3.64 (1.27)	3.35 (0.68)	0.01	3.26 (0.65)	3.95 (1.68)	<0.001
Total	39.38 (10.72)	39.88 (10.72)	0.02	41.06 (8.96)	46.12 (11.16)	0.02
Bedtime Resistance				7.88 (2.39)	9.04 (3.38)	0.03
Daytime Sleepiness				4.91 (4.13)	6.35 (4.97)	0.03
SCAS						
Physical Injury Fears	4 (2.59)	4.85 (3.44)	0.04			

Table 4: Age Differences

	TD (n=102)		FASD (n=91)	
	β	***p***	**β**	***p***
CSHQ				
Bedtime Resistance	-0.28	0.04		
Sleep Duration	-0.3	<0.001		
Night Wakings	-0.21	0.04		
Parasomnias	-0.44	<0.001		
Daytime Sleepiness	-0.5	<0.001		
CSHQ Total	-0.48	<0.001		
SCAS				
Panic			0.27	0.01
Separation Anxiety			0.25	0.02
Social Phobia			0.33	<0.001

Table 5: Results of t-tests comparing TD and FASD groups on CSHQ and SCAS

	TD (n= 102)		FASD (n= 91)		t	*p*	df*
	M	**SE**	**M**	**SE**			
CSHQ							
Bedtime Resistance	7.47	2.68	8.35	2.87	-2.22	0.03	0.19
Sleep Onset Delay	1.23	1.00	1.88	0.70	-5.19	<0.001	21.00
Sleep Duration	3.83	2.16	4.99	1.85	-3.97	<0.001	6.78
Sleep Anxiety	6.13	2.22	7.25	2.87	-3.08	<0.001	12.26
Night Wakings	3.93	1.18	4.69	1.64	-3.73	<0.001	16.47
Parasomnias	8.73	2.36	9.04	2.72	-0.87	0.39	0.98
Sleep Disordered Breathing	3.49	1.02	3.54	1.22	-0.33	0.74	0.32
Daytime Sleepiness	6.95	3.79	5.49	4.52	2.44	0.02	4.68
CSHQ Total	38.70	9.48	41.93	10.46	-2.26	0.02	1.00
SCAS							
Panic	1.71	2.685	6.27	4.50	-8.693	<0.001	14.38
Separation Anxiety	5.42	4.52	9.11	4.12	-5.917	<0.002	3.23
Physical Injury Fears	3.22	3.07	5.57	4.46	-2.468	0.01	0.19
Social Phobia	6.07	4.48	8.74	4.60	-4.087	<0.001	0.01
Obsessive Compulsive	1.98	2.52	4.49	3.20	-6.113	<0.001	5.58
Generalised Anxiety	4.61	3.27	7.65	3.77	-6.004	<0.001	0.80
SCAS Total	24.24	16.35	41.84	18.16	-7.099	<0.001	0.07

****degrees of freedom***

The following tables are intended as supplements:

Supplemental Table 1: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Panic

			Overall Model			**Change Statistics**		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	0.06	1.27		0.02	1.23	0.004
n= 102		Age	0.01	0.01	0.16*			
		Sex	0.05	0.51	0.01			
	2	(Constant)	-5.27	2.40		0.16	2.25*	0.096
		Age	0.02	0.01	0.22*			
		Sex	0.34	0.51	0.07			
		Bedtime Resistance	-0.20	0.15	-0.20			
		Sleep Onset Delay	0.35	0.38	0.13			
		Sleep Duration	0.10	0.20	0.08			
		Sleep Anxiety	0.24	0.19	0.20			
		Night Wakings	0.02	0.25	0.01			
		Parasomnia	0.23	0.15	0.21			
		Sleep Disordered Breathing	0.58	0.28	0.22			
		Daytime Sleepiness	-0.10	0.10	-0.15			
FASD	1	(Constant)	1.11	2.21		0.078	3.706*	0.057
n=91		Age	0.04	0.01	0.28			
		Sex	0.69	0.94	0.08			
	2	(Constant)	-8.24	2.98		0.196	2.71*	0.183
		Age	0.05	0.01	0.37			
		Sex	-0.78	0.95	-0.09			
		Bedtime Resistance	0.28	0.28	0.18			
		Sleep Onset Delay	0.35	0.78	0.05			
		Sleep Duration	0.21	0.30	0.09			
		Sleep Anxiety	0.23	0.26	0.15			
		Night Wakings	0.05	0.29	0.02			
		Parasomnia	0.25	0.23	0.15			
		Sleep Disordered Breathing	0.60	0.39	0.16			
		Daytime Sleepiness	-0.05	0.13	-0.05			

