

Sleep disruption in children and adolescents with epilepsy

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RUNNING HEAD: SLEEP DISRUPTION IN CHILDHOOD EPILEPSY

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**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

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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

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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].

134 The bidirectional association between sleep and epilepsy is underpinned by various
 135 mechanisms, which are more and less well understood and are reviewed in detail elsewhere
 136 [12,13,14]. Its impact can extend beyond neurological and physiological changes to impact
 137 overall wellbeing, including poor cognitive and behavioural outcomes [8,15], problems with
 138 reading and writing [16], attentional deficits [17] and difficulties managing emotions [18].
 139 CWE experience considerable negative psychological and social consequences, which can be
 140 partially attributed to underlying sleep disturbances, highlighting the need for clinical
 141 acknowledgement. Moreover, a recent randomised controlled trial found the use of a sleep
 142 intervention during hospital visits resulted in improvements in sleep quality and sleep
 143 duration in CWE, compared to those who did not receive the intervention [19]. These results
 144 illustrate that sleep habits can be modified. An accurate quantification of the nature and range
 145 of sleep difficulties experienced by CWE is therefore potentially beneficial to help design
 146 interventions which can ameliorate negative clinical, psychological and social outcomes in
 147 this group.

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

153 This meta-analysis was conducted with the following goals:

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

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

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METHODS

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We performed a systematic review and meta-analysis in accordance with the Preferred

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Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [20].

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166 **Search strategy**

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A systematic literature search was conducted using the databases Medline, Embase,

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PsychINFO and PubMed in April 2019. Examples of key terms used included “sleep” OR “sleep

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problem*” OR “sleep disturbance” AND “Epilep*” OR “Epilepsy” OR “Paediatric Epilepsy”

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AND “child*” OR “adolescen*” (see Table 1 for a full list of search terms).

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+++++INSERT TABLE 1 HERE+++++

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174 **Study selection**

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Selection of papers for inclusion in the review was conducted by AW. Figure 1 illustrates the

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search process and results. The initial literature search returned 14,951 papers. After duplicates

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were removed 8838 papers were screened via the titles and abstracts. Papers that met the

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following criteria at this stage of eligibility screening were included for further review: 1)

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available in English, 2) reported on paediatric patients with epilepsy and included a measure of

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sleep 3) not animal studies 4) not review articles, case studies, editorials, letters or comments 5)

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reported on children or adolescents aged ≤ 18 years 6) sample size > 5 . Following the eligibility

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screening, the full text articles of the remaining studies were retrieved and screened against these

183 criteria *and* the following additional inclusion criteria: 1) No intellectual disability (ID) 2)
 184 Suitable data to extract for pooling of effect sizes (i.e. measures of means and SDs) 3) Inclusion
 185 of a healthy control group.

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187 ++++++INSERT FIGURE 1 HERE+++++

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190 **Data Extraction and Quality Review**

191 Nineteen papers met the eligibility criteria at full text screening and were included in the
 192 final analyses. Data extraction was performed by AW. A quality criteria checklist adapted
 193 from previous meta-analyses [21,22] was used to review the overall quality of studies (see
 194 Table 2). Each study was reviewed for their sample identification, instruments used to
 195 measure sleep and epilepsy classification based on a scale of 0 to 3 (poor to excellent). Each
 196 score was coded with a colour, 0 was coded as red for a poor score, 1 as orange for an
 197 adequate score, 2 as yellow for a good score and 3 as green for an excellent score. This
 198 resulted in a total score between 0-9. The total score was then divided by the maximum
 199 possible score of 9 to produce a quality value between 0 and 1.

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

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207 ++++++INSERT TABLE 2 HERE ++++++

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209 **Sleep measures**

210 The sleep parameters of interest were: 1) TST 2) Sleep difficulties 3) Sleep efficiency and 4)
 211 Sleep architecture. TST was measured with a combination of methods including PSG, 24-hour
 212 video-electroencephalography (EEG), actigraphy and self-report. Sleep difficulties in the
 213 retrieved papers were assessed via two questionnaires. The Children’s Sleep Habits
 214 Questionnaire (CSHQ) [23] is a parent report sleep measure. It consists of a global score and
 215 eight additional subscales, where higher scores are indicative of more severe sleep difficulties. A
 216 separate analysis was conducted using the subscales ‘parasomnias’, ‘sleep disordered breathing
 217 (SDB)’, ‘sleep onset delay’, ‘sleep duration’, ‘bedtime resistance’, ‘night wakings’, ‘sleep
 218 anxiety’ and ‘daytime sleepiness’. Other studies used the Sleep Behaviour Questionnaire (SBQ)
 219 [18] which is also a parent report questionnaire designed to measure duration and quality of
 220 sleep. It consists of a global score and 5 subscales: ‘parasomnias’, ‘parent/child interaction’,
 221 ‘sleep fragmentation’, ‘daytime drowsiness’ and ‘bedtime difficulties’, where higher scores are
 222 again indicative of more frequent sleep difficulties. Note that the SBQ and the CSHQ were
 223 initially treated separately, after which a subgroup analysis was conducted. This did not reveal
 224 significant differences, indicating that the type of questionnaire did not contribute substantially
 225 to the results. They were subsequently combined into one composite analysis for overall sleep
 226 difficulties. Sleep efficiency was measured via a combination of PSG and actigraphy. Finally,
 227 sleep architecture was measured via PSG and 24-hour video-EEG, as the only methods capable
 228 of providing this information.

