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

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SUMMARY

This systematic review and meta-analysis aims to assess and quantify putative differences in sleep architecture, sleep efficiency, sleep timing and broadly-defined sleep difficulties between children with and without epilepsy. Databases were searched systematically, and studies identified in PubMed, EMBASE, PsychINFO and Medline. The meta-analysis included 19 studies comparing a total of 901 children with epilepsy to 1470 healthy children. Relative to healthy children, children with epilepsy experienced reduced sleep time, sleeping on average 34 minutes less across self-report, actigraphy, 24-hour video-EEG and polysomnography measures. They had more sleep difficulties specifically in the domains of night waking, parasomnias and sleep disordered breathing. The analysis also revealed a significantly increased percentage of N2 sleep and decreased sleep efficiency in children with epilepsy compared to healthy children. These results illustrate that children with epilepsy are vulnerable to more sleep difficulties compared to healthy children. This suggests that screening for sleep difficulties should be an integral part in a diagnosis of epilepsy to ensure that clinically relevant sleep difficulties are identified and treated. Such an approach may ultimately aid in the development of treatment strategies which can contribute to improvements in both developmental and diagnostic outcomes for children with epilepsy.

Keywords: Epilepsy, Sleep, Children, Adolescents, Meta-analysis

Abbreviations

AASM: American Academy of Sleep Medicine
AED: Antiepileptic drug
CSHQ: Children's sleep habits questionnaire
CWE: Children with epilepsy
EEG: Electroencephalography
ID: Intellectual disability
IED: interictal epileptiform discharges
NREM: Non-rapid eye movement sleep
PDSS: Paediatric daytime sleepiness scale
PRISM: Preferred Reporting Items for Systematic reviews and Meta-analyses
PSG: Polysomnography
PSQ: Paediatric sleep questionnaire
QOL: Quality of life
R&K: Rechtschaffen & Kales
REM: Rapid eye movement sleep
SBQ: Sleep behaviour questionnaire
SE: Sleep efficiency
SMD: Sleep disordered breathing
SDB: Standardised mean difference
TST: Total sleep time

INTRODUCTION

Epilepsy is the most frequently occurring neurological disease in childhood and often presents in early development [1]. 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 overall well-being as well as its link with seizures. In order to accurately quantify the differences between children with epilepsy (CWE) and healthy children, it is essential to assess a variety of sleep parameters (e.g., sleep timing, sleep efficiency, sleep architecture and sleep difficulties) to achieve a complete picture.

For the purpose of this meta-analysis, sleep difficulties are defined as 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. The prevalence of such sleep difficulties in healthy children and adolescents is estimated to range between 25 – 40%, with common presentations including night waking and bedtime resistance [2,3]. These rates are significantly higher in CWE than in healthy children, irrespective of whether seizures occur during sleep [4]. Existing observational studies demonstrate that sleep difficulties such as excessive daytime sleepiness, night awakenings and reduced sleep duration are more common in CWE than healthy children [5,6,7] and that these difficulties can appear very early in the epilepsy trajectory [8].

Similarly, polysomnography (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 [9,10] reported in CWE compared to healthy children. 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 [11].

The bidirectional association between sleep and epilepsy is underpinned by various mechanisms, which are more and less well understood and are reviewed in detail elsewhere [12,13,14]. Its impact can extend beyond neurological and physiological changes to impact overall wellbeing, including poor cognitive and behavioural outcomes [8,15], problems with reading and writing [16], attentional deficits [17] and difficulties managing emotions [18]. CWE experience considerable negative psychological and social consequences, which can be partially attributed to underlying sleep disturbances, highlighting the need for clinical acknowledgement. Moreover, a recent randomised controlled trial found 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 [19]. These results illustrate that sleep habits can be modified. An accurate quantification of the nature and range of sleep difficulties experienced by CWE is therefore potentially beneficial to help design interventions which can ameliorate negative clinical, psychological and social outcomes in this group.

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

This meta-analysis was conducted with the following goals:

i. To assess differences in sleep timing, sleep efficiency, sleep architecture and sleep difficulties in CWE compared to healthy children
ii. To assess heterogeneity between studies and provide recommendations in order to reduce between-study heterogeneity for future research

iii. To examine possible moderators for differences in sleep timing, efficiency, architecture and difficulties between CWE and healthy children including method of sleep assessment, quality of study and demographic variables including sex and age.

METHODS

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [20].

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 1 for a full list of search terms).

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Study selection

Selection of papers for inclusion in the review was conducted by AW. Figure 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 intellectual disability (ID) 2) Suitable data to extract for pooling of effect sizes (i.e. measures of means and SDs) 3) Inclusion of a healthy control group.

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Data Extraction and Quality Review

Nineteen papers met the eligibility criteria at full text screening and were included in the final analyses. Data extraction was performed by AW. A quality criteria checklist adapted from previous meta-analyses [21,22] was used to review the overall quality of studies (see Table 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.

Two authors (AW and SB) reviewed the quality of each paper 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, $p<.001$)

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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-electroencephalography (EEG), actigraphy and self-report. Sleep difficulties in the retrieved papers were assessed via two questionnaires. The Children's Sleep Habits Questionnaire (CSHQ) [23] is a parent report sleep measure. 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) [18] which is also a parent 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. They 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.

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 [24]. 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 we used the Sidik-Jonkman estimator rather than the DerSimonian-Laird estimator which can lead to false positives when heterogeneity is high, and number of studies are low [25], which was the case in our 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 [26]. 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 removal 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 less [27].

RESULTS

Study characteristics

Nineteen 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 in 17 studies) and 1470 healthy children with a mean age of 10.8 years (reported in 17 studies). Nine studies used PSG to assess sleep parameters, of which three [9,30,37] used an adaptation night (data were reported for only the second night across all these studies), six [28,32,33,34,38,39] used one night of sleep only with no adaptation night and one study used 24-hour video-EEG [36]. Of the remaining nine studies, eight [6,8,16,18,29,31,40,41] used parent reported sleep questionnaires and one [35] used both actigraphy and questionnaires. Table 3 presents characteristics of the studies included in the meta-analysis.

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Total sleep time

Of the 12 studies that reported TST in CWE in comparison to healthy children, six studies reported TST via PSG, one via 24-hour video-EEG, one used actigraphy and four used self-reported sleep time. The study by Barreto et al. (2002) [28] consisted of two subgroups: 'idiopathic generalised epilepsy' and 'idiopathic focal epilepsy'. They 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. Two studies were conducted by Gogou et al (2016, 2017) [33,34]

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 than the 'rolandic epilepsy' group, which was omitted.

The random effects model revealed that CWE experienced significantly shorter TST in comparison to healthy children (SMD= -0.55, [95% CI -1.08; -0.02] p=0.04), see Figure 2). Mean weighted difference comparison found that CWE slept on average 34 minutes less than healthy controls, 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 outlier and sensitivity analysis by the leave one out method, which revealed no influential cases.

++++++++++++++++++INSERT FIGURE 2 HERE++++++++++++++++++

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. Leave one out sensitivity analysis and outlier analysis revealed that the study by Batista et al. (2007) [29] was an outlier as evidenced by clear distortion on the effect size estimate. This outlier was removed, and 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 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 healthy children. Batista et al. (2007) [29] was excluded in further analysis.

++++++++++++++++++INSERT FIGURE 3 HERE++++++++++++++++++

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 4). We 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.

++++++++++++++++++INSERT FIGURE 4 HERE++++++++++++++++++

Sleep Efficiency

Of 6 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 sleep efficiency compared to healthy children (SMD= -0.71, [95% CI [-1.23; -0.19], p=0.02), see Figure 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.

++++++++++++++++++INSERT FIGURE 5 HERE++++++++++++++++++

Sleep Architecture

Separate meta-analyses were conducted for percentage of sleep stages (see Figure 6): N1% (5 studies), N2% (6 studies), N3% (5 studies) and REM% (6 studies). The meta-analyses initially revealed no significant differences for all sleep stages. Sensitivity analyses was conducted and revealed two outliers [36,38] in N2% and one outlier [38] 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 healthy children. There was no substantial heterogeneity detected (I^2=0%, Q=1.27, p=0.74), thus no further analyses were conducted.