******p*=<0.05, *****p*=<0.001.**

Supplemental Table 2: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Separation Anxiety

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	8.91	2.11		0.05	2.83	0.035
n= 102		Age	-0.04	0.02	-0.23*			
		Sex	0.32	0.85	0.04			
	2	(Constant)	-5.27	3.63		0.29	5.01**	0.271
		Age	-0.02	0.02	-0.13			
		Sex	0.72	0.78	0.08			
		Bedtime Resistance	0.28	0.23	0.17			
		Sleep Onset Delay	0.38	0.57	0.09			
		Sleep Duration	-0.05	0.30	-0.02			
		Sleep Anxiety	0.27	0.29	0.13			
		Night Wakings	0.62	0.37	0.16			
		Parasomnia	0.21	0.22	0.11			
		Sleep Disordered Breathing	1.27	0.42	0.29*			
		Daytime Sleepiness	-0.14	0.15	-0.12			
FASD	1	(Constant)	10.18	2.00		0.10	4.63*	0.075
n=91		Age	-0.03	0.01	-0.23*			
		Sex	1.51	0.85	0.18			
	2	(Constant)	2.08	2.47		0.31	5.23**	0.332
		Age	-0.02	0.01	-0.15			
		Sex	0.33	0.79	0.04			
		Bedtime Resistance	0.48	0.23	0.33*			
		Sleep Onset Delay	0.08	0.64	0.01			
		Sleep Duration	-0.24	0.25	-0.11			
		Sleep Anxiety	0.27	0.21	0.19			
		Night Wakings	0.18	0.24	0.07			
		Parasomnia	0.43	0.19	0.29*			
		Sleep Disordered Breathing	-0.28	0.33	-0.08			
		Daytime Sleepiness	0.00	0.11	0.00			

***p*=<0.05, ** *p*=<0.001.**

Supplemental Table 3: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Physical Injury

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	4.20	1.44		0.04	1.78	0.015
n= 102		Age	-0.01	0.01	-0.10			
		Sex	0.95	0.58	0.16			
	2	(Constant)	-1.58	2.60		0.24	3.67*	0.190
		Age	-0.01	0.01	-0.07			
		Sex	1.18	0.56	0.20*			
		Bedtime Resistance	0.06	0.17	0.05			
		Sleep Onset Delay	-0.08	0.41	-0.03			
		Sleep Duration	-0.35	0.21	-0.25			
		Sleep Anxiety	0.34	0.21	0.25			
		Night Wakings	0.53	0.27	0.21*			
		Parasomnia	0.10	0.16	0.07			
		Sleep Disordered Breathing	0.38	0.30	0.13			
		Daytime Sleepiness	-0.04	0.11	-0.05			
FASD	1	(Constant)	4.14	1.63		0.02	0.71	0.007
n=91		Age	0.01	0.01	0.13			
		Sex	0.04	0.69	0.01			
	2	(Constant)	-2.51	2.08		0.30	4.35**	0.228
		Age	0.02	0.01	0.21			
		Sex	-1.12	0.66	-0.17			
		Bedtime Resistance	0.10	0.20	0.09			
		Sleep Onset Delay	0.83	0.54	0.18			
		Sleep Duration	-0.13	0.21	-0.07			
		Sleep Anxiety	0.40	0.18	0.36*			
		Night Wakings	-0.08	0.20	-0.04			
		Parasomnia	0.17	0.16	0.15			
		Sleep Disordered Breathing	0.43	0.27	0.16			
		Daytime Sleepiness	0.00	0.09	0.00			

***p*=<0.05, ****p*=<0.001.**

Supplemental Table 4: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Social Phobia

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	3.75	2.13		0.02	0.75	-0.005
n= 102		Age	0.02	0.02	0.12			
		Sex	0.20	0.86	0.02			
	2	(Constant)	-8.27	3.97		0.19	2.64*	0.112
		Age	0.04	0.02	0.26*			
		Sex	0.69	0.85	0.08			
		Bedtime Resistance	-0.17	0.26	-0.10			
		Sleep Onset Delay	0.15	0.63	0.03			
		Sleep Duration	0.27	0.33	0.13			
		Sleep Anxiety	0.28	0.32	0.14			
		Night Wakings	0.04	0.41	0.01			
		Parasomnia	0.32	0.24	0.17			
		Sleep Disordered Breathing	1.21	0.46	0.28*			
		Daytime Sleepiness	0.00	0.16	0.00			
FASD	1	(Constant)	5.62	2.20		0.12	6.26*	0.105
n=91		Age	0.04	0.01	0.31*			
		Sex	-1.23	0.94	-0.13			
	2	(Constant)	-1.86	2.79		0.27	4.43**	0.317
		Age	0.05	0.01	0.38**			
		Sex	-2.43	0.89	-0.27*			
		Bedtime Resistance	0.38	0.26	0.24			
		Sleep Onset Delay	1.26	0.73	0.19			
		Sleep Duration	-0.55	0.28	-0.22			
		Sleep Anxiety	0.24	0.24	0.15			
		Night Wakings	0.19	0.27	0.07			
		Parasomnia	0.35	0.21	0.21			
		Sleep Disordered Breathing	-0.30	0.37	-0.08			
		Daytime Sleepiness	0.12	0.12	0.12			