229

230 **Statistical analyses**

231 All statistical analyses were performed in R, version 3.6.0 with RStudio, using the meta and
 232 metafor packages. Standard deviations and means for each of the sleep parameters across CWE
 233 and control groups were inputted into a spreadsheet. Separate meta-analyses were conducted to

234 produce pooled overall effect size estimates for sleep timing, sleep difficulties, sleep architecture
 235 and sleep efficiency. Each pooled effect size was expressed as a standardised mean difference
 236 (SMD, Hedge's g) with corresponding 95% confidence intervals. All analyses were computed
 237 using a random effect model. This model assumes that the true effect size varies between studies
 238 for two reasons: 1) sampling error within the studies and 2) differences in study population
 239 which result in real differences in effect size between studies [24]. It was therefore beneficial to
 240 use this model, given the range of participant characteristics across all studies, such as age and
 241 diagnoses of patient. For all analyses we used the Sidik-Jonkman estimator rather than the
 242 DerSimonian-Laird estimator which can lead to false positives when heterogeneity is high, and
 243 number of studies are low [25], which was the case in our sample.

244 Cochran's Q was used to assess whether there was statistically significant between-study
 245 heterogeneity present in the analysis. The amount of heterogeneity present was then quantified
 246 using Higgins I^2 with cut off values placed at 0, 25%, 50% and 75% corresponding to 'no',
 247 'moderate', 'substantial' and 'high' heterogeneity [26]. Between-study heterogeneity was
 248 explored when possible through subgroup analyses and meta-regressions in a mixed effect model
 249 across different variables, which were established *a priori*. The purpose of this was to understand
 250 whether the methodological approach of the studies had an impact on the overall results. Type of
 251 sleep instrument e.g., PSG, 24-hour video-EEG, actigraphy or questionnaire, was used as the
 252 categorical variable in the subgroup analyses. Meta-regression analyses were performed using
 253 age (years), sex (male %) and study quality score as continuous variables.

254 The robustness of the results was assessed in sensitivity analyses using outlier removal and
 255 the leave-one-out method, where, as studies are omitted one at a time, effect sizes are
 256 recalculated to assess the influence of individual studies on the overall effect size estimate. Risk
 257 of publication bias was assessed using visual inspection of contour-enhanced funnel plots, which
 258 plot standardised mean difference (Hedges g) in the x-axis against standard error, as a measure

259 for size of studies in the y-axis. Statistical testing for funnel plots was conducted using the
 260 Eggers test, and only for analyses consisting of 10 studies or more as the power of the test is too
 261 low to detect reliable bias estimates with less [27].

262

263 **RESULTS**

264 **Study characteristics**

265 Nineteen studies met the inclusion criteria and were used to assess the differences in sleep
 266 parameters between a total of 901 CWE with a mean age of 10.8 years (reported in 17 studies)
 267 and 1470 healthy children with a mean age of 10.8 years (reported in 17 studies). Nine studies
 268 used PSG to assess sleep parameters, of which three [9,30,37] used an adaptation night (data
 269 were reported for only the second night across all these studies), six [28,32,33,34,38,39] used
 270 one night of sleep only with no adaptation night and one study used 24-hour video-EEG [36]. Of
 271 the remaining nine studies, eight [6,8,16,18,29,31,40,41] used parent reported sleep
 272 questionnaires and one [35] used both actigraphy and questionnaires. Table 3 presents
 273 characteristics of the studies included in the meta-analysis.

274

275 +++++INSERT TABLE 3 HERE+++++

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278 ***Total sleep time***

279 Of the 12 studies that reported TST in CWE in comparison to healthy children, six studies
 280 reported TST via PSG, one via 24-hour video-EEG, one used actigraphy and four used self-
 281 reported sleep time. The study by Barreto et al. (2002) [28] consisted of two subgroups:
 282 ‘idiopathic generalised epilepsy’ and ‘idiopathic focal epilepsy’. They were initially treated with
 283 two separate analyses in order to avoid unit of analysis error. One subgroup (‘idiopathic focal
 284 epilepsy’) was revealed to be an outlier in subsequent sensitivity analysis so was not included in
 285 the meta-analysis for TST. Two studies were conducted by Gogou et al (2016, 2017) [33,34]

286 using the same control group. In this case, the ‘focal and generalised epilepsy’ group was kept in
287 the analysis as it had a larger sample size than the ‘rolandic epilepsy’ group, which was omitted.