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Heterogeneity Analysis

In order 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. 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.

Total sleep time

No significant subgroup differences were found between PSG, 24-hour video-EEG, self-report and actigraphy (Q=3.17*;* p=0.37) indicating that the type of sleep measure did not have an effect on 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%)

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=0.16, R^2= 22.71%), sex (p=0.33, R^2=2.78%) or quality of the study (p=0.15, R^2=20.70%)

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%).

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 [42]. This was confirmed via the Eggers test which revealed a non-significant effect p=0.17 (see S1 for funnel plot).

DISCUSSION

Summary of findings

Sleep difficulties are often reported by parents of CWE, however this relationship continues to be under-recognized clinically. To our knowledge, this is the first meta-analysis to quantify differences across self-reported and objective measures of sleep variables between CWE and healthy children. 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

391 incorporate a variety of findings and approaches. In addition, the use of a systematic search
392 strategy with inclusive terms optimised the breadth of literature captured. The use of robust
393 assessments of study quality strengthened the confidence in our findings and, as anticipated,
394 CWE experienced deficits across a wide range of sleep parameters. Our analysis indicated that
395 CWE have significantly reduced TST and sleep efficiency, increased percentage of N2 and more
396 frequent and severe sleep difficulties across various domains compared to healthy children.
397 Previous research has consistently highlighted that poor sleep in CWE can impact seizure control
398 and also increase the risk of poorer behavioural and psychological outcomes in comparison to
399 healthy children. Therefore, this evidence of sleep disruptions in CWE warrants further
400 investigation and a greater degree of clinical acknowledgment.
401 Analysis of TST found CWE slept on average 34 minutes less in comparison to healthy
402 children (this ranged from 151 minutes less to 9 minutes more across studies). This meta-analytic
403 finding confirms previous empirical studies [37,43]. It is clinically relevant to the management
404 of CWE, given that insufficient sleep can act as a precipitating factor for IEDs and seizure
405 control. Reduced sleep duration also increases daytime sleepiness which will have an impact on
406 behaviour, learning and overall quality of life (QOL) [44].
407 Our results also revealed significantly more frequent sleep difficulties in CWE, which were
408 most pronounced in relation to the subscales of night waking, SDB and parasomnias as assessed
409 via the CSHQ. This demonstrates that both objective and subjective measures are consistently
410 highlighting poorer sleep parameters in CWE in comparison to healthy children. Moreover, as
411 sleep difficulties often contribute to and prefigure the development of sleep disorders, they pose
412 a clinical problem in their own right. They should therefore be addressed in order to mitigate the
413 risk of these difficulties worsening and complicating the presentation of the epilepsy.
414 Sleep difficulties including parasomnias and SDB are commonly observed in CWE [45] and
415 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 [46,47]. 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 [48], which is why video monitoring forms such a crucial part of the diagnostic workflow. It is therefore possible that parent reports 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 antiepileptic drugs (AEDs) (see below) and disturbed sleep [49]. 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 [33].

Our analysis of PSG variables revealed alterations to sleep architecture, specifically increased N2% in CWE compared to healthy children. 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 [50]. Similarly, poor sleep efficiency was also apparent in CWE, averaging 83%, which is below the average of 90% [51] in the healthy population and may be indicative of poor seizure control as suggested by previous research [52].

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 [53,54]. In addition, polytherapy is found to exacerbate the occurrence of parasomnias [8] and ultimately lead to more severe sleep difficulties in comparison to those on monotherapy [29]. 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 [49,50]. SDB is also associated with dysfunction of the cardiovascular system which is speculated to play a role in sudden unexpected death in epilepsy, highlighting the potentially devastating consequences of

sleep disturbances in CWE [55]. 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.

Strengths and Limitations

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 subjective and objective quantification of sleep disturbances in CWE. This also allowed us to investigate 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 healthy children. 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 [43,52,56,57] were consistent with those in the review. They also emphasised the association with behavioural and psychiatric co-morbidities [56,57]. We did not have the scope 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 [58]. This review highlighted the need for longitudinal designs to be conducted, in order to draw stronger conclusions on the association between sleep and epilepsy. It was also noted that results from parent-report measures are likely to be influenced by their own anxieties. However, the current meta-analysis demonstrates that regardless of whether subjective or objective measures are used, there are clear and consistent differences between CWE and healthy children across sleep parameters.

The majority of 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 [45], while interictal manifestations of focal epilepsies vary across the sleep-wake cycle [59]. 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 [60]. These and other issues concerning the relationship between epilepsy and sleep are discussed in detail in several reviews [61,62]. Finally sleep disturbances appeared to be more pronounced in those with drug resistant epilepsy, as supported by previous research [38]. 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 [63]. 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 [64].

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 [45,50], and issues such as drowsiness are commonly experienced [65]. Despite reporting treatment use, many of the studies failed to subdivide participants by AED type, and hence we were not able 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.

We excluded studies 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 [22]. 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 [66].

Finally, studies measuring sleep architecture used two different scoring systems for sleep: Rechtschaffen & Kales (R&K) [67] and American Academy of Sleep Medicine (AASM) [68]. Previous research has found significant differences between the two when measuring children's and adolescents' sleep, including differences in N1, N2 and REM [69]. 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.

Methodological considerations

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 subjective (e.g., sleep diaries, questionnaires) tools. Within the context of our statistical analysis (see the Heterogeneity Analysis section above), the overall conclusions did not depend on the details of these instruments. Due to the limited number of papers in this area, we believe 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 our analyses for sleep problems, the majority of the data were derived from parent 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 [70]. 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 [71]. Another problem that arises with parent report measures, which has been previously discussed, is the difficulty faced when distinguishing nocturnal seizures from NREM parasomnias. In order to resolve this issue, we recommend that studies should not rely heavily on questionnaire measures in such cases but rather consider videos or preferably video-EEG. Future research should also aim to use parent-proxy 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. We have previously found that actigraphy is well tolerated, even in children with severe ID [72].

In our analysis of sleep architecture, one study [38] measured percentage of sleep stages in reference to sleep period time 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. We recommend 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.

Conclusion

This meta-analysis found that CWE suffer from widespread objective and subjective sleep disruptions in comparison to healthy children. 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 QOL in the child and family. 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 in order to reduce the detrimental impacts the disease and additional co-morbidities may have on developmental outcomes.

Practice points

1) Children with epilepsy experience both objective and subjective disruptions to their sleep in comparison to healthy children that require clinical acknowledgment.
2) Co-occurring intellectual disability were excluded as this group are understood to be at an increased risk for sleep disturbances. This raises the possibility that our results likely capture the lower estimate of the range of sleep disruptions. It is important that clinicians consider the impact of these factors in epilepsy management.
3) Children with drug resistant epilepsy appear to be most vulnerable to sleep disturbances, although the relative contribution of anti-epileptic medications or recurrent seizures is not clear.
4) Routine screening of sleep habits and the inclusion of a sleep specialist as part of the diagnostic process are recommended for children with epilepsy.

Research Agenda

1) Further studies should place more emphasis on investigating individual epilepsy syndromes with consistent etiologies in order to understand the differences in sleep patterns across epilepsies.
2) Future research should aim to extend current findings to investigate whether poor quality of sleep with co-occurring epilepsy has a greater consequence on quality of life, academic attainment and mental health, than in healthy children.
3) The current studies had various methodological limitations which posed restrictions to extracting and synthesising data. To mitigate this problem, future research should aim to develop standardised sleep questionnaires for paediatric epilepsy patients, to aid in comparing across groups, and ensure routine reporting of AEDs for individual patients.
4) Future research should encourage the use of wearable devices in clinical settings as they provide considerable value in gathering accurate information on sleep habits, which can help to better understand the role in epilepsy.
5) Studies on interventions should be conducted to investigate whether improving sleep habits has an impact on health-related quality of life and seizures.

Conflicts of 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

++++++++++++++++++++INSERT FIGURE S1 HERE++++++++++++++++++++

REFERENCES*

[1] Aaberg KM, Gunnes N, Bakken IJ, Søraas CL, Berntsen A, Magnus P, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. *Pediatrics* 2017; 1**39**: 1-9.