******p*=<0.05,**

*******p*=<0.001.**

Supplemental Table 5: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Obsessive Compulsive

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	2.15	1.20		0.01	0.29	-0.014
n= 102		Age	0.00	0.01	0.04			
		Sex	-0.33	0.49	-0.07			
	2	(Constant)	-5.03	2.23		0.20	2.80*	0.115
		Age	0.02	0.01	0.21			
		Sex	-0.14	0.48	-0.03			
		Bedtime Resistance	-0.11	0.14	-0.12			
		Sleep Onset Delay	0.10	0.35	0.04			
		Sleep Duration	0.21	0.18	0.18			
		Sleep Anxiety	0.23	0.18	0.20			
		Night Wakings	0.17	0.23	0.08			
		Parasomnia	0.16	0.14	0.15			
		Sleep Disordered Breathing	0.43	0.26	0.17			
		Daytime Sleepiness	0.02	0.09	0.04			
FASD	1	(Constant)	3.90	1.63		0.01	0.34	-0.015
n=91		Age	0.01	0.01	0.08			
		Sex	-0.18	0.69	-0.03			
	2	(Constant)	-1.55	2.28		0.15	1.79	0.053
		Age	0.01	0.01	0.14			
		Sex	-1.11	0.73	-0.17			
		Bedtime Resistance	-0.01	0.22	-0.01			
		Sleep Onset Delay	0.66	0.60	0.14			
		Sleep Duration	-0.06	0.23	-0.03			
		Sleep Anxiety	0.09	0.20	0.08			
		Night Wakings	0.19	0.22	0.10			
		Parasomnia	0.30	0.17	0.25			
		Sleep Disordered Breathing	0.25	0.30	0.10			
		Daytime Sleepiness	0.02	0.10	0.03			

******p*=<0.05,**

*******p*=<0.001.**

Supplemental Table 6: Hierarchical multiple regression results for TD children and children with FASD for SCAS Subscale Generalised Anxiety

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	4.52	1.57		0.00	0.00	-0.020
n= 102		Age	0.00	0.01	0.00			
		Sex	0.03	0.63	0.01			
	2	(Constant)	-4.74	2.82		0.24	3.68*	0.162
		Age	0.02	0.01	0.16			
		Sex	0.61	0.60	0.10			
		Bedtime Resistance	-0.27	0.18	-0.22			
		Sleep Onset Delay	0.65	0.45	0.20			
		Sleep Duration	-0.02	0.23	-0.01			
		Sleep Anxiety	0.44	0.23	0.3*			
		Night Wakings	-0.25	0.29	-0.09			
		Parasomnia	0.43	0.17	0.31			
		Sleep Disordered Breathing	0.58	0.33	0.18			
		Daytime Sleepiness	0.03	0.11	0.04			
FASD	1	(Constant)	3.81	1.88		0.05	2.25	0.027
n=91		Age	0.02	0.01	0.20			
		Sex	0.94	0.80	0.12			
	2	(Constant)	-0.91	2.69		0.11	1.35	0.057
		Age	0.03	0.01	0.23*			
		Sex	0.00	0.85	0.00			
		Bedtime Resistance	-0.10	0.25	-0.08			
		Sleep Onset Delay	0.38	0.70	0.07			
		Sleep Duration	0.19	0.27	0.09			
		Sleep Anxiety	0.35	0.23	0.27			
		Night Wakings	0.21	0.26	0.09			
		Parasomnia	-0.03	0.20	-0.02			
		Sleep Disordered Breathing	0.29	0.36	0.10			
		Daytime Sleepiness	0.10	0.12	0.12			

******p*=<0.05,**

*******p*=<0.001.**

Supplemental Table 7: Hierarchical multiple regression results for TD children and children with FASD for Total SCAS