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

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

297 *Sleep difficulties*

298 Nine studies were pooled into the meta-analysis for sleep difficulties. Five measured sleep
299 difficulties via the total scores on CSHQ and four via the SBQ. The random effects model for the
300 full sample initially revealed a non-significant effect (SMD= 2.08, 95% CI [-0.53, 4.69], $p=0.10$)
301 and substantial heterogeneity $I^2=97.3\%$, $Q=299.44$, $p<0.01$. Leave one out sensitivity analysis
302 and outlier analysis revealed that the study by Batista et al. (2007) [29] was an outlier as
303 evidenced by clear distortion on the effect size estimate. This outlier was removed, and the
304 random effects model was computed again and found to yield a significant result (SMD= 0.97,
305 95% CI [0.48, 1.46], $p=0.002$, see Figure 3) with reduced heterogeneity $I^2= 88.1\%$, $Q=59.04$,
306 $p<0.01$. This indicated that CWE suffer significantly more frequent and severe sleep difficulties
307 compared to healthy children. Batista et al. (2007) [29] was excluded in further analysis.

308

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

311 *Type of sleep difficulties*

312 A separate analysis was conducted on studies measuring sleep difficulties via the CSHQ,
313 taking advantage of the subscales which examine different aspects of sleep difficulties. Each
314 subscale of the questionnaire was separated as eight different outcomes and one total outcome to
315 conduct subgroup analyses (see Figure 4). We found that CWE had significantly higher scores
316 on the following subscales: night waking (SMD=0.42, 95% CI [0.16; 0.68], $p=0.01$),
317 parasomnias (SMD= 0.68, 95% CI [0.21; 1.15], $p=0.02$), sleep disordered breathing (SMD=
318 0.34, 95% CI [0.09; 0.59], $p=0.02$) and total sleep difficulties (SMD=0.92, 95% CI [-0.00; 1.83],
319 $p=0.05$). All remaining subscales yielded non-significant estimates.

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

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325 **Sleep Efficiency**

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327 Of 6 studies that measured sleep efficiency, five reported sleep efficiency via PSG and one
328 used actigraphy, all of which were pooled into the meta-analysis. The random effects model
329 revealed that CWE experience significantly reduced sleep efficiency compared to healthy
330 children (SMD= -0.71, [95% CI [-1.23; -0.19], $p=0.02$), see Figure 5. CWE had an average sleep
331 efficiency of 83% (compared to controls mean sleep efficiency of 89%). The mean difference
332 was 6% less for CWE and this ranged between 0.2% more to 10% less than controls across
333 studies. There was low heterogeneity amongst the studies ($Q= 8.22$, $I^2= 39.2$, $p=0.14$).
334 Sensitivity and outlier analysis did not reveal any influential cases, confirming the robustness of
335 the results.

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

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339 **Sleep Architecture**

340 Separate meta-analyses were conducted for percentage of sleep stages (see Figure 6): N1% (5
341 studies), N2% (6 studies), N3% (5 studies) and REM% (6 studies). The meta-analyses initially
342 revealed no significant differences for all sleep stages. Sensitivity analyses was conducted and
343 revealed two outliers [36,38] in N2% and one outlier [38] in N3% and REM%. Removal of all
344 outliers did not have a significant effect on the overall effect size estimate for N3% and REM%.
345 However, when the outliers for N2% were removed, the overall effect size estimate was found to
346 be of borderline significance (SMD=0.44, 95% CI [0.00; 0.87], $p=0.05$), indicating that CWE
347 had a higher percentage of N2 compared to healthy children. There was no substantial
348 heterogeneity detected ($I^2=0%$, $Q=1.27$, $p=0.74$), thus no further analyses were conducted.

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350 ++++++INSERT FIGURE 6 HERE+++++

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353 **Heterogeneity Analysis**

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

360 ***Total sleep time***

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

365 ***Sleep difficulties***

366 No significant subgroup differences were detected between the SBQ and CSHQ on the overall
367 effect size estimates for sleep difficulties ($Q=0.21$, $p=0.64$). The meta-regression analysis found
368 no significant associations between sleep difficulties and age ($p=0.16$, $R^2=22.71\%$), sex ($p=0.33$,
369 $R^2=2.78\%$) or quality of the study ($p=0.15$, $R^2=20.70\%$)

370 *Sleep Efficiency*

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

375

376 **Publication Bias**

377 Assessment of publication bias was conducted using a graphical approach and statistical
378 testing when there were ≥ 10 studies available. For TST the contour enhanced funnel plot
379 indicated some asymmetry. Closer inspection demonstrated that most of the studies fell in the
380 area of non-statistical significance (white shading) rather than the areas of significance (light
381 blue and blue shading), hence the funnel asymmetry was unlikely to be attributed to publication
382 bias [42]. This was confirmed via the Eggers test which revealed a non-significant effect $p=0.17$
383 (see S1 for funnel plot).