[2] Byars KC, Yolton K, Rausch J, Lanphear B, Beebe DW. Prevalence, patterns, and persistence of sleep problems in the first 3 years of life. *Pediatrics* 2012; **129**:276-84.

[3] Mindell JA, Meltzer LJ. Behavioural sleep disorders in children and adolescents. *Ann Acad Med Singapore*, 2008; **37:**722-8.

[4] Gibbon FM, Maccormac E, Gringras P. Sleep and epilepsy: unfortunate bedfellows. *Archives of disease in childhood*, 2019; **104**:189-92.*

[5] Larson AM, Ryther RC, Jennesson M, Geffrey AL, Bruno PL, Anagnos CJ, et al. Impact of pediatric epilepsy on sleep patterns and behaviors in children and parents. *Epilepsia* 2012; 53**:**1162-9.

[6] Maganti R, Hausman N, Koehn M, Sandok E, Glurich I, Mukesh BN. Excessive daytime sleepiness and sleep complaints among children with epilepsy. *Epilepsy & Behavior* 2006; **8**:272-7.

[7] Shaki D, Goldbart A, Daniel S, Fraser D, Shorer Z. Pediatric epilepsy and parental sleep quality. *Journal of clinical sleep medicine* 2011; **7**: 502-6.

[8] Byars AW, Byars KC, Johnson CS, degrauw TJ, Fastenau PS, Perkins S, Austin JK, Dunn DW. The relationship between sleep problems and neuropsychological functioning in children with first recognized seizures. *Epilepsy & Behavior* 2008; **13**: 607-13.

[9] Maganti R, Sheth RD, Hermann BP, Weber S, Gidal BE, Fine J. Sleep architecture in children with idiopathic generalized epilepsy. *Epilepsia* 2005; **46**:104-9.

[10] Pereira AM, Bruni O, Ferri R, Palmini A, Nunes ML. The impact of epilepsy on sleep architecture during childhood. *Epilepsia* 2012; 53:1519-25.

665 [11] Tezer FI, Rémi J, Erbil N, Noachtar S, Saygi S. A reduction of sleep spindles heralds
666 seizures in focal epilepsy. *Clinical Neurophysiology* 2014, **125**: 2207-11.
667 [12] Matos G, Tufik S, Scorza FA, Cavalheiro EA, Andersen ML. Sleep and epilepsy:
668 exploring an intriguing relationship with a translational approach. *Epilepsy & Behavior* 2013;
669 **26:**405-9.
670 [13] Sinha SR. Basic mechanisms of sleep and epilepsy. *Journal of Clinical Neurophysiology*
671 2011; **28**:103-10.
672 [14] Takagi S. Sleep and epilepsy. *Sleep and Biological Rhythms* 2017;**15**:189-96.
673 [15] Piccinelli P, Borgatti R, Aldini A, Bindelli D, Ferri M, Perna S, et al. Academic
674 performance in children with rolandic epilepsy. *Developmental Medicine & Child Neurology*
675 2008; **50**:353-6.
676 [16] Ekinci O, Isik U, Gunes S, Ekinci N. Understanding sleep problems in children with
677 epilepsy: associations with quality of life, attention-deficit hyperactivity disorder and
678 maternal emotional symptoms. *Seizure* 2016; **40:**108-13.
679 [17] Stores G, Wiggs L, Campling G. Sleep disorders and their relationship to psychological
680 disturbance in children with epilepsy. *Child: care, health and development* 1998; **24**:5-19.
681 [18] Cortesi F, Giannotti F, Ottaviano S. Sleep problems and daytime behavior in childhood
682 idiopathic epilepsy. *Epilepsia* 1999, **40:**1557-65.
683 [19] Tsai SY, Lee WT, Lee CC, Jeng SF, Weng WC. Behavioural-educational sleep
684 interventions for pediatric epilepsy: a randomized controlled trial. *Sleep* 2020; **43**:zsz211.*
685 [20] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic
686 reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8:** 336-41.
687 [21] Richards C, Jones C, Groves L, Moss J, Oliver C. Prevalence of autism spectrum disorder
688 phenomenology in genetic disorders: a systematic review and meta-analysis. *The Lancet*
689 *Psychiatry* 2015; **2:** 909-16.

690 [22] Surtees AD, Oliver C, Jones CA, Evans DL, Richards C. Sleep duration and sleep quality
691 in people with and without intellectual disability: a meta-analysis. *Sleep medicine reviews*
692 2018; **40:** 135-50.
693 [23] Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ):
694 psychometric properties of a survey instrument for school-aged children. *Sleep-New York-*
695 2000; **23:**1043-52.
696 [24] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *Bmj*
697 2011; **342:**d549.
698 [25] IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for
699 random effects meta-analysis is straightforward and considerably outperforms the standard
700 DerSimonian-Laird method. *BMC medical research methodology* 2014; **14:** 25.
701 [26] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-
702 analyses. *Bmj.* 2003; **327:** 557-60.
703 [27] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations
704 for examining and interpreting funnel plot asymmetry in meta-analyses of randomised
705 controlled trials. *Bmj* 2011; **343:** d4002.
706 [28] Barreto JR, Fernandes RM, Sakamoto AC. Correlation of sleep macrostructure
707 parameters and idiopathic epilepsies. *Arquivos de neuro-psiquiatria* 2002; **60:** 353-7.
708 [29] Batista BH, Nunes ML. Evaluation of sleep habits in children with epilepsy. *Epilepsy &*
709 *Behavior* 2007; **11:**60-64.
710 [30] Bruni O, Novelli L, Luchetti A, Zarowski M, Meloni M, Cecili M, et al. Reduced NREM
711 sleep instability in benign childhood epilepsy with centro-temporal spikes. *Clinical*
712 *neurophysiology* 2010; **121:** 665-71.

[31] Chan B, Cheong EY, Ng SF, Chan YC, Lee QU, Chan KY. Evaluation of sleep disturbances in children with epilepsy: A questionnaire-based case–control study. Epilepsy & Behavior 2011; **21:**437-40.

[32] Chan S, Pressler R, Boyd SG, Baldeweg T, Cross JH. Does sleep benefit memory consolidation in children with focal epilepsy?. *Epilepsia* 2017; **58:** 456-66.

[33] Gogou M, Haidopoulou K, Eboriadou M, Pavlidou E, Hatzistylianou M, Pavlou E. Sleep respiratory parameters in children with idiopathic epilepsy: A cross-sectional study. *Epilepsy research* 2016; **126:** 10-15.

[34] Gogou M, Haidopoulou K, Eboriadou M, Pavlou E. Sleep disturbances in children with rolandic epilepsy. *Neuropediatrics* 2017; **48:**030-5.

[35] Holley S, Whitney A, Kirkham FJ, Freeman A, Nelson L, Whitlingum G, et al. Executive function and sleep problems in childhood epilepsy. *Epilepsy & Behavior* 2014; **37:** 20-5.

[36] Myatchin I, Lagae L. Sleep spindle abnormalities in children with generalized spike-wave discharges. Pediatric neurology. 2007 Feb 1;36(2):106-11.

[37] Nunes LM, Ferri R, Arzimanoglou A, Curzi L, Appel CC, Costa da Costa J. Sleep organization in children with partial refractory epilepsy. *Journal of child neurology* 2003; **18:**763-6.

[38] Pereira AM, Bruni O, Ferri R, Nunes ML. Sleep instability and cognitive status in drug-resistant epilepsies. *Sleep medicine* 2012;**13:** 536-41.

[39] Shaheen HA, El-Kader AA, El Gohary AM, El-Fayoumy NM, Afifi LM. Obstructive sleep apnea in epilepsy: a preliminary Egyptian study. *Sleep and Breathing* 2012; **16:**765-71.

[40] Tang SS, Clarke T, Owens J, Pal DK. Sleep behavior disturbances in rolandic epilepsy. *Journal of child neurology* 2011; **26:** 239-43.