			Overall Model			Change Statistics		
Group	**Block**	**Predictors**	***B***	***SE B***	**ß**	**ΔR^2**	**ΔF^2**	***Adjusted R^2***
TD	1	(Constant)	23.58	7.82		0.00	0.09	0.00
n= 102		Age	-0.01	0.05	-0.02			
		Sex	1.22	3.16	0.04			
	2	(Constant)	-30.16	13.76		0.28	4.38**	0.27
		Age	0.07	0.06	0.13			
		Sex	3.39	2.94	0.11			
		Bedtime Resistance	-0.41	0.89	-0.07			
		Sleep Onset Delay	1.54	2.17	0.10			
		Sleep Duration	0.16	1.13	0.02			
		Sleep Anxiety	1.80	1.10	0.24			
		Night Wakings	1.14	1.41	0.08			
		Parasomnia	1.45	0.85	0.21			
		Sleep Disordered Breathing	4.45	1.60	0.27*			
		Daytime Sleepiness	-0.24	0.56	-0.05			
FASD	1	(Constant)	28.76	9.12		0.03	1.38	0.01
n=91		Age	0.09	0.06	0.17			
		Sex	1.76	3.89	0.05			
	2	(Constant)	-12.99	11.52		0.31	4.58**	0.30
		Age	0.14	0.05	0.26*			
		Sex	-5.12	3.66	-0.14			
		Bedtime Resistance	1.13	1.09	0.18			
		Sleep Onset Delay	3.56	3.00	0.14			
		Sleep Duration	-0.57	1.16	-0.06			
		Sleep Anxiety	1.57	0.99	0.25			
		Night Wakings	0.74	1.12	0.07			
		Parasomnia	1.47	0.88	0.22			
		Sleep Disordered Breathing	0.99	1.52	0.07			
		Daytime Sleepiness	0.20	0.49	0.05			

***p*=<0.05,**
****p*=<0.001.**

Figures:

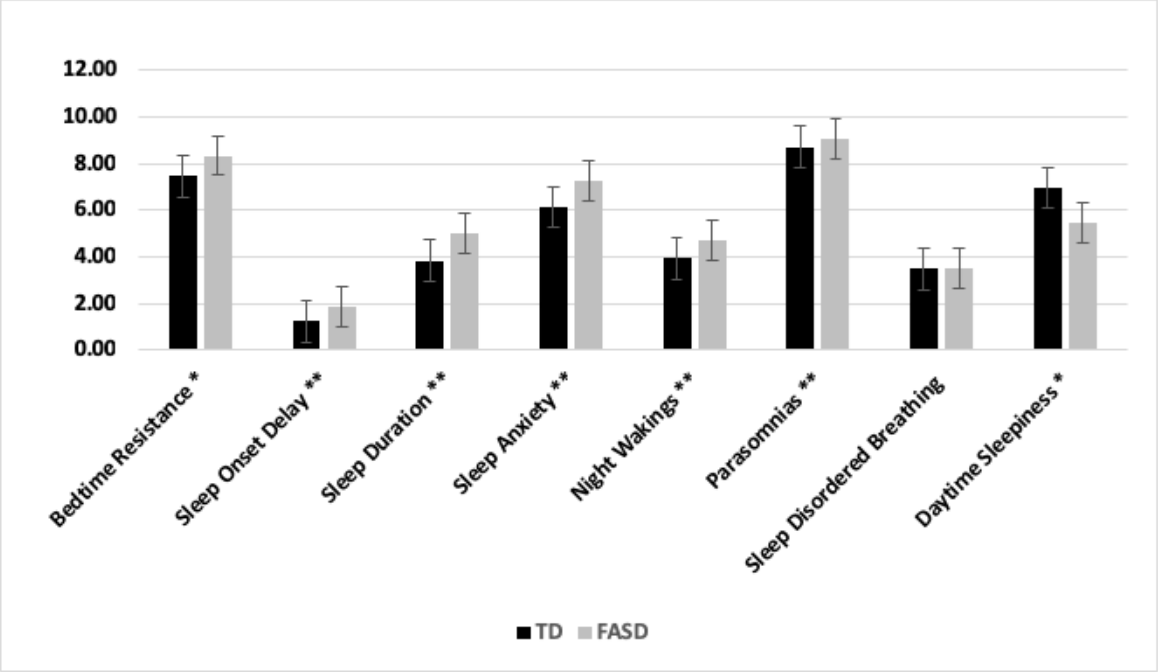

*Figure 1: Comparison between TD and FASD children on CSHQ Subsets. * p<0.05. **p<0.001*