384

384 **DISCUSSION**

385 **Summary of findings**

386 Sleep difficulties are often reported by parents of CWE, however this relationship continues
387 to be under-recognized clinically. To our knowledge, this is the first meta-analysis to quantify
388 differences across self-reported and objective measures of sleep variables between CWE and
389 healthy children. A wide range of sleep parameters were considered within the meta-analysis
390 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

416 triggered at times of anxiety, which is heightened in CWE given the unpredictable nature of
417 seizures [46,47]. Additionally, it is important to note that commonly experienced parasomnias
418 such as confusional arousals and night terrors share similar gross semiology and behavioural
419 features to nocturnal seizures [48], which is why video monitoring forms such a crucial part of
420 the diagnostic workflow. It is therefore possible that parent reports are unable to capture this
421 difference in the absence of video-EEG data. SDB in CWE can be attributed to multiple factors
422 including side effect of antiepileptic drugs (AEDs) (see below) and disturbed sleep [49]. SDB
423 has been associated with a range of deficits including alterations to sleep and neurocognitive
424 impairments, and thus presents a risk for the developmental progress of CWE [33].

425 Our analysis of PSG variables revealed alterations to sleep architecture, specifically increased
426 N2% in CWE compared to healthy children. This may relate to the higher rates of SDB
427 observed, which often results in frequent arousals during sleep, increasing the time children
428 spend within the lighter stages of sleep [50]. Similarly, poor sleep efficiency was also apparent in
429 CWE, averaging 83%, which is below the average of 90% [51] in the healthy population and
430 may be indicative of poor seizure control as suggested by previous research [52].

431 Interestingly, nearly all studies within the meta-analysis included CWE on AED treatment,
432 which may in part contribute to the differences observed in sleep macro-structure and respiratory
433 parameters. AEDs can have varying effects on sleep architecture and sleep efficiency [53,54]. In
434 addition, polytherapy is found to exacerbate the occurrence of parasomnias [8] and ultimately
435 lead to more severe sleep difficulties in comparison to those on monotherapy [29]. Another side
436 effect of some AEDs is increased weight gain, which is a risk factor for apnoea events during
437 sleep due to the heightened risk of blockages of the upper airways [49,50]. SDB is also
438 associated with dysfunction of the cardiovascular system which is speculated to play a role in
439 sudden unexpected death in epilepsy, highlighting the potentially devastating consequences of

440 sleep disturbances in CWE [55]. Therefore, consideration of the type of AEDs administered and
441 the possible presence of an underlying sleep disorder is vital in the overall assessment of CWE.

442

443 **Strengths and Limitations**

444 In the current meta-analysis, strict inclusion criteria were set in order to produce the most
445 reliable findings, which has both strengths and limitations. One strength was the inclusion of
446 studies employing a variety of sleep instruments, as this provides both subjective and objective
447 quantification of sleep disturbances in CWE. This also allowed us to investigate a range of
448 aspects related to sleep, which is important given the complexity of sleep as a behaviour.
449 Another criterion was only including studies comparing CWE to healthy children. This provided
450 a reference point for understanding the specific sleep disruptions that are present in CWE, but
451 also resulted in the loss of potentially informative studies that did not include a control group.
452 Nonetheless, the findings from studies that were not included as they did not have a control
453 group [43,52,56,57] were consistent with those in the review. They also emphasised the
454 association with behavioural and psychiatric co-morbidities [56,57]. We did not have the scope
455 to examine the impact of psychopathologies on sleep within this meta-analysis, however this is
456 an important area of future research given the importance of these issues to patients.

457 Similarly, this meta-analysis extends the results of a previous review investigating sleep
458 problems in CWE, by providing the first empirical synthesis of the data [58]. This review
459 highlighted the need for longitudinal designs to be conducted, in order to draw stronger
460 conclusions on the association between sleep and epilepsy. It was also noted that results from
461 parent-report measures are likely to be influenced by their own anxieties. However, the current
462 meta-analysis demonstrates that regardless of whether subjective or objective measures are used,
463 there are clear and consistent differences between CWE and healthy children across sleep
464 parameters.