[41] Wirrell E, Blackman M, Barlow K, Mah J, Hamiwka L. Sleep disturbances in children with epilepsy compared with their nearest-aged siblings. *Developmental medicine and child neurology* 2005; **47:**754-9.

[42] Palmer TM, Sutton AJ, Peters JL, Moreno SG. Contour-enhanced funnel plots for meta-analysis. *The STATA* journal 2008; **8:** 242-54.

[43] Tsai SY, Lee WT, Jeng SF, Lee CC, Weng WC. Sleep and Behavior Problems in Children with Epilepsy. *Journal of Pediatric Health Care* 2019; **33**:138-45.

[44] Giorelli AS, Passos P, Carnaval T, Gomes MD. Excessive daytime sleepiness and epilepsy: a systematic review. *Epilepsy research and treatment* 2013; **2013:** 629469.

[45] Al-Biltagi MA. Childhood epilepsy and sleep. *World journal of clinical pediatrics* 2014; **3:**45.*

[46] Caplan R, Siddarth P, Gurbani S, Hanson R, Sankar R, Shields WD. Depression and anxiety disorders in pediatric epilepsy. *Epilepsia* 2005; **46:**720-30.

[47] Reilly C, Agnew R, Neville BG. Depression and anxiety in childhood epilepsy: a review. *Seizure* 2011; **20:** 589-97.

[48] Walker MC, Eriksson SH. Epilepsy and sleep disorders. *European Neurological Review* 2011; **6**:60-3.*

[49] Sivathamboo S, Perucca P, Velakoulis D, Jones NC, Goldin J, Kwan P, et al. Sleep-disordered breathing in epilepsy: epidemiology, mechanisms, and treatment. *Sleep* 2018; **41:**zsy015.

[50] Gogou M, Haidopoulou K, Eboriadou M, Pavlou E. Sleep apneas and epilepsy comorbidity in childhood: a systematic review of the literature. *Sleep and Breathing* 2015; **19:**421-32.*

759 [51] Bazil, CW. Parasomnias, sleep disorders, and narcolepsy—sleep-time imitators of
760 epilepsy. In: Kaplan, PW, Fisher, RS, eds. Imitators of Epilepsy. 2nd ed. New York: Demos;
761 2005. p.217-230.
762 [52] Kaleyias J, Cruz M, Goraya JS, Valencia I, Khurana DS, Legido A, et al. Spectrum of
763 polysomnographic abnormalities in children with epilepsy. *Pediatric neurology* 2008;
764 **39:**170-6.
765 [53] Shvarts V, Chung S. Epilepsy, antiseizure therapy, and sleep cycle parameters. *Epilepsy*
766 *research and treatment 2013*;2013.*
767 [54] Jain SV, Glauser TA. Effects of epilepsy treatments on sleep architecture and daytime
768 sleepiness: an evidence-based review of objective sleep metrics. *Epilepsia* 2014; **55:**26-37.
769 [55] Billakota S, Odom N, Westwood AJ, Hanna E, Pack AM, Bateman LM. Sleep-disordered
770 breathing, neuroendocrine function, and clinical SUDEP risk in patients with epilepsy.
771 *Epilepsy & Behavior* 2018; **87:** 78-82.
772 [56] Becker DA, Fennell EB, Carney PR. Daytime behavior and sleep disturbance in
773 childhood epilepsy. Epilepsy & Behavior 2004; **5:** 708-15.*
774 [57] Hansen BH, Alfstad KÅ, van Roy B, Henning O, Lossius MI. Sleep problems in children
775 and adolescents with epilepsy: Associations with psychiatric comorbidity. *Epilepsy &*
776 *Behavior* 2016; **62:**14-9.
777 [58] Schlarb AA, Christen R, Claßen M, Bien CG. Sleep and dreaming in children and
778 adolescents with epilepsy. *Somnologie* 2016; **20:**242-50.*
779 [59] Bagshaw AP, Jacobs J, LeVan P, Dubeau F, Gotman J. Effect of sleep stage on interictal
780 high-frequency oscillations recorded from depth macroelectrodes in patients with focal
781 epilepsy. *Epilepsia* 2009; **50**:617-28.

[60] Leresche N, Lambert RC, Errington AC, Crunelli V. From sleep spindles of natural sleep to spike and wave discharges of typical absence seizures: is the hypothesis still valid?. *Pflügers Archiv-European Journal of Physiology* 2012; **463:** 201-12.

[61] Kotagal P, Yardi N. The relationship between sleep and epilepsy. *In Seminars in pediatric neurology* 2008; **15:** 42-49.*

[62] Frauscher B, Gotman J. Sleep, oscillations, interictal discharges, and seizures in human focal epilepsy. *Neurobiology of disease* 2019; **127:** 545-553*

[63] Manokaran RK, Gulati S. Sleep and drug resistant epilepsy in children. *Sleep Med Dis Int J*. 2018; **2:** 96-8.

[64] Dahl RE. Sleep and the developing brain. *Sleep* 2007;**30:**1079.

[65] Placidi F, Scalise A, Marciani MG, Romigi A, Diomedi M, Gigli GL. Effect of antiepileptic drugs on sleep. *Clinical Neurophysiology* 2000; **111:**115-9.

[66] Trickett J, Heald M, Oliver C, Richards C. A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. *Journal of neurodevelopmental disorders* 2018; **10:**9.

[67] Rechtschaffen A. Kales, A. A manual for standardized terminology, techniques and scoring system for sleep stages in human subjects, editors. Brain Research Institute, UCLA. 1968.

[68] Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.

[69] Novelli L, Ferri R, Bruni O. Sleep classification according to AASM and Rechtschaffen and Kales: effects on sleep scoring parameters of children and adolescents. *Journal of sleep research* 2010; **19**:238-47.

[70] Baca CB, Vickrey BG, Hays RD, Vassar SD, Berg AT. Differences in child versus parent reports of the child's health-related quality of life in children with epilepsy and healthy siblings. *Value in Health. 2010*; **13:**778-86.

[71] Short MA, Gradisar M, Lack LC, Wright HR, Chatburn A. Estimating adolescent sleep patterns: parent reports versus adolescent self-report surveys, sleep diaries, and actigraphy. *Nature and science of sleep* 2013; **5**:23.

[72] Trickett J, Oliver C, Heald M, Denyer H, Surtees A, Clarkson E, et al. Sleep in children with Smith–Magenis syndrome: a case–control actigraphy study. *Sleep* 2019; 1-12.

Figure Legends

Figure 1. Flowchart of search process

Figure 2. Forest plot for standardised mean difference (Hedge's g) in sleep time between children with epilepsy and healthy controls. 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 and the corresponding confidence interval.

Figure 3. Forest plot for standardised mean difference (Hedge's g) in total sleep problems between children with epilepsy and healthy children. 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 and the corresponding confidence interval.

Figure 4. Forest plot for standardised mean difference (Hedge's g) in type of sleep difficulties on CSHQ between children with epilepsy and healthy children. 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 and the corresponding confidence interval.

Figure 5. Forest plot for standardised mean difference (Hedge's g) in sleep efficiency (%) between children with epilepsy and healthy children. 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 and the corresponding confidence interval.

Figure 6. Forest plot for standardised mean difference (Hedge's g) in percentage of N1,N2, N3 and rapid eye movement sleep between children with epilepsy and healthy children. 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 and the corresponding confidence interval.

Appendix A: Supplementary data

Figure S1: Contour enhanced funnel plot. Standardised mean difference in total sleep time between children with epilepsy and healthy children 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.