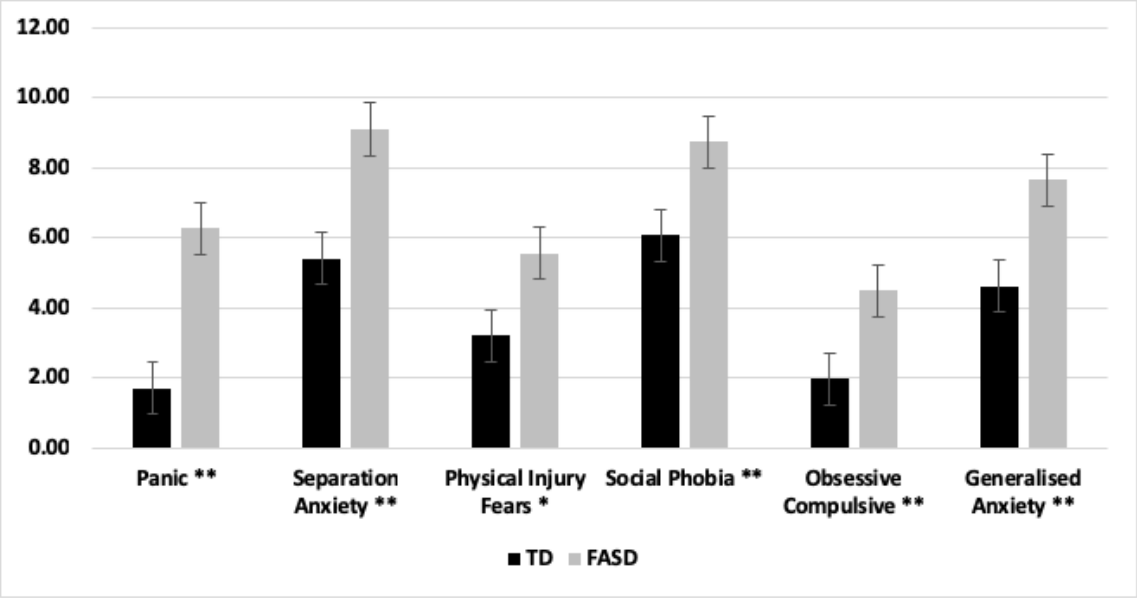

*Figure 2: Comparison between TD and FASD children on SCAS Subsets. * p<0.05. **p<0.001*

References

Alberry, B., & Singh, S. M. (2016). Developmental and behavioral consequences of early life maternal separation stress in a mouse model of fetal alcohol spectrum disorder. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2016.04.031

Alfano, C. A., Zakem, A. H., Costa, N. M., Taylor, L. K., & Weems, C. F. (2009). Sleep problems and their relation to cognitive factors, anxiety, and depressive symptoms in children and adolescents. *Depression and Anxiety*. https://doi.org/10.1002/da.20443

Alvaro, P. K., Roberts, R. M., & Harris, J. K. (2013). A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep*. https://doi.org/10.5665/sleep.2810

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM). *CoDAS*.

Ashworth, A., Hill, C. M., Karmiloff-Smith, A., & Dimitriou, D. (2014). Sleep enhances memory consolidation in children. *Journal of Sleep Research*, *23*(3), 302–308. https://doi.org/10.1111/jsr.12119

B.R., L., J., L., R., D., R.E., W., T.W., T., G., H., … M., C. (2016). Gross motor performance in children prenatally exposed to alcohol and living in remote Australia. *Journal of Paediatrics and Child Health*.

Baglioni, C., Spiegelhalder, K., Lombardo, C., & Riemann, D. (2010). Sleep and emotions: A focus on insomnia. *Sleep Medicine Reviews*. https://doi.org/10.1016/j.smrv.2009.10.007

Baglioni, C., Spiegelhalder, K., Nissen, C., & Riemann, D. (2011). Clinical implications of the causal relationship between insomnia and depression: How individually tailored treatment of sleeping difficulties could prevent the onset of depression. *EPMA Journal*. https://doi.org/10.1007/s13167-011-0079-9

Bowlby, J. (1973). *Attachment and Loss. Separation, Anxiety and Anger. Basic Books*. https://doi.org/0-465-07691-2 Cloth

Brown, W. J., Wilkerson, A. K., Boyd, S. J., Dewey, D., Mesa, F., & Bunnell, B. E. (2018). A review of sleep disturbance in children and adolescents with anxiety. *Journal of Sleep Research*. https://doi.org/10.1111/jsr.12635

Carskadon, M. A., & Dement, W. C. (2011). Normal Human Sleep : An Overview. *Principles and Practice of Sleep Medicine*, 16–26. https://doi.org/10.1016/B978-1-4160-6645-3.00141-9

Chase, R. M., & Pincus, D. B. (2011). Sleep-Related Problems in Children and Adolescents With Anxiety Disorders. *Behavioral Sleep Medicine*. https://doi.org/10.1080/15402002.2011.606768