465 The majority of included studies combined epilepsy types into one broad group e.g.,
466 generalised and focal epilepsy. This is particularly problematic given that ictal and interictal
467 indicators of epilepsy vary with the sleep/wake cycle in a way which is specific to the type of
468 epilepsy, e.g., focal epilepsies with secondary generalisation are more vulnerable to sleep
469 disturbances compared to generalised epilepsies [45], while interictal manifestations of focal
470 epilepsies vary across the sleep-wake cycle [59]. In addition, the underlying neurobiological
471 basis of some epilepsies may tie in closely with the brain networks involved in sleep generation
472 and regulation, e.g., the suggestion that generalised spike-wave discharges make use of
473 thalamocortical networks normally involved in the generation of sleep spindles [60]. These and
474 other issues concerning the relationship between epilepsy and sleep are discussed in detail in
475 several reviews [61,62]. Finally sleep disturbances appeared to be more pronounced in those
476 with drug resistant epilepsy, as supported by previous research [38]. This is to be expected given
477 the use of multiple AEDs and experience of recurrent uncontrollable seizures, all of which
478 contribute to disruptions to sleep [63]. However, the relative contribution of AEDs and recurrent
479 seizures to sleep habits is difficult to disentangle. Furthermore, the lack of reporting on seizure
480 control using standardised measures meant we did not have the ability to investigate the
481 influence of this factor. Future studies are needed which are focussed much more closely on
482 individual epilepsy syndromes in terms of their relationship with sleep, with a specific need for
483 investigation of paediatric epilepsies, given the importance of adequate sleep for brain
484 development [64].

485 Another important factor which has been briefly mentioned above is that across the majority
486 of included studies, children were receiving AEDs. The majority of AEDs have been established
487 to impact sleep architecture [45,50], and issues such as drowsiness are commonly experienced
488 [65]. Despite reporting treatment use, many of the studies failed to subdivide participants by
489 AED type, and hence we were not able to investigate the impact of AEDs specifically. The fact

490 that studies of rolandic epilepsy, which is generally not treated with AEDs, showed a similar
491 tendency to the overall results, suggests that the effects we observed are not entirely the result of
492 treatment. However, future studies should detail the type and dose of AEDs in order to allow
493 specific investigation of their impact.

494 We excluded studies involving co-morbid IDs, on the basis that they would affect
495 interpretation of the results, making it too difficult to differentiate the effects of epilepsy from the
496 effects of an ID, which are known to impact sleep [22]. This ultimately led to the exclusion of
497 studies focussed on the more severe epilepsies e.g., epileptic encephalopathies, which are
498 typically associated with serious cognitive and neuropsychological deficits. However, in practice
499 this would suggest that the clinical importance of sleep disturbances across the full range of
500 epilepsies would be expected to be higher than estimated by our meta-analysis, with our results
501 representing a lower bound. Nevertheless, previous research investigating sleep habits in
502 children with ID where epilepsy is prevalent, such as Angelman syndrome and tuberous sclerosis
503 complex, have demonstrated that the presence of epilepsy in ID can have a cumulative effect on
504 sleep disturbances [66].

505 Finally, studies measuring sleep architecture used two different scoring systems for sleep:
506 Rechtschaffen & Kales (R&K) [67] and American Academy of Sleep Medicine (AASM) [68].
507 Previous research has found significant differences between the two when measuring children's
508 and adolescents' sleep, including differences in N1, N2 and REM [69]. Unfortunately, sensitivity
509 analysis could not be conducted to assess the influence of scoring systems, as there were
510 insufficient studies. This limitation does not affect the majority of the results, and indeed the
511 effects seen in terms of sleep architecture were generally smaller than for other measures of sleep
512 disturbance.

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514

515 **Methodological considerations**

516 There are several methodological considerations that may aid with standardisation between
517 studies in the future. **The first is that within this meta-analysis, some sleep parameters were**
518 **extracted from a broad range of measurements including both objective (e.g., actigraphy, PSG)**
519 **and subjective (e.g., sleep diaries, questionnaires) tools. Within the context of our statistical**
520 **analysis (see the Heterogeneity Analysis section above), the overall conclusions did not depend**
521 **on the details of these instruments. Due to the limited number of papers in this area, we believe**
522 **that including as wide a range of studies as possible and analysing the impact of their**
523 **heterogeneity statistically was the most favourable approach. However, more broadly, comparing**
524 **sleep parameters derived from different methodological approaches is not ideal, and points**
525 **towards the need for more widespread adoption of some standard and widely tolerated tools such**
526 **as actigraphy and questionnaires within future studies of this type.**

527 In our analyses for sleep problems, the majority of the data were derived from parent report
528 measures. Parents of children with chronic diseases such as epilepsy have heightened parental
529 anxiety and stress, and reports may be influenced by parents' own perceptions and result in
530 overestimation of problem [70]. Similarly, parents are less involved in their child's bedtime
531 routines as they grow older, so may be less aware of their sleep patterns, especially in
532 adolescence [71]. Another problem that arises with parent report measures, which has been
533 previously discussed, is the difficulty faced when distinguishing nocturnal seizures from NREM
534 parasomnias. In order to resolve this issue, we recommend that studies should not rely heavily on
535 questionnaire measures in such cases but rather consider videos or preferably video-EEG. Future
536 research should also aim to use parent-proxy measures in younger children and self-reports in
537 older groups or preferably use objective measures such as actigraphy to provide a more accurate
538 measure of habitual sleep patterns. We have previously found that actigraphy is well tolerated,
539 even in children with severe ID [72].