Tables

Table 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)

Table 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

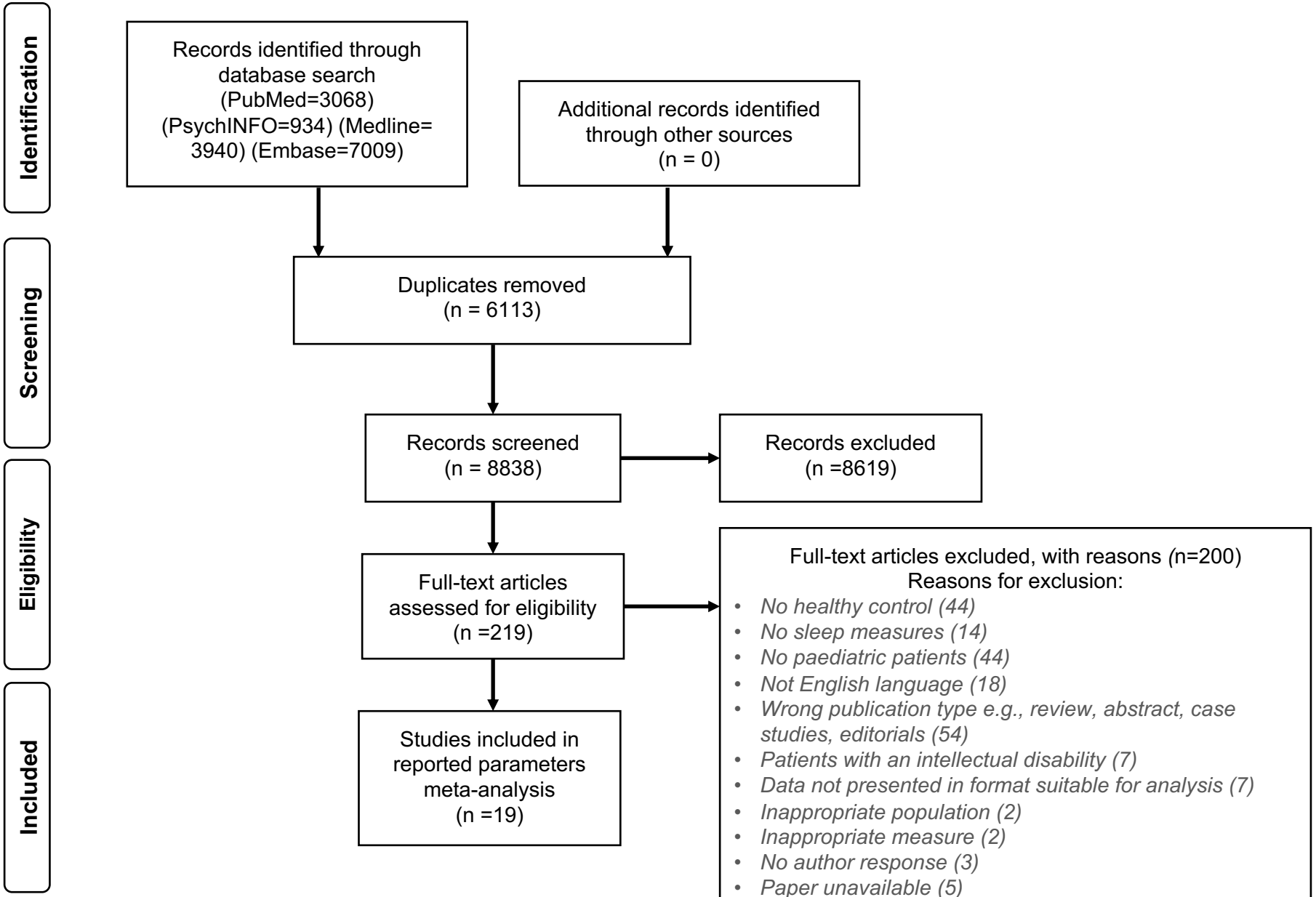
Table 3. Study characteristics

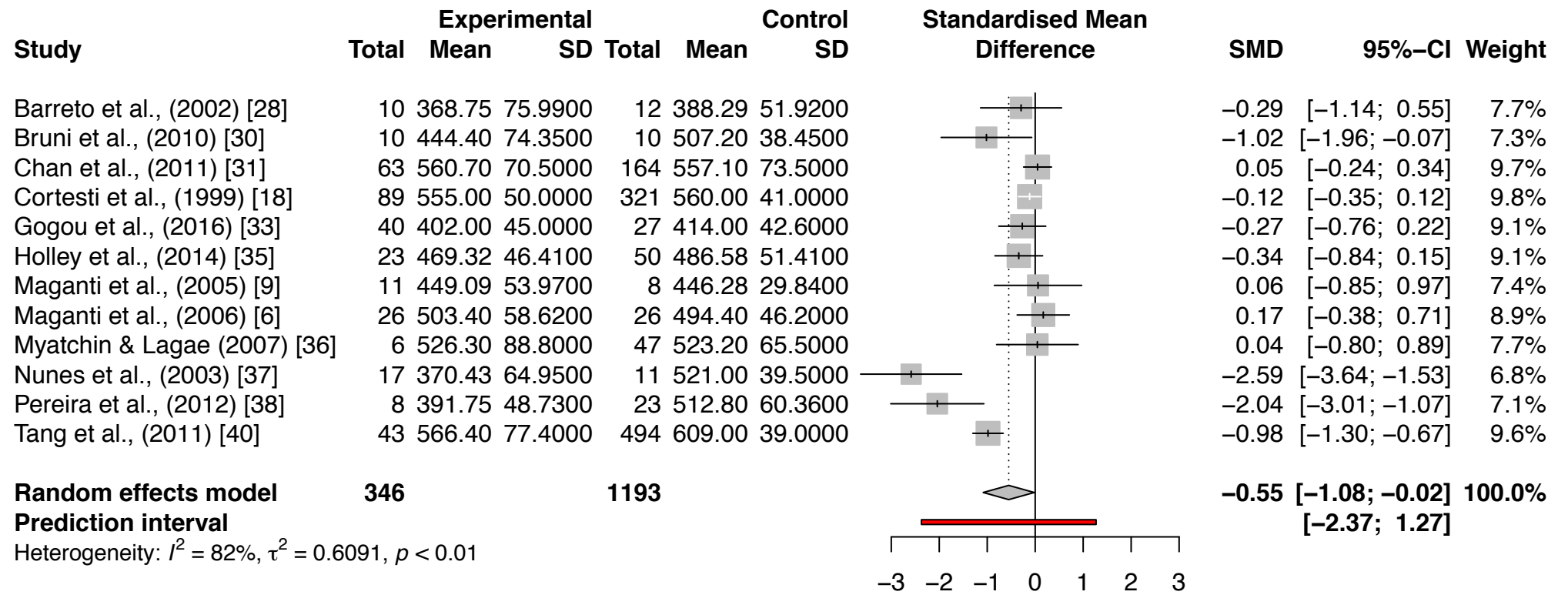
Study	Sample size		Age(Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Barreto *et al,* 2002[28]	10 13	12	12.2 8.9	10.8	40 54	33	10 Idiopathic 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[29]	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 [30]	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 [8]	332	321	9.6	9.6	49	48	Various epilepsy syndromes	SBQ	Parent reported sleep time SBQ total score	50% monotherapy 2% polytherapy 48% no AEDs	N/A	3	2	1	**0.67**
Chan *et al,* 2011 [31]	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 [32]	22	21	11.5	10.6	64	43	Focal epilepsy	PSG	TST, N1, N2, N3, REM%	Yes (% unknown)	No	2	1	2	**0.56**
Cortesi *et al,* 1999 [18]	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 [16]	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**
Gogou *et al,* 2016 [33]	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 [34]	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**