Chen, M. L., Olson, H. C., Picciano, J. F., Starr, J. R., & Owens, J. (2012). Sleep problems in children with fetal alcohol spectrum disorders. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine*, *8*(4), 421–429. https://doi.org/10.5664/jcsm.2038; 10.5664/jcsm.2038

Chen, M., Olson, H., Picciano, J., Starr, J., & Owens, J. (2012). Sleep Problems in Children with Fetal Alcohol Spectrum Disorders. *Journal of Clinical Sleep Medicine*, *8*(4), 421–429. https://doi.org/10.5664/jcsm.2038

Cox, R. C., & Olatunji, B. O. (2016). A systematic review of sleep disturbance in anxiety and related disorders. *Journal of Anxiety Disorders*. https://doi.org/10.1016/j.janxdis.2015.12.001

Duval, E. R., Javanbakht, A., & Liberzon, I. (2015). Neural circuits in anxiety and stress disorders: A focused review. *Therapeutics and Clinical Risk Management*. https://doi.org/10.2147/TCRM.S48528

Espie, C. A., & Morin, C. M. (2012). *The Oxford Handbook of Sleep and Sleep Disorders*. *The Oxford Handbook of Sleep and Sleep Disorders*. https://doi.org/10.1093/oxfordhb/9780195376203.001.0001

Essau, C. A., Muris, P., & Ederer, E. M. (2002). Reliability and validity of the Spence Children's Anxiety Scale and the Screen for Child Anxiety Related Emotional Disorders in German children. *Journal of Behavior Therapy and Experimental Psychiatry*, *33*(1), 1–18. https://doi.org/10.1016/S0005-7916(02)00005-8

Fletcher, F. E., Conduit, R., Foster-Owens, M. D., Rinehart, N. J., Rajaratnam, S. M. W., & Cornish, K. M. (2018). The Association Between Anxiety Symptoms and Sleep in School-Aged Children: A Combined Insight From the Children's Sleep Habits Questionnaire and Actigraphy. *Behavioral Sleep Medicine*. https://doi.org/10.1080/15402002.2016.1180522

Frank, M. G., & Heller, H. C. (2003). The ontogeny of mammalian sleep: A reappraisal of alternative hypotheses. *Journal of Sleep Research*. https://doi.org/10.1046/j.1365-2869.2003.00339.x

Gareri, J., Lynn, H., Handley, M., Rao, C., & Koren, G. (2008). Prevalence of fetal ethanol exposure in a regional population-based sample by meconium analysis of fatty acid ethyl esters. *Therapeutic Drug Monitoring*, *30*(2), 239–245.

https://doi.org/10.1097/FTD.0b013e318167cfe5

Goril, S., Zalai, D., Scott, L., & Shapiro, C. M. (2016). Sleep and melatonin secretion abnormalities in children and adolescents with fetal alcohol spectrum disorders. *Sleep Medicine*, *23*, 59–64. https://doi.org/10.1016/j.sleep.2016.06.002

Gregory, A. M., Caspi, A., Eley, T. C., Moffitt, T. E., O'Connor, T. G., & Poulton, R. (2005). Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *Journal of Abnormal Child Psychology*. https://doi.org/10.1007/s10802-005-1824-0

Gregory, A. M., & Eley, T. C. (2005). Sleep problems, anxiety and cognitive style in school-aged children. *Infant and Child Development*. https://doi.org/10.1002/icd.409

Hellemans, K. G. C., Sliwowska, J. H., Verma, P., & Weinberg, J. (2010). Prenatal alcohol exposure: Fetal programming and later life vulnerability to stress, depression and anxiety disorders. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2009.06.004

Hill, C. M., Hogan, A. M., & Karmiloff-Smith, A. (2007). To sleep, perchance to enrich learning? *Archives of Disease in Childhood*, *92*(7), 637–643. https://doi.org/10.1136/adc.2006.096156

Hutson, J. R., Magri, R., Gareri, J. N., & Koren, G. (2010). The incidence of prenatal alcohol exposure in Montevideo Uruguay as determined by meconium analysis. *Therapeutic Drug Monitoring*, *32*(3), 311–317. https://doi.org/10.1097/FTD.0b013e3181dda52a

Ipsiroglu, O. S., McKellin, W. H., Carey, N., & Loock, C. (2013). " They silently live in terror..." why sleep problems and night-time related quality-of-life are missed in children with a fetal alcohol spectrum disorder. *Social Science and Medicine*. https://doi.org/10.1016/j.socscimed.2012.10.027