540 In our analysis of sleep architecture, one study [38] measured percentage of sleep stages in
541 reference to sleep period time whereas the remaining studies used TST. Interestingly, this study
542 was detected as an outlier in sensitivity analysis and when removed, revealed a significant result
543 for percentage of N2. This suggests that the non-significant result was driven by differences in
544 sleep scoring rather than differences in sleep architecture. Other studies were not able to be
545 included in the analysis of some sleep stages due to studies combining stages, which made it
546 difficult to compare them. We recommend that future studies explicitly state what scoring
547 parameters were used for sleep variables and to report sleep stages individually, rather than
548 collating them together e.g., N1+N2. Finally, future studies should specify the type of epilepsy
549 and seizures, and when possible the epilepsy syndromes, aetiology, disease severity and AED
550 use, given the potential influence of these factors in CWE. Introducing such modifications to
551 future studies would result in easier comparison of studies and allow for richer data to be meta-
552 analysed.

553

554 **Conclusion**

555 This meta-analysis found that CWE suffer from widespread objective and subjective sleep
556 disruptions in comparison to healthy children. Improving the specificity of this finding requires
557 future studies which investigate individual epilepsy syndromes, with standardised subjective and
558 objective sleep markers, and clear reporting of AEDs. **At the present time, habitual sleep patterns**
559 **are not consistently evaluated by specialists in the routine care or diagnosis for CWE**, which is
560 likely to be attributed to the complexity of the disease and the primary goal of treating seizures.
561 However, epilepsy is a chronic and unpredictable disease, and the association with sleep
562 disruptions only further negatively impacts the QOL in the child and family. **The present results**
563 **indicate the potential benefit for childhood epileptologist to consider the importance of sleep in**
564 **epilepsy management.** Furthermore, future research should aim to develop behavioural

565 interventions to tackle sleep difficulties early on in childhood epilepsy in order to reduce the
566 detrimental impacts the disease and additional co-morbidities may have on developmental
567 outcomes.

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Practice points

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1) Children with epilepsy experience both objective and subjective disruptions to their
573 sleep in comparison to healthy children that require clinical acknowledgment.

574

2) Co-occurring intellectual disability were excluded as this group are understood to be at
575 an increased risk for sleep disturbances. This raises the possibility that our results
576 likely capture the lower estimate of the range of sleep disruptions. It is important that
577 clinicians consider the impact of these factors in epilepsy management.

578

3) Children with drug resistant epilepsy appear to be most vulnerable to sleep
579 disturbances, although the relative contribution of anti-epileptic medications or
580 recurrent seizures is not clear.

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4) Routine screening of sleep habits and the inclusion of a sleep specialist as part of the
582 diagnostic process are recommended for children with epilepsy.

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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.

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617

618 **Authors contributions**

619 All authors contributed to the manuscript as follows:

620 *Study design and concept:* AW, AB, CR.

621 *Acquisition and analysis of data:* AW

622 *Interpretation of the data:* All authors.

623 *Drafting of the manuscript:* All authors.

624 *Approval of the final manuscript:* All authors.

625

626 **APPENDIX A**

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

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830 **Figure Legends**

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832 **Figure 1.** Flowchart of search process

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834 **Figure 2.** Forest plot for standardised mean difference (Hedge's g) in sleep time between
835 children with epilepsy and healthy controls. The bold vertical line in the middle represents the
836 line of null effect. Black horizontal lines represent 95% confidence intervals and the squares are
837 the point estimate of the study result. The prediction interval represents the range in which the
838 point estimate of 95% of future studies will be expected to fall in. The diamond at the bottom of
839 the figure plots the overall effect and the corresponding confidence interval.

840

841 **Figure 3.** Forest plot for standardised mean difference (Hedge's g) in total sleep problems
842 between children with epilepsy and healthy children. The bold vertical line in the middle
843 represents the line of null effect. Black horizontal lines represent 95% confidence intervals and
844 the squares are the point estimate of the study result. The prediction interval represents the range
845 in which the point estimate of 95% of future studies will be expected to fall in. The diamond at
846 the bottom of the figure plots the overall effect and the corresponding confidence interval.