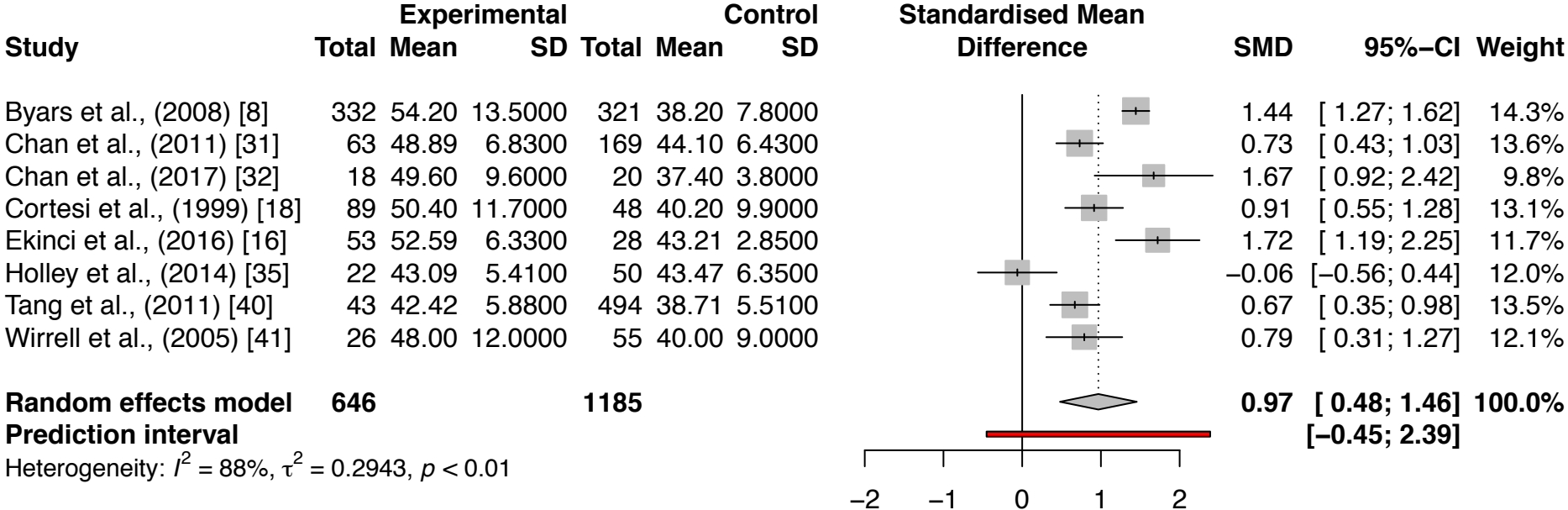
Holley *et al,* 2014 [35]	23	50	10	9.3	48	44	Childhood absence epilepsy, generalised tonic clonic seizures, focal seizures and not known	CSHQ Actigraphy	CSHQ total score and subscales Actigraphy	96% on AEDs	N/A	3	2	3	**0.89**
Maganti *et al,* 2005 [9]	11	8	13.4	14.3	45	50	5 Childhood absence, 4 juvenile absence, 2 juvenile myoclonic epilepsy	PSG	TST, SE(%),N1, N2, N3, REM%	73% monotherapy 27% polytherapy	Yes	3	1	3	**0.78**
Maganti *et al,* 2006 [6]	26	26	14.6	14.7	35	35	14 Idiopathic generalised epilepsy 12 Localisation related epilepsy	PDSS PSQ	Parent reported sleep duration	100% on AEDs	N/A	3	1	1	**0.56**
Myatchin & Lagae 2007 [36]	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 [37]	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**
Pereira et *al,* 2012 [38]	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 [39]	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 [40]	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 [41]	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.

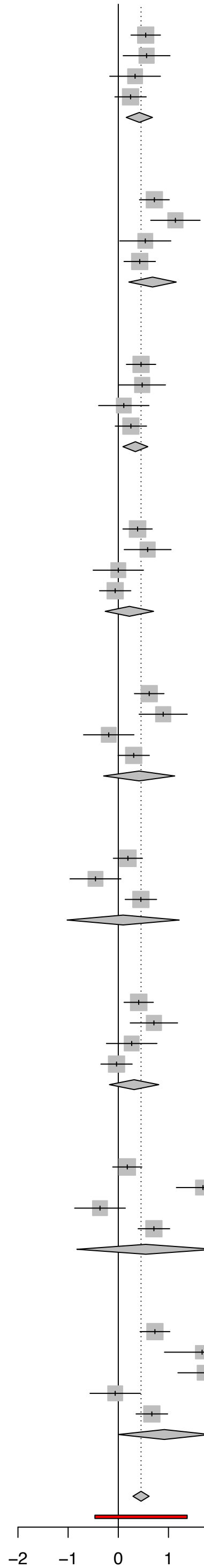
Figure

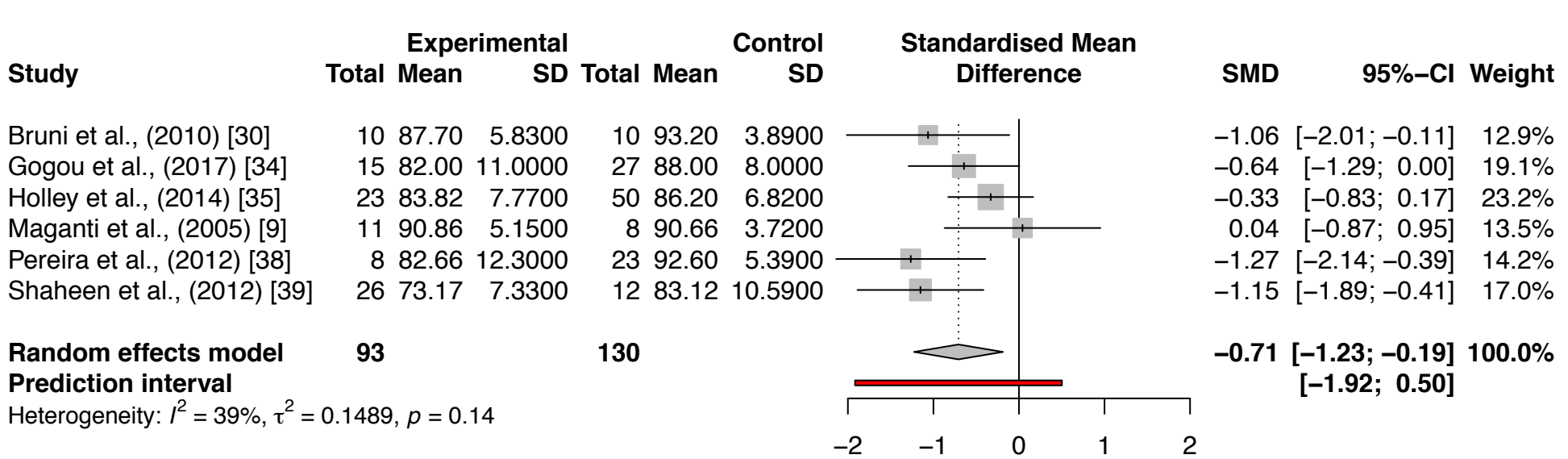

Identification
Screening
Eligibility
Included
Records identified through database search (PubMed=3068) (PsychINFO=934) (Medline= 3940) (Embase=7009)
Additional records identified through other sources (n = 0)
Duplicates removed (n = 6113)
Records screened (n = 8838)
Records excluded (n =8619)
Full-text articles assessed for eligibility (n =219)
Full-text articles excluded, with reasons (n=200)
Reasons for exclusion:
No healthy control (44)
No sleep measures (14)
No paediatric patients (44)
Not English language (18)
Wrong publication type e.g., review, abstract, case studies, editorials (54)
Patients with an intellectual disability (7)
Data not presented in format suitable for analysis (7)
Inappropriate population (2)
Inappropriate measure (2)
No author response (3)
Paper unavailable (5)
Studies included in reported parameters meta-analysis (n =19)


Study
Experimental
Total
Mean
SD
Control
Total
Mean
SD
Standardised Mean Difference
SMD
95%−CI
Weight
Barreto et al., (2002) [28] 10 368.75 75.9900 12 388.29 51.9200 −0.29 [−1.14; 0.55] 7.7%
Bruni et al., (2010) [30] 10 444.40 74.3500 10 507.20 38.4500 −1.02 [−1.96; −0.07] 7.3%
Chan et al., (2011) [31] 63 560.70 70.5000 164 557.10 73.5000 0.05 [−0.24; 0.34] 9.7%
Cortesti et al., (1999) [18] 89 555.00 50.0000 321 560.00 41.0000 −0.12 [−0.35; 0.12] 9.8%
Gogou et al., (2016) [33] 40 402.00 45.0000 27 414.00 42.6000 −0.27 [−0.76; 0.22] 9.1%
Holley et al., (2014) [35] 23 469.32 46.4100 50 486.58 51.4100 −0.34 [−0.84; 0.15] 9.1%
Maganti et al., (2005) [9] 11 449.09 53.9700 8 446.28 29.8400 0.06 [−0.85; 0.97] 7.4%
Maganti et al., (2006) [6] 26 503.40 58.6200 26 494.40 46.2000 0.17 [−0.38; 0.71] 8.9%
Myatchin & Lagae (2007) [36] 6 526.30 88.8000 47 523.20 65.5000 0.04 [−0.80; 0.89] 7.7%
Nunes et al., (2003) [37] 17 370.43 64.9500 11 521.00 39.5000 −2.59 [−3.64; −1.53] 6.8%
Pereira et al., (2012) [38] 8 391.75 48.7300 23 512.80 60.3600 −2.04 [−3.01; −1.07] 7.1%
Tang et al., (2011) [40] 43 566.40 77.4000 494 609.00 39.0000 −0.98 [−1.30; −0.67] 9.6%
Random effects model 346 1193 −0.55 [−1.08; −0.02] 100.0%
Prediction interval [−2.37; 1.27]
Heterogeneity: I^2 = 82%, τ^2 = 0.6091, p < 0.01
−3
−2
−1
0
1
2
3