Jan, J., Asante, K., Conry, J., Fast, D., Bax, M., Ipsiroglu, O., … Wasdell, M. (2010). Sleep health issues for children with FASD: clinical considerations. *International Journal of Pediatrics*, *2010*, 1–7. https://doi.org/10.1155/2010/639048

Kocevska, D., Muetzel, R. L., Luik, A. I., Luijk, M. P. C. M., Jaddoe, V. W., Verhulst, F. C., … Tiemeier, H. (2017). The Developmental Course of Sleep Disturbances Across Childhood Relates to Brain Morphology at Age 7: The Generation R Study. *Sleep*. https://doi.org/10.1093/sleep/zsw022

Kozanian, O. O., Rohac, D. J., Bavadian, N., Corches, A., Korzus, E., & Huffman, K. J. (2018). Long-Lasting Effects of Prenatal Ethanol Exposure on Fear Learning and Development of the Amygdala. *Frontiers in Behavioral Neuroscience*. https://doi.org/10.3389/fnbeh.2018.00200

Litwiller, B., Snyder, L. A., Taylor, W. D., & Steele, L. M. (2017). The relationship between sleep and work: A meta-analysis. *Journal of Applied Psychology*. https://doi.org/10.1037/apl0000169

Lussier, A. A., Weinberg, J., & Kobor, M. S. (2017). Epigenetics studies of fetal alcohol spectrum disorder: Where are we now? *Epigenomics*. https://doi.org/10.2217/epi-2016-0163

Martin, J., Hiscock, H., Hardy, P., Davey, B., & Wake, M. (2007). Adverse Associations of Infant and Child Sleep Problems and Parent Health: An Australian Population Study. *PEDIATRICS*. https://doi.org/10.1542/peds.2006-2569

May, P. A., Blankenship, J., Marais, A. S., Gossage, J. P., Kalberg, W. O., Joubert, B., … Seedat, S. (2013). Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): Quantity, frequency, and timing of drinking. *Drug and Alcohol Dependence*. https://doi.org/10.1016/j.drugalcdep.2013.07.013

May, P. A., Chambers, C. D., Kalberg, W. O., Zellner, J., Feldman, H., Buckley, D., … Hoyme, H. E. (2018). Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2017.21896

McLachlan, K., Rasmussen, C., Oberlander, T. F., Loock, C., Pei, J., Andrew, G., … Weinberg, J. (2016). Dysregulation of the cortisol diurnal rhythm following prenatal alcohol exposure and early life adversity. *Alcohol*. https://doi.org/10.1016/j.alcohol.2016.03.003

McQuire, C., Mukherjee, R., Hurt, L., Higgins, A., Greene, G., Farewell, D., … Paranjothy, S. (2018). Screening prevalence of fetal alcohol spectrum disorders in a region of the United Kingdom: A population-based birth-cohort study. *Preventive Medicine*, *118*, 344–351.

Meltzer, L. J., & Mindell, J. A. (2006). Sleep and Sleep Disorders in Children and Adolescents. *Psychiatric Clinics of North America*. https://doi.org/10.1016/j.psc.2006.08.004

Office of National Statistics (ONS) (2019). The National Statistics Socio-economic classification (NS-SEC) REtrieved on 2nd

February 2019 from https://www.ons.gov.uk/methodology/classificationsandstandards/otherclassifications/thenationalstatisticssocioeconomicclassificationnssecrebasedonsoc2010#toc

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*. https://doi.org/10.1093/sleep/27.7.1255

Owens, J. A., Spirito, A., & McGuinn, M. (2000). The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep*, *23*(8), 1043–1051. https://doi.org/10.1111/j.1469-8749.2001.tb00204.x

Pei, J., Denys, K., Hughes, J., & Rasmussen, C. (2011). Mental health issues in fetal alcohol spectrum disorder. *Journal of Mental Health*, *20*(5), 473–483. https://doi.org/10.3109/09638237.2011.577113

Popova, S., Lange, S., Burd, L., & Rehm, J. (2016). The economic burden of fetal alcohol spectrum disorder in Canada in 2013. *Alcohol and Alcoholism*. https://doi.org/10.1093/alcalc/agv117

Popova, S., Lange, S., Shield, K., Mihic, A., Chudley, A. E., Mukherjee, R. A. S., … Rehm, J. (2016). Comorbidity of fetal alcohol spectrum disorder: A systematic review and meta-analysis. *The Lancet*. https://doi.org/10.1016/S0140-6736(15)01345-8

Price, A., Cook, P. A., Norgate, S., & Mukherjee. (2017). Prenatal alcohol exposure and traumatic childhood experiences: A systematic review. *Neuroscience & Biobehavioral Reviews*, *80*, 89–98. https://doi.org/10.1016/J.NEUBIOREV.2017.05.018

