



# The contribution of sleep and co-occurring neurodevelopmental conditions to quality of life in children with epilepsy

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## ABSTRACT

**Background:** Health-related quality of life (HRQOL) in children with epilepsy (CWE) is multifactorial and can be affected not only by epilepsy-specific variables but also co-occurring conditions such as sleep disturbances, autism, and attention deficit hyperactivity disorder (ADHD). While highly prevalent in CWE, these conditions are underdiagnosed despite having a significant impact on HRQOL. Sleep problems have a complex relationship with epilepsy and neurodevelopmental characteristics. However, little is known about how these issues interact and contribute to HRQOL.

**Objectives:** The current study aims to explore the relationship between sleep and neurodevelopmental characteristics on HRQOL in CWE.

**Methods:** 36 CWE aged 4–16 years old were recruited from two hospitals and asked to wear an actiwatch for a period of 14 days and caregivers completed a series of questionnaires assessing co-occurrences and epilepsy-specific variables.

**Results:** A high proportion of CWE (78.13%) presented significant sleep problems. Informant-reported sleep problems were significantly predictive of HRQOL above seizure severity and the number of antiseizure medications. Interestingly, informant-reported sleep problems were no longer significantly predictive of HRQOL when neurodevelopmental characteristics were considered, indicating a possible mediating effect. Similarly, actigraphy-defined sleep (variability in sleep onset latency) displayed a similar effect but only for ADHD characteristics, whereas autistic characteristics and variability in sleep onset latency continued to exert an individual effect on HRQOL.

**Conclusion:** These data from our study shed light on the complicated relationship between sleep, neurodevelopmental characteristics and epilepsy. Findings suggest that the impact of sleep on HRQOL in CWE is possibly mediated by neurodevelopmental characteristics. Furthermore, the impact this triangular relationship exerts on HRQOL is dependent on the type of tool used to measure sleep. These findings highlight the importance of a multidisciplinary approach to epilepsy management.

**Abbreviations:** ADHD, Attention deficit hyperactivity disorder; ANOVA, Analysis of variance; ASD, Autism spectrum disorder; ASM, Antiseizure medication; CSHQ, Children's sleep habits questionnaire; CWE, Children with epilepsy; CWOE, Children without epilepsy; HASS, Hague seizure severity scale; HRQOL, Health related quality of life; ID, Intellectual disability; IIV, Intra individual variability; NDCTS, neurodevelopmental characteristics; QOLCE, Quality of life in childhood epilepsy; SCQ, Social communication questionnaire; SE, Sleep efficiency; SELECTS, Self-Limited Epilepsy with Centrottemporal Spikes; SOL, Sleep onset latency; TD, Typically developing; TST, Total sleep time; WASO, Wake after sleep onset.

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## 1. Introduction

Children with epilepsy (CWE) experience lower health related quality of life (HRQOL) compared to their typically developing (TD) peers (Cianchetti et al., 2015; Conde-Guzón et al., 2020; Nadkarni et al., 2011). Several epilepsy-specific variables such as epilepsy severity, longer disease duration and poor treatment adherence negatively impact HRQOL (Aggarwal et al., 2011; Kaenkrai et al., 2021; Liu and Han, 2015; Nagabushana et al., 2019). However, co-occurrences also impact HRQOL and have been found to exert a stronger influence (Miller et al., 2003). Moreover, this impact can last even after seizures have remitted (Baca et al., 2011). Together, this cumulative evidence indicates that whilst managing seizures is necessary, it is likely not sufficient to achieve optimal HRQOL in CWE (Wood, 2012).

Sleep disturbances are common co-occurrences in CWE and are up to 12 times more likely to occur in CWE compared to children without epilepsy (CWOE), (Gutter et al., 2013; Winsor et al., 2021). Most research rely on informant reports to measure sleep, which have clinical utility but are prone to biases in reporting. To overcome such issues, objective measures of sleep such as actigraphy are recommended in combination with subjective tools (Perpétuo et al., 2020). Actigraphy characterise sleep based on movement, through a small, non-invasive devices normally worn on the wrist. Informant reports are convergent with actigraphy results for sleep scheduling variables, such as the timing and duration of sleep, but not others, such as quality of sleep (Holley et al., 2010; Perpétuo et al., 2020; Werner et al., 2008). Whilst informant reports can capture observable behavioural sleep features (Esbensen et al., 2018), actigraphy provides Supporting information in their interpretation and mitigates reporting bias (Perpétuo et al., 2020; Wiggs et al., 2005). Therefore, use of both measures is recommended, to shed light on specific areas of sleep disturbances.

To date, there is limited research using actigraphy in CWE. One study (Holley et al., 2014) found that CWE displayed more severe sleep problems across several Children's Sleep Habits Questionnaire (CHSQ) subscales, compared to CWOE. By contrast, this was not corroborated in the actigraphy data, with no significant differences identified between CWE and CWOE in total sleep time, sleep efficiency or sleep period time. Similarly, a more recent study has shown that higher CHSQ scores were related to poorer behavioural outcomes in CWE but not actigraphy-defined sleep parameters (Tsai et al., 2019). This discrepancy may relate to the aspect of sleep being measured (Holley et al., 2014) and the varying sensitivity of questionnaires versus actigraphy. A recent meta-analysis no significant differences in sleep parameters such as TST, between CWE and CWOE, irrespective of the measurement methods used (Winsor et al., 2021).

The aforementioned studies have focused only on sleep parameters averaged over several nights. However, this approach fails to capture the complexity and variability of sleep patterns. Intra-individual variability of sleep represents the level of variability from night to night (Becker et al., 2017). A prior review emphasised the need for the inclusion of intra-individual variability of sleep as a second construct, in combination with mean sleep parameters (Bei et al., 2016). A previous study (Tsai et al., 2018) investigated intra-individual variability in sleep duration in CWE and found a negative association with maternal knowledge of their child's sleep. However, this study lacked a control group to assess whether sleep parameters significantly differed from CWOE, or whether these were predictive of child outcomes such as HRQOL. Therefore, the current study affords the opportunity to build the limited evidence base on actigraphy defined sleep parameters in CWE.

Autism and attention deficit hyperactivity disorder (ADHD) are the two most commonly occurring neurodevelopmental conditions and traits (NDCTS) reported (Lo-Castro and Curatolo, 2014). Interestingly sleep disturbances are also commonly observed in NDCTS (Singh and Zimmerman, 2015), suggesting a potential triangular relationship between epilepsy, NDCTS and sleep disturbance. CWE and co-occurring

ADHD experience significantly more severe sleep problems compared to children with ADHD or epilepsy alone (Ekinci et al., 2017). In addition, autistic children with autism and ADHD show higher rates of sleep problems compared to TD children and CWE, while perhaps surprisingly, CWE did not experience a higher prevalence of sleep problems compared to TD children (Tsai et al., 2012). This finding has been attributed due to the recruitment of CWE without co-occurring NDCTS, indicating that NDCTS can increase the risk of sleep problems in CWE. In summary, NDCTS need to be isolated to assess their contribution to sleep problems and HRQOL in CWE.

There are few studies which have investigated the association between sleep and HRQOL in CWE. Although these studies found that sleep problems were more frequent and severe in CWE compared to CWOE (Gutter et al., 2013; Wirrell et al., 2005) and that these were associated with poorer HRQOL independently of epilepsy (Ekinci et al., 2016; Zhao et al., 2022), there were several methodological constraints which reduced their generalisability. In the study by (Zhao et al., 2022) most of the sample were on monotherapy and experienced few seizures. Similarly, Gutter et al., 2013 focused on children with focal epilepsy only. Furthermore, in the study sample by (Wirrell et al., 2005) siblings without epilepsy were used as the comparison group. However, the sleep of the wider family is also likely to have been affected (Larson et al., 2012).

Given the heterogeneity of epilepsy, it is important to consider the differences in co-occurrences and HRQOL across epilepsy types. Previous research points to poorer HRQOL in children with focal epilepsy compared to generalised epilepsy (Aggarwal et al., 2011; Ferro, 2014; Fong et al., 2018; Nadkarni et al., 2011), although this is not always found (Pachange et al., 2021). Most studies combine epilepsy types into one group, which leads to difficulties in investigating syndrome-specific profiles of HRQOL (Mellish et al., 2015). In the current study, Self-Limited Epilepsy with Centrotemporal Spikes (SELECTS) has been included as a specific epilepsy type of interest, in addition to the broader groups of focal and generalised epilepsy. SELECTS is presumed to be genetically determined with seizure onset between 1 and 14 years of age with peak frequency between aged 6–7 years of age (Camfield and Camfield, 2002; Lee et al., 2017; Xiong and Zhou, 2017). Few studies have assessed HRQOL in SELECTS, 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). Furthermore, SELECTS is recognised as the most commonly occurring epilepsy type with a prevalence rate of around 15% in CWE (Amrutkar and Riel-Romero, 2023; Camfield and Camfield, 2002), meaning that these reductions in HRQOL are experienced by a large group of CWE. Although SELECTS has a low seizure burden, the impact on sleep may be greater than in other epilepsy types, given that activation of IEDs can result in epileptic encephalopathy with spike-wave activation in sleep (Pereira-Nunes et al., 2023). Nevertheless inclusion of SELECTS also allows the impact of epilepsy more broadly to be dissociated from the impact of seizures more specifically on both sleep and HRQOL.

The aim of the current study was:

- (1) To assess differences in sleep, NDCT and HRQOL scores across epilepsy types.
- (2) To explore differences in actigraphy-defined sleep parameters will be explored between CWE and CWOE, in addition to self-report measures.
- (3) To explore the contribution of NDCT and epilepsy-specific variables to the relationship between sleep and HRQOL in CWE.

## 2. Materials and methods

### 2.1. Participants

#### 2.1.1. Children with epilepsy

This study was cross-sectional. Participants were recruited from the

Departments of Neurophysiology of The Birmingham Children's Hospital and Worcestershire Royal Hospital from September 2019 to May 2021. The inclusion criteria for the CWE were: (1) Age between 4 and 16 years; (2) Confirmed diagnosis of epilepsy; (3) Absence of co-occurring intellectual disability (ID); (4) Parents with a sufficient level of spoken English to ensure that the study instructions and questionnaires could be understood; (5) A minimum of seven days and nights of usable actigraphy data. Further clinical information was retrieved from participants' medical records. The study was approved by the North West - Preston Research Ethics Committee (REC reference 19/NW/0337).

### 2.1.2. Children without epilepsy

Socio-demographic and actigraphy data for CWOE were collected from an existing participant database for families of children who had taken part in a previous study by the Cerebra Network for Neurodevelopmental Disorders (Trickett et al., 2019, 2020). Within this study, children aged 4–15 years old with no medical or neurodevelopmental 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 14 day period.

## 2.2. Measures

### 2.2.1. Child sleep

**2.2.1.1. Children's Sleep Habits Questionnaire (CHSQ).** The CHSQ (Owens et al., 2000) is a retrospective informant report questionnaire designed to assess sleep habits in school-age children. It consists of 45 items, 33 of which are scored, and 7 provide additional information on sleep. Parents were required to detail sleep patterns which occurred over the past week across a 3-point scale ranging from 1 (rarely) to 3 (usually). Item ratings were categorised into eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing and Daytime Sleepiness. The CHSQ 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 (Owens et al., 2000).

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

**2.2.1.3. Actigraphy.** Habitual sleep patterns were measured using an actigraphy device (Actiwatch2, Phillips Respironics Inc) for a period of 14 consecutive nights. Actiwatches are non-invasive wearable devices, that measure body movements to provide information on sleep-wake patterns. Actiwatches use an accelerometer to detect movements and translate these into activity counts. These activity data are summed within epochs that can then be used to represent sleep and wake periods. A 30-second period was selected for the epoch length 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 epoch as sleep, and anything above this value was coded as wake. 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.

Data were cleaned in the Actiware software using an established protocol (Agar et al., 2023; Trickett et al., 2017) to remove 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 intervals 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 a 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 when the watch was taken off, periods of inactivity, and naps were also removed. The mean and intraindividual variability (IIV) of the following parameters were studied:

- Total sleep time (TST): Proportion of time spent asleep within a 24-hour period as recorded by the actiwatch.
- Sleep onset latency (SOL): The amount of time taken to fall asleep from bedtime.
- Sleep efficiency (SE): Proportion of time actually spent asleep whilst in bed.
- 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 they are commonly assessed in research utilising actigraphy as reliable measures. Furthermore, given the limited actigraphy data available for 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.

### 2.2.2. Neurodevelopmental characteristics

**2.2.2.1. Social communication questionnaire (SCQ).** SCQ (Rutter et al., 2003) is a questionnaire developed using the revised Autism Diagnostic Interview (Lord et al., 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 used clinically 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).

**2.2.2.2. 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. The questionnaire consists of 10 items derived from the DSM-5 criteria (American Psychiatric Association, 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 were calculated for the ADHD sum index, where higher index scores indicate higher severity of ADHD characteristics. A T score of 65 is indicative of scores similar to children with diagnosed ADHD (Conners, 2008).

### 2.2.3. Health related quality of life

**2.2.3.1. Quality of life in childhood epilepsy scale (QOLCE-55).** QOLCE-55 (Goodwin et al., 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). 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.

## 2.2.4. Seizure severity

**2.2.4.1. 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. 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).

## 3. Statistical analysis

All data were initially assessed for normality using the Shapiro-Wilk test, and where data were not normally distributed ( $p < 0.05$ ) a non-parametric test was used. Descriptive statistics were reported for demographic variables across CWE and CWOE. Continuous data were presented as mean (SD) and categorical data in the form of frequencies (%). All statistical analyses were carried out using R (R Core Team, 2022).

### 3.1. Group comparisons

Parametric one way analysis of variance or non-parametric Kruskal-Wallis tests were used to assess differences in CSHQ, SCQ, CONNERS and QOLCE scores across the epilepsy types. As the above questionnaire data was not available for CWOE, the same statistical tests were used to compare differences in demographic characteristics between CWE and CWOE only.

The mean of actigraphy sleep parameters was calculated by averaging data for each parameter across the total number of nights. IIV of sleep parameters were also calculated (SD/Mean). Parametric independent sample t-tests or non-parametric Mann-Whitney test were conducted to assess differences in sleep parameters between CWE and CWOE. 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, which were revealed to be non-significant (see details in [Supplementary materials](#)).

### 3.2. Regression analyses

Separate hierarchical linear regression analyses were conducted to assess the contribution of various factors to the relationship between sleep and HRQOL, controlling for age and conducted with both informant report and actigraphy assessments of sleep. Regression analyses were created with the additional factors included as possible predictors: (1) autistic characteristics; (2) ADHD characteristics; (3) seizure severity and (4) number of ASMs. As the number of ASMs are defined as a categorical variable, this was dummy coded, where no medication was assigned as a reference category. Prior to regression models utilising actigraphy sleep parameters, a correlational analysis was calculated to explore the association between actigraphy sleep parameters and HRQOL. Sleep parameters which were significantly correlated with the total QOLCE score ( $p < 0.05$ ) were then carried into the hierarchical linear regression models. However, due to the small sample size, the number of ASMs was not entered in the actigraphy sleep-based regression models.

To correct for multiple comparisons, an adjusted p-value was computed using Bonferroni correction by dividing the p-value of 0.05 by the number of comparisons within a family of tests.

## 4. Results

### 4.1. Demographic data

From an initial sample of 70 recruited 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).

The final sample of CWE consisted of 36 CWE ( $M=9.47$  y,  $SD=2.62$  y, range= 4–14 y). 17 of whom had a focal epilepsy type (5 x temporal lobe epilepsy, 3 occipital lobe epilepsy, 1 x focal cortical dysplasia, 1 x parietal occipital lobe, 1 x frontal lobe epilepsy, 1 x genetic focal epilepsy, 2 x structural with right hemispheric origin, 3 x no further detail); 10 generalised (1 x Jeavons syndrome, 9 x no further detail) and 9 SELECTS. 85% of CWE wore the actiwatch for a period of 14 days. 14 CWOE ( $M=8.29$  y,  $SD=3.12$  y, range= 4–15 y) wore the actiwatch for an average of 10 days (range = 7–12 days). Sample characteristics are presented in [Tables 1 and 2](#).

An epilepsy diagnosis was determined by a neurophysiologist and confirmed by a neurologist according to International League Against Epilepsy (ILAE) 2017 classification. Epilepsy type was based on electroencephalogram (EEG) presentation, more specifically which hemisphere the epileptiform activity was present.

### 4.2. Informant reported sleep and actigraphy data

It was found that 78.13% of CWE scored above the clinical cut-off for a significant sleep disturbance according to the CSHQ cut off score ( $>41$ ). Comparison of mean and IIV of actigraphy sleep parameters between CWE and CWOE revealed no significant differences. Initially a significant difference between IIV of actigraphy sleep parameters was detected but this was not retained following Bonferroni correction. Data are summarised in [Tables 3 and 4](#).

### 4.3. Within group differences in informant reported sleep, NDCT and HRQOL

To address the first aim, total CSHQ, SCQ, CONNERS and QOLCE scores were compared across epilepsy types. Kruskal-Wallis tests found no significant differences for autistic characteristics ( $\chi^2(2) = 5.45$ ,  $p = 0.07$ ), ADHD characteristics ( $\chi^2(2) = 3.27$ ,  $p = 0.20$ ) and CSHQ scores ( $\chi^2(2) = 0.88$ ,  $p = 0.64$ ). An ANOVA revealed no significant differences in HRQOL ( $F(2,29) = 2.86$ ,  $p = 0.07$ ) across epilepsy types.

### 4.4. Between group differences in actigraphy defined sleep parameters

To investigate the second aim, there were no significant differences between epilepsy types in mean TST ( $F(2,33) = 2.04$ ,  $p = 0.15$ ), SE ( $\chi^2(2) = 1.80$ ,  $p = 0.41$ ), SOL ( $\chi^2(2) = 1.82$ ,  $p = 0.40$ ) or WASO ( $\chi^2(2) = 0.41$ ,  $p = 0.81$ ). Similarly, comparing the IIV of each sleep parameter across the three epilepsy groups revealed no differences. There was no significant difference between the three epilepsy types for IIV of TST ( $\chi^2(2) = 4.06$ ,  $p = 0.13$ ), SOL ( $F(2,33) = 0.47$ ,  $p = 0.63$ ), SE ( $\chi^2(2) = 1.34$ ,  $p = 0.51$ ), WASO ( $\chi^2(2) = 1.49$ ,  $p = 0.47$ ).

### 4.5. Relationship between informant reported sleep and HRQOL

To examine the second aim, hierarchical linear regressions were used to compare the contribution of co-occurring characteristics and epilepsy specific variables to predicting the impact of informant reported sleep problems on child HRQOL. The age of the 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 ([Fig. 1](#)), ADHD characteristics ([Fig. 2](#)), seizure severity ([Fig. 3](#)) or number of ASMs ([Fig. 4](#)) were entered across the four regression models. All data met the

**Table 1**  
Sample characteristics of CWE (N = 36). Values are shown as mean (SD).

	Focal <sup>a</sup> (N = 17)	Generalised <sup>b</sup> (N = 10)	SELECTS (N = 9)	CWOE (N=14)	F/ $\chi^2$	DF	p value*	Post Hoc Analyses
<b>Demographics</b>					0.07	2	0.94	
Age, Years (SD)	9.41(2.67)	9.40(3.57)	9.67(1.22)	8.29(3.12)				
Age Range, Years	5–14	4–14	8–12	4–15				
<b>Sex</b>					2.56	2	0.28	
Male	12	4	6					
Female	5	6	3					
<b>Number of ASMs</b>					10.83	2	<b>0.004</b>	F,G>RE
0	2	1	6					
1	8	7	3					
2	7	2	0					
<b>Type of ASM</b>								
Levetiracetam	4	5	1					
Carbamazepine	8	1	1					
Lamotrigine	2	3	1					
Topiramate	2							
Sodium valproate	3	2						
Clobazam	2							
Ethosuximide	1							

a: 5 x temporal lobe epilepsy, 3 occipital lobe epilepsy, 1 x focal cortical dysplasia, 1 x parietal occipital lobe, 1 x frontal lobe epilepsy, 1 x genetic focal epilepsy, 2 x structural with right hemispheric origin, 3 x no further detail

b: 1 x Jeavons syndrome, 9 x no further detail.

\*  $p < 0.05$ , Adjusted  $p = 0.02$  applied. Differences which remained significant following Bonferroni correction are denoted in bold.

**Table 2**  
Sample characteristics of CWE (N = 36) vs CWOE (N = 14). Values are shown as mean (SD).

	CWE (N = 36)	CWOE (N = 14)	F/ $\chi^2$	DF	p value*
<b>Demographics</b>		85	1	0.18	
Age (Year)	9.47(2.62)	8.29(3.12)			
<b>Sex</b>			2.57	1	0.11
Male	22	5			
Female	14	9			

**Table 3**  
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)	p value
<b>Total sleep time (mins)</b>	506.23(45.31)	504.86(47.67)	0.92
<b>Sleep onset latency (mins)</b>	20.73(18.29)	23.97(18.83)	0.42
<b>Sleep efficiency (%)</b>	83.81(4.67)	77.06(21.48)	0.20
<b>Wake after sleep onset (mins)</b>	60.20(29.19)	55.64(16.41)	0.89

\*  $p < 0.05$ , Adjusted  $p = 0.01$  applied. Differences which remained significant following Bonferroni correction are denoted in bold.

**Table 4**  
IIV of actigraphy defined sleep parameters between CWE and CWOE. Values are shown as mean.

Actigraphy	CWE (n = 36) Mean	CWOE (n = 14) Mean	p value
<b>Total sleep time (mins)</b>	0.10	0.09	0.04
<b>Sleep onset latency (mins)</b>	1.20	0.90	0.30
<b>Sleep efficiency (%)</b>	0.08	0.13	0.67
<b>Wake after sleep onset (mins)</b>	0.31	0.30	0.67

\*  $p < 0.05$ , Adjusted  $p = 0.01$  applied. Differences which remained significant following Bonferroni correction are denoted in bold.

assumptions of collinearity and independent errors.

As indicated in Figs. 1 and 2, sleep problems were a significant predictor of HRQOL [ $\beta = -0.41$ ,  $t(29) = -2.39$ ,  $p = .02$ ]. The addition of CSHQ score significantly improved the fit of both models, increasing the variance accounted for by 16.5% in the autistic characteristics [F

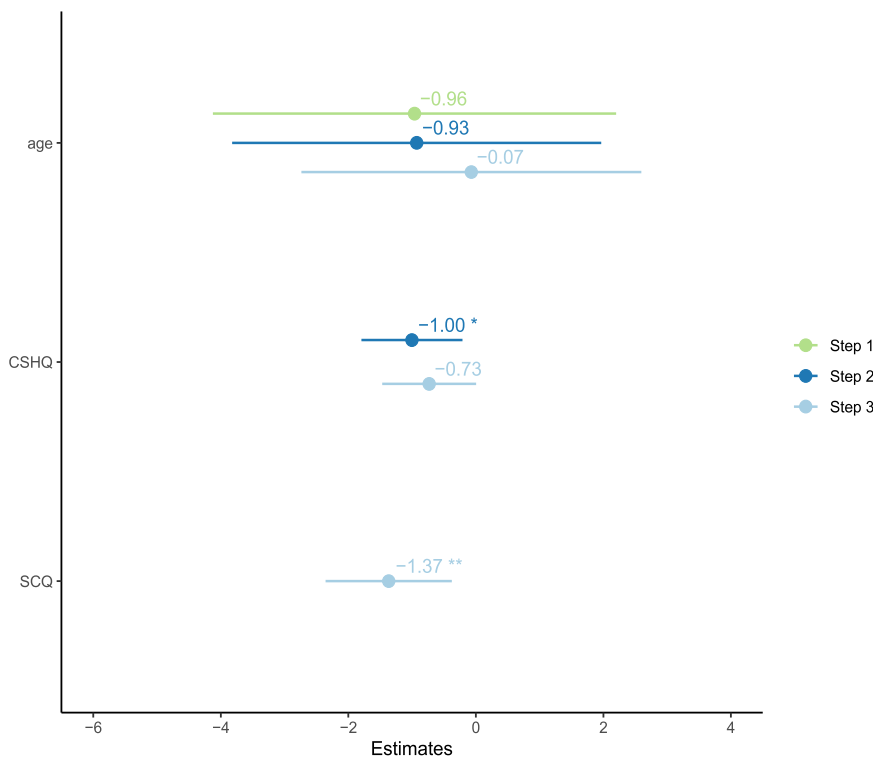
(1,28) = 5.70,  $p = 0.02$ ] and ADHD model [F(1,29) = 5.91,  $p = 0.02$ ]. Once autistic and ADHD characteristics were inputted in model 1 and 2 respectively, this led to a significant increase in explained variance by 18.3% [F(1,27) = 5.35,  $p = 0.01$ ] and 22.6% [F(1,28) = 6.64,  $p = 0.002$ ] respectively. In contrast the regression coefficient for the association between sleep problems and HRQOL was reduced to [ $\beta = -0.30$ ,  $t(28) = -1.93$ ,  $p = 0.07$ ] and [ $\beta = -0.16$ ,  $t(28) = 0.98$ ,  $p = 0.34$ ] in the two models. This observation suggests a potential mediating effect of neurodevelopmental characteristics on the relationship between sleep problems and HRQOL.

For the models relating to epilepsy-specific variables (seizure severity, number of ASMs, Figs. 3 and 4), when sleep problems were inputted, they were a significant predictor of HRQOL [ $\beta = -0.41$ ,  $t(29) = -2.29$ ,  $p = 0.02$ ] and contributed to an improvement in the variance of the overall model by 16.5% in both models. Once seizure severity and number of ASMs were added in models 1 and 2, this led to a non-significant change in the amount of variance by 0.1% and 5.4% respectively. Sleep problems remained significant predictors when seizure severity [ $\beta = -0.40$ ,  $t(28) = -2.29$ ,  $p = 0.03$ ] and number of ASMs [ $\beta = -.39$ ,  $t(28) = -2.17$ ,  $p = 0.04$ ] were included. Neither of these variables were significant predictive of HRQOL. This indicates that sleep problems exerted a significant unique contribution to HRQOL above and beyond epilepsy specific variables.

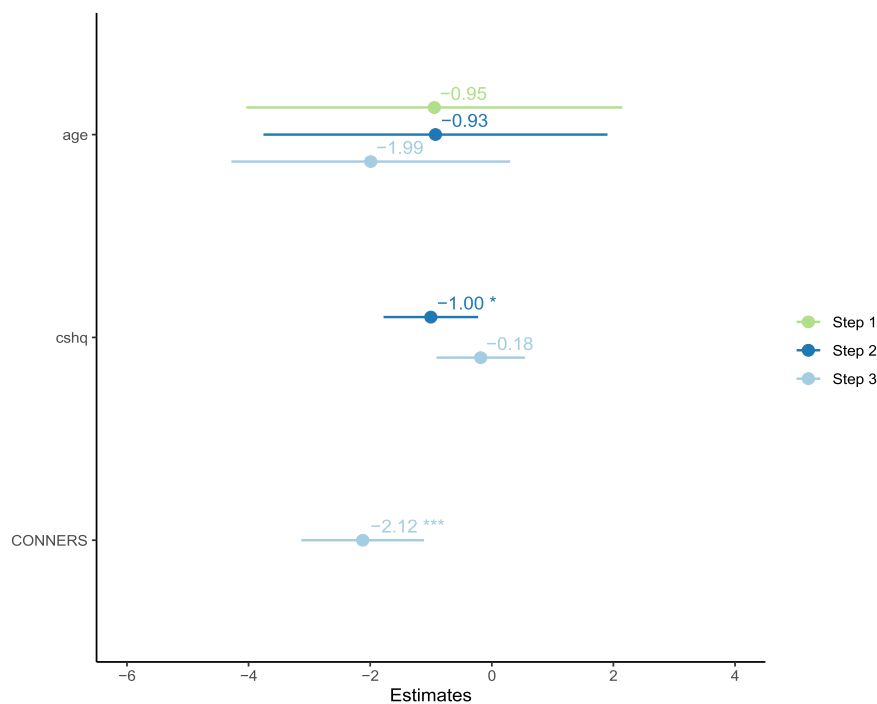
#### 4.6. Relationship between actigraphy defined sleep parameters and HRQOL

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). HRQOL was significantly associated with mean SOL [ $r(32) = 0.36$ ,  $p = 0.04$ ], IIV of SOL [ $r(32) = -0.44$ ,  $p = 0.01$ ] and mean WASO [ $r(32) = -.40$ ,  $p = .02$ ].

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 regression analyses. The actigraphy-defined sleep variables which were significantly associated with HRQOL (see Table 5) were taken forward for inclusion in the second step across all the regression analyses. In the third step, autistic characteristics (Fig. 5), ADHD characteristics (Fig. 6), or seizure severity



**Fig. 1.** Regression coefficient plot for hierarchical regression predicting HRQOL from informant reported sleep (CSHQ total score) and autistic characteristics (SCQ total score). The y axis represents the variables of interest inputted at each step. The x axis represents the strength of the unstandardised beta coefficient estimate. Coefficients from the first model are presented in green, second model in dark blue and the third model in light blue. The horizontal line represents the 95% confident intervals and the circles represent the point estimate of the unstandardised beta coefficient.



**Fig. 2.** Regression coefficient plot for hierarchical regression predicting HRQOL from informant reported sleep (CSHQ total score) and ADHD characteristics (CONNERS total score).

(Fig. 7) were entered across the three regression analyses respectively.

Across all analyses, when actigraphy-defined sleep variables were entered in step two, they were found to lead to a significant improvement in all analyses. More specifically, only IIV of SOL was significantly predictive of HRQOL. This led to a significant increase in explained variance across the analyses by 31.8%, 31.0% and 31.0% respectively. In Fig. 5, when autistic characteristics were entered, both autistic

characteristics [ $\beta = -0.49$ ,  $t(25) = -3.47$ ,  $p = .002$ ] and IIV of SOL retained significance [ $\beta = -0.51$ ,  $t(25) = -2.40$ ,  $p = .02$ ], thus the two variables were found to exert a unique contribution to HRQOL.

In Fig. 6, when ADHD characteristics were entered, this led to a significant improvement in the overall regression 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 [ $\beta = -0.36$ ,  $t$

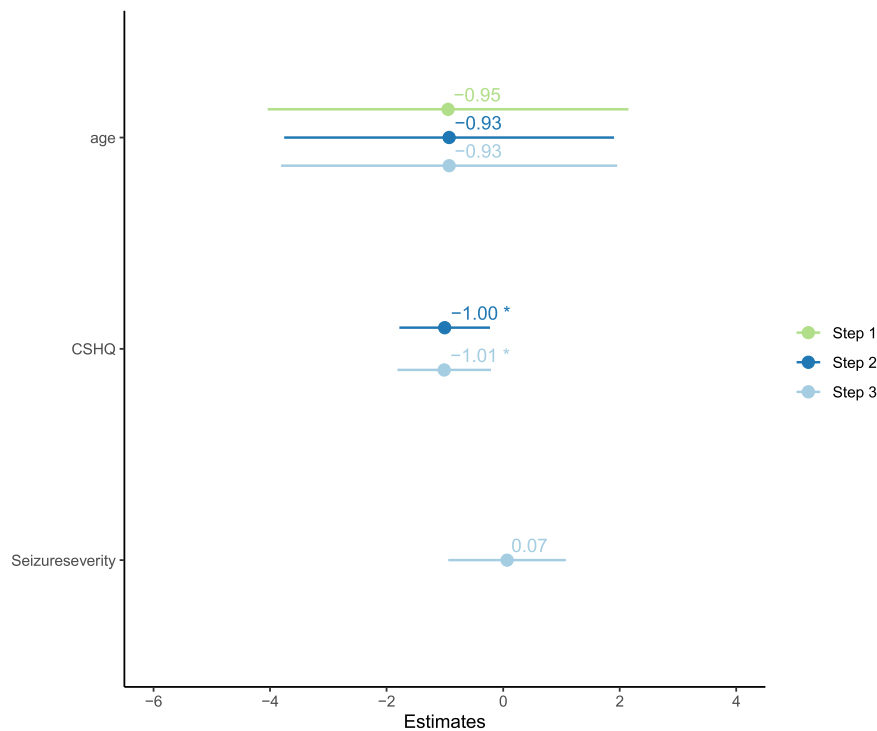


Fig. 3. Regression coefficient plot for hierarchical regression predicting HRQOL from informant reported sleep (CSHQ total score) and seizure severity (HASS score).

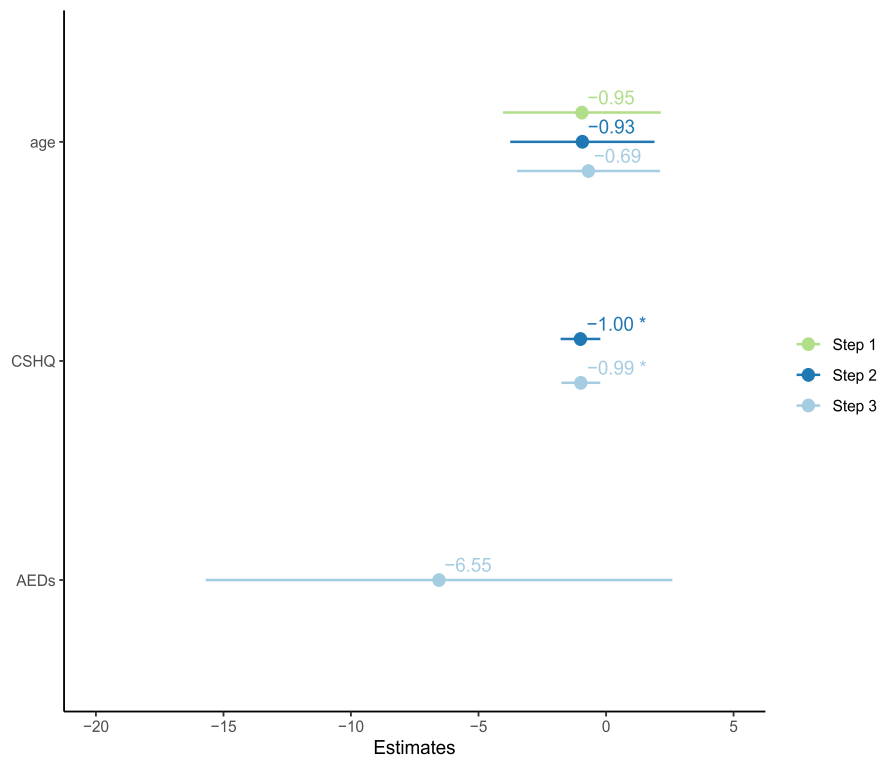


Fig. 4. Regression coefficient plot for hierarchical regression predicting HRQOL from informant reported sleep (CSHQ total score) and number of ASMs.

(26) = -1.72,  $p = 0.10$ ]. Moreover, the beta value of IIV of SOL on HRQOL reduced from  $\beta = -0.54$  to  $\beta = -0.36$ , following the inclusion of ADHD characteristics into the regression, suggesting that they possibly mediate the relationship between IIV of SOL and HRQOL.

Finally, in Fig. 7, the addition of seizure severity did not contribute significantly to the overall regression [ $F(1,26) = 0.33, p = 0.57$ ],

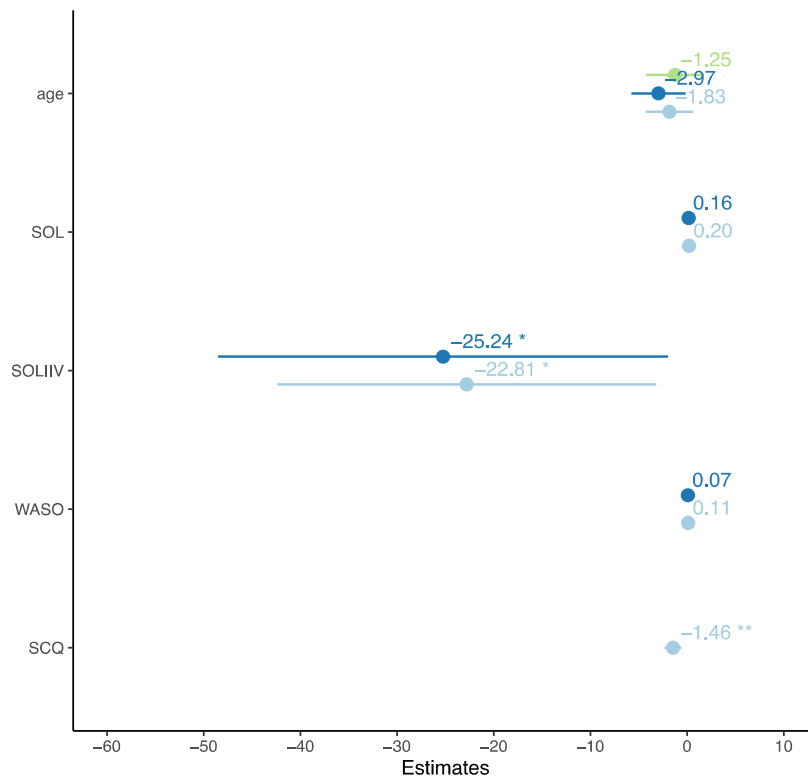
(0.01%). Although IIV of SOL was no longer significantly predictive of HRQOL following input of seizure severity, there was minimal change in the beta value from [ $\beta = -0.54, t(27) = -2.18, p = 0.04$ ] to [ $\beta = -0.51, t(26) = -1.97, p = 0.06$ ] indicating that seizure severity had little impact on the predictive power of IIV of SOL.

**Table 5**  
Correlations between total HRQOL score and actigraphy defined sleep parameters.

	TST (M) <sup>a</sup>	TST (IIV) <sup>a</sup>	SOL (M) <sup>b</sup>	SOL (IIV) <sup>a</sup>	SE (M) <sup>b</sup>	SE (IIV) <sup>a</sup>	WASO (M) <sup>b</sup>	WASO (IIV) <sup>b</sup>
QOLCE	0.04	-0.13	0.36*	-0.44*	0.09	-0.06	-0.40*	-0.15

p values were derived from Pearson correlation coefficients<sup>a</sup> or Spearman correlation coefficients<sup>b</sup>.

\* p < .05,



**Fig. 5.** Regression coefficient plot for hierarchical regression predicting HRQOL from actigraphy sleep measures (SOL, SOL(IIV), WASO) and autistic characteristics (SCQ total score).

## 5. Discussion

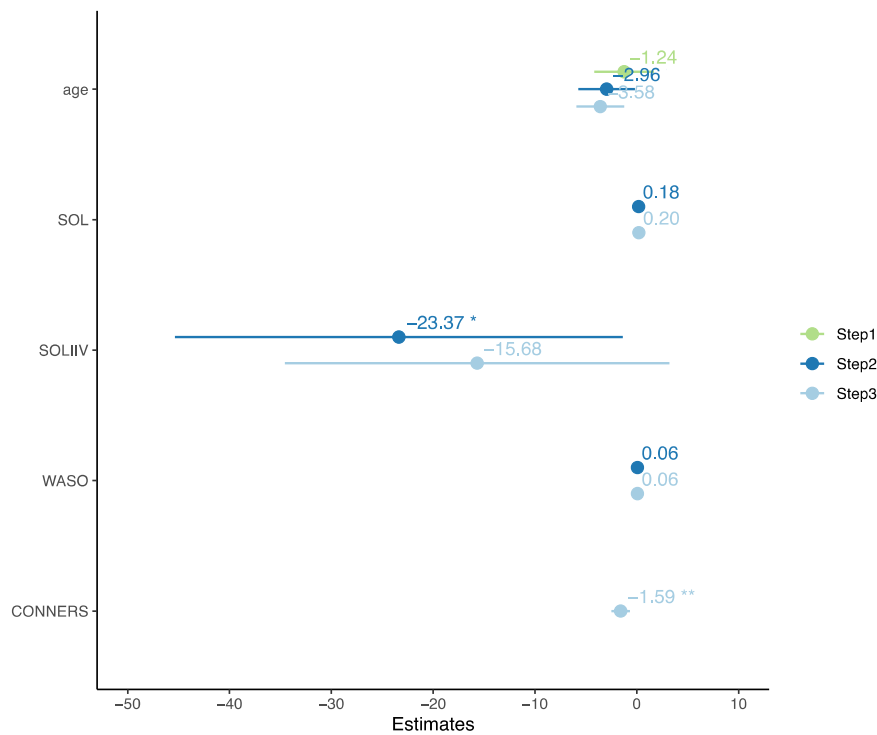
There has been an increased recognition of the importance of HRQOL as an outcome measure for CWE, both in research and clinical practice (Alnaamani et al., 2023; Rozensztrauch and Koltuniuk, 2022). However, most studies have focused exclusively on the role of seizures in predicting HRQOL without capturing the potential role of commonly co-occurring conditions like NDCT and sleep disturbances. Recognition of the role of these factors is important for comprehensive epilepsy management due to the persistence of their impact (Baca et al., 2011). The current study aimed to examine the differences in sleep, NDCT, and HRQOL across epilepsy types. Secondly, differences in actigraphy-defined sleep parameters were analysed between CWE and CWOE. Finally, the impact of epilepsy-specific variables and NDCTs on the relationship between sleep and HRQOL was explored, using an epilepsy-specific measure of HRQOL to provide an accurate measure of the impact on CWE. Similarly, the use of actigraphy as a sleep tool helps to overcome the caveats associated with informant-reports and provides richer information on specific sleep parameters. Finally, the inclusion of neurodevelopmental characteristics rather than relying on diagnoses allows for better representation of the findings due to the potential diagnostic overshadowing of such conditions within this group (Biswas and Casey, 2022).

### 5.1. Differences in sleep, NDCTs and HRQOL across epilepsy types

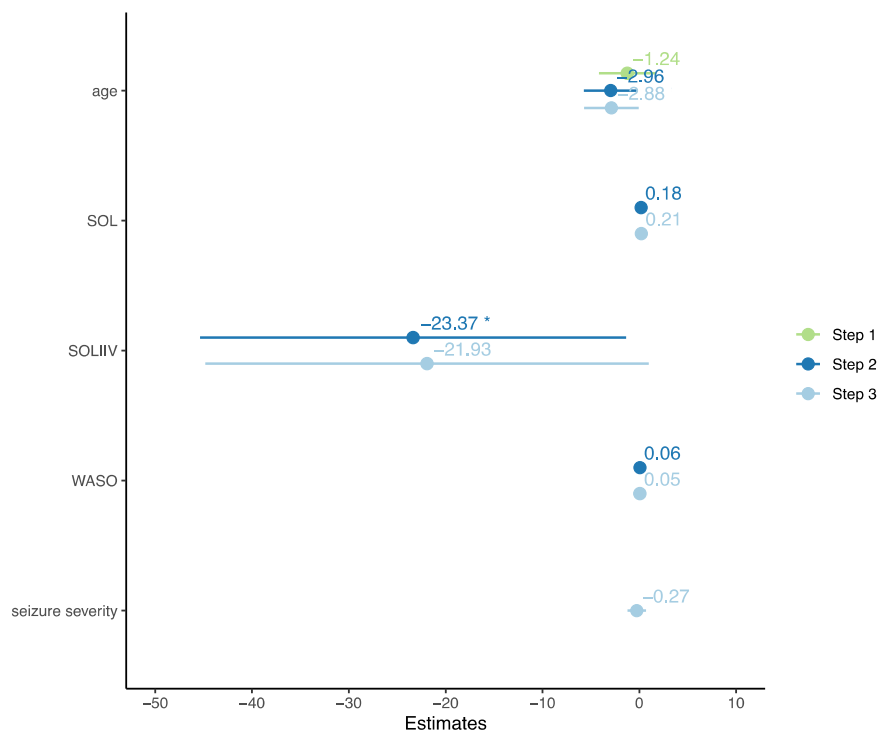
The comparative analysis of the impact of epilepsy type on sleep, NDCTs and HRQOL did not reveal significant differences. This is broadly consistent with prior literature. There is currently no clear consensus regarding how NDCTs are represented across epilepsy types (Berg et al., 2011; Lee et al., 2011; Spence and Schneider, 2009). There is some literature to indicate that HRQOL is poorer in children with focal epilepsy compared to others (Ferro et al., 2017; Nadkarni et al., 2011), although the majority of the literature suggests there are no differences (Aggarwal et al., 2011; Arya et al., 2014; Liu and Han, 2015; Pachange et al., 2021). The literature regarding differences in sleep problems across epilepsy types is also inconsistent (Batista and Nunes, 2007; Chan et al., 2011).

In our data, the categorisation of epilepsy type into focal, generalised and SELECTS miss nuances in these relationships associated with finer-grained categories. However, there is no current data to support this suggestion. In addition, the inclusion of SELECTS as a specific group does point towards commonalities in the relationship of epilepsy with sleep, NDCTs and HRQOL that do not depend on the specific details of epilepsy. SELECTS generally has a low seizure burden and had been classified as 'benign' based on the fact that it is often self-limiting and remits in adolescence (Amrutkar and Riel-Romero, 2023). This is no longer considered the case, and it is clear that children with SELECTS can have poorer outcomes than CWOE (Liu and Han, 2015; Smith et al., 2015). However, in the current context, SELECTS would be considered





**Fig. 6.** Regression coefficient plot for hierarchical regression predicting HRQOL from actigraphy sleep measures (SOL, SOL(IIV), WASO) and ADHD characteristics (CONNERS total score).



**Fig. 7.** Regression coefficient plot for hierarchical regression predicting HRQOL from actigraphy sleep measures (SOL, SOL(IIV), WASO) and seizure severity (HASS score).

as the less severe of the epilepsy types investigated, and any associations with sleep disturbances, NDCTs and HRQOL would be unlikely to be driven by seizures or ASMs but rather the underlying presence of epilepsy such as through activation of IEDs (e.g., see Table 1). Future work using EEG based methods in larger cohorts will be needed to confirm

this, but our finding is potentially clinically useful as it suggests that even in self-limited epilepsies, the severity of sleep problems, NDCTs and HRQOL is not significantly lower than in epilepsies with higher seizure count and ASM number.

## 5.2. Sleep problems in CWE

In our sample, 78.13% of the children displayed sleep problems that exceeded the clinical threshold on the CSHQ. This figure is consistent with a previous study by (Zhao et al., 2022) who found that 73.70% of CWE experienced sleep problems above this threshold also. 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 et al., 2015). Despite this, the actigraphy analysis did not find any significant differences between CWE and CWOE. This is in line with the findings of Holley et al. (2014) who also found no significant differences in actigraphy sleep measures between CWE and CWOE, and with the general point that objective and subjective measures of sleep often do not agree. Another possible explanation for these findings could relate to the issue that sleep quality measures calculated from actigraphy (WASO and SE) do not capture all aspects of sleep quality, some of which are known to be disturbed in CWE (Winsor et al., 2021). One exception was IIV in SOL, which was found to be higher in CWE compared to CWOE, although this was no longer significant following correction for multiple comparisons. Prior studies in adults have suggested that variability in sleep patterns is correlated with seizure likelihood (Cobabe et al., 2015; Dell et al., 2021; Haut et al., 2007). 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 et al., 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 due to insufficient data, and future actigraphy studies are required to elucidate these potentially important findings. As above, it is worth reiterating that children with SELECTS did not have significantly better sleep than those with other focal or generalised epilepsies, suggesting that seizures are not the primary determinant of poor or variable sleep in CWE. Overall, our results indicate that CWE experience sleep difficulties and suggest that future research should examine what variables affect the discrepancy between informant report and actigraphy measures of sleep in CWE.

## 5.3. Contribution of NDCTs vs sleep to HRQOL

The regression analyses suggested that NDCTs mediate the relationship between informant-reported sleep problems and HRQOL. For actigraphy data, a similar effect was seen but only for ADHD characteristics and IIV of SOL. This is particularly interesting for two reasons: (i) it suggests that the apparent negative impacts of sleep disturbance in CWE are in reality the result of the NDCTs they are associated with; and (ii) it suggests that the manner in which NDCTs modify the relationship between sleep and HRQOL differs depending on the type of sleep measurement tool. This is relevant to prior studies, which have suggested that while 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). However there are yet to be any studies utilising these two sleep tools to assess the impact on HRQOL in CWE, which hampers the ability to compare previous results. Therefore these differences in the trimodal relationship between sleep, NDCTs and HRQOL according to which sleep measure is used require further investigation.

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., 2011; Moreau et al., 2014; Ziegler et al., 2021). This is consistent with prior research which indicates that sleep problems may be secondary to ADHD characteristics (Hvolby, 2015; Owens, 2009). The literature regarding the relationship between the variability of sleep and autistic characteristics is not as convincing or consistent

(Anders et al., 2011; Goodlin-Jones et al., 2008). Therefore, the current findings suggest that ADHD characteristics are the fundamental driver of HRQOL, and sleep disruption occurs as secondary to these characteristics. On the other hand, co-occurrences of autistic characteristics and variable SOL uniquely contribute to poor HRQOL. However, as it was not possible to conduct a mediation analysis due to the small sample size, the details of these relationships require further exploration with a larger sample.

## 5.4. Contribution of epilepsy specific variables vs sleep to HRQOL

In our data, more severe sleep problems assessed by CSHQ and actigraphy (IIV of SOL) significantly contributed to HRQOL above seizure severity and number of ASMs, neither of which added substantial variance (0–5.4%) and were non-significant contributors to HRQOL. Few studies have investigated informant-reported sleep as measured by the CSHQ and HRQOL in CWE. They documented that more severe and adverse sleep problems were associated with poorer HRQOL (Ekinci et al., 2016; Gutter et al., 2013; Wirrell et al., 2005; Zhao et al., 2022). These studies and our data support the suggestion that sleep problems contribute to HRQOL and need to be considered in epilepsy management, although we would also suggest that their influence is over-estimated as the effect of NDCTs are not considered. Although some studies have demonstrated that a higher number of ASMs and seizure severity worsens HRQOL (Aggarwal et al., 2011; Nadkarni et al., 2011), others have found that epilepsy-specific variables such as seizure severity were not predictive of HRQOL (Sherman et al., 2006; Speechley et al., 2012). A possible explanation for these differences may be the high heterogeneity in the type of measures used to record seizure severity, a mixed group of epilepsies and the number of medications. Nevertheless, self-reports from CWE have reported similar findings to this study, suggesting that HRQOL is not primarily determined by epilepsy-specific variables (Fayed et al., 2015; Hussain et al., 2020).

## 5.5. Limitations

There are some limitations within this study that should be recognised when interpreting our findings. Firstly, this study was limited by the small sample size, which may have prevented differences between epilepsy types from being determined. It should also be noted that there are some drawbacks to actigraphy in determining sleep parameters, largely because actigraphy relies on motion as a surrogate marker of sleep (Martin and 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, over-estimating SOL (Fekedulegn et al., 2020). Nevertheless, steps were taken to address this issue, and the impact of other sleep variables which would also be wrongly interpreted. These steps included following a rigorous cleaning protocol and ensuring that 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). There were also some methodological limitations associated with this study. For example, defining seizure severity based on the HASS, can be skewed by parents' memory recall (Love et al., 2016). There are more sophisticated methods currently being developed utilising wearable technologies, such as smartphones, smartwatches and armbands. However, these have yet to be implemented in routine clinical practice as require replication in larger samples to improve the understanding of their usability to people with epilepsy (Brinkmann et al., 2021). Therefore, the HASS was the most feasible and clinically available option. Nevertheless, other epilepsy-specific variables, namely the number of ASMs and epilepsy type, showed a consistent lack of association with HRQOL, supporting the robustness of our findings.

## 5.6. Future research

The findings from this study 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, to identify how it changes over development in the context of changing sleep patterns and NDCTs. Secondly, informant reports were the main measurement tool 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. For example, a previous study found that when children rated their own HRQOL, NDCTs were not as strongly correlated compared to when parents rated their HRQOL (Baca et al., 2011). Therefore, introduction of a multi-modal approach to measuring sleep via use 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. CWE were divided into distinct groups based on their epilepsy type, although, characterised by large heterogeneity. However, the small sample size prevented further stratification based on etiology or syndrome. Future studies would benefit from larger samples to address the question of the role of etiology vs syndrome in unpacking the relationship between epilepsy and sleep. Clinically, the findings also point towards the need to screen for co-occurrences including sleep problems and neurodevelopmental characteristics as part of the epilepsy assessment process, in order to provide the most appropriate support for parents and children as early as possible.

## 6. Conclusions

A multifaceted approach was taken within this study, combining sleep, neurodevelopmental and epilepsy research in the hope to better understand HRQOL in CWE. The findings indicate that the perceived impact of sleep problems on HRQOL could be explained by NDCTs, whereby sleep problems may behave as a marker of these characteristics rather than of the epilepsy. Most notably, the trimodal interaction between sleep, epilepsy and NDCTs appears to be dependent on the method by which sleep was measured. This finding emphasises the contribution of actigraphy, which is limited in paediatric epilepsy research. Further use of actigraphy holds large utility in studying sleep patterns in CWE and co-occurring NDCTs.

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## Declaration of Competing Interest

The authors declare no conflict of interest in relation to this work.

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## Authors contributions

All authors contributed to the manuscript as follows: Study design and concept: AW, AB, CR. Acquisition and analysis of data: AW. Interpretation of the data: All authors. Drafting of the manuscript: All authors. Approval of the final manuscript: All authors.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the

online version at doi:10.1016/j.eplepsyres.2023.107188.

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