Study
Experimental
Total
Mean
SD
Control
Total
Mean
SD
Standardised Mean Difference
SMD
95%–CI
Weight
Byars et al., (2008) [8] 332 54.20 13.5000 321 38.20 7.8000 1.44 [1.27; 1.62] 14.3%
Chan et al., (2011) [31] 63 48.89 6.8300 169 44.10 6.4300 0.73 [0.43; 1.03] 13.6%
Chan et al., (2017) [32] 18 49.60 9.6000 20 37.40 3.8000 1.67 [0.92; 2.42] 9.8%
Cortesi et al., (1999) [18] 89 50.40 11.7000 48 40.20 9.9000 0.91 [0.55; 1.28] 13.1%
Ekinci et al., (2016) [16] 53 52.59 6.3300 28 43.21 2.8500 1.72 [1.19; 2.25] 11.7%
Holley et al., (2014) [35] 22 43.09 5.4100 50 43.47 6.3500 –0.06 [–0.56; 0.44] 12.0%
Tang et al., (2011) [40] 43 42.42 5.8800 494 38.71 5.5100 0.67 [0.35; 0.98] 13.5%
Wirrell et al., (2005) [41] 26 48.00 12.0000 55 40.00 9.0000 0.79 [0.31; 1.27] 12.1%
Random effects model 646 1185 0.97 [0.48; 1.46] 100.0%
Prediction interval [–0.45; 2.39]
Heterogeneity: I^2 = 88%, τ^2 = 0.2943, p < 0.01
–2
–1
0
1
2

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	Standardised Mean Difference	SMD	95%–CI	Weight
Measure = Night Waking										
Chan et al., (2011) [31]	63	3.79	1.1400	169	3.28	0.8400		0.55	[0.25; 0.84]	3.0%
Ekinci et al., (2016) [16]	53	3.73	0.9900	28	3.25	0.4400		0.56	[0.10; 1.03]	2.6%
Holley et al., (2014) [35]	22	3.91	1.3100	50	3.55	0.9400		0.33	[–0.17; 0.84]	2.5%
Tang et al., (2011) [40]	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) [31]	63	9.37	2.1400	169	8.07	1.6600		0.72	[0.42; 1.02]	3.0%
Ekinci et al., (2016) [16]	53	8.88	2.0300	28	6.92	0.7600		1.14	[0.65; 1.63]	2.6%
Holley et al., (2014) [35]	22	10.00	2.0900	50	9.00	1.7200		0.54	[0.03; 1.05]	2.5%
Tang et al., (2011) [40]	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) [31]	63	3.75	1.0300	169	3.33	0.8800		0.45	[0.16; 0.75]	3.0%
Ekinci et al., (2016) [16]	53	3.84	1.4800	28	3.25	0.4400		0.48	[0.01; 0.94]	2.6%
Holley et al., (2014) [35]	22	3.70	1.0600	50	3.59	0.9600		0.11	[–0.39; 0.61]	2.5%
Tang et al., (2011) [40]	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) [31]	63	9.46	2.8100	169	8.46	2.5100		0.38	[0.09; 0.68]	3.1%
Ekinci et al., (2016) [16]	53	10.86	4.0100	28	8.92	0.8100		0.58	[0.12; 1.05]	2.6%
Holley et al., (2014) [35]	22	7.00	1.4100	50	7.00	1.7100		0.00	[–0.50; 0.50]	2.5%
Tang et al., (2011) [40]	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) [31]	63	1.67	0.8000	169	1.29	0.5300		0.62	[0.32; 0.91]	3.0%
Ekinci et al., (2016) [16]	53	6.73	1.1500	28	5.78	0.8300		0.89	[0.42; 1.37]	2.6%
Holley et al., (2014) [35]	22	1.61	0.7800	50	1.76	0.7800		–0.19	[–0.69; 0.31]	2.5%
Tang et al., (2011) [40]	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) [31]	63	4.76	1.6400	169	4.47	1.4600		0.19	[–0.10; 0.48]	3.1%
Holley et al., (2014) [35]	22	3.91	1.1300	50	4.63	1.7200		–0.45	[–0.96; 0.05]	2.5%
Tang et al., (2011) [40]	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) [31]	63	5.98	2.0300	169	5.21	1.8300		0.41	[0.12; 0.70]	3.1%
Ekinci et al., (2016) [16]	53	5.53	1.7000	28	4.50	0.6900		0.71	[0.24; 1.18]	2.6%
Holley et al., (2014) [35]	22	4.96	1.7500	50	4.59	1.1700		0.27	[–0.24; 0.77]	2.5%
Tang et al., (2011) [40]	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) [31]	63	13.37	3.1600	169	12.79	3.2600		0.18	[–0.11; 0.47]	3.1%
Ekinci et al., (2016) [16]	53	14.03	2.7400	28	10.00	1.3800		1.69	[1.16; 2.22]	2.5%
Holley et al., (2014) [35]	22	10.35	3.3000	50	11.47	2.9200		–0.36	[–0.87; 0.14]	2.5%
Tang et al., (2011) [40]	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) [31]	63	48.89	6.8300	169	44.10	6.4300		0.73	[0.43; 1.03]	3.0%
Chan et al., (2017) [32]	18	49.60	9.6000	20	37.40	3.8000		1.67	[0.92; 2.42]	2.0%
Ekinci et al., (2016) [16]	53	52.59	6.3300	28	43.21	2.8500		1.72	[1.19; 2.25]	2.5%
Holley et al., (2014) [35]	22	43.09	5.4100	50	43.47	6.3500		–0.06	[–0.56; 0.44]	2.5%
Tang et al., (2011) [40]	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										



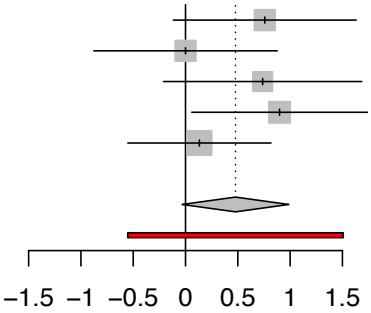

Experimental
Control
Standardised Mean Difference
Study
Total
Mean
SD
Total
Mean
SD
SMD
95%−CI
Weight
Bruni et al., (2010) [30] 10 87.70 5.8300 10 93.20 3.8900 −1.06 [−2.01; −0.11] 12.9%
Gogou et al., (2017) [34] 15 82.00 11.0000 27 88.00 8.0000 −0.64 [−1.29; 0.00] 19.1%
Holley et al., (2014) [35] 23 83.82 7.7700 50 86.20 6.8200 −0.33 [−0.83; 0.17] 23.2%
Maganti et al., (2005) [9] 11 90.86 5.1500 8 90.66 3.7200 0.04 [−0.87; 0.95] 13.5%
Pereira et al., (2012) [38] 8 82.66 12.3000 23 92.60 5.3900 −1.27 [−2.14; −0.39] 14.2%
Shaheen et al., (2012) [39] 26 73.17 7.3300 12 83.12 10.5900 −1.15 [−1.89; −0.41] 17.0%
Random effects model 93 130 −0.71 [−1.23; −0.19] 100.0%
Prediction interval [−1.92; 0.50]
Heterogeneity: I^2 = 39%, τ^2 = 0.1489, p = 0.14
−2
−1
0
1
2

Figure

1. N1%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002) [28]	10	4.79	3.9300	12	2.36	2.1600	0.76	[−0.12; 1.63]	18.7%
Bruni et al., (2010) [30]	10	9.40	3.5600	10	9.40	3.7600	0.00	[−0.88; 0.88]	18.7%
Maganti et al., (2005) [9]	11	7.19	3.2700	8	4.87	2.5800	0.74	[−0.21; 1.69]	16.6%
Pereira et al., (2012) [38]	8	8.67	8.2900	23	3.80	3.8500	0.90	[0.06; 1.74]	19.9%
Shaheen et al., (2012) [29]	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]**	

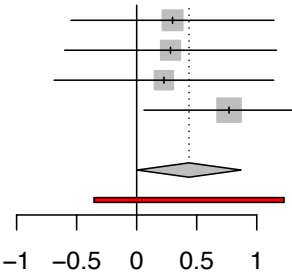
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0710$, $p = 0.44$



2. N2%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002) [28]	10	53.25	12.6700	12	50.11	7.3900	0.30	[−0.55; 1.14]	24.0%
Bruni et al., (2010) [30]	10	44.50	10.4600	10	42.10	4.8400	0.28	[−0.60; 1.16]	22.2%
Maganti et al., (2005) [9]	11	49.49	8.9000	8	47.46	8.0200	0.23	[−0.69; 1.14]	20.7%
Shaheen et al., (2012) [29]	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]**	

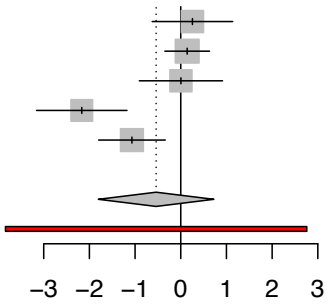
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0153$, $p = 0.74$



3. N3%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Bruni et al., (2010) [30]	10	27.50	6.0600	10	26.20	3.2900	0.26	[−0.63; 1.14]	19.4%
Gogou et al., (2016) [33]	40	32.00	10.4800	27	30.69	6.8900	0.14	[−0.35; 0.63]	22.3%
Maganti et al., (2005) [9]	11	17.33	5.4500	8	17.31	5.7700	0.00	[−0.91; 0.91]	19.2%
Pereira et al., (2012) [38]	8	9.37	9.1200	23	23.70	5.3100	−2.17	[−3.16; −1.18]	18.5%
Shaheen et al., (2012) [39]	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]**	

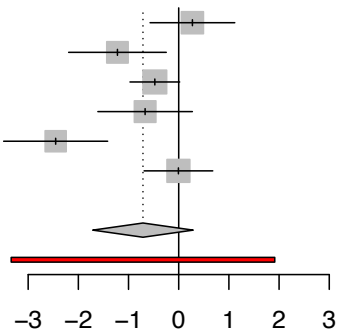
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.8664$, $p < 0.01$



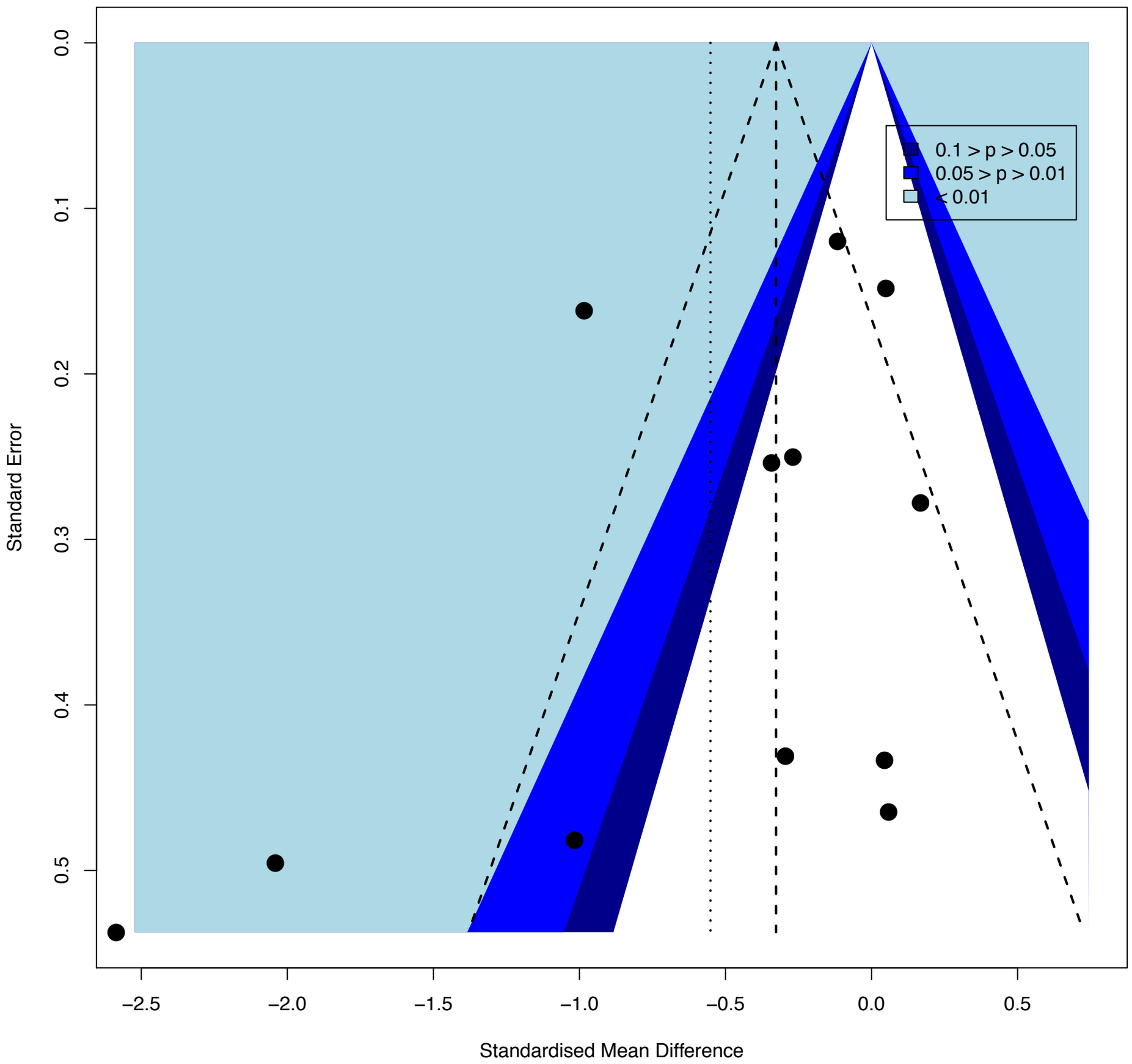
4. REM%

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%–CI	Weight
Barreto et al., (2002) [28]	10	24.92	8.2200	12	22.71	7.4000	0.27	[−0.57; 1.12]	16.6%
Bruni et al., (2010) [30]	10	15.50	4.6000	10	21.20	4.3400	−1.22	[−2.19; −0.25]	15.6%
Gogou et al., (2016) [33]	40	18.63	5.8800	27	21.24	4.6500	−0.48	[−0.97; 0.02]	19.1%
Maganti et al., (2005) [9]	11	17.91	3.8400	8	22.03	7.9300	−0.67	[−1.61; 0.27]	15.8%
Pereira et al., (2012) [38]	8	9.73	5.7900	23	22.90	5.0400	−2.45	[−3.49; −1.42]	15.1%
Shaheen et al., (2012) [39]	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: $I^2 = 76\%$, $\tau^2 = 0.7432$, $p < 0.01$



Figure


0.1 > p > 0.05
0.05 > p > 0.01
< 0.01
Standard Error
0.0
0.1
0.2
0.3
0.4
0.5
−2.5
−2.0
−1.5
−1.0
−0.5
0.0
0.5
Standardised Mean Difference