Rasmussen, C., Andrew, G., Zwaigenbaum, L., & Tough, S. (2008). Neurobehavioural outcomes of children with fetal alcohol spectrum disorders: A Canadian perspective. *Paediatrics and Child Health*. https://doi.org/10.1093/pch/13.3.185

Schlarb, A. A., Jaeger, S., Schneider, S., In-Albon, T., & Hautzinger, M. (2016). Sleep Problems and Separation Anxiety in Preschool-Aged Children: A Path Analysis. *Journal of Child and Family Studies*. https://doi.org/10.1007/s10826-015-0262-z

Sharma, V., & Mazmanian, D. (2003). Sleep loss and postpartum psychosis. *Bipolar Disorders*, *5*(15), 98–105. https://doi.org/10.1034/j.1399-5618.2003.00015.x

Spence, S H. (1997). Structure of anxiety symptoms among children: a confirmatory factor-analytic study. *Journal of Abnormal Psychology*, *106*(2), 280–297. https://doi.org/10.1037/0021-843X.106.2.280

Spence, Susan H. (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy*, *36*(5), 545–566. https://doi.org/10.1016/S0005-7967(98)00034-5

Spruyt, K., Ipsiroglu, O., Stockler, S., & Reynolds, J. N. (2018). Challenging sleep-wake behaviors reported in informal, conversational interviews of caregivers of children with fetal alcohol spectrum disorder. *International Journal of Developmental Disabilities*, *64*(2), 65–74. https://doi.org/10.1080/20473869.2016.1229395

Staner, L. (2010). Comorbidity of insomnia and depression. *Sleep Medicine Reviews*. https://doi.org/10.1016/j.smrv.2009.09.003

Steinhausen, H. C., & Spohr, H. L. (1998). Long-term outcome of children with fetal alcohol syndrome: psychopathology, behavior, and intelligence. *Alcohol Clin Exp Res*, *22*(2), 334–338. https://doi.org/10.1111/j.1530-0277.1998.tb03657.x

Streissguth, a P., Bookstein, F. L., Barr, H. M., Press, S., & Sampson, P. D. (1998). A fetal alcohol behavior scale. *Alcoholism, Clinical and Experimental Research*, *22*(2), 325–333. https://doi.org/10.1111/j.1530-0277.1998.tb03656.x

Streissguth, A. P., Bookstein, F. L., Barr, H. M., Sampson, P. D., O'Malley, K., & Young, J. K. (2004). Risk factors for adverse life outcomes in Fetal Alcohol Sydnrome and Fetal Alcohol Effects. *Journal of Developmental and Behavioral Pediatrics*. https://doi.org/10.1097/00004703-200408000-00002

Touchette, E., Petit, D., Séguin, J. R., Boivin, M., Tremblay, R. E., & Montplaisir, J. Y. (2007). Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep*. https://doi.org/10.1093/sleep/30.9.1213

Trejos-Castillo, E., Bedore, S., Davis, G., & Hipps, T. (2015). Emotional Well-being of Youth in Foster Care: An Exploratory Study. *Revista Ces Psicologia*.

Tsang, T. W., Lucas, B. R., Carmichael Olson, H., Pinto, R. Z., & Elliott, E. J. (2016). Prenatal Alcohol Exposure, FASD, and

Child Behavior: A Meta-analysis. *Pediatrics*, *137*(3), e20152542. https://doi.org/10.1542/peds.2015-2542

Wenar, C., & Kerig, P. (2000). *Developmental psychopathology: From infancy through adolescence*. *Developmental psychopathology: From infancy through adolescence (4th ed.)*.

Wengel, T., Hanlon-dearman, A. C., Fjeldsted, B., Ot, D., & Mb, O. T. R. (2011). Sleep and Sensory Characteristics in Young Children With fetal alcohol spectrum disorder. *J Dev Behav Pediatr*, *32*(5), 384–392.

Wieczorek, L., Fish, E. W., O'Leary-Moore, S. K., Parnell, S. E., & Sulik, K. K. (2015). Hypothalamic-pituitary-adrenal axis and behavioral dysfunction following early binge-like prenatal alcohol exposure in mice. *Alcohol*. https://doi.org/10.1016/j.alcohol.2015.01.005

Williams, P., Catterick, M., & Calder, E. (2012). "As I see it..." Using social media to bring out the voices of people with FASD, their families and carers. *Journal of Population Therapeutics and Clinical Pharmacology*.

World Health Organization. (2014). Global Status Report on Alcohol and Health. Retrieved September 1, 2017, from http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf