THE IMPACT OF SLEEP AND NEURODEVELOPMENTAL CHARACTERISTICS ON QUALITY OF LIFE IN CHILDREN WITH EPILEPSY

by

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ABSTRACT

This thesis set out to explore the complex relationship between sleep and health related quality of life (HRQOL) in children with epilepsy (CWE). Sleep disturbances and neurodevelopmental characteristics are common co-occurrences in CWE; however, they are often overlooked in epilepsy management. In CWE, their impact on HRQOL is expected to be amplified. Despite this, there is limited relevant research, thus it is unknown whether sleep disturbances directly impact HRQOL or whether they behave as a marker of neurodevelopmental characteristics, which are indeed driving this impact. Furthermore, HRQOL is multifactorial, and epilepsy does not occur in isolation, but can have a systemic impact on parents. Consequently, the contribution of parental variables compared to child variables, specifically co-occurrences were also considered, in order to construct a broad picture of HRQOL.

The first study based on informant reports of sleep showed that sleep problems were significantly predictive of HRQOL above seizure severity and number of AEDs. In contrast, sleep problems were no longer predictive of HRQOL when neurodevelopmental characteristics were considered. There were also no significant differences in sleep, neurodevelopmental characteristics or HRQOL across epilepsy types. The second study based on actigraphy defined sleep revealed that there were no significant differences between CWE and children without epilepsy (CWOE), or between epilepsy types. However, there was a trend for higher intra-individual variability in sleep onset latency (SOL) in CWE compared to CWOE. Variability in SOL did not significantly predict HRQOL above seizure severity. However, it was shown that inclusion of ADHD characteristics possibly mediated the relationship between sleep and HRQOL. Interestingly, both autistic characteristics and variability in SOL were found to uniquely predict HRQOL. In the third study, parents of CWE were found to be vulnerable to poor sleep quality and mental health symptoms.

Furthermore, all parental variables were initially significantly predictive of HRQOL, however when considered in the presence of co-occurrences, this effect was no longer significant.

In summary this research elucidates the consistent role of co-occurrences in impacting HRQOL, which holds important clinical and research implications. Improvement of HRQOL in CWE requires an integrated approach, consisting of input from both neurodevelopmental and epilepsy fields.

DEDICATION

To 'Uncle Tony', thank you for everything.

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Publications

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ABBREVIATIONS

AASM: American Academy Of Sleep Medicine

ADHD: Attention Deficit Hyperactivity Disorder

AED: Antiepileptic Drugs

ANOVA: Analysis Of Variance

ASD: Autism Spectrum Disorder

BECTS: Benign Epilepsy With Centrotemporal Spikes

CNND: Cerebra Network For Neurodevelopmental Disorder

CSHQ Children's Sleep Habits Questionnaire

CWE: Children With Epilepsy

CWOE: Children Without Epilepsy

ECG: Electrocardiogram

EEG: Electroencephalography

EMG: Electromyography

EOG: Electrooculogram

GABA: Gamma-Aminobutyric Acid

HADS: Hospital Anxiety And Depression Scale

HASS: Hague Seizure Severity Scale

HRA: Health Research Authority

HRQOL: Health Related Quality Of Life

ICSD-3: International Classification Of Sleep Disorders

ID: Intellectual Disability

IED: Interictal Epileptiform Discharge

IIV: Intraindividual Variability

ILAE: International League Against Epilepsy

NHS: National Health Service

NREM: Non Rapid Eye Movement Sleep

PCA: Principal Component Analysis

PDS: Paroxysmal Depolarising Shift

PDSS: Paediatric Daytime Sleepiness Scale

PRISM: Preferred Reporting Items For Systematic Reviews And Meta-Analyses

PSG: Polysomnography

PSQ Paediatric Sleep Questionnaire

PSQI: Pittsburgh Sleep Quality Index

QOL: Quality Of Life

QOLCE: Quality Of Life In Childhood Epilepsy Scale

R&K: Rechtschaffen & Kales

RE: Rolandic Epilepsy

REC: Research Ethics Committee

REM: Rapid Eye Movement Sleep

SBQ Sleep Behaviour Questionnaire

SCQ: Social Communication Questionnaire

SD: Standard Deviation

SDB Sleep Disordered Breathing

SE: Sleep Efficiency

SMD Standardised Mean Difference

SOL: Sleep Onset Latency

SPT: Sleep Period Time

SUDEP: Sudden Unexpected Death In Epilepsy

SWS: Slow Wave Sleep

TD: Typically Developing

TIB: Time In Bed

TMS: Transcranial Magnetic Stimulation

TST: Total Sleep Time

V-EEG: Video Electroencephalography

VIF: Variance Inflation Factor

WASO: Wake After Sleep Onset

WHO: World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 Epilepsy

1.1.1. Epidemiology of epilepsy

Epilepsy is defined as a group of diseases characterised by an underlying vulnerability to recurrent seizures (Sirven, 2015). The first definition of epilepsy was defined by the occurrence of two or more seizures of an unprovoked nature, occurring more than a day apart (Fisher et al., 2014a). However, given the heterogeneity of the disease, this definition was extended to include additional criteria (see Table 1.1). The global epilepsy report by the World Health Organisation (WHO, 2019) estimates that 50 million people worldwide are affected by epilepsy. Furthermore, it is recognised as one of the most frequently occurring neurological diseases in children, with a prevalence of up to 1% in childhood (Aaberg et al., 2017). According to WHO (2019), epilepsy has been estimated to contribute 0.5% to overall disease burden across the world, highlighting the health-related impact of epilepsy.

Table 1.1. *Criteria for an epilepsy diagnosis according to the ILAE.*

1. Two or more unprovoked seizures which occur more than 24 hours apart
2. One unprovoked seizure combined with at least a 60% risk of further seizures in a 10-year period
3. Epilepsy syndrome diagnosis

Note. Adapted from "A practical clinical definition of epilepsy" by Fisher et al. (2014a), *Epilepsia*, 55(4), 475-482. Wiley Periodicals, Inc. Copyright 2014 by International League Against Epilepsy

1.2. Definition and Classification of Epilepsies

Over the decades there has been a refinement to the classification system governing definitions of epilepsies and seizures. The current classification system proposed by the International League Against Epilepsy (ILAE; Scheffer et al., 2017) is multi-level and constructed to allow classification of epilepsy across various settings with varying levels of resources (see Figure 1.1). Use of a classification system is a beneficial tool for clinicians to evaluate diagnoses, additional risks of co-

occurring conditions including intellectual disability (ID) and neurodevelopmental conditions. It is also helpful for identifying risk of sudden unexpected death in epilepsy (SUDEP) and for guiding selection of antiepileptic drugs (AEDs) (Scheffer et al., 2017).

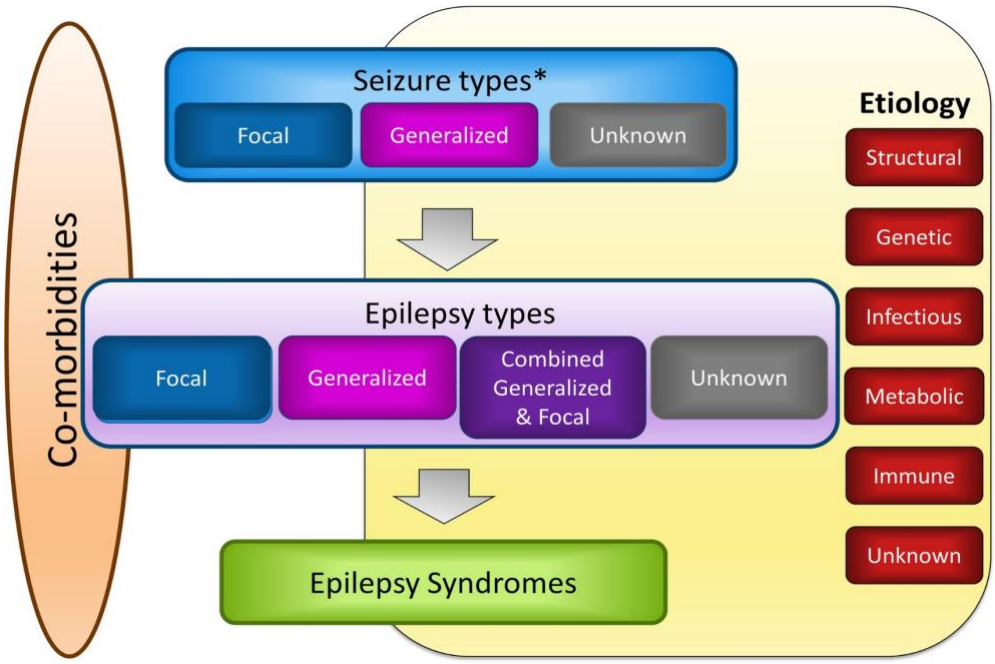


Figure 1.1. *ILAE 2017 epilepsy classification framework*. Reprinted from "ILAE Classification of the epilepsies: Position paper of the ILAE Commission of Classification and Terminology" by Scheffer et al. (2017), Epilepsia, 58(4), 512-521. Wiley Periodicals, Inc. Copyright 2017 by International League Against Epilepsy

Note. *Represents seizure onset.

1.2.1. Seizure Classification

Seizure types are positioned at the beginning of the classification system (Figure 1.1) Seizures are described as "transient occurrence of signs and/ or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2017, p.476). As outlined in Table 1.1, the occurrence of one seizure only is not sufficient for an epilepsy diagnosis, therefore seizures require their own classification system, which underpins the epilepsy diagnostic classification

system. Seizures are divided into three types based on their onset: focal, generalised, or unknown. Another classification system was produced to provide a detailed description of each seizure type, which expands on the epilepsy classification framework (see Figure 1.2). In this framework, focal onset seizures are then further subdivided into two types based on whether the individual is aware during the seizure or not. This can then be further characterised by whether motor or non-motor symptoms are displayed. Focal seizures are also recognised in some cases to evolve into bilateral tonic-clonic seizures. Generalised seizures are divided into motor and non- motor, the latter are recognised as absence seizures. Compared to focal onset seizures, where an individual's awareness level is considered, this is not the case for seizures of generalised onset, as almost all involve loss of awareness (Fisher et al., 2017). It is important to consider that in some cases this may be the final level of diagnosis where an individual can experience seizures, without having an epilepsy diagnosis. This may be due to the lack of resources available (e.g., diagnostic tests) or it may be that the patient does not fulfil the criteria for an epilepsy diagnosis (see Table 1.1.) (Fisher et al., 2014a; Scheffer et al., 2017).

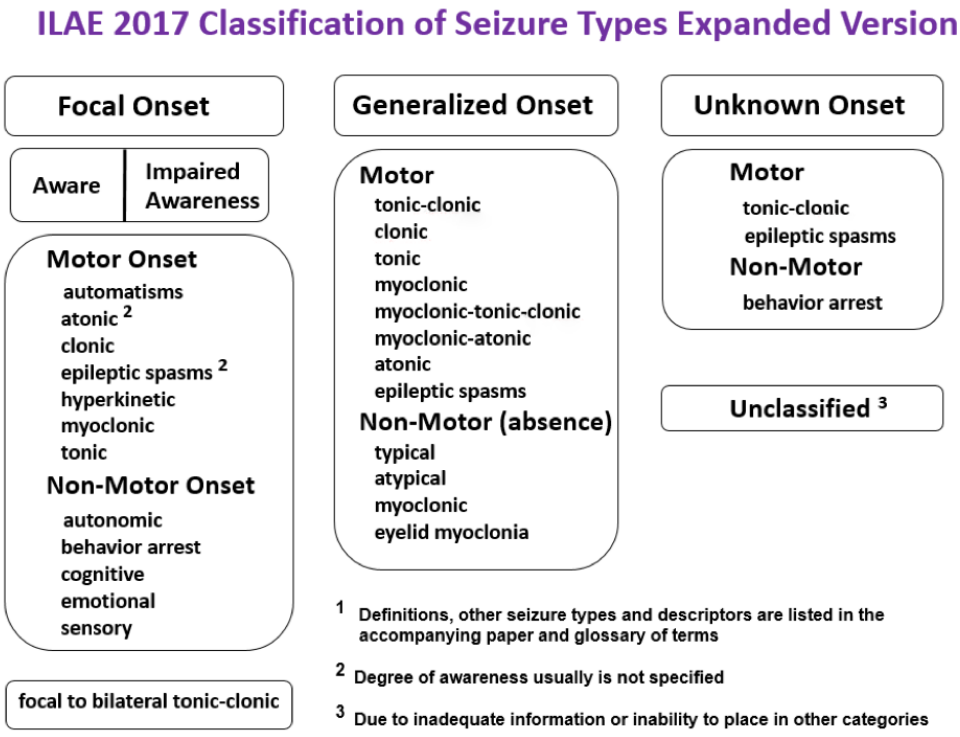


Figure 1.2. *ILAE 2017 Seizure type classification*. Reprinted from "Instruction manual for the ILAE 2017 operational classification of seizure types" by Fisher et al. (2017), Epilepsia, 58(4), 531-542. Wiley Periodicals, Inc. Copyright 2017 by International League Against Epilepsy

1.2.2. Epilepsy Classification

If an individual fulfils the epilepsy diagnosis criteria as outlined in Table 1.1, the type of epilepsy would then be specified. To provide an epilepsy type, the second level of the initial classification system is referred to again (Figure 1.1). Epilepsy types are divided into focal, generalised, combined focal and generalised and unknown onset (Scheffer et al., 2017). To assign an epilepsy type, information is taken from electroencephalography (EEG) data (see section 1.3.2 for a description). An epilepsy diagnosis can be the final level of classification, or if there is sufficient information, a refined diagnosis of an epilepsy syndrome can be made.

1.2.3. Epilepsy Syndrome classification

The final level of the epilepsy classification system is a diagnosis of an epilepsy syndrome. This refers to a "cluster of features incorporating seizure types, EEG and imaging features that tend to occur together" (Scheffer et al., 2017, p.6). Epilepsy syndromes are defined based on shared characteristics including, features appearing or remitting at a similar age across children, daytime presentation, similar triggers, or shared co-occurrences (Commission of ILAE, 1989). An epilepsy syndrome diagnosis can be clinically useful to guide epilepsy management, however it is important to note that there is not yet an operationalised classification system for childhood epilepsy syndromes. Nevertheless, there are current attempts being made to achieve this by the ILAE nosology task force (Specchio et al., 2021).

1.2.4. Rolandic Epilepsy

As described above, one of the commonalities of epilepsy syndromes can be the age at which features appear. While a full description of childhood epilepsy syndromes is beyond the scope of this thesis (see Pearl, 2018 for more detail), a particular focus of this thesis is the childhood epilepsy syndrome, rolandic epilepsy (RE). RE was previously recognised as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes (BECTS). This is a self-limited epilepsy syndrome (Scheffer et al., 2017), which is clinically recognised as benign. This is due to most seizures occurring during sleep, the low seizure burden and lack of need for AED treatment (Camfield & Camfield, 2001; Ambrosetto & Tassinari, 1990). The term 'benign' was replaced with the term 'self-limited' due to the increased acknowledgement of the negative co-occurrences attached to this epilepsy type and the probable remission of the syndrome (Scheffer et al., 2017). The main rationale for including this epilepsy type as a subgroup and focus for this thesis, is because RE is recognised as the most commonly occurring epilepsy type in childhood with a prevalence rate of "15%" in children with epilepsy (CWE) (Amrutkar & Riel-Romero, 2018; Camfield & Camfield, 2002). In addition, the "benign" nature will allow a dissociation between the impact of epilepsy more broadly and the impact of seizures more specifically on both sleep and health related quality of life (HRQOL).

The aetiology of RE is presumed to be genetically determined however the exact cause is yet to be established (Xiong & Zhou, 2017). Seizure onset in RE occurs between 1 and 14 years of age, with peak frequency between aged 6-7 years of age (Camfield & Camfield, 2002; Lee, Hwang & Kwon, 2017). However, the prognosis of RE is relatively positive as seizures usually remit before children reach age 16 (Guliyeva, Tatishvili & Kaiyrzhanov, 2021). In addition, seizure frequency in RE is relatively low, with up to 20% of children experiencing one event during their diagnosis. Most children experience less than 10 seizures, where children who experience a higher number of

seizures tend to experience them earlier in the disease trajectory (Amrutkar & Riel-Romero, 2018). If seizures occur at a frequent rate, they tend to cluster together, and the next attack may not occur for several months (Panayiotopoulos, 2010). Children primarily experience focal seizures which are of short duration (a few minutes), usually occurring during the night and characterised by one-sided facial motor features, difficulties with speech and excessive saliva (Panayiotopoulos, Michael, Sanders, Valeta & Koutroumanidis, 2008). Around 50% of children with RE experience secondary generalisation of seizures (Lee et al., 2017). Finally due to the positive prognosis of RE, treatment of seizures is optional (Camfield & Camfield, 2002).

In clinical practice an epilepsy classification system is followed (see Figure 1.1). To improve the clinical translation of these findings, the sample within this thesis has been divided using this system. These included (1) Focal epilepsy (2) Rolandic epilepsy and (3) Generalised epilepsy. As conceptualisation goes beyond the epilepsy classification, the following section outlines the mechanisms underlying the progression of a seizure through to epilepsy.

1.3. Mechanisms in Epilepsy

1.3.1. Epileptogenesis

Epileptogenesis refers to a chronic process in which tissue develops, which is vulnerable to seizure generation. This results in the initiation of epilepsy and eventual progression of seizure frequency and intensity (Pitkänen, Lukasiuk, Dudek & Staley, 2015; Pitkänen & Engel, 2014). Epileptogenesis is considered to involve three steps: (1) initial epilepsy event (2) latent period where no seizures occur, and previously normal networks begin to transform into abnormal networks (3) seizure initiation (Maguire, 2016). The aetiology of epilepsy is multifactorial and can occur for congenital reasons or acquired factors such as infections or stroke (Pitkänen et al., 2007). The latent period is considered to be where epileptogenesis is completed and can last from a period of several weeks to months (Kandratavicius et al., 2014). However, this process continues to occur

beyond seizure initiation (Reddy, 2013), evidenced by observations of increased seizure frequency and progression to drug resistance (Dudek & Staley, 2011; Maguire, 2016). This suggests that epileptogenesis is not a staged process but rather evolves continuously, and the seizure trajectory can differ after the initial impact on the brain (Pitkänen, 2010).

1.3.2. EEG in Epilepsy

As outlined in section 1.2.1, seizures are characterised by excessive neuronal activity which can manifest as physical features e.g., change in awareness level, motor manifestations or behavioural changes (Fisher et al., 2017). In clinical settings, type of seizure or an epilepsy diagnosis is supported with a combination of clinical and EEG data (Fisher, Scharfman & DeCurtis, 2014b). EEG is described as a recording of neuronal activity from the brain. In this process, the individual is fitted with scalp electrodes to record the underlying activity (Bromfield, Cavazos & Sirven, 2006; Binnie & Prior, 1994). The EEG typically consists of five frequency bands: delta ("1-4Hz"), theta ("4-8Hz"), alpha ("8-13Hz"), beta ("13-30Hz) and gamma ("30-80Hz") (Tsipouras, 2019). In some cases, a video is used as an adjunct to the EEG. This can support diagnosis by recording movements and differentiating these from other behavioural or neurological causes (Loddenkemper & Wyllie, 2005).

In people with epilepsy, there are distinctive patterns on the EEG, referred to as epileptiform discharges. These are not typically seen in people without epilepsy and are indicative of a vulnerability to seizures (Smith, 2005). Epileptiform activity is divided into three states: interictal, ictal and postictal (Fisher et al., 2014b). EEG is recognised as gold standard for visualisation of interictal epileptiform discharges (IED). Typically, EEGs are conducted when the individual is awake (wake-EEG), however this only detects IEDs on the first EEG recording in 50% of people with epilepsy (Smith, 2005). For some people, there may be difficulties in detecting IEDs using a

wake EEG due to age of the person, type of epilepsy syndrome, location of seizure onset or frequency of seizures (Smith, 2005). Other methods can be used to improve identification of IEDs. These include activation procedures such as hyperventilation, induced sleep through methods such as melatonin or sleep deprivation, and photic stimulation (Pillai & Sperling, 2006).

1.3.3. Interictal epileptiform discharges

IEDs are defined as pathological transient electrophysiological activity which **occur in-between seizures** and act as an indicator of the presence of epileptic tissue (De Curtis, Jefferys & Avoli, 2012; Chvojka et al., 2021). IEDs occur without any physical manifestation of a seizure (Cheng, Yan, Xu, Zhou & Chen, 2020). On the EEG, IEDs can present with various morphologies within and between people with epilepsy, including spikes and sharp waves, which can be attached or not to a slow wave (So, 2010). They have considerable clinical significance as a diagnostic marker for epilepsy and can be used to assess disease progression or remission, type of epilepsy, monitor reaction to AEDs and when seizures are remitted (Chvojka et al., 2021; Avoli, Biagini & De Curtis, 2006).

At an extracellular level, a single IED represents a state of hypersynchronous activity across cortical neurons. This is supported by observations at a cellular level, where it is characterised by a paroxysmal depolarising shift (PDS) (De Curtis & Avanzini, 2001). The duration of the depolarisation is between 80 and 200ms (Chvojka et al., 2021), which is considerably longer than that of an excitatory post synaptic potential (10-16ms). The relevance of this much longer depolarisation state is attributed to its capability to produce a run of action potentials (Holmes and Ben-Ari, 2001). The current consensus regarding the generation of a PDS suggests it is due to disinhibition of the neurotransmitter gamma-aminobutyric acid (GABA) or influx of calcium ions (Chvojka et al., 2021; Kubista, Boehm & Hotka, 2019). The mechanisms by which the network

changes from the interictal (before seizure) to ictal (during seizure) state is a topic of continued debate (Jacob et al., 2019). It is possible that IEDs play a protective role in seizure generation (Avoli, 2001). However, a debate has yet to reach a conclusion as to whether IEDs may facilitate seizure onset or have no impact at all (Kubista et al., 2019). It may be useful to take a dynamic approach to the role of IEDs in seizure generation, where the interaction between the brain network and IEDs are considered in combination (Chvojka et al., 2021; see Figure 1.3). The theory posits various mechanisms for seizure generation. A general mechanism considered is that over time the brain slowly loses stability and eventually shifts into a seizure state. Interestingly, two other mechanisms were put forward, which were considered in the context of IEDs. The authors suggested that when the brain is in a state of high stability, high amplitude IEDs cannot exert a strong enough impact to tip the brain into a seizure state. In this situation, the IED may have a protective effect on the system and help the brain move into a more stable state. However if the system is not stable, then an IED can swiftly shift the brain into a seizure state and holds a 'pro-ictogenic effect' (Chvojka et al., 2021).

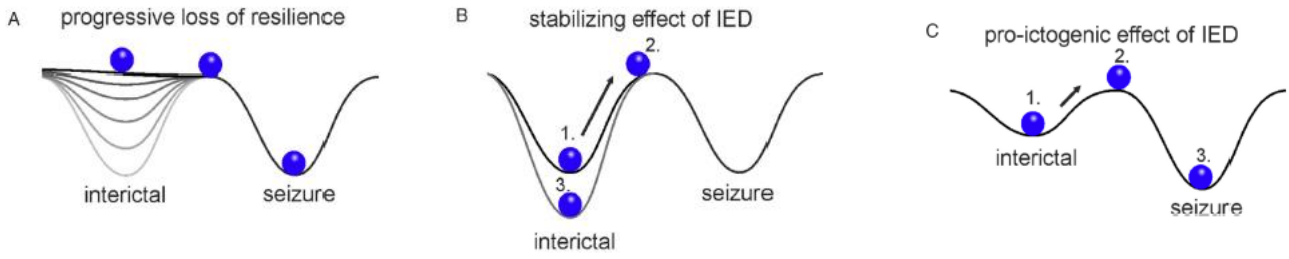


Figure 1.3 *Impact of IEDs on seizure generation.* Reprinted from "The role of interictal discharges in ictogenesis – A dynamical perspective" by Chvojka et al. (2021), Epilepsy & Behaviour, 121, 106591. Copyright 2021 by Elsevier, Inc.

1.3.4. Seizure Generation

Seizures are referred to as ictal discharges and the process where a seizure is generated is referred to as ictogenesis. Initiation of a seizure consists of two main features (1) Rapid occurrence of action potentials and (2) synchronisation of neurons (Bromfield et al., 2006). Generation of seizure occurs when there is a sufficient synchronisation of action potentials producing an ictal discharge on the EEG. There is no definitive conclusion on the electrographic pattern of a seizure (ictal EEG). Various EEG patterns have been suggested to reflect seizures including (1) spike waves (2) rhythmic waves (3) seizures with no accompanying EEG pattern (4) fast waves of low amplitude or (5) rhythmic spiking (Fisher et al., 2014b). Due to the limitations of scalp EEG (see section 1.3.2), intracranial recordings are recommended to record ictal EEG patterns. Such recordings suggest that the most commonly occurring EEG pattern observed during the occurrence of a seizure are low amplitude (beta/gamma frequency range) spike waves, which occur in fast succession (Fisher et al., 2014b). The neuronal mechanisms underlying seizure generation has been considered to be due to the delicate balance between excitation and inhibition (Bromfield et al., 2006). This delicate balance is proposed to lean towards a hyper excitable state in the case where there are changes in depolarising ionic movements (e.g., sodium or calcium influx) or an increase in transmission of glutamate. Similarly, this balance can shift when GABAergic activity is decreased (loss of inhibitions) or ions which hyperpolarise the membrane are enhanced (reduction in extracellular potassium or increase in intracellular chloride) (Bromfield et al., 2006; Shao, Habela & Stafstrom, 2019).

This brief overview outlined the basic features of epilepsy and the mechanisms underlying the appearance of seizures and markers of epilepsy. These epilepsy mechanisms can intertwine with sleep systems; therefore, the following section will focus on describing sleep across development, sleep methodology and the interaction with epilepsy.

1.4. Sleep

1.4.1. Sleep Architecture in adults

Sleep is described as a state of reduced responsiveness to the environment and reduced motor movement (Siegel, 2005). Sleep architecture refers to the structure of sleep (Nayak & Anilkumar, 2021). There are two types of sleep, non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). NREM sleep is further divided into three stages N1, N2 and N3. N3 is typically referred to as slow wave sleep (SWS)[i] (American Academy of Sleep Medicine; Iber, 2007). Sleep onset starts with N1, descending into N2, N3 and finally REM sleep. This equates to one cycle of sleep and takes on average 90 minutes. Individuals alternate between REM and NREM sleep throughout the night, experiencing around 4 to 5 sleep cycles per night. NREM sleep occupies nearly 80% of the total sleep time whereas REM occupies approximately 20% of sleep time (Carskadon & Dement, 2011). The proportion of time spent within sleep stages varies in length as the night progresses, where REM and N2 sleep tend to occupy the cycle towards the end of the night, whereas N3 sleep tends to be higher in the early night and reduce during the course of the night (Carskadon & Dement, 2011; Colten & Altevogt, 2006).

Similar to epilepsy, EEG is used to visually represent sleep architecture. The wake state is defined on the EEG by a dominance of alpha activity, which dissipates when N1 sleep begins. In N1, there is a mix of theta and beta activity, which replaces the alpha waves from wake. This stage lasts for around 1-7 minutes in typically developing (TD) adults with an appearance of vertex sharp waves (a negative potential which is obvious from the activity in the background) towards the end (Malhotra & Avidan, 2013). Following this stage, individuals enter N2 which is characterised by theta activity (4-7Hz) and the appearance of sleep spindles and K-complexes. Sleep spindles are visually presented on the EEG as an oscillation which occurs in the 10-16Hz range, lasting for up

[i] Previously, SWS consisted of N3 and N4 sleep (Rechtschaffen & Kales, 1968).

to three seconds. K-complexes are visually represented as a biphasic waveform composed of a high negative wave followed by a small positive wave, which lasts for half a second (Malhotra & Avidan, 2013; Kryger, Roth & Dement, 2010). This stage typically lasts for around 20 minutes. N3 is also referred to as SWS and lasts around 40 minutes. This stage is characterised by high amplitude slow waves/delta waves (0.5-2Hz) on the EEG. Following NREM sleep, an individual enters REM sleep which lasts for 5 minutes in the first cycle of sleep; however, this extends in time in later sleep cycles. It is also referred to as 'paradoxical sleep' due to the similarities to the waking stage on the EEG. This stage is characterised by desynchronised EEG activity including theta activity and 'sawtooth' shaped waves. During this stage, individuals display muscle atonia and rapid movements of the eye (Carskadon & Dement, 2005).

1.4.2. Sleep architecture across development

There are key differences in sleep architecture in adults compared to children. In new-borns, sleep is divided into quiet (NREM sleep), active (REM sleep) and intermediate sleep (Davis, Parker & Montgomery, 2004). The sleep cycle in newborns is still present, however in adults this takes around 90 minutes whereas in newborns, this takes between 50 – 60 minutes (Carskadon & Dement, 2011). This difference is attributed to the lack of a developed circadian rhythm, which is described as the body rhythm that plays a role in regulating the sleep/wake system and other body functions including hunger and hormonal changes (Colten & Altevogt, 2006). The circadian rhythm begins to emerge as early as two months, where sleep architecture becomes more obvious and the cyclical interaction between REM and NREM sleep emerges. Once infants reach the age of one, they sleep for 14 hours a day, and there is an increased night-time sleep and fewer daytime naps (Anders, Sadeh & Appareddy, 1995). Through childhood, the amount of time spent asleep decreases to 11 hours a day by age five for various reasons, including physiological changes, social cues, sleep needs and schedules (Colten & Altevogt, 2006). The length of the sleep cycle begins

to resemble that of adults, extending to 75 minutes by age two and 90 minutes by age five (Guion & Avis, 2011; Davis et al, 2004). By adolescence, the amount of time children sleep for decreases to between nine and 10 hours (Colten & Altevogt, 2006). Therefore, sleep can be recognised as a developmental process which undergoes predictable changes throughout childhood.

1.4.3. Sleep difficulties in children

Sleep disorders are diagnosed using the international classification of sleep disorders 3 (ICSD-3; Sateia, 2014), which divides them into seven domains including: "Insomnia, central disorders of hypersomnolence, parasomnias, circadian rhythm sleep wake disorders, sleep related movement disorders, sleep related breathing disorders and other" (Bruni & Novelli, 2010). Sleep problems are broader and distinguished from sleep disorders and do not have a diagnostic system as such. They can include problems with settling to sleep, amount of sleep achieved and sleep quality. They can also be recognised as symptoms of sleep disorders and form one aspect of a diagnosis (Cormier, 1990). For the purpose of this thesis, the terms sleep problems or sleep disorder will be used. In cases where there is less clarity, sleep difficulties will be used to describe a combination of diagnosable clinical sleep disorders (e.g., insomnia) and/or components of diagnosable sleep disorders (e.g., difficulties settling to sleep) measured by widely used instruments.

Sleep difficulties are prevalent in children and can arise from both medical and behavioural factors (Meltzer, Johnson, Crosette, Ramos & Mindell, 2010; Hannan & Hiscock, 2015). Behavioural sleep difficulties are the most commonly occurring in childhood, with up to 30% of children experiencing some difficulty with sleep (Turnbull, Reid & Morton, 2013). These include night awakenings, behavioural insomnia (i.e., bedtime resistance, sleep onset delay or refusal to go to sleep) and resistance at bedtime (Moturi & Avis, 2010; Honaker & Meltzer, 2014). Such sleep difficulties can arise for various reasons including poor sleep hygiene resulting from the use of

stimulants, unstructured bedtime routines (poor sleep associations) or use of electronic devices (Esposito et al., 2019; Honaker & Meltzer, 2014). Sleep difficulties with medical origin can be caused by neurological diseases such as epilepsy, for example nocturnal seizures can disrupt sleep. It is recognised that if sleep difficulties are left untreated, they can lead to poor outcomes in the child including behavioural and learning difficulties, poor HRQOL and mood problems (Carter, Hathaway & Lettieri, 2014). Similarly, this can extend to impact the family, where parents of children with maladaptive sleep patterns are more vulnerable to psychological health problems (Honaker & Meltzer, 2014; Bayer, Hiscock, Hampton & Wake, 2007).

Despite these consequences and high prevalence rates across childhood, sleep difficulties are usually under-recognised at both a parent and service level (Meltzer et al., 2010). Prior studies have demonstrated that despite children in the general population displaying symptoms of sleep problems, less than half of parent's report this at their routine paediatrician's appointment (Stein, Mendelsohn, Obermeyer, Amromin & Benca., 2001). There are various reasons for this lack of reporting. Qualitative findings demonstrate that parents have concerns that reporting their child's sleep problems may reflect poorly on their parenting ability (Cook, Appleton & Wiggs, 2020). Similarly, parents may not be given the opportunity to engage in discussions about children's sleep due to a primary medical focus at appointments or lack of training around sleep in children (Chervin, Archbold, Panahi & Pituch, 2001; Cook et al., 2020). Another reason for the lack of recognition of sleep difficulties, is that parents may lack understanding of sleep problems and their impact on children's functioning (Blunden et al., 2004). Moreover, specific sleep problems including napping or snoring may not be recognised by parents as maladaptive and as a result are under-reported (Byars, Yolton, Rausch, Lanphear & Beebe, 2012). On the other hand, there is a lack of screening of sleep problems as part of routine clinical care, where appointments usually

involve one question about sleep at most, which is not comprehensive enough to capture the breadth of sleep problems which exist in the general population (Byars et al., 2012; Owens, 2001).

As noted above, sleep problems can be screened for by questioning, as part of routine clinical care. Within sleep research, there are various assessment tools which can be used to measure sleep problems or sleep disorders in addition to questioning. The next section outlines the type of sleep assessments available to quantify sleep with a particular focus on measurement of sleep habits in childhood, and strengths and weaknesses of these.

1.5. Sleep Methodology

1.5.1. Polysomnography

Polysomnography **(**PSG) is generally a laboratory-based technique for overnight sleep assessment. It combines EEG, with measurement of muscle activity and limb movement (EMG), eye movements (EOG), electrical activity of the heart (ECG) and oxygen saturation level using pulse oximetry (Rundo & Downey, 2019). PSG is recognised as the "gold standard" for objective assessment of sleep, particularly for sleep architecture and it can also capture a variety of sleep-related disorders such as sleep apnoea and movement disorders (Rundo & Downey, 2019). Although PSG is recognised as the most accurate measure of sleep, **t**here are some caveats to its use. As it is usually delivered within a laboratory setting, the artificial environment, uncomfortable nature of electrodes or being observed can disrupt sleep patterns, hence it is not wholly representative of sleep patterns at home (Jaworski, Roshan, Tae & Park, 2019). The effect of these variables has not been extensively evaluated across age groups, but they are likely to pose challenges with young children, especially those with neurological conditions such as autism or epilepsy due to their increased sensitivity to change and/or difficulty with specialised equipment (Sitnick, Goodlin-Jones & Anders, 2008).

Another limitation of PSG is that it is typically used for one or two nights only, due to the high cost attached. However, there can be a 'first night effect' where sleep architecture can be particularly affected on the first night of the sleep study, thus not representative of a usual sleep period (Tamaki, Nittono, Hayashi & Hori, 2005). Conversely, some participants may experience a reverse first night effect where they achieve better sleep on the first night, with differences in the type of effect being dependent on the type of sleep disorder experienced (Byun, Kim, Moon, Motamedi & Cho, 2019). This again points to sleep data acquired with PSG not being representative of an individual's habitual sleep at home. Alternatives to laboratory-based PSG to allow at home or ambulatory recording can be used to minimise the first night effect and are less costly (Sharpley, Solomon & Cowen, 1988; Edinger et al., 1997).

1.5.2. Actigraphy

Actigraphy measures sleep objectively via an actigraph, which is a non-invasive wearable device that measures body movements to provide proxy information on sleep-wake patterns. It is usually worn on the wrist or ankle and uses an accelerometer to detect movements and translate these into activity counts (Ancoli-Israel et al., 2003). The built-in algorithm transforms this activity data into sleep and wake periods. Actigraphy is a cost-effective approach that can be used to record for a longer period of time compared to PSG, as studies recommend a minimum of 5-7 nights for a reliable measurement of sleep (Acebo et al., 1999; Sadeh & Acebo, 2002). The main sleep parameters drawn from the watch include total sleep time (TST), sleep onset latency (SOL) wake after sleep onset (WASO) and sleep efficiency (SE). (See section 3.5.4.2 for description of these terms) (Fekedulegn et al., 2020). Whereas PSG might be used to diagnose a sleep disorder, actigraphy measures sleep/wake cycles to describe habitual sleep and can be used to support diagnosis but is not sufficient for diagnostic purposes.

Actigraphy provides a cheaper alternative to PSG and can record for longer periods of time within naturalistic settings (Spruyt, Gozal, Dayyat, Roman & Molfese, 2011b). It has also been found to be well tolerated in children with neurodevelopmental conditions such as autism and attention deficit hyperactivity disorder (ADHD) due to its non-invasive nature (Earnest et al., 2020). Actigraphy also holds value for use in CWE, as it has been demonstrated to record seizures with motor features by changes in velocity and direction, achieving approximately 79% agreement with informant reports (Lockman, Fisher & Olson, 2011; Beniczky, Polster, Kjaer & Hjalgrim, 2013). This is supported by other research which shows that actigraphy proves useful in detecting sleep even in children with refractory epilepsy, a group where sleep can be greatly fragmented due to seizure activity and IEDs (Sadaka et al., 2014). Furthermore, actigraphy has also been shown to be sensitive to detecting pharmacological induced changes in sleep (Sadeh, 2011). This is particularly important in CWE because of the observed impact of AEDs on sleep architecture (Jain & Glauser, 2014).

Despite its utility across a variety of populations, actigraphy does hold some limitations. As it utilises an accelerometer which measures physical movements, this can lead to over and underestimation of sleep and wake periods. If a child is still for periods of time, the device may interpret this as sleep, or if the child is asleep but in a moving vehicle, this may be detected as wake (Sadeh, Sharkey & Carskadon, 1994). Nevertheless, strategies can be used to overcome these errors, such as the use of the event marker to signal times when the child goes into and out of bed (Martin & Hakim, 2011). Similarly, completion of a sleep diary alongside the actigraph, can also help in mitigating errors and discrepancies (Acebo et al., 1999). Other caveats include human error if the watch is attached incorrectly, removed for periods of time, or has technical errors affecting the data recorded (Sadeh, 2008). There are also methodological issues associated with actigraphy which restrict its utility. Such issues include the lack of standardisation across actiwatches, and

measurement and scoring methods which makes it difficult to compare across studies (Sadeh, 2011; Meltzer & Westin, 2011). This is particularly evident with daytime sleep parameters such as naps which have not been assessed as much as night-time sleep parameters (Galland, Meredith-Jones, Terrill & Taylor, 2014; Meltzer, Montgomery-Downs, Insana & Walsh, 2012a) and for which no established scoring system has been developed. However, one study of CWE found that actigraphy was accurate in detecting sleep periods during the day (Sadaka et al., 2014). Some studies have begun to address some of these issues using standardised scoring protocols which may help limit individual variability (Patel et al., 2015; Fekedulegn et al. 2020).

1.5.3. Actigraphy compared to PSG

As highlighted above, actigraphy has considerable strengths compared to PSG in terms of cost and recording time. As the use of actigraphy becomes more common, work has been undertaken to validate its use against PSG. Overall, the consensus indicates that in children and adolescents, actigraphy shows relatively good agreement (89 to 97%) with PSG in terms of sensitivity (accuracy in determining sleep periods). However, specificity (accuracy in determining wake periods) is lower (54-77%) (Meltzer, Walsh, Traylor & Westin, 2012b; Marino et al., 2013; Spruyt et al., 2011b; Sitnick et al., 2008; Sadeh et al., 2014; Hyde et al., 2007). This finding also extends to research with other populations, which has demonstrated poor specificity in identifying awakenings during the night across chronic conditions such as epilepsy and asthma (Ward, Lentz, Kieckhefer & Landis, 2011). As actigraphy can record lack of movement as sleep, this may explain why PSG is likely to be more accurate in determining sleep onset and wake, since it directly records brain activity (Paquet, Kawinska & Carrier, 2007). However, discrepancies between the two may also relate to the type of scoring system used. This was demonstrated by a study which showed that concordance between the two measures for determining SOL improved, when sleep onset was

defined as the beginning of the first continuous 20 minutes of sleep rather than within the first minute of sleep (Cole, Kripke, Gruen, Mullaney & Gillin, 1992).

1.5.4. Informant report measures

Another method that is commonly used in sleep research with children is informant report measures. These can include questionnaires or sleep diaries. Sleep questionnaires consist of questions which assess sleep patterns retrospectively from a specific point in time. These can be reported by either the informant (parent) or self-reported (child). The purpose of sleep questionnaires is generally to screen for sleep problems, and they are typically structured to map onto ICSD-3 diagnostic criteria (Sateia, 2014) . Sleep diaries as highlighted above are usually used in conjunction with actigraphy to improve its accuracy. They involve parents or carers documenting the child's sleep for prolonged periods of time, producing estimates on sleep/wake cycle and sleep parameters such as SOL, WASO, SE and TST (Carney et al., 2012).

Sleep questionnaires can also be used to provide information on sleep patterns over a certain time period (Sadeh, 2015). They have strengths as they are inexpensive, do not require additional assistance and can be completed anywhere (Ibáñez, Silva & Cauli, 2018). Limitations with informant reported questionnaires include the issue of bias such as social desirability and recall, as questionnaires often ask for a retrospective account. Sleep diaries have various strengths including documenting sleep longitudinally in a natural environment and having less risk of reporting bias, as parents can record sleep daily rather than retrospectively compared to sleep questionnaires (Martin & Hakim, 2011). However, sleep diaries do hold some limitations as they use retrospective reporting, which can lead to unreliable information due to memory accuracy (Iwasaki et al., 2010). Compliance in completing sleep diaries is also affected by the length of reporting and decreases with time.

1.5.5. Actigraphy vs informant report measures

The literature regarding the concordance between actigraphy and informant report measures is mixed. One study found poor agreement between actigraphy and the Children's Sleep Habits Questionnaire (CSHQ, Owens, Spirito & McGuinn, 2000b) for several sleep variables including sleep onset and offset times, TST and WASO (Perpétuo, Fernandes & Veríssimo, 2020). This is supported by Werner, Molinari, Guyer & Jenni (2008) who compared actigraphy and sleep diaries for children aged 4-7 years of age. They found satisfactory agreement rates for sleep onset, offset and presumed sleep duration. However, agreement for actual sleep duration and night awakenings were poor. Similarly, comparison between actigraphy and informant reported sleep diaries in children within the general population, revealed that parents were reliable reporters for sleep start and end times as evidenced by the strong correlation between the two measures. However, parents were less reliable in their reports for sleep quality parameters (night waking's and SE) (Tikotzky & Sadeh, 2001). Studies showed poor agreement rates for sleep duration and SE (Bélanger, Simard, Bernier & Carrier, 2014; Dayyat, Spruyt, Molfese, Gozal, 2011). Similarly, Mazza, Bastuji & Rey (2020) also found good agreement levels between the two measures for sleep onset/offset, and for TST, however this was only significant for school days. This agreement was poor for sleep variables including WASO and SOL. Overall, these findings show a trend towards good agreement for some parameters including start and end time of sleep but not for sleep quality and night wakings, whereby parents tended to overestimate sleep quality and underestimate awakenings. Furthermore, as actigraphy is recognised to overestimate sleep time compared to PSG (Danzig, Wang, Shah & Trotti, 2019), informant reports are likely to sit on the upper bound of this estimate.

There are a variety of reasons for the discrepancies between informant reported measures and actigraphy. One reason may include physical proximity, where studies of CWE have documented

increased parental accuracy for sleep estimates when parents engage in co-sleeping (Tsai, Lee, Lee, Jeng & Weng, 2018). Similarly, discrepancies can also arise due to the age of child, where older children are able to self-regulate better, thus do not require as much parental intervention or signal their parents if they have woken up during the night (Sadeh, 2008; Werner et al., 2008). Another factor which may impact accuracy of findings is the discrepancy between weekend and weekday sleep, whereby parents are found to be more accurate in their estimate of sleep patterns such as TST and wake times during weekdays (Dayyat et al., 2011; Mazza et al., 2020). This is likely explained by parent's higher involvement in children's sleep patterns when preparing them for school. Another factor that could impact the congruency between objective and informant reports is the subjective perception of one's own sleep. One study found that parents' own sleep quality impacted their reports of their child's sleep, where worse sleep quality was associated with exacerbation of their child's (perceived) sleep problems (Rönnlund, Elovainio, Virtanen, Matomäki & Lapinleimu, 2016). This is particularly relevant to CWE where studies have found that poor sleep habits in children also have a systemic impact on family sleep and well-being (Shaki, Goldbart, Daniel, Fraser & Shorer, 2011). Another reason for poor concordance may be explained by the retrospective nature of sleep questionnaires, which often ask about general sleep patterns in the preceding weeks. Whereas with actigraphy, sleep is recorded in real time thus is not prone to recall errors. Others have found that the discrepancy between objective and informant reported measures can be impacted by the child's SE. Parents of children with higher SE reported better concordance for sleep parameters between the objective and subjective measures compared to children who had lower SE (Mazza et al., 2020). This suggest that the level of sleep disturbance can negatively impact parent's perception of their child's sleep. However, this finding is refuted by Kushnir and Sadeh (2013) who compared concordance of actigraphy and informant reported questionnaires between controls and a clinical sleep disturbed group. They found that discrepancies between the two measures were larger in the control group compared to children

with sleep disturbances. This may be because parents of children with sleep problems were more involved in their child's sleep patterns. Presence of sleep problems may therefore improve concordance between the measures.

Overall, this evidence demonstrates that both actigraphy and informant report measures are reliable for gathering information on children's sleep patterns, however each provides useful information for different parameters and are thus recommended to be used together.

1.5.6 Concordance between informant reported and self-reports of sleep

As outlined above, there are a various sleep tools including objective, informant, and subjective reports. However, literature has largely focused on comparison of the concordance rates between objective and informant/subjective reported methods of sleep. There has been less attention paid to the concordance between different reporters (child vs parent). A previous study (Combs et al., 2019) assessed the concordance between informant and subjective reports compared to actigraphy defined sleep parameters. They found that although concordance was similar for TST between parent and child, there was lower concordance for SOL and even less for SE. Several explanations were put forward, such as parents were typically awake at their child's sleep onset, thus may be more reliable reporters for SOL. Alternatively, children may not signal to their parents when they wake up during the night so may provide more accurate reports for SE compared to their parents. Another study (Liu, Wang, Ji, Cui & Liu, 2018) compared informant reports of sleep to child reports of sleep in pre-adolescents. They found significantly low agreement across the following subscales: sleep disordered breathing, daytime sleepiness and parasomnias. Interestingly discrepancies decreased with age, female gender and higher parental education. These findings suggest there are specific factors which may impact concordance between different reporters. However, the findings from this study were refuted by a previous study assessing concordance for

reports of sleep disturbances in adolescents compared to parents. It was shown that sleep disturbance scores were significantly higher when reported by children compared to parents, however differences in these scores were not affected by age or gender (Roeser, Eicholz, Schwerdtle, Schlarb & Kubler, 2012). Overall the literature regarding concordance between reporters is largely mixed due to the heterogeneity of measures and age groups studied but do indicate that both informant and subjective reports of sleep should be utilised if possible.

1.6. Sleep and Epilepsy

1.6.1. Effect of sleep on epilepsy

The relationships between sleep and epilepsy are recognised to be bidirectional. Being able to shed light on these factors can help to improve our understand of epilepsy and its impacts. For example, sleep is suggested to have a pronounced role on IEDs. There is typically a higher rate of IEDs in NREM sleep compared to REM sleep and wakefulness (Ng & Pavlova, 2013; Okanari et al., 2015; Sammaritano, Gigli & Gotman, 1991). This indicates that NREM sleep has an activating role on IEDs whereas REM plays an inhibiting role, where the spread of IEDs is suppressed (Jin, Aung, Geng & Wang, 2020). Research has also found a positive relationship between IED occurrence and depth of NREM sleep, where IEDs are more likely to occur in N3 compared to lighter stages (N1 & N2) (Lanigar & Bandyopadhyay, 2017; Sammariatno et al., 1991; Malow, Kushwaha, Lin, Morton & Aldrich, 1997). The facilitating role of NREM sleep has been postulated to occur due to synchronisation mechanisms within the thalamocortical projection neurons (Al-Biltagi, 2014; Malow et al., 1997). In REM sleep, there is a state of desynchronization due to cholinergic input which desynchronises the thalamocortical network (Ng & Pavolva, 2013) and reduces the emergence of sleep spindles and slow waves. Instead, oscillations in the alpha and theta band emerge, which restrict spread of IEDs (Ferrillo, Beelke & Nobli, 2000; Díaz-Negrillo, 2013).

Some studies have found that seizures are more likely to occur in lighter stages of sleep (N2) (Herman, Walczak & Bazil, 2001; Minecan, Natarajan, Marzec & Malow, 2002). Arousal mechanisms have been implicated to play a role in this relationship. It is suggested that after arousal from sleep, on the transition back to sleep from lighter to deeper stages, seizures are usually likely to occur (Minecan et al., 2002; Sinha, 2011). This is reflected in disrupted sleep architecture and fragmented sleep observed in people with epilepsy (Dell et al., 2021). Another area of sleep that has been recognised to impact epilepsy is circadian rhythm, specifically clock genes which regulate this rhythm. Clock genes can contribution to an imbalance between inhibition and excitation, a mechanism which impacts seizure occurrence (see section 1.5) (Jin et al., 2020).

1.6.2. Effect of sleep deprivation on epilepsy

Sleep deprivation is commonly used as an activating procedure in clinical EEG to elicit IEDs or seizures (Aird, Masland & Woodbury, 1984), and can be used to support diagnosis by aiding in localising IEDs or seizures, to determine epilepsy classification. The role of sleep deprivation is supported by studies where following sleep deprivation, there was an increased number of IEDs compared to routine wake EEG (Rowan, Veldhuisen & Nagelkerke, 1982). Initially, there was uncertainty surrounding whether sleep deprivation independently activates IEDs or whether this was the effect of sleep onset leading to NREM sleep activating IEDs (Malow, 2004). However, research has refuted this latter view. One study compared the number of IEDs across wake and sleep stages in sleep deprived EEGs and found that the number of IEDs was not significantly different across stages. In addition, participants where IEDs occurred during sleep in routine EEGs were excluded, suggesting that the findings were solely attributed to sleep deprivation (Fountain, Kim & Lee, 1998). Similarly, it has been demonstrated that the rates of IEDs are higher in wake EEGs following sleep deprivation than within sleep EEGs (Lanigar & Bandyopadhyay, 2017). The action of the mechanism of sleep deprivation is not completely established, however it is presumed

to increase excitability within the cortex (Van Diessen, Otte, Braun, Stam & Jansen, 2014) which ultimately lowers the threshold for recurrent seizures to occur (Scalise et al. 2006). This is supported by previous studies using transcranial magnetic stimulation (TMS) which showed heightened cortical excitability following sleep deprivation in people with and without epilepsy (Badawy, Curatolo, Newton, Berkovic & Macdonell, 2006; Huber et al., 2013).

1.6.3. Effect of epilepsy on sleep

On the other side of the bidirectional relationship, epilepsy is known to exert a detrimental impact on sleep. Sleep problems are commonly reported in CWE, however there are various causes including AEDs, seizures, and epilepsy itself (Nunes, 2010). Nocturnal seizures disrupt sleep architecture and can lead to night awakenings and increase in WASO (Lanigar & Bandyopadhyay, 2017; Peter-Derex et al., 2020). Sleep quality following a seizure is also likely to be disturbed which can lead to daytime sleepiness (Bazil, 2003). Research has demonstrated that even on seizure free nights, sleep was still disrupted (Bazil, 2003; Lanigar & Bandyopadhyay, 2017). This suggests that sleep problems may be an inherent part of some epilepsies.

Another precipitating factor in sleep difficulties is medical treatment of epilepsy itself, since AEDs can alter sleep architecture and increase fatigue (Lanigar & Bandyopadhyay, 2017). However, the effect on sleep can be difficult to establish given the differing effects of different AEDs. Some drugs have a negative effect on sleep, whereas others may indeed improve sleep (Wang, Zhang, Li, Qu & Huang, 2018). Not only does the type of drug impact sleep, but also the number. Research has shown that polytherapy (use of two or more drugs) impacts sleep in a worse manner than monotherapy or no AEDs (Al-Biltagi, 2014; Byars et al., 2008; Batista & Nunes, 2007).

In terms of the effect of IEDs on sleep, there is evidence to suggest that IEDs contribute to arousals during sleep and ultimately fragment sleep (Bonakis & Koutroumanidis, 2009; Cortesi, Giannotti & Ottaviano, 1999; Al-Biltagi, 2014). This state of fragmentation then facilitates the occurrence of sleep related disturbances such as parasomnias, which results in more IEDs via a cyclical mechanism (Gibbs et al., 2016). Finally, prior research also indicates that IED also trigger sleep spindles which ultimately disrupt network functioning (Dahal et al., 2019).

1.7. Epilepsy and neurodevelopmental conditions

As described in the previous section, sleep disturbances are recognised to co-occur with epilepsy. There are other conditions which frequently co-occur with epilepsy such as neurodevelopmental conditions, which will be explored below. There are various mechanisms postulated for the relationship between epilepsy and neurodevelopmental conditions, which has led to a push to consider epilepsy in the grouping of neurodevelopmental conditions (Shankar, Perera & Thomas, 2020). Therefore, it is important to recognise these conditions when assessing HRQOL in CWE. The section below evaluates the co-occurrence between epilepsy and neurodevelopmental variables including autism and ADHD.

Prior to this, clarification surrounding the language use for co-occurrences/ comorbidities is outlined below. The term ‘co-morbidity’ is used in the majority of research in paediatric epilepsy. It is used to describe cases where an individual reaches the diagnostic threshold for more than one condition which occur together (Kaplan, Crawford, Cantell, Kooistra & Dewey, 2006). The use of this term has been under continuous debate, as the consensus around the distinction between disease and symptoms is often not clarified (Kaplan, Dewey, Crawford & Wilson, 2001). For the purpose of this thesis, the term ‘co-occurrence’ has been used, which is used to describe conditions which occur at the same point in time, which can have either a common aetiology or not (Kaplan

et al., 2006; Tyrer, 2017) (see Figure 1.4 for an example). The rationale for using this term is based on the lack of certainty regarding the aetiology of the relationship between neurodevelopmental conditions and epilepsy. In addition, as these neurodevelopmental conditions are defined as characteristics rather than diagnostically in this thesis (see section 1.9), they cannot be recognised as co-comorbid to epilepsy.

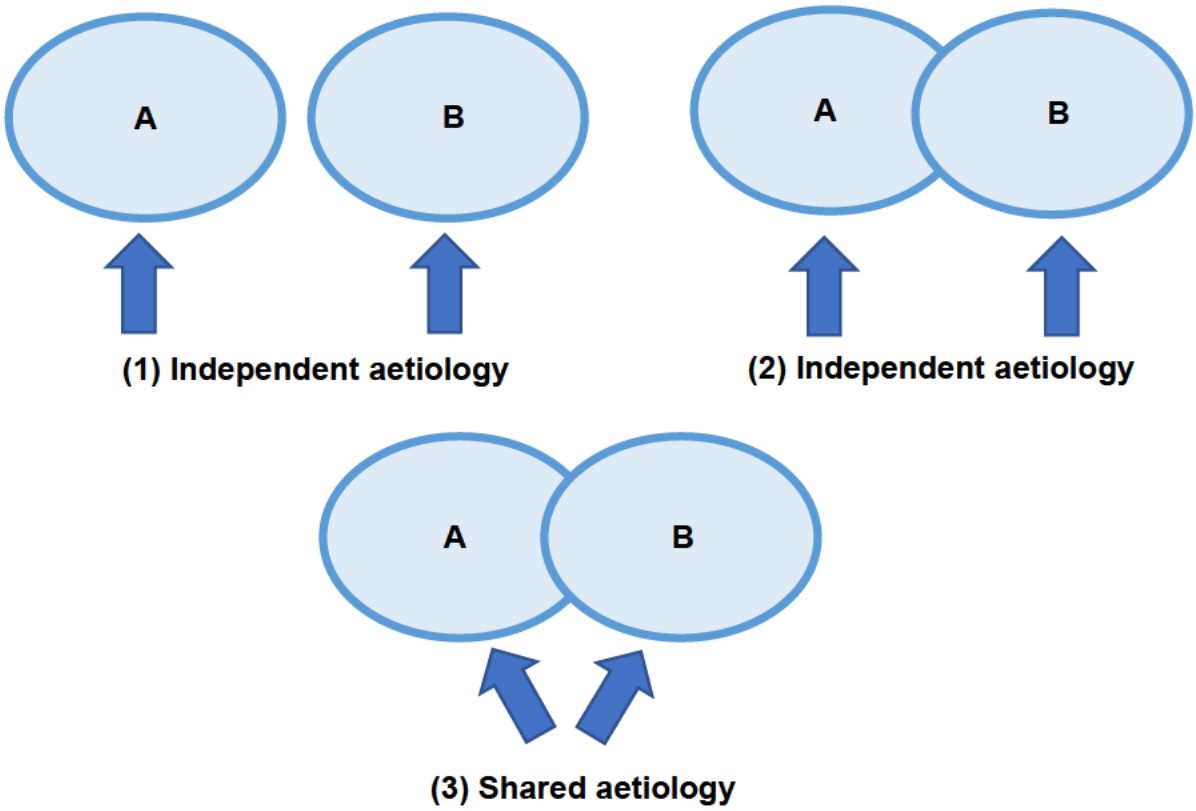


Figure 1.4. *Schematic representations of co-morbidity vs co-occurrence.* Adapted from "Comorbidity, co-occurrence, continuum: what's in the name?" by Kaplan, Crawford, Cantell, Kooistra & Dewey, (2006), 32(6), 723-731. *Note. (1) Comorbidity characterised by independent aetiology (2) co-occurrences with independent aetiologies (3) co-occurrence with shared aetiology.*

1.7.1. Epilepsy and Autism

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterised by differences in social communication and repetitive and restricted behaviours (DSM-5; American Psychiatric Association, 2013). For the purpose of this thesis, identity first language will be used throughout[ii]. The prevalence of autism in the general population across both adults and children, is estimated to be 1% (Bralten et al., 2018). In comparison, the prevalence rate of an autism diagnosis in epilepsy is estimated to be 6.3% (Strasser, Downes, Kung, Cross & De Haan, 2018). However, autism is often underdiagnosed in CWE as demonstrated by a study which found that 32% of CWE reached the diagnostic threshold for a diagnosis of autism, yet the majority of this group had not received a diagnosis (Clarke et al., 2005). For this reason, along with the discussion in section 1.9, autistic characteristics rather than autism diagnosis are explored within this thesis.

Although autistic characteristics are recognised to be heightened in CWE, the consensus regarding the direction of the co-occurrence is unclear. It has been previously found that autistic children have a heightened prevalence of IEDs, even in those who do not experience seizures or epilepsy (Kim, Donnelly, Tournay, Book & Filipek, 2006; Rossi, Posar & Parmeggiani, 2000; Veerappan et al., 2018). The role of IEDs is continuously questioned (Ghacibeh & Fields, 2015). Some research has shown that the presence of IEDs is related to more severe outcomes including social and behavioural problems and autistic characteristics (Veerappan et al., 2018; Mulligan & Trauner, 2014). Some have suggested that the occurrence of seizures early in developmental trajectory can affect the plasticity of the brain and ultimately the excitatory state of the brain, which can leave individuals vulnerable to poorer outcomes (Strasser et al., 2018; Milovanovic & Grujicic, 2021). As IEDs are recognised as a diagnostic marker for epilepsy, this would lend weight to the theory

[ii] There has been a debate regarding use of identity first ("autistic person") or person first ("individual with autism") language when referring to an autism diagnosis (Kenny et al., 2016; Vivanti, 2020). Although no consensus has yet to be reached, the consensus among the autism community is to favour the use of identity first language, which places the condition before the person (Botha, Hanlon & Williams, 2021).

that epilepsy causes autism. This is supported by prior a study which found that nearly 50% of children experienced their first seizure prior to an autism diagnosis (Matsuo, Maeda, Sasaki, Ishii & Hamasaki, 2010). However, given that autism is typically diagnosed later in development, this may lead to an overshadowing of its occurrence if epilepsy has an early onset. More research is necessary to ascertain the direction of the two.

Nevertheless, most research leans towards the theory that autism and epilepsy share an underlying mechanism (Besag, 2018). A possible pathway is the disruptions in the networks producing glutamate and GABA, which are neurotransmitters which have linked to the production of IED and seizures (Hirosawa et al., 2018, see section 1.3.4.). Similarly, abnormalities in transmission of GABA and glutamate have also been suggested to underlie the development of autism (Horder et al., 2018; Coghlan et al., 2012). Alternative explanations for the underling aetiology between the two conditions have been proposed, however this is not within the scope of this thesis (see Besag & Vasey, 2020 for a review).

1.7.2. Epilepsy and ADHD

The second most prevalent neurodevelopmental condition in CWE is ADHD. ADHD is described as a neurodevelopmental condition which is characterised by difficulties in the hyperactivity and impulsivity domains of attention, (APA, 2013). Up to 9% of children in the general population have a diagnosis of ADHD, whereas in epilepsy, these rates are estimated to increase to 40% (Williams, Giust, Kronenberger & Dunn, 2016). Various mechanisms have been proposed to underlie this co-occurrence (Kaufmann, Goldberg-Stern & Shuper, 2009; Ravi & Ickowicz, 2016). IEDs have been recognised to hold considerable clinical importance, whereby they are suggested to disrupt the networks governing attention and higher order functions (Lee, Choi, Yoon & Bahn, 2016). Some suggest that side effects of AEDs can contribute to an increased risk of ADHD

symptoms (Tan & Appleton, 2005; Matricardi, Farello, Operto, Coppola & Verrotti, 2020) depending on the type and number of medications. However, as ADHD symptoms can often be present before children's first seizure and prior to the use of AEDs (Hesdorffer et al., 2004; Hermann et al., 2007; Austin et al., 2001), this indicates that ADHD is more likely to be co-occurring with epilepsy rather than due to the impact of treatment or seizures (Williams et al., 2016; Austin et al., 2001). This points towards the consensus that there is an underlying shared aetiology. Prior research has demonstrated higher familial risk of ADHD in people with epilepsy compared to those without, suggesting shared genetic predispositions may underlie the co-occurrence between epilepsy and ADHD (Brikell, Burton, Mota & Martin, 2021). Overall, although there are several theories which postulate a relationship between epilepsy and ADHD, there are yet no clear conclusions (Chou et al., 2013).

As outlined above, neurodevelopmental conditions including autism and ADHD are prevalent in epilepsy. Sleep problems are also prevalent across these conditions and suggested to be higher in autism and ADHD compared to CWE (Tsai et al., 2012). Therefore, when assessing the relationship between sleep and HRQOL, it is crucial in understanding how autism and ADHD characteristics alters this relationship is crucial.

1.8. Sleep and neurodevelopmental conditions

1.8.1. Autism and sleep

Sleep problems are commonly co-occurring in autism. Prior research estimates a prevalence of sleep problems in 40 to 80% of autistic children compared to 10 to 50% of those without autism (Surtees et al., 2019; Elrod & Hood, 2015; Richdale & Schreck, 2009; Chen et al., 2021). There are a variety of sleep disturbances reported in autistic children as measured using informant reports and actigraphy. The most commonly occurring sleep disturbance in autistic children is reduced sleep duration (Souders et al., 2017; Accardo & Malow, 2015). This can be attributed to the

frequently reported issues with night waking, sleep anxiety and delayed sleep onset (Krakowiak, Goodlin-Jones, Hertz-Picciotto, Croen & Hansen, 2008; Cortesi, Giannotti, Ivanenko & Johnson, 2010; Wiggs & Stores, 2004). Sleep disruptions including reduced sleep duration, sleep onset delay and sleep disordered breathing (SDB) have also been shown to be associated with higher autistic characteristics and behavioural difficulties (Schreck, Mulick & Smith, 2004; Hoffman et al., 2005; Goldman et al., 2011; Tudor, Hoffman & Sweeney, 2012). The direction of this relationship has been a continued debate (Mazzone, Postorino, Siracusano, Riccioni & Curatolo, 2018) as many studies explore the relationship in a cross-sectional manner, and propose a bidirectional relationship (Adams, Matson, Cervantes & Goldin, 2014). However, evidence from a longitudinal study suggests that whilst sleep problems are present, they develop over time in autistic children and did not contribute to increased severity of autistic characteristics (Verhoeff et al., 2018). Therefore, managing sleep problems may not be the most appropriate approach in improving HRQOL if autistic characteristics are the perpetuating factor.

1.8.2. ADHD and sleep

Sleep disruptions are also common in children with ADHD (Cortese, Faraone, Konofal & Lecendreux, 2009) with between 50 and 70% of parents reporting significant sleep problems (Sung, Hiscock, Sciberras & Efron, 2008). Informant report and actigraphy measures have demonstrated more severe sleep problems including sleep duration, SOL and bedtime resistance, in children with ADHD compared to children without ADHD (Owens, Maxim, Nobile, McGuinn & Msall, 2000a). Consistent with this, PSG studies demonstrated significantly lower REM latency and higher percentage of REM sleep in children with ADHD compared to those without (Busby, Firestone & Pivik, 1981; O'Brien et al., 2003). Similarly other sleep disorders detected include SDB and movement disorders (Picchietti, England, Walters, Willis & Verrico, 1998; Crabtree, Ivanenko & Gozal, 2003). Sleep disruptions and ADHD characteristics share a complex

relationship (Hvolby, 2015). On one hand symptoms of ADHD such as difficulties with impulsivity may increase difficulties around bedtime and ultimately increase SOL (Gruber et al., 2012). In addition, medication such as methylphenidate to manage ADHD characteristics, can lead to sleep problems such as insomnia (Stein et al., 2003). Alternatively sleep disturbances may stem from an unstable sleep wake system (Owens, 2009). On the other hand, sleep disruptions may mask as ADHD characteristics such as problems with hyperactivity, attention, and behavioural difficulties (O'Brien, 2011). Similarly sleep problems can also worsen ADHD characteristics (Kirov & Brand, 2014). Although the literature regarding the relationship between sleep problems and ADHD is well developed, investigations on the impact on HRQOL is limited.

1.9. Categorical vs Dimensional to Neurodevelopmental conditions

There are two main overarching approaches used to assess neurodevelopmental conditions in research: Categorical or Dimensional. Categorical approaches are based on diagnostic categories such as those provided by the DSM-5 to establish whether an individual has a condition (e.g., autism/ADHD) or not. Whereas a dimensional approach views the conditions on a continuum with varying symptom severity (Moreland & Dumas, 2008). Within clinical practice, autism is viewed categorically where a diagnosis is given or not. However, the continuum approach to autism is supported by the broad autism phenotype, which lends to the hypothesis that autistic characteristics gradually merge with subthreshold characteristics in the general population (Abu-Akel, Allison, Baron-Cohen, Heinke, 2019). This is evidenced by studies which have found that families members of an autistic individual are at higher chance of displaying autistic characteristics irrespective of having an autism diagnosis (Bailey, Palferman, Heavey & Le Couteur, 1998). Similarly, taxometric research by Frazier, Youngstrom & Naugle (2007) found no evidence of shared diagnostic indicators across groups using neuropsychological or behavioural tests, which would reflect an ADHD diagnosis. They suggested that a dimensional approach to identifying

individuals at risk of ADHD characteristics would be preferred. In support of these findings, interventions and medication effects are also related to severity of symptoms rather than DSM categories and specific thresholds (McLennan, 2016). This evidence is therefore in favour of a dimensional approach to neurodevelopment .

Within this thesis a dimensional approach will be taken, as categories can fail to consider the requirements of all children across the continuum who display symptoms which may not reach threshold. This means that children who present with lower difficulties, but which still affect their day-to-day functioning, are not considered (Astle, Holmes, Kievit & Gathercole, 2021). Furthermore, as the overarching rationale is to explore mechanisms to understand variations in HRQOL, dichotomising children intro groups based on whether they fit threshold criteria limits the exploratory power given the small sample size (Cohen, 1983). In conclusion, consideration of a dimensional approach is important to the aims of this thesis, as it enables accurate measurement of how sleep and neurodevelopmental conditions contribute to HRQOL in CWE.

1.10. Health Related Quality of Life in CWE

HRQOL is a comprehensive term, which describes the impact of an individual's health on their overall quality of life (QOL) (Karimi & Brazier, 2016). Within this broad construct there are various areas considered in addition to health status, including physical, psychological, and social wellbeing. The goal in epilepsy management is to ensure families and CWE are able to live a life as independently from seizures and side effects of AEDs as possible (Ronen, Streiner & Rosenbaum, 2003; Momen, Abareian & Malamiri, 2019; Lach et al., 2006). However, the impact of epilepsy goes beyond these factors alone. Furthermore, there is a growing recognition amongst clinicians and researchers to include HRQOL as a broader goal in management of epilepsy (Ronen, Streiner & Rosenbaum, 2003; Cianchetti et al., 2015).

Prior research has demonstrated that CWE have worse overall HRQOL compared to children without epilepsy (CWOE) (Miller, Palermo & Grewe, 2003; Riechmann et al., 2019; Haneef et al., 2010). The detrimental impact of epilepsy on HRQOL can emerge early in the epilepsy trajectory. This is demonstrated by a study which found poorer HRQOL in children with newly diagnosed epilepsy and in those who had experienced only one seizure, compared to CWOE (Modi et al., 2009). These finding are also concordant with self-reports by children with newly diagnosed epilepsy (Taylor, Jacoby, Baker & Marson, 2011). A possible reason for such findings is outlined by one study, which suggests that poor HRQOL in these children may indicate that these children have not yet adjusted to the disease (Jacoby & Baker, 2008). HRQOL appears to fluctuate, whereby some studies have documented declining HRQOL over time. This is evidenced by poor HRQOL in children with chronic epilepsy compared to newly diagnosed epilepsy (Cianchetti et al., 2015), as well as within two years following diagnosis (Loiselle, Ramsey, Rausch & Modi, 2016). In contrast, one study showed that the majority of CWE (62%) show improvements in HRQOL across a 28-month period (Ferro et al., 2017). Variability in these findings were attributed to the role of factors other than epilepsy characteristics, such as co-occurring conditions and psychosocial factors (Puka & Smith, 2015; Modi, Ingerski, Rausch & Glauser, 2011). This is supported by research which noted that CWE display worse HRQOL compared to children and adolescents with other chronic health conditions such as asthma. However worse HRQOL was not found to be associated with epilepsy related variables including seizure severity or disease control, thus control of seizures would not be sufficient for HRQOL improvements (Austin, Smith, Risinger & McNelis, 1994; Wang, Wang, Wang, Xu & Zhang, 2012; Taylor et al., 2011). Collectively, these findings suggest that whilst epilepsy confers a unique risk to decreased HRQOL, there are a wide variety of factors other than epilepsy specific variables, which can impact HRQOL (Stevanovic, Tadić & Novakovic, 2017). These need to be explored and understood if HRQOL in CWE is to be maximised.

1.10.1. Concordance between child and informant reports of child HRQOL.

HRQOL, as previously outlined above, is typically defined from the person's perspective. However, the majority of literature assessing HRQOL in CWE has utilised informant reports. These are advantageous in assessing views of children who are too young to report or lack the cognitive ability to do so (Fong et al., 2018). However, some studies have found that parents tend to report lower HRQOL compared to CWE themselves (Baca, Vickrey, Hays, Vassar & Berg, 2010). This has been attributed to the aspect of HRQOL being measured. Some studies found that children reported lower scores for domains including implicit thoughts such as secrecy around the disease compared to more external domains such as health outcomes (Baca et al., 2010; Verhey et al., 2009). It has been suggested that children do not openly express these feelings, thus parents are unaware of the impact of such factors (Verhey et al., 2009). Similarly, another study found that whilst informant reports of poor HRQOL were strongly correlated with the presence of a neurodevelopmental condition, children's perceived HRQOL was not (Baca et al., 2011). These findings suggest that children ascribe different importance to determinants for HRQOL compared to parents.

Despite these findings, most studies have found that there is generally a good agreement between parent and child reports of HRQOL (Ferro et al., 2017; Cianchetti, 2015; Haneef et al., 2010). Moreover, a recent study by Fayed et al. (2019) adopted a novel approach using longitudinal growth analysis to assess the degree of concordance between parent and child reports. This is particularly useful given that the majority of research is cross sectional and has mainly quantified discrepancy using correlations, thus may fail to consider the difference in discrepancy and impact of variability over time (Eiser & Morse, 2001). They found that parents do indeed serve as reliable informants for children's HRQOL. Most interestingly, risk factors for either negative or positive

parental responses were associated with children's social experiences and parental stress rather than epilepsy specific variables

1.11. Health Related Quality of Life: Framework

Use of HRQOL as an outcome can provide useful and important information to improve management of epilepsy. One barrier to maximising our understanding of HRQOL in CWE is the too narrow a focus on the role of epilepsy specific variables such as seizure control and medication (Nadkarni, Jain & Dwivedi, 2011). As noted earlier, whilst these are important, epilepsy extends beyond seizures, and there are many factors aside to epilepsy specific variables which contribute to HRQOL. Research in paediatric epilepsy has raised the importance of considering HRQOL in epilepsy within a framework (Lach et al., 2006; Fayed et al., 2015). The use of frameworks in HRQOL can help to assess how different factors interact (Ronen, Streiner & Rosenbaum, 2003) and their predictive value, which can ultimately improve our understanding of the trajectory of HRQOL in CWE (Jacoby & Baker, 2008). Moreover, the authors emphasised that as epilepsy related variables only show a modest relationship with HRQOL, future research should shed light on the role of other variables such as co-occurring conditions, parental wellbeing, and family variables. Within this thesis, the framework devised by Lach et al. (2006) (see Figure 1.5) is used to guide the research questions outlined in section 1.16.

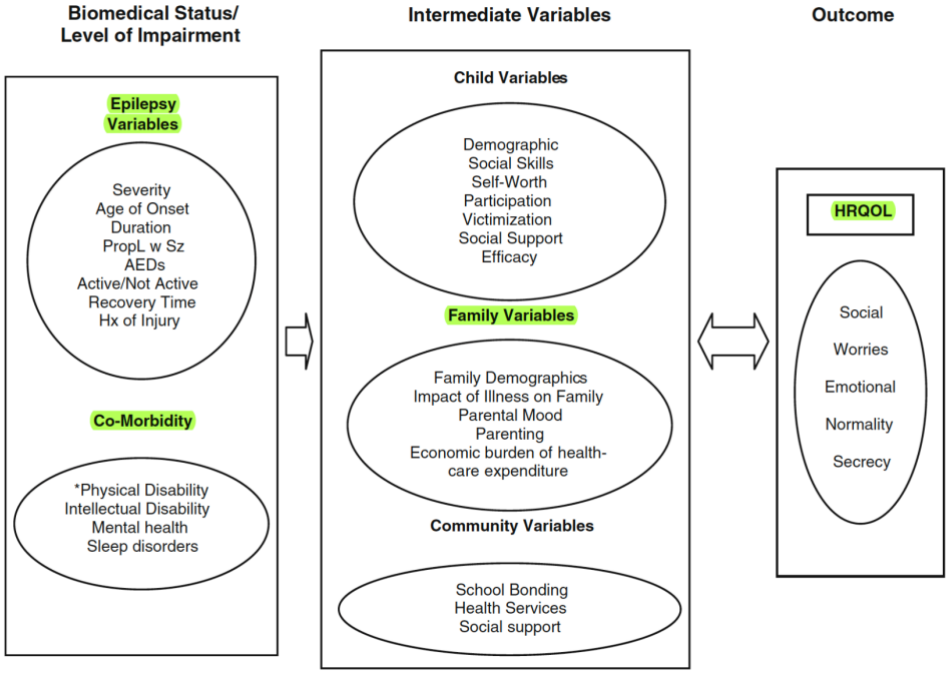


Figure 1.5. *Theoretical framework for HRQOL in CWE*. Adapted from "Health-related quality of life in youth with epilepsy: Theoretical model for clinicians and researchers. Part I: The role of epilepsy and co-morbidity" by Lach et al. (2006), 15, 1161-1171. Copyright 2006, Springer

1.11.1. Epilepsy Variables

The first domain of interest is "Epilepsy variables". For the purpose of this thesis the following variables are considered in relation to HRQOL: seizure severity, number of AEDs and epilepsy type. The justification for these variables is based on prior research and methodological constraints. In terms of methodological constraints, information regarding age of onset and duration of epilepsy, which have been previously shown to impact HRQOL (Ferro, 2014; Ronen et al., 2010), could not be extracted from the child's medical records due to the inconsistency of reporting. Seizure severity is a core component of epilepsy which has been shown to adversely impact HRQOL in CWE (Liu & Han, 2015; Aggarwal, Datta & Thakur, 2011; Lach et al., 2006), thus it is imperative to include this within the study. In terms of the number of AEDs, most studies have found that polytherapy is a strong predictor of poor HRQOL (Miller et al., 2003; Nadkarni et

al., 2011; Shakya, Shakya, Poudel & Shrestha, 2020). This is likely attributed to the instance that children who are on polytherapy often have 'drug resistant' epilepsy types, which are characterised by uncontrolled seizures, which negatively impact on HRQOL (Verrotti et al., 2020).

Another area, which is largely understudied, is the comparison of HRQOL across epilepsy types. This is particularly important given that comprehensive epilepsy management requires recognition of epilepsy types. The main body of research points towards worse HRQOL in children with focal epilepsy compared to generalised epilepsy (Ferro et al., 2014; Nadkarni et al., 2011 & Aggarwal, et al., 2011; Fong et al., 2018), although this is not always found (Pachange, Dixit, Arjun & Goel, 2021). When examining epilepsy type, majority of research mixes epilepsy types including focal and generalised into one group, which leads to difficulties in investigating profiles of HRQOL (Mellish, Dunkley, Ferrie & Pal, 2015). Furthermore, previous research has largely focused on refractory epilepsy types (Liu & Han, 2015; Elliott, Lach & Smith, 2005; Sabaz, Cairns, Lawson, Bleasel & Bye, 2001) thus limiting the representativeness of the findings.

Assessing variation in HRQOL across epilepsy types can help identify groups at risk of poorer outcomes. In this study, rolandic epilepsy has been included as a specific epilepsy type of interest, in addition to the broader groups of focal and generalised epilepsy. Few studies have assessed HRQOL in rolandic epilepsy, but despite the favourable prognosis and low seizure burden, HRQOL has been shown to be adversely impacted (Connolly et al., 2006; Sabaz et al., 2003). This again emphasises that epilepsy variables such as seizure severity and medication may not play the dominant role in HRQOL. Moreover, before analysing the predictive value of overall HRQOL in CWE, consideration needs to be made as to whether there is a significant difference between epilepsy types. Moreover, as previously discussed in section 1.2.4, when considering sleep in

relation to HRQOL, RE offers the opportunity to gain an in-depth understanding due to infrequent number of seizures disrupting sleep.

1.11.2. Co-occurring conditions

The second domain of interest is "Co-occurring conditions", which can be divided into neurological, psychological, and physical co-occurrences (Wei & Lee, 2015). As depicted in the epilepsy classification system outlined in Figure 1.1, co-occurrences are increasingly recognised in paediatric epilepsy and should be routinely considered as part of epilepsy management (Scheffer et al., 2017). Co-occurring conditions are prevalent in CWE, with up to 80% of CWE experiencing at least one co-occurring condition (Sillanpää & Cross, 2009; Reilly et al., 2014). It has been demonstrated that even when seizures have remitted, CWE continue to show poor HRQOL because of co-occurring conditions. These persist into adulthood, again consistent with the view that seizure variables may not hold as strong of a role in determining HRQOL as other variables (Baca et al., 2011). The impact of co-occurring conditions on HRQOL can exceed that of epilepsy as demonstrated by Haneef et al (2010), who found that both parent and self-reported perceptions of HRQOL were higher for epilepsy alone compared to when epilepsy presented with co-occurring neurological and psychological conditions. Similarly, previous research has emphasised that co-occurring conditions can further complicate epilepsy management and that acknowledgment of these early on in epilepsy trajectory can improve HRQOL (Sirven, 2016). Although studies have examined factors which impact HRQOL, the focus has typically been on the role of epilepsy related variables as outlined above. However, as outlined in Lach et al. (2006) model of HRQOL and given the prevalence of co-occurring conditions, they need to be accounted for to provide a comprehensive picture that is specific to each patient.

For the purpose of this thesis, the focus will be on sleep problems (neurological co-occurrence; section 1.11.3), ADHD characteristics and autistic characteristics (psychological co-occurrences; section 1.11.4).

1.11.3. Co-occurrences: Sleep problems

Epilepsy and sleep share a bi-directional relationship as described previously. The majority of research has focused on sleep problems and their relationship with outcomes which may contribute to poor HRQOL but have rarely directly assessed this relationship. For example, poor quality sleep and sleep anxiety in CWE has been linked with behavioural disturbance (Stores, Wiggs & Campling, 1997; Tsai et al., 2018). This is also found with the use of objectively measured sleep whereby Becker, Fennell and Carney (2004) found that inattentiveness and depressive symptoms were significantly associated with longer REM latency. Whilst most research has demonstrated that poor sleep is related to worse outcomes, there are only two studies which have investigated the association between sleep and HRQOL in CWE (Wirrell, Blackman, Barlow, Mah & Hamiwka, 2005; Gutter, Brouwer & DeWeerd, 2013). Although both studies found that sleep problems were more frequent and severe in CWE compared to CWOE, and that these were independently associated with poorer HRQOL, there were several methodological constraints which reduced the generalisability of such findings. In the study by Gutter et al. (2013), only children with focal epilepsy were included, limiting the generalisability of the findings to children with other epilepsies. Furthermore, in the study by Wirrell et al. (2005), siblings without epilepsy were used as the comparison group. However, as sleep problems have been previously shown to disturb not only the child with epilepsy but can have a systemic impact on the family (Larson et al., 2012), the sleep of this group is also likely to be affected. Thus, more studies are needed with representative samples. Finally, both studies used informant report measures, and none have yet

to investigate other sleep parameters (e.g., variability). Therefore, the understanding of the role of sleep is greatly limited by the type of sleep disturbance examined and measure of recording sleep.

1.11.4. Co-occurrences: ADHD and Autism

Despite the evidence that neurodevelopmental conditions are commonly co-occurring with epilepsy, there has been very little attention paid to the role of these co-occurrences in HRQOL. Three studies in this area have examined the co-occurrence of ADHD and epilepsy to HRQOL with consistent results. Studies by Ekinci et al. (2017), Sherman, Slick, Connolly and Eyrl (2007) and Wagner, Mueller, Hellier, Smith and Modi (2021) found that HRQOL was poorer in children with ADHD and epilepsy compared to epilepsy alone. Whilst these findings are beneficial, there are limitations which must be considered when extending these findings. Firstly, in the study by Ekinci et al. (2017), all children were on medication to treat ADHD characteristics, therefore these findings likely reflect the lower bound estimates of the impact on HRQOL. Therefore, it is necessary to examine HRQOL in children who are not treated with medication to conceptualise a clearer understanding of HRQOL, which this thesis enables. Another caveat which limits these findings is that all the studies used the child's clinical records to gather information on number of seizures experienced. However, this cannot sensitively capture the experience of seizures, given the differences in presentation of seizure types (see Figure 1.2) (Cramer & French, 2001). Therefore, the use of a measure such as seizure severity may reveal differing findings.

In terms of the relationship between HRQOL and autism in CWE, there is no research to our knowledge which has investigated the direct contribution of co-occurring autism to HRQOL in CWE. Nevertheless, a previous meta-analysis demonstrated QOL to be lower in autistic children compared to TD children across development (Van Heijst & Geurts, 2015). Therefore, it is plausible that co-occurring epilepsy would amplify the impact on poor HRQOL. Demonstrating

the impact of these conditions on HRQOL in CWE can encourage clinicians to consider screening as part of epilepsy assessment and provide a more holistic view of the challenges facing individual CWE. Overall, understanding the individual contribution of all co-occurrences can help priorities areas of need in clinical care and is necessary to improving HRQOL (Salpekar & Mula, 2019).

Finally, given that sleep disturbances are highly prevalent in children with ADHD, autism, and epilepsy (Neto, Noschang & Nunes, 2016, Ekinci, Isik, Gunes & Ekinci, 2016; Besag, 2018; Accardo & Malow, 2015), it is important to consider the impact of both of these neurodevelopmental conditions when assessing the impact of sleep on HRQOL in CWE (see section 1.8). This can help us to disentangle whether sleep disturbances are acting as a proxy of these conditions, which prior research often fails to account for.

1.11.5. Family Variables

The third domain of interest is "Family variables". Within this thesis, focus will be placed on parental mental health and sleep quality. Epilepsy adjustment is not only based on epilepsy variables but also involves major adjustment to daily life. These include anxiety surrounding seizures, administering medication etc., which can represent challenges for the whole family. This can leave parents vulnerable to poorer wellbeing compared to parents of CWOE (Jones & Reilly, 2016; Bompori, Niakas, Nakou, Siamopoulou-Mavridou & Tzoufi, 2014). Previous research has documented links between parental anxiety and depression and child HRQOL (Lv et al., 2009; Williams et al., 2003; Adewuya, 2006; Ferro, 2014; Yong, Cheng-Ye, Jiong & Zhang, 2008). Moreover, parental anxiety has also been demonstrated to exert a stronger contribution to HRQOL compared to epilepsy variables (Yong, Chengye & Jiong, 2006). Similarly, a previous study examining self-reported HRQOL in CWE demonstrated that parental support was a stronger determinant than seizure variables (Fayed et al., 2015). Given that parents' wellbeing affects

children's ability to adapt to their disease (Kerne & Chapieski, 2015), this can ultimately worsen their HRQOL. Therefore, these findings suggest that HRQOL in CWE is not only determined by epilepsy specific variables, but rather parental variables exert a large impact. However, few have yet to compare whether parental wellbeing predicts HRQOL beyond co-occurrences, and whether the strength of parental contribution still holds in determining HRQOL.

On the other hand, parents of CWE have been found to have difficulties across various sleep parameters including shortened sleep duration and reduced sleep quality (Reilly et al., 2018a; Shaki, et al., 2011; Larson et al., 2012). Interestingly, Shaki et al. (2011) found that sleep disturbances in parents were not associated with severity of the child's epilepsy, suggesting other factors are implicated in poor parental sleep. Given that studies have also shown that poor mental health in parents of CWE are associated with poor sleep quality (Hesdorffer et al., 2020; Liu, Yin, Zhu, Zhang & Sheng, 2021), it is surprising that very little attention has been paid to the role of parental sleep in HRQOL. To maximise the understanding of HRQOL in CWE, research needs to holistically assess the individual contribution of these factors and the how they relate together.

1.16. Aims of thesis

The literature above has described the complex relationship between sleep, neurodevelopmental conditions, and epilepsy. The consideration of co-occurrences within epilepsy management is often lacking and whilst some work has been conducted to understand the relationship between sleep and HRQOL, consideration of the impact of neurodevelopmental characteristics within this context has yet to be examined. In addition, HRQOL is complex and not solely determined by child variables, however there is a gap within the literature assessing the contribution of child variables compared to parental variables. Therefore, assessment of all these variables and the relationships between them are necessary when constructing a coherent model of HRQOL in

CWE. There are several overarching aims of the current thesis which correspond to each subsequent chapter.

1.16.1. To systematically review the current literature on sleep in CWE and quantify the type of sleep disturbances which CWE experience compared to CWOE.

1.16.2. Firstly, to assess the differences in co-occurrences and HRQOL across epilepsy types. Secondly, to explore the contribution of neurodevelopmental characteristics and epilepsy specific variables to the relationship between informant reported sleep and HRQOL in CWE.

1.16.3. Firstly, to compare actigraphy reported sleep in between CWE and CWOE, as well as between epilepsy types. Secondly, to determine the contribution of neurodevelopmental characteristics and epilepsy specific variables to the relationship between actigraphy reported sleep and HRQOL in CWE.

1.16.4. To assess parental sleep and overall wellbeing and the contribution of these variables compared to child variables in determining HRQOL in CWE.

CHAPTER TWO

SLEEP DISRUPTION IN CHILDREN AND ADOLESCENTS WITH EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

2.1. Preface

In the previous Chapter, the complex relationship between sleep and epilepsy was described. In addition, the limited evidence based surrounding the impact of sleep disturbances on HRQOL in CWE was highlighted. To improve the understanding of how sleep affects HRQOL, quantification of the nature and type of sleep problems experienced in CWE is necessary. Therefore, to address this, this Chapter (Winsor et al., 2021) aims to systematically review previous studies which have investigated sleep using objective and informant reported measures between CWE and CWOE. Furthermore, the types of sleep difficulties will also be meta-analysed (Aim 1.16.1.).

2.2. Introduction

Epilepsy is the most frequently occurring neurological disease in childhood and often presents in early development (Aaberg et al., 2017). While the primary clinical issue is seizures, over the years there has been an increased focus on the role of sleep in people with epilepsy, and its impact on daily functioning and overall well-being. It is essential to assess a variety of sleep parameters to accurately quantify the differences between CWE and CWOE. The prevalence of sleep difficulties in CWOE and adolescents is estimated to range between 25 – 40%, with common presentations including night waking and bedtime resistance (Byars et al., 2012; Mindell & Meltzer, 2008). These rates are significantly higher in CWE than in CWOE, irrespective of whether seizures occur during sleep (Gibbon, Maccormac & Gringras, 2019). Existing observational studies demonstrate that sleep difficulties such as excessive daytime sleepiness, night awakenings and reduced sleep duration are more common in CWE than CWOE (Larson et al., 2012; Maganti et al., 2006; Shaki et al., 2011) and that these difficulties can appear very early in the epilepsy trajectory (Byars et al., 2008).

Similarly, PSG has demonstrated differences in sleep architecture at a macro-structural level with reductions in REM sleep, increased sleep latency and frequent shifting of sleep stages, reported in CWE compared to CWOE (Maganti et al., 2005; Pereira, Bruni, Ferri, Palmini & Nunes, 2012b). Abnormalities in sleep micro-structure are also reported in CWE. In particular, seizure type can be associated with severity of sleep difficulty, as evidenced by greater reduction in sleep spindles in patients with secondary generalised seizures compared to patients with focal seizures (Tezer, Rémi, Erbil, Noachtar & Saygi, 2014).

Looking at the influence of sleep on epilepsy, NREM sleep can serve as an activating environment to an epileptic brain, increasing the occurrence and spread of IEDs, whereas the desynchronised state in REM exerts an opposite influence (Gibbon et al., 2019; Bagshaw, Jacobs, LeVan., Dubeau & Gotman, 2009). Reduced sleep duration can have various effects on IEDs, altering their frequency and shape in childhood epilepsies (Kotagal & Yardi, 2008). Circadian rhythmicity has also been found to exert a modulating influence on seizure timing in different epilepsies along with various other factors e.g., type of epilepsy or seizure and age of onset (Khan et al., 2018). Sleep and epilepsy therefore have a bidirectional association which is supported by several more and less well understood mechanisms as outlined in section1.6. Ultimately, by synthesising empirical data on sleep timing, sleep architecture, sleep efficiency and sleep difficulties in CWE compared to CWOE, evidence will be provided that may elucidate these mechanisms.

This cyclical interaction between sleep and epilepsy can extend beyond neurological and physiological changes to impact HRQOL. Optimal and good quality sleep has been recognised as a possible predictor for HRQOL in the adult epilepsy literature (Alanis-Guevara et al., 2005). In contrast, there is little data on the direct predictive value of disrupted sleep on HRQOL in the paediatric population (Gutter et al., 2013; Wirrell et al., 2005). Nevertheless, there are studies that have assessed the link between sleep difficulties and factors contributing to HRQOL. For example, sleep disturbances were associated with behavioural problems including attentional difficulties and hyperactivity in CWE (Stores et al., 1998; Tsai, Lee, Jeng, Lee & Weng, 2019). Likewise previous research has demonstrated that sleep difficulties were associated with poorer neuropsychological performance in this population compared to CWOE (Byars et al., 2008), placing them at risk of future academic difficulties. This is evident even in children with rolandic epilepsy, which is considered generally self-limiting, and which has an

overall burden of seizures that is less than in many paediatric epilepsies (see section 1.2.4). Despite this, children with this epilepsy syndrome have been found to suffer from difficulties with reading and writing (Piccinelli et al., 2008). Moreover, such academic difficulties were associated with greater IED activity during sleep (Ebus, Overvliet, Arends & Aldenkamp, 2011). CWE and poor sleep patterns were also found to have difficulties managing emotions (Cortesi et al., 1999), as well as attentional and cognitive difficulties (Stores et al., 1998; Becker et al., 2004). There is also a negative impact on HRQOL in parents of CWE, who show high rates of mental health problems such as depression and anxiety (Reilly et al., 2018c; Jones & Reilly, 2016). These studies demonstrate that CWE experience considerable negative psychological and social consequences, which can be partially attributed to underlying sleep disturbances, highlighting the need for clinical acknowledgement. Overall, these can ultimately affect children's HRQOL and may have a more detrimental impact than the seizures themselves (Fayed et al., 2015; Ekinci et al., 2016).

Moreover, a previous randomised controlled trial found that the use of a sleep intervention during hospital visits resulted in improvements in sleep quality and sleep duration in CWE, compared to those who did not receive the intervention (Tsai, Lee, Lee, Jeng & Weng, 2020b). These results illustrate that sleep habits can be modified. Therefore, an accurate quantification of the nature and range of sleep difficulties experienced by CWE is potentially beneficial to ameliorate negative psychological and social outcomes in this group.

Although previous research has investigated the association between sleep and epilepsy in children, no meta-analysis has yet to be conducted to characterise the types of sleep difficulties present in this population in reference to CWOE. We aim to synthesise and collate previous studies investigating sleep parameters in CWE compared to CWOE in order to quantify these

differences. It is anticipated that by quantifying what aspects of sleep are affected in CWE, possible treatment implications may be identified e.g., screening for sleep difficulties as part of routine diagnostic care in epilepsy.

2.3. Study Aims

This systematic review and meta-analysis was conducted with the following goals:

1. To assess differences in sleep timing, sleep difficulties, sleep efficiency and sleep architecture in CWE compared to CWOE
2. To assess heterogeneity between studies and provide recommendations in order to reduce between-study heterogeneity for future research
3. To examine possible moderators for differences in sleep timing, efficiency, architecture, and difficulties between CWE and CWOE including method of sleep assessment, quality of study and demographic variables including sex and age.

2.4. Methods

A systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff & Altman, 2010) .

2.4.1. Search strategy

A systematic literature search was conducted using the databases Medline, Embase, PsychINFO and PubMed in April 2019. Examples of key terms used included “sleep” OR “sleep problem*” OR “sleep disturbance” AND “Epilep*” OR “Epilepsy” OR “Paediatric Epilepsy” AND “child*” OR “adolescen*” (see Table 2.1 for a full list of search terms).

Table 2.1. *Database search terms*

1	Sleep	Sleep* or Non 24 hour sleep wake disorder or Non 24 hour sleep wake syndrome or Non 24 hour sleep wake rhythm disorder or Free running disorder or Hypernychthemeral disorder or N24HSWD or Non 24 hour circadian rhythm disorder or somniloquy or sleep talking or night talking or Sub wakefulness Syndrome or hypnagogic hallucination* or confusional arousal* or sleep enuresis or nocturnal enuresis or night enuresis or night* wet* or nocturnal bed wet* or rapid* eye movement behavi* disorder* or REM behavi* disorder* or Nightmare disorder* or dream anxiety disorder* or nightmare syndr* or Non* Rapid Eye Movement Arousal or NREM arousal or Nocturnal eat* or nocturnal drink* or night eat* or night drink* or nocturnal Bruxism or sleep bruxism or nocturnal tooth* or nocturnal teeth* or night* walking or sleep terror* or night* terror* or Parasomni* or Circadian rhythm disorder* or circadian rhythm sleep* or CRSD or Central Alveolar Hypoventilation or central alveolar hypovent* or Central hypoventilat* or Narcolepsy or narcolep* or hypersomnolen* or hypersomni* or insomni* or sleep problems or sleep difficulties or sleep disturbance or sleep disorder or sleepiness or daytime sleepiness or sleep quality or insomnia or sleep apnea or Obstructive sleep apnea or total sleep time or sleep onset latency or Sleep efficiency or sleep onset time or wake or nocturnal or snoring or sleep disordered breathing or restless leg syndrome
2	Epilepsy	Childhood epilepsy or epilepsy or epilep* or Epilepsy syndrome or Adolescent epilepsy or paediatric epilepsy or Seizures or west syndrome or infantile spasms or dravet syndrome or Lennox Gastaut syndrome or Doose syndrome or Myoclonic Astatic epilepsy or Progressive myoclonic epilepsy or Benign Rolandic epilepsy or Benign Epilepsy with centro-temporal spikes or Panayiotopoulos syndrome or childhood absence epilepsy or Juvenile myoclonic epilepsy
3	Childhood	children or child* or paediatr* or adolescen*
4		(1 AND 2 AND 3)

2.4.2. Study selection

Figure 2.1 illustrates the search process and results. The initial literature search returned 14,951 papers. After duplicates were removed 8838 papers were screened via the titles and abstracts. Papers that met the following criteria at this stage of eligibility screening were included for further

review: 1) available in English, 2) reported on paediatric patients with epilepsy and included a measure of sleep 3) not animal studies 4) not review articles, case studies, editorials, letters or comments 5) reported on children or adolescents aged ≤18 years 6) sample size > 5. Following the eligibility screening, the full text articles of the remaining studies were retrieved and screened against these criteria *and* the following additional inclusion criteria: 1) No ID 2) Suitable data to extract for pooling of effect sizes (i.e., measures of means and SDs) 3) Inclusion of a TD control group.

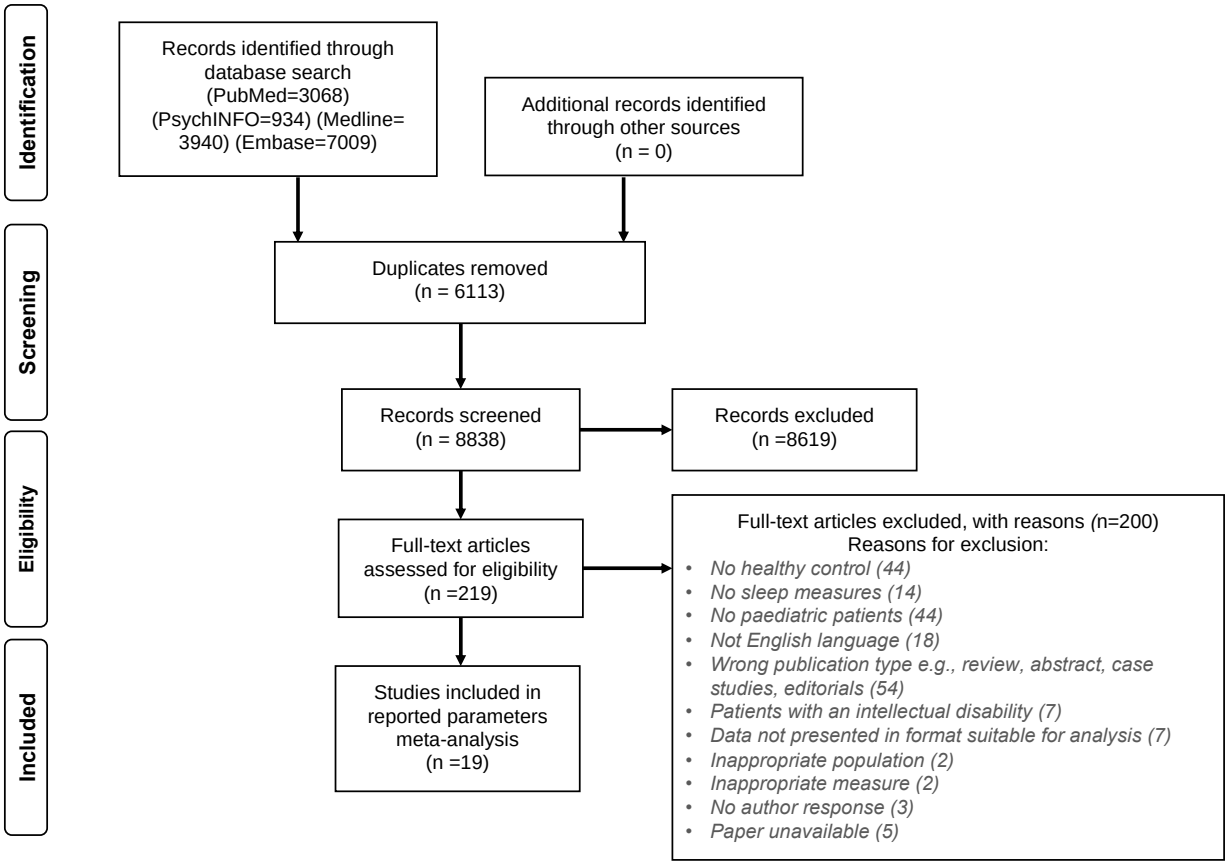


Figure 2.1. Flowchart of search process

2.4.3. Data Extraction and Quality Review

19 papers met the eligibility criteria at full text screening and were included in the final analyses. A quality criteria checklist adapted from previous meta-analyses (Richards, Jones, Groves, Moss & Oliver, 2015; Surtees, Oliver, Jones, Evans & Richards, 2018) was used to review the overall

quality of studies (see Table 2.2). Each study was reviewed for their sample identification, instruments used to measure sleep and epilepsy classification based on a scale of 0 to 3 (poor to excellent). Each score was coded with a colour, 0 was coded as red for a poor score, 1 as orange for an adequate score, 2 as yellow for a good score and 3 as green for an excellent score. This resulted in a total score between 0-9. The total score was then divided by the maximum possible score of 9 to produce a quality value between 0 and 1.

The quality of each paper was reviewed by two researchers independently and inter-rater reliability was established using weighted Cohen's kappa statistic. Inter-rater reliability of the two authors was excellent for the overall scale (Kappa= 0.95, $p<.001$). The individual item ratings varied between good (epilepsy diagnosis, Kappa=0.81, $p<.001$), almost perfect (sample identification, Kappa=0.87, $p<.001$) and perfect agreement (sleep measurement, Kappa=1, $p<.001$).

Table 2.2. *Quality Rating Framework.*

	0 – Poor (Red)	1 – Adequate (Orange)	2 – Good (Yellow)	3 – Excellent (Green)
Epilepsy diagnosis	Not specified / reported	Seizure type Focal, generalised or unknown	Epilepsy type Focal, generalised, combined generalised and focal	Epilepsy syndrome Must specify the type of syndrome
Sample Identification	Not specified / reported	Single restricted or non-random sample (specialist clinic or previous research study)	Multiple restricted or non-random samples (multi-region specialist clinics)	Random or total population sample
Sleep measurement	Response to a single question	Validated sleep questionnaire. Note any form of validation is applicable (for instance clinician judgement to make adaptations for population)	Self/parent monitoring through diaries Atypical use of polysomnography/ actigraphy	Polysomnography (following at least 1 day for adaptation) Actigraphy of 7 days or more

2.4.4. Sleep measures

The sleep parameters of interest were: 1) TST 2) Sleep difficulties 3) Sleep efficiency and 4) Sleep architecture. TST was measured with a combination of methods including PSG, 24-hour video-EEG, actigraphy and informant-report. Sleep difficulties in the retrieved papers were assessed via two questionnaires. The CSHQ (Owens et al., 2000b) is an informant report measure (see section 3.5.4.1 for detailed description). It consists of a global score and eight additional subscales, where higher scores are indicative of more severe sleep difficulties. A separate analysis was conducted using the subscales 'parasomnias', 'sleep disordered breathing (SDB)', 'sleep onset delay', 'sleep duration', 'bedtime resistance', 'night wakings', 'sleep anxiety' and 'daytime sleepiness'. Other studies used the Sleep Behaviour Questionnaire (SBQ) (Cortesi et al., 1999) which is also an informant report questionnaire designed to measure duration and quality of sleep. It consists of a global score and 5 subscales: 'parasomnias', 'parent/child interaction', 'sleep fragmentation', 'daytime drowsiness' and 'bedtime difficulties', where higher scores are again indicative of more frequent sleep difficulties. Note that the SBQ and the CSHQ were initially treated separately, after which a subgroup analysis was conducted. This did not reveal significant differences, indicating that the type of questionnaire did not contribute substantially to the results. Therefore, the SBQ and CSHQ were subsequently combined into one composite analysis for overall sleep difficulties. Sleep efficiency was measured via a combination of PSG and actigraphy. Finally, sleep architecture was measured via PSG and 24-hour video-EEG, as the only methods capable of providing this information.

2.5. Statistical analyses

All statistical analyses were performed in R, version 3.6.0 with RStudio, using the 'meta' and 'metafor' packages. Standard deviations and means for each of the sleep parameters across CWE and control groups were inputted into a spreadsheet. Separate meta-analyses were conducted to produce pooled overall effect size estimates for sleep timing, sleep difficulties, sleep architecture

and sleep efficiency. Each pooled effect size was expressed as a standardised mean difference (SMD, Hedge's g) with corresponding 95% confidence intervals. All analyses were computed using a random effect model. This model assumes that the true effect size varies between studies for two reasons: 1) sampling error within the studies and 2) differences in study population which result in real differences in effect size between studies (Riley, Higgins & Deeks, 2011). It was therefore beneficial to use this model, given the range of participant characteristics across all studies, such as age and diagnoses of patient. For all analyses the Sidik-Jonkman estimator was used rather than the DerSimonian-Laird estimator which can lead to false positives when heterogeneity is high, and number of studies are low (IntHout, Ioannidis & Borm, 2014), which was the case in this sample.

Cochrane's Q was used to assess whether there was statistically significant between-study heterogeneity present in the analysis. The amount of heterogeneity present was then quantified using Higgins I^2 with cut off values placed at 0, 25%, 50% and 75% corresponding to 'no', 'moderate', 'substantial' and 'high' heterogeneity (Higgins, Thompson, Deeks & Altman, 2003). Between-study heterogeneity was explored, when possible, through subgroup analyses and meta-regressions in a mixed effect model across different variables, which were established a *priori*. The purpose of this was to understand whether the methodological approach of the studies had an impact on the overall results. Type of sleep instrument e.g., PSG, 24-hour video-EEG, actigraphy or questionnaire, was used as the categorical variable in the subgroup analyses. Meta-regression analyses were performed using age (years), sex (male %) and study quality score as continuous variables.

The robustness of the results was assessed in sensitivity analyses using outlier detection and the leave-one-out method, where, as studies are omitted one at a time, effect sizes are recalculated to

assess the influence of individual studies on the overall effect size estimate. Risk of publication bias was assessed using visual inspection of contour-enhanced funnel plots, which plot standardised mean difference (Hedges *g*) in the x-axis against standard error, as a measure for size of studies in the y-axis. Statistical testing for funnel plots was conducted using the Eggers test, and only for analyses consisting of 10 studies or more as the power of the test is too low to detect reliable bias estimates with fewer than 10 studies (Sterne et al., 2011).

2.6. Results

2.6.1. Study characteristics

19 studies met the inclusion criteria and were used to assess the differences in sleep parameters between a total of 901 CWE with a mean age of 10.8 years (reported by authors in 17 studies) and 1470 CWOE with a mean age of 10.8 years (reported by authors in 17 studies). Nine studies used PSG to assess sleep parameters, of which three used an adaptation night (data were reported for only the second night across the original studies, six used one night of sleep only with no adaptation night. One study used 24-hour video-EEG. Of the remaining nine studies, eight used informant reported sleep questionnaires. Finally, only one study used both actigraphy and questionnaires. Table 2.3 presents characteristics of the studies included in the meta-analysis.

Table 2.3. *Study characteristics*

Study	Sample size		Age (Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Barreto et al. (2002)	10 13	12	12.2 8.9	10.8	40 54	33	10 Idiopathic generalised epilepsy 13 Benign epilepsy with centrotemporal spikes	PSG	TST, N1, N2, N3, N4, REM%	74% on AEDs	No	3	1	2	**0.67**
Batista & Nunes. (2007)	81	81	9.3	9.3	48	N/A	21 Focal seizures 28 Focal seizures with secondary generalisation 32 Generalised seizures	SBQ	SBQ total score	27.1% polytherapy	N/A	1	1	1	**0.33**
Bruni et al. (2010)	10	10	8.1	7.8	N/A	N/A	10 Rolandic epilepsy	PSG	TST, SE (%), N1, N2, N3, REM%	Unknown	Yes	3	1	3	**0.78**
Byars et al. (2008)	332	321	9.6	9.6	49	48	Various epilepsy syndromes	SBQ	Informant reported sleep time SBQ total score	50% monotherapy 2% polytherapy 48% no AEDs	N/A	3	2	1	**0.67**

Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency, TST= Total sleep time.

Table 2.3. *Study characteristics*

Study	Sample size		Age (Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Chan et al. (2011)	63	169	8.4	7.7	49	49	40 Generalised epilepsy 23 Partial epilepsy	CSHQ	CSHQ total and subscales	62% monotherapy 25% polytherapy	N/A	2	2	1	**0.56**
Chan et al. (2017)	22	21	11.5	10.6	64	43	Focal epilepsy	PSG	TST, N1, N2, N3, REM%	45% monotherapy 46% polytherapy 9% no AEDs	No	2	1	2	**0.56**
Cortesi et al. (1999)	89	48	9.7	9.2	56	48	63 Primary generalised epilepsy 26 Primary partial epilepsy	SBQ	SBQ total score	100% monotherapy	N/A	2	1	1	**0.44**
Ekinci et al. (2016)	53	28	11.8	12.14	55	61	24 Partial seizures 16 Generalised-tonic clonic seizures 13 Absence seizures	CSHQ	CSHQ total score and subscales	77% monotherapy	N/A	1	1	1	**0.33**

Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency, TST= Total sleep time.

Table 2.3. *Study characteristics*

Study	Sample size		Age (Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Gogou et al. (2016)	40	27	10.6	11	N/A	N/A	22 Generalised epilepsy 18 Focal epilepsy	PSG	TST, N3%, N1+N2%, REM%,	80% monotherapy 12.5% polytherapy 7.5% no AEDs	No	2	1	2	**0.56**
Gogou et al, (2017)	15	27	10.5	11	N/A	N/A	Rolandic Epilepsy	PSG	TST, SE(%), N1+N2, N3, REM%	73.3% monotherapy 13.3% polytherapy 13.3% no AEDs	No	3	1	2	**0.67**
Holley et al. (2014)	23	50	10	9.3	48	44	Childhood absence epilepsy, generalised tonic clonic seizures, focal seizures and not known	CSHQ Actigraphy	CSHQ total score and subscales Actigraphy	96% on AEDs	N/A	3	2	3	**0.89**
Maganti et al. (2005)	11	8	13.4	14.3	45	50	5 Childhood absence, 4 juvenile absence, 2 juvenile myoclonic epilepsy	PSG	TST, SE(%),N1, N2, N3, REM%	73% monotherapy 27% polytherapy	Yes	3	1	3	**0.78**

Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency, TST= Total sleep time.

Table 2.3. *Study characteristics*

Study	Sample size		Age(Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Maganti *et al,* 2006	26	26	14.6	14.7	35	35	14 Idiopathic generalised epilepsy 12 Localisation related epilepsy	PDSS PSQ	Informant reported sleep duration	100% on AEDs	N/A	3	1	1	**0.56**
Myatchin & Lagae 2007	6	47	9.7	8.6	67	56	4 Childhood absence, 1 myoclonic absence, 1 juvenile myoclonic epilepsy	24-hour Video-EEG	TST, N2%	100% monotherapy	No	3	1	2	**0.67**
Nunes et al., 2003	17	11	4.7-16.2	7.17-18.8	47	73	3 Idiopathic localisation related epilepsy 14 Symptomatic localisation related epilepsy	PSG	TST, N1, N2, N3-N4%, REM%	100% on AEDs	Yes	2	2	3	**0.78**

Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency, TST= Total sleep time.

Table 2.3. *Study characteristics*

Study	Sample size		Age(Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Pereira et *al*, 2012a	8	23	11.9	8.3	50	39	5 Idiopathic localisation elated epilepsy 3 Symptomatic localisation related epilepsy	PSG	TST, SE(%), N1, N2, N3 and REM%	100% on AEDs	No	2	1	2	**0.56**
Shaheen *et al*, 2012	26	12	12.6	11.8	62	50	4 Generalised epilepsy 12 Focal epilepsy 10 Focal epilepsy with secondary generalisation	PSG	TST, SE(%), N1%, N2%, N3%, REM%	38.5% monotherapy 38.5% polytherapy	No	2	1	2	**0.56**
Tang *et al,* 2011	43	494	9.8	7.6	56	51	Rolandic epilepsy	CSHQ	CSHQ total and subscales	31% treated with AEDs	N/A	3	2	1	**0.67**
Wirrell *et al,* 2005	26	55	N/A	10.4	N/A	N/A	Reported but not quantified for subgroup	SBQ	SBQ total	Reported but not quantified for subgroup	N/A	3	1	1	**0.56**

Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency, TST= Total sleep time.

2.6.2. Total sleep time

Of the 12 studies that reported TST in CWE in comparison to CWOE, six studies reported TST via PSG, one via 24-hour video-EEG, one used actigraphy and four used informant-reported sleep time. The study by Barreto et al. (2002) consisted of two subgroups: 'idiopathic generalised epilepsy' and 'idiopathic focal epilepsy'. These two groups were initially treated with two separate analyses in order to avoid unit of analysis error. One subgroup ('idiopathic focal epilepsy') was revealed to be an outlier in subsequent sensitivity analysis so was not included in the meta-analysis for TST (see Appendix 2.1). Two studies were conducted by Gogou et al (2016, 2017) using the same control group. In this case, the 'focal and generalised epilepsy' group was kept in the analysis as it had a larger sample size (N=22) than the 'rolandic epilepsy' group (N=18), which was omitted.

The random effects model revealed that CWE experienced significantly shorter TST in comparison to CWOE (SMD= -0.55, [95% CI -1.08; -0.02] p=0.04), see Figure 2.2). Mean weighted difference comparison found that CWE slept on average 34 minutes less than CWOE, and this ranged between 151 minutes less to 9 minutes more. Significantly high heterogeneity among the studies was detected (Q= 62.34, I^2=82.4%, p<0.01). The robustness of the results was tested via sensitivity analysis by the leave one out method, which revealed no influential cases.

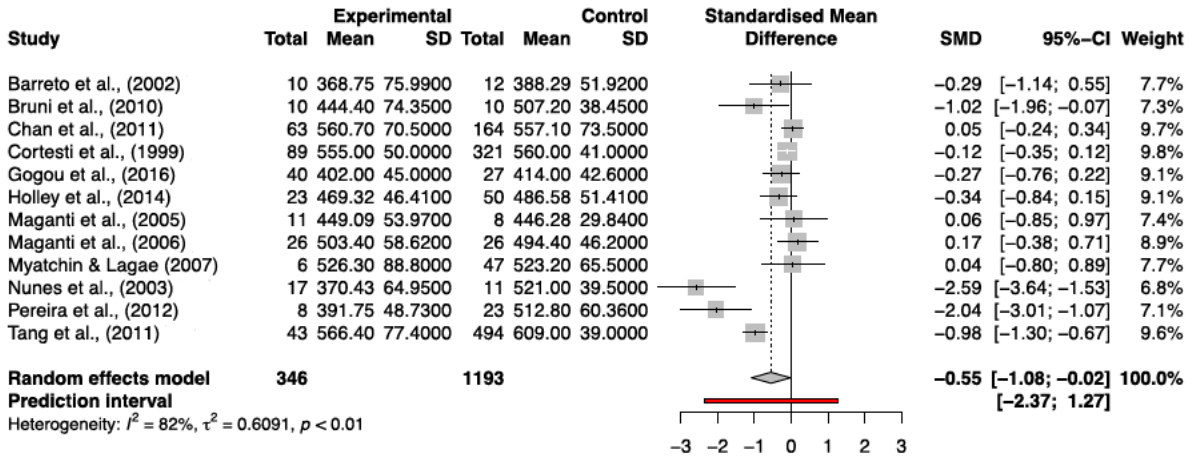


Figure 2.2. *Forest plot for standardised mean difference (Hedge's g) in sleep time between CWE and CWOE.* The bold vertical line in the middle represents the line of null effect. Black horizontal lines represent 95% confidence intervals, and the squares are the point estimate of the study result. The prediction interval represents the range in which the point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of the figure plots the overall effect (centre point of diamond) and the corresponding confidence intervals (horizontal points of the diamond).

2.6.3. Sleep difficulties

Nine studies were pooled into the meta-analysis for sleep difficulties. Five measured sleep difficulties via the total scores on CSHQ and four via the SBQ. The random effects model for the full sample initially revealed a non-significant effect (SMD= 2.08, 95% CI [-0.53, 4.69], p=0.10) and substantial heterogeneity I^2=97.3%, Q=299.44, p<0.01. Sensitivity analyses revealed that the study by Batista et al. (2007) was an outlier as evidenced by clear distortion on the effect size estimate (see appendix 2.2). This outlier was removed from the current and all future analyses. The random effects model was computed again and found to yield a significant result (SMD= 0.97, 95% CI [0.48, 1.46], p=0.002, see Figure 2.3) with reduced heterogeneity I^2= 88.1%, Q=59.04, p<0.01. This indicated that CWE suffer significantly more frequent and severe sleep difficulties compared to CWOE.

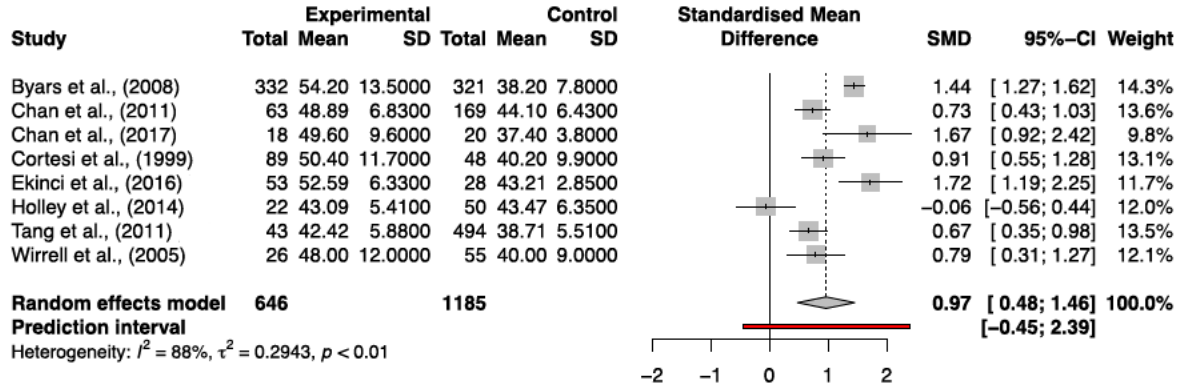


Figure 2.3. *Forest plot for standardised mean difference (Hedge's g) in total sleep problems between CWE and CWOE.* The bold vertical line in the middle represents the line of null effect. Black horizontal lines represent 95% confidence intervals, and the squares are the point estimate of the study result. The prediction interval represents the range in which the point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of the figure plots the overall effect (centre point of diamond) and the corresponding confidence intervals (horizontal points of the diamond).

2.6.4. Type of sleep difficulties

A separate analysis was conducted on studies measuring sleep difficulties via the CSHQ, taking advantage of the subscales which examine different aspects of sleep difficulties. Each subscale of the questionnaire was separated as eight different outcomes and one total outcome to conduct subgroup analyses (see Figure 2.4). It was found that CWE had significantly higher scores on the following subscales: night waking (SMD=0.42, 95% CI [0.16; 0.68], p=0.01), parasomnias (SMD= 0.68, 95% CI [0.21; 1.15], p=0.02), sleep disordered breathing (SMD= 0.34, 95% CI [0.09; 0.59], p=0.02) and total sleep difficulties (SMD=0.92, 95% CI [-0.00; 1.83], p=0.05). All remaining subscales yielded non-significant estimates.

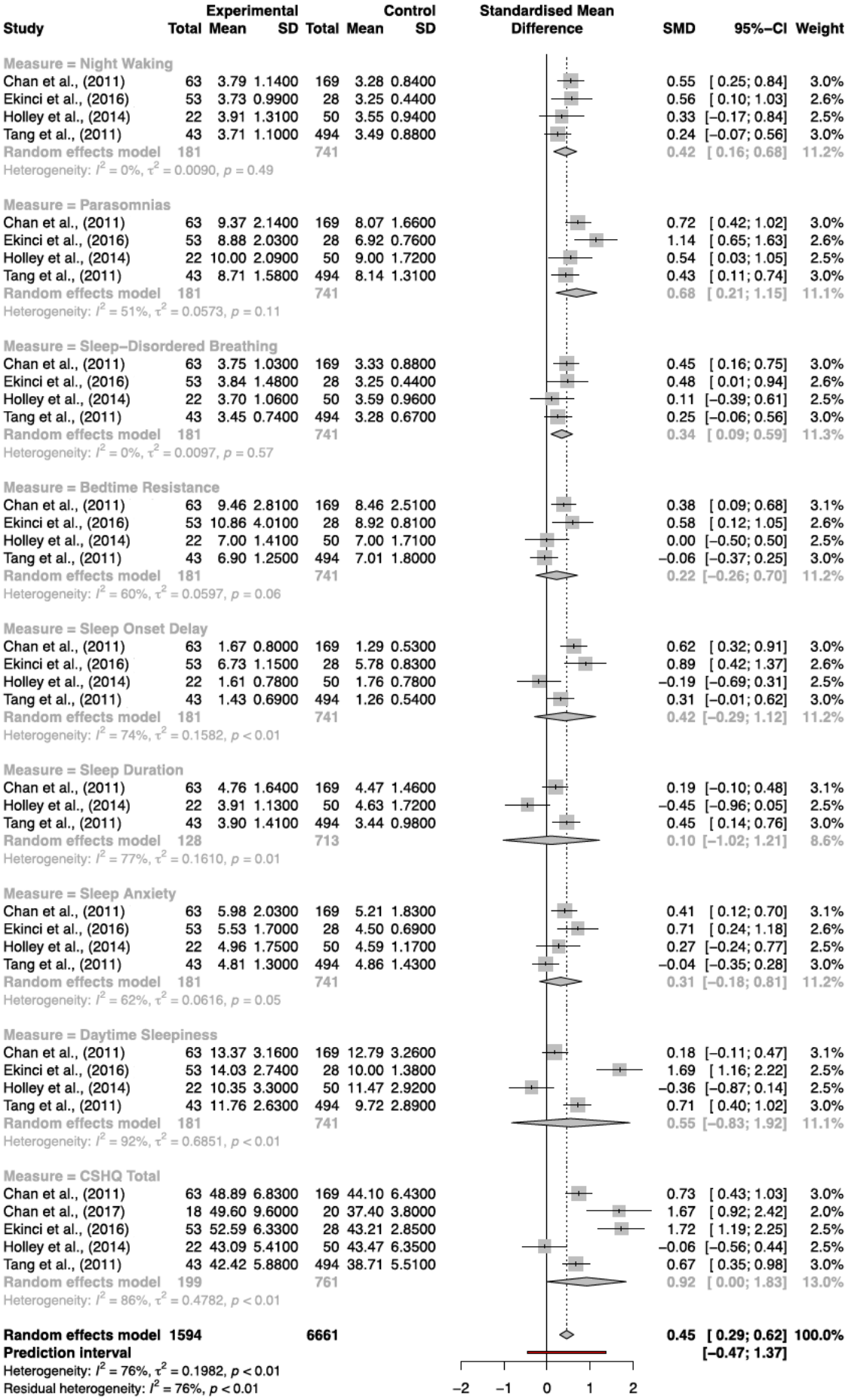

Study
Experimental
Total Mean SD
Control
Total Mean SD
Standardised Mean Difference
SMD 95%–CI Weight
Measure = Night Waking
Chan et al., (2011) 63 3.79 1.1400 169 3.28 0.8400 0.55 [0.25; 0.84] 3.0%
Ekinci et al., (2016) 53 3.73 0.9900 28 3.25 0.4400 0.56 [0.10; 1.03] 2.6%
Holley et al., (2014) 22 3.91 1.3100 50 3.55 0.9400 0.33 [−0.17; 0.84] 2.5%
Tang et al., (2011) 43 3.71 1.1000 494 3.49 0.8800 0.24 [−0.07; 0.56] 3.0%
Random effects model 181 741 0.42 [0.16; 0.68] 11.2%
Heterogeneity: I^2 = 0%, τ^2 = 0.0090, p = 0.49
Measure = Parasomnias
Chan et al., (2011) 63 9.37 2.1400 169 8.07 1.6600 0.72 [0.42; 1.02] 3.0%
Ekinci et al., (2016) 53 8.88 2.0300 28 6.92 0.7600 1.14 [0.65; 1.63] 2.6%
Holley et al., (2014) 22 10.00 2.0900 50 9.00 1.7200 0.54 [0.03; 1.05] 2.5%
Tang et al., (2011) 43 8.71 1.5800 494 8.14 1.3100 0.43 [0.11; 0.74] 3.0%
Random effects model 181 741 0.68 [0.21; 1.15] 11.1%
Heterogeneity: I^2 = 51%, τ^2 = 0.0573, p = 0.11
Measure = Sleep–Disordered Breathing
Chan et al., (2011) 63 3.75 1.0300 169 3.33 0.8800 0.45 [0.16; 0.75] 3.0%
Ekinci et al., (2016) 53 3.84 1.4800 28 3.25 0.4400 0.48 [0.01; 0.94] 2.6%
Holley et al., (2014) 22 3.70 1.0600 50 3.59 0.9600 0.11 [−0.39; 0.61] 2.5%
Tang et al., (2011) 43 3.45 0.7400 494 3.28 0.6700 0.25 [−0.06; 0.56] 3.0%
Random effects model 181 741 0.34 [0.09; 0.59] 11.3%
Heterogeneity: I^2 = 0%, τ^2 = 0.0097, p = 0.57
Measure = Bedtime Resistance
Chan et al., (2011) 63 9.46 2.8100 169 8.46 2.5100 0.38 [0.09; 0.68] 3.1%
Ekinci et al., (2016) 53 10.86 4.0100 28 8.92 0.8100 0.58 [0.12; 1.05] 2.6%
Holley et al., (2014) 22 7.00 1.4100 50 7.00 1.7100 0.00 [−0.50; 0.50] 2.5%
Tang et al., (2011) 43 6.90 1.2500 494 7.01 1.8000 −0.06 [−0.37; 0.25] 3.0%
Random effects model 181 741 0.22 [−0.26; 0.70] 11.2%
Heterogeneity: I^2 = 60%, τ^2 = 0.0597, p = 0.06
Measure = Sleep Onset Delay
Chan et al., (2011) 63 1.67 0.8000 169 1.29 0.5300 0.62 [0.32; 0.91] 3.0%
Ekinci et al., (2016) 53 6.73 1.1500 28 5.78 0.8300 0.89 [0.42; 1.37] 2.6%
Holley et al., (2014) 22 1.61 0.7800 50 1.76 0.7800 −0.19 [−0.69; 0.31] 2.5%
Tang et al., (2011) 43 1.43 0.6900 494 1.26 0.5400 0.31 [−0.01; 0.62] 3.0%
Random effects model 181 741 0.42 [−0.29; 1.12] 11.2%
Heterogeneity: I^2 = 74%, τ^2 = 0.1582, p < 0.01
Measure = Sleep Duration
Chan et al., (2011) 63 4.76 1.6400 169 4.47 1.4600 0.19 [−0.10; 0.48] 3.1%
Holley et al., (2014) 22 3.91 1.1300 50 4.63 1.7200 −0.45 [−0.96; 0.05] 2.5%
Tang et al., (2011) 43 3.90 1.4100 494 3.44 0.9800 0.45 [0.14; 0.76] 3.0%
Random effects model 128 713 0.10 [−1.02; 1.21] 8.6%
Heterogeneity: I^2 = 77%, τ^2 = 0.1610, p = 0.01
Measure = Sleep Anxiety
Chan et al., (2011) 63 5.98 2.0300 169 5.21 1.8300 0.41 [0.12; 0.70] 3.1%
Ekinci et al., (2016) 53 5.53 1.7000 28 4.50 0.6900 0.71 [0.24; 1.18] 2.6%
Holley et al., (2014) 22 4.96 1.7500 50 4.59 1.1700 0.27 [−0.24; 0.77] 2.5%
Tang et al., (2011) 43 4.81 1.3000 494 4.86 1.4300 −0.04 [−0.35; 0.28] 3.0%
Random effects model 181 741 0.31 [−0.18; 0.81] 11.2%
Heterogeneity: I^2 = 62%, τ^2 = 0.0616, p = 0.05
Measure = Daytime Sleepiness
Chan et al., (2011) 63 13.37 3.1600 169 12.79 3.2600 0.18 [−0.11; 0.47] 3.1%
Ekinci et al., (2016) 53 14.03 2.7400 28 10.00 1.3800 1.69 [1.16; 2.22] 2.5%
Holley et al., (2014) 22 10.35 3.3000 50 11.47 2.9200 −0.36 [−0.87; 0.14] 2.5%
Tang et al., (2011) 43 11.76 2.6300 494 9.72 2.8900 0.71 [0.40; 1.02] 3.0%
Random effects model 181 741 0.55 [−0.83; 1.92] 11.1%
Heterogeneity: I^2 = 92%, τ^2 = 0.6851, p < 0.01
Measure = CSHQ Total
Chan et al., (2011) 63 48.89 6.8300 169 44.10 6.4300 0.73 [0.43; 1.03] 3.0%
Chan et al., (2017) 18 49.60 9.6000 20 37.40 3.8000 1.67 [0.92; 2.42] 2.0%
Ekinci et al., (2016) 53 52.59 6.3300 28 43.21 2.8500 1.72 [1.19; 2.25] 2.5%
Holley et al., (2014) 22 43.09 5.4100 50 43.47 6.3500 −0.06 [−0.56; 0.44] 2.5%
Tang et al., (2011) 43 42.42 5.8800 494 38.71 5.5100 0.67 [0.35; 0.98] 3.0%
Random effects model 199 761 0.92 [0.00; 1.83] 13.0%
Heterogeneity: I^2 = 86%, τ^2 = 0.4782, p < 0.01
Random effects model 1594 6661 0.45 [0.29; 0.62] 100.0%
Prediction interval [−0.47; 1.37]
Heterogeneity: I^2 = 76%, τ^2 = 0.1982, p < 0.01
Residual heterogeneity: I^2 = 76%, p < 0.01
−2 −1 0 1 2

Figure 2.4. *Forest plot for standardised mean difference (Hedge's g) in type of sleep difficulties on CSHQ between CWE and CWOE.* The bold vertical line in the middle represents the line of null effect. Black horizontal lines represent 95% confidence intervals and the squares are the point estimate of the study result. The prediction interval represents the range in which the point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of the figure plots the overall effect (centre point of diamond) and the corresponding confidence intervals (horizontal points of the diamond).

2.6.5. Sleep Efficiency

Of six studies that measured sleep efficiency, five reported sleep efficiency via PSG and one used actigraphy, all of which were pooled into the meta-analysis. The random effects model revealed that CWE experience significantly reduced SE compared to CWOE (SMD= -0.71, [95% CI [-1.23; -0.19], p=0.02), see Figure 2.5. CWE had an average sleep efficiency of 83% (compared to controls mean sleep efficiency of 89%). The mean difference was 6% less for CWE and this ranged between 0.2% more to 10% less than controls across studies. There was low heterogeneity amongst the studies (Q= 8.22, I^2= 39.2, p=0.14). Sensitivity and outlier analysis did not reveal any influential cases, confirming the robustness of the results.

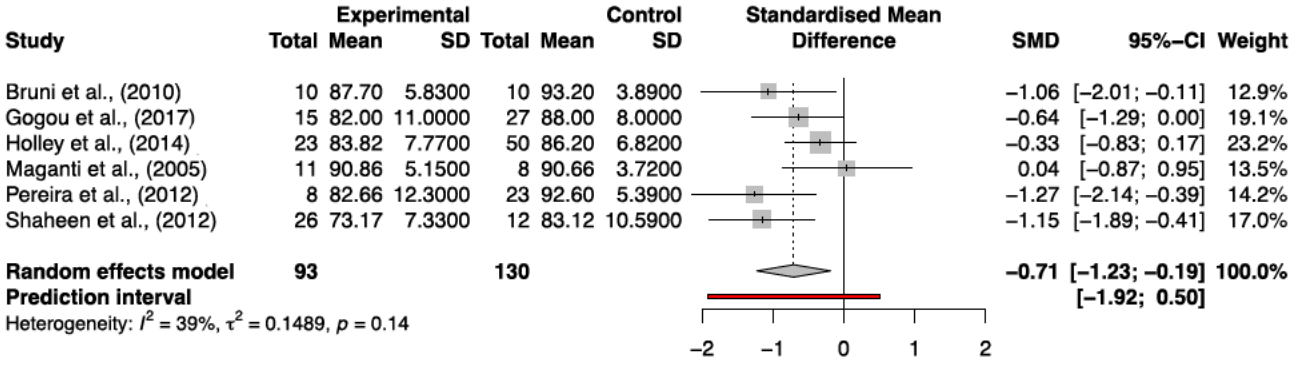


Figure 2.5. *Forest plot for standardised mean difference (Hedge's g) in sleep efficiency (%) between CWE and CWOE.* The bold vertical line in the middle represents the line of null effect. Black horizontal lines represent 95% confidence intervals, and the squares are the point estimate of the study result. The prediction interval represents the range in which the point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of the figure plots the overall effect (centre point of diamond) and the corresponding confidence intervals (horizontal points of the diamond).

2.6.6. Sleep Architecture

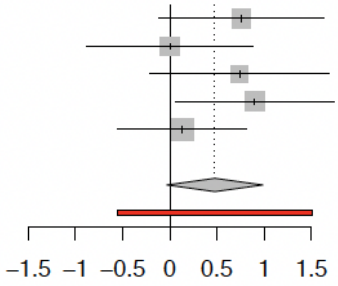
Separate meta-analyses were conducted for percentage of time spent in sleep stages (see Figure 2.6): N1% (5 studies), N2% (6 studies), N3% (5 studies) and REM% (6 studies). Three studies were excluded prior to analyses including Gogou et al. (2016,2017) as N1 and N2% could not be separated for analysis. The study by Chan et al. (2017) was also removed as some participants underwent sleep restrictions as part of the experimental procedure and others underwent a natural sleep procedure, however as the data could not differentiated, the study was excluded. The meta-analyses initially revealed no significant differences for all sleep stages. Sensitivity analyses was conducted and revealed two outliers (Myatchin & Lagae, 2007; Pereira Bruni, Ferri & Nunes, 2012a, see appendix 2.3) in N2% and one outlier (Pereira et al., 2012a) in N3% and REM%. Removal of all outliers did not have a significant effect on the overall effect size estimate for N3% and REM%. However, when the outliers for N2% were removed, the overall effect size estimate was found to be of borderline significance (SMD=0.44, 95% CI [0.00; 0.87], p=0.05), indicating that CWE had a higher percentage of N2 compared to CWOE. There was no substantial heterogeneity detected (I^2=0%, Q=1.27, p=0.74), thus no further analyses were conducted.

1. N1%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002)	10	4.79	3.9300	12	2.36	2.1600	0.76	[–0.12; 1.63]	18.7%
Bruni et al., (2010)	10	9.40	3.5600	10	9.40	3.7600	0.00	[–0.88; 0.88]	18.7%
Maganti et al., (2005)	11	7.19	3.2700	8	4.87	2.5800	0.74	[–0.21; 1.69]	16.6%
Pereira et al., (2012)	8	8.67	8.2900	23	3.80	3.8500	0.90	[0.06; 1.74]	19.9%
Shaheen et al., (2012)	26	8.18	7.1800	12	7.22	6.8600	0.13	[–0.55; 0.82]	26.2%
Random effects model	**65**			**65**			**0.48**	**[–0.03; 0.99]**	**100.0%**
Prediction interval								**[–0.55; 1.51]**	

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0710$, $p = 0.44$

Standardised Mean Difference

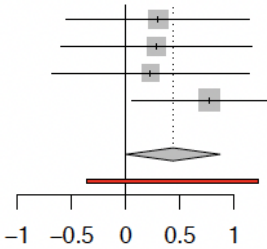


2. N2%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002)	10	53.25	12.6700	12	50.11	7.3900	0.30	[–0.55; 1.14]	24.0%
Bruni et al., (2010)	10	44.50	10.4600	10	42.10	4.8400	0.28	[–0.60; 1.16]	22.2%
Maganti et al., (2005)	11	49.49	8.9000	8	47.46	8.0200	0.23	[–0.69; 1.14]	20.7%
Shaheen et al., (2012)	26	57.01	17.1200	12	44.05	14.9800	0.77	[0.06; 1.48]	33.1%
Random effects model	**57**			**42**			**0.44**	**[0.00; 0.87]**	**100.0%**
Prediction interval								**[–0.36; 1.23]**	

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0153$, $p = 0.74$

Standardised Mean Difference

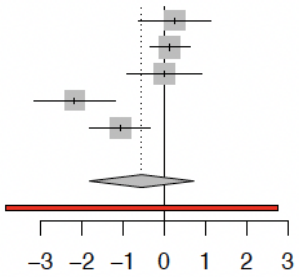


3. N3%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Bruni et al., (2010)	10	27.50	6.0600	10	26.20	3.2900	0.26	[–0.63; 1.14]	19.4%
Gogou et al., (2016)	40	32.00	10.4800	27	30.69	6.8900	0.14	[–0.35; 0.63]	22.3%
Maganti et al., (2005)	11	17.33	5.4500	8	17.31	5.7700	0.00	[–0.91; 0.91]	19.2%
Pereira et al., (2012)	8	9.37	9.1200	23	23.70	5.3100	–2.17	[–3.16; –1.18]	18.5%
Shaheen et al., (2012)	26	23.11	10.2700	12	36.08	14.9000	–1.07	[–1.80; –0.34]	20.6%
Random effects model	**95**			**80**			**–0.54**	**[–1.80; 0.73]**	**100.0%**
Prediction interval								**[–3.84; 2.76]**	

Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.8664$, $p < 0.01$

Standardised Mean Difference



4. REM%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002)	10	24.92	8.2200	12	22.71	7.4000	0.27	[–0.57; 1.12]	16.6%
Bruni et al., (2010)	10	15.50	4.6000	10	21.20	4.3400	–1.22	[–2.19; –0.25]	15.6%
Gogou et al., (2016)	40	18.63	5.8800	27	21.24	4.6500	–0.48	[–0.97; 0.02]	19.1%
Maganti et al., (2005)	11	17.91	3.8400	8	22.03	7.9300	–0.67	[–1.61; 0.27]	15.8%
Pereira et al., (2012)	8	9.73	5.7900	23	22.90	5.0400	–2.45	[–3.49; –1.42]	15.1%
Shaheen et al., (2012)	26	12.57	9.3300	12	12.62	6.2800	–0.01	[–0.69; 0.68]	17.8%
Random effects model	**105**			**92**			**–0.71**	**[–1.71; 0.29]**	**100.0%**
Prediction interval								**[–3.34; 1.91]**	

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.7432$, $p < 0.01$

Standardised Mean Difference

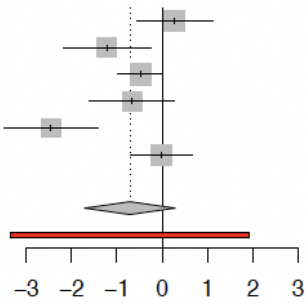


Figure 2.6. *Forest plot for standardised mean difference (Hedge's g) in percentage of time (mins) spent in N1, N2, N3 and REM sleep between CWE and CWOE*. The bold vertical line in the middle represents the line of null effect. Black horizontal lines represent 95% confidence intervals, and the squares are the point estimate of the study result. The prediction interval represents the range in which the point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of the figure plots the overall effect (centre point of diamond) and the corresponding confidence intervals (horizontal points of the diamond).

2.7. Heterogeneity Analysis

To explore other sources of heterogeneity and their potential impact on the results, subgroup and meta-regression analyses were conducted on the TST, sleep difficulties and sleep efficiency data only[3]. Subgroup analyses were performed using categorical variables (type of sleep instrument) and meta-regression analyses were performed using continuous variables (age, % of male individuals and quality of study), to assess whether the overall effect size in the above datasets were impacted by these variables.

2.7.1. Total sleep time

No significant subgroup differences were found between PSG, 24-hour video-EEG, informant-report and actigraphy (Q=3.17*;* p=0.37) indicating that the type of sleep measure did not influence TST. The meta regression analyses revealed no significant associations between TST and age (p=0.79, R^2= 0%), sex (p=0.89, R^2= 0%) or quality of the study (p=0.67, R^2= 0%)

[3] Subgroup analysis for sleep architecture could not be conducted, as a minimum of 6 studies are required to produce clinically meaningful findings (Fu et al., 2011)

2.7.2. Sleep difficulties

No significant subgroup differences were detected between the SBQ and CSHQ on the overall effect size estimates for sleep difficulties (Q=0.21, p=0.64). The meta-regression analysis found no significant associations between sleep difficulties and age (p=0.79, R^2= 0%), sex (p=0.10, R^2=47.88%) or quality of the study (p=0.09, R^2=42.08%)

2.7.3. Sleep Efficiency

No significant subgroup differences were found between actigraphy or PSG on the overall sleep efficiency estimates (Q=2.06, p=0.15). The meta-regression analysis found no significant associations between sleep efficiency and age (p=0.20, R^2=37.7%), sex (p=0.10, R^2=47.9%) or quality of the study (p=0.09, R^2=42.08%).

2.8. Publication Bias

Assessment of publication bias was conducted using a graphical approach and statistical testing when there were ≥ 10 studies available. For TST the contour enhanced funnel plot indicated some asymmetry. Closer inspection demonstrated that most of the studies fell in the area of non-statistical significance (white shading) rather than the areas of significance (light blue and blue shading), hence the funnel asymmetry was unlikely to be attributed to publication bias (Palmer, Sutton, Peters & Moreno, 2008). This was confirmed via the Eggers test which revealed a non-significant effect p=0.17 (Figure 2.7).

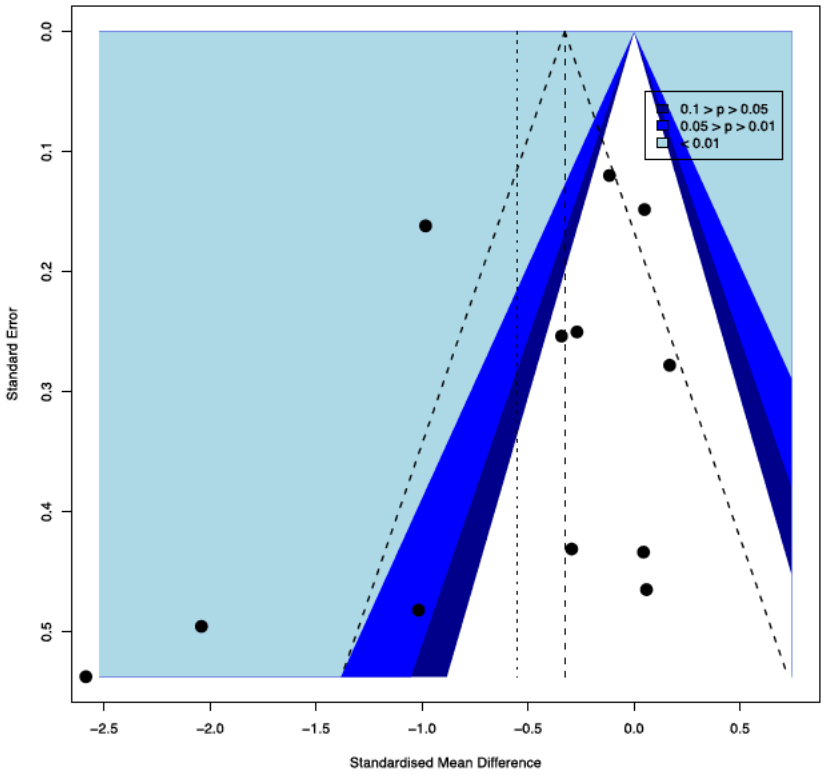


Figure 2.7. *Contour enhanced funnel plot. Standardised mean difference in total sleep time between CWE and CWOE plotted against standard errors.* Black circles refer to the included studies. The light blue shaded region corresponds to p-values below 0.01, the blue shaded region corresponds to p-values between 0.05 and 0.01, the dark blue shaded region corresponds to p-values between 0.1 and 0.05.

2.9. Discussion

Sleep difficulties are often reported by parents of CWE, however the relationship between sleep difficulties and epilepsy continues to be under-recognized clinically. This is the first meta-analysis to quantify differences across informant-reported and objective measures of sleep variables between CWE and CWOE. A wide range of sleep parameters were considered within the meta-analysis including sleep timing, sleep difficulties, sleep efficiency and sleep architecture in order to incorporate a variety of findings and approaches. In addition, the use of a comprehensive, systematic search strategy with inclusive terms optimised the breadth of

literature captured. The use of robust assessments of study quality strengthened the confidence in the findings and, as anticipated, CWE experienced deficits across a wide range of sleep parameters. Our analysis indicated that CWE have significantly reduced TST and sleep efficiency, increased percentage of N2 and more frequent and severe sleep difficulties across various domains compared to CWOE. Previous research has consistently highlighted that poor sleep in CWE can impact seizure control and increase the risk of poorer behavioural and psychological outcomes in comparison to CWOE. Therefore, this evidence of sleep disruptions in CWE warrants further investigation and a greater degree of clinical acknowledgment.

Analysis of TST found that CWE slept on average 34 minutes less in comparison to CWOE (this ranged from 151 minutes less to 9 minutes more across studies). This meta-analytic finding confirms previous empirical studies (Lahorgue Nunes et al., 2003; Tsai et al., 2019). It is clinically relevant to the management of CWE, given that insufficient sleep can act as a precipitating factor for IEDs and seizure control. Reduced sleep duration also increases daytime sleepiness which will have an impact on behaviour, learning and overall HRQOL (Giorelli, Passos, Carnaval & Gomes, 2013).

The results also revealed significantly more frequent sleep difficulties in CWE, which were most pronounced in relation to the subscales of night waking, SDB and parasomnias as assessed via the CSHQ. This demonstrates that both objective and informant reported measures are consistently highlighting poorer sleep parameters in CWE in comparison to CWOE. Moreover, as sleep difficulties often contribute to and prefigure the development of sleep disorders, they pose a clinical problem in their own right. They should therefore be addressed in order to mitigate the risk of these difficulties worsening and complicating the presentation of the epilepsy.

Sleep difficulties including parasomnias and SDB are commonly observed in CWE (Al-Biltagi, 2014) and there are various mechanisms underlying these disturbances. NREM parasomnias can be triggered at times of anxiety, which is heightened in CWE given the unpredictable nature of seizures (Caplan et al., 2005; Reilly, Agnew & Neville, 2011). Additionally, it is important to note that commonly experienced parasomnias such as confusional arousals and night terrors share similar gross semiology and behavioural features to nocturnal seizures (Walker & Eriksson, 2011), which is why video monitoring forms such a crucial part of the diagnostic workflow. It is therefore possible that informant report tools are unable to capture this difference in the absence of video-EEG data. SDB in CWE can be attributed to multiple factors including side effect of AEDs (see below) and disturbed sleep (Sivathamboo et al., 2018). SDB has been associated with a range of deficits including alterations to sleep and neurocognitive impairments, and thus presents a risk for the developmental progress of CWE (Gogou et al., 2016).

The analysis of PSG variables revealed alterations to sleep architecture, specifically increased N2% in CWE compared to CWOE. This may relate to the higher rates of SDB observed, which often results in frequent arousals during sleep, increasing the time children spend within the lighter stages of sleep (Gogou, Haidopoulou, Eboriadou & Pavlou, 2015). Similarly, poor sleep efficiency was also apparent in CWE, averaging 83%, which is below the average of 90% (Bazil, 2005) in the TD population and may be indicative of poor seizure control as suggested by previous research (Kaleyias et al., 2008).

Interestingly, nearly all studies within the meta-analysis included CWE on AED treatment, which may in part contribute to the differences observed in sleep macro-structure and respiratory parameters. AEDs can have varying effects on sleep architecture and sleep

efficiency (Shvarts & Chung, 2013; Jain & Glauser, 2014). In addition, polytherapy is found to exacerbate the occurrence of parasomnias (Shaki et al., 2011) and ultimately lead to more severe sleep difficulties in comparison to those on monotherapy (Batista & Nunes, 2007). Another side effect of some AEDs is increased weight gain, which is a risk factor for apnoea events during sleep due to the heightened risk of blockages of the upper airways (Sivathamboo et al., 2018; Gogou et al., 2015). SDB is also associated with dysfunction of the cardiovascular system, which is speculated to play a role in SUDEP, highlighting the potentially devastating consequences of sleep disturbances in CWE (Billakota et al., 2018). Therefore, consideration of the type of AEDs administered and the possible presence of an underlying sleep disorder is vital in the overall assessment of CWE.

In the current meta-analysis, strict inclusion criteria were set in order to produce the most reliable findings, which has both strengths and limitations. One strength was the inclusion of studies employing a variety of sleep instruments, as this provides both informant reported and objective quantification of sleep disturbances in CWE. This enabled investigation of a range of aspects related to sleep, which is important given the complexity of sleep as a behaviour. Another criterion was only including studies comparing CWE to CWOE. This provided a reference point for understanding the specific sleep disruptions that are present in CWE, but also resulted in the loss of potentially informative studies that did not include a control group. Nonetheless, the findings from studies that were not included as they did not have a control group, were consistent with those in the review (Tsai et al., 2019; Kaleyias et al., 2008; Becker et al., 2004; Hansen, Alfstad, Van Roy, Henning, & Lossius, 2016). They also emphasised the association with behavioural and psychiatric co-occurrences (Becker et al., 2004; Hansen et al., 2016). It was not possible to examine the impact of psychopathologies on sleep within this

meta-analysis, however this is an important area of future research given the importance of these issues to patients.

Similarly, this meta-analysis extends the results of a previous review investigating sleep problems in CWE, by providing the first empirical synthesis of the data (Schlarb, Christen, Claβen & Bien, 2016). This review highlighted the need for longitudinal designs to be conducted, to draw stronger conclusions on the association between sleep and epilepsy. It was also noted that results from informant-report measures are likely to be influenced by their own anxieties. However, the current meta-analysis demonstrates that regardless of whether informant reported or objective measures were used, there are clear and consistent differences between CWE and CWOE across sleep parameters.

Most included studies combined epilepsy types into one broad group e.g., generalised and focal epilepsy. This is particularly problematic given that ictal and interictal indicators of epilepsy vary with the sleep/wake cycle in a way which is specific to the type of epilepsy, e.g., focal epilepsies with secondary generalisation are more vulnerable to sleep disturbances compared to generalised epilepsies (Al-Biltagi, 2014), while interictal manifestations of focal epilepsies vary across the sleep-wake cycle (Bagshaw et al., 2009). In addition, the underlying neurobiological basis of some epilepsies may tie in closely with the brain networks involved in sleep generation and regulation, e.g., the suggestion that generalised spike-wave discharges make use of thalamocortical networks normally involved in the generation of sleep spindles (Leresche, Lambert, Errington & Crunelli, 2012). These and other issues concerning the relationship between epilepsy and sleep are discussed in detail in several reviews (Kotagal & Yardi, 2008; Frauscher & Gotman, 2019). Finally sleep disturbances appeared to be more pronounced in those with drug resistant epilepsy, as supported by previous research (Pereira,

et al., 2012a). This is to be expected given the use of multiple AEDs and experience of recurrent uncontrollable seizures, all of which contribute to disruptions to sleep (Manokaran & Gulati, 2018). However, the relative contribution of AEDs and recurrent seizures to sleep habits is difficult to disentangle. Furthermore, the lack of reporting on seizure control using standardised measures meant we did not have the ability to investigate the influence of this factor. Future studies are needed which are focussed much more closely on individual epilepsy syndromes in terms of their relationship with sleep, with a specific need for investigation of paediatric epilepsies, given the importance of adequate sleep for brain development (Dahl, 2007).

Another important factor which has been briefly mentioned above is that across the majority of included studies, children were receiving AEDs. The majority of AEDs have been established to impact sleep architecture (Al-Biltagi, 2014; Gogou et al., 2015) and issues such as drowsiness are commonly experienced (Placidi et al., 2000). Despite reporting treatment use, many of the studies failed to subdivide participants by AED type, and hence it was not possible to investigate the impact of AEDs specifically. The fact that studies of rolandic epilepsy, which is generally not treated with AEDs, showed a similar tendency to the overall results, suggests that the effects we observed are not entirely the result of treatment. However, future studies should detail the type and dose of AEDs in order to allow specific investigation of their impact.

Studies were excluded involving co-morbid IDs, on the basis that they would affect interpretation of the results, making it too difficult to differentiate the effects of epilepsy from the effects of an ID, which are known to impact sleep (Surtees et al., 2018). This ultimately led to the exclusion of studies focussed on the more severe epilepsies e.g., epileptic encephalopathies, which are typically associated with serious cognitive and

neuropsychological deficits. However, in practice this would suggest that the clinical importance of sleep disturbances across the full range of epilepsies would be expected to be higher than estimated by our meta-analysis, with our results representing a lower bound. Nevertheless, previous research investigating sleep habits in children with ID where epilepsy is prevalent, such as Angelman syndrome and tuberous sclerosis complex, have demonstrated that the presence of epilepsy in ID can have a cumulative effect on sleep disturbances (Trickett, Heald, Oliver & Richards, 2018).

Finally, studies measuring sleep architecture used two different scoring systems for sleep: Rechtschaffen & Kales (1968) (R&K) and American Academy of Sleep Medicine (AASM) (Iber et al., 2007). Previous research has found significant differences between the two when measuring children's and adolescents' sleep, including differences in N1, N2 and REM (Novelli, Ferri & Bruni, 2010). Unfortunately, sensitivity analysis could not be conducted to assess the influence of scoring systems, as there were insufficient studies. This limitation does not affect the majority of the results, and indeed the effects seen in terms of sleep architecture were generally smaller than for other measures of sleep disturbance.

There are several methodological considerations that may aid with standardisation between studies in the future. The first is that within this meta-analysis, some sleep parameters were extracted from a broad range of measurements including both objective (e.g., actigraphy, PSG) and informant reported (e.g., sleep diaries, questionnaires) tools. Within the context of the statistical analysis within this study (see section 2.7), the overall conclusions did not depend on the details of these instruments. Due to the limited number of papers in this area, it was concluded that including as wide a range of studies as possible and analysing the impact of their heterogeneity statistically was the most favourable approach. However, more broadly,

comparing sleep parameters derived from different methodological approaches is not ideal, and points towards the need for more widespread adoption of some standard and widely tolerated tools such as actigraphy and questionnaires within future studies of this type.

In the analyses for sleep problems, the majority of the data were derived from informant report measures. Parents of children with chronic diseases such as epilepsy have heightened parental anxiety and stress, and reports may be influenced by parents' own perceptions and result in overestimation of problem (Baca et al., 2010). Similarly, parents are less involved in their child's bedtime routines as they grow older, so may be less aware of their sleep patterns, especially in adolescence (Short, Gradisar, Lack, Wright & Chatburn, 2013). Another problem that arises with informant report measures, which has been previously discussed, is the difficulty faced when distinguishing nocturnal seizures from NREM parasomnias. In order to resolve this issue, it is recommended that studies do not rely heavily on questionnaire measures in such cases, but rather consider videos or preferably video-EEG. Future research should also aim to use informant reported measures in younger children and self-reports in older groups or preferably use objective measures such as actigraphy to provide a more accurate measure of habitual sleep patterns. It has been previously found that actigraphy is well tolerated, even in children with severe ID (Trickett et al., 2019).

In the analysis of sleep architecture, one study (Pereira et al., 2012a) measured percentage of sleep stages in reference to sleep period time (SPT) whereas the remaining studies used TST. Interestingly, this study was detected as an outlier in sensitivity analysis and when removed, revealed a significant result for percentage of N2. This suggests that the non-significant result was driven by differences in sleep scoring rather than differences in sleep architecture. Other studies were not able to be included in the analysis of some sleep stages due to studies

combining stages, which made it difficult to compare them. It is recommended that future studies explicitly state what scoring parameters were used for sleep variables and to report sleep stages individually, rather than collating them together e.g., N1+N2. Finally, future studies should specify the type of epilepsy and seizures, and when possible, the epilepsy syndromes, aetiology, disease severity and AED use, given the potential influence of these factors in CWE. Introducing such modifications to future studies would result in easier comparison of studies and allow for richer data to be meta-analysed.

Another limitation that must be considered is that the analysis of sleep architecture was combined across studies which included an adaptation night (N=3) and others without an adaptation night (N=6). Prior research has highlighted that as PSG typically utilises one night of sleep, this may lead to a first night effect where recorded sleep may not be reflective of natural sleep patterns (see section 1.5.1). As data could not be analysed separately, this may affect the accuracy of the sleep parameters measured. This is supported by a previous meta-analysis (Ding, Chen, Dai & Li, 2022) which demonstrated that across the lifespan, sleep parameters including TST, SE, REM and N1 were significantly affected by the first night effect. However no significant effect of the first night was observed across both N2 and N3. These findings suggest that future research should consider the role of the first night effect when combining sleep architecture data across nights.

This meta-analysis found that CWE suffer from widespread objective and informant reported sleep disruptions in comparison to CWOE. Improving the specificity of this finding requires future studies which investigate individual epilepsy syndromes, with standardised subjective and objective sleep markers, and clear reporting of AEDs. At the present time, habitual sleep patterns are not consistently evaluated by specialists in the routine care or diagnosis for CWE,

which is likely to be attributed to the complexity of the disease and the primary goal of treating seizures. However, epilepsy is a chronic and unpredictable disease, and the association with sleep disruptions only further negatively impacts the HRQOL in the child and family, which needs to be assessed. The present results indicate the potential benefit for childhood epileptologist to consider the importance of sleep in epilepsy management. Furthermore, future research should aim to develop behavioural interventions to tackle sleep difficulties early on in childhood epilepsy to reduce the detrimental impacts the disease and additional co-morbidities may have on developmental outcomes.

CHAPTER THREE

METHODS AND MEASURES

3.1. Preface

The previous Chapter performed a systematic review and meta-analysis quantifying the type of sleep difficulties which exist in CWE, whilst highlighting areas for future research which are addressed throughout this thesis. As highlighted in Chapter 1 there is a high prevalence of neurodevelopmental characteristics in CWE (see section 1.7). In addition, these characteristics also contribute to poor sleep and HRQOL in CWOE thus need to be considered when assessing the relationship between sleep and HRQOL (see section 1.8). Finally, in order to provide a coherent representation of HRQOL, the impact of parental sleep and mental health are also considered (see section 1.11.5). Therefore, this Chapter aims to outline the general methodology to conduct more detailed phenotyping of sleep profiles in CWE using both, informant report measures and actigraphy to extend the findings of Chapter 2. The methods used to measure epilepsy specific variables, neurodevelopmental characteristics and parental variables linking specifically with HRQOL will also be outlined. The specific methodology, analyses and results are outlined in the individual Chapters.

3.2. Study Design

The current study adopted a cross sectional design with the aim to assess how sleep impacts HRQOL, and the contribution of neurodevelopmental characteristics and epilepsy specific variables in this relationship (See Figure 3.1). In Chapter 4 (Study 1) the association between informant reported sleep and HRQOL was assessed. Chapter 5 (study 2) employed the same design using actigraphy assessed sleep, which offered the scope to examine the extent to which the type of sleep measure impacts this relationship. Furthermore, HRQOL cannot be fully explained by child variables only, suggesting other variables may be implicated. Therefore, in Chapter 6 (study 3), the contribution of parental variables vs child variables in HRQOL was explored with the aim to elucidate potential pathways in understanding HRQOL in CWE.

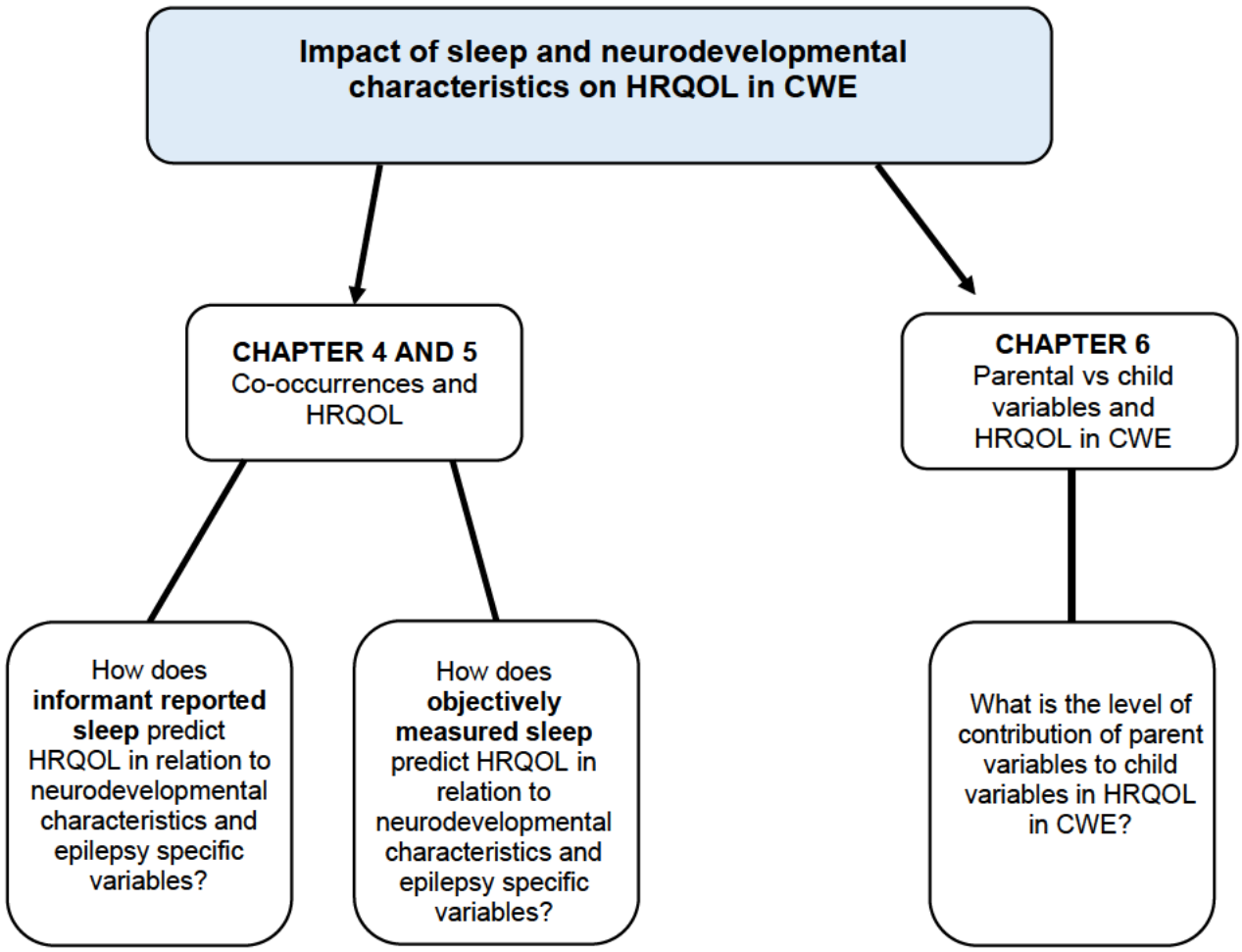


Figure 3.1. Flowchart of overall study design

3.3. Participants

3.3.1. Eligibility Criteria

Children attending the neurophysiology departments for a routine nap video-electroencephalography (V-EEG) appointment at either of two hospitals (Birmingham Children's Hospital and Worcestershire Royal Hospital), were recruited from September 2019 to May 2021. Due to the design of the recruitment routes, the following inclusion criteria were applied at the time of recruitment: (1) Children aged between 4 and 16 years old and (2) Parents had sufficient level of spoken English to ensure that the study instructions could be understood. Upon completion of the study and once the nap V-EEG were reviewed by a consultant neurologist, a diagnosis could then be sought via the National Health Service (NHS) neurophysiology database. At this point of recruitment, the following inclusion criteria were applied: (3) Diagnosis of epilepsy and (4) absence of a co-occurring ID (ID is recognised to be associated with increased risk of sleep disturbances which may have confounded the findings if included). See Figure 3.2 for participant recruitment flow chart.

3.3.2. Recruitment Process

3.3.2.1. Recruitment of control group

The study described in Chapter 5 included a group of CWOE for comparison of actigraphy defined sleep parameters to CWE. Data for these participants was collected from an existing participant database for families of children who had previously taken part in the 'Exploring Sleep in Neurodevelopmental disorders through Online and Remote evaluations' study by the Cerebra Network for Neurodevelopmental Disorders (CNND). Within this study, children aged 4-15 years old with no medical conditions were recruited through social media. Following expression of interest, they were administered an information sheet and consent form. Once

consented, families were provided with an Actiwatch, which their child were required to wear across a 10 day period.

3.3.2.2. Recruitment of children with epilepsy

Prior to the COVID-19 pandemic, there were two recruitment routes: prospective and retrospective, which children were recruited to between September 2019 and March 2020.

- **Prospective route:** Eligible participants aged between 4 and 16 years of age were screened against the NHS database for nap V-EEG appointments in the upcoming weeks. A prospective information pack was then mailed out and they were approached at their clinic appointment to discuss the study in further detail.
- **Retrospective route:** Eligible participants with a diagnosis of rolandic epilepsy aged between 4 and 16 years of age were screened against the NHS database for nap V-EEG appointments in the previous 18-24 months. Participants were mailed a retrospective information pack.

Recruitment was paused between April 2020 and July 2020 due to the COVID-19 pandemic. Following this, a remote recruitment method was adopted between August 2020 until May 2021.

- **Remote recruitment route:** Eligible participants aged between 4 and 16 years of age were screened against the NHS database for upcoming nap V-EEG appointments. Participants were mailed an information pack.

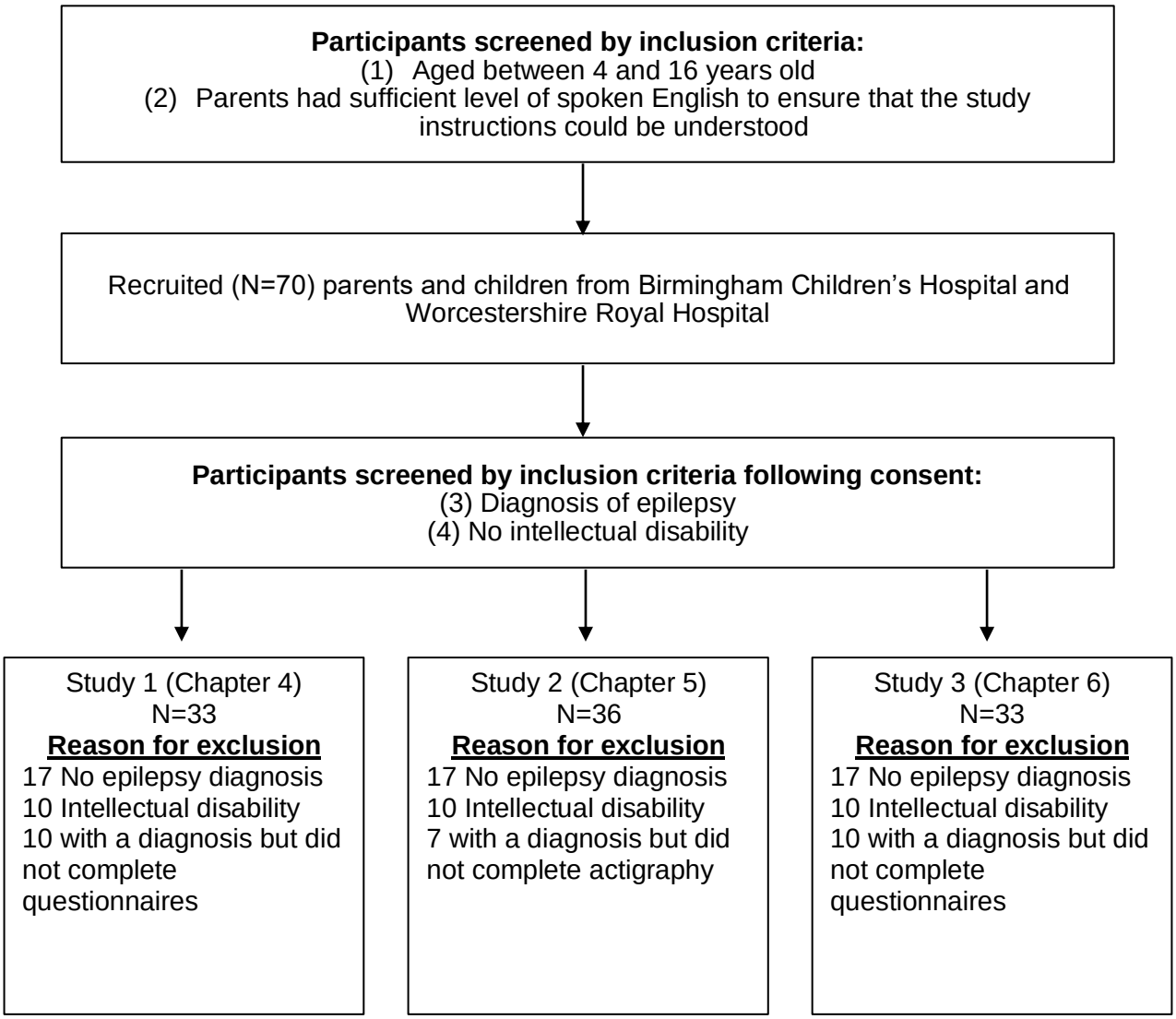


Figure 3.2. Flowchart detailing participant recruitment across each study

Table 3.1. *Sample characteristics of CWE (N=36). Values are shown as mean (SD)*

	Focal (N=17)	**Generalised (N=10)**	**Rolandic (N=9)**	**F/χ^2**	***DF***	***p* value***	**Effect size**	**Post Hoc Analyses**
Demographics				0.07	2	0.94	0.01	
Age, Year (SD)	9.41(2.67)	9.40(3.57)	9.67(1.22)					
Age Range, Year	5-14	4-14	8-12					
Sex				2.56	2	0.28	0.01	
Male	12	4	6					
Female	5	6	3					
Number of AEDs				10.83	2	**0.004***	0.31	F,G>RE
0	2	1	6					
1	8	7	3					
2	7	2	0					
Type of AED								
Levetiracetam	4	5	1					
Carbamazepine	8	1	1					
Lamotrigine	2	3	1					
Topiramate	2							
Sodium valproate	3	2						
Clobazam	2							
Ethosuximide	1							

*p<.05, Adjusted p=0.02 applied. Differences which remained significant following Bonferroni correction are denoted in bold.

Table 3.2. *Sample characteristics of CWE and TD control group from the CNND database. Values are shown as mean (SD)*

	CWE (N=36)	**Control (N=14)**	**F/χ^2**	***DF***	***p* value***	**Effect size**
Demographics			1.85	1	0.18	0.04
Age, Year (SD)	9.47(2.62)	8.29(3.12)				
Age Range, Year	4-14	4-15				
Sex			2.57	1	0.11	0.05
Male	12	5				
Female	5	9				

*$p<.05$, Adjusted $p=0.03$ applied. Differences which remained significant following Bonferroni correction are denoted in bold.

3.4. Procedure

Across all recruitment routes, eligible families were initially mailed a study information and consent pack, enabling permission to contact the researcher about participation in the study (see appendix 3.1). If families expressed an interest in the study, they were given the opportunity to ask questions and made aware that participation within the study was voluntary and that it would not affect the standard of care received. If no contact was made two weeks after receiving the pack, the researcher contacted families by telephone to establish whether they were interested in taking part in the study.

In the prospective route, the information and consent pack would usually be received one to two weeks prior to their clinic appointment. If no contact was made before this time, the researcher then met with eligible families at the appointment to discuss the study. If families had mailed back their consent form prior to their appointment, they were provided with a questionnaire pack, sleep diary and actiwatch for the study weeks (see section 3.5.). If no consent form had been received yet, they were asked to complete a consent pack in their appointment if they were interested. In the retrospective and remote recruitment routes, similar material was mailed out following receipt of the consent pack.

All parents were provided with separate prepaid envelopes to return the completed questionnaires, study materials and consent pack. Following consent to take part within the study, clinical information on medication, diagnosis and co-occurrences were taken from the child's clinical records on the NHS database. After the two-week study period, parents were notified of the study completion and a feedback report summarising the questionnaire and actigraphy data were posted out to families. See Figure 3.3 for a visual description of the overall study procedure for recruiting CWE.

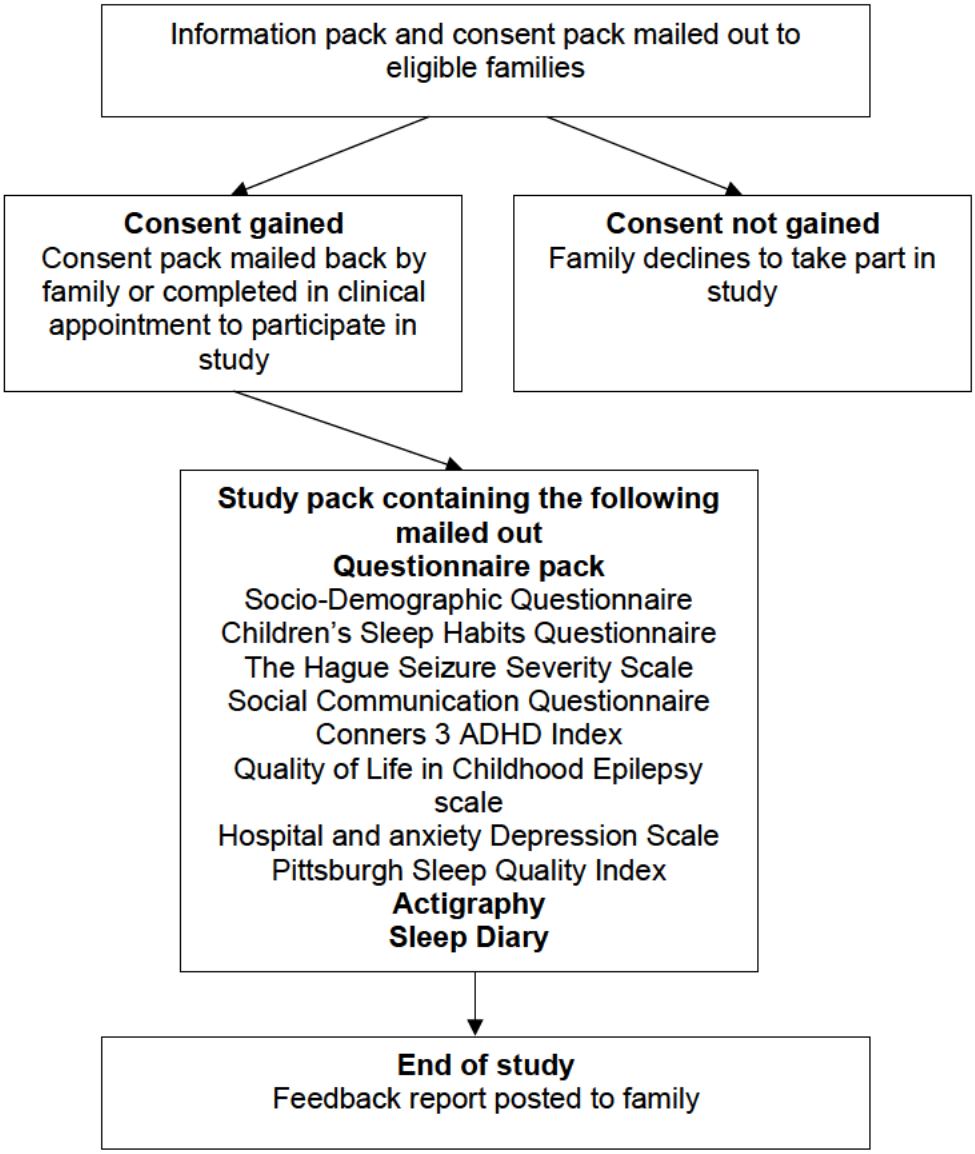


Figure 3.3. Flowchart of general procedure for recruiting CWE.

3.5. Measures

Following consent to take part in the study, families were provided with the following informant report measures and an actiwatch to be worn by the child.

3.5.1. Clinical data

Participants' clinic records were reviewed for epilepsy diagnosis, age, AEDs, and socio-demographic information.

3.5.2. Background Questionnaire

A background questionnaire was used to gain information on participants age, sex, epilepsy diagnosis, medication, and other diagnoses. Additional information regarding school and family was also gathered (see Appendix 3.2.)

3.5.3. Epilepsy specific variables

3.5.3.1 Hague Seizure Severity Scale (HASS)

The HASS (Carpay et al., 1997) is a 13-item informant report questionnaire which quantifies a child's seizure behaviour during the pre- and post-ictal state and is used as an index for severity of seizures in the past three months (see appendix 3.3). The items are rated along a 4-point scale (or 5 in the case of two questions) from the least severe to most severity rating. Scores range from 13 (low severity) to 54 (high severity). The questionnaire is based on the Liverpool severity scale (Baker, Smith, Jacoby, Hayes & Chadwick, 1998), but was modified to allow informant report specific to childhood epilepsy. Use of the questionnaire in children has demonstrated both high internal consistency (Cronbach alpha 0.85) and high-test retest reliability (r = 0.93) (Carpay et al., 1997).

3.5.4. Child sleep

3.5.4.1 Children's Sleep Habits Questionnaire (CHSQ)

The CHSQ (Owens et al., 2000b), is a retrospective informant report questionnaire designed to assess sleep habits in school aged children (see Appendix 3.4). The CSHQ consists of 45 items:

33 items are scored, and 7 items provide additional information on sleep. Parents were required to detail sleep patterns which occurred over the past week. These were scored on a 3-point scale: "usually" (occurs 5-7 times per week), "sometimes" (occurs 2-4 times per week) and "rarely" (occurs 0-1 time per week). Higher scores are indicative of more severe sleep behaviours, and some items are reverse scored to indicate this. Item ratings are categorised into eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing and Daytime Sleepiness. The CSHQ subscales were collated to produce a total sleep disturbance score ranging from 33 to 99, where a score greater than 41 is recognised as a clinical threshold for significant sleep disturbance. The CSHQ has demonstrated acceptable internal consistency (Cronbach α= 0.68) and test-reliability (0.62), when used as a screening tool for sleep problems in a normative sample. Sensitivity and specificity of the threshold score for delineating between children with and without a significant sleep disturbance was demonstrated to be adequate (0.80 and 0.72, respectively) (Owens et al., 2000b).

3.5.4.2 Actigraphy

Habitual sleep patterns were measured using an actiwatch (Actiwatch2, Phillips Respironics Inc) for a period of 14 consecutive nights for CWE and 10 nights for CWOE (see section 5.3.1 for detailed description of participants). This is a non-invasive wearable device, which measures body movements to provide information on sleep-wake patterns. It uses an accelerometer to detect movements and translate these into activity counts. The built-in algorithm in the watch transforms this activity data into epochs that represent sleep and wake periods. A 30 second period was selected for epoch count and sleep parameters were automatically detected using the Actiware software (Version 6.0.7) using the default wake threshold of medium sensitivity. This was specified using 40 activity counts per each epoch as sleep, and anything above this value was coded as wake. Concordance of this Actiwatch model

to PSG has been previously studied. It is shown to have a good agreement for TST and SE, and the medium threshold setting showed a sensitivity score of 0.94 in detecting sleep and accuracy score of 0.92 in children ages 3 to 18 years old (Meltzer et al., 2012b). Parents were asked to press the button (event marker) on the side of the watch to indicate when the child got into bed and when they woke up. In conjunction with this, they were also asked to complete a sleep diary (see section 3.5.4.3.) to aid in interpretation of the actigraphy data.

Data was cleaned in the Actiware software (Version 6.0.7) using a protocol devised by Trickett et al. (2017) (see Appendix 3.5) to remove any artefacts, which have been recognised to affect the reliability of actigraphy (Sadeh, 2011). In this cleaning process, data from the actigraph were compared to completed sleep diaries, automatically calculated sleep interval and the event marker timings to corroborate sleep and wake times. Sleep or wake times were adjusted based on the activity count threshold described above when there was mismatch between the timings. Similarly sleep intervals would be extended or restricted if the software automatically scored sleep amount incorrectly. Artefacts including periods of time where the watch was taken off, periods of inactivity, and naps were also removed. Data was then transferred to an excel spreadsheet, where the mean and intraindividual variability (IIV) of following parameters were studied within this thesis:

1. Total sleep time (TST): Proportion of time spent asleep within a 24-hour period as recorded by the Actiwatch.
2. Sleep onset latency (SOL): The amount of time taken to fall asleep from bedtime.
3. Sleep efficiency (SE): Proportion of time actually spent asleep whilst in bed.
4. Wake after sleep onset (WASO): The total number of minutes spent awake between sleep onset time and get up time.

These parameters were chosen as are commonly assessed in research utilising actigraphy. Furthermore, given the limited evidence based on actigraphy in CWE, parameters which had been assessed by the only previous study comparing actigraphy based sleep parameters in CWE vs CWOE (Holley et al., 2014) were used to enable cross comparison.

In order to calculate the mean of the above sleep parameters, data for each parameter was averaged across the number of nights. In addition, to assess the IIV of the sleep parameters, for each child, the standard deviation of each parameter was extracted and divided by the mean of the parameter, this was then averaged over the number of nights. Alongside the data cleaning process outlined above, other factors which can impact the robustness of the results were considered during statistical analysis including the impact of weekday vs weekends, school time vs non-school time and pre vs post COVID (see section 5.4.2).

3.5.4.3 Sleep diary

Parents were asked to complete a sleep diary (see Appendix 3.6). This enabled information to be collected on informant reported bedtime, sleep onset time, wake time, times actiwatch taken off, sleep quality and perceived stresses at night. These data were used for the purpose of cleaning artefacts and to aid in interpretation of the actigraphy data.

3.5.5. Autistic characteristics

3.5.5.1 Social Communication Questionnaire (SCQ)

SCQ (Rutter, Bailey & Lord, 2003) is a questionnaire developed using the revised Autism Diagnostic Interview (Lord, Rutter, & Le Couteur, 1994) to screen for autistic characteristics over the previous three months. The questionnaire consists of 40 items which parents answer with a ‘yes’ or ‘no’, corresponding to the presence or absence of a particular behaviour. Higher

scores are indicative of more severe ASD symptomology. The scores are split into three domains: reciprocal social interaction; communication; and restrictive, repetitive, and stereotyped patterns of behaviour. A total score of 15 is to distinguish between autism and no autism symptoms, indicating that the child requires further screening. The higher threshold of 22 provides stronger evidence for an autism diagnosis (Snow, 2013). The predictive value of the SCQ in determining autism diagnosis is indicated as good (AUC=.95, Hanley & McNeil, 1982).

3.5.6. ADHD characteristics

3.5.6.1. Conners 3 ADHD Index (Conners 3AI)

Conners 3AI (Conners, 2008) is a screening measure for ADHD symptoms, which forms part of the wider Conners rating scale 3rd edition (Conners, 2008). The questionnaire consists of 10 items derived from the DSM-5 criteria (APA, 2013) and scored across a four-point scale as (0) not true at all, (1) just a little true, (2) pretty much true, (3) very much true, referring to the frequency of behaviours in the past month. The total raw score and T-score was calculated for the ADHD sum index, where higher index scores indicate higher severity of ADHD characteristics. A T score of $\geq$65 is indicative of scores similar to children with ADHD (Conners, 2008). The measure has demonstrated high internal reliability scores with both parent and teacher versions of this form (Morales-Hidalgo, Hernández-Martínez, Vera, Voltas & Canals, 2017).

3.5.7. Health related Quality of Life

3.5.7.1 Quality of Life in Childhood Epilepsy scale (QOLCE-55)

QOLCE-55 (Goodwin, Lambrinos, Ferro, Sabaz & Speechley, 2015) is a gold standard informant report epilepsy-specific measure consisting of four domains: physical functioning (9

items), cognition functioning (22 items), social functioning (7 items) and emotional functioning (17 items) (see appendix 3.7). The measure consists of 76 items that are rated along a five-point scale based on behaviours in the past 4 weeks, ranging from (0) very often, (1) fairly often, (2) sometimes, (3) almost never, and (4) never. The total score is the mean of the four domains from 0 to 100, where higher scores are indicative of better HRQOL. Reliability (α=0.92) was rated as good and validity was moderate to strong compared to similar measures (Goodwin et al., 2015)

3.5.8. Parental Mental Health

3.5.8.1 Hospital Anxiety and Depression Scale (HAD scale)

Parental mental health was measured using the HAD scale (Zigmond & Snaith, 1983). This is a self-report measure which consists of two subscales for anxiety (HADS-A) and depression (HADS-D) (see Appendix 3.8). Questions are scored on a scale ranging from 0 to 3 to produce a total score between 1 and 21. A score between 0 and 7 corresponds to "normal" symptoms, a score between 8 and 10 suggest the scores fall in the "borderline' range and scores of 11 and over correspond to clinically significant range (Snaith, 2003). The psychometric properties of the HAD scale including the reliability and correlation between variables are recognised as good (Mykletun, Stordal & Dahl, 2001).

3.5.9. Parental Sleep

3.5.9.1 Pittsburgh Sleep Quality Index (PSQI)

Parental sleep was measured using the PSQI (Buysse, Reynolds, Monk, Berman & Kupfer, 1989) which is widely used clinically (see Appendix 3.9). The self-report measure assesses sleep disturbance across seven components including subjective sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime

sleepiness. The sum of the seven components produces a global PSQI score ranging from 0 to 21, where a cut off score of 5 or more indicates poor sleep quality. The validity and reliability of the measure are recognised as adequate (Buysse et al., 1989).

3.6. Ethical Approval

Health research authority (HRA) and NHS ethical approval was obtained from the Northwest – Preston Research Ethics Committee (REC reference 19/NW/0337) for the study research protocol in July 2019 (see Appendix 3.10). Research and developmental approval were also gained for the participating hospitals to enable recruitment of participants (R&D no: 19/BC/DTS/PO/247).

3.7. General statistical analysis

The specific statistical analyses employed are detailed in the methods section of each Chapter. All statistical analyses were carried out using R, version 3.6.0, and R studio (Version 1.4.1717), using the "stats" and "psych" packages. Packages for more specific analyses are outlined within each Chapter. All data were initially assessed for normality using Shapiro Wilk test, where data was not normally distributed ($p<.05$) a non-parametric test was used. Where appropriate descriptive statistics are also presented for subscale or total scores.

3.7.1. Between group Analyses

To investigate differences between groups, statistical tests were performed based on normality tests. In addition, homogeneity of variance was tested where appropriate using Levene's test, where $p<.05$ indicates that the assumption of equal variance is not met. For comparison between two groups (CWE vs CWOE) either an independent sample t-test (parametric) or Mann-Whitney U test (non-parametric) was conducted. For comparison between three groups (Focal vs Generalised vs Rolandic) a one-way analysis of variance (ANOVA) (parametric) or

Kruskal Wallis χ^2 Test (non-parametric) was conducted. Effect sizes were reported for between group comparisons due to the small sample size (Tomczak & Tomczak, 2014). Guidelines for interpreting these effect sizes are outlined in the specific methods of each Chapter.

3.7.2. Correlational Analyses

When assessing for associations between variables, data were initially checked for normality. If data met the assumptions of normality, Pearson correlation tests were conducted. If data did not meet the assumptions for normality, Spearman rho correlation test were conducted.

3.7.3. Regression Analyses

To investigate the contribution of predictor variables on HRQOL, separate hierarchical linear regressions were conducted. In the case of categorical variables, these were converted to dummy variable for use within the regression. Prior to running the regression analyses, the appropriate assumptions of multicollinearity, autocorrelations and linearity were assessed (Barbara, Tabachnick & Fidell, 2001). A variance inflation factor (VIF) value of higher than 10 or a tolerance with a value lower than 0.10 indicates multicollinearity (Myers & Myers, 1990). The Durbin Watson test was used to measure autocorrelation where values between 1.5 and 2.5 are deemed acceptable. As these statical assumptions were satisfied, the hierarchical linear regressions were appropriate to run (see Appendix 3.11).

3.7.4. Multiple comparison corrections

Statistical significance level was set at $p<0.05$ for tests. In cases where multiple comparisons were conducted, Bonferroni corrections were applied to correct for this. As the regression analyses were conducted for exploratory purposes, these were not corrected due to the

conservative nature (Perneger, 1998). Both unadjusted and adjusted p-values (denoted by bold) are reported for completeness.

3.7.5. Missing data

For Chapters 4-6, data were initially reviewed for missing values prior to running analyses. For dealing with missing data across participants, data for measures where 20% or less of the items were missing across the measure were pro-rated via averaging the remaining items. Questionnaires where more than 20% of data missing were excluded from the analysis.

CHAPTER FOUR

THE CONTRIBUTION OF SLEEP AND CO-OCCURRING CHARACTERISTICS TO QUALITY OF LIFE IN CHILDREN WITH EPILEPSY

4.1. Preface

In Chapter 2, a systematic review and meta-analysis identified that CWE experienced more frequent and severe sleep disruptions across both informant reports and objective measures of sleep. Various limitations were discussed and proposals for future research were put forward, some aspects of which will be addressed within this Chapter. These include (1) to examine the impact of sleep difficulties on HRQOL and (2) to understand the differences in sleep across epilepsy types. Furthermore, as discussed in Chapter 1, sleep difficulties are also related to autistic and/or ADHD characteristics, which are commonly co-occurring in CWE. Consequently, when examining the impact of sleep on HRQOL, it is important to delineate the impact of neurodevelopmental co-occurrences on HRQOL. Finally, Chapter 3 outlined various assessments for these parameters, including objective vs informant report measures of sleep. To address aim 1.16.2. within this thesis, this Chapter will examine the contribution of neurodevelopmental characteristics and epilepsy specific factors to the relationship between informant reported sleep and HRQOL in CWE.

4.2. Introduction

HRQOL is recognised to be poorly affected in CWE (Conde-Guzón et al., 2020; Nadkarni et al., 2011; Cianchetti et al., 2015). Several epilepsy specific variables have been found to negatively impact HRQOL including epilepsy severity, seizure frequency, longer disease duration and poor treatment adherence (Kaenkrai, Pattoomwan, Wongvatunyu & Lusawat, 2021; Nagabushana, Praveen-Kumar & Agadi, 2019; Liu & Han, 2015; Aggarwal et al., 2011). However, epilepsy is not only defined by epilepsy specific variables such as seizures and AEDs, but also by co-occurrences, which were included in the epilepsy classification system (see Figure 1.1). A previous study indicated that co-occurring problems including neurological difficulties i.e learning difficulties, were stronger predictors of HRQOL than seizure severity and epilepsy duration (Miller et al., 2003). These findings were reflected in a self-report study which showed that HRQOL in CWE was significantly associated with psychological health and peer support (Fayed et al., 2015) but not seizures. Moreover, evidence indicates that not only are co-occurrences stronger predictors of HRQOL than epilepsy specific variables, but their effects last even after seizures have remitted (Baca et al., 2011). This accumulating evidence indicates that the traditional approach to epilepsy management of treating seizures is necessary, but likely not sufficient to achieve optimal HRQOL in CWE (Wood, 2012).

Across previous literature, there is a consistent focus on epilepsy-specific variables such as seizures or side effects of AEDs, as determinants of HRQOL, which ultimately shifts the focus away from co-occurrences. As outlined in Chapter 1, co-occurrences are common in CWE and can include sleep disturbances and neurodevelopmental conditions such as autism or ADHD (see Section 1.7-1.8). When left unaddressed, such co-occurrences have the potential to further complicate epilepsy diagnosis and negatively impact HRQOL.

The first co-occurrence of focus is sleep disturbances. As outlined in Chapter 2, CWE are vulnerable to both objective and informant-reported sleep difficulties (Winsor et al., 2021). Previous studies suggest that sleep problems can negatively impact overall HRQOL due to daytime sleepiness, contributing to impairments in academic attainment, overall health, and interactions with peers (Ekinci et al., 2016). Similarly, poor sleep may impact children's ability to cope with the side effects of medication and the impact of epilepsy on HRQOL (Shaki et al., 2011). Traditionally, optimal and good quality sleep has been continually recognised as an important predictor for HRQOL in adults with epilepsy (Alanis-Guevara et al., 2005; Piperidou et al., 2008; Gutter et al., 2019). In contrast, far less attention has been paid to the direct predictive value of disrupted sleep on HRQOL in CWE. Only two studies have directly assessed this association (Wirrell et al., 2005; Gutter et al., 2013). These studies found that CWE not only had more severe sleep problems but that these problems were associated with poorer HRQOL and more behavioural problems. However, both studies were limited by sample constraints including epilepsy type and use of a sibling control group, affecting the generalisability of these findings (see section 1.11.3). Therefore, the current study provides the opportunity to extend the understanding of sleep problems on HRQOL in CWE.

It is also important to note that sleep problems in CWE frequently co-occur with neurodevelopmental conditions including autism (Cortesi et al., 2010; Stafstrom & Benke, 2015; Accardo & Malow, 2015) and ADHD (Cortese et al., 2009; Dunn, Austin, Harezlak & Ambrosius, 2003). Supporting evidence has found that CWE and co-occurring ADHD experience significantly more severe sleep problems compared to children with ADHD or epilepsy alone (Ekinci et al., 2016). Another study found that rates of sleep problems were higher in autistic children and those with ADHD compared to TD children and CWE. Surprisingly, CWE did not experience higher sleep problems compared to TD children (Tsai

et al., 2012). The authors suggested this finding was due to recruitment of CWE and no co-occurring neurodevelopmental conditions, indicating that neurodevelopmental characteristics heighten the risk of sleep problems in CWE. In summary, autistic characteristics and ADHD characteristics need to be isolated to better clarify the level of contribution of sleep problems to HRQOL in CWE.

A high prevalence of autistic characteristics in CWE can only further complicate epilepsy management due to additional care needs and ultimately contributes to poor HRQOL (Szemere & Jokeit, 2015). This is demonstrated by prior research, which reported that CWE and co-occurring autism showed more severe challenging behaviours and social difficulties compared to autistic children with no epilepsy (Turk et al., 2009). A similar study by Ko, Kim, Kim, Song and Cheon (2016) found that autistic CWE had more difficulties in responding to social cues and displays of appropriate social communication, than autistic children alone, indicating that co-occurrence of both conditions contributed to worse outcomes. Despite this evidence, no studies have investigated the contribution of autistic characteristics to HRQOL in CWE. This research is necessary, as given HRQOL is emerging within clinical management as a core outcome, quantifying this impact will ultimately encourage clinical recognition.

Another neurodevelopmental condition, which is recognised to commonly co-occur in CWE is ADHD. As concluded in Chapter 1, few studies have explored the contribution of ADHD characteristics to HRQOL in CWE, highlighting the research gap. A study by Sherman et al. (2007) found that children with severe epilepsy types were at higher risk of an ADHD diagnosis and that this was significantly predictive of HRQOL. However, as most children were drawn from referrals to neuropsychological services, this study was affected by selection bias. As this sample is more likely to have heightened ADHD characteristics, thus it may not be fully

representative of all CWE. Nevertheless, these findings were supported by Ekinci et al. (2017). They found that CWE with co-occurring ADHD had poorer HRQOL compared to children with ADHD or epilepsy alone. In addition, children with ADHD alone had worse HRQOL than those with epilepsy alone. This study demonstrates the detrimental impact that ADHD characteristics can exert on HRQOL in CWE. A caveat of the aforementioned studies is that both used generic HRQOL measures as opposed to disease specific measures. Unfortunately, generic measures are unable to sensitively capture the impact of epilepsy (Wiebe, Guyatt, Weaver, Matijevic & Sidwell, 2003) compared to a disease specific measure. Therefore, the approach to measuring HRQOL within this study enhances the clinical and research utility of these findings.

Not only is the examination of the overall impact of co-occurrences in HRQOL important but given the heterogeneity of epilepsies, an understanding of how these present broadly across epilepsy types is also important. Most studies to date examining the co-occurrence of autism and epilepsy have considered autism in the context of ID (Berg & Plioplys, 2012). In addition, one study suggested that poorer outcomes in children with co-occurring epilepsy and autism was largely explained by additional ID (Viscidi et al., 2013). However, ID is typically present in more severe epilepsy syndromes, where risk of neurodevelopmental characteristics is high and the presentation is more obvious to clinicians (Lukmanji et al., 2019; Tuchman, 2017). This fails to include epilepsy types where ID is not present and further entrains the representativeness of the findings. Thus, exclusion of ID within this study allows the effect of ID to be disentangled from neurodevelopmental characteristics alone and ultimately maximising the understanding of the impact on HRQOL in CWE.

Another limitation of prior research is that studies typically adopt a categorical approach to measuring autism and ADHD. This is particularly relevant, as recent evidence from clinical services (Holmes, Sawer & Clark, 2021) suggest that autistic characteristics may present differently in CWE compared to CWOE, and thus may not fit the symptomology for a diagnosis. Furthermore, CWE may demonstrate autistic characteristics which do not reach the threshold for a diagnosis, yet these difficulties can continue to leave CWE at risk of poor outcomes (Holmes et al., 2021). Therefore, more studies which adopt a dimensional approach are needed to encourage interventions based on inclusion of characteristics rather than diagnosis.

The literature above highlights the role of co-occurring conditions such as autistic characteristics, ADHD characteristics and sleep problems in HRQOL in CWE. Chapter 2 identified a broad range of sleep problems in CWE and put forward several recommendations, aspects of which will be addressed within this Chapter. Alongside these recommendations, the rationale for the present study is also to extend the current evidence base regarding the contribution of sleep problems on HRQOL. Given the close relationship of neurodevelopmental characteristics with sleep and epilepsy, it is important to consider how much of the variance in HRQOL are explained by neurodevelopmental characteristics compared to sleep problems.

4.2.1. Study Aims

The specific aims of the current study are:

1. To compare profiles of HRQOL and co-occurrences including sleep, autistic characteristics, and ADHD characteristics in children across three groups of epilepsies: (1) Focal epilepsy (2) Generalised epilepsy and (3) Rolandic epilepsy.

2. To investigate whether sleep problems predict HRQOL above or beyond other co-occurrences including autistic characteristics, ADHD characteristics, or epilepsy specific variables.

4.3. Methods

The methods specific to this Chapter are outlined below. For detailed descriptions of the methods common to other Chapters, please refer to Chapter 3.

4.3.1. Participants

From an initial sample of 70 participants, 17 children were excluded as they did not receive an epilepsy diagnosis, ten due to the presence of an ID and ten who did not complete the measures to be included in the analysis. The final sample consisted of 33 CWE (M=9.72, SD=2.50, range=4-14 years). Table 4.1. describes the sample characteristics between each epilepsy type. Significant differences between the groups were found only for the number of AEDs.

Table 4.1. *Sample characteristics of children with epilepsy (N=33). Values are shown as mean (SD)*

	Focal (N=15)	Generalised (N=10)	Rolandic (N=8)	F/χ^2	*DF*	*p* value*	Effect size	Post Hoc Analyses
Demographics				0.09	2	0.92[a]	.001	
Age, Year (SD)	9.93(2.37)	9.40(3.57)	9.75(1.28)					
Sex				3.36	2	0.19[b]	0.01	
Male	12	4	6					
Female	5	6	3					
Number of AEDs				11.14	2	**0.004***[b]		F, G>RE
0	2	1	6					
1	8	7	3					
2	7	2	0					
Type of AED								
Levetiracetam	4	5						
Carbamazepine	7	1	1					
Lamotrigine	2	3	1					
Topiramate	2							
Sodium valproate	2	2						
Clobazam	2							
Ethosuximide	1							

*$p<.05$, Adjusted $p=0.02$ applied. Differences which remained significant following Bonferroni correction are denoted in bold.
p values were derived from one-way ANOVA[a] or Kruskal Wallis test[b]

4.3.2. Procedure

Parents were asked to complete a battery of questionnaires, see section 3.4 for a detailed description of the procedure. Due to partial or no completion of the questionnaires, one response was not recorded for the CSHQ, one for CONNERS, two for SCQ and one for QOLCE, thus sample sizes were different across analyses.

4.3.3. Measures

4.3.3.1 Clinical data

Participants' clinic records were reviewed for epilepsy diagnosis, type and number of AEDs and socio-demographic information including sex and age.

4.3.3.2 Epilepsy Specific variables

Parents completed the Hague Seizure Severity Scale (HASS, Carpay et al., 1997) which provided information on children's seizure severity.

4.3.3.3 Child Sleep

Parents completed the Children's Sleep Habits Questionnaire (CHSQ, Owens et al., 2000b) in order to assess children's sleep habits from the past week.

4.3.3.4 Autistic characteristics

In order to screen for autistic characteristics, parents completed the Social Communication Questionnaire (current) (SCQ; Rutter et al., 2003).

4.3.3.5 ADHD characteristics

To screen for ADHD characteristics, parents also completed the Conners 3 ADHD Index (Conners 3AI; Conners, 2008).

4.3.3.6. Health related quality of life

To assess for HRQOL, parents completed the Quality of Life in Childhood Epilepsy scale (QOLCE-55; Goodwin et al., 2015).

4.4.4. Statistical Analysis

Descriptive statistics were provided for the CSHQ subscales, which were compared to the normative data from Owens et al. (2000b) community sample. Boxplots were produced for total CSHQ, SCQ, Conners and HRQOL scores to visually represent the differences across three groups of epilepsies: (1) Generalised epilepsy, (2) Focal epilepsy and (3) Rolandic epilepsy. To test for these differences a one-way ANOVA (parametric) or Kruskal Wallis test (non-parametric) was performed, as appropriate. Across each analysis, an adjusted *p* value was computed via Bonferroni correction based on the number of comparisons.

Effect size for one way ANOVA and Kruskal Wallis tests were calculated using partial eta squared ($\eta^2_{p)}$ and epsilon squared (ε^2; Kelley, 1935) respectively. Both were interpreted using Cohen's guidelines; small= .01, medium=.06, large=.14 (Cohens, 1988).

Finally, separate hierarchical linear regression models were conducted to assess the contribution of epilepsy specific variables (seizure severity and number of AEDs) and neurodevelopmental characteristics to the relationship between sleep and HRQOL. As the

number of AEDs are defined as a categorical variable, this was dummy coded, where no medication was assigned as a reference category.

4.4.5. Control Analyses

As recruitment was conducted prior to and during the COVID-19 pandemic, considerations of how sleep may have been affected was important to examine. This is based on recent research, which has demonstrated the negative impact of the COVID-19 pandemic on sleep patterns in children (Lokhandwala et al., 2021; Sharma, Aggarwal, Madaan, Saini & Bhutani, 2021; Wearick-Silva, Richter, Viola, Nunes & COVID-19 Sleep Research Group, 2021).

To assess differences in sleep problems before and during the COVID-19 pandemic, independent sample t-tests (parametric) and Mann Whitney U test (non-parametric) were conducted. The effect size for the independent sample t test were calculated using Cohens *d* and interpreted based on Cohen (1988) guidelines; small=.20, medium=.50 and large=.80. Similarly effect sizes were calculated for Mann Whitney U tests using Cohens *r* and interpreted using the following cut offs; small=.10, medium=.30 and large =.50 (Cohens, 1988). There were no significant differences between groups across all these analyses, the results are presented in Appendix 4.1.

4.5. Results

To examine the first aim, CSHQ (sleep problems), SCQ (autistic characteristics), Conners (ADHD characteristics) and total QOLCE score (HRQOL) were compared across epilepsy types (see Figure 4.1).

4.5.1. Sleep Problems

All CSHQ subscale scores were higher in CWE compared to the scores of those in Owens et al. (2000b) community sample (see Table 4.2).The mean total CSHQ score was 48.00, this was highest in the focal group (M=49.07, SD=8.22) and lowest in rolandic epilepsy (M=46.75, SD=13.57). Scores in the generalised epilepsy group were M=47.50, SD=5.06. The Kruskal Wallis test demonstrated that these differences were not statistically significant (χ^2 (2) =0.88, p=0.64, ε^2=0.03, small effect size). Although differences were not significant, across all groups, 78.13% of participants scored above the clinical cutoff for a significant sleep disturbance.

Table 4.2. *Descriptive statistics for CSHQ subscales in CWE compared to CWOE. Values are shown as mean (SD)*

CSHQ subscales	CWE (n=33) Mean (SD)	Community sample[a] (n=469) Mean (SD)
Bedtime resistance	7.24(3.06)	7.06(1.89)
Sleep onset delay	1.52(0.83)	1.25(0.53)
Sleep anxiety	5.18(2.26)	4.89(1.49)
Sleep duration	4.48(1.94)	3.41(0.93)
Night waking	4.15(1.82)	3.51(0.89)
Parasomnias	9.48(2.91)	8.11(1.25)
Sleep disordered breathing	3.55(1.58)	3.24(0.63)
Daytime sleepiness	11.64(3.95)	9.64(2.80)

[a]Community sample data retrieved from Owens et al. (2000b)

4.5.2. Autistic Characteristics

The mean total score was 9.87 (SD=6.97). 25% of children achieved above the threshold for autism. There were no significant differences for autistic characteristics across all three groups

($\chi^2(2)$ =5.45, p=0.07, ε^2=0.18, large effect size), focal epilepsy (M=13.15, SD=7.72), generalised epilepsy (M=8.80, SD=5.41) and rolandic epilepsy (M=5.88, SD=5.36).

4.5.3. ADHD characteristics

The mean ADHD index score was 8.40 (SD=6.65) and 67% of children within the study achieved a T score of $\geq$65 indicating elevated scores above the threshold. ADHD characteristics were higher in the focal (M=9.93, SD=7.09) and generalised (M=9.10, SD=6.12) epilepsy groups compared to the rolandic epilepsy group (M=4.88, SD=5.92). The Kruskal Wallis test demonstrated that these differences were not statistically significant ($\chi^2(2)$=3.27, p=0.20, ε^2=0.11, medium effect size).

4.5.4. HRQOL

Descriptive statistics for HRQOL subscales were provided in Table 4.3. The overall total HRQOL score was 63.00 (SD=20.55) across all groups. This was highest in the rolandic epilepsy group (M=76.83, SD=13.09), lowest in the focal epilepsy group (M=56.50, SD=24.00), and intermediate for the generalised epilepsy group (M=61.04, SD=15.81). The one-way ANOVA demonstrated that these differences were not statistically significant (F(2,29) =2.86, p=0.07, η^2_p=0.17, large effect size).

Table 4.3. Descriptive statistics of QOLCE subscales. *Values are shown as mean (SD)*

	Cognitive	**Emotional**	**Social**	**Physical**	**Total**
QOLCE	56.84(28.86)	68.69(17.13)	76.24(27.71)	52.19(23.60)	63.00(20.55)

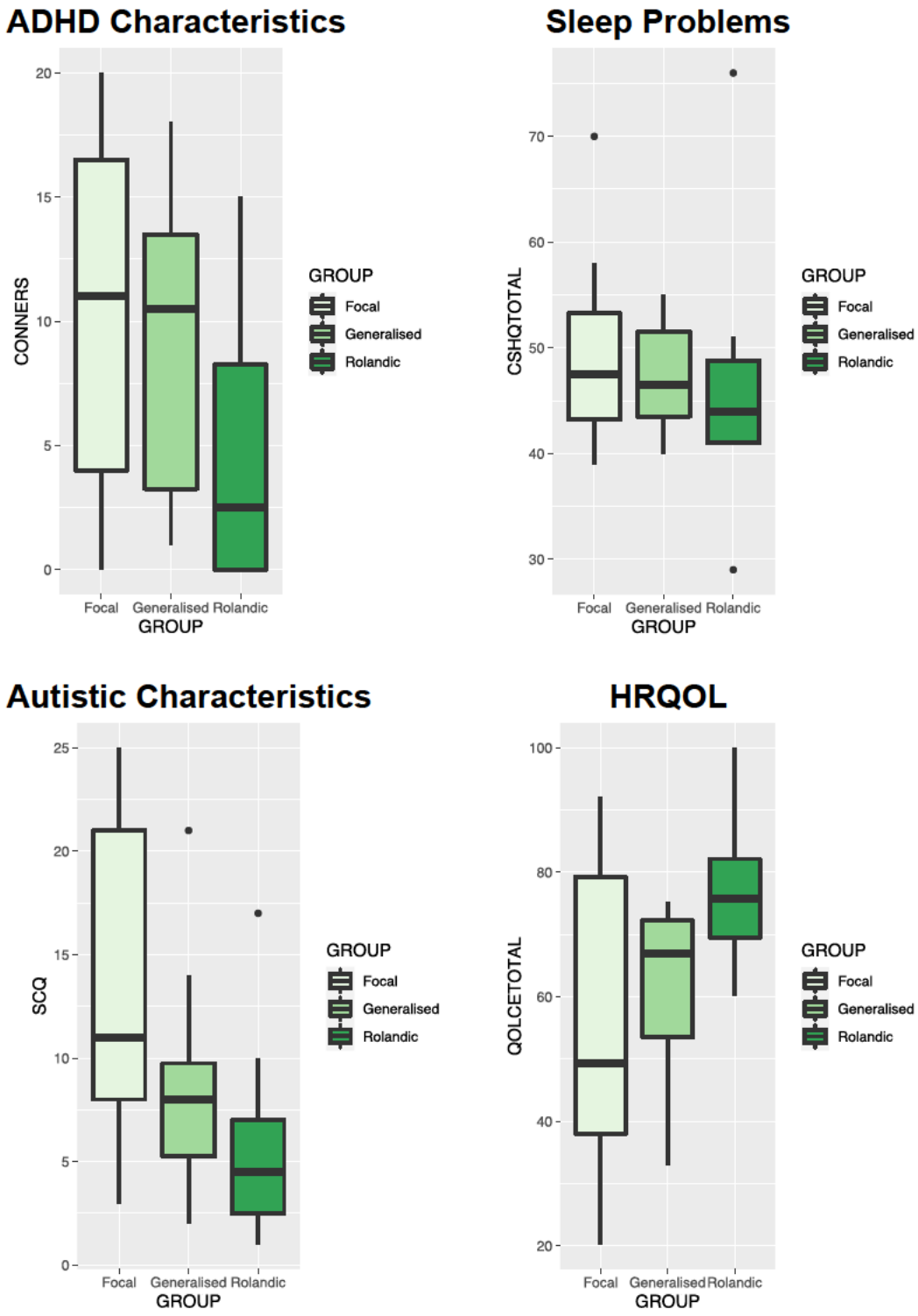


Figure 4.1. Box plots for total SCQ, Conners, CSHQ and QOLCE scores across the epilepsy types. Horizontal lines denote the median and interquartile range. Whiskers represent maximum and minimum points.

4.5.5 Contribution of co-occurring characteristics and epilepsy specific variables to the relationship between sleep problems and HRQOL

To examine the second aim, hierarchical linear regressions were used to compare the contribution of co-occurring characteristics and epilepsy specific variables in predicting the impact of sleep problems on child HRQOL. Age of child was entered into the first step and sleep problems in the second step, across all the regression models. In the third step, autistic characteristics (Table 4.4), ADHD characteristics (Table 4.5), seizure severity (Table 4.6) or number of AEDs (Table 4.7) were entered across the regression models. See Figure 4.2 for representation of regression models.

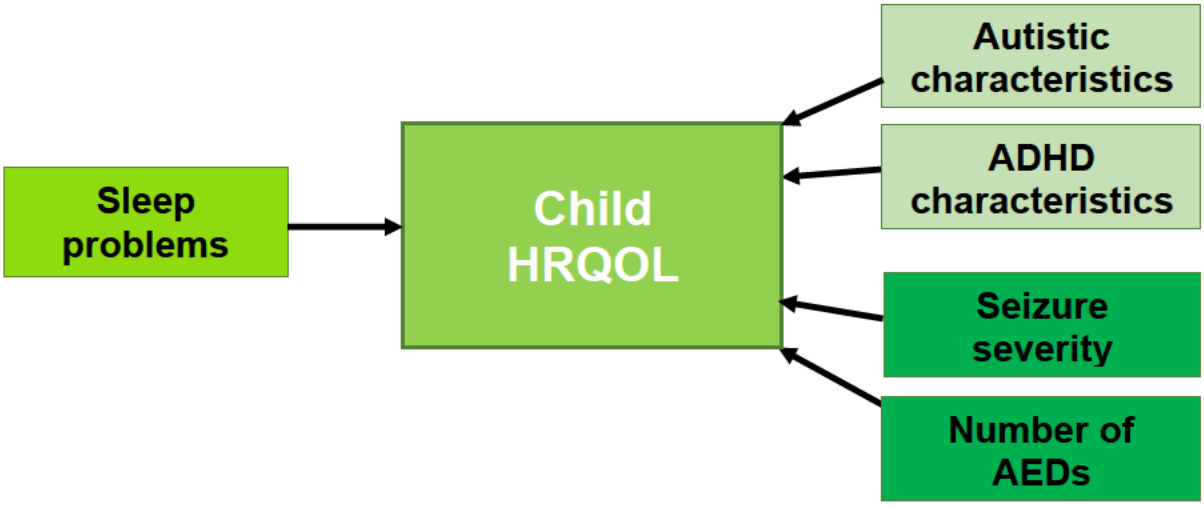


Figure 4.2. Schematic representation of hierarchical linear regression for aim 1.16.2.

4.5.5.1. Severity of sleep problems vs autistic characteristics in child HRQOL

In the first model when age of child was entered in the first step, it was found to account for 2.5% of the variance and the model was not significantly predictive of HRQOL F(1, 29) =.73, p=.40. When CSHQ score was added in step two, it was found to significantly improve the predicted variance in HRQOL (16.5%), F(1,28)=5.70, p=.02. Finally in the third step, the addition of autistic characteristics led to a significant improvement in the overall model, F (1,27) =5.35, p=.01 and an increase in 18.3% of the variance in HRQOL. However, sleep

problems were no longer a significant predictor of child HRQOL (β=-.30, t (27) =-1.93, p=.07). These findings indicate that the extent to which severity of sleep problems predict variance in HRQOL is conditional upon autistic characteristics, suggesting that autistic characteristics possibly mediate the relationship between severity of sleep problems and child HRQOL.

Table 4.4. *Hierarchical linear regression predicting child HRQOL from sleep problems and autistic characteristics in children*

Model 1	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.03	-.01
Age	-1.25	1.47	-.16	-.86		
Step 2					.19	.13
Age	-1.16	1.36	-.15	-.86		
CSHQ[a]	-.94	.40	-.41	-2.39*		
Step 3					.37	.30
Age	-.24	1.26	-.03	-.19		
CSHQ	-.70	.37	-.30	-1.93		
SCQ[b]	-1.37	.49	-.46	**-2.81***		

Note. N= 31, * p<.05, adjusted p=0.01 applied.
Differences which remained significant following Bonferroni correction are denoted in bold
[a]Missing data, N= 1
[b]Missing data, N= 2

4.5.5.2. Severity of sleep problems vs ADHD characteristics in child HRQOL

Within the second model, when age of child was included in step one, it accounted for 2.4% of the variance in HRQOL F (1,30) =.75, p=.39. In the second step when sleep problems were entered, the model contributed significantly to the variance in HRQOL (16.5%), F (1,29) =5.91, p=.02. In step 3, addition of ADHD characteristics led to a significant improvement in the variance of the overall model (22.6%) F (1,28) =6.64, p=.002. Similar to the previous analysis, severity sleep problems were no longer predictive (β=-.38, t (28) =-.98, p=.34) of HRQOL following addition of ADHD characteristics, which were significant (β=-.56, t (28) =-3.29,

p=.003) and explained an additional 22.6% of variance. Taken together, these results indicate that not only do ADHD characteristics predict children's HRQOL above sleep problems, but possibly mediate the impact of sleep problems on child HRQOL.

Table 4.5. *Hierarchical linear regression predicting child HRQOL from sleep problems and ADHD characteristics in children*

Model 2	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.02	-.01
Age	-1.24	1.44	-.16	-.87		
Step 2					.19	.13
Age	-1.17	1.33	-.15	-.88		
CSHQ[a]	-.94	.39	-.41	-.24*		
Step 3					.42	.35
Age	-.24	1.21	-.30	-1.98		
CSHQ	-.37	.38	-.16	-.98		
CONNERS[b]	-1.72	.52	-.56	**-3.29***		

Note. N= 32, * *p*<.05, adjusted *p*=0.01 applied.
Differences which remained significant following Bonferroni correction are denoted in bold
[a,b]Missing data, N= 1

4.5.5.3. Severity of sleep problems vs seizure severity in child HRQOL

In the third model, age of child accounted for 2.4% of the variance and the model was not significantly predictive of child HRQOL F (1,30) =.75, *p*=.39. In the second step when sleep problems were entered, they were found to significantly contribute to an increased variance in HRQOL (16.5%) F (1,29) =5.91, *p*=.02. In the final step of the model, addition of seizure severity led to an increase in variance of HRQOL by 0.1%, however this did not significantly improve the overall model F (1,28) =2.20, *p*=.11. Sleep problems (β=-.40, t (28) =-2.29, p=.03) remained as a significant predictor of HRQOL following this addition. Taken together, these

results suggest that sleep problems exerted a significant unique contribution to HRQOL above seizure severity.

Table 4.6. *Hierarchical linear regression predicting child HRQOL from sleep problems and seizure severity in children*

Model 3	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.02	-.01
Age	-1.24	1.33	-.16	-.87		
Step 2					.19	.13
Age	-1.17	1.33	-.15	-.88		
CSHQ[a]	-.94	.39	-.41	-2.43*		
Step 3					.19	.10
Age	-1.15	1.36	-.15	-.85		
CSHQ	-.93	.40	-.40	-2.29*		
HSSS	-.09	.49	-.03	-.19		

Note. N= 32, *p<.05, adjusted p=0.01 applied.
Differences which remained significant following Bonferroni correction are denoted in bold
[a]Missing data, N= 1

4.5.5.4. Sleep problems vs number of AEDs in child HRQOL

In the fourth model, age of child accounted for 2.4% of the variance and the model was not significantly predictive of child HRQOL F (1,30) =.75, p=.39. In the second step when sleep problems were entered, this was found to significantly contribute to an improvement in the variance of HRQOL (16.5%) F (1,29) =5.91, p=.02. However, in the final step of the model, inclusion of number of AEDs led to an increase in variance by 5.4%. This increase did not significantly contribute to an improvement in the overall model F (1,27) =2.17, p=.10. Within this model, sleep problems remained a significant unique predictor of HRQOL (β=-.39, t (28) =-2.17, p=.04).

Table 4.7. *Hierarchical linear regression predicting HRQOL from sleep problems and number of antiepileptic drugs*

Model 4	B	SE	β	t	R^2	Adjusted R^2
Step 1					.02	-.01
Age	-1.24	1.44	-.16	-.87		
Step 2					.19	.13
Age	-1.17	1.33	-.15	-.88		
CSHQ[a]	-.94	.39	-.41	-2.43*		
Step 3					.24	.13
Age	-.92	1.36	-.12	-.67		
CSHQ	-.90	.42	-.39	-2.17*		
Monotherapy	-4.85	8.55	-.12	-.57		
Polytherapy	-12.57	9.10	-.28	-1.38		

Note. N= 32, * $p<.05$, adjusted $p=0.01$ applied.
Differences which remained significant following Bonferroni correction are denoted in bold
[a]Missing data, N= 1

4.6. Discussion

The purpose of the current study was (1) To examine the differences in sleep, HRQOL and autistic and ADHD characteristics across epilepsy types. (2) To explore the impact of epilepsy specific variables and neurodevelopmental characteristics on the relationship between informant reported sleep and HRQOL. There has been an increased recognition of the importance of HRQOL as an outcome measure for CWE, both in research and clinical practice (Baker, 2001; Ronen et al., 2003). Unfortunately, most studies focus exclusively on the role of seizures in predicting HRQOL, which neglects the role of co-occurring conditions. Recognition of these factors are important for comprehensive epilepsy management due to the persistence of their impact (Baca et al., 2011). The use of an epilepsy specific measure of HRQOL, improves the accuracy of the impact measured in CWE. Similarly, inclusion of neurodevelopmental characteristics rather than relying on diagnoses, allows for better

representation of the findings due to the diagnostic overshadowing of such conditions within this group. Overall, the study revealed that there were no significant differences between epilepsy types in sleep problems, autistic characteristics, ADHD characteristics or HRQOL. Furthermore, severity of sleep problems predicted poorer HRQOL above seizure severity and number of AEDs. It was also found that ADHD and autistic characteristics predicted HRQOL above sleep problems, and possibly mediated the relationship between sleep and HRQOL.

In terms of overall HRQOL, the mean total HRQOL score (62.72) was consistent with the scores from prior research in CWE of 62.52 (21.52) (Aggarwal et al., 2011) and 66.7(4.83) (Arya, Gehlawat, Kaushik, Gathwala, 2014). In addition, there were no significant differences in these scores between the epilepsy types. Whilst there is some literature to indicate that HRQOL is poorer in children with focal epilepsy types compared to others (Nadkarni et al., 2011; Ferro et al., 2017), most literature suggests there are no differences (Arya et al., 2014; Aggarwal et al., 2011; Liu & Han, 2015; Pachange, Dixit, Arjun & Goel, 2021). The latter view is consistent with the findings of this study. A possible reason for inconsistencies with prior studies may relate to differences in the HRQOL measure used, where some were disease specific, and others were generic measures. As a result, the impact of epilepsy may be quantified differently, and consequently not fully reflect the effect of epilepsy type on HRQOL. Another reason for the lack of differences may be due to use of epilepsy type, which is a broad categorisation. This limitation was also emphasised in Chapter 2, where lack of stratification prevented further analysis of sleep problems by epilepsy type. Recent research has adopted such approach, whereby Baggio et al. (2022) performed a cross syndrome comparison study on predictors of HRQOL including cognitive and behavioural co-occurrences in three epilepsy syndromes. Such approach revealed that the cognitive and behavioural profile of CWE differed across epilepsy syndromes, and this difference was related to seizure freedom. Therefore future

research may benefit from using a more granule approach, such as stratifying by epilepsy syndromes to better delineate profiles of HRQOL and ultimately inform treatment decisions.

The results also revealed that the 78.13% of the children within our sample displayed sleep problems that surpassed the clinical threshold. This is supported by prior research which has indicated that CWE have disturbed sleep compared to CWOE (Winsor et al., 2021). Although the present study did not include a control group, supporting evidence using the same measure in a similar age group (6-12 years) found that 33% of CWOE had a sleep disturbance score above the threshold (Markovich, Gendron & Corkum, 2015). In addition to this, normative subscale data by Owens et al. (2000b) was compared to the data within the sample of CWE. This revealed that CWE displayed heightened scores across all subscales compared to CWOE. This is consistent with the descriptive findings within Chapter 2, which showed that across the studies CWE had more severe sleep problems across all subscales compared to CWOE. However as statistical analyses could not be conducted on this data, the statistical significance of these findings could not be determined. Nevertheless, these findings suggest that use of an index score for sleep problems did not limit the interpretations of these findings greatly. The comparative analysis into the impact of epilepsy type on overall sleep problems did not reveal significant differences. The literature regarding this relationship is mixed, whereby one study found that children with generalised and drug resistant epilepsies were more likely to experience more frequent sleep problems (Batista & Nunes, 2007). However, Chan et al. (2011) found that severity of sleep problems was not significantly different between those with partial and generalised epilepsy. A possible reason for this difference may relate to how sleep problems were defined. While the study by Batista and Nunes (2007) explored the incidence of sleep problems, the study by Chan et al. (2011) explored the severity of sleep problems. Thus, the two measures are sensitive to different constructs of sleep. Despite this lack of

consistency, our finding is potentially clinically useful as it suggests that even in less severe or self-limited epilepsies, severity of sleep problems was not significantly lower than in the more severe epilepsy subgroups.

In addition to this finding, more severe sleep problems predicted poorer HRQOL above seizure severity and number of AEDs, which were not significant predictors. These findings are in line with studies of adults with epilepsy (Gutter, Callenbach, Brouwer & De Weerd, 2019; Piperidou et al., 2008). They are also in line with previous studies in demonstrating the impact of poor sleep habits on HRQOL in CWE (Gutter et al., 2013; Wirrell et al., 2005). However, given the inclusion of only focal epilepsy and use of a sibling control group, the representativeness of these studies was poor. Therefore, these findings extend the current literature and illustrate the need to consider the role of sleep problems in epilepsy management.

Furthermore, the regression analyses found that epilepsy-specific variables including seizure severity and number of AEDs were not significantly predictive of HRQOL across all analyses. This is consistent with quantitative and qualitative studies which indicated that parent's perception of their child's HRQOL are not significantly related to seizure severity (Cianchetti et al., 2015; Ronen et al., 2003). This also complements a previous study which employed self-report measures, which reported that children weigh factors such as social and emotional functioning as more debilitating than seizure factors when determining HRQOL (Fayed et al., 2015). In contrast, one longitudinal study suggested that side effects, type of AEDs and frequency of seizures do impact long term HRQOL in CWE (Modi et al., 2011). However as noted by the authors, given the short follow up period of seven months, parents may still be adapting to their child's epilepsy and overestimate the impact of these variables on HRQOL. Moreover, parents are often not aware of co-occurring conditions early in the epilepsy

trajectory (Lewis, Noyes & Mackereth, 2010). Therefore, it is possible that parents may become more aware of these conditions over time and ultimately their perception of HRQOL may improve. Within this study it was not possible to gain information on length of time since epilepsy diagnosis thus this pathway could not be explored. To disentangle this impact, future studies should aim to conduct longitudinal assessments examining how epilepsy-specific variables and co-occurrences impact HRQOL over disease trajectory.

The results also indicated that autistic characteristics were not significantly different between epilepsy type, which is supported by a previous studies (Berg, Caplan & Hesdorffer, 2011; Lee, Kang, Kim, Kim, Chung, 2011; Spence & Schneider, 2009). In addition, when both autistic characteristics and sleep problems were considered, higher autistic characteristics predicted poorer HRQOL above sleep problems, and possibly mediated this relationship. As previously discussed, sleep problems are common in autistic children and increased autistic characteristics can predict higher sleep disturbance (Adams et al., 2014). These findings should be interpreted with caution as a mediation analysis could not be conducted, due to the small number of participants. Nevertheless, the total SCQ score (9.87) within this sample was higher than those reported in TD children (2.54) of a similar age group (Mouti, Dryer & Kohn, 2019) indicating that CWE display higher autistic characteristics than CWOE. In sum these results suggest that autistic characteristics, which do not necessarily meet the threshold for further assessment can also have an impact on HRQOL. This is also supported by the result that only 25.82% of the sample achieved a score which would warrant a diagnostic assessment for autism. This has clinical implications for epilepsy management, as these difficulties continue to go undetected, they can place a considerable care burden on parents (Holmes et al., 2021).

Similarly, when both ADHD characteristics and sleep problems were considered in the regression analysis, higher ADHD characteristics predicted poorer HRQOL, and sleep problems no longer accounted for unique variance. A possible reason is that ADHD characteristics exert a mediating effect on the relationship between sleep and HRQOL. This is consistent with previous research, which suggests that sleep problems may mask as ADHD characteristics (Hvolby, 2015). Although previous research has documented the strong association between sleep problems and ADHD characteristics in CWE (Wirrell et al., 2005; Becker et al., 2004; Ekinci et al., 2016). The direction of the relationship between sleep and ADHD characteristics is difficult to establish due to difficulties recognising the point of onset (Neto et al., 2016). Despite this, the impact of ADHD characteristics on HRQOL is evident and as previously outlined, can be worse than epilepsy alone (Ekinci et al., 2017; Sherman et al., 2007). Therefore, future research should aim to conduct a full mediation analysis to elucidate the inter-relationships between ADHD and autistic characteristics vs sleep problems more definitively.

There were some methodological limitations associated with this study. For example, defining seizure severity within the last three months based on the HASS, can be skewed by parents' memory recall. Parents who are more knowledgeable about their child's seizures may also be more accurate in their reports (Love et al., 2016). An alternative approach would be to use seizure diaries, which are clinically recognised, and this would enable close and reliable tracking of seizure rates (Fisher et al., 2012). However, there is the possibility that children may experience seizures when their parents are not present such as during school time or due to specific seizures type which are not salient to parents (e.g., nocturnal or absence seizures) (Becker et al., 2004). Although there are more sophisticated methods currently being developed, these have yet to be implemented in clinical practice (Brinkmann et al., 2021).

Therefore, the current screening tool used within this study was the most feasible and clinically available option. Nevertheless, other epilepsy-specific variables, including number of AEDs and epilepsy type, showed a consistent lack of association with HRQOL, supporting the robustness of our findings. Another caveat was the use of only informant reports for sleep. Prior research has shown that informant-reported sleep patterns were related to poorer behavioural outcomes in CWE but not actigraphy defined sleep parameters (Tsai et al., 2019). This indicates that the two measures provide independent information about sleep patterns. Future research would benefit in exploring whether the type of measure may yield a different result (see Chapter 5).

Although gold standard measures were used to assess HRQOL (Goodwin et al., 2015) there are some drawbacks regarding the discrepancies between child and informant reports (see section 1.10.1). Some studies were found to have discordance between the two groups for reporting HRQOL. Baca et al. (2011) found that informant reports revealed an association between neurodevelopmental conditions and HRQOL, however this was not found for self-reports. This may be attributed to the different importance children and parents' place on determinants of HRQOL. This was supported by Verhey et al. (2009) found discrepancies were largest when reporting an introspective viewpoint (i.e children's ratings were higher than parents) and presenting issues (i.e children's ratings lower than parents). This is also consistent with a study conducted by Fayed et al. (2015), found that children's emotional and social functioning were strongly related to self-reported HRQOL rather than disease characteristics. This suggests that children ascribe a higher importance to factors other than their epilepsy. Despite these findings, a recent study by Fayed et al. (2019) indicates that parents of CWE can provide accurate reports for their child's HRQOL. However, the accuracy of reports can be impacted by parent's ability to cope with their child's disease and children's peer support.

However, factors such as seizure severity or depression symptoms did not affect this accuracy. Future research should aim to improve these factors in order to reduce the discrepancy between child and adult ratings.

4.7. Conclusion

Autistic and ADHD characteristics were found to be predictive of overall HRQOL in CWE. Most of the sample of CWE also exceeded the clinical threshold for sleep problems. Both sleep and neurodevelopmental conditions require clinical acknowledgement, as these co-occurring conditions can complicate an epilepsy diagnosis in a child, as well as impact family networks. Routine screening of autistic and ADHD characteristics is recommended at the epilepsy diagnostic stage, to provide parents with support to help navigate around their child's difficulties. Interestingly, despite the majority of children displaying sleep problems which surpassed clinical threshold and across all subscales compared to CWOE, these were not significantly predictive of HRQOL when neurodevelopmental characteristics were considered. A study using an objective measure of sleep is required to explore whether sleep is generally not predictive of HRQOL, or whether these differences are due to the use of informant report measures, Therefore, the aim of the next Chapter is to replicate the current study with the use of actigraphy to elucidate the potential discrepancies between the two measures and whether this impacts HRQOL.

CHAPTER FIVE

THE CONTRIBUTION OF ACTIGRAPHY DEFINED SLEEP PARAMETERS AND CO-OCCURRING CHARACTERISTICS TO QUALITY OF LIFE IN CHILDREN WITH EPILEPSY

5.1. Preface

In Chapter 2, a systematic review and meta-analysis was conducted, which demonstrated poorer sleep across both objective and informant reported measures in CWE compared to CWOE. The study in Chapter 4 built on these findings, by exploring how informant reported sleep contributes to HRQOL in CWE in relation to neurodevelopmental characteristics and epilepsy specific variables. It was found that whilst more severe sleep problems were independently predictive of poorer HRQOL, epilepsy specific variables including seizure severity and AEDs number were not. Interestingly, the relationship between sleep and HRQOL was no longer retained when autistic and ADHD characteristics were included in the model. This indicates that these neurodevelopmental characteristics potentially mediate the relationship between sleep and HRQOL. However, there are various caveats associated with informant-reported sleep, which can skew the accuracy of these reports. Therefore, the use of objective measures such as actigraphy can reveal a clearer picture of the role of sleep in HRQOL. In addition, Chapter 4 used the CSHQ overall score as an index of sleep disturbance. Although this is informative, viewing sleep as a multi-dimensional construct can shed light on whether there are specific sleep problems unique to HRQOL in CWE. Consequently, the current study addresses aim 1.16.3 of this thesis, by firstly comparing actigraphy defined sleep parameters in CWE to CWOE. Secondly, the study design used in Chapter four will be followed to assess whether objective sleep measurement reveals a different relationship with HRQOL.

5.2. Introduction

Sleep disturbances are commonly reported in CWE and are up to 12 times more likely to occur in this group compared to CWOE (Gutter et al., 2013; Bazil, 2003; Winsor et al., 2021). Informant reports of child sleep hold great clinical utility due to their cost and time effectiveness. In addition, young children may lack the capacity to reliably report about their own sleep patterns (Mazza et al., 2020). However, informant reports can be prone to different biases. For example, as sleep problems are recognised to affect not only the child but the wider family in CWE (Shaki et al., 2011; Larson et al., 2012, Tsai et al., 2020a), the impact on family well-being can negatively skew parents' perception of a child's sleep. Similarly in parents of CWE, knowledge of sleep is indicated to be inadequate (Tsai et al., 2018), a factor which has been shown to be negatively associated with poor sleep in children in the general population (McDowall, Elder & Campbell, 2017). Therefore, given the drawbacks of informant report measures, research should consider the use of objective measurements of sleep.

Other studies have utilised objective methods to measure sleep in CWE such as PSG and demonstrated that CWE experience disturbed sleep architecture (Maganti et al., 2005; Bruni et al., 2010; Pereira et al., 2012b; Winsor et al., 2021). Although PSG is regarded as a gold standard objective measure for sleep, as discussed in Chapter 1, issues surrounding the cost and time it can record limits its use in clinical practice. Its validity as a measure of habitual sleep is also unclear, given the unusual settings that it is typically recorded in. Other measures such as actigraphy are easier to implement and better tolerated in children with neurodevelopmental conditions compared to PSG (Yavuz-Kodat et al., 2019). As these conditions are commonly co-occurring in CWE (see section1.7.), actigraphy can be a useful tool to use alongside informant-reports. However, the literature regarding the agreement between informant reports and objective measures of sleep is mixed. Most studies have

demonstrated that informant reports are convergent with actigraphy for some variables, such as timing around sleep, but not others, such as quality of sleep (Holley, Hill & Stevenson, 2010; Werner et al., 2008; Perpétuo et al., 2020). This inconsistency may lie in the fact that these tools are indeed measuring different aspects of sleep (Holley et al., 2010). Whilst informant-reports can provide suitable information on observable behavioural sleep issues (Esbensen, Hoffman, Stansberry & Shaffer, 2019), actigraphy can help provide clarity when interpreting this information and overcome issues with reporting bias (Perpétuo et al., 2020; Wiggs Montgomery & Stores, 2005). It can also provide a more precise measure of specific sleep parameters, which can be an issue in CWE as highlighted earlier in Chapter 2. Therefore, use of both measures is recommended, and can possibly help guide treatment options for CWE.

Use of both sleep tools offers the opportunity to extract richer information on specific variables, which is particularly important when understanding their role in HRQOL. In Chapter 4, a single score for severity of sleep problems, as measured via the CSHQ was used to predict HRQOL. Although there are benefits with this approach in identifying children at risk of significant sleep disturbance (Owens et al., 2000b), it limits the understanding of the specific sleep parameters underlying this disturbance. This is supported by a previous study which found that the CSHQ was beneficial in detecting risk of sleep disturbance, however, it did not correlate well with actigraphy variables such as sleep duration and sleep efficiency (Duraccio, Carbine, Barnett, Stevens & Jensen, 2018). In addition to this caveat, another study demonstrated significant sleep disturbances across several actigraphy domains (TST, SOL and WASO) did not correlate with the related CSHQ subscales in children (Markovich et al., 2015). This raises the risk that the degree of sleep disturbances may be underrepresented by the CSHQ, if used on its own. In summary, use of both tools can provide a clearer picture of sleep patterns within this group.

To date there are very few studies which have utilised actigraphy for measuring sleep in CWE. Of the limited literature, one study compared both objective and informant reported sleep using actigraphy and the CSHQ in CWE (Holley et al., 2014). They found that CWE displayed more severe sleep problems compared to CWOE across several CHSQ subscales, including night waking, parasomnias, and sleep duration. By contrast, these results were not replicated by actigraphy, in which no significant differences were detected between CWE and CWOE in TST, SE or SPT. These results support prior research, that the two measures are capturing different information on sleep (Holley et al., 2010). Furthermore, the sample of children within this study had well controlled epilepsy with no additional co-occurrences such as psychological or learning difficulties and were on monotherapy only. As highlighted in Chapter 4, co-occurring conditions are highly prevalent in this group and are of specific importance when considering HRQOL. These results may not be wholly representative of actigraphy defined sleep parameters in CWE. This is emphasised by prior studies which have demonstrated poorer sleep as measured by actigraphy in children with neurodevelopmental conditions compared to children without (Melegari et al., 2020; Baker, Richdale, Short & Gradisar, 2013). Consequently, further evidence from a sample of heterogenous epilepsies and inclusion of co-occurrences may provide a more representative understanding of objectively measured sleep in CWE.

In addition to exploring actigraphy defined sleep in CWE and co-occurrences, it is important to examine the association between sleep parameters and outcomes such as HRQOL. Prior research using questionnaire measures demonstrates that poorer sleep is significantly associated with worse HRQOL in adults (Piperidou et al., 2008; Gutter et al., 2019; Alanis-Guevara et al., 2005) and CWE (Chapter 4, Gutter et al., 2013, Wirrell et al., 2005). However, at the current time there are no studies which have assessed the association between actigraphy

defined sleep and HRQOL. One study examined the relationship between informant-reported and actigraphy defined sleep in predicting behavioural problems (Tsai et al., 2019). They found that informant reported sleep problems were associated with poor behavioural outcomes. However, actigraphy defined sleep did not significantly predict this. Nevertheless, despite the lack of association with behavioural outcomes, it was found that over 83% of their sample had a WASO value of an hour or more. They also found that around 80% of children had a total sleep time of under 10 hours, which is less than the national recommended amount (10-14 hours) for children within this age group (1.5 to 6 years) (Paruthi et al., 2016). These results suggest that there are sleep disturbances present within CWE as evaluated by actigraphy, however this could not be validated against normative data, as no control group was used. Therefore, this study affords the opportunity to build the limited evidence base on actigraphy defined sleep parameters in CWE compared to CWOE.

Finally, another probable reason for the findings regarding the lack of difference in actigraphy defined sleep parameters between CWE and CWOE (Holley et al., 2014), may relate to the aspect of sleep being measured. The aforementioned studies have focused only on mean sleep parameters; however, this does not take account of the richness of the data and limits its interpretation. A type of measurement of sleep to consider, that is typically underreported, is IIV of sleep, which represents the level of variability from night to night (Becker, Sidol, Van Dyk, Epstein & Beebe, 2017). A prior review emphasised the need for inclusion of IIV of sleep as a second construct, in combination with mean sleep parameters (Bei, Wiley, Trinder & Manber, 2016). One study has previously investigated IIV variability in sleep duration in CWE and found that higher variability was negatively associated with poorer maternal knowledge of sleep (Tsai et al., 2018). However, in this study no control group was used to assess whether sleep parameters significantly differed from CWOE, or whether these were predictive of child

outcomes e.g., HRQOL. Interestingly, it has been found that IIV of sleep parameters such as TST are stronger predictors of overall well-being than mean sleep parameters in CWOE (Lemola, Ledermann & Friedman, 2013; Slavish, Taylor & Lichstein, 2019). Therefore, investigation of the relationship between IIV of sleep parameters and child outcomes in CWE, would assist in drawing stronger conclusions on the contribution of actigraphy defined sleep to HRQOL.

Therefore, the rationale for the present Chapter was to extend the currently limited literature regarding actigraphy defined sleep in CWE. The overall aim was to elucidate whether the method of quantifying sleep (i.e., informant-report vs actigraphy) can affect the observed relationship between sleep, neurodevelopmental characteristics and HRQOL. The first step to achieving this aim is to explore actigraphy-defined sleep in CWE compared to CWOE, which has only been investigated in one previous study (Holley et al., 2010). Furthermore, only two studies have examined how actigraphy relates to child outcomes, these included behaviour (Tsai et al., 2019) and executive functioning (Holley et al., 2014). Both studies controlled for specific variables such as type of epilepsy and excluded co-occurrences, thus limiting generalisation of these findings to CWE. Therefore, examination of sleep across different epilepsy types and consideration of co-occurrences may reveal a different picture. Finally, some research argues that IIV of sleep, may be a stronger predictor of overall health and wellbeing than mean sleep parameters (Bei et al., 2016), but no studies have yet been carried out between CWE and CWOE.

5.2.1. Study Aims

1. To compare actigraphy evaluated sleep parameters in children with epilepsy to children without epilepsy

2. To explore differences between actigraphy defined mean and IIV of sleep across three groups of epilepsies: (2) Focal epilepsy (2) Generalised epilepsy and (3) Rolandic epilepsy
3. To investigate the potential impact of epilepsy variables and other co-occurring conditions, in the relationship between sleep and QOL.

5.3. Methods

Methods and measures unique to this Chapter are given below and recruitment and eligibility criteria are summarised in Chapter 3.

5.3.1. Participants

5.3.1.1 Children with epilepsy

From an initial sample of 70 participants, 17 children were excluded as they did not receive an epilepsy diagnosis, ten due to the presence of an ID, and seven who did not complete the minimum number of nights for actigraphy (seven nights). A minimum number of seven nights for CWOE was required across both groups. According to this criteria, four participants were excluded as did not wear the watch. Two participants were excluded as they wore the watch less than seven nights. Finally, one participant was excluded as the watch failed to record during the two-week period. It was also important to note that two children shared a room with their parents on some occasions during the study weeks, which may have affected their sleep patterns. This was not used an exclusion criteria given the small sample size and inconsistency of reporting.

The final sample for this study consisted of 36 CWE (M=9.47, SD=2.62, range= 4-14 years) who wore an actiwatch for an average of 14 days (range = 7-15 days). 85% of CWE wore the watch for a period of 14 days. Sample characteristics are presented in Table 3.1.

5.3.1.2. Children without epilepsy

14 CWOE (M=8.29, SD=3.12, range= 4-15 years) wore the actiwatch for an average of 10 days (range = 7-12 days). No CWOE were excluded as all had a minimum of seven nights Demographic information is presented in Table 3.2.

5.3.2. Procedure

Parents were required to complete a set of questionnaires and children wore an actiwatch (Actiwatch2, Phillips Respironics Inc) for a period of two weeks. Some questionnaires were partial or fully completed (see section 4.3.2), thus sample sizes differed across analyses. See section 3.4 for a detailed description of the study procedure.

5.3.3. Measures

Clinic records of CWE were reviewed for epilepsy diagnosis, type and number of AEDs and socio-demographic information including sex and age (see Table 3.1). All informant report measures for this Chapter are the same as those used in Chapter 4, except for the measure on sleep problems (CSHQ) which was not used. Alternatively, sleep was measured objectively using actigraphy where mean and IIV of TST, SOL, SE and WASO were computed (see section 3.5.4.2 for description). Socio demographic information including age and gender, as well as actigraphy parameters (see section 3.5.4.2) of CWOE were extracted from the CNND participants database (Cerebra Network).

5.4. Statistical Analysis

5.4.1. Primary Analyses

To investigate group differences, an independent sample t-test (parametric) or Mann Whitney U test (non-parametric) was performed for mean and IIV of actigraphy between CWE and CWOE. Visual representation via boxplots was used for comparisons between the three groups of epilepsies: (1) Generalised epilepsy, (2) Focal epilepsy and (3) Rolandic epilepsy. To test for the differences between epilepsy types, a one-way ANOVA (parametric) or Kruskal Wallis test (non-parametric) was performed. Bonferroni corrections were applied throughout between group analyses and a new statistical significance level was set depending on the number of comparisons. Effect sizes were calculated for group comparisons, see section 4.4.4 for guidelines for interpretation.

Exploratory analyses were calculated to explore which sleep variables were associated with HRQOL scores. Firstly, Pearson's correlation coefficients were applied to parametric data and Spearman's correlation coefficient were applied to non-parametric data. Actigraphy variables which were significantly correlated with overall HRQOL score ($p<0.05$) were then carried into the hierarchical linear regression models to assess the contribution of epilepsy specific variables (seizure severity) and neurodevelopmental characteristics to the relationship between sleep and HRQOL. Number of AEDs were not inputted into a model due to the low sample size.

5.4.2. Control Analyses

Separate control analyses were conducted for various reasons. As outlined in Chapter 4, consideration of the effect of COVID-19 pandemic was evaluated. In addition, as actigraphy was conducted throughout school and non-school times, control analyses were conducted to

ensure there were no significant differences between the two time periods (Mazza et al., 2020). Similarly, previous research has documented differences in weekday vs weekend sleep (Tsai et al., 2018) thus analyses were also conducted to control for this.

To investigate differences between weekday and weekend sleep, paired sample t-tests (parametric) and Wilcoxon signed rank tests (non-parametric) were conducted. To assess differences between sleep during school vs non-school times and pre vs during the COVID-19 pandemic, independent sample t-tests (parametric) and Mann Whitney U test (non-parametric) were conducted. No significant differences were found across any of these analyses, results are presented in Appendix 5.1.

5.5. Results

5.5.1. Differences in actigraphy defined sleep between CWE and CWOE

The first aim of the study was to assess differences in actigraphy defined sleep parameters between CWE and CWOE. No significant differences were detected across all mean sleep parameters (adjusted *p* value=0.01) including mean TST (Mann Whitney U=257.00, *p*=0.92, *r*=0.02, small effect size), mean SOL (Mann Whitney U=290.00, *p*=0.42, *r*=0.15, small effect size), mean SE (Mann Whitney U=192.00, *p*=0.20, *r*=0.24, small effect size), mean WASO (Mann Whitney U=245.00, *p*=0.89, *r*=0.03, small effect size). These analyses are presented in Table 5.1.

For the second half of the first aim, the IIV of each sleep parameter was compared between CWE and CWOE. The Mann Whitney U test revealed a significant difference between IIV of SOL (Mann Whitney U=156.00, *p*=0.04, *r*=0.04, small effect size), however this was not retained following Bonferroni correction (adjusted *p* value=0.01). No significant differences

were detected across the other sleep parameters including IIV of TST (Mann Whitney U=204.00, p=0.30, r=0.19, small effect size), IIV of SE (Mann Whitney U=272.00, p=0.67, r= 0.08, small effect size) and IIV of WASO (Mann Whitney U=231.50, p=0.67, r=0.08, small effect size) between the two groups. These analyses are presented in Table 5.2.

Table 5.1. *Mean actigraphy defined sleep parameters between CWE and CWOE. Values are shown as mean (SD).*

Actigraphy	CWE (n=36) Mean (SD)	CWOE (n=14) Mean (SD)
Bed time	20:49:00	21:00:56
Sleep onset time	22:51:46	21:24:32
Total sleep time	506.23(45.31)	504.86(47.67)
Sleep onset latency	20.73(18.29)	23.97(18.83)
Sleep efficiency	83.81(4.67)	77.06(21.48)
Wake after sleep onset	60.20(29.19)	55.64(16.41)

Table 5.2. *IIV of actigraphy defined sleep parameters between CWE and CWOE*. Values are shown as mean.

Actigraphy	CWE (n=36)	CWOE (n=14)
	Mean	Mean
Total sleep time	0.10	0.09
Sleep onset latency	1.20	0.90
Sleep efficiency	0.08	0.13
Wake after sleep onset	0.31	0.30

5.5.2. Differences in actigraphy based sleep parameters across epilepsy types

The second aim of the study was to explore actigraphy defined sleep across different epilepsy types. Depending on the normality of the data, either a one-way ANOVA (parametric) or Kruskal-Wallis test (non-parametric) was conducted. There were no significant differences between the three epilepsy types in mean TST (F (2,33) =2.04, p=0.15, η^2_p=0.11, medium effect size), SE (Kruskal Wallis $\chi^2(2)$ =1.80, p=0.41, ε^2=0.05, small effect size), SOL (Kruskal Wallis $\chi^2(2)$ =1.82, p=0.40, ε^2=0.05, small effect size) and WASO (Kruskal Wallis χ^2 (2) =0.41, p=0.81, ε^2=0.02, small effect size). These analyses are presented in Figure 5.1.

For the other arm of the second aim, the IIV of each sleep parameter was compared across the three epilepsy groups. There was no significant difference between the three epilepsy types for IIV of TST (Kruskal Wallis χ^2 (2)=4.06, p=0.13, ε^2 =0.12, medium effect size), SOL (F(2,33)=0.47, p=0.63, η_p^2=0.03, small effect size), SE (Kruskal Wallis χ^2 (2)=1.34, P=0.51, ε^2=.04, small effect size), WASO (Kruskal Wallis χ^2 (2)=1.49, p=0.47, ε^2=.04, small effect size). These analyses are presented in Figure 5.2.

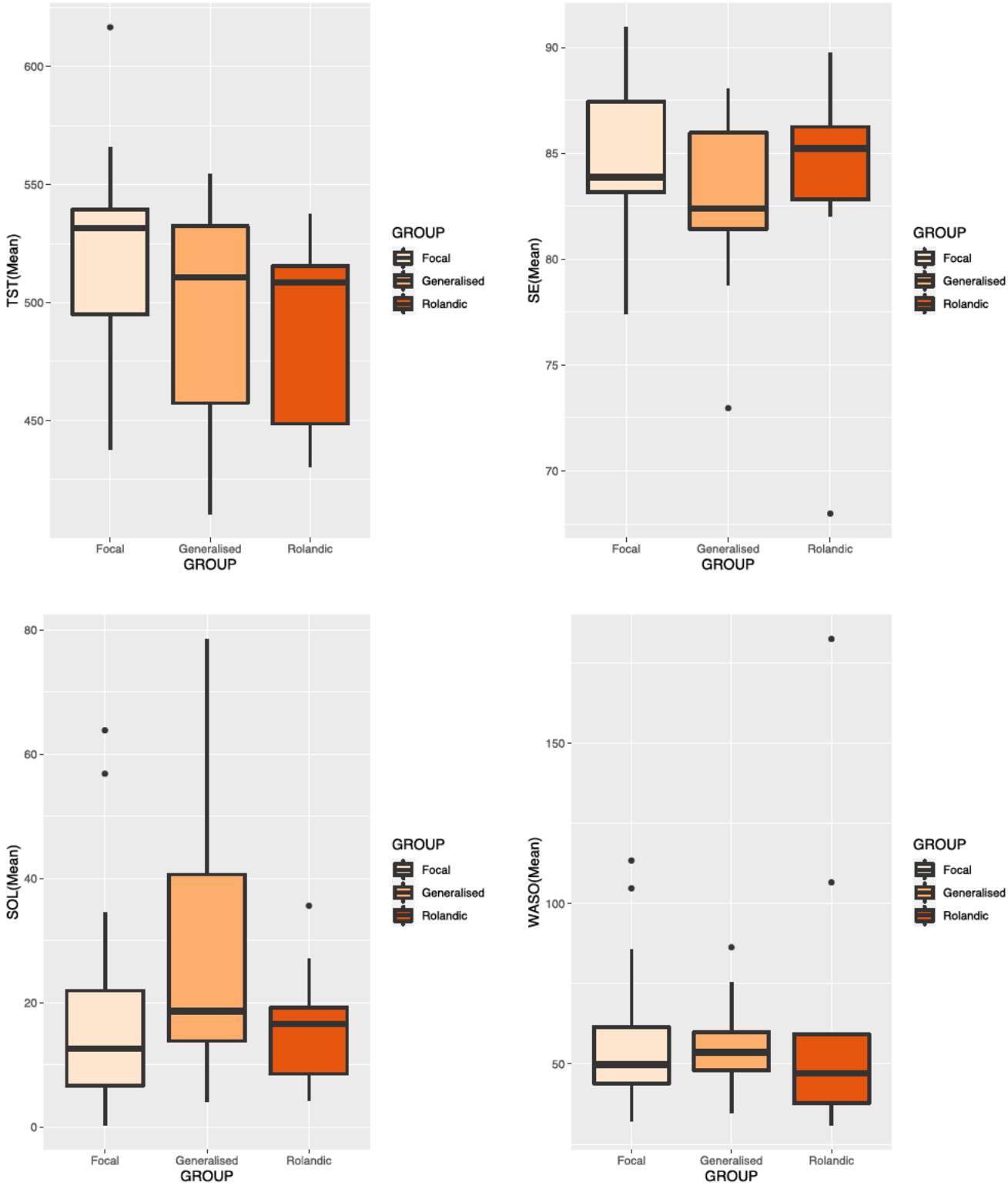


Figure 5.1. Boxplots for mean of actigraphy defined sleep parameters across epilepsy types. Horizontal lines denote the median and interquartile range. Whiskers represent maximum and minimum points.

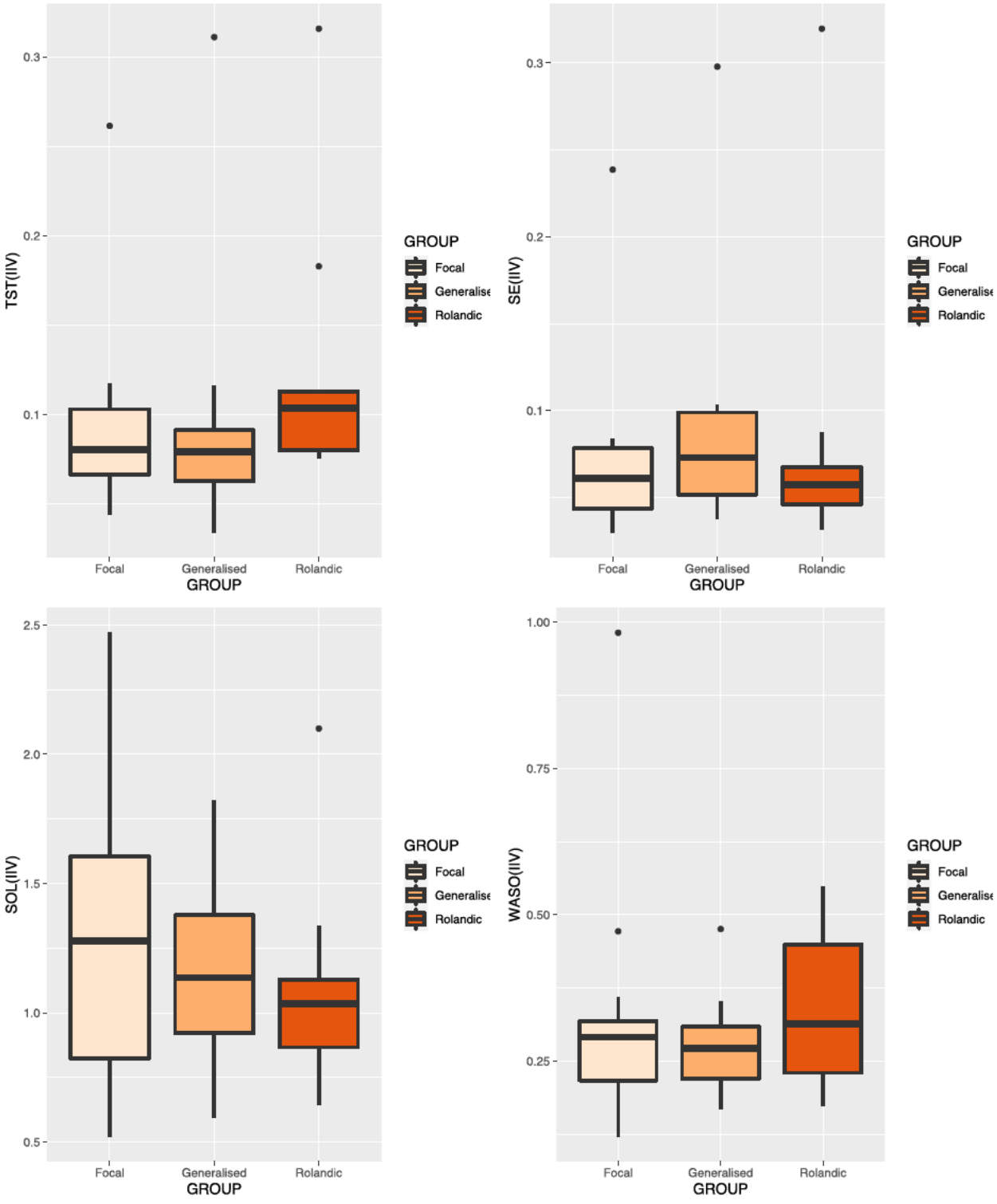


Figure 5.2. Box plots for IIV of actigraphy defined sleep parameters across epilepsy types. Horizontal lines denote the median and interquartile range. Whiskers represent maximum and minimum points.

5.5.3. Associations between HRQOL and actigraphy defined sleep parameters

Exploratory correlational analyses were carried out between the total HRQOL score, and both mean and IIV of actigraphy defined sleep parameters to select predictor variables for entry into the regression analyses (see Table 5.3). It was found that HRQOL was significantly associated with mean SOL (*rho* (32) =0.36, p=0.04), IIV of SOL (r (32) =-0.44, *p*=.01) and mean WASO (*rho* (32) =-.40, *p*=.02).

Table 5.3. *Correlations between total HRQOL score and actigraphy defined sleep parameters*

	TST(M)[a]	**TST(IIV)[a]**	**SOL(M)[b]**	**SOL(IIV)[a]**	**SE(M)[b]**	**SE(IIV)[a]**	**WASO(M)[b]**	**WASO(IIV)[b]**
QOLCE	0.04	-0.13	**0.36***	**-0.44***	0.09	-0.06	**-0.40***	-0.15

**p<.05,*
p values were derived from Pearson correlation coefficents[a] or Spearman correlation coefficients[b].

5.5.4. Contribution of co-occurring characteristics and epilepsy specific variables to the relationship between actigraphy defined sleep parameters and HRQOL

To examine aim two, separate hierarchical linear regressions were performed to compare the contribution of co-occurring characteristics and epilepsy specific variables in predicting the impact of actigraphy defined sleep on child HRQOL. Age was entered into the first step in all models. The actigraphy defined sleep variables which were significantly associated with HRQOL (see Table 5.3) were taken forward for inclusion in the second step across all the regression models. In the third step, autistic characteristics (Table 5.4), ADHD characteristics (Table 5.5), or seizure severity (Table 5.6) were entered across the three regression models respectively. See Figure 5.3 for representation of the regression models.

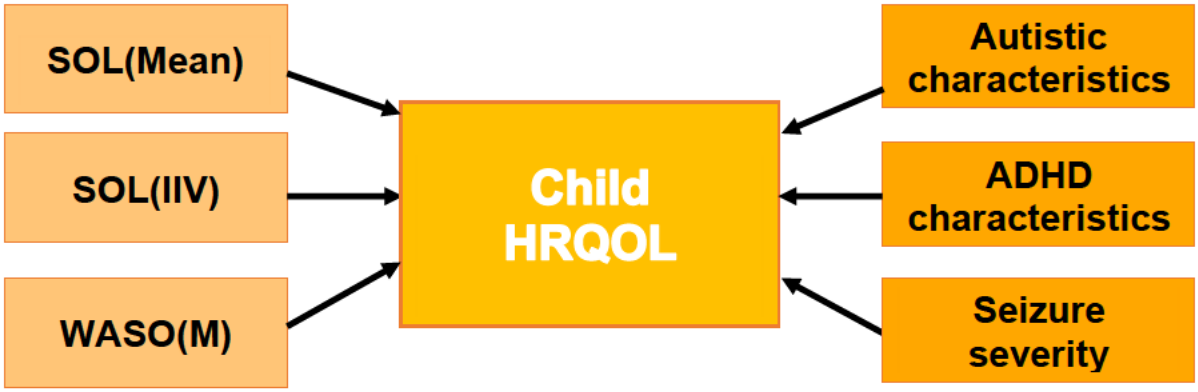


Figure 5.3. Schematic representation of hierarchical linear regression for aim 1.16.3.

5.5.4.1. Contribution of actigraphy defined sleep variables vs autistic characteristics in child HRQOL

In the first model when age of child was entered in the first step it was found to account for 2.5% of the variance and was not significantly predictive of HRQOL F(1,29) =0.73, p=.40. When actigraphy defined sleep variables were entered into step 2, they were found to lead to a significant improvement in the overall model F (4,36) =3.39, *p*=.02, accounting for an increase in 31.8% of the explained variance in HRQOL. More specifically only IIV of SOL was significantly predictive of HRQOL (β=-.57, t (26) =-2.23, *p*=.03). Finally in the final step of the model, addition of autistic characteristics led to a significant improvement in the model F(5,25) =6.26, p<.001, accounting for an additional 21.3% of variance in HRQOL. In this step, both autistic characteristics (β=-49, t (25)=-3.47, *p*=.002) and IIV of SOL retained significance (β=-0.51, t(25)=-2.40, p=.02), thus the two variables were found to exert a unique contribution to HRQOL.

Table 5.4. *Hierarchical linear regression predicting HRQOL from actigraphy defined sleep parameters and autistic characteristics*

Model 1	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.03	-.01
Age	-1.25	1.47	-.16	-.86		
Step 2					.34	.24
Age	-2.96	1.37	-.37	-2.17		
SOL(M)	.16	.22	.14	.70		
SOL(IIV)	-25.26	11.31	-.57	-2.23*		
WASO(M)	.07	.14	.11	.52		
Step 3					.56	.47
Age	-1.83	1.19	-.23	-1.54		
SOL(M)	.20	.19	.18	1.06		
SOL(IIV)	-22.85	9.51	-.51	-2.40*		
WASO(M)	.11	.12	.16	.96		
SCQ[a]	-1.46	.42	-.49	**-3.47***		

Note. N= 31, * $p<.05$, adjusted $p=0.02$ applied.
Differences which remained significant following Bonferroni correction are denoted in bold.
[a]Missing data, N= 5

5.5.4.2. Contribution of actigraphy defined sleep parameters vs ADHD characteristics in child HRQOL

In the second model, when age of child was adjusted for in the first step this was not significantly predictive F (1,30) =.75, $p=.39$ and accounted for 2.4% of the variance in HRQOL. When the actigraphy variables were entered into the second step of the model, this predicted a statistically significant proportion of variance in overall HRQOL F(4,27)=3.39, $p=.02$, (31.0%). Within this model, only IIV of SOL was significantly predictive of HRQOL (β=-0.54, t(27)=-2.19, $p=0.04$). In the third step of the model when ADHD characteristics were entered, this led to a significant improvement in the overall model for HRQOL (F(5,26)=6.48, $p<.001$) (22.1%). However, within this step, the contribution of IIV of SOL to HRQOL was

no longer significant of HRQOL (β=-0.36, t(26)=-1.72, p=0.10). Moreover, the beta value of IIV of SOL on HRQOL reduced from β= -0.54 to β=-0.36, following inclusion of ADHD characteristics into the model suggesting that they possibly mediate the relationship between IIV of SOL and HRQOL.

Table 5.5. *Hierarchical linear regression predicting HRQOL from actigraphy defined sleep parameters and ADHD characteristics*

Model 1	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.02	-.01
Age	-1.24	1.44	-.16	-.87		
Step 2					.33	.24
Age	-2.96	1.35	-.37	-2.20		
SOL(M)	.18	.22	.16	.84		
SOL(IIV)	-23.37	10.71	-.54	-2.19*		
WASO(M)	.07	.14	.10	.48		
Step 3					.55	.47
Age	-3.59	1.14	-.45	-3.15		
SOL(M)	.20	1.8	.18	1.12		
SOL(IIV)	-15.76	9.18	-.36	-1.72		
WASO(M)	.07	.11	.10	.57		
CONNERS[a]	-1.59	.44	-.51	**-3.59***		

Note. N= 32, * p<.05, adjusted p=0.02 applied.
Differences which remained significant following Bonferroni correction are denoted in bold.
[a]Missing data, N= 4

5.5.4.3. Contribution of actigraphy defined sleep variables vs seizure severity in child HRQOL

In the first model when age of child was entered in the first step it was found to account for 2.4% of the variance and was not significantly predictive of overall HRQOL F (1,30) =0.75,

p=.40. When actigraphy sleep variables were entered into step 2, they were found to lead to a significant improvement in the overall model F (4,27) =3.39, *p*=.02 accounting for an additional 31.0% of the variance in HRQOL. Only IIV of SOL was significantly predictive of HRQOL (β=-0.54, t (27) =-2.19, *p*=0.04). In the final step of the model, addition of seizure severity did not contribute significantly to the overall model F (5,26) =2.71, *p*=0.04, (0.01%). Although IIV of SOL was no longer significantly predictive of HRQOL, there was minimal change in the beta value (β=-0.51, t (27) =-2.19, *p*=0.04) indicating that seizure severity had little impact on the predictive power of IIV of SOL.

Table 5.6. *Hierarchical linear regression predicting HRQOL from actigraphy defined sleep parameters and seizure severity score*

Model 1	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.02	-.01
Age	-1.24	1.44	-.16	-.87		
Step 2					.33	.24
Age	-2.96	1.35	-.37	-2.20		
SOL(M)	.18	.22	.16	.84		
SOL(IIV)	-23.41	10.71	-.54	-2.19*		
WASO(M)	.07	.14	.10	.48		
Step 3					.34	.22
Age	-2.88	1.37	-.36	-2.10		
SOL(M)	.21	.22	.18	.93		
SOL(IIV)	-21.97	11.13	-.51	-1.97		
WASO(M)	.05	.14	.08	.37		
HSSS[a]	-.27	.46	-.10	-.58		

Note. N= 32, * *p*<.05, adjusted *p*=0.02 applied.
Differences which remained significant following Bonferroni correction are denoted in bold.
[a]Missing data, N= 4

5.6. Discussion

This is the first study to evaluate the contribution of neurodevelopmental characteristics and epilepsy specific variables to the relationship between actigraphy defined sleep parameters and HRQOL in CWE. The use of actigraphy as a sleep tool improves the precision of measured sleep patterns, as it can help to overcome the caveats associated with informant-reports and provides richer information on specific sleep parameters. Inclusion of a group of CWOE enabled better understanding of whether actigraphy defined sleep in CWE deviates from normative values. This extends prior research, whereby only one study has compared both groups of children (Holley et al. 2014). Finally, by exploring the contribution of co-occurrences within the sample, this also improves the clinical applicability of the study findings.

The study revealed that across epilepsy types, there was no significant difference between CWE and CWOE, across mean and IIV of actigraphy defined sleep variables. One exception was IIV of SOL, which was found to be higher in CWE compared to CWOE. However, this finding was not retained following Bonferroni correction, which future research should explore. Consistent with the findings from Chapter 4, seizure severity was not found to be predictive of HRQOL. However, IIV of SOL and autistic characteristics were found to exert a significant independent contribution to HRQOL. Furthermore, the results suggest that ADHD characteristics act as a mediator between IIV of SOL and HRQOL in CWE. These findings illustrate differences in the relationship between sleep and HRQOL to those in Chapter 4, where an informant-report of sleep was used. This suggest that in epilepsy management, a multifaceted approach is required to assessing sleep, which should also include screening of neurodevelopmental characteristics.

This study indicates that there are no significant differences in actigraphy defined sleep parameters in CWE compared to CWOE, which is line with the findings of a prior study by Holley et al. (2014). Within this study, IIV in SOL was found to be significantly higher in CWE compared to CWOE, but this was no longer significant following correction of multiple testing. Nevertheless, prior studies in adults have demonstrated that variability in sleep patterns is correlated with seizure likelihood (Dell et al., 2021; Cobabe et al., 2015; Haut, Hall, Masur & Lipton, 2007). This trend may reflect the unpredictability of seizures occurring. It is possible that children who experience a seizure on one night may take longer to fall asleep the subsequent night, due to the fear of a seizure re-occurring (Ong, Yang, Wong, AlSiddiq & Khu, 2010; Stores et al., 1998). Alternatively, they may also fall asleep more readily in the night following a seizure due to a lack of opportunity to sleep in the previous night. It was not possible to assess the temporal association between seizures and sleep patterns in this study. This is an area future research should aim to develop in CWE. In addition, only one previous study of CWE has measured IIV of sleep, however this was only for one parameter (sleep duration) (Tsai et al., 2018). Therefore, further research is required to explore sleep in CWE using actigraphy, to replicate these potentially important findings.

The results also confirmed that there were no differences in sleep parameters across epilepsy types, which is consistent with findings in Chapter 4 (see section 4.5.1). There are no actigraphy studies to date assessing sleep differences between epilepsy type, however some studies have used other objective measures such as PSG. Our findings converge with those of Kaleyias et al. (2008) who did not find differences in PSG sleep between generalised and focal epilepsy. However, prior research reported that children with focal epilepsy with secondary generalisation or idiopathic epilepsy types, experienced higher vulnerability to fragmented sleep than children with generalised epilepsy (Al-Biltagi et al., 2014). It is possible that due to

the small sample size of children within each group, this may have also hindered the possibility of finding differences. Future research should aim to explore actigraphy defined sleep in CWE using larger samples with more defined epilepsy aetiologies to define sleep profiles in a way that can be clinically meaningful.

The regression analysis also suggests that both that co-occurring autistic characteristics significantly contribute to decreased HRQOL in CWE, consistent with the findings from Chapter 4. Despite the well-recognised relationship between autism and epilepsy, as well as the heightened risk of mortality (Lukmanji et al., 2019; Strasser et al., 2018) no empirical study has directly investigated the contribution of autistic characteristics to HRQOL in CWE. A recent report by Reilly (2021) put forward various factors which may contribute to poorer HRQOL in autistic individuals with epilepsy, as assessed through qualitative methods. This included lack of timely autism diagnosis, failure to consider adaptations to the sensory and communication needs of children in diagnostic appointments, and impact on wider family. Such issues have also been raised by other researchers (Tye, Runicles, Whitehouse & Alvares, 2019; Holmes et al., 2021). Ultimately many of these difficulties may stem from the lack of communication between epilepsy and autism fields. Given the consistency of these findings, there is a pressing need to recognise the influence of neurodevelopmental characteristics early in the epilepsy diagnostic process. Through early identification, the appropriate support and management can be put in place for families and ultimately improve HRQOL in children (Akhter, 2021).

The finding that higher IIV of SOL is associated with poorer HRQOL are consistent with the general sleep literature, which suggests that variable sleep patterns are a stronger predictor of poor psychological and physical outcomes than mean sleep variables (Becker et al., 2017; Bei,

Seeman, Carroll & Wiley, 2017; Slavish et al., 2019). It has been previously suggested that this association can occur via circadian misalignment or behavioural factors such as poor sleep hygiene (Bei et al., 2016; Slavish et al., 2019).

Mean SOL of CWE did not significantly differ from CWOE, however despite both groups being put to bed at similar times (20.49 PM vs 21.00 PM), CWE had a later sleep onset time of 27 minutes across the weeks compared to CWOE. This would imply that the time CWE are put to sleep is not consistent with their chronotype (Trickett et al., 2019), thus a circadian misalignment may explain these findings. As all subscales of the CSHQ were higher in CWE compared to CWOE, it is difficult to gain a better understanding on the type of sleep problems which may underlie this disturbance. Alternatively, as there was no information regarding specific bedtime routines, it's possible that the later sleep onset time is not reflective of a sleep onset issue but rather a bedtime routine in place by the parents. Further research should therefore aim to include more detailed assessments of bedtime routines and chronotype to elucidate the pathways by which variability in sleep impacts HRQOL in CWE.

When ADHD characteristics were entered in the regression analysis, IIV of SOL was no longer a significant predictor, but ADHD characteristics remained significant. This could imply that the relationship between variability in SOL and HRQOL is possibly mediated by ADHD characteristics. Prior research has consistently shown that children with ADHD have a higher variability in sleep patterns compared to children without ADHD (Hvolby, Jørgensen & Bilenberg, 2008; Langberg et al., 2019; Gruber & Sadeh, 2004). In addition, a study by Gruber, Sadeh & Raviv (2000) proposed that variability in sleep patterns may be a marker of ADHD characteristics. This may stem from an unstable underlying pathway involving the pre-frontal cortex, which is responsible for modulating arousal levels (Owens, 2009; Hiscock, et al., 2015;

Gruber et al., 2000). Consistent with this, there is also evidence to suggest sleep disturbances can manifest as ADHD symptoms (Spruyt & Gozal, 2011a; Owens, 2009). As a result, it is possible that improving ADHD characteristics may improve the relationship between SOL and HRQOL. Refuting evidence from a prior study showed that a behavioural sleep intervention led to short- and long-term improvements in sleep, ADHD characteristics and HRQOL in CWOE (Hiscock et al., 2015), supporting the possibility that sleep problems underlie ADHD characteristics. Ultimately, given the complexity in untangling this relationship, further investigation is necessary. Finally, as observed in Chapter 4, seizure severity was not predictive of HRQOL which is consistent with prior literature (Ferro et al., 2017; Reilly et al., 2019), which implies that epilepsy management should focus on factors in addition to seizures.

There are some limitations within this study that should be recognised when interpreting these findings. Firstly, this study was limited by the small sample size, which may have prevented effects being determined between epilepsy types. Also, it should be noted that there are some drawbacks with actigraphy in determining SOL (Martin & Hakim, 2011; Meltzer et al., 2016). For example, when children are resting in bed but awake, this can lead to misinterpretation of the length of time taken to fall asleep (Fekedulegn et al., 2020). Nevertheless, steps were taken to address this issue. This included following a rigorous cleaning protocol, where both the child's sleep diary and actigraphy defined, times were compared to refine the accuracy of time in bed to sleep time. In addition, most children wore the watch for a period of 14 days (85%), which is indicated to improve the accuracy of this sleep parameter (Rowe et al., 2008).

5.7. Conclusions

Despite these limitations, this is the first study to assess the contribution of actigraphy defined sleep compared to co-occurrences and epilepsy specific variables in HRQOL of CWE. Firstly, the findings confirmed that seizure severity did not significantly contribute to HRQOL and the

relationship between IIV of SOL and HRQOL was potentially mediated by ADHD characteristics, which was consistent with the findings within Chapter 4. However, IIV of SOL and autistic characteristics were found to be independently associated with HRQOL, which was not consistent with the findings from Chapter 4. These findings require acknowledgment as they suggest that the role of neurodevelopmental characteristics in the relationship between sleep and HRQOL is altered depending on the measure used to assess sleep. Furthermore, these findings support the need to screen for these characteristics within the epilepsy management process. Finally, there is also a need for improved communication between neurodevelopmental and epilepsy fields, to determine how to provide the most appropriate support to families of CWE.

CHAPTER SIX

QUALITY OF LIFE IN CHILDREN WITH EPILEPSY: THE ROLE OF PARENTAL MENTAL HEALTH AND SLEEP QUALITY

6.1. Preface

In Chapter 1, a theoretical framework for determinants of HRQOL in CWE was presented, of which epilepsy specific variables, sleep and neurodevelopmental characteristics have been investigated throughout this thesis. In Chapters 4 and 5, sleep and neurodevelopmental characteristics were shown to significantly contribute to HRQOL. However, epilepsy specific variables were shown not to be significantly associated, across both Chapters. Finally, no model was able to explain all the variance in HRQOL. Therefore, this emphasises that additional factors need to be considered when evaluating HRQOL in CWE. Thus far within this thesis, only variables about the child have been considered in relation to HRQOL, however the impact of epilepsy extends beyond this to the whole family. As such in line with aim 1.16.4, the current chapter will explore to what extent family variables such as parental sleep quality and mental health impact HRQOL compared to child variables.

6.2. Introduction

Paediatric epilepsy is recognised for its chronic nature (Hamiwka & Wirrell, 2009) and is associated with a range of co-occurrences such as sleep disturbances, behavioural difficulties, and neurodevelopmental characteristics. Within this thesis and across previous literature, they have been shown to impact HRQOL beyond epilepsy specific variables (Nadkarni et al., 2011; Cianchetti et al., 2015; Reilly et al., 2015). These co-occurrences not only impact the child but extend to impact families (Riechmann et al., 2019; Ferro, 2014). Raising CWE can be particularly difficult for parents, as it can introduce daily uncertainties which require adjustments for the whole family (Duffy & Vessey, 2016). The occurrence of even a single seizure can introduce significant disruptions to parents including increased stress, anxiety, depression, and sleep disturbances (Lv et al., 2009; Reilly et al., 2018a,b,c; Larson et al., 2012; Shaki et al., 2011). However, there has been little examination of how parental variables impact child HRQOL, and even less investigation of the relative contribution of parental variables compared to child variables in predicting HRQOL. Understanding the contribution of these two domains can help to optimise epilepsy management and determine what areas of need to prioritise, when aiming to improve HRQOL.

Previous literature indicates that parents of CWE are vulnerable to heightened stress and psychopathologies including anxiety and depression (Yang, Feng, Zhu, Qiao, Xiao & Feng, 2020; Zhang et al., 2021). This is supported by two prior systematic reviews, which estimated that 47% of parents of CWE experience symptoms of depression (Ferro & Speechley, 2009) and up to 60% of parents experience anxiety symptoms (Jones & Reilly, 2016). Poor well-being in parents can arise due to a variety of factors. One factor includes seizure outcomes, with the severity and frequency of seizures predicting family stress (Yong et al., 2006). Moreover, the psychological impact on families is unique in epilepsy compared to other

chronic conditions. According to past studies, this is likely due to the unpredictability of seizures, which can leave parents in a constant state of worry (Berg et al., 2019; Chiou & Hsieh, 2008). Alternatively, evidence from some research suggests that parental well-being does not solely stem from epilepsy specific variables, but rather co-occurring factors such as behavioural difficulties (Reilly et al., 2018c; Shore, Austin, Huster & Dunn, 2002; Wood, Sherman, Hamiwka, Blackman & Wirrell, 2008). This is supported by Williams et al. (2003) who found that anxiety symptoms were significantly higher in parents of CWE with co-occurring learning and behavioural disabilities compared to parents of children with no co-occurrences. Similarly, behavioural difficulties in CWE can lead to increased parental stress (Rani & Thomas, 2019). Therefore, the role of co-occurrences is important to consider when assessing parental variables and their contribution to HRQOL.

The aforementioned studies demonstrate that parents are vulnerable to poor mental health and that various factors can impact this. Another important putative contributor to well-being is parental sleep. Prior research has demonstrated that parents of CWE are at risk of sleep disturbances and that this needs to be monitored in addition to parental mental health (Reilly et al., 2018a,b). Disturbed sleep patterns have been documented in 38% to 62% of parents of CWE (Reilly et al., 2018a; Liu et al., 2021) and can arise because of various factors. As demonstrated earlier in Chapter 2, CWE are vulnerable to both objective and informant reported sleep disturbances (Winsor et al., 2021), which can extend to impact parental sleep (Shaki et al., 2011). Furthermore, parents are more likely to engage in poor sleep hygiene habits such as co-sleeping due to worries about nocturnal seizures in their child (Larson et al., 2012; Cottrell & Khan, 2005; Wirrell & Turner, 2001). Poor sleep and mental health in parents can have large ramifications on parental functioning and adaptation to disease (Wu, Follansbee-

Junger, Rausch &Modi, 2014; Reilly et al., 2018a,c). Therefore, it is important to study the prevalence of these outcomes to estimate the level of support required for parents of CWE.

So far, some research has considered the contribution of parental mental health to HRQOL. In the wider literature, parental worries about epilepsy have been shown to be related to a decline in child HRQOL (Cianchetti et al., 2015). Some studies have also shown that parental anxiety and depression are negatively related to children's HRQOL (Li, Ji, Qin & Zhang, 2008; Williams et al., 2003; Yong et al., 2006). However, across these studies the eligibility criteria were largely permissive, limiting their external validity. In contrast, children with ID were included within these studies which would likely amplify impact the relationship between parental wellbeing and HRQOL (Thompson, Kerr, Glynn & Linehan, 2014).

In addition to parental mental health, another important factor is parental sleep quality. The findings from Chapter 4 showed that over 78.13% of children experienced sleep problems (see section 4.4.2). Poor sleep in CWE extends to negatively impact parental sleep quality (Reilly et al., 2018a; Shaki et al., 2011). Poor sleep quality in parents of CWE has also been shown to be associated with more severe mental health symptoms (Cottrell & Khan, 2005; Larson et al., 2012), which ultimately contributes to poor child HRQOL in children. Despite this no studies have investigated the relationship between parental sleep and child HRQOL; thus, this study aims to address this research gap.

Given the impact of parental variables and child variables (see Chapters 4 and 5) in HRQOL, understanding the level of contribution to HRQOL can help to prioritise treatment needs. Broader research has assessed the contribution of parental coping vs epilepsy severity to child HRQOL, which showed that parental coping was a stronger predictor in determining HRQOL

than epilepsy specific variables (McLaughlin, Schraegle, Nussbaum & Titus, 2018). Similarly, Yong et al. (2006) found that parental anxiety was more strongly predictive of HRQOL compared to epilepsy specific variables such as seizure outcomes and AEDs. These findings are consistent with previous research, which emphasised that epilepsy goes beyond epilepsy specific variables (Puka, Ferro, Anderson & Speechley, 2019; Puka, Widjaja & Smith, 2017) and that family variables can further complicate management of the disease (Engel, Shanley, Scal & Kunin-Batson, 2021). However, these studies failed to include co-occurrences limiting the interpretation of the impact of this distribution on HRQOL.

Contrastingly, Bilgiç, Işık, Çolak, Derin, & Çaksen (2018) evaluated the contribution of parents and child psychological symptoms, as well as epilepsy specific variables. They found that parental variables were not significant contributions to child HRQOL. In comparison, they did show that both epilepsy specific factors and psychological co-occurrences were significant predictors in HRQOL, but co-occurrences held the strongest contribution. This study demonstrates that comparison of the contribution parental variables to co-occurring conditions could provide a better understanding of what role parental variables hold in HRQOL. Moreover, this can have clinical utility for assessing which areas should be addressed when aiming to improve HRQOL. Therefore, future research needs to empirically evaluate the relative contribution, whilst controlling for co-occurring conditions which can also exert an additional influence.

In summary, poor mental health and sleep problems are common in parents of CWE. However, when estimating the impact on HRQOL, previous research is limited as it has mainly considered the contribution of epilepsy related variables to parental variables, which fails to allow for the impact of co-occurring conditions. To comprehensively assess HRQOL in CWE,

it is important to understand the prevalence of mental health symptoms and sleep difficulties in parents. Once these are established, evaluating whether these variables also contribute to HRQOL in addition to child variables will provide a more comprehensive and clinically valuable model of HRQOL in CWE.

6.2.1. Study Aims

1. To investigate the prevalence of sleep disturbances, anxiety, and depression symptoms in parents of CWE
2. To examine the association between parental sleep quality and anxiety and depression symptoms.
3. To explore the contribution of parental mental health and sleep compared to co-occurring conditions in CWE to child HRQOL.

6.3. Methods

The methods specific to this Chapter are provided in detail below. For a detailed description of the measures used, please refer to Chapter 3.

6.3.1. Participants

6.3.1.1. Children with epilepsy

From an initial sample of 70 participants, 17 children were excluded as they did not receive an epilepsy diagnosis, ten due to the presence of an ID and ten who did not complete the measures to be included in the analysis. The final sample consisted of 33 CWE (M= 9.72, SD 2.50, range = 4-14 years). Demographic information is presented in Table 4.1.

6.3.1.2. Parents of children with epilepsy

Demographic information was reported for 29 parents in total. This sample consisted of 25 mothers (M=39.64, SD=5.98, range=26-49, three mothers ages missing) and four fathers (M=48.25, SD=4.43, range=44 -53).

6.3.2. Procedure

Parents were asked to complete a battery of questionnaires. See Chapter 3 for a complete list of measures and outline of the procedure. Similar to previous Chapters, due to partial or non-completion of the questionnaires one response was not recorded for the CSHQ, two for the SCQ, one for the Conners, one for the QOLCE and three for the PSQI. Consequently, the sample size across analyses are different.

6.3.3. Measures

Clinic data of CWE were extracted from health records including epilepsy diagnosis, type and number of AEDs and socio-demographic information including sex and age (see Table 5.1). The informant reported outcomes for children assessed within this Chapter are the same as those outlined in Chapter 4 (see section 4.3.3.). In addition to these, parental mental health was assessed using the Hospital Anxiety and Depression Scale (HADs, Zigmond & Snaith, 1983) and parental sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989).

6.4. Statistical Analysis

Descriptive statistics were used to describe the scores on the PSQI and HADs, the prevalence of parents scoring above the clinical cut off for each questionnaire was calculated. Correlation analyses were conducted to assess the relationship between parental sleep quality to depression

(Spearman rho) and anxiety (Pearson coefficient) symptoms. Bonferroni correction was used to correct for multiple comparisons. In addition, exploratory hierarchical linear regressions were used to compare the contribution of child outcomes (Autistic characteristics, ADHD characteristics and sleep problems) and parental outcomes (Sleep quality, anxiety, and depression symptoms) to HRQOL.

Prior to conducting the regressions, the number of child variables were reduced using Principal Component Analysis (PCA), due to the small sample size within the study. PCA with varimax rotation was conducted using the "stats" and "psych" packages in R software. To determine the suitability of data for the PCA, the Kaiser Meyer Olkin (Kaiser, 1974) of sampling adequacy and the Bartlett's test of sphericity (1951) were used. The Kaiser Meyer Olkin test revealed a Figure of 0.62 indicating the data was suitable for the PCA. The Bartlett's test of sphericity was significant $\chi^2(6) = 12.75$, $p=0.04$, indicating that there was sufficient correlation between the items. Using Kaisers (1960) criterion, examination of the scree plot led to retainment of one component with eigenvalue of greater than one (eigenvalue = 1.8) (see Figure 6.1). This component was defined by three variables (autistic characteristics, ADHD characteristics and sleep problems) which loaded the most strongly and accounted for 45% of the variance (see Table 6.1). Subsequently this component was used in the hierarchical linear regression analyses as a summary index for the child co-occurring variables, which have been investigated more specifically in previous Chapters.

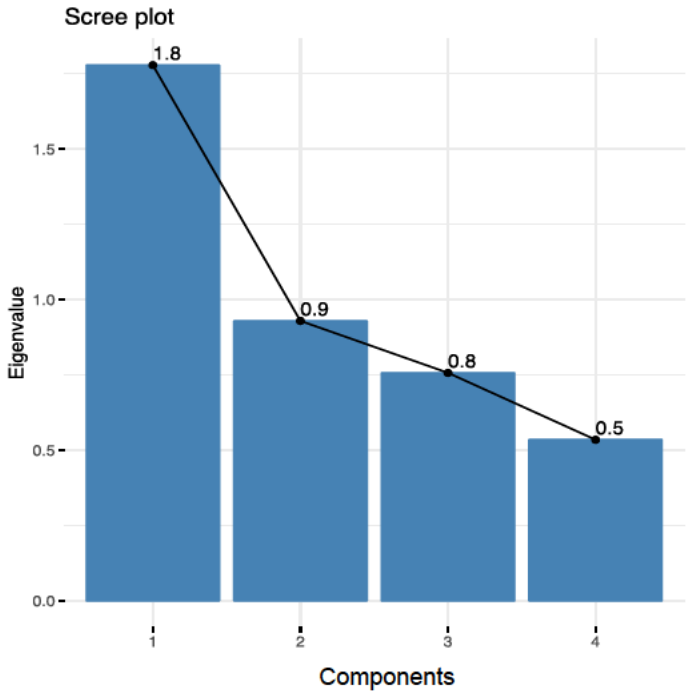


Figure 6.1 Scree Plot indicating one component to be retained based on Kaiser's rule for eigenvalues

Table 6.1. *Loadings of Principle Component Analysis using four child variables*

	Component			
Child composite scores	**1**	**2**	**3**	**4**
Sleep disturbances	**.57**	-.33	-.47	.56
Seizure severity	-.06	**.88**	-.43	-.14
ADHD characteristics	**.53**	.33	.74	-.75
Autistic characteristics	**-.63**	-.10	.23	.32
Proportion of variance explained	44.47%	23.24%	18.92%	13.37%
Cumulative Variance Explained	44.47%	67.72%	86.63%	100.00%

Note N=30, values in bold indicate strongest loading, Rotation Method: Varimax
1 component extracted

6.5. Results

6.5.1. Descriptive statistics for parental variables

To examine aim one, parental anxiety, depression and sleep quality scores were calculated, along with prevalence rates. The mean parental scores for depressive and anxiety symptoms were 4.64 ± 4.16 and 8.24 ± 4.08 respectively (see Figure 6.2). In terms of prevalence rates, 33.33% of parents had a score of ≥11 on the anxiety scale, while 12.12% of parents had a score of ≥11 on the depression scale. The mean total PSQI score was 7.54 ± 4.10 and 67.86% of parents scored above the global cut off (>5) for clinically disturbed sleep quality.

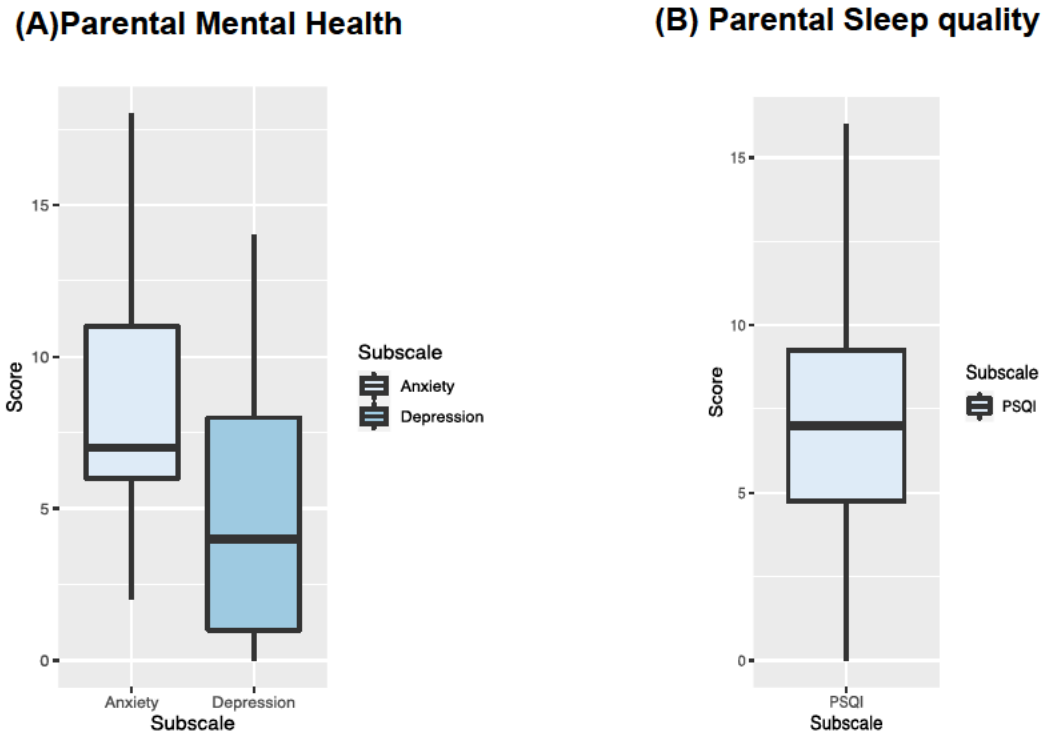


Figure 6.2 Boxplots for (A) parental anxiety and depression symptoms and (B) sleep quality scores. Horizontal lines denote the median and interquartile range. Whiskers represent maximum and minimum points.

6.5.2. Relationship between parental sleep quality and mental health

To address aim two, correlational analyses were conducted to examine the association between parental sleep quality to anxiety, and depression symptoms. The analyses revealed a significant positive correlation between parental sleep quality and anxiety symptoms (r(28)=0.51, *p*=.01). A trend was also revealed for the association between parental sleep quality and depression symptoms (*rho* (28)=0.38, *p*=0.05) (see Figure 6.3).

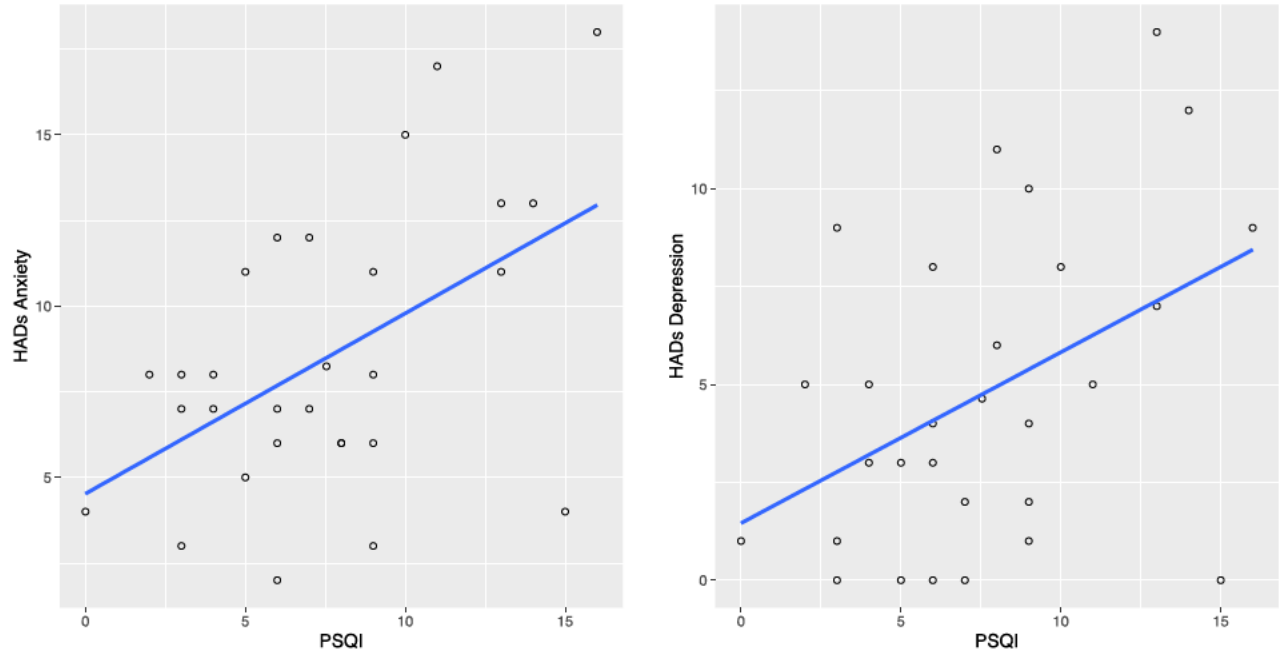


Figure 6.3. Scatter plot depicting (A) Correlation between sleep quality and parental anxiety symptoms and (B) correlation between sleep quality and parental depression symptoms

6.5.3 Contribution of parental variables compared to child variables in determining HRQOL

To address aim three, hierarchical linear regressions were used to compare the contribution of parental and child co-occurring variables (component one) to child HRQOL. Age of child was

entered into the first step; parental variables were inputted in the second step and the child variables were inputted in the final step within all the regression models. The parental variables across the three models included sleep quality (Table 6.2), anxiety symptoms (Table 6.3) and depression symptoms (Table 3.4). See Figure 6.4 for a schematic representation of regression models.

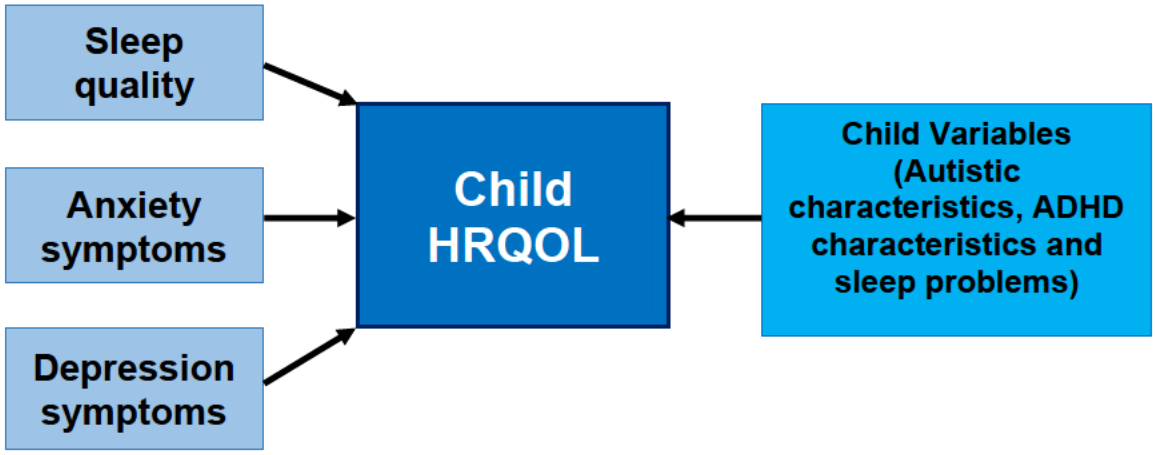


Figure 6.4. Schematic representation of hierarchical linear regression for aim 1.16.4.

6.5.3.1. Parental Sleep Quality vs Co-occurring conditions in child HRQOL

In the first model, age of child was entered in the first step of the model, with the addition of parental sleep quality in the second step and child co-occurrences in step three. In step one, age accounted for 3.0% of the variance and the model was not significant F (1,26) =.81, p=.38. In step two, introduction of parental sleep quality led to a significant improvement in the model accounting for an additional 20.0% of the variance F(2,25) =3.74, p=.04. Finally in the third step, addition of the child variables led to a significant improvement in the overall model F(3,24) =6.36, p=.003, accounting for an additional 21.2% of the variance. However, parental sleep quality was no longer a significant predictor of child HRQOL (β=-.09, t(24) =-.49, p=.63). Overall, these findings indicate that co-occurrences in CWE not only significantly

predict child HRQOL, but possibly mediated the relationship between parental sleep quality and child HRQOL.

Table 6.2. *Hierarchical linear regression predicting child HRQOL from parental sleep quality and co-occurring conditions*

Model 1	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.03	-.01
Age	-1.43	1.59	-.17	-.90		
Step 2					.23	.17
Age	-.93	1.45	-.11	-.64		
PSQI	-2.42	.95	-.45	**-2.55***		
Step 3					.44	.37
Age	-1.25	1.27	-.15	-.99		
PSQI	-.51	1.04	-.09	-.49		
Component one	-9.30	3.08	-.58	**-3.03****		

Note. N= 28, * p<.05, **p<.01, ***p<.001

6.5.3.2. Parental Anxiety vs Co-occurring conditions in child HRQOL

In the second model, when age was entered in the step one, it was found to account for 2.5% of the variance and the model was not significant F (1,29) =.73, *p*=0.40. In step two, when parental anxiety symptoms were entered, this contributed significantly to the model F (1,28) =4.81, *p*=.04, accounting for additional 14.3% of variance in HRQOL. Finally in the third step, when child co-occurrences were inputted, they led to a significant improvement in the overall model F (3,27) =7.01, *p*=.001 (27.0%). Whilst child co-occurrences were significant within this step (*β*=-.59, t(27)=-3.60, *p*=.001), anxiety symptoms were no longer a significant predictor of overall HRQOL (*β*=-.09, t(27)=-.56, *p*=.58). These findings suggest that co-occurrences in CWE may possibly mediate the relationship between parental anxiety and child HRQOL.

Table 6.3. *Hierarchical linear regression predicting child HRQOL from parental anxiety symptoms and co-occurring conditions*

Model 2	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.03	-.01
Age	-1.25	1.47	-.16	-.86		
Step 2					.17	.11
Age	-1.48	1.38	-.19	-.19		
Anxiety	-1.92	.87	-.39	**-.38***		
Step 3					.44	.38
Age	-1.33	1.16	-.17	-.17		
Anxiety	-.47	.83	-.09	-.09		
Component one	-9.29	2.58	-.59	**-.59****		

Note. N= 31, * p<.05, **p<.01, ***p<.001
Note

6.5.3.3 Parental Depression vs Co-occurring conditions in child HRQOL

In the third model, age of child was entered in the first step with the addition of parental depression symptoms in the second step and child co-occurrences in step three. In step one, age accounted for 2.5% of the variance and the model was not significant F (1,29) =.73, p=0.40. In step two, parental depression symptoms significantly improved the overall model and variance F (2,28) =5.01, p=.01, (23.9%). Finally in the third step, when child variables were entered this led to a significant improvement in the overall model F (3,27) =7.63, p<.001, and accounted for an increase in 19.5% of the variance of HRQOL. However parental depression symptoms were no longer a significant predictor of child HRQOL (β=-.20, t(27)=-1.17, p=.25). Overall, these findings indicate that co-occurrences in CWE not only significantly predict child HRQOL, but possibly mediate the relationship between parental depression symptoms and child HRQOL.

Table 6.4. *Hierarchical linear regression predicting child HRQOL from parental depression symptoms and co-occurring conditions*

Model 3	**B**	**SE**	**β**	**t**	**R^2**	**Adjusted R^2**
Step 1					.03	-.01
Age	-1.25	1.47	-.16	-.86		
Step 2					.26	.21
Age	-.44	1.32	-.06	-.34		
Depression	-2.61	.87	-.50	**-3.01****		
Step 3					.46	.40
Age	-.94	1.17	-.12	-.81		
Depression	-1.06	.91	-.20	-1.17		
Component one	-8.28	2.66	-.53	**-3.12****		

Note. N= 31, * p<.05, **p<.01, ***p<.001

6.6. Discussion

The purpose of the current study was (1) to examine the prevalence of poor sleep quality and mental health symptoms in parents of CWE. (2) To examine the interaction between parental mental health and sleep quality. (3) To explore the contribution of parental variables compared to child variables in predicting overall HRQOL. With respect to the first aim, the study revealed that for anxiety and depression symptoms, 33.33% and 12.12% of parents scored above the threshold. In addition to this, 67.86% of parents experienced clinically disturbed sleep quality. In terms of the second aim, the findings also revealed that parents of CWE showed a significant relationship between disturbed sleep and poor anxiety symptoms, and a trend for poor depression symptoms. Finally, in terms of the third aim, it was demonstrated that parental sleep quality, anxiety, and depression symptoms independently predicted children's overall HRQOL. However, when child variables were considered, parental variables were no longer significantly predictive. Rather, the severity of children's co-occurrences significantly

predicted HRQOL above these. This indicates that co-occurrences possibly mediate the relationship between parental variables and child HRQOL. This extends previous research which has mainly focused on the level of contribution between parental variables and epilepsy specific variables in HQOL. These findings have significant clinical utility, as they present consistent evidence for the role of co-occurring conditions in HRQOL, which are rarely screened for in the epilepsy management process.

The current study revealed that parents scored 8.70 and 4.96 on the anxiety and depression subscales of the HADs respectively; this data is similar to those of Wojtas, Oskedra, Cepuch & Świderska (2014) where parents of CWE scored 8.25 and 6.02 on these subscales. In addition to this, prevalence rates of parents who scored above the clinical thresholds for anxiety and depression symptoms were calculated. The results revealed that 33.33% and 12.12% of parents scored above the clinical threshold for anxiety and depression symptoms respectively. In comparison to other studies which have used the same measure in parents of CWE, the values within this study are considerably lower. For example, Shariff et al. (2013) found that 55% and 38.7% and Yong et al. (2006) found that 58% and 42% of parents of CWE scored above the clinical thresholds for anxiety and depression subscales. The differences between the prevalence rates within these studies and this study, may be explained by various factors. As noted in the study by Yong et al. (2006) over 30% of the CWE sample were suggested to have mental development in the "abnormal" range, however in our study, children with co-occurring ID were excluded. Prior research has found that parents of children with a significant developmental delay or ID experienced heightened stress levels (Buelow, McNelis, Shore & Austin, 2006; Reilly et al., 2018b). This is due to the increased demands required of the parents in their role, due to the need to manage both seizures and additional behavioural and cognitive differences (Shatla, Sayyah, Azzam & Elsayed, 2011). In addition to increased caring responsibilities, co-occurring ID has been found to be associated with higher stigma and poorer

child-parent relationship (Reilly et al., 2018b). This has been shown to increase stress in parents (Rani & Thomas, 2019), which can ultimately contribute to increased risk of psychopathologies such as depression and anxiety.

Despite discrepancies between the rates of mental health symptoms across studies, there were consistencies between studies when observing the difference within anxiety and depression symptoms. Consistent with the findings in the current study, most previous studies indicated that anxiety symptoms were higher than depression symptoms in parents CWE. Higher anxiety symptoms can arise due to the unpredictable and chronic nature of epilepsy (Li et al., 2008), which can leave them in a constant state of worry. Although it was not possibly to use a control group within this study, comparison of HADs scores were made to a similarly aged sample of people. It was found that 17.33% of people score above the clinical threshold for anxiety symptoms whereas 7.70% of people scored above the clinical threshold for depression symptoms (Breeman, Cotton, Fielding & Jones, 2015). These scores are lower compared to the current study, which showed that 33.33% and 12.12% of parents scored above the clinical cut off for anxiety and depression symptoms respectively. These findings emphasise that parents of CWE are vulnerable to increased mental health difficulties and the need to consider these outcomes in the epilepsy management process.

Within this study, the mean total PSQI score (7.14) was consistent with the scores of prior studies (6.33-7.70), which have compared sleep quality in parents of CWE to parents of CWOE (Yang et al., 2020; Larson et al., 2012). In addition to these scores, percentage for proportion of parents which scored above the threshold for poor sleep quality were also calculated. However, these scores were higher than of those studies, which have reported poor sleep quality in 37.6 to 59.9% of parents (Cottrell & Khan, 2005). In addition, this study revealed

that parental sleep quality was significantly associated with parental anxiety symptoms. This is in line with prior research (Yang et al., 2020; Cottrell & Khan, 2005; Reilly et al., 2018a) which have also documented associations between parental wellbeing and sleep. Due to the cross-sectional nature of this study, a causal relationship could not be confirmed. However, the majority of research indicates that this association is likely to be bidirectional (Alvaro, Roberts, & Harris, 2013). Sleep problems may be a symptom of poor emotional functioning, preventing parents from being able to settle at the onset of sleep. In addition, parental anxiety about children's seizures during the night (Wiggs, Cook, Hiscock, Pal & Gringras, 2021) or the possibility of SUDEP, may contribute to poor sleep hygiene such as co-sleeping (Williams et al., 2000; Larson et al., 2012). Conversely, sleep problems in parents may exacerbate emotional problems such as stress and depression (Yang et al., 2020; Shaki et al., 2011). These findings require clinical acknowledgement, given that sleep disturbances are also shown to significantly contribute to physical health outcomes in parents of CWE (Edelstein, Shorer, Shorer & Bachner, 2019).

The results of this study also indicated that parental anxiety, depression, and sleep quality were initially all significantly predictive of child HRQOL. Consistent with this finding, prior studies have found that parental mental health is strongly associated with HRQOL in CWE (Williams et al., 2003; Wu et al., 2014; Yong et al., 2008). One possible explanation is that parents are concerned about their child's epilepsy and their inability to control the seizures can shape their parenting behaviours (Li et al., 2008), such as imposing excessive restrictions on their child's everyday activities (Williams et al., 2003; Rani & Thomas, 2019). It is important to recognise that informant-reports of child HRQOL have been criticised in prior research, as negative emotions including anxiety and depression symptoms can influence parents' reporting (Wood et al., 2008; Caplan, 2015). Nevertheless, research has demonstrated a relationship between

parental mental health and adolescents' self-reports of HRQOL (Adewuya, 2006). Finally, the current study also revealed that parental sleep quality was significantly predictive of child HRQOL. This relationship may arise due to the impact of poor sleep on parental functioning, reducing their ability to provide optimal support for their child's needs. To date, there is no research which has focused on the association between parental sleep and HRQOL in children. A possible reason for the lack of research is that poor sleep quality may be masked by symptoms of anxiety and depression, thus exert an indirect association with HRQOL, which is not captured. Despite this, the potential indirect impact of poor sleep on child HRQOL is demonstrated by previous studies. One study found that poor parental sleep quality was negatively associated with parent's ability to cope with their child's disease (Liu et al., 2021). This is also emphasised by a study which found that children's perception of their HRQOL was related to parents' ability to support their needs (Fayed et al., 2015). Overall, these findings expand on current literature and point towards the need to better understand the impact of parental variables compared to child variables in determining child HRQOL.

The study also revealed that when child co-occurring variables (component 1) were considered in association with parental variables (sleep quality, anxiety, and depression symptoms), these may mediate the relationship between parental variables and HRQOL. The strong role of co-occurrences above parental variables is supported by prior research (Bilgiç et al., 2018). The role of co-occurring conditions in parental variables and child HRQOL may reflect the lack of support parents receive for coping with these difficulties. Outcomes focused on epilepsy specific variables are routinely addressed in clinical practice. However, this leaves co-occurrences such as sleep problems and neurodevelopmental characteristics vulnerable to diagnostic overshadowing, whereby they may be attributed to side effects of AEDs or effects of seizures (Holmes et al., 2021). Co-occurrences can have direct and significant impact on

various aspects of children's functioning, as highlighted in the literature presented in Chapters 4 and 5. If left unaddressed, they can complicate the diagnosis leading to additional strain on parental wellbeing and sleep. Similarly, they can also leave parents feeling unsupported in their role and vulnerable to negative emotions (Rani & Thomas, 2019). Nevertheless, it is important to note that these findings do not undermine the influence or importance of parental variables, as a mediation analysis could not be conducted to confirm this relationship. Rather parental variables still needed to be considered in epilepsy management to maximise the well-being of the whole family (Cianchetti et al., 2018).

There are several limitations that must be considered when interpreting these findings. Due to the small sample size, all child variables could not be inputted into the regression alongside the parental variables. Therefore, a PCA analysis was used to create a composite index measure for child variables. As a result, the effect of individual variables within this composite could not be separated out. However, this limitation does not affect the results greatly given that all three variables including sleep and neurodevelopmental characteristics often co-occur in CWE and CWOE (Ekinci et al., 2016; Reilly et al., 2019; Tsai et al., 2012), thus it is acceptable that intervening with one can contribute to improvements in the others. Another caveat is that although the results revealed poor sleep quality and heightened anxiety and depression symptoms in parents, they did not infer a cause and effect. Gaining information on parental mental health or sleep history could shed light on the direction of this relationship. Nevertheless, our findings complement prior research which found that co-occurrences predict HRQOL above parental variables (Bilgiç et al., 2018).

6.7. Conclusion

In conclusion, this study confirms the need for assessment and support of co-occurring conditions in CWE. The results also demonstrated that parents of CWE are at risk of poor mental health and sleep quality, which may be bidirectional in nature. However, whilst these variables were initially predictive of HRQOL, their effect was not retained following inclusion of co-occurrences. Therefore, future research should aim to focus on intervening with these co-occurrences, which may ultimately improve the relationship between parental outcomes and HRQOL.

CHAPTER 7

GENERAL DISCUSSION

7.1. Preface

In order to gain an in-depth understanding of HRQOL, the study within Chapter 6 investigated the contribution of parental variables to child variables (co-occurrences), in predicting HRQOL. The results demonstrated that parents of CWE were at risk of poor mental health symptoms and poor sleep quality. In addition, parental anxiety was significantly associated with poor sleep quality. The findings revealed that although parental variables were significantly predictive of HRQOL in CWE, this effect was lost following the inclusion of child variables (co-occurrences). Consequently, it is possible that child variables may exert a mediating effect on the relationship between parental variables and HRQOL. These findings suggest that by addressing co-occurrences in CWE, this may not only improve the HRQOL of CWE, but have a systemic impact on the interaction between parental wellbeing, sleep and HRQOL. Within this Chapter, the aims and evaluation of the findings from Chapters 2-6 will be discussed. Following this, the clinical implications of these findings will be outlined.

7.2. Introduction

The main purpose of this thesis was to examine the relationship between sleep, neurodevelopmental characteristics and HRQOL in CWE. The use of a multi-method assessment of sleep, helped to establish an in-depth understanding of the type of sleep disturbances which exist in CWE. This was also supported with the use of standardised screening measures for neurodevelopmental characteristics, which enabled a robust assessment of their role in HRQOL. With the exception of the review presented in Chapter 2, only one other review has examined the type of sleep disturbances in children and adolescents with epilepsy (Schlarb et al., 2016). This review indicated that CWE experienced various sleep problems including, night wakings, parasomnias, daytime sleepiness and anxieties surrounding sleep. Objective sleep problems including shorter TST and SE were also detected in CWE. However, there were drawbacks of this review, including the lack of a comparative analysis of sleep disturbances in CWE to CWOE and no meta-analysis was conducted. These caveats are significant, as inclusion of a comparison group would enable conclusions to be drawn on the extent to which sleep is disturbed in CWE. Moreover, a meta-analysis would aid in providing an accurate quantification of the sleep disturbances present. Therefore, to address these limitations, Chapter 2 (Winsor et al., 2021) provided the first systematic review and meta-analysis quantifying the type of sleep disturbances that exist in CWE compared to CWOE. This review revealed several methodological limitations within the literature. For example, to prevent a large loss of data due to the small number of studies available, results were synthesised across different type of sleep measurements. In addition, only one study within this review included actigraphy, comparing sleep between CWE and CWOE, which is reflective of the limited evidence base available on actigraphy defined sleep in CWE (Holley et al., 2014). These limitations were addressed in Chapters 4 and 5, which set out to delineate the type of sleep disturbances experienced by CWE as measured by both informant reports and actigraphy.

Recommendations were proposed within Chapter 2 for future research to extend these findings. which formed the over-arching aims within this thesis. Current studies on sleep and HRQOL in CWE (Gutter et al., 2013; Wirrell et al., 2005) are limited and have failed to address the role of neurodevelopmental characteristics, which are commonly co-occurring in CWE. This is problematic, as lack of consideration of neurodevelopmental characteristics can lead to an inaccurate estimation of the impact of sleep on HRQOL in CWE, reducing the representativeness of the results (Ferro et al., 2017). Therefore, to provide a more accurate picture of the association between sleep and HRQOL in CWE, the contribution of the two most commonly co-occurring neurodevelopmental characteristics in CWE, including autism and ADHD were examined in Chapters 4 and 5.

Finally, the theoretical framework produced by Lach et al. (2006) highlighted the different variables which can contribute to poor HRQOL. A notable area was family variables, in order to generate a complete picture of HRQOL in CWE, Chapter 6 considered the contribution of parental variables to co-occurrences in predicting HRQOL. Parental sleep quality and mental health symptoms were considered as the variables of interest, given the high prevalence of these outcomes (Jones & Reilly, 2016; Larson et al., 2012; Zhang et al., 2021). Whilst previous studies have examined the contribution of epilepsy related variables to parental variables, only one study has considered the role of child co-occurrences to parental variables (Bilgiç et al., 2018). Gaining an understanding of how parental variables contribute to HRQOL compared to child variables, can help future research to synthesise possible interventions. Findings from the Chapter 2 and empirical Chapters 4, 5 and 6 are discussed below. The strengths and limitations of these results are evaluated and integrated within the current literature. Finally, the clinical implications and directions for future research are also outlined.

7.3. Summary of findings

Table 7.1 *Summary of Chapter aims and findings within this thesis*

Chapter	Aims	Main findings
Two	To systematically quantify the type of sleep difficulties experienced in CWE compared to CWOE. To assess the heterogeneity between current studies examining sleep difficulties in CWE. To explore potential moderators for differences in sleep parameters including type of sleep assessment, quality of study and demographic variables.	This systematic review and meta-analysis demonstrated that relative to CWOE, CWE experienced more frequent and worse sleep difficulties including night wakings, parasomnias and sleep disordered breathing. In addition, CWE also experienced significantly higher percentage of N2 sleep, reduced sleep efficiency and total sleep time compared to CWOE.
Four	To compare HRQOL and co-occurrences between epilepsy types including (1) Focal epilepsy (2) Generalised epilepsy (3) Rolandic epilepsy. To examine the contribution of neurodevelopmental co-occurrences and epilepsy specific variables to the relationship between informant reported sleep and HRQOL.	The results of this study revealed that most children (78%) experienced significant sleep problems. Sleep problems, autistic characteristics, ADHD characteristics and HRQOL did not significantly differ between epilepsy types. Furthermore, more frequent sleep problems independently predicted HRQOL above epilepsy specific variables. These included seizure severity and number of AEDs, which showed no significant association. Importantly, when either ADHD characteristics or autistic characteristics were considered, the contribution of sleep problems was no longer significant. Consequently, neurodevelopmental characteristics were suggested to exert a mediating effect on the relationship between sleep and HRQOL in CWE.

Table 7.1 *Summary of Chapter aims and findings within this thesis*

Chapter	Aims	Main findings
Five	To compare mean and IIV of actigraphy defined sleep parameters between CWE and CWOE. To compare these sleep parameters between epilepsy types including (1) Focal epilepsy (2) Generalised epilepsy (3) Rolandic epilepsy. To examine the contribution of neurodevelopmental characteristics and epilepsy specific variables to the relationship between actigraphy measured sleep and HRQOL.	Only IIV of SOL was significantly different between CWE and CWOE but was not retained following Bonferroni correction. There was no significant difference across all sleep parameters between epilepsy types. Finally, seizure severity did not significantly contribute to HRQOL. However, IIV of SOL and autistic characteristics showed an independent significant contribution to HRQOL. Variability in SOL was no longer significantly predictive, following inclusion of ADHD characteristics suggesting that they also exerted a mediating effect.
Six	To examine the prevalence and relationship of sleep problems and mental health symptoms in parents of CWE. To explore the contribution of child variables to parental variables in HRQOL.	The majority of parents (67.86%) experienced poor sleep quality above the clinical threshold. Parental sleep quality was shown to be significantly associated with anxiety symptoms and a trend towards an association with depression symptoms. Initially parental sleep quality, anxiety and depression symptoms significantly contributed to HRQOL. These were no longer significant following inclusion of child variables. More specifically, the findings indicated that co-occurrences in children possibly mediated the relationship between parental variables and HRQOL.

7.4 Synthesis of findings within literature

The findings of this thesis are discussed within the themes below: Prevalence and type of sleep disturbances, the complex relationship between sleep and HRQOL and clinical implications for epilepsy management.

7.4.1. Prevalence and type of sleep disturbances in CWE

The first aim of this thesis was to estimate and quantify the type of sleep disturbances which exist in CWE. As noted earlier, only one previous review has been conducted (Schlarb et al., 2016), which had limited internal validity due to lack of a control group. The findings from Chapter 2 demonstrated that relative to CWOE, CWE experienced more severe sleep difficulties including night wakings, parasomnias and SDB. In addition, CWE experienced significantly higher percentage of N2 sleep, reduced SE and TST compared to CWOE. These findings were extended by the experimental Chapters 4 and 5, which enabled assessment of both informant and objectively assessed sleep in CWE. Chapter 4 indicated that 78.13% of CWE experienced significant sleep problems, which is line with previous research using the same measure (Reilly et al., 2018a). Although a control group was not utilised within this study, comparison to a previous study assessing sleep problems in a similar age group, estimated that 33% of CWOE experience significant sleep problems (Markovich et al., 2015). This emphasises that CWE are vulnerable to increased sleep difficulties compared to CWOE.

Importantly, this thesis extends prior literature by including an objective assessment of sleep, given that only one study in the systematic review (Chapter 2) utilised this approach. In addition, using actigraphy also afforded the scope to explore not only mean sleep parameters, but variability in sleep parameters, which is particularly relevant to HRQOL. This is supported by a previous review, which indicated that variability of sleep parameters were more strongly correlated with physical and psychological outcomes, than mean sleep parameters (Bei et al., 2016). Therefore, the analyses within Chapter 5 sought to address these gaps. The findings revealed that there were no significant differences in mean sleep parameters in CWE compared to CWOE, which was consistent with the only previous comparative study of CWE using actigraphy (Holley et al., 2014). By contrast, the findings also revealed that only variability in

SOL was significantly higher in CWE compared to CWOE. However, following Bonferroni correction this was no longer significant, so future research is needed to improve the robustness of these results. The results contrast those of Chapter 4, which suggested that most of the sample of CWE experience significant sleep problems. These findings do not underscore that CWE experience sleep difficulties, but do indicate that future research should examine what variables affect the discrepancy between informant report and actigraphy measures of sleep in CWE.

Finally, across both Chapters, sleep was assessed across epilepsy types, to further delineate whether specific groups of CWE at are risk of poor sleep. No differences were demonstrated in both informant reports and actigraphy defined sleep parameters. However, these findings should be interpreted with caution, given that division of the sample into epilepsy types greatly reduced the sample size of participants. A larger sample would be preferred to confirm these results and to better delineate the sleep profiles of the children across epilepsy type.

7.4.2. The relationship between sleep and HRQOL

In addition to providing a description of the prevalence and type of sleep disruptions in CWE the second and third aim of this thesis was to assess the relationship between sleep and HRQOL. A multi method approach to measuring sleep was used, including both informant measures and actigraphy. Several pathways were considered in understanding the impact of sleep disturbances on HRQOL including epilepsy specific variables and neurodevelopmental characteristics.

7.4.2.1 Contribution of epilepsy specific factors to the relationship between sleep and HRQOL

To better understand the influence of epilepsy specific variables on the relationship between sleep and HRQOL, this outcome was compared across epilepsy types. Following this, several hierarchical linear regression analyses were conducted. In Chapter 4, HRQOL was found not to be significantly different across epilepsy type, which is particularly important given the inclusion of rolandic epilepsy. As noted in section 1.2.4, rolandic epilepsy is characterised by low seizure frequency and is rarely treated with AEDs. Therefore, this finding supports the view that the HRQOL is not strongly related to epilepsy specific variables (Wood, 2012; Baca et al., 2011).

In Chapter 4, the results of the hierarchical regression analyses showed that more severe sleep problems significantly contributed to HRQOL. Moreover, when seizure severity and number of AEDs were inputted, they added little variance (0-5.4%) and were non-significant contributors to HRQOL. Whereas sleep problems remained significantly associated with HRQOL. These findings extend the current literature, whereby only two studies have investigated informant reported sleep and HRQOL in CWE. Both studies documented that more severe and adverse sleep problems were associated with poorer HRQOL (Wirrell et al., 2005; Gutter et al., 2013). These findings were consistent with those of Gutter et al. (2013), who found that children with co-occurring epilepsy and sleep problems had poorer HRQOL compared to CWE, but no sleep problems. This illustrates that sleep problems are associated with poor HRQOL and need to be considered in epilepsy management. Although some studies have demonstrated that higher number of AEDs and seizure severity worsen HRQOL (Aggarwal et al., 2010; Nadkarni et al., 2011), other studies have found that epilepsy specific variables such as seizure severity were not predictive of HRQOL (Speechley et al., 2012; Sherman, Slick & Eyrl, 2006). A possible explanation for these differences may be explained

by the high heterogeneity in the type of measures used to record seizure severity and number of medications. Nevertheless, self-reports from CWE have reported similar findings to this study, suggesting that HRQOL is not mainly determined by epilepsy specific variables (Hussain et al., 2020; Fayed et al., 2015).

In Chapter 5, the impact of actigraphy defined sleep parameters on HRQOL were then considered. It was found that in the first model, IIV of SOL was the only significant predictor of HRQOL in CWE. However, the predictive value was lost in the presence of seizure severity, which also did not significantly contribute to overall HRQOL. Despite this, the change in the beta coefficient was minimal, thus seizure severity had little impact. To date, no published study has explored the contribution of actigraphy sleep parameters to HRQOL in CWE. This adds to the complexity in interpreting these findings but does highlight the need future research to assess a full spectrum of sleep disruptions.

7.4.2.2 Contribution of neurodevelopmental characteristics to the relationship between sleep and HRQOL

In line with aims two and three, both Chapters 4 and 5 explored the contribution of autistic and ADHD characteristics in relation to sleep disruptions on HRQOL. Previous research has emphasised the importance of epilepsy specific variables in the relationship between sleep and HRQOL. However, few studies have considered the role of other co-occurrences such as neurodevelopmental characteristics in the relationship between sleep and HRQOL in CWE. In Chapter 5, correlation analyses were initially conducted between actigraphy defined sleep parameters and HRQOL to identify predictor variables for input into the regression analyses. It was found that both mean and IIV of SOL and mean WASO were significantly correlated with HRQOL, thus were entered as sleep predictors within the regression analyses. In the

regression analyses in Chapter 4 and 5, it was demonstrated that in the second step, both informant-reported sleep problems and IIV of SOL were found to be significantly predictive of HRQOL. Following this, when autistic characteristics or ADHD characteristics were inputted in the final step, they also accounted for a significant contribution to the variance in HRQOL. However, the effect of informant reported sleep problems was not retained in both cases. Similarly, in Chapter 5 when ADHD characteristics were introduced, the significant effect of IIV of SOL was lost, suggesting that ADHD characteristics potentially mediated the relationship between variability in sleep and HRQOL (see Figure 7.1). However, when autistic characteristics and IIV of SOL were considered together, both exerted a unique contribution to HRQOL (see Figure 7.2). This is particularly interesting as this suggests that the manner in which neurodevelopmental characteristics modify the relationship between sleep and HRQOL, differs depending on the type of sleep tool. This is relevant to prior studies, which suggest that whilst the CSHQ may be a useful tool in screening for sleep problems, actigraphy is also needed to compensate for the limitations of informant reports and to assess specific sleep parameters (Duraccio et al., 2018; Perpétuo et al., 2020).

These differences in the trimodal relationship between IIV in SOL, neurodevelopmental characteristics and HRQOL should be acknowledged. Variability in sleep patterns, specifically higher variability in SOL has been recognised to be negatively affected in children with ADHD vs TD children (Gruber et al., 2000; Moreau, Rouleau, & Morin, 2014; Ziegler et al., 2021). This is consistent with prior research which indicates that sleep problems may be secondary to ADHD characteristics (Owens, 2009; Hvolby, 2015). Whereas the literature regarding the relationship between variability of sleep and autistic characteristics is not as convincing (Goodlin-Jones, Tang, Liu & Anders, 2008; Anders, Iosif, Schwichtenberg, Tang & Goodlin-Jones, 2011). Therefore, the findings suggest that ADHD characteristics are the fundamental

driver of HRQOL, and sleep disruption occurs as secondary to these characteristics. Whereas co-occurrences of autistic characteristics and variable SOL uniquely contribute to poor HRQOL. This consistent role of ADHD characteristics in predicting HRQOL in CWE, has been supported by prior research (Ekinci et al., 2017), which found that children with ADHD alone had worse HRQOL than CWE alone.

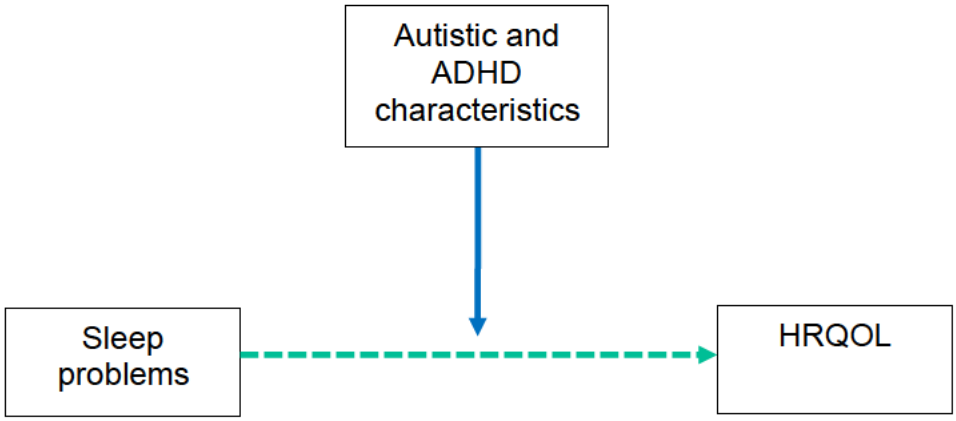


Figure 7.1. Conceptual diagram for the role of autistic and ADHD characteristics on the relationship between informant reported sleep problems and HRQOL (Chapter 4).

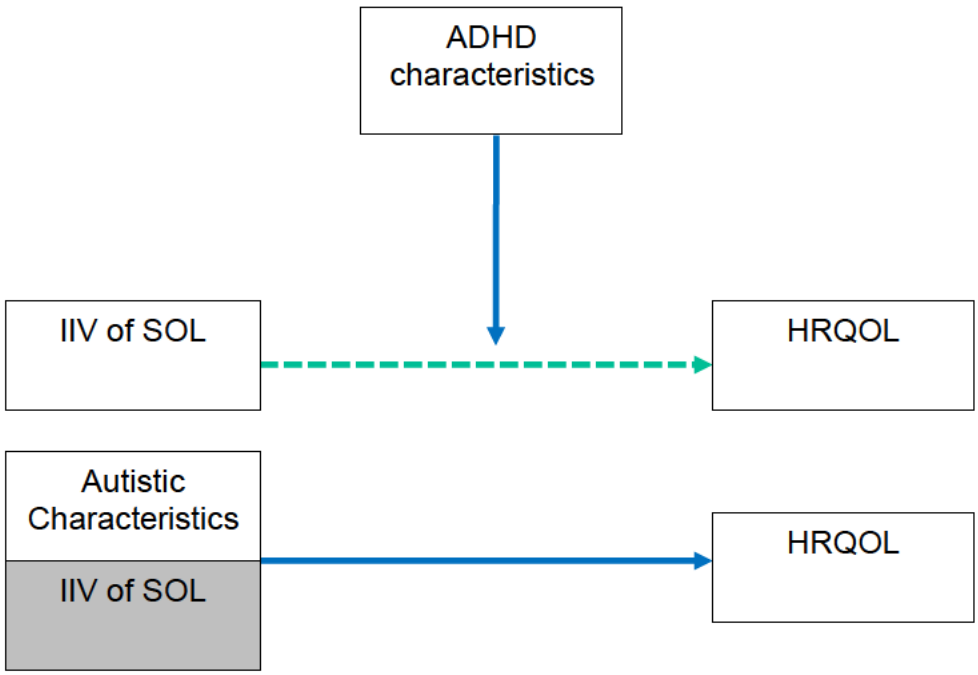


Figure 7.2 Conceptual diagram for the interaction between neurodevelopmental characteristics, IIV of SOL and HRQOL (Chapter 5)

7.4.3. Contribution of parental variables vs child variables in HRQOL

The final aim of this thesis was to examine prevalence of sleep quality and mental health symptoms in parents of CWE. Within Chapter 6, the results showed that the 67.86% of parents experienced poor sleep quality above the clinical threshold. Similarly, the proportion of parents scoring above the threshold for anxiety (33.33%) and depression (12.12%) symptoms was higher than those previously reported in the general population (Breeman et al., 2015). Moreover, poor sleep quality was found to be significantly associated with anxiety scores and a trend was observed for depression scores. These findings provide convergent evidence for the systemic impact that raising a child with epilepsy can have on family systems.

In addition to the final aim, the contribution of these parental variables was compared to child variables (co-occurrences) in determining HRQOL. Taken together, the findings from Chapters 4 and 5 indicated that higher co-occurrences including sleep, autistic and ADHD characteristics negatively impact HRQOL above and beyond epilepsy specific variables. To gain an in-depth understanding of HRQOL, the investigation in Chapter 6 set out to the extend these results. Previous research has documented a negative association between parental anxiety, depression, and child HRQOL (Williams et al., 2003; Adewuya, 2006; Li et al., 2008). However, few studies have investigated the relative contribution of child vs parental variables in CWE, in which the findings have been mixed. A previous study found that parental anxiety was the strongest predictor, above epilepsy related variables for poor HRQOL (Yong et al., 2006). Furthermore, prior studies have found that when parental anxiety and coping are considered in conjunction to epilepsy specific variables, parental variables predict worse HRQOL above epilepsy specific variables (Yong et al., 2006; McLaughlin et al., 2018). However, the failure to consider co-occurrences in this relationship is particularly problematic, due to the high prevalence of these issues in CWE and their contribution to HRQOL (see Sections 1.11.4). In

contrast, a previous study compared parental variables to child epilepsy specific variables and co-occurrences. They found that co-occurrences predicted HRQOL above these variables and parental variables no longer played a significant role (Bilgiç et al., 2018). Therefore, inclusion of co-occurrences may elucidate the role of parental variables in HRQOL and is an area that warrants further acknowledgment.

Within Chapter 6, a PCA was initially conducted to reduce the number of child variables. This analysis showed that no component including an epilepsy specific factor remained above the threshold of an eigen value of 1, thus were not carried forward into the regression analyses. This resulted in a component of co-occurrences only. The analysis showed that all parental variables (sleep quality, anxiety, and depression symptoms) were initially predictive of HRQOL, however following input of co-occurrences, they were no longer significant. This suggests that co-occurrences mediate the relationship between parental variables and HRQOL (see Figure 7.3). A possible explanation for these findings may be attributed to the additional care burden co-occurrences can add to parents' role (Pokharel et al., 2020; Wei & Lee, 2015). This combined burden can negatively impact parental outcomes and the quality of care that parents can provide to their child (Abd El-Mouty & Salem, 2019), impacting HRQOL. Therefore, maximising support for co-occurrences may have an indirect effect on the relationship between parental outcomes and HRQOL in children. However due to the limited sample size within this study, more research is needed to improve the robustness of the findings. Nevertheless, across all chapters co-occurrences are indicated to have the strongest impact on HRQOL. In the context of epilepsy management and with the aim of improving HRQOL, this suggests that the focus should be on co-occurrences such as sleep problems and neurodevelopmental characteristics. However, it's important to note that this does not underestimate the poor outcomes which exist in parents'. This finding holds clinical

implications for epilepsy management, suggesting a triage approach may be necessary if aiming to improve HRQOL (see Figure 7.4 for a proposed approach).

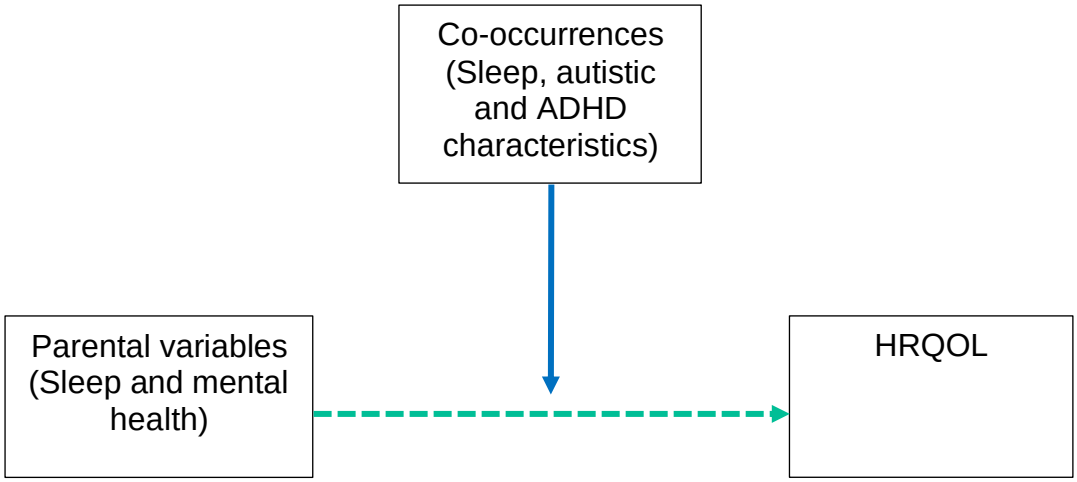


Figure 7.3. Conceptual diagram demonstrating the impact of co-occurrences on the relationship between parental variables and HRQOL (Chapter 6)

7.5. Strengths and limitations

7.5.1. Strengths

A main strength of this thesis is that it was driven by gaps in both the research and clinical fields, thus a balanced approach was taken to assessing the variables which contribute to HRQOL. There is a limited evidence base focusing on the impact of co-occurrences on HRQOL, despite the high prevalence rates in CWE (Reilly et al., 2019). Therefore, a key first step was to explore the contribution of different determinants including co-occurrences. Following this, parental variables were also explored to provide a more in-depth understanding of which variables drive poor HRQOL, beyond epilepsy specific variables. In addition to this, from the data presented, various pathways were put forward for improving HRQOL, which future research should assess.

The findings within this thesis were supported with the use of a disease specific HRQOL tool. The use of this tool was also supported by a previous review, which found that the QOLCE-55 (Goodwin et al., 2015) was recognised as a gold standard measure for HRQOL in CWE (Crudgington et al., 2020a; 2020b). This is particularly important as it ensures that the impact of epilepsy on HRQOL is captured as accurately as possible (Desai, Gadgil, Saad, Raskin & Lam, 2019). Moreover, given the sensitivity of disease specific measures, it would be anticipated that epilepsy related variables would be more strongly correlated (Wu et al., 2014). However, this was not found within this study and strengthens the findings that epilepsy goes beyond epilepsy related variables.

Another strength of this thesis is that a multimodal approach to measuring sleep was used. This has various advantages including the opportunity to illuminate the discrepancies between the sleep measures and facilitates convergence of data. This extends prior research where assessment of sleep has generally been restricted to the use of informant reports (Holley et al., 2014). As outlined in Chapter 1, use of informant reports holds strengths, particularly in younger children, who may not be able to reliably report their own sleep patterns due to cognitive capacity (Mazza et al., 2020). However, such reports are still subject to bias due to variables such as memory recall and parents' own sleep can affect their ratings on child sleep, which is negatively affected in CWE (Larson et al., 2012). The use of objective measures of sleep not only overcomes issues surrounding bias but by capturing sleep in a naturalistic setting, it also enables deeper exploration of the data for measures such as night-to-night variability, which are rarely explored in the general sleep literature (Bei et al., 2016). Moreover, the two measures have been recognised to measure different aspects of sleep (Perpétuo et al., 2020). Thus, the use of both measures ensures that a more comprehensive picture of child sleep is captured when assessing the impact of sleep on HRQOL.

7.5.2. Limitations

A consistent finding throughout this thesis was the lack of influence of epilepsy specific variables including seizure severity and number of AEDs to HRQOL (Chapter 4 & 5), which is consistent with both adult (Jacoby & Baker, 2008) and paediatric literature (Fayed et al., 2015). Despite this, these findings raise issues surrounding seizure measurement, which has been a continuing discussion within the epilepsy field (Hoppe, Poepel & Elger, 2007; Elger & Hoppe, 2018). Within the study, parents were required to rate their child's seizure severity using a well validated scale (HASS, Carpay et al., 1997). However, there are various variables which impact the accuracy of parent's identification of seizures and in turn their reports on severity outcome. These include younger age of the child, lack of knowledge about seizures and type of epilepsy. Furthermore, it has also been indicated that their ability is also limited, especially in cases regarding absence or nocturnal seizures where parents may not be present for these (Akman et al., 2009). Therefore, the observation regarding the lack of impact of epilepsy specific variables may be impacted by the way in which they were measured. Although methods such as video-EEG would enable more accurate assessment of seizures, however, these are currently limited by the short time period that they can be administered for (Akman et al., 2009; Aghaei-Lasboo & Fisher, 2016). Currently there are strides being made towards developing wearable technologies for seizure detection, which have good accuracy for more specific seizure types such as motor or generalised tonic-clonic seizures. However, their detection rate is not as strong for less pronounced seizure types (Brinkmann et al., 2021). Furthermore, these have yet to be applied to clinical settings, thus the screening measures chosen for use within this study were the most appropriate choice within this study.

Another limitation that must be considered when interpreting the findings within this thesis is the small sample size. This has been previously discussed and was particularly relevant to the

analyses including comparison of scores across epilepsy type (Chapter 4 and 5) and control analyses (see appendix 5.1). In the between group comparison it is possible that lack of group differences may reflect a lack of statistical power causing large variance in the scores. Similarly comparison of IIV of SOL between weekend and weekday was shown to approach significance (0.054) thus care needs to be taken when interpreting this result. Nevertheless, to address these limitations, effect sizes were reported to measure the strength of associations and ultimately improve the clarity of the findings (Aarts, Van Den Akker & Winkens, 2014). These were found to be small across majority of analyses, therefore suggests that these findings also have little practical significance, thus are not affected by the lack of statistical significance. In terms of other statistical limitations, it was noted earlier in section 3.7.3., that the regression analyses were conducted for exploratory purposes, and as a result correction for multiple testing was not conducted. This inflates the likelihood of type two error, which should be considered when interpreting these results. On the other hand, use of Bonferroni correction has been previously criticised for being too conservative in their approach (Perneger, 1998; Bender & Lange, 1999), thus would not be appropriate for the exploratory analyses. Nevertheless, similar caution should be taken in interpretation of the significant findings within the regression analyses. According to Field (2009), when conducting linear regression analysis with three or more predictor variables, a sample size of 40 or more is required to achieve a large effect size of 0.8 (Cohens, 1988). As a result, the regression analyses within this thesis are likely underpowered. However, the findings that epilepsy related variables do not play a large role in HRQOL are in line with previous studies in CWE (Bilgiç et al., 2018; Ferro et al., 2017). Nevertheless, future research is necessary with larger samples to conduct more robust statistical analyses.

Another limitation that should be considered when interpreting our findings is that the sample of CWE were recruited from a tertiary hospital setting. This may capture children with more

complex epilepsies and as a result present with higher rates of co-occurrences, which has been raised by another study (Hansen et al., 2016). Therefore, these findings may not be generalised to CWE with less complex epilepsy types. Future research should aim to recruit from various recruitment routes including primary and secondary care services, which was not possible within this study.

A final limitation of this thesis is the construct validity of neurodevelopmental characteristics, in particularly autistic characteristics in CWE. As previously discussed, there are strengths to using a dimensional approach and the measures chosen are both reliable and valid for quantifying autistic characteristics in the general population (Eaves, Wingert, Ho & Mickelson, 2006; Chesnut, Wei, Barnard-Brak & Richman, 2017). However, there has been a recent debate on whether extending the findings based on autistic characteristics to the autism community is most appropriate (Sasson & Bottema-Beutel, 2021). This is further complicated by the lack of understanding of the presentation of autistic characteristics in CWE and whether these differ to autistic children alone (Holmes et al, 2021). In addition, exclusion of children with ID likely resulted in a smaller range of autistic and ADHD characteristics than exists in the population of CWE (Viscidi et al., 2013). However, inclusion of ID would confound the accuracy of the screening measure, by measuring overall development rather than autistic characteristics (Strasser et al., 2018). Therefore, this strengthens both the practical significance and validity of these characteristics.

7.6. Clinical Implications for epilepsy management

The findings from this thesis have clinical implication in several areas which are addressed below:

7.6.1. Assessment of sleep in the diagnostic process

As evidenced in Chapter 2 of this thesis, sleep is significantly disturbed in CWE across both informants reported and objective sleep methods. This was supported by the findings in Chapter 4 which showed that 78.18% of children experienced significantly frequent sleep disturbance. This is higher than the rates (33%) detected using the same measure in a sample of CWOE of similar age (Markovich et al., 2015). Alongside these finding, the results from Chapters 4 and 5 demonstrated that both informant reported sleep problems and higher IIV of SOL were significantly predictive of poorer HRQOL. This extends the limited evidence base on the relationship between sleep and HRQOL (Gutter et al., 2013; Wirrell et al. 2005). A recent review put forward by Nobili et al. (2021), outlined a diagnostic pathway for assessing and treating sleep problems in clinical appointments. This consisted of a robust sleep assessment involving discussions between the clinician and patient, as well as completion of questionnaires based on the problems identified. The proposed pathway to improving sleep problems and disorders holds large clinical utility for adults with epilepsy. Future research should aim to implement similar pathways in paediatric settings (Jain, Simakajornboon & Glauser, 2013).

Another area of consideration required regarding the diagnostic process is the type of measurement tool used. In Chapter 4 the findings indicated that CWE experience frequent sleep problem across all subscales compared to CWOE. However in Chapter 5 no significant sleep problems were detected using actigraphy between the two groups, indicating a lack of concordance between the measures. A possible explanation for this may relate to the different control groups used across the chapters. In addition, comparison to a previous systematic review and meta-analysis (Galland et al., 2018) establishing normative actigraphy data found similar values to the control group used in Chapter 5, confirming the lack of concordance.

However no prior study has established normative values for variability in sleep, thus interpretation of the degree of concordance is limited to mean actigraphy values only. Other possible reasons for discordance may relate to reporting bias, which is particularly relevant in parents of CWE. A previous study comparing actigraphy and informant reported sleep in CWE found similar findings to the present study and suggested that parental anxiety may contribute to this lack of concordance (Holley et al., 2014). Future research is necessary to assess contributory factors to the agreement between informant and objective measures.

7.6.2. Integration of neurodevelopmental and epilepsy fields.

There is a current gap in the care of people with co-occurring epilepsy and neurodevelopmental conditions. The findings from this thesis demonstrated that autistic and ADHD characteristics uniquely explained between 18.3 to 21.3% and 22.0 to 22.6%, respectively of the variance in HRQOL. Moreover, the results indicated that neurodevelopmental characteristics possibly exert a mediation effect on the relationship between sleep disturbances and HRQOL, further emphasising their role. A dimensional approach was taken to examining autistic characteristics and ADHD characteristics, which helped to extend the limited evidence base available on the contribution of neurodevelopmental conditions on HRQOL. A recent editorial outlined that although ADHD and autism are prevalent in CWE, they continue to be underdiagnosed in this group (Shankar et al., 2020). This is supported by prior research which showed that autistic CWE receive an autism diagnosis at a later point in the developmental trajectory compared to autistic children only (25% vs 6.67% by age 8) (Turk et al., 2009). These findings were attributed this to the lack of communication between clinicians and barriers to accessing specialised treatments.

Similarly, a previous study incorporated an integrated approach to epilepsy and autism within epilepsy clinics. They reported that delayed or under-diagnoses in CWE may be attributed to diagnostic overshadowing issues or differences in presentations, compared to neurodevelopmental conditions alone (Holmes et al, 2021). Diagnostic overshadowing has considerable clinical implications, as it reduces the timeframe to initiate early interventions and support (Robinson, 2012). Therefore, improved communication between the two fields is necessary to support differential diagnoses and improve access to support for families. A step to achieving this may lie in the acknowledgment of epilepsy as part of the group of neurodevelopmental conditions (Shankar et al., 2020). Moreover, given the findings within this study, clinical practice should aim to routinely screen for autistic characteristics in CWE as opposed to diagnoses only.

7.6.3. Implementation of specialised referral pathways

The overall findings within this thesis have significant clinical implications, suggesting that co-occurrences impair HRQOL beyond parental variables and epilepsy specific variables. As co-occurring conditions appear to be present early in the epilepsy trajectory (Austin et al., 2001), there is an urgent need to address them within epilepsy management. However, due to barriers such as those outlined above, they remain under recognised. A previous study demonstrated successful implementation of psychological screening and targeted intervention routes in paediatric epilepsy clinics (George et al., 2021). However, children with neurodevelopmental conditions were excluded from this study due to the lack of suitability of the measure for this group. Nevertheless, a similar study showed strong effectiveness of a screening and referral programme for neurodevelopmental co-occurrences within epilepsy (Eom, Fisher, Dezort & Berg, 2014). However, a drawback of this study was that screening was conducted within specialised epilepsy settings, where parents had additional time to fill in

the questionnaires. Whilst this is advantageous, this approach may not be possible in wider settings. Future research should aim to build on the findings within secondary care settings, to pilot screening of co-occurring conditions.

In calls for a holistic approach to epilepsy management by prior research (Caplan, 2015) and to improve the pathway from initial epilepsy assessment to referral to specialised services, the pathway in Figure 7.4 is proposed. This proposes a triage approach where children are stratified depending on the severity of co-occurrences. Within this framework, children are initially screened for co-occurrences such as those investigated within this thesis. Following this, children are triaged to the appropriate level of support depending on the severity of their co-occurrences. (1) In the first case, when there are no co-occurrences reported, no additional input is needed. (2) In the second case, if children present with moderate co-occurrences, self-management materials will be provided. At the follow up appointment, children are assessed again and if co-occurrences are continuing to exert a significant impact, the child is then referred to further assessment. (3) In this step, children are referred to specialised services to undergo an assessment for their differences. If a diagnosis is given, children are referred to the appropriate interventions route. If no diagnosis is received, parents are then provided with appropriate support material for managing their child's differences and support for their own outcomes.

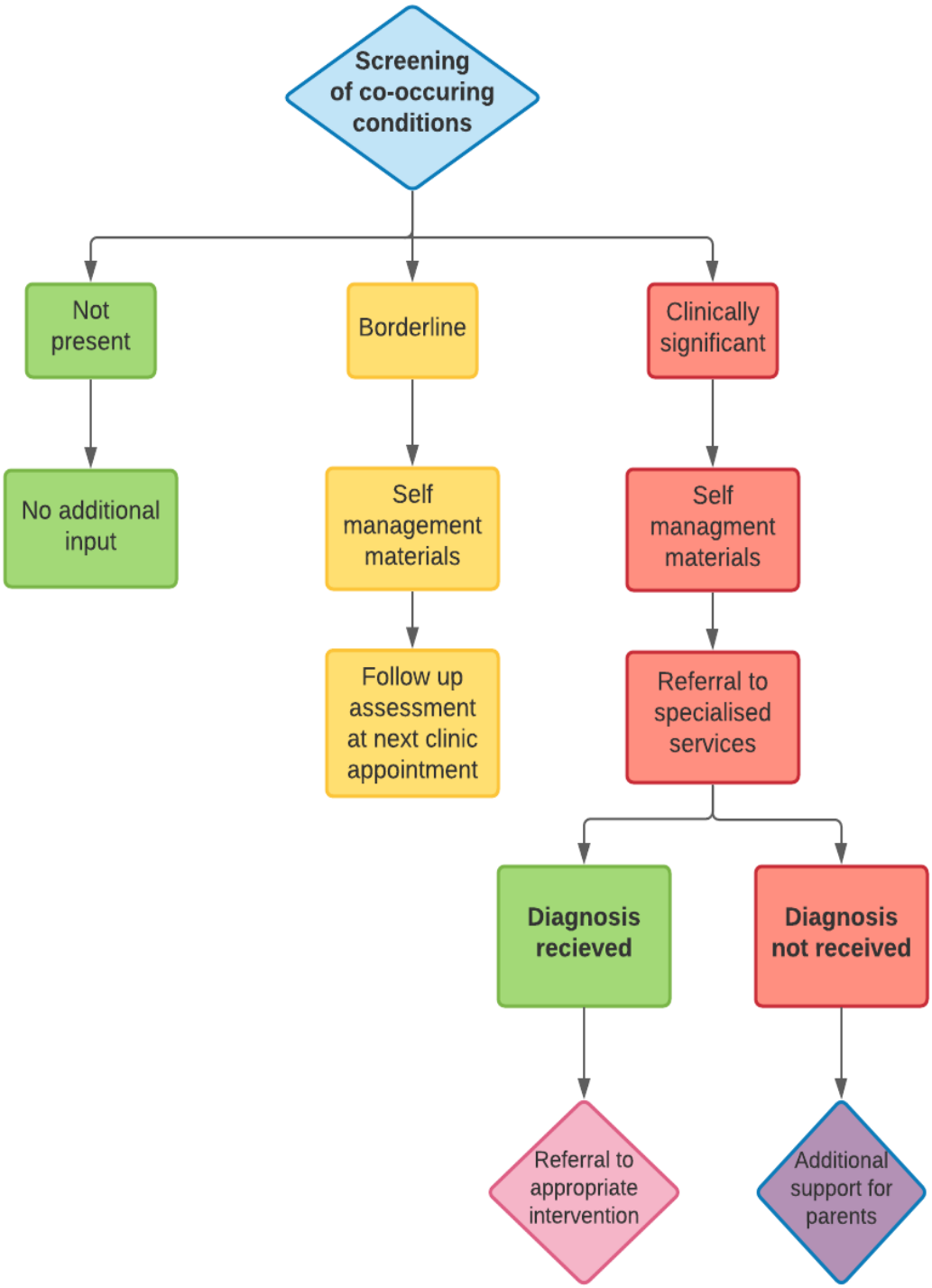


Figure 7.4. Schematic presentation of clinical pathway for screening co-occurring conditions in CWE

7.7. Clinical Implications for Intervention

7.7.1. Interventions targeting child sleep

As outlined above, assessment of sleep problems in CWE should be encouraged and included as part of routine clinical practice. Such assessments can help shed light on the aetiology of sleep problems (Nobili et al., 2021). The appropriate interventions can then be established to mitigate these disturbances. If the aim is to *improve sleep* in CWE, promotion of good sleep habits should be a key priority, given the wider association with family sleep, as demonstrated in Chapter 6. A previous randomised controlled trial delivered a behavioural sleep intervention during routine clinical appointments (Tsai et al., 2020b). They found that following a 12-month period, CWE in the intervention group had significant improvements in night-time sleep quality and lengthened night-time sleep as measured by actigraphy, compared to children who did not receive the intervention. This finding is particularly promising as it indicates that sleep interventions can be integrated within routine epilepsy care. However, improvements in maternal sleep quality were not observed suggesting interventions aimed at only child sleep may not map onto improvements for parental sleep. Contrastingly, a recent online sleep intervention has been co-developed with parents of CWE, which ensures that the needs of both parents and children are met. This approach may help not only to engage parents but in turn improve their own sleep (Wiggs et al., 2021).

7.7.2. Interventions aimed at optimising support for neurodevelopmental characteristics

In Chapters 4 and 5, neurodevelopmental characteristics were indicated to likely mediate the impact of severity of sleep problems on HRQOL. This is crucial to consider if one goal of a sleep intervention is to *improve HRQOL*, as it suggests that targeting sleep would not be the optimal approach. Prior studies have brought attention to the lack of screening of neurodevelopmental characteristics in clinical services, despite their association with poor

HRQOL (Sherman et al., 2007). These research findings also suggest that there are benefits for interventions aimed at improving neurodevelopmental characteristics in CWE to improve overall HRQOL. Interventions could be aimed at directly maximising support for neurodevelopmental characteristics. Alternatively, another approach is to provide parents with more information on the prevalence of co-occurrence in CWE compared to CWOE (Robinson, 2012; Ekinci et al., 2017). This may ultimately aid in helping parents cope with negative emotions such as anxiety (England, Liverman, Schultz & Strawbridge, 2012).

Current intervention approaches to ADHD are primarily focused on medical approaches with the use of methylphenidate (Cortese et al., 2018). However, the use of methylphenidate has been linked with sleep problems (Feldman & Reiff, 2014; Stein, Weiss & Hlavaty, 2012), and thus may adversely impact HRQOL based on the findings within this study. In addition, prior research has found that when ADHD is not addressed, the effect of ADHD on HRQOL in later adulthood exerts a stronger impact than the epilepsy itself (Gulko, 2018). Behavioural management interventions in children with ADHD have been shown to be effective in CWOE (Pfiffner & Haack, 2015). Furthermore as highlighted in Chapter 5, a behavioural intervention aimed at improving sleep, also led to improvements in ADHD characteristics and HRQOL (Hiscock et al., 2015). Similar perpetuating variables have been found to be associated with diminished HRQOL in both children with ADHD + epilepsy and ADHD alone, therefore it is possible that similar interventions may be applicable to this group. In addition, such intervention suggests that targeting sleep can also lead to improvements in ADHD characteristics, therefore interventions solely targeted towards neurodevelopmental co-occurrences may not be the only route but rather interventions aimed at addressing general co-occurrences can aid in improving HRQOL (Im, Cho & Kim, 2019; Rodenburg, Meijer, Deković & Aldenkamp, 2007; McLaughlin et al., 2018).

The findings within the current study also highlight the need to support management of autistic characteristics in CWE, however the current evidence base on intervention support is minimal. A possible reason may relate to the lack of agreement regarding the pathophysiology of their co-occurrences. Similarly, as noted previously, CWE and co-occurring autism are often diagnosed at a later stage compared to children with autism alone (Turk et al. 2009). A possible explanation is that the presentation of behaviours in autistic children and co-occurring epilepsy compared to autism alone may differ and complicate the diagnosis (Holmes et al., 2021). Within this study an informant reported index score for autistic characteristics was used, and no further delineation on the type of characteristics e.g., language, behaviour, or social competence, were made. These caveats limit the interpretation on the type of intervention which would be useful in this group, however given the impact on HRQOL, interventions are needed.

It is important to note that in the general autism literature, there are concerns regarding the ethics of certain behavioural interventions designed to reduce autistic characteristics. Therefore, psychosocial approaches which target broader outcomes are recommended and have been found to be effective in CWE (Snead et al., 2004; Jones, Blocher, Jackson, Sung & Fujikawa, 2014). Prior to implementing these targeted interventions, more studies are needed to establish whether there are clear phenotypic differences and whether there are differences during development of autism in children across the two groups (Holmes et al., 2021).

Another factor to consider in regard to the interventions discussed above is that they are based on interventions with children diagnosed with a neurodevelopmental conditions. However as highlighted earlier, there are merits to utilising a dimensional approach in understanding neurodevelopment, especially in CWE (see section 1.9). A previous study by Langberg et al.

(2010) administered a behavioural intervention to children aimed at improving ADHD characteristics. They found that the intervention was most effective for children with low to moderate symptoms compared to those with high symptoms. This suggests that interventions are not dependent on a threshold effect, thus adopting a categorical approach may exclude participants who still display significant difficulties. A possible method proposed by prior research is to approach interventions adaptively, where they initially start with the focus on the environment and progress to managing specific neurodevelopmental characteristics. Depending on the child's response, the intervention will be adapted appropriately, increased in specificity e.g targeting specific difficulties or decrease in specificity e.g general behavioural maintenance (Finlay-Jones et al., 2019). Overall, there is a need for future research to assess the cost and benefit ratio of structured adaptive interventions in order to replicate these across children.

7.8. Future research

The findings from this thesis were based on a cross sectional design. Consequently, the direction or causality of relationships could not be determined. Future research would benefit from a longitudinal approach to studying HRQOL in CWE. Although neurodevelopmental characteristics are recognised to be stable across childhood (Taylor, Gillberg, Lichtenstein & Lundström, 2017), there are suggestions that autistic characteristics in CWE may fluctuate across development (Holmes et al., 2021). This is particularly important in children since typical development occurs at the same time, thus the relationship between the variables might change, as well as the impact on HRQOL. This supports the use of a longitudinal design to better understand their trajectory and the underling mechanisms linking with sleep and HRQOL.

Various clinical implications have been postulated above for epilepsy management; however future research should aim to develop trials which assess such implications. As described in Figures 7.1 and 7.2, neurodevelopmental characteristics impact HRQOL greatly. However other co-occurrences including sleep and parental variables also contribute significantly when neurodevelopmental co-occurrences are not present. The findings therefore indicate that a stepped approach is necessary to improving HRQOL in CWE, such as that proposed in Figure 7.4. Moreover, the priority for intervention development should be aimed to optimise support for co-occurrences in particularly.

The total variance predicted by the overall models in explaining HRQOL was between 19% to 56%. Although this is a large proportion, there is still some unexplained variance in HRQOL. The theoretical model presented in section 1.10. (Lach et al., 2006) was integrated with the findings from this thesis (see Figure 7.5). Overall the data emphasises the role of 'epilepsy variables', 'co-occurrences' and 'family variables'. However little focus is given to 'child variables' and 'community variables'. This is particularly interesting as lower HRQOL scores were observed in the physical and cognitive domain which may be more strongly related to the variables of interest in the model. Whereas, the social and emotional domain were the highest areas of HRQOL observed, which may be more strongly associated to the variables not assessed in this thesis (community/child variables). Assessment of a wider range of variables would allow for better understanding of the pathways to poor HRQOL in CWE. For example prior research by Fayed et al. (2015) showed that epilepsy variables such as seizure status demonstrated a relationship with HRQOL, only through child mental health. This highlights the role the child's emotional state can play in HRQOL. Future research would benefit from assessment of the contribution of variables across the whole of the theoretical model in order to provide an accurate understanding of HRQOL.

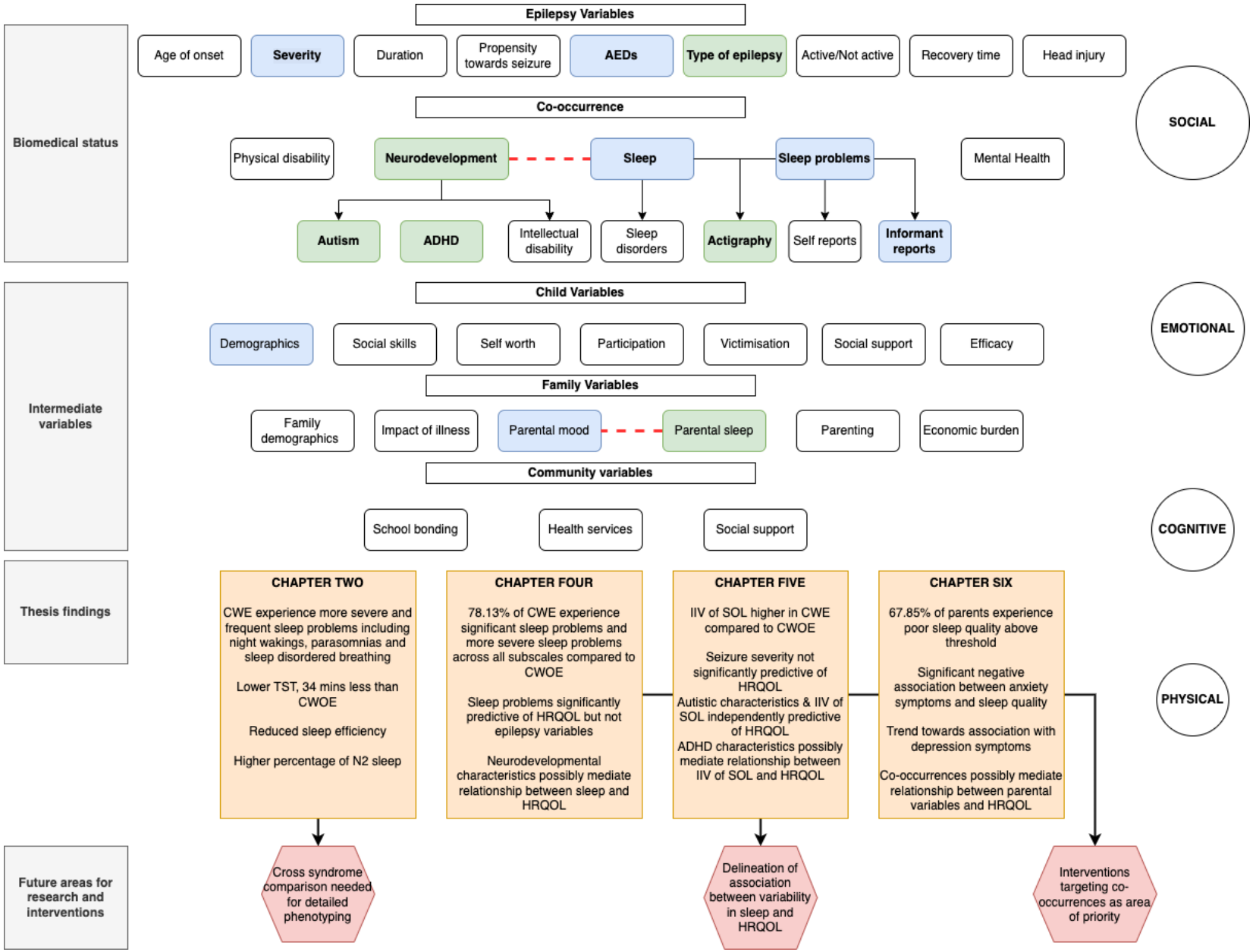


Figure** 7.5. Adapted model of HRQOL by Lach et al. (2006).** White boxes denote factors extracted from the initial model. Green boxes denote factors added to the model and blue boxes represent variables of interest studied from original model. Orange boxes represent findings from thesis and red hexagons indicate areas for future research and interventions. Dashed red lines highlighted presumed relationships.

As highlighted throughout this thesis, informant reports were the main measurement used. Whilst previous research has shown that informant reports are reliable measures of HRQOL (Fayed et al., 2019), there is a risk that these findings may reflect a common method variance. As previously noted, one study found that when children rated their own HRQOL, neurodevelopmental characteristics were not as strongly correlated compared to when parents rated their HRQOL (Baca et al., 2011). Therefore, introduction of self-reports alongside informant reports can aid in not only capturing the voice of the child but assessing the robustness of these findings across measures.

7.9. Conclusion

A multifaceted approach was taken within this thesis, combining sleep, neurodevelopmental and epilepsy research in the hope to better understand HRQOL in CWE. This thesis showed that sleep is largely disrupted in CWE and can extend to impact HRQOL. However, the findings also indicate that this perceived impact of sleep problems on HRQOL could be explained by neurodevelopmental characteristics. This suggests that sleep problems may behave as a marker of these characteristics rather than of the epilepsy. Moreover, the trimodal interaction between sleep, epilepsy and neurodevelopmental characteristics appear to be dependent on the method by which sleep was measured. In one case, actigraphy defined variability in SOL displayed an independent contribution to HRQOL that was not affected by the inclusion of neurodevelopmental characteristics. Finally, this thesis presented additional evidence for poor sleep and wellbeing in parents of CWE, and more importantly that co-occurrences may mediate the impact of poor parental outcomes on child HRQOL. Consequently, the concept that sleep may be driven by neurodevelopmental characteristics deserves recognition and has large clinical implications for epilepsy management. Future research including larger samples with a multi-modal measurement of sleep, will help improve

the robustness of these findings. Clinically, the findings also point towards the need to screen for co-occurrences as part of the epilepsy diagnostic process, in order to provide the most appropriate support for parents as early as possible.

APPENDICES

Appendix 1.1 Copyright permission for inclusion of Figure 1.3

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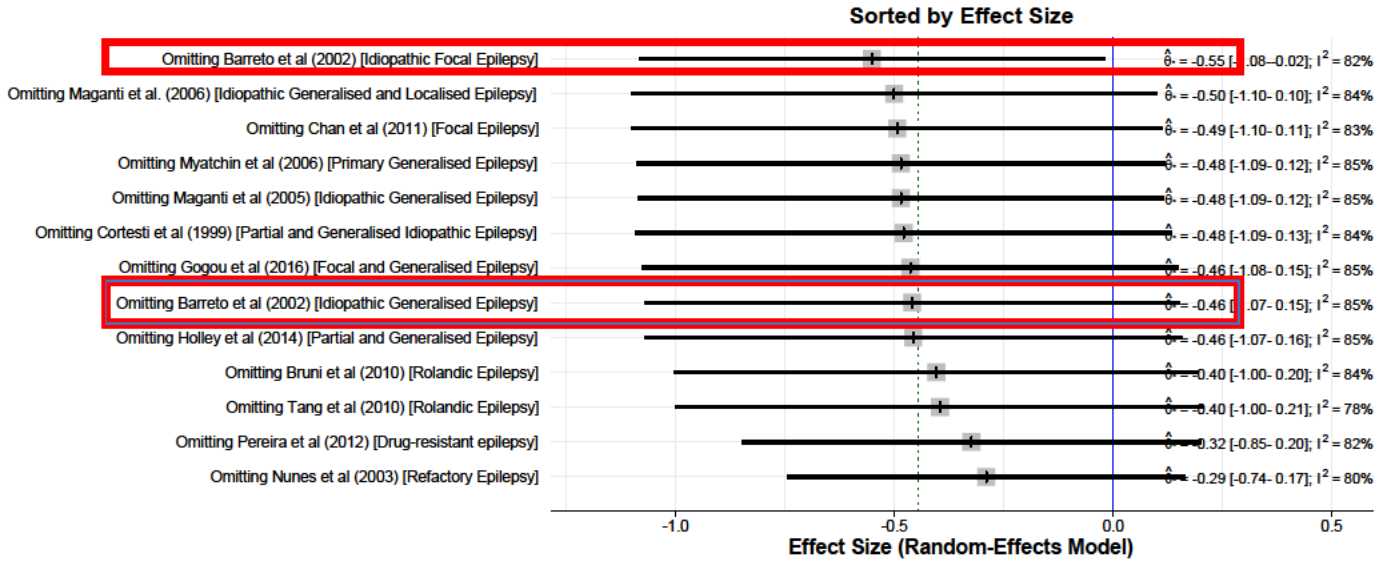
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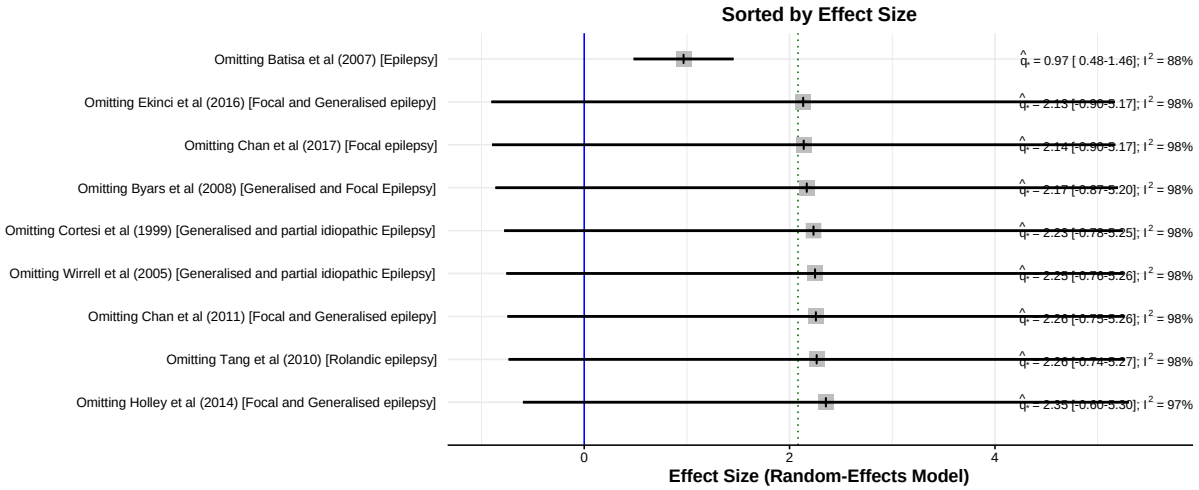
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Appendix 2.1 Leave one out forest plot for total sleep time meta-analysis



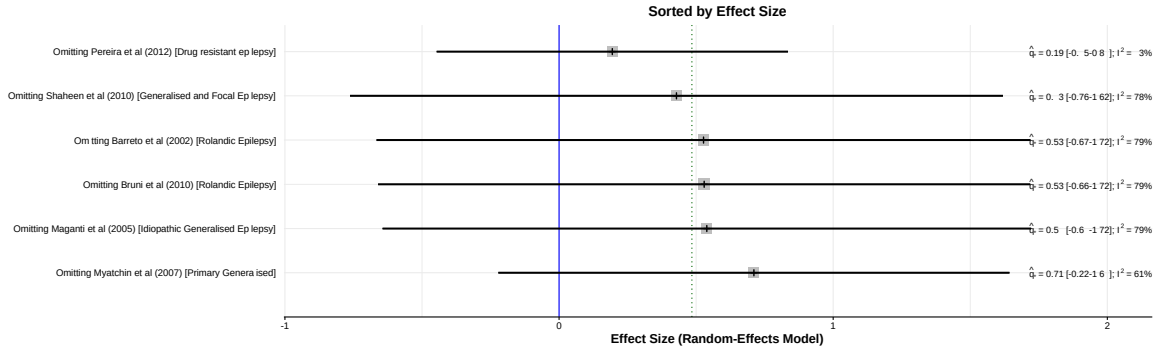
Appendix 2.1 Figure 1. Leave one out comparison of the idiopathic generalised and idiopathic focal epilepsy subgroups of Barreto et al. (2002). Larger dispersion of effect size for idiopathic focal epilepsy compared to idiopathic generalised epilepsy

Appendix 2.2 Leave one out forest plot for sleep problems meta-analysis



Appendix 2.2 Figure 1. Leave one out comparison of sleep problems meta-analysis. Note the study Batista et al. (2007) shows clear distortion of effect size estimate

Appendix 2.3 Leave one out forest plot for N2% meta-analysis



Appendix 2.3 Figure 1. Leave one out comparison of sleep problems meta-analysis. Note the study Pereira et al. (2012) and Myatchin & Lagae (2007) shows distortion of effect size estimate.

Appendix 3.1. Recruitment material for children with epilepsy

Ms Alice Winsor (PhD Student)

Tel: [redacted]

Email: [redacted]

Dear Parent/Carer

We are contacting you about a research project that is being conducted at the Centre for Human Brain Health at the University of Birmingham. This project is looking into how sleep habits and sleeping brain activity relate to children's and parent's quality of life.

We are contacting you because your child is undergoing a sleep video-EEG at Birmingham children's hospital which makes them eligible for this study and we would like to invite you and your child/ the child that you care for to participate.

We have enclosed detailed information about what this study will involve. If you think that you and your child might be interested in taking part in the study but you would like to discuss it with a member of the research team first then please contact Ms Alice Winsor (please see contact details above). Alternatively, if you happy for you and your child to participate then please follow the instructions and return all appropriate forms in the pre-paid envelopes provided. We understand that some forms may not be applicable to your child but please try to answer all other questions as best as possible.

Thank you very much for your time.

Kind regards,

Alice Winsor

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENT/GUARDIAN INFORMATION SHEET

Research study: Sleep and Quality of Life

Part 1
Introduction to the research and invitation to take part:

We are inviting your child to take part in a research study being conducted at the Centre for Human Brain Health, University of Birmingham. This research work being led by Dr Andrew Bagshaw, Dr Caroline Richards and Ms Alice Winsor will examine how sleep habits and sleeping brain activity relate to children's and parents' quality of life.

It is important that you understand why the research is being done and what it will involve before you decide whether your child can take part or not. Please read the following information carefully and discuss this with others if you wish. Feel free to ask us if there is anything that is not clear or if you would like more information (see contact details at the end of part 1 of the information sheet).

Once you are happy that you have sufficient information to be able to decide whether or not you want your child to take part in the study, please complete the enclosed consent forms and questionnaires and post all back to us at your earliest convenience **(before your clinic appointment)** in the separate pre-paid envelopes provided. We will also provide you with a copy of the parent/guardian information sheet and consent form to keep.

What is the purpose of the study?

The purpose of this study is to investigate the link between sleep and waking behaviour and quality of life in children with neurological disorders and their parents. This will allow us to understand how different neurological disorders disrupt, and are disrupted by, sleep. In the future, this could help us to develop ways to improve quality of life for the whole family.

Why has my child been invited to take part in the study?

Your child has been invited to take part in this study because they are aged between 4 and 16 years old and will be attending the Neurophysiology department at Birmingham Children's Hospital to undergo a sleep video-EEG as part of routine care. The data from this appointment will form the basis for our analysis. We aim to investigate as many participants as possible during the time-frame (currently until 2021). We do not have your contact details and we do not know your name or your child's name. The health facility that your child attends has sent out this information on behalf of the research team so please be assured that we do not have access to any of your personal information.

Does my child have to take part in this research project?
Participation in this research study is voluntary. If you decide that you do not wish your child to take part in this study, they do not have to. This will not affect the standard of care your child receives and your child will continue to undergo their sleep V-EEG appointment as planned.

What will happen if my child/ the person I care for decides to participate?

Where will the research take place?
The research will take place at Birmingham Children's Hospital during your child's scheduled appointment. We will provide you with some questionnaires to complete at home before and after their appointment. We may also ask you to complete a brief interview over the phone with us after your appointment.

Who will be involved in collecting the data?
Members of the research team at the Centre for Human Brain Health based at University of Birmingham including Dr Andrew Bagshaw, Dr Caroline Richards and Ms Alice Winsor.

Before appointment
Prior to your child's clinic appointment, we will post out a study pack which includes this information sheet, a consent form and a set of questionnaires. You will be asked to sign a consent form and provide us with a few personal details (name, postal address, telephone number, email address). We have also included an easy to read information sheet with visual aids in this pack for you to use with your child/person you care for. This can be used to include your child/person you care for in the consent process and to prepare them ahead of their appointment at Birmingham Children's Hospital.

You will be asked to complete a number of background questionnaires at home, these will take between 30-40 minutes in total to complete, they are not required to be completed in one sitting. You will be required to post the completed questionnaires and consent forms back to the research team in the separate prepaid envelopes provided. Alternatively, if you need further clarification or are unable to understand the questionnaires, you can contact a member of the research team and arrange to have them administered over the telephone if you prefer.

During appointment
At your scheduled appointment, you will be asked to complete some additional questionnaires assessing various aspects of quality of life whilst your child is undergoing their sleep test. These questionnaires should take no more than an hour to complete. If you are unable to complete the questionnaires during your appointment, we can provide copies to be completed at home and posted back to us.

After appointment
1. You will be provided with a wrist activity monitor, similar to a Fitbit and a paper sleep diary, which will provide us with an assessment of your child's sleep habits at home. The activity monitor should be worn by your child for a period of two weeks in order to measure day and night time movements. You will be

required to fill in a paper sleep diary each day over this time period (takes no more than 5 minutes). Once the two weeks are over, you will be required to post the activity monitor and diary back to us in the prepaid envelopes provided.

2. You may be contacted by the research team to schedule a time in the following 6-8 weeks after your appointment to take part in a telephone interview. This will depend on your child's diagnosis and is optional.

Will the interview be recorded?
The telephone interview will be audio recorded by the research team for later typing up (transcription). The interview will be fully anonymised when it is transcribed, any personal information, names etc. will be removed during typing up. The University of Birmingham will hold the copyright for the audio recordings so that the confidentiality of these recordings will be protected. But the University of Birmingham will not be able to edit or use the recordings for teaching purposes unless you give us your written permission to do this.

How long will participation in the study take?
Completing all questionnaires is expected to take around two hours of your time in total. The activity monitor will be worn for a period of two weeks, with input into the sleep diary each day (5 minutes). The interview should take up to an hour to complete.

We will be collecting information from participants between August 2019 and August 2021. Following data collection, we will spend some time analysing the information and writing reports. We expect that families will receive feedback reports 2-3 months after returning study materials and the study to reach completion by September 2021.

What are the risks or disadvantages of taking part?
There are no risks involved in carrying out the tests. Since the tests are simple paper-and-pencil or non-invasive computer-based measures, there is nothing to go wrong.

What are the possible benefits of taking part?
The study will not help your child directly, but it will help us to better understand how sleep interacts with neurological disorders. This may then be helpful in developing future assessment and treatment options.

Furthermore, after your child has completed the study, you will be provided with a feedback report tailored to your child based on your responses to the questionnaires and results from the activity monitor. These individualised feedback reports may be useful for you to highlight particular difficulties that your child might face. We are happy for you to share a copy of this report with professionals involved in your child's care if you wish to do so.

What happens at the end of the research study?
Once the research study is over, you will receive an end of participation letter and feedback report. The results from the research will be used to inform our understanding of the role of sleep in neurological disorders and develop future assessment and diagnosis methods. The data will also form the basis of Ms Alice Winsor's PhD project and may be reported in scientific papers and at relevant conferences.

What if there is a problem?
Any complaint about the way the study has been conducted or any possible harm you may have suffered will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:
Please contact Ms Alice Winsor (PhD Student), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Or Dr Andrew Bagshaw (Reader In Imaging neuroscience), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Or Dr Caroline Richards (Lecturer in Neurodevelopmental Disorders), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Alternatively, you can contact Birmingham Community Healthcare - Patient Advice and Liaison Service (PALS), Moseley Hall Hospital Alcester Road, Birmingham, B13 8JL for independent advice about the study
Tel: 0800 917 2855 (Freephone)
Email: PALS@bhamcommunity.nhs.uk.

This completes Part 1 of the Information Sheet.
If the information in part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision**.**

Part 2

What will happen to my data I provide?
Any personal identifying information including names, ages, addresses, telephone number and email addresses, which are found on the consent form will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998 & 2018. This information will be stored for the duration of the study on a password protected portable hard drive which will be kept in a locked filing cabinet at the University of Birmingham.

The audio recordings are considered to necessarily contain personal identifying information. These recordings will not be labelled with your names or any other personal identifying information but will be labelled with your special reference number. Recordings will be stored on a password protected portable drive, which will be kept in a locked cabinet at the University of Birmingham and only members of our research team will have access to them.

Your completed questionnaires and your child's wrist activity monitor data will be stored separately from the personal identifying information in a locked filing cabinet at the University of Birmingham. Similarly, your child's nap study data will be stored on a password protected portable encrypted hard drive. The data from these will be allocated a unique participant number and this will appear on the assessments instead of names ensuring your data is kept anonymous. An electronic file will be created which links the participant number to the participant name and will be stored on a password protected portable drive in a locked filing cabinet at the University of Birmingham. Only members of the research team will have access to the research project filing cabinet.

What will happen the data once the study is over?
Data collected from the questionnaires, activity monitor, interview and medical records (e.g medication history and MRI scans) will be destroyed 10 years following the end of the project, unless you have provided written consent for the information to be used for teaching and/or dissemination.

Records of your personal information will be destroyed immediately after the end of the study unless you tell us otherwise. This means that we would no longer be able to trace the results of your child's assessments back to you. If you withdraw from the project, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible. The section below on ***"Participant database information"*** gives you information about the database that we use to store the personal details of some participants. Please read the section below in order to decide whether you'd like to join that database.

Withdrawal
Even after you have provided consent for your child's participation in the study, you can request for your child to be withdrawn from the study. This will not restrict access or affect the right to any health services. Your personal and research data collected up until the point of withdrawal will be retained by the research team.

What if there is a problem?
If you have any problems with the conduct of the study then you can phone the Research Governance Committee of the University of Birmingham, who have considered this project, on 0121-414-7618, who will arrange for your concerns to be investigated. Otherwise please contact Dr Andrew Bagshaw at the School of Psychology, University of Birmingham (0121 414 3683). In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds to claim compensation against Birmingham

and Solihull NHS Mental Health Foundation NHS Trust, but you may have to pay your legal costs. If the negligence was by a member of the NHS, then you may have grounds for legal action for compensation against the NHS trust concerned.

Participant Database information

Drs. Bagshaw and Richards will create a database for the purpose of this research study where we will store the names and contact details of participants. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. It will only be accessible to members of the research team. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Consent to be included in the "Participant database" is separate to consent for the study and you are welcome to participate in the study without being included in the database.

If you would like us to, we can add your details to this database. We would use this information for two things:

1) We will contact you with information about future research work to find out whether or not you would like to participate.
2) It is often important to find out how things change over time. By keeping your details, we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Your information could be used for research in any aspect of health or care and could be combined with information about you from other sources held by researchers, the NHS or government. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Who would have access to my details?

Only approved members of our research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?

You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?

All you would need to do is contact Dr. Bagshaw on 0121 414 3683 or Dr. Richards on 01214158098 or at the School of Psychology, University of Birmingham,

Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Will my taking part in this study be kept confidential?
Our procedures for handling, processing, storing and destroying your data are all compliant with the General Data Protection Regulation (GDPR). All information that is collected about you during the course of the research will be kept strictly confidential. Your data will be collected from your medical records and from the activity monitor and questionnaires. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Who is organising and funding the research?
The research is funded by the Waterloo Foundation (http://www.waterloofoundation.org.uk/).

Who has reviewed the study?
This study has been reviewed and given a favourable opinion by North West - Preston Research Ethics Committee.

The University of Birmingham is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Birmingham will keep identifiable information about you for 6 months following receipt of your completed questionnaires.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at https://www.birmingham.ac.uk/privacy and/or by contacting our data protection manager.

The University of Birmingham will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Birmingham and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

Birmingham Women's and Children's NHS Foundation Trust will pass these details to the University of Birmingham along with the information collected from you. The only people in the University of Birmingham who will have access to information that identifies you will be people who need to contact you to about your participation in the study, send a feedback report or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). Our Data Protection Officer is Mrs. Carolyn Pike OBE and you can contact them at legalservices@contacts.bham.ac.uk.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you for considering taking part and taking the time to read this information sheet.

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENT/GUARDIAN INFORMATION SHEET

Research study: Sleep and Quality of Life

Part 1
Introduction to the research and invitation to take part:
You are being invited to take part in a research study being conducted at the Centre for Human Brain Health, University of Birmingham. This research work being led by Dr Andrew Bagshaw and Dr Caroline Richards, will examine how sleep habits and sleeping brain activity relate to children's and parents' quality of life.

It is important that you understand why the research is being done and what it will involve before you decide whether or not to take part. Please read the following information carefully and discuss this with others if you wish. Feel free to ask us if there is anything that is not clear or if you would like more information (see contact details at the end of part 1 of the information sheet).

Once you are happy that you have sufficient information to be able to decide whether or not you want your child to take part in the study. If you would like to participate in the study, please complete the enclosed forms and post all back to us at your earliest convenience in the separate pre-paid envelopes provided. We will also provide you with a copy of the parent/guardian information and consent form to keep.

What is the purpose of the study?
The purpose of this study is to investigate the link between sleep and waking behaviour and quality of life in children with neurological disorders and their parents. This will allow us to understand how different neurological disorders disrupt, and are disrupted by, sleep. In the future, this could help us to develop ways to improve quality of life for the whole family.

Why has my child been invited to take part in the study?
Your child has been invited to take part in this study because they are aged between 4 and 16 years old and have previously attended the Neurophysiology department at Birmingham Children's Hospital for a sleep V-EEG study and may still be under clinical care. The data from this appointment will form the basis for our analysis. We aim to investigate as many participants as possible during the time-frame (currently until 2021)

Does my child have to take part in this research project?

Participation in this research study is voluntary. If you decide that you do not wish your child to take part in this study, they do not have to. This will not affect the standard of care your child receives if still under clinical care.

What will happen if my child/ the person I care for decides to participate?

There are two parts to this study. You can choose to sign up to part 1 or both parts.

Part 1: You will be asked to sign a consent form for us to access your child's sleep V-EEG data, background questionnaire and provide us with a few personal details (name, postal address, telephone number, email address). You will be required to post back the forms in the pre-paid envelopes provided, back to the research team. If a completed consent form is not received within two weeks, a member of the research team will directly contact you to see if you're still interested in participating in the research and to answer any additional questions you have.

Part 2:
You will be asked to complete a number of questionnaires at home, these will take between 1hr 30 to 1hr 45 hours in total to complete- they are not required to be completed in one sitting. Alternatively, if you need further clarification or are unable to understand the questionnaires, you can contact a member of the research team and arrange to have them administered over the telephone if you prefer.

You will be provided with a wrist activity monitor, similar to a Fitbit and a paper sleep diary, which will provide us with an assessment of your child's sleep habits at home. The activity monitor should be worn by your child for a period of two weeks in order to measure day and night time movement. You will be required to fill in a paper sleep diary each day over this time period (takes no more than 5 minutes). Once the two weeks are over, you will be required to post the activity monitor and diary back to us in the prepaid envelopes provided.

You may be contacted by the research team to schedule a time in the following 6-8 weeks after your appointment to take part in a telephone interview. This will depend on your child's diagnosis and is optional.

Will the interview be recorded?
The telephone interview will be audio recorded by the research team for later typing up (transcription). The interview will be fully anonymised when it is transcribed, any personal information, names etc will be removed during typing up. The University of Birmingham will hold the copyright for the audio recordings so that the confidentiality of these recordings will be protected. But, the University of Birmingham will not be able to edit or use the recordings for teaching purposes unless you give us your written permission to do this.

How long will participation in the study take?
Completing all questionnaires is expected to take around two hours of your time in total. The activity monitor will be worn for a period of two weeks, with input into the sleep diary each day (5 minutes). The interview should take up to an hour to complete.

Who will be involved in collecting the data?
Members of the research team at the Centre for Human Brain Health based at University of Birmingham including Dr Andrew Bagshaw, Dr Caroline Richards and Ms Alice Winsor.

What are the risks or disadvantages of taking part?
There are no risks involved in carrying out the tests. Since the tests are simple paper-and-pencil or non-invasive computer-based measures, there is nothing to go wrong.

What are the possible benefits of taking part?
The study will not help your child directly, but it will help us to better understand how sleep interacts with neurological disorders. This may then be helpful in developing future assessment and treatment options.

If you decide to participate in **both parts** of the study, you will be provided with a feedback report tailored to your child based on your responses to the questionnaire and results from the activity monitor upon completion of the study. These individualised feedback reports may be useful for you to highlight particular difficulties that your child might face. We are happy for you to share a copy of this report with professionals involved in your child's care if you wish to do so.

What happens at the end of the research study?
We will be collecting information from participants between August 2019 and August 2021. Once the study is over, you will receive an end of participation letter. The results from the research will be used to inform basic understanding of the role of sleep and develop future assessment and diagnosis methods. The data will also form the basis of Ms Alice Winsor's PhD project and may be reported in scientific papers and at relevant conferences

What if there is a problem?
Any complaint about the way the study has been conducted or any possible harm you may have suffered will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:
Please contact Ms Alice Winsor (PhD Student), School of Psychology, University of Birmingham, B15 2TT

Tel: [redacted]
Email: [redacted]

Or Dr Andrew Bagshaw (Reader In Imaging neuroscience), School of Psychology, University of Birmingham, B15 2TT
Tel: [redacted]
Email: [redacted]

Or Dr Caroline Richards (Lecturer in Neurodevelopmental Disorders), School of Psychology, University of Birmingham, B15 2TT
Tel: [redacted]
Email: [redacted]

Alternatively, you can contact Birmingham Community Healthcare - Patient Advice and Liaison Service (PALS), Moseley Hall Hospital Alcester Road, Birmingham, B13 8JL for independent advice about the study

Tel: 0800 917 2855 (freephone)
Email: PALS@bhamcommunity.nhs.uk.

This completes Part 1 of the Information Sheet.
If the information in part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision**.**

Part 2

What will happen to my data I provide?
Any personal identifying information including names, ages, addresses, telephone number and email addresses, which are found on the consent form will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998 & 2018. This information will be stored for the duration of the study on a password protected portable hard drive which will be kept in a locked filing cabinet at the University of Birmingham.

The audio recordings are considered to necessarily contain personal identifying information. These recordings will not be labelled with your names or any other personal identifying information but will be labelled with your special reference number. Recordings will be stored on a password protected portable drive, which will be kept in a locked cabinet at the University of Birmingham and only members of our research team will have access to them.

Your completed questionnaires and your child's wrist activity monitor data will be stored separately from the personal identifying information in a locked filing cabinet at

the university of Birmingham. Similarly, your child's nap study data will be stored on a password protected portable encrypted hard drive. The data from these will be allocated a unique participant number and this will appear on the assessments instead of names ensuring your data is kept anonymous. An electronic file will be created which links the participant number to the participant name and will be stored on a password protected portable drive in a locked filing cabinet at the University of Birmingham. Only members of the research team will have access to the research project filing cabinet.

What will happen the data once the study is over?
Data collected from your questionnaires, activity monitor and medical records (e.g medication history and MRI scans) will be destroyed 10 years following the end of the project unless you have provided written consent for the information to be used for teaching and/or dissemination.

Records of your personal information will be destroyed immediately after the end of the study **unless you tell us otherwise.** This means that we would no longer be able to trace the results of your child's assessments back to you. If you withdraw from the project, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible. The section below on ***"Participant database information"*** gives you information about the database that we use to store the personal details of some participants. Please read the section below in order to decide whether you'd like to join that database.

Withdrawal
Even after you have provided consent for your child's participation in the study, you can request for your child to be withdrawn from the study. This will not restrict access or affect the right to any health services. Your personal and research data collected up until the point of withdrawal will be retained by the research team.

What if there is a problem?
If you have any problems with the conduct of the study then you can phone the Research Governance Committee of the University of Birmingham, who have considered this project, on 0121-414-7618, who will arrange for your concerns to be investigated. Otherwise please contact Dr Andrew Bagshaw at the School of Psychology, University of Birmingham (0121 414 3683). In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds to claim compensation against Birmingham and Solihull NHS Mental Health Foundation NHS Trust, but you may have to pay your legal costs. If the negligence was by a member of the NHS, then you may have grounds for legal action for compensation against the NHS trust concerned.

Participant Database information

Drs. Bagshaw and Richards will create a database for the purpose of this research study where we will store the names and contact details of participants. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. It will only be accessible to members of the research team. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Consent to be included in the "Participant database" is separate to consent for the study and you are welcome to participate in the study without being included in the database.

If you would like us to, we can add your details to this database. We would use this information for two things:

1)We will contact you with information about future research work to find out whether or not you would like to participate.
2)It is often important to find out how things change over time. By keeping your details, we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Your information could be used for research in any aspect of health or care and could be combined with information about you from other sources held by researchers, the NHS or government. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Who would have access to my details?
Only approved members of our research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact Dr. Bagshaw on 0121 414 3683 or Dr. Richards on 01214158098 or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Will my taking part in this study be kept confidential?
Our procedures for handling, processing, storing and destroying your data are all compliant with the General Data Protection Regulation (GDPR). All information that is collected about you during the course of the research will be kept strictly confidential. Your data will be collected from your medical records and from the activity monitor and questionnaires. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Who is organising and funding the research?
The research is funded by the Waterloo Foundation (http://www.waterloofoundation.org.uk/).

Who has reviewed the study?
This study has been reviewed and given a favourable opinion by North West - Preston Research Ethics Committee.

The University of Birmingham is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Birmingham will keep identifiable information about you for 6 months following receipt of your completed questionnaires.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at https://www.birmingham.ac.uk/privacy and/or by contacting our data protection manager.

The University of Birmingham will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Birmingham and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

Birmingham Women's and Children's NHS Foundation Trust will pass these details to the University of Birmingham along with the information collected from you. The only people in the University of Birmingham who will have access to information that identifies you will be people who need to contact you to about your participation in the study, send a feedback report or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). Our Data Protection Officer is Mrs. Carolyn Pike OBE and you can contact them at legalservices@contacts.bham.ac.uk.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you for considering taking part and taking the time to read this information sheet.

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENT/GUARDIAN INFORMATION SHEET

Research study: Sleep and Quality of Life

Part 1
Introduction to the research and invitation to take part:
We are inviting your child to take part in a research study being conducted at the Centre for Human Brain Health, University of Birmingham. This research work being led by Dr Andrew Bagshaw, Dr Caroline Richards and Ms Alice Winsor will examine how sleep habits and sleeping brain activity relate to children's and parents' quality of life.

It is important that you understand why the research is being done and what it will involve before you decide whether your child can take part or not. Please read the following information carefully and discuss this with others if you wish. Feel free to ask us if there is anything that is not clear or if you would like more information (see contact details at the end of part 1 of the information sheet).

Once you are happy that you have sufficient information to be able to decide whether or not you want your child to take part in the study, please complete the enclosed consent forms and questionnaires and post all back to us at your earliest convenience in the separate pre-paid envelopes provided. We will also provide you with a copy of the parent/guardian information sheet and consent form to keep.

What is the purpose of the study?
The purpose of this study is to investigate the link between sleep and waking behaviour and quality of life in children with neurological disorders and their parents. This will allow us to understand how different neurological disorders disrupt, and are disrupted by, sleep. In the future, this could help us to develop ways to improve quality of life for the whole family.

Why has my child been invited to take part in the study?
Your child has been invited to take part in this study because they are aged between 4 and 16 years old and have attended the Neurophysiology department at Birmingham Children's hospital to undergo a sleep video-EEG as part of routine care. The data from this appointment will form the basis for our analysis. We aim to investigate as many participants as possible during the time-frame (currently until 2021).

Does my child have to take part in this research project?

Participation in this research study is voluntary. If you decide that you do not wish your child to take part in this study, they do not have to. This will not affect the standard of care your child receives/

What will happen if my child/ the person I care for decides to participate?

If you would like to take part in the research, you will be asked to sign a consent form and provide us with a few personal details (name, postal address, telephone number and email address). We have also included an easy to read information sheet with visual aids in this pack for you to use with your child/person you care for. This can be used to include your child/person you care for in the consent process. You can return this to the research team using the pre-paid envelope provided.

1. You, as an informant for your child's sleep and behaviour, will be asked to complete a questionnaire pack. The research team will also contact you to arrange a date where we can post to you the study equipment that your child will need to complete the next assessment. We will send you an Actiwatch (similar to a Fitbit) that your child will be asked to wear on their wrist continuously for 2 weeks. We will thoroughly disinfect the Actiwatch before positing it to you and will place it in the postage bag while wearing gloves. We will also provide you with gloves and disinfectant wipes to use to clean the watch before you send it back to us. Whilst your child wears the Actiwatch, you will be asked to report daily on your child's sleep patterns using a sleep diary (takes no more than 5 minutes per day)
2. You may be contacted by the research team to schedule a time in the following 6-8 weeks after your appointment to take part in a telephone interview. This will depend on your child's diagnosis and is optional.

Where will the study activities take place?
You can complete the questionnaires at your convenience and post these back to the research team. The research team will provide remote support while your child completes the Actiwatch assessment and you report your child's sleep behaviours on the sleep diary.

Who will be involved in collecting the data?
Members of the research team at the Centre for Human Brain Health based at University of Birmingham including Dr Andrew Bagshaw, Dr Caroline Richards and Ms Alice Winsor.

How long will participation in the study take?
Completing all questionnaires is expected to take around two hours of your time in total. The activity monitor will be worn for a period of two weeks, with input into the sleep diary each day (5 minutes).

If you are invited to complete the interview in the future, this should take up to an hour to complete.

We will be collecting information from participants between September 2019 to July 2021. Following data collection, we will spend some time analysing the information and writing reports. We expect that families will receive feedback reports by the end of the study period and the study to reach completion by July 2021.

Will the interview be recorded? (Optional)
The telephone interview will be audio recorded by the research team for later typing up (transcription). The interview will be fully anonymised when it is transcribed, any personal information, names etc will be removed during typing up. The University of Birmingham will hold the copyright for the audio recordings so that the confidentiality of these recordings will be protected. But, the University of Birmingham will not be able to edit or use the recordings for teaching purposes unless you give us your written permission to do this.

What are the risks or disadvantages of taking part?
There are no risks involved in carrying out the tests. Since the tests are simple paper-and-pencil or non-invasive computer-based measures, there is nothing to go wrong.

What are the possible benefits of taking part?
The study will not help your child directly, but it will help us to better understand how sleep interacts with neurological disorders. This may then be helpful in developing future assessment and treatment options.

Furthermore, after your child has completed the study, you will be provided with a feedback report tailored to your child based on your responses to the questionnaires and results from the activity monitor. These individualised feedback reports may be useful for you to highlight particular difficulties that your child might face. We are happy for you to share a copy of this report with professionals involved in your child's care if you wish to do so.

If I decide to participate in the project, what should I do now?
Please remember that participation in the project is optional and the decision not to participate will not restrict access or affect the right to any health services. When you are satisfied that you have all the information you need to be able to decide whether or not you would like your child to take part in the study, and if you decide that you would like to participate, please complete the enclosed consent form and return it to us in the prepaid envelope provided.

You can then complete the questionnaire pack and return this to us using a second prepaid envelope that has been provided. It is important that you return the consent forms and questionnaire pack separately so that your personal information and data cannot be linked in the unlikely event that it is lost in the post. This is for your safety and to ensure your data is kept confidential.

What happens at the end of the research study?
Once the research study is over, you will receive an end of participation letter and feedback report. The results from the research will be used to inform our understanding of the role of sleep in neurological disorders and develop future assessment and diagnosis methods. The data will also form the basis of Ms Alice Winsor's PhD project and may be reported in scientific papers and at relevant conferences.

What if there is a problem?
Any complaint about the way the study has been conducted or any possible harm you may have suffered will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:
Please contact Ms Alice Winsor (PhD Student), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Or Dr Andrew Bagshaw (Reader In Imaging neuroscience), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Or Dr Caroline Richards (Lecturer in Neurodevelopmental Disorders), School of Psychology, University of Birmingham, B15 2TT
Tel:
Email:

Alternatively, you can contact Birmingham Community Healthcare - Patient Advice and Liaison Service (PALS), Moseley Hall Hospital Alcester Road, Birmingham, B13 8JL for independent advice about the study
Tel: 0800 917 2855 (freephone)
Email: PALS@bhamcommunity.nhs.uk.

This completes Part 1 of the Information Sheet.
If the information in part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision**.**

Part 2

What will happen to my data I provide?

While government regulations are in place advising workers to continue their work remotely from home, the research team will operate as such. During this period, physical data will be stored in a secure lockbox at Ms Alice Winsor's home. Electronic data will be password protected and stored on an encrypted online server held by the University of Birmingham. Only approved members of the research team will have access to this data. When such restrictions end, physical data will be transferred in the lockbox to the University of Birmingham and be stored in a locked filing cabinet in a lockable office. Once government regulations are relaxed normal data storage procedures will ensue, as described below.

Any personal identifying information including names, ages, addresses, telephone number and email addresses, which are found on the consent form will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998 & 2018. This information will be stored for the duration of the study on a password protected portable hard drive which will be kept in a locked filing cabinet at the University of Birmingham.

The audio recordings are considered to necessarily contain personal identifying information. These recordings will not be labelled with your names or any other personal identifying information but will be labelled with your special reference number. Recordings will be stored on a password protected portable drive, which will be kept in a locked cabinet at the University of Birmingham and only members of our research team will have access to them.

Your completed questionnaires will be stored separately from the personal identifying information in a locked filing cabinet at the university of Birmingham. Sleep and activity data collected via the actiwatch is stored on the device and is not transmitted via a server. Once the device is returned to the research team the data will be transferred to University of Birmingham computers. Similarly, your child's nap study data will be stored on a password protected portable encrypted hard drive. The data from these will be allocated a unique participant number and this will appear on the assessments instead of names ensuring your data is kept anonymous. An electronic file will be created which links the participant number to the participant name and will be stored on a password protected portable drive in a locked filing cabinet at the University of Birmingham. Only members of the research team will have access to the research project filing cabinet.

What will happen the data once the study is over?
Data collected from the questionnaires, activity monitor, interview and medical records (e.g medication history and MRI scans) will be destroyed 10 years following the end of the project, unless you have provided written consent for the information to be used for teaching and/or dissemination.

Records of your personal information will be destroyed immediately after the end of the study unless you tell us otherwise. This means that we would no longer be able to trace the results of your child's assessments back to you. If you withdraw from the project, we will keep the information we have already obtained but, to safeguard your rights, we will use the minimum personally-identifiable information possible. The section below on ***"Participant database information"*** gives you information about the database that we use to store the personal details of some participants. Please read the section below in order to decide whether you'd like to join that database.

Withdrawal
Even after you have provided consent for your child's participation in the study, you can request for your child to be withdrawn from the study. This will not restrict access or affect the right to any health services. Your personal and research data collected up until the point of withdrawal will be retained by the research team.

What if there is a problem?
If you have any problems with the conduct of the study then you can phone the Research Governance Committee of the University of Birmingham, who have considered this project, on 0121-414-7618, who will arrange for your concerns to be investigated. Otherwise please contact Dr Andrew Bagshaw at the School of Psychology, University of Birmingham (0121 414 3683). In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds to claim compensation against Birmingham and Solihull NHS Mental Health Foundation NHS Trust, but you may have to pay your legal costs. If the negligence was by a member of the NHS, then you may have grounds for legal action for compensation against the NHS trust concerned.

Participant Database information
Drs. Bagshaw and Richards will create a database for the purpose of this research study where we will store the names and contact details of participants. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. It will only be accessible to members of the research team. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Consent to be included in the "Participant database" is separate to consent for the study and you are welcome to participate in the study without being included in the database.

If you would like us to, we can add your details to this database. We would use this information for two things:

1) We will contact you with information about future research work to find out whether or not you would like to participate.
2) It is often important to find out how things change over time. By keeping your details, we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Your information could be used for research in any aspect of health or care and could be combined with information about you from other sources held by researchers, the NHS or government. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Who would have access to my details?
Only approved members of our research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact Dr. Bagshaw on 0121 414 3683 or Dr. Richards on 01214158098 or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Will my taking part in this study be kept confidential?
Our procedures for handling, processing, storing and destroying your data are all compliant with the General Data Protection Regulation (GDPR). All information that is collected about you during the course of the research will be kept strictly confidential. Your data will be collected from your medical records and from the activity monitor and questionnaires. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Who is organising and funding the research?

The research is funded by the Waterloo Foundation (http://www.waterloofoundation.org.uk/).

Who has reviewed the study?
This study has been reviewed and given a favourable opinion by North West - Preston Research Ethics Committee.

The University of Birmingham is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Birmingham will keep identifiable information about you for 6 months following receipt of your completed questionnaires.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at https://www.birmingham.ac.uk/privacy and/or by contacting our data protection manager.

The University of Birmingham will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Birmingham and regulatory organisations may look at your medical and research records to check the accuracy of the research study.

Birmingham Children's and Women's NHS foundation Trust will pass these details to the University of Birmingham along with the information collected from you. The only people in the University of Birmingham who will have access to information that identifies you will be people who need to contact you to about your participation in the study, send a feedback report or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

Our Data Protection Officer is Mrs. Carolyn Pike OBE and you can contact them at legalservices@contacts.bham.ac.uk.

You will be given a copy of the information sheet and a signed consent form to keep.

Thank you for considering taking part and taking the time to read this information sheet.

Hi,



We are a team from the University of Birmingham.





We work with a lot of children at different hospitals.

We would like you to take part in a study to find out about your sleep.





We will ask your parents/the person who looks after you some questions about you and how you sleep at home.





We will give you a special watch to wear at home for two weeks. This watch will measure your sleep and when you move.



The information we collect is confidential- this means only we will look at it, we won't tell anyone else you took part in the study.



If you have any questions, you can speak to us, your parents/person who looks after you and your doctor.

Thank you!

Sleep and Quality of life

Information sheet for children 8-12 years

What is research?

A research project is a way of finding out answers to questions that we don't know enough about.

Your Invitation:

We would like to ask you if you would like to join our research project. Your brain is amazing, it's always awake, even when you're sleeping! We want to find out more about your brain by looking at how it behaves when you're asleep and how this is linked to you and your family's quality of life.







Before you say whether you want to join in, it is very important for you to understand why we are doing this research and what we want you to do. Once you read this sheet, talk to your family, friends or doctor and ask us any questions if you want to.

Why have you asked me to take part?



We are looking for children between the ages of **4-16** who are coming for an appointment at the Neurophysiology department at Birmingham Children's Hospital to have a sleep video test.

What will I have to do if want to take part?

As part of your hospital appointment you will have a video sleep test. The doctor will first place some pads on your head, these will be connected to a computer. You will then be allowed to sleep. Whilst you're sleeping the doctor will watch your brain patterns on the computer. **This test will happen even if you do or do not take part in this research study.**

1. **If you decide that you want to take part in this research project**, you will be given this form and another to sign to say that you understand the study and what will happen. You will be given your own copy of the form to keep as well as this information sheet.



2. We will also ask your parents/the person who looks after you to fill in some forms to tell us a bit about how you sleep and behave at home.



3. You will be required to wear a special watch for two weeks which will record your daytime and night-time movements. Your parent/person who looks after you will also fill in a diary about your sleep each day.

Do I have to say yes?

You do not have to take part in this study. If you decide to take part but change your mind later, that's ok, it will not change the standard of medical care you receive, and **you will still be required to attend your clinic appointment.**

What will happen to my information?

The information we collect from you and your parents will remain confidential- this means only we will look at it, we won't tell anyone else you took part in the study.

What will you do with the results?

The research team will write about the results and send this to the University of Birmingham which will help us understand more about sleep and the brain and help other children with sleep issues. You will also receive a feedback paper explaining what these results mean.

Will the study upset or help me?

No- the study will not change how you are looked after at the hospital. There are no specific benefits of the study however you will receive a certificate for participating!

Will anyone check the study?

Before any research is allowed to happen in the hospital it has to be checked by a group of people called the 'Research Ethics Committee'. They make sure that the research is fair. This project has been checked by the North West - Preston Research Ethics Committee.

What happens if I don't want to carry on?

If at any time you wish to not be a part of the research just let your parents or the doctors and nurses know, and you can stop at any time



If you have any further questions, please contact Ms Alice Winsor on 07736336640.

Thank you very much for taking the time to read the information provided.

Sleep and Quality of life

Information sheet for young people 13-16 years

We would like to invite you to take part in a research study exploring the link between sleep and quality of life in children and young people.

Before you decide whether you would like to take part, it is important for you to understand why the study is being done and what it will involve. This information sheet is divided in two parts. Part 1 tells you about the study and what will happen if you choose to take part. Part 2 gives you detailed information about how the research will be run.

Please read this information sheet carefully. You can talk about it to your family, friends, doctors or us. Please **ask us** if there is anything you do not understand or if you want more information.

Thank you for reading this!

PART 1

Why have you asked me to take part?

You have been asked to take part in this study because you are aged between 4 and 16 years and will be attending an appointment at the Neurophysiology department at Birmingham Children's Hospital to have a sleep video EEG.

Do I have to take part?

You do not have to take part in this study. If you decide to take part but change your mind later, that's ok, it will not change the standard of medical care you receive, and **you will still be required to attend your clinic appointment.**

What will I be asked to do if I take part?

Prior to your appointment, your parent/carer will be mailed a study pack alongside your clinic appointment letter. The pack includes this information sheet, a consent form and a set of background questionnaires, which they will complete and return back in the envelope provided.

You will be required to read this information sheet and sign an assent form to say you understand the study and what will happen. You will be given your own copy of the form to keep as well as this information sheet. If you would like to hear more about the study, you can speak to your parent/carer to arrange a time to talk to us.

As part of your planned hospital appointment you will be asked to attend your clinic appointment where you will undergo your sleep video EEG. **This procedure will happen regardless of whether you take part in this research study.** If you do choose to participate, the data from this appointment will be used for our study. This

sleep video EEG will record the electrical activity of your brain whilst you're awake and then asleep. It involves placing small discs to your head using gel in order to record your brain activity. The appointment will take around 2 hours. Whilst you're asleep, we will provide your parents with several questionnaires to fill in. These questionnaires will measure different aspects of quality of life and your sleep patterns at home.

Once your appointment is over, we will provide you with a wrist activity monitor called an Actiwatch (similar to a Fitbit). It will measure your sleeping and movement patterns and should be worn for a period of two weeks after your appointment. Your parent/carer will also complete a sleep diary for this period of time, it will include questions such as the time you fall asleep, how long you sleep for and the number of times you wake up. Once the two weeks are over, your parent/carer will post this back to us in the prepaid envelope provided.

What are the risks or disadvantages of taking part?

There are no risks involved in this study.

What are the possible benefits of taking part?

The study will not help you directly, but it will help us to better understand how sleep interacts with different aspects of quality of life. This may then be helpful in developing future assessment and treatment options.

Furthermore, after you have completed the study, your parent/carer will be provided with a feedback report tailored to you based on their responses to the questionnaire and your results from the activity monitor. These individualised feedback reports may be useful for you to look through.

What happens at the end of the research study?

After the study stops, you will continue to access medical care if you still need it. The results from the research will be used to inform our understanding of the role of sleep in neurological disorders and develop future assessment. The data will also form the basis of this project, if you want to know the study results, let us know and we can send them to you.

PART 2

Consent

When you come to see us, we will ask you and your parent or guardian whether they will allow you take part and if they say yes, they will be asked to fill in a CONSENT form. You will be required to fill in an ASSENT form to agree to take part.

What will happen to the information you collect about me?

It is very important that all the information you give is completely confidential. The information we collect about you from your test, questionnaires and the Actiwatch will be encrypted and password protected (so no one else can see them). They will be stored on a secure university of Birmingham computer.

We only use a research ID to identify you. No name or personal information will be on the questionnaires we provide to your parents. All personal details that can identify you will be kept in a securely locked cabinet in locked offices or password protected on secure University of Birmingham computers. We will use the results when we write about this project, but we will take your name and any information off, so no one will know it's your information.

What will happen to the results of the study?

This study will provide us information on the importance of sleep in quality of life. We aim to publish these results in journals to help other children and young people who may require this information and raise the knowledge of this topic.

What should I do if I have a problem with this study?

If you have any problems with this study, please speak to your parents/carers. You can also speak to Ms Alice Winsor or any member of the research team. Their contact information can be found at the end of this sheet.

You can also complain to the NHS in the usual way through Patient Advice and Liaison Service (PALS), Tel: 0800 917 2855 (freephone).

Ethical Approval

This study has been reviewed and given a favourable opinion by North West - Preston Research Ethics Committee.

Who can I contact for further information?

Ms Alice Winsor (PhD Student), School of Psychology, University of Birmingham, B15 2TT
Tel: [redacted]
Email: [redacted]

Or Dr Andrew Bagshaw (Reader in Imaging neuroscience), School of Psychology, University of Birmingham, B15 2TT
Tel: [redacted]
Email: [redacted]
Or Dr Caroline Richards (Lecturer in Neurodevelopmental Disorders), School of Psychology, University of Birmingham, B15 2TT
Tel: [redacted]
Email: [redacted]

Thank you very much for taking the time to read the information provided!

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENTAL CONSENT FORM
Research study: Sleep and Quality of Life

If you are reading this information on behalf of someone you care for who is a child aged 4-16y, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete the consent form and post back in the pre-paid envelope provided.

Centre Number:

Please initial box…

1. I confirm I have read and understand the attached information sheet dated V3.0 05/07/19 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that the participation of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reasons, without that of my child's/person I care for's medical care or legal rights being affected. I agree that data collected prior to withdrawal can still be used in the research analysis. ☐

3. I understand that all information collected during the study will be confidential. Only members of the research team at the University of Birmingham will know who has participated in the study. All information collected during the study will be stored in locked cabinets that only members of the research team will have access to. No names will be published in any reports. Information will be treated as strictly confidential and handled in ☐

accordance with the provisions of the General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018.

4. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals involved in the research. I give permission for these individuals to have access to my records. ☐

5. I understand that as part of the above study, a voice recording may be made of me, and members of my family who are present at the time of the recording may also be captured on the audio. I consent for this recording to be made of me and stored for further review. ☐

6. I understand that the University of Birmingham will hold the copyright of any voice recordings collected during the study but that this does not entitle the University of Birmingham to edit, copy or use the recordings for teaching purposes without my written permission. ☐

7. I understand that my contact details will only be used by the research team for the purpose of this study only. ☐

8. I agree on behalf of myself for my child/person I care for taking part in the above study ☐

Optional clauses: The statements below are <u>optional</u>: ☐

1. I agree to being contacted with information about participating in future parts of the above study using the contact details I provide.

2. I agree for my contact information to be kept so that feedback can be sent to me ☐

Please complete the details below

Name of Parent / Carer: _____

Your relationship to the participant: _____

Signed: _____ **Date:** _____

Researcher name (if present) _____ **Countersigned:** _____

Child's gender: Male Female

Age of Child: _____years _____months.

Telephone number: _____

Address: _____

Email: _____

Completed Consent Form Filing
Completed consent forms will be filed in a secure and safe location at the University of Birmingham. Participants will be provided with a photocopy of the completed consent form for their own filing.

OFFICE USE
To be removed following return of consent form

ID number:

Centre for Human Brain Health

University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENTAL CONSENT FORM
Research study: Sleep and Quality of Life

If you are reading this information on behalf of someone you care for who is a child aged 4-16y, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete the consent form and post it back in the pre-paid envelope provided.

Centre Number:

Please initial box…

1. I confirm I have read and understand the attached information sheet dated V3.0 05/07/19 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that the participation of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reasons, without that of my child's/person I care for's medical care or legal rights being affected. I agree that data collected prior to withdrawl can stil be used in the research analysis. ☐

3. I understand that all information collected during the study will be confidential. Only members of the research team at the University of Birmingham will know who has participated in the study. All information collected during the study will be stored in locked cabinets that only members of the research team will have ☐

access to. No names will be published in any reports. Information will be treated as strictly confidential and handled in accordance with the provisions of the General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018.

4. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals involved in the research. I give permission for these individuals to have access to my records. ☐

5. I understand that as part of the above study, a voice recording may be made of me, and members of my family who are present at the time of the recording may also be captured on the audio. I consent for this recording to be made of me and stored for further review. ☐

6. I understand that the University of Birmingham will hold the copyright of any voice recordings collected during the study but that this does not entitle the University of Birmingham to edit, copy or use the recordings for teaching purposes without my written permission. ☐

7. I understand that my contact details will only be used by the research team for the purpose of this study only. ☐

8. I agree on behalf of myself for my child/person I care for taking part in part 1 of the study ☐

9. I agree on behalf of myself for my child/person I care for taking part in part 1 and 2 of the study ☐

Optional clauses: The statements below are <u>optional</u>:

1. I agree to being contacted with information about participating in future parts of the above study using the contact details I provide. ☐

2. I agree for my contact information to be kept so that feedback can be sent to me ☐

Please complete the details below

Name of Parent / Carer: _____

Your relationship to the participant: _____

Signed: _____ **Date:** _____

Researcher name (if present) _____ **Countersigned:** _____

Child's gender: Male Female

Age of Child: _____years _____months.

Telephone number: _____

Address: _____

Email: _____

Completed Consent Form Filing
Completed consent forms will be filed in a secure and safe location at the University of Birmingham. Participants will be provided with a photocopy of the completed consent form for their own filing.

OFFICE USE
To be removed following return of consent form

ID number:

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARENTAL CONSENT FORM
Research study: Sleep and Quality of Life

If you are reading this information on behalf of someone you care for who is a child aged 4-16y, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete the consent form and post back in the pre-paid envelope provided.

Centre Number:

Please initial box…

10. I confirm I have read and understand the attached information sheet dated 06/07/2020 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

11. I understand that the participation of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reasons, without that of my child's/person I care for's medical care or legal rights being affected. I agree that data collected prior to withdrawl can stil be used in the research analysis. ☐

12. I understand that all information collected during the study will be confidential. Only members of the research team at the University of Birmingham will know who has participated in the study. No names will be published in any reports. Information will be treated as strictly confidential and handled in accordance with the provisions of the General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018. ☐

13. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals involved in the research. I give permission for these individuals to have access to my records. ☐

14. I understand that as part of the above study, a voice recording may be made of me, and members of my family who are present at the time of the recording may also be captured on the audio. I consent for this recording to be made of me and stored for further review. ☐

15. I understand that the University of Birmingham will hold the copyright of any voice recordings collected during the study but that this does not entitle the University of Birmingham to edit, copy or use the recordings for teaching purposes without my written permission. ☐

16. I understand that my contact details will only be used by the research team for the purpose of this study only. ☐

17. I agree on behalf of myself for my child/person I care for taking part in the above study ☐

Optional clauses: The statements below are <u>optional</u>:

3. I agree to being contacted with information about participating in future parts of the above study using the contact details I provide. ☐

4. I agree for my contact information to be kept so that feedback can be sent to me ☐

Please complete the details below

Name of Parent / Carer: _____

Your relationship to the participant: _____

Signed: _____ **Date:** _____

Researcher name (if present) _____ **Countersigned:** _____

Child's gender: Male Female

Age of Child: _____years _____months.

Telephone number: _____

Address: _____

Email: _____

Completed Consent Form Filing
Completed consent forms will be filed in a secure and safe location at the University of Birmingham. Participants will be provided with a photocopy of the completed consent form for their own filing.

OFFICE USE
To be removed following return of consent form

ID number:

ASSENT FORM FOR CHILD/ YOUNG PERSON

Research study: Sleep and Quality of Life

Child (or if unable, parent on their behalf)/ young person to circle all they agree with:

1. Has somebody else explained the project to you? YES/NO
2. Do you understand what the project is about? YES/NO
3. Have you asked all of the questions you want? YES/NO
4. Have you had your questions answered in a way you understand? YES/NO
5. Do you understand it is OK to stop taking part at any time? YES/NO
6. Are you happy to take part? YES/NO

If any answers are 'no' or you don't want to take part, don't sign your name!

If you **do** want to take part, you can write your name below

Your name: _____

Date: _____

You can also choose if you want to say 'yes' to these questions:

7. If your Doctor asks to see your results from this project is that OK? YES/NO
8. Are you happy for us to contact you again in the future? YES/NO

The person who explained this project to you needs to sign too. If you are under the age of 16, this should be your parent/guardian.

Print name:_____ Sign:_____

Researcher name (if present): _____ Countersigned:_____

Date:_____

Centre for Human Brain Health
University of Birmingham
Edgbaston
Birmingham B15 2TT

PARTICIPANT DATABASE CONSENT FORM
Research study: Sleep and Quality of Life

This is <u>optional</u> and allows you to provide continuing consent for us to keep your personal details on our Participant Database. See section titled 'Participant Database' in the information sheet

Please initial box…

1. I have read and understood the section titled 'Participant Database' and I would like my personal details to be added to the database. ☐

2. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018 and I may be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

3. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child / person I care for so that they can look at changes over time if I take part in future projects. ☐

4. I understand that even after I have agreed for my details to be added to the database. I can request that they be removed by contacting Drs Bagshaw and Richards or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT. ☐

5. I understand that Drs Bagshaw and Richards hold ultimate responsibility for the database. ☐

Print Name: _____

Signature: _____

Researcher name (if present): _____

Countersigned:_____

Date: _____

OFFICE USE
To be removed following return of consent form

ID number:

Appendix 3.2 Socio Demographic Questionnaire

SOCIO DEMOGRAPHIC QUESTIONNAIRE

1. BACKGROUND INFORMATION

*Information obtained from **parent/carer:***
Parent's Gender: Male ☐ Female ☐ Other ☐
Parent's age: ☐

Please answer the following about the person you care for:

1.1 Gender of child : Male ☐ Female ☐ Other ☐

1.2 Date of birth: ___/___/____

1.3 Has the person you care for been diagnosed with any of the following conditions? Yes/No (Delete as appropriate)

If yes, please indicate which condition and answer question 1.4. If no please continue to question 1.5.

Generalised Epilepsy ☐
Focal Epilepsy ☐
Generalised and Focal Epilepsy ☐
Epilepsy Syndrome ☐
Other ☐

1.4 When was the person you care for diagnosed? _____

1.5 Please select whether your child has ever experienced any of the following types of seizures. Please tick and write any further details in the comment box (e.g. Myoclonic, tonic clonic, epileptic spasms, atonic, motor, non-motor or absence seizure types):

Focal aware seizure (Simple partial) ☐
Focal impaired awareness seizure (Complex partial) ☐
Generalised Onset seizures ☐
Unknown Onset seizures ☐

1.6 Please describe any prescribed medications your child is currently taking (name and dosage taken):

Anti-epileptic drugs:……

Medication to aid sleep (e.g. Melatonin)……

Neuroleptics (e.g. Risperidone)……

Anti-depressants (e.g. Amitriptyline)……

Psychostimulants (e.g. Methylphenidate)……

Other Medications:……

1.7 Has the person you care for had any medical/health difficulties in the last six months? If yes, please give details

_____

_____

2. SCHOOL

2.1 Start of school

☐ Early ☐ Regular age ☐ Late ☐ Not known

2.2 Repeating of year

☐Repeated year ☐ None ☐ One ☐ Several ☐ Not known

Dropped out of school ☐ No ☐ Yes ☐ Not known

2.3 How many changes of schools due to academic or behavioural problems:

☐ None ☐ 1 x ☐ 2x ☐ >3x ☐ Not known

2.4 Current and past schools attended

Primary school ☐ yes ☐ No

If 'yes': ☐ Mainstream ☐ Special Education ☐ Not known

Secondary school ☐ yes ☐ No

If 'yes': ☐ Mainstream ☐ Special Education ☐ Not known

2.5 Current School year (e.g. year 5, 6, 7, etc…): _____

2.6 Current school attendance (proportion of required time)

☐ 100% ☐ ≥ 60% ☐ < 60% ☐ <20% ☐ Not known/Applicable

The following questions ask for background information about you and your family. Please tick boxes or write in the spaces provided.

3. SOCIAL INFORMATION

3.1 Child/Adolescent lives with:

Female person:

(Please note: question is single choice, only tick once)

☐ Biological mother ☐stepmother ☐adoptive mother ☐foster mother

☐Female relative, other responsible female carer ☐not applicable

Male person:

(Please note: question is single choice, only tick once)

☐Biological father ☐stepfather ☐adoptive father ☐foster father

☐Male relative, other responsible male carer ☐not applicable

Grandparents:

Grandmother: ☐ yes ☐ no

Grandfather: ☐ yes ☐no

Alternative living conditions:

(Please note: question is single choice, only tick once)

☐Lives alone ☐no permanent residence/homeless

☐Assisted living /shared flat/care taker ☐not applicable

If 'assisted living/shared flat/care taker': since_____ _____ (month/year)

3.2 Living area

Number of persons in household: _____ Adults _____ Children _____

Number of rooms (without kitchen/bathroom) _____

Does your child share a room? ☐ yes ☐no

If yes, with how many people? _____

3.3 Siblings

Number of siblings: ☐ 0 ☐ 1 ☐2 ☐3 ☐ 4 ☐ >4

Age of siblings: from |_|_| years to |_|_| years

3.4 What is your current marital status?

Married, and living with spouse..... ☐

Living with partner..... ☐

Divorced/Separated/Widowed/Single and NOT living with a partner..... ☐

3.5 Education of parents / Caregivers

Parent 1

Relationship to child: Mother / Father (please circle)

No formal educational qualifications.....

Fewer than 5 GCSE or O level (grades A-C), NVQ 1, or BTEC First Diploma…….

5 or more GCSE or O level (grades A-C), NVQ 2, or equivalent……..……..

3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent.....

Polytechnic/University degree, NVQ 4, or equivalent.....

Masters/Doctoral degree, NVQ 5, or equivalent…….....

Parent 2

Relationship to child: Mother / Father (please circle)

No formal educational qualifications.....

Fewer than 5 GCSE or O level (grades A-C), NVQ 1, or BTEC First Diploma…….

5 or more GCSE or O level (grades A-C), NVQ 2, or equivalent……..……..

3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent.....

Polytechnic/University degree, NVQ 4, or equivalent.....

Masters/Doctoral degree, NVQ 5, or equivalent…….....

3.6 Ethnic group

White	Child
English/welsh/Scottish/Northern Irish/British	
Irish	☐
Gypsy or Irish Traveller	☐
Any other white background …….	☐
	☐

Mixed/Multiple Ethnic Groups	
White and Black Caribbean	☐
White and Black African	☐
White and Asian	☐
Any other Mixed/Multiple ethnic background……..	☐

Asian/Asian British	
Indian	
Pakistani	☐
Bangladeshi	☐
Chinese	☐
Any other Asian Background……..	☐
	☐

Black/African/Caribbean/Black British	
African	
Caribbean	☐
Any other Black/African/Caribbean Background…….	☐
	☐

Other ethnic group	
Arab	
Any other ethnic group…….	☐
	☐

Appendix 3.3 Hague Seizure severity Scale

THE HAGUE SEIZURE SEVERITY SCALE for children with epilepsy

Questions relate to your child's condition in the past 3 months.

1. How often do you notice a decrease of consciousness during a seizure in your child?
    a. always
    b. usually
    c. sometimes
    d. never

2. How long does such a decrease of consciousness last? (From time of onset to time of normal consciousness)
    a. very long
    b. long
    c. short
    d. very short
    e. does not apply, there is no decrease of consciousness

3. How severe have the seizures been overall?
    a. very severe
    b. fairly severe
    c. not very severe
    d. not at all severe

4. Are there any muscle jerks or cramps in the arms or legs during an attack?
    a. always
    b. usually
    c. sometimes
    d. never

5. How long do the jerks or cramps last during an attack?
    a. very long
    b. long
    c. short
    d. very short
    e. does not apply, there are no jerks or cramps

6. How noticeable are the symptoms of an attack?
    a. very noticeable, everyone will notice an attack
    b. fairly noticeable, most people will notice an attack
    c. not very noticeable, most people will not notice
    d. not at all noticeable, you have to be very alert to notice an attack

7. During or after an attack, how often does your child seem confused?
    a. always
    b. usually
    c. sometimes
    d. never

8. During an attack, how often does your child wet him/herself?
    a. always
    b. usually
    c. sometimes
    d. never (or unknown)

9. During an attack, how often does your child bite his/her tongue?
    a. always
    b. usually
    c. sometimes
    d. never

10. How often does your child become injured during an attack (other than biting the tongue)?
    a. always
    b. usually
    c. sometimes
    d. never

11. After the attack has finished, is your child sleepy? (Including sleepiness caused by the use of rescue medication like Diazepam)
    a. always
    b. usually
    c. sometimes
    d. never

12. After an attack, does your child complain of sickness, headache and/or pain in the muscles?
    a. always
    b. usually
    c. sometimes
    d. never (or unknown, my child would not be able to complain about that)

13. After an attack, how long does it take, until your child can resume to normal activity?
    a. very long
    b. long
    c. short
    d. very short or direct after an attack

Appendix 3.4 Children's Sleep Habits Questionnaire

Child's Sleep Habits
(Preschool and School-Aged)

_____
Coding

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if something occurs **5 or more times** in a week; answer SOMETIMES if it occurs **2-4 times** in a week; answer RARELY if something occurs **never or 1 time** during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A).

Bedtime

Write in child's bedtime: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child goes to bed at the same time at night **(R) (1)**	☐	☐	☐	Yes	No	N/A
Child falls asleep within 20 minutes after going to bed **(R) (2)**	☐	☐	☐	Yes	No	N/A
Child falls asleep alone in own bed **(R) (3)**	☐	☐	☐	Yes	No	N/A
Child falls asleep in parent's or sibling's bed **(4)**	☐	☐	☐	Yes	No	N/A
Child falls asleep with rocking or rhythmic movements	☐	☐	☐	Yes	No	N/A
Child needs special object to fall asleep (doll, special blanket, etc.)	☐	☐	☐	Yes	No	N/A
Child needs parent in the room to fall asleep **(5)**	☐	☐	☐	Yes	No	N/A
Child is ready to go to bed at bedtime	☐	☐	☐	Yes	No	N/A
Child resists going to bed at bedtime	☐	☐	☐	Yes	No	N/A
Child struggles at bedtime (cries, refuses to stay in bed, etc.) **(6)**	☐	☐	☐	Yes	No	N/A
Child is afraid of sleeping in the dark **(7)**	☐	☐	☐	Yes	No	N/A
Child is afraid of sleep alone **(8)**	☐	☐	☐	Yes	No	N/A

Sleep Behavior

Child's usual amount of sleep each day: _____ hours and _____ minutes (combining nighttime sleep and naps)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child sleeps too little **(9)**	☐	☐	☐	Yes	No	N/A
Child sleeps too much	☐	☐	☐	Yes	No	N/A
Child sleeps the right amount **(R) (10)**	☐	☐	☐	Yes	No	N/A
Child sleeps about the same amount each day **(R) (11)**	☐	☐	☐	Yes	No	N/A
Child wets the bed at night **(12)**	☐	☐	☐	Yes	No	N/A
Child talks during sleep **(13)**	☐	☐	☐	Yes	No	N/A
Child is restless and moves a lot during sleep **(14)**	☐	☐	☐	Yes	No	N/A
Child sleepwalks during the night **(15)**	☐	☐	☐	Yes	No	N/A
Child moves to someone else's bed during the night (parent, brother, sister, etc.) **(16)**	☐	☐	☐	Yes	No	N/A

Coding

Sleep Behavior (continued)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child reports body pains during sleep. If so, where? _____	☐	☐	☐	Yes	No	N/A
Child grinds teeth during sleep (your dentist may have told you this) **(17)**	☐	☐	☐	Yes	No	N/A
Child snores loudly **(18)**	☐	☐	☐	Yes	No	N/A
Child seems to stop breathing during sleep **(19)**	☐	☐	☐	Yes	No	N/A
Child snorts and/or gasps during sleep **(20)**	☐	☐	☐	Yes	No	N/A
Child has trouble sleeping away from home (visiting relatives, vacation) **(21)**	☐	☐	☐	Yes	No	N/A
Child complains about problems sleeping	☐	☐	☐	Yes	No	N/A
Child awakens during night screaming, sweating, and inconsolable **(22)**	☐	☐	☐	Yes	No	N/A
Child awakens alarmed by a frightening dream **(23)**	☐	☐	☐	Yes	No	N/A

Waking During the Night

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child awakes once during the night **(24)**	☐	☐	☐	Yes	No	N/A
Child awakes more than once during the night **(25)**	☐	☐	☐	Yes	No	N/A
Child returns to sleep without help after waking	☐	☐	☐	Yes	No	N/A

Write the number of minutes a night waking usually lasts: _____

Morning Waking

Write in the time of day child usually wakes in the morning: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child wakes up by him/herself **(26) (R)**	☐	☐	☐	Yes	No	N/A
Child wakes up with alarm clock	☐	☐	☐	Yes	No	N/A
Child wakes up in negative mood **(27)**	☐	☐	☐	Yes	No	N/A
Adults or siblings wake up child **(28)**	☐	☐	☐	Yes	No	N/A
Child has difficulty getting out of bed in the morning **(29)**	☐	☐	☐	Yes	No	N/A
Child takes a long time to become alert in the morning **(30)**	☐	☐	☐	Yes	No	N/A
Child wakes up very early in the morning	☐	☐	☐	Yes	No	N/A
Child has a good appetite in the morning	☐	☐	☐	Yes	No	N/A

Coding

Daytime Sleepiness

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child naps during the day	☐	☐	☐	Yes	No	N/A
Child suddenly falls asleep in the middle of active behavior	☐	☐	☐	Yes	No	N/A
Child seems tired **(31)**	☐	☐	☐	Yes	No	N/A

During the past week, your child has appeared very sleepy or fallen asleep during the following (check all that apply):

	1 Not Sleepy	2 Very Sleepy	3 Falls Asleep
Play alone	☐	☐	☐
Watching TV **(32)**	☐	☐	☐
Riding in car **(33)**	☐	☐	☐
Eating meals	☐	☐	☐

Appendix 3.5 Sleep Diary

PARENT INFORMATION PACK

Sleep and Quality of life

Dear Parent and Guardians,

Thank you for agreeing to take part in the study. In this pack is all the information you'll need over the next two weeks in order for us to understand more about your child's sleep. You are under no obligation to complete any of the measures and can choose to stop the study at any stage. If you have any questions at all, please do contact us.

If anything's not clear, please do call us and we'd be happy to talk you through it.

Contact Information: Your contact for the weeks is Ms Alice Winsor

ACTIWATCHES



What do they do? An Actiwatch measures movement, this can help us to know when your child is awake or asleep.

Why are we using them? Directly measuring sleep this way can give us the most accurate picture of sleep/wake patterns.

Who should wear them? Your child should wear the watch.

How do they wear them? Children should wear the Actiwatch on either their non-dominant wrist or ankle, whichever they find most comfortable. The watch should fit snuggly but doesn't need to be too tight. We have also included a hospital band with a child-proof fastening for you to use with the Actiwatch for your child if you think that it would help them to keep the Actiwatch on. **Please remember to press the "marker" button on the left of the Actiwatch when you turn off the lights for your child to go to sleep and when they wake up in the morning.** We would really like you to encourage your child to wear the Actiwatch for as much of the day and night as possible, however we recommend taking it off during bath time and replacing it immediately after. Please make a note on the sleep diary of the timings of when the watch was removed and replaced. Once the watch is being worn, you do not need to press any buttons, it is recording data automatically.

When should they wear them? Your child should wear the watch from the first opportunity, after they return from their clinic appointment until a researcher collects the watch from you or is mailed back.

What if the Actiwatch stops working? Please contact us. We'll get a replacement to you as soon as we can.

What if the Actiwatch is uncomfortable? Loosening the strap a little might help. If there are any signs of reddening or inflammation, please stop using the watch and give us a call. This doesn't happen often.

What if my child doesn't want to wear it? That's fine. If you do feel comfortable to start another day, that would be great. If you would like any advice in encouraging your child to wear the watch, please contact Ms Alice Winsor.

Green column: To be completed in the evening when your child is going to sleep
Blue column: To be completed in the morning when your child wakes up
Yellow column: To be completed throughout the day

SLEEP DIARIES

On the following pages, you'll find the paper versions of the sleep diaries

What do they do? The sleep diary is a way to get a picture of your child's routine.

Why are we using it? The actiwatches don't tell the full story. The diaries can let us know what you see in your child's sleeping pattern.

How often do I fill it in? Please try and do this every day. Some people find it easiest to do when they get up in the morning or after their child has gone to school.

How do I fill it in? You will receive a text message reminder to complete the sleep diary. Hopefully it should be clear on the diary itself. Each day has a row and we'd like you to fill in: when your child goes to bed, when they get up, how many times they get up in the night…

What if I forget to fill it in? Don't worry, if you can still remember what happened then fill it in, if not, start again on the next day. We will send you a number of prompts by text message throughout the day to help remind you to fill these in.

What if I don't want to fill it in? That's fine. If you do feel comfortable to start another day, that would be great.

What if I have any problems? Please contact us.

1st day of study: Please put your child's Actiwatch on at the first opportunity after your child returns from their appointment. Please note this time and date here _____.

15th day of study: Please remove your child's actiwatch and follow instructions for return of Actiwatch.

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Day of the week							
Time got into bed?							
Time lights turned off?							
Child's behaviour at bedtime?							
What did you do to handle the problem?							
Estimated time taken to fall asleep?							
Time woken up in morning?							
Time got out of bed?							
Fell asleep: 1. Easily 2. After some time							

W/ difficulty							
How many times woke up during the night?							
How long awake?							
Timing of awakenings?							
Behaviour during wakings?							
What did you do to handle the problem?							
Estimated total amount of sleep?							

Perceived sleep quality: 1-5 (1 poor and 5 very good)	[redacted]						
List of stresses of the day							
Did they nap during the day/night? If so, how long for?							
Rate how he/she felt today 1. Tired 2. Somewhat tired 3. Fairly alert 4. Wide awake							
Irritability level 1. None 2. Some/ moderate 3. Fairly high 4. High							
Medications							

Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
If your child had a seizure: 1. Were they asleep/awake? 2. Did they occur in the day/night? 3. What time and how long did they occur for?							

N.B. Please remove the Actiwatch when showering/bathing. Please note any reason for why your child's sleep quality may have been poor, e.g. if ill.

	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14
Day of the week							
Time got into bed?							
Time lights turned off?							
Child's behaviour at bedtime?							
What did you do to handle the problem?							
Estimated time taken to fall asleep?							
Time woken up in morning?							
Time got out of bed?							
Fell asleep: 1. Easily							

2. After some time W/ difficulty							
How many times woke up during the night?							
How long awake?							
Timing of awakenings?							
Behaviour during wakings?							
What did you do to handle the problem?							
Estimated total amount of sleep?							

Perceived sleep quality: 1-5 (1 poor and 5 very good)							
List of stresses of the day							
Did they nap during the day/night? If so, how long for?							
Rate how he/she felt today 1. Tired 2. Somewhat tired 3. Fairly alert 4. Wide awake							
Irritability level 1. None 2. Some/ moderate 3. Fairly high 4. High							
Medications							

Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
If your child had a seizure: 1. Were they asleep/awake? 2. Did they occur in the day/night? 3. What time and how long did they occur for?							

	DAY 15	DAY 16	DAY 17	DAY 18	DAY 19	DAY 20	DAY 21
Day of the week							
Time got into bed?							
Time lights turned off?							
Child's behaviour at bedtime?							
What did you do to handle the problem?							
Estimated time taken to fall asleep?							
Time woken up in morning?							
Time got out of bed?							
Fell asleep: 3. Easily 4. After some time W/ difficulty							

How many times woke up during the night?							
How long awake?							
Timing of awakenings?							
Behaviour during wakings?							
What did you do to handle the problem?							
Estimated total amount of sleep?							

Perceived sleep quality: 1-5 (1 poor and 5 very good)							
List of stresses of the day							
Did they nap during the day/night? If so, how long for?							
Rate how he/she felt today 1. Tired 2. Somewhat tired 3. Fairly alert 4. Wide awake							
Irritability level 1. None 2. Some/ moderate 3. Fairly high 4. High							
Medications							

Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
Time Actiwatch removed							
Time Actiwatch replaced							
If your child had a seizure: 1. Were they asleep/awake? 2. Did they occur in the day/night? 3. What time and how long did they occur for?							

Appendix 3.6 Protocol for cleaning Actigraphy



UNIVERSITY OF BIRMINGHAM

Actigraphy Cleaning Protocol

Jayne Trickett, Mary Heald, Andrew Surtees, Emma Clarkson, Georgie Agar, Chris Oliver and Caroline Richards

Cerebra Centre for Neurodevelopmental Disorders
School of Psychology
University of Birmingham

Please use this reference when citing this work:
Trickett J., Heald, M., Surtees, A., Clarkson, E., Agar, G., Oliver, C., & Richards, C. (2017). *Actigraphy Cleaning Protocol*. University of Birmingham, Birmingham.

Data cleaning

Needed to complete cleaning:

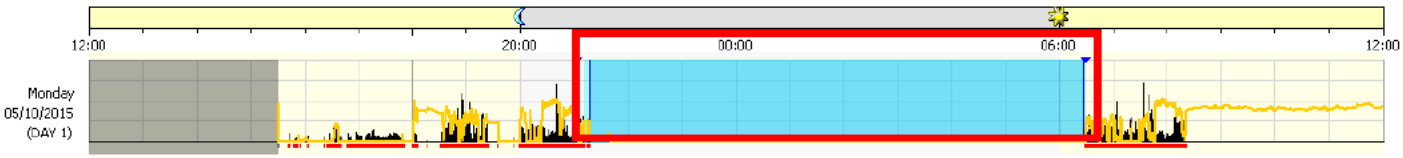
a) Open file on Philips Actiware
b) Child diary.

Step-1: Exclude any automatically-coded intervals which occur after the watch has been collected (E, Shift E, Ctrl E). This information can be gained from the sleep diary.



Step-2: Exclude any nights during which the parent identifies a time when the watch was taken off.

- Open child diary to the relevant night and confirm if parent reports any times that watch was taken off between lights out and wake-up time. If there are any such times check against actogram for consistency (i.e., no movement at this time). If consistent, exclude this night from data in actogram (E, Shift E, Ctrl E). If parent reports that the watch has been removed, but this is not evident on the actogram (i.e., evidence of movement during this time), keep the existing interval as it is and continue to step 3.



** Parent has recorded that the watch was removed on the night of Monday 6th. Inspection of the actogram suggests that there was no evidence of activity, and therefore appears to be consistent with parent report. The interval has therefore been excluded.*



** Parent has recorded that the watch was removed for part of the night of Thursday 10th. Inspection of the actogram suggests that there was activity throughout the interval, and this therefore appears to be inconsistent with parent report. The automatically-calculated interval has therefore been left.*

Step-3: Exclude any nights during which the watch appears to have been taken off, but this was not noted in parent diary.

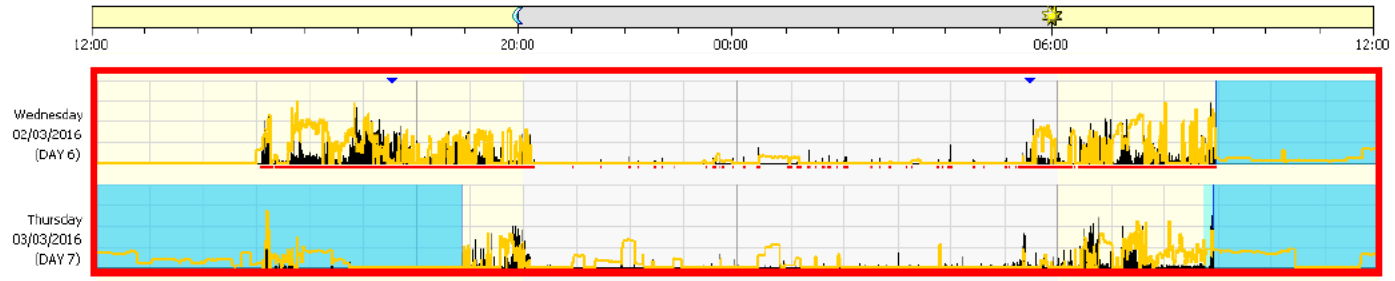
- Visually inspect each night on actogram. If on any night, there is no recorded activity (**0 in <u>activity</u> column** of data list) for a period of 2 hours or more, exclude this whole night from actogram (E, Shift E, Ctrl E).



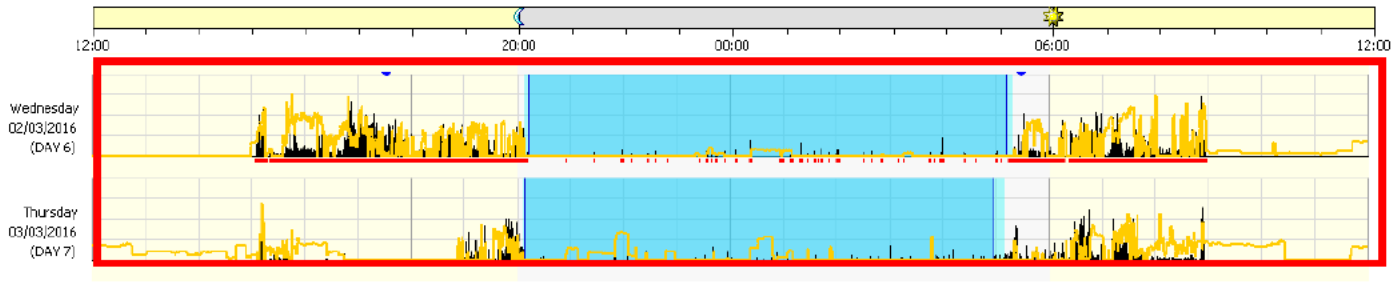
** Parent has not recorded that the watch was removed during the night of Monday 21st, but inspection of the actogram suggests that there were periods greater than 2hours without any evidence of activity. This would suggest that the watch was removed, and the automatically-calculated interval has therefore been excluded.*

Step-4: Clear any automatically-calculated sleep intervals from the daytime and insert interval to night time

- Note any occasions on which the software has coded the sleep interval as in the day-time. Criteria for this is if the automatically-coded interval both starts and ends outside of period noted as sleep in parent diary. For any intervals on which this is the case, clear the sleep interval (Right click, clear interval).
- New interval should be inserted.
- To allocate start time of new interval: 1. Find first period of 20 minutes of sleep after lights out in diary (40 epochs coded as **0 in sleep/wake column** in data list). From there, go back to the last period of 10 minutes of activity (20 epochs coded as **1 in sleep/wake column**). Start time is first 0 after this.
- To allocate end time: 1. Find last period of 20 minutes of sleep before wake-up time in diary (40 epochs coded as **0 in sleep/wake column**). From there, go forward to the first period of 10 minutes of activity (20 epochs coded as **1 in sleep/wake column**). End time is first 0 before this.

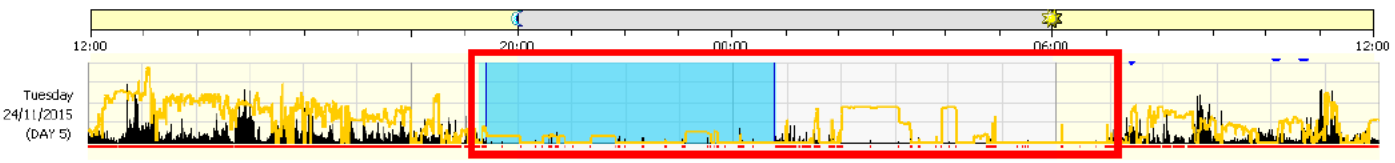


** Sleep interval has been automatically-calculated to fall between 9am and 7pm on Thursday 3rd. When consulting the parent diary, it can be seen that this interval falls outside of the time that the parent reported the child to be in bed, and so we can assume that the interval has been calculated incorrectly. As a result, we can clear the incorrect intervals, and insert new intervals.*



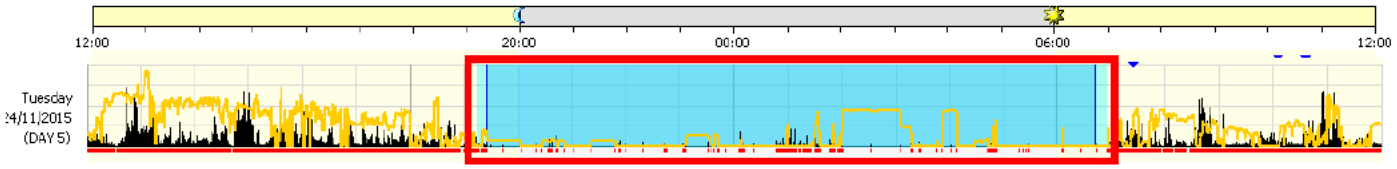
Step-5: Extend any intervals that have not captured entire night sleep.

- Locate any 20 minute periods coded as sleep in the actogram (40 epochs coded as 0 in sleep/wake column), that are **not** found within the automatically calculated sleep interval but **are** between lights out and wake-up in sleep diary.
- If period is after the automatically calculated interval, extend interval from sleep period to last point before 10 minutes coded as awake (20 consecutive scores coded as 1 in sleep/wake column on datalist). To do this, clear the original interval and add a new one with the original start time and the new end time.
- If period is before the automatically calculated interval, extend interval from sleep period to first point after 10 minutes coded as awake (20 consecutive epochs coded as 1 in sleep/wake column on datalist). To do this, clear the original interval and add a new one with the original end time and the new start time.



** The automatically-calculated sleep interval suggests that child is awake from 1 am on Wednesday 25th. However, inspection of the actogram suggests that there are several periods of non-activity after 1 am. Looking at the actogram more closely, it can be seen that some of these periods are greater than 20 mins,*

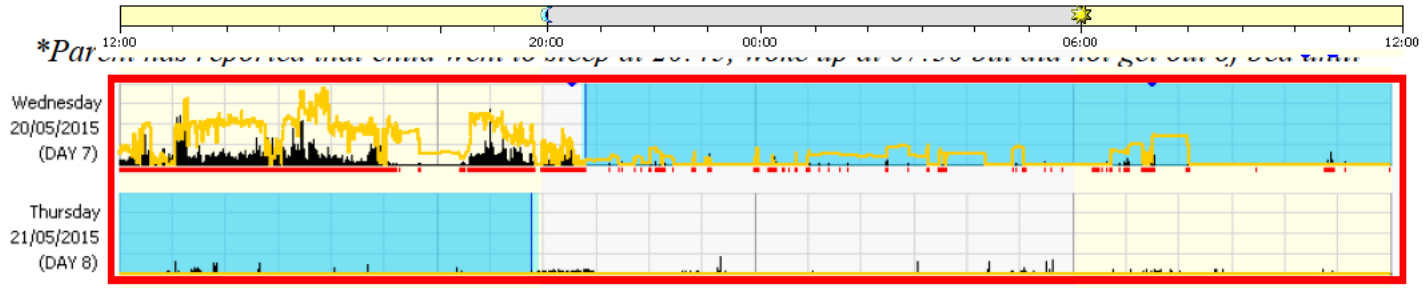
which implies that the child has returned to sleep and the automatically-calculated sleep interval has incorrectly estimated the child's final waking time as being too early. As a result, we can clear the incorrect interval, and insert a new interval.



** A new sleep interval has been calculated using the data list, to identify the time at which the child is likely to have awoken in the morning based on the data in the sleep/wake column. The original time at which the sleep interval was automatically estimated to have begun has remained the same. The original start time, and new end time have therefore been used to insert a new interval.*

Step-6: Exclude any intervals that have twice the duration of the average Total Sleep Time

- Note any occasion where the software has created a sleep interval where the duration of Total Sleep Time and/or the sleep diary has stated that time between lights out and waking up time is twice that of the average TST. Exclude sleep interval.



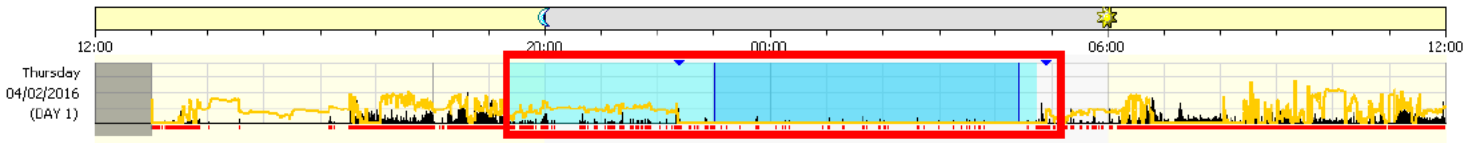
**Par[illegible]*

19:45. Total Sleep Time for this night is > twice as long as average Total Sleep Time across the whole week and therefore sleep interval has been excluded.

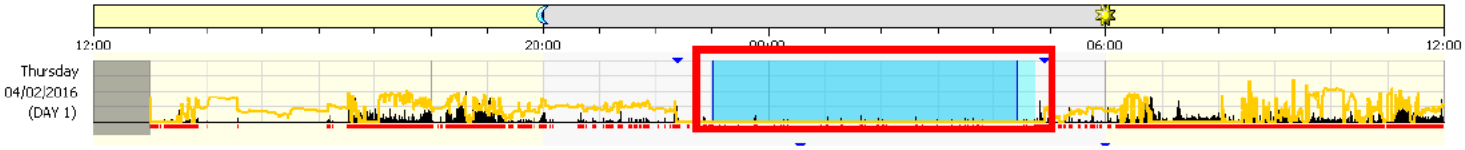
Step-7: Exclude nights where parents reported that children had a sleepover with a friend

Step-8: Change any sleep intervals where it includes parent report sedentary activity.

- Check if the automatically-calculated sleep interval overlaps with the parent reported sedentary activity in the diary.
- If the sedentary activity in the sleep diary ends before the sleep interval in the actigraphy, do not change the sleep interval.
- If sleep interval starts during the period of sedentary activity, delete the sleep interval and create a new sleep interval. Extract the end of the sleep interval from the summary statistics and input the start of the sleep interval using the following guidance:
    - a) If the diary 'time lights turned off' and the event marker are congruent (+/- 15 minutes) use the time the event marker was pressed as the start of the newly created sleep interval.
    - b) If the diary 'time lights turned off' and event marker are incongruent (> +/- 15 minutes) use the time the event marker was pressed as the start of the newly created sleep interval **unless** the event marker was pressed during the sedentary activity (if this is the case, use the diary 'time lights turned off' as the start of the newly created sleep interval).
    - c) If the event marker was **not** pressed, use parent reported 'time lights turned off' as the start of the newly created sleep interval.
    - d) If the event marker was not pressed and the parent diary does not report 'time lights turned off' use the end of the period of sedentary activity in the sleep diary as the start of the newly created sleep interval.



** The automatically-calculated sleep interval suggests that parent has been in bed from 7:30pm on*



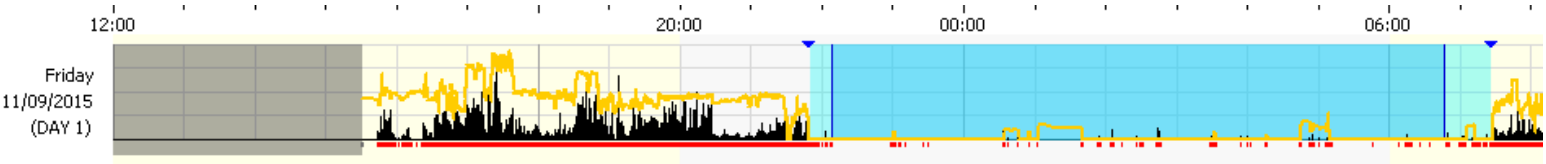
Thursday 4th. The parent diary reported sedentary activity between 7:30pm and 11:00pm. The diary and the event marker are incongruent, and the event marker was pressed during the sedentary activity. As a result, we clear this sleep interval and insert a new one using the parent reported 'time lights turned off'.

Step 9 – Changing the start of the rest interval

- Look over the whole week of the sleep diary. If on the majority of nights (e.g., 4/7) the following apply:
  - Event marker is missing
  - Event marker has been pressed multiple times within two hours of the automatic interval
  - Parent indicated that the event marker was pressed at the incorrect time

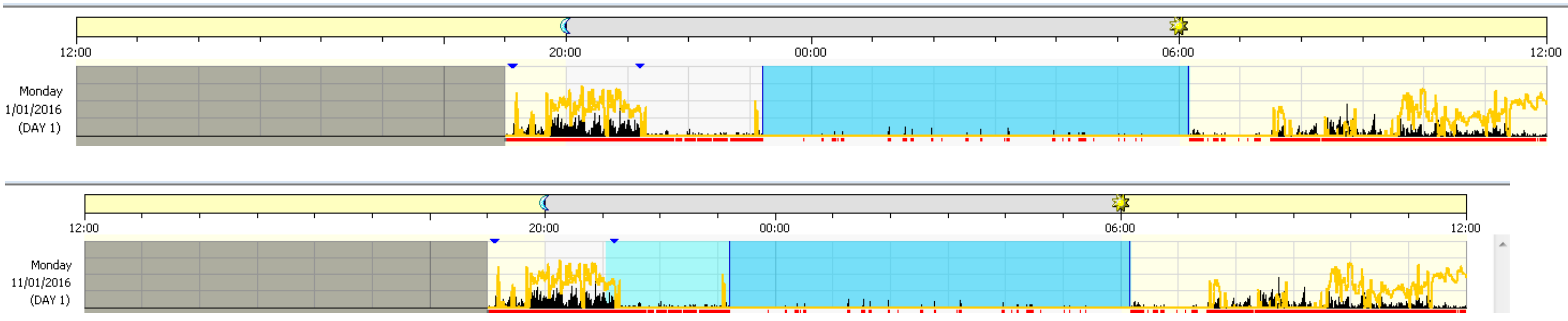
Then use the sleep diary to adjust the start of the sleep intervals for each day. Use adjusted algorithms on page 10. For each day that the event marker is inaccurate (even if this is just 1/7) use the adjusted algorithm for that day specifically.

- Look at the event marker, sleep diary and the automatically calculated rest interval. If they are concordant (all three within +/-15 minutes of each other) then leave the automatically calculated rest interval.



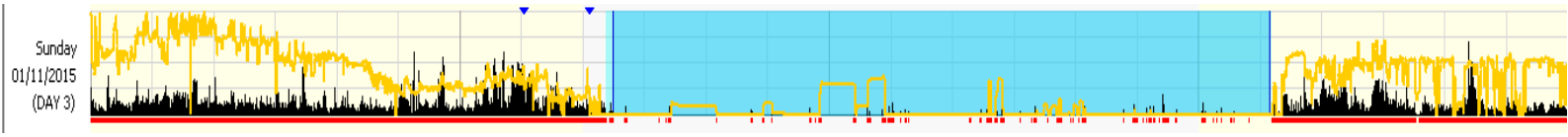
**The sleep diary, event marker and automatically calculated interval all indicate that the lights were turned off at 21:45, so the automatically calculated interval is left.*

- If the event marker and sleep diary are concordant but discordant with the automatically calculated rest interval, delete this interval and replace it with a new interval. The new start time should be the time indicated by the event marker.



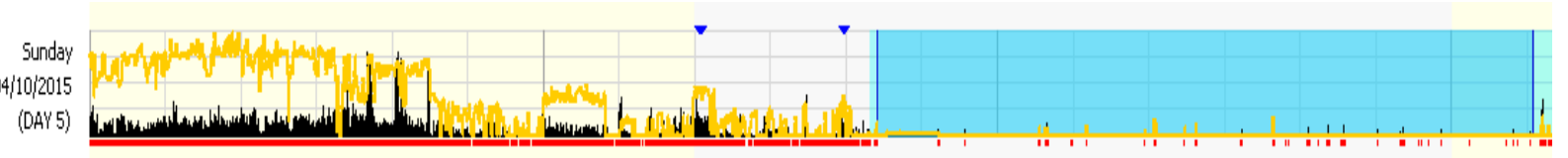
**The parent diary and event marker indicate that the lights were turned off at around 21:15. However, the automatically calculated rest interval begins at 23:13. Since they are discordant, the event marker is used to indicate when the child went to sleep and a new rest interval is added.*

- If the event marker is discordant with the sleep diary but concordant with the automatically calculated rest interval, leave the automatically calculated rest interval.



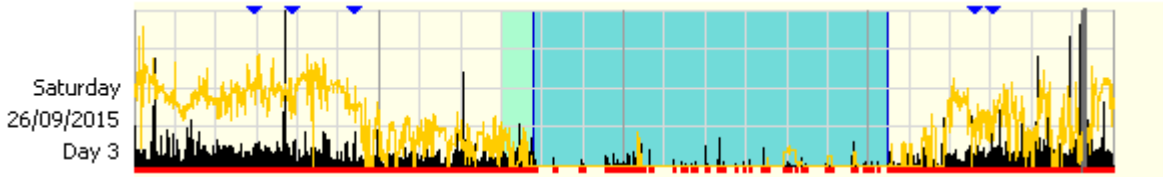
**The event marker has been pressed at 20:06:30, but the parent reports in the sleep diary that they are not sure when it was pressed or when the lights were turned off. The automatically calculated rest interval begins within 15 minutes of the event marker being pressed, so no change is made to the start of the rest interval.*

- If the sleep diary is discordant with the event marker but concordant with the automatically calculated rest interval, leave the automatically calculated rest interval.

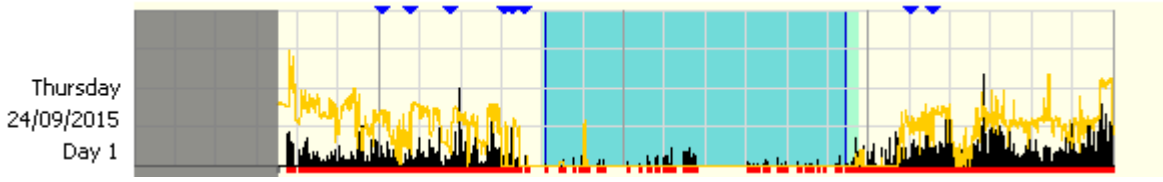


**The sleep diary indicates that the lights were turned off at 22:30, but the event marker has been pressed at 21:59. The automatically calculated interval suggests the child fell asleep at 22:24:30. Since this is within 15 minutes of the time indicated by the parent sleep diary, leave the automatically calculated interval.*

- If the sleep diary, event marker and automatically calculated rest interval are all discordant, leave the automatically calculated rest interval.



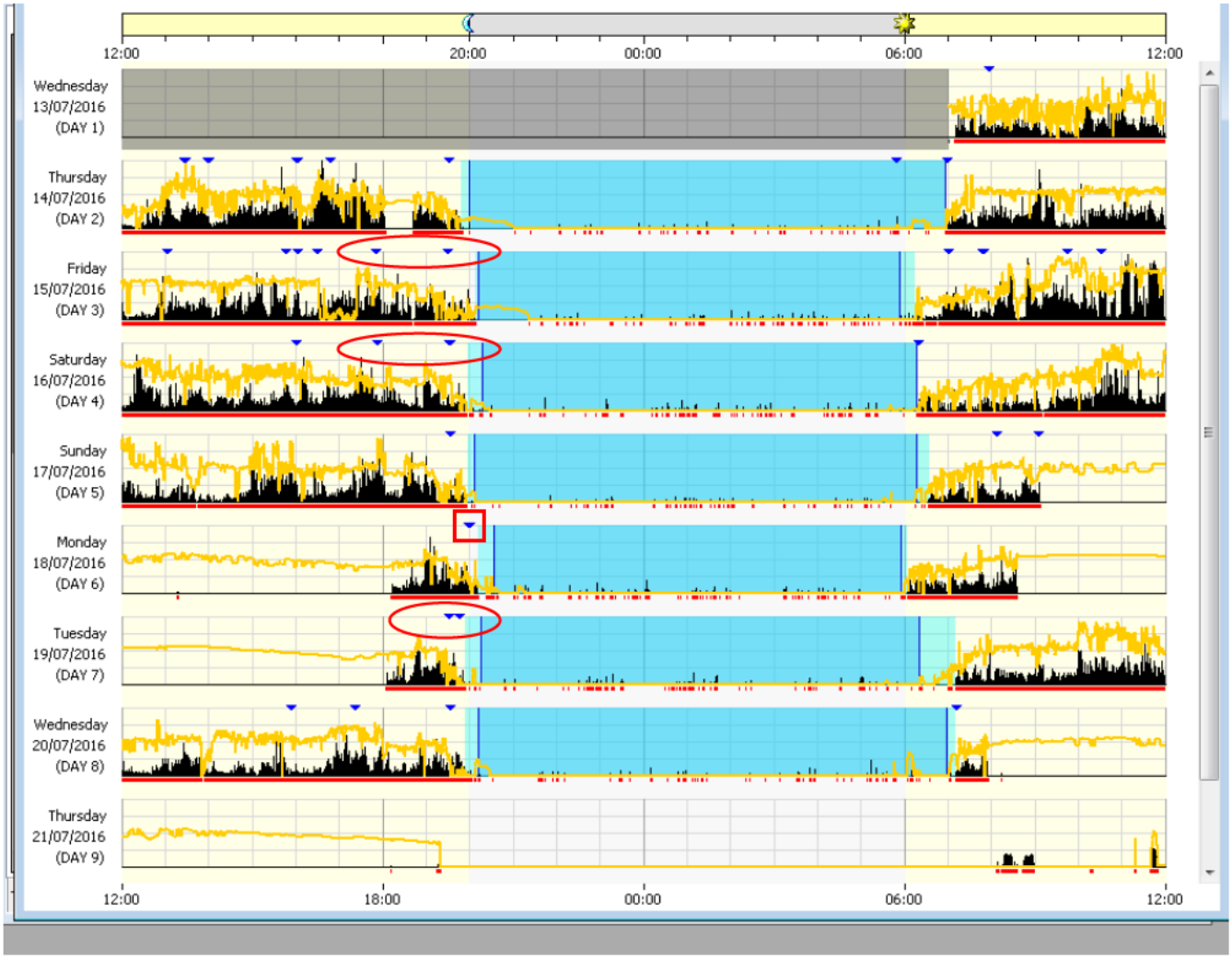
**Sleep diary indicated lights out at 20:15, this is discordant with light and activity levels by 45 mins. Sleep diary lights out time is earlier than automatic interval. No sedentary activity overlap with sleep period- used automatically calculated sleep interval.*



**Sleep diary indicated lights out at 22:30, this is discordant with lights and activity levels by 30 mins. Sleep diary lights out time is later than automatic interval. No sedentary activity overlap with sleep period- used automatically calculated sleep interval*

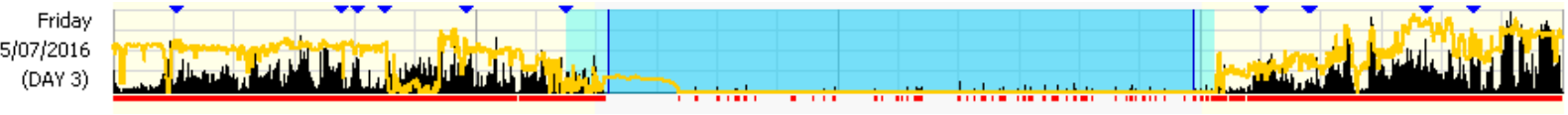
ALTERNATIVE ALGORITHMS

- If the event marker has been identified as missing or inaccurate on a majority of nights, then it should be discounted.



**On several nights (Friday, Saturday, Tuesday) the event marker has been pressed multiple times within two hours of the automatically calculated rest interval. Additionally, on Monday, the event marker has been pressed at 20:02, but the parent diary indicates it was pressed at 19:30. This means that the event marker is inaccurate for the majority of nights (4/7), and so should be discounted. This means that only alternative algorithms 1 and 2 should be used to clean the data.*

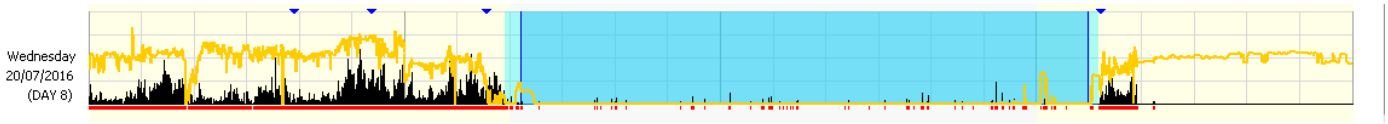
- If the event marker has been identified as inaccurate, but the sleep diary and automatically calculated rest interval are concordant, leave the



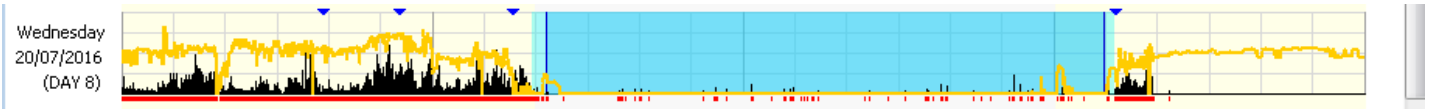
automatically calculated rest interval.

**The event marker has been pressed several times. The sleep diary and automatically calculated interval indicate that the child went to sleep at around 19:45, so the automatically calculated interval is left.*

- If the event marker has been identified as inaccurate and the sleep diary is discordant with the automatically calculated interval, use the sleep diary to insert a new interval.



**The event marker has been pressed multiple times throughout this participant's sleep week, so the event marker is discounted. The sleep diary says that the lights were turned off at 19:35pm, but this is discordant with the automatically calculated sleep interval by 20 minutes. Therefore, the automatic interval is cleared and a new interval is inserted, which begins at 19:35pm.*



Appendix 3.7 Quality of life in childhood epilepsy questionnaire

Quality of Life in Childhood Epilepsy Questionnaire: QOLCE-55
Version 1.0 (English)

Goodwin SW, Lambrinos AI, Ferro MA, Sabaz M, Speechley KN. Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). Epilepsia 2015;56(6):864-72.

USER INFORMATION

Citation:

Individuals using the QOLCE-55 should cite the following reference in their work:

> Goodwin SW, Lambrinos AI, Ferro MA, Sabaz M, Speechley KN. Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). Epilepsia 2015;56(6):864-72.

QOLCE-55 Item Allocation:

1. Cognitive functioning (22 items): section 1.1 a-v.
2. Emotional functioning (17 items): section 2.1 a-k and section 2.2 a-f.
3. Social functioning (7 items): section 3.1 a-g.
4. Physical functioning (9 items): section 4.1 a-i.

Scoring Instructions:

1. Recode all items such that higher scores indicate higher well-being.
2. Convert the pre-coded numeric values of items to a 0-100 point scale, with higher converted scores always reflecting better quality of life. Responses should now be coded as 0, 25, 50, 75, 100.
3. Calculate the mean value of the items in each subscale. Adjust the denominator to include only items answered.
4. To calculate the total score, take the unweighted mean of the four subscales.

Quality of Life in Childhood Epilepsy Questionnaire: QOLCE-55
Version 1.0 (English)

Goodwin SW, Lambrinos AI, Ferro MA, Sabaz M, Speechley KN. Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). Epilepsia 2015;56(6):864-72.

INSTRUCTIONS

The following questions ask about your child's health and well-being. Answer the questions by ticking the appropriate box. Certain questions may look alike but each one is different. Some questions may ask about problems your child does not have. Please try to answer each question as it is important for us to know when your child does not have these problems. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can.

SECTION 1: YOUR CHILD'S COGNITIVE FUNCTIONING

The following questions ask about some problems children have with concentrating, remembering, and speaking.

1.1 Compared to other children of his/her own age, how often during the past 4 weeks has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not Applicable
a. had difficulty attending to an activity?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said and done?	☐	☐	☐	☐	☐	☐
i. found it hard remembering things?	☐	☐	☐	☐	☐	☐
j. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
k. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
l. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
n. planned to do something then forgot?	☐	☐	☐	☐	☐	☐

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not Applicable
o. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
p. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐
q. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
r. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
s. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
t. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
u. had trouble writing?	☐	☐	☐	☐	☐	☐
v. had trouble talking?	☐	☐	☐	☐	☐	☐

SECTION 2: YOUR CHILD'S EMOTIONAL FUNCTIONING

Below is a list that describes how your child might feel in general.

2.1 During the past 4 weeks, how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not Applicable
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt happy?	☐	☐	☐	☐	☐	☐
c. wished s/he was dead?	☐	☐	☐	☐	☐	☐
d. felt frustrated?	☐	☐	☐	☐	☐	☐
e. worried a lot?	☐	☐	☐	☐	☐	☐
f. felt confident?	☐	☐	☐	☐	☐	☐
g. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
h. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
i. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
j. felt valued?	☐	☐	☐	☐	☐	☐
k. felt no one cared?	☐	☐	☐	☐	☐	☐

Below are statements that describe some children's behaviour.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.

2.2 Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not Applicable
a. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
b. angered easily	☐	☐	☐	☐	☐	☐
c. hit or attacked people	☐	☐	☐	☐	☐	☐
d. swore in public	☐	☐	☐	☐	☐	☐
e. was obedient	☐	☐	☐	☐	☐	☐
f. demanded a lot of attention	☐	☐	☐	☐	☐	☐

SECTION 3: YOUR CHILD'S SOCIAL FUNCTIONING

Below are statements that describe some children's social interactions and activities.
Please try to answer all questions as well as you can, even if some do not seem to apply to your child.

3.1 During the past 4 weeks, how often has your child's epilepsy:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not Applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours)?	☐	☐	☐	☐	☐	☐
b. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
c. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
d. isolated him/her from others?	☐	☐	☐	☐	☐	☐
e. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐
f. frightened other people?	☐	☐	☐	☐	☐	☐
g. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?	☐ Yes, limited a lot	☐ Yes, limited some	☐ Yes, limited a little	☐ Yes, but rarely	☐ No, not limited	

SECTION 4: YOUR CHILD'S PHYSICAL FUNCTIONING

The following questions ask about physical activities your child might do.

4.1. In his/her daily activities during the past 4 weeks, how often has your child:

	Very Often	Fairly Often	Some-times	Almost Never	Never	Not Applicable
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
c. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. gone swimming (i.e., swam independently)?	☐	☐	☐	☐	☐	☐
e. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
f. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
g. played with friends away from you or your home?	☐	☐	☐	☐	☐	☐
h. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
i. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

Appendix 3.8 Hospital Anxiety and Depression Scale

The following questionnaire focuses on your thoughts and feelings as a person- **this is a questionnaire about you as a parent/carer not your child.**

Tick the box beside the reply that is closest to how you have been feeling in the past week. Do not take too long with your replies as your immediate reaction to each item will probably be more accurate than a long thought out response

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Appendix 3.9 Pittsburgh Sleep Quality Index

Name:_____ Date: _____

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Appendix 3.10 NHS Ethical Approvals

North West - Preston Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ
Telephone: 0207 104 8196

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

05 July 2019

Dr Andrew Bagshaw
School of Psychology
University of Birmingham
B15 2TT

Dear Dr Bagshaw

Study title:	**The mechanisms and impact of sleep disruption in children with Rolandic Epilepsy**
REC reference:	**19/NW/0337**
Protocol number:	**ERN_18-0695**
IRAS project ID:	**247899**

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Andrew Bagshaw
School of Psychology
University of Birmingham
B15 2TT

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

05 July 2019

Dear Dr Bagshaw

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The mechanisms and impact of sleep disruption in children with Rolandic Epilepsy**
IRAS project ID:	**247899**
Protocol number:	**ERN_18-0695**
REC reference:	**19/NW/0337**
Sponsor	**University of Birmingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

Appendix 3.11 Regression Diagnostic Tests

Table 1. *Autocorrelation and collinearity statistics across regression models within Chapter 4*

Model	Durbin Watson	VIF	Tolerance value
1	2.12	1.06-1.12	0.89-0.94
2	1.74	1.08-1.36	0.73-0.93
3	1.90	1.01-1.06	0.95-0.99
4	1.99	1.04-1.57	0.64-0.96

Model 1: Age, CSHQ, SCQ
Model 2: Age, CSHQ, CONNERS
Model 3: Age, CSHQ, HSSS
Model 4: Age, CSHQ, Polytherapy, Monotherapy

Table 2. *Autocorrelation and collinearity statistics across regression models within Chapter 5*

Model	Durbin Watson	VIF	Tolerance value
1	2.36	1.11-2.55	0.39-0.90
2	2.02	1.19-2.63	0.38-0.83
3	2.34	1.18-2.61	0.28-0.94

Model 1: Age, SOL(M), SOL(IIV), WASO(M), SCQ
Model 2: Age, CSHQ, SOL(M), SOL(IIV), WASO(M), CONNERS
Model 3: Age, CSHQ, SOL(M), SOL(IIV), WASO(M), HSSS

Table 3. *Autocorrelation and collinearity statistics across regression models within Chapter 6*

Model	Durbin Watson	VIF	Tolerance value
1	1.85	1.03-1.62	0.62-0.98
2	1.84	1.01-1.31	0.76-0.99
3	1.96	1.06-1.43	0.67-0.94

Model 1: Age, PSQI, Composite 1
Model 2: Age, HADS-A, Composite 1
Model 3: Age, HADS-D, Composite 1

Appendix 4.1 Control Analyses for Chapter 4

Table 1. *Comparison of sleep parameters assessed by the CSHQ score before and during the COVID-19 pandemic. Values are presented as means (SD)*

	Prior to COVID-19 (N=18)	**During COVID-19 (N=14)**	W	*P* value
CSHQ[a]	49.33(10.87)	46.29(5.17)	147	0.44

Note. N=32, *p<.05
[a]Missing data, N=1

Appendix 5.1 Control Analyses for Chapter 5

Table 1. *The comparison of mean actigraphy variables between weekend vs weekday*

	Weekday		Weekend		Between group comparisons		
Actigraphy parameters	**Mean**	**SD**	**Mean**	***SD***	***p***	**df**	***t/Z***
Total sleep time (h:mm)[a]	506.66	46.11	506.49	56.87	0.98	35	0.03
Sleep onset latency (mins)[b]	21.90	21.15	17.83	17.90	0.11		412.00
Sleep efficiency (%)[b]	83.82	5.02	85.01	4.48	0.07		203.00
Wake after sleep onset (mins)[b]	60.09	30.24	56.12	21.28	0.22		391.00

p values were derived from paired sample t-tests[a] or Wilcoxon signed-ranked test[b]

Table 2. *The comparison of IIV in actigraphy variables between weekend vs weekday*

	Weekday		Weekend		Between group comparisons		
Actigraphy parameters	**Mean**	**SD**	**Mean**	***SD***	***p***	**df**	***t/Z***
Total sleep time (h:mm)[b]	0.09	0.07	0.08	0.05	0.47		360.00
Sleep onset latency (mins)[a]	1.15	0.54	0.90	0.59	0.05	35	2.02
Sleep efficiency (%)[a]	0.07	0.07	0.06	0.04	0.24	35	1.19
Wake after sleep onset (mins)[b]	0.29	0.10	0.25	0.15	0.21		392.00

p values were derived from paired sample t-tests[a] or Wilcoxon signed-ranked test[b]

Table 3. *The comparison of actigraphy variables between school and non-school times*

	School (*n=23*)		**Non-school (*n=13*)**		**Between group comparisons**		
Actigraphy parameters	**Mean**	**SD**	**Mean**	***SD***	***p***	**df**	***t/Z***
Total sleep time (mins)[a]	508.79	45.02	501.72	47.29	0.66	34	0.44
Sleep onset latency (mins)[b]	17.84	17.63	25.85	10.01	0.15		105.00
Sleep efficiency (%)[a]	83.93	5.04	83.61	4.12	0.85	34	0.20
Wake after sleep onset (mins)[b]	62.56	33.85	56.02	18.84	0.67		163.00

p values were derived from independent sample t-tests[a] or Mann Whitney test[b]

Table 4. *The comparison of IIV of actigraphy variables between school and non-school time*

	School (n=23)		**Non-school (n=13)**		**Between group comparisons**		
Actigraphy parameters	**Mean**	**SD**	**Mean**	***SD***	***P***	**df**	***t/Z***
Total sleep time (h:mm)[b]	0.11	0.07	0.10	0.07	0.41		175.00
Sleep onset latency (mins)[a]	1.25	0.44	1.11	0.56	0.42	34	0.81
Sleep efficiency (%)[b]	0.08	0.07	0.08	0.07	0.64		164.00
Wake after sleep onset (mins)[b]	0.33	0.17	0.28	0.10	0.30		181.50

p values were derived from independent sample t-tests[a] or Mann Whitney tests[b]

Table 5. *Comparison of mean sleep parameters assessed by the actigraphy before and during the COVID-19 pandemic. Values are presented as means (SD)*

Actigraphy parameters	**Prior to COVID-19 (N=22)**	**During COVID-19 (N=14)**	t/W	*P* value	Effect size
Total sleep time (mins)[a]	512.12(43.25)	496.97(48.52)	0.98	0.34	0.33
Sleep onset latency (mins)[b]	17.04(16.00)	26.52(20.68)	112	0.18	0.27
Sleep efficiency (%)[b]	84.25(4.58)	83.13(4.90)	182	0.38	0.18
Wake after sleep onset (mins)[b]	62.60(34.07)	56.42(19.83)	164	0.76	0.07

p values were derived from independent sample t-tests[a] or Mann Whitney tests[b]

Table 6. *Comparison of IIV of sleep parameters assessed by the actigraphy before and during the COVID-19 pandemic. Values are presented as means (SD)*

Actigraphy parameters	**Prior to COVID-19 (N=22)**	**During COVID-19 (N=14)**	t/W	*P* value	Effect size
Total sleep time (mins)[a]	512.12(43.25)	496.97(48.52)	211	0.07	0.37
Sleep onset latency (mins)[b]	1.26(0.46)	1.09(0.51)	1.05	0.30	0.36
Sleep efficiency (%)[b]	0.08(0.07)	0.08(0.07)	167	0.68	0.08
Wake after sleep onset (mins)[b]	0.34(0.18)	0.27(0.09)	189	0.26	0.23

p values were derived from independent sample t-tests[a] or Mann Whitney tests[b]

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