847

848 **Figure 4.** Forest plot for standardised mean difference (Hedge's g) in type of sleep difficulties on
849 CSHQ between children with epilepsy and healthy children. The bold vertical line in the middle
850 represents the line of null effect. Black horizontal lines represent 95% confidence intervals and
851 the squares are the point estimate of the study result. The prediction interval represents the range
852 in which the point estimate of 95% of future studies will be expected to fall in. The diamond at
853 the bottom of the figure plots the overall effect and the corresponding confidence interval.

854

855 **Figure 5.** Forest plot for standardised mean difference (Hedge's g) in sleep efficiency (%)
856 between children with epilepsy and healthy children. The bold vertical line in the middle
857 represents the line of null effect. Black horizontal lines represent 95% confidence intervals and
858 the squares are the point estimate of the study result. The prediction interval represents the range
859 in which the point estimate of 95% of future studies will be expected to fall in. The diamond at
860 the bottom of the figure plots the overall effect and the corresponding confidence interval.

861

862 **Figure 6.** Forest plot for standardised mean difference (Hedge's g) in percentage of N1, N2, N3
863 and rapid eye movement sleep between children with epilepsy and healthy children. The bold
864 vertical line in the middle represents the line of null effect. Black horizontal lines represent 95%
865 confidence intervals and the squares are the point estimate of the study result. The prediction
866 interval represents the range in which the point estimate of 95% of future studies will be
867 expected to fall in. The diamond at the bottom of the figure plots the overall effect and the
868 corresponding confidence interval.

869

870 **Appendix A:** Supplementary data

871

872 **Figure S1:** Contour enhanced funnel plot. Standardised mean difference in total sleep time
873 between children with epilepsy and healthy children plotted against standard errors. Black circles
874 refer to the included studies. The light blue shaded region corresponds to p-values below 0.01,
875 the blue shaded region corresponds to p-values between 0.05 and 0.01, the dark blue shaded
876 region corresponds to p-values between 0.1 and 0.05.

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 Hypnerychthemeral 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)

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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

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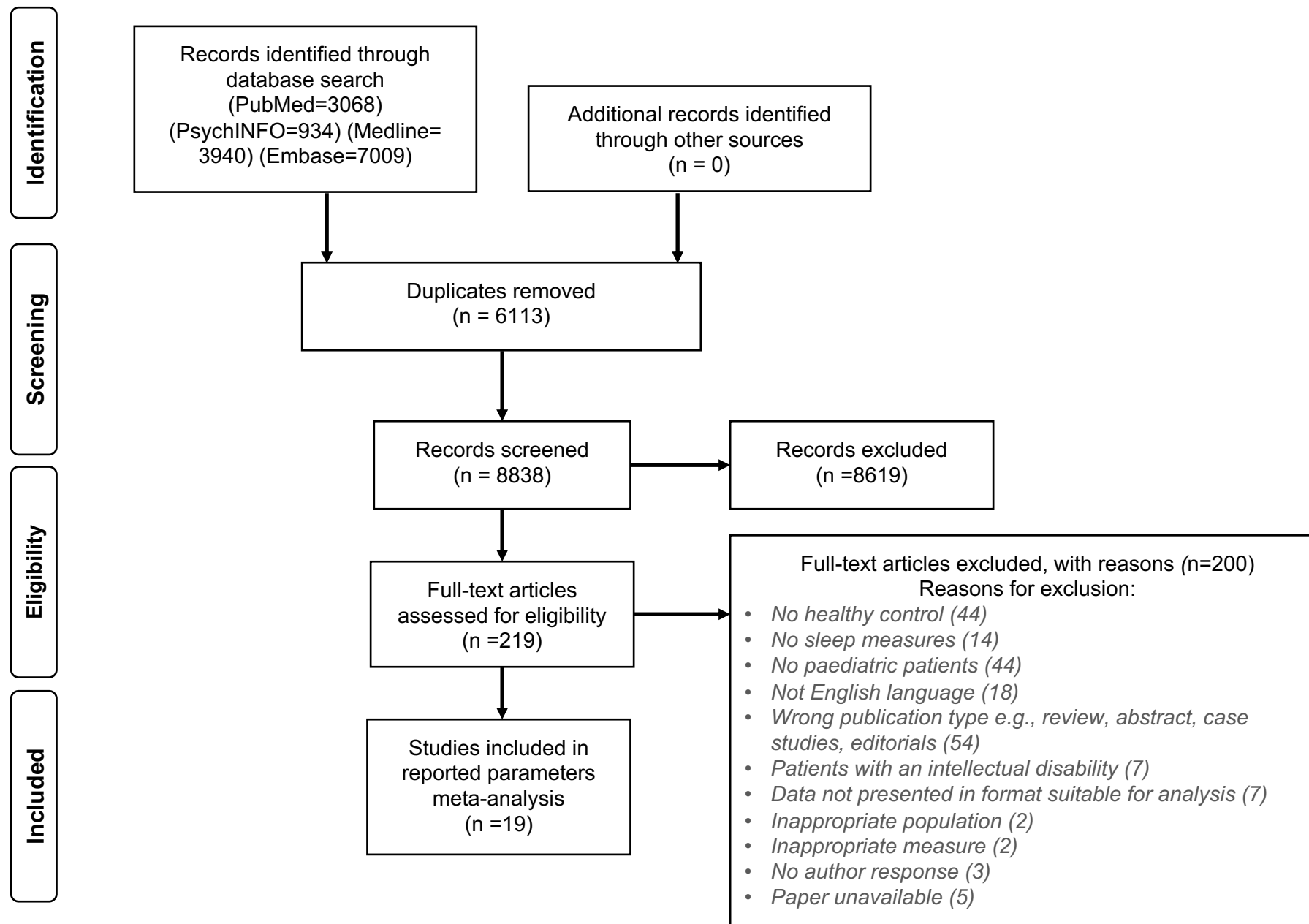
Table 3. Study characteristics

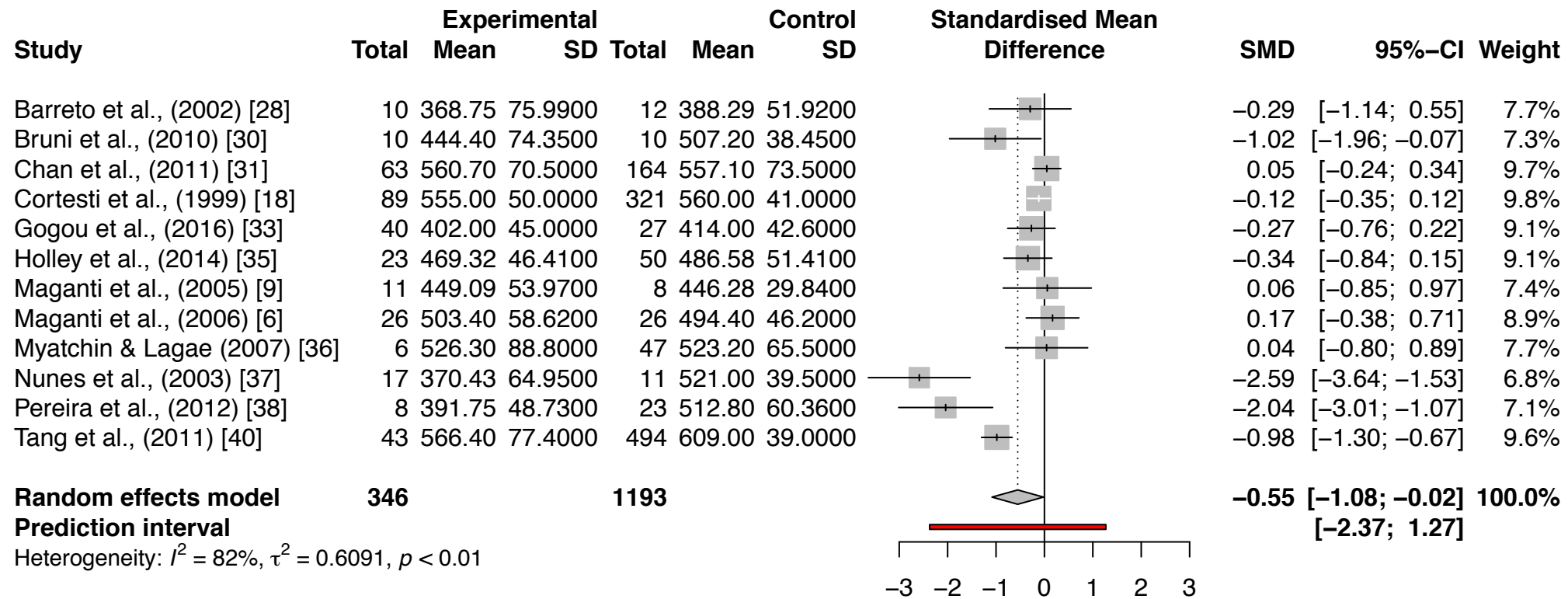
Study	Sample size		Age(Y, mean)		Sex (male%)		Diagnosis	Sleep measure	Sleep variable	Medication	Adaptation night	Quality criteria			Overall quality
	Epilepsy	Controls	Epilepsy	Controls	Epilepsy	Controls						Epilepsy	Sample	Sleep	
Barreto <i>et al</i> , 2002[28]	10	12	12.2	10.8	40	33	10 Idiopathic generalised 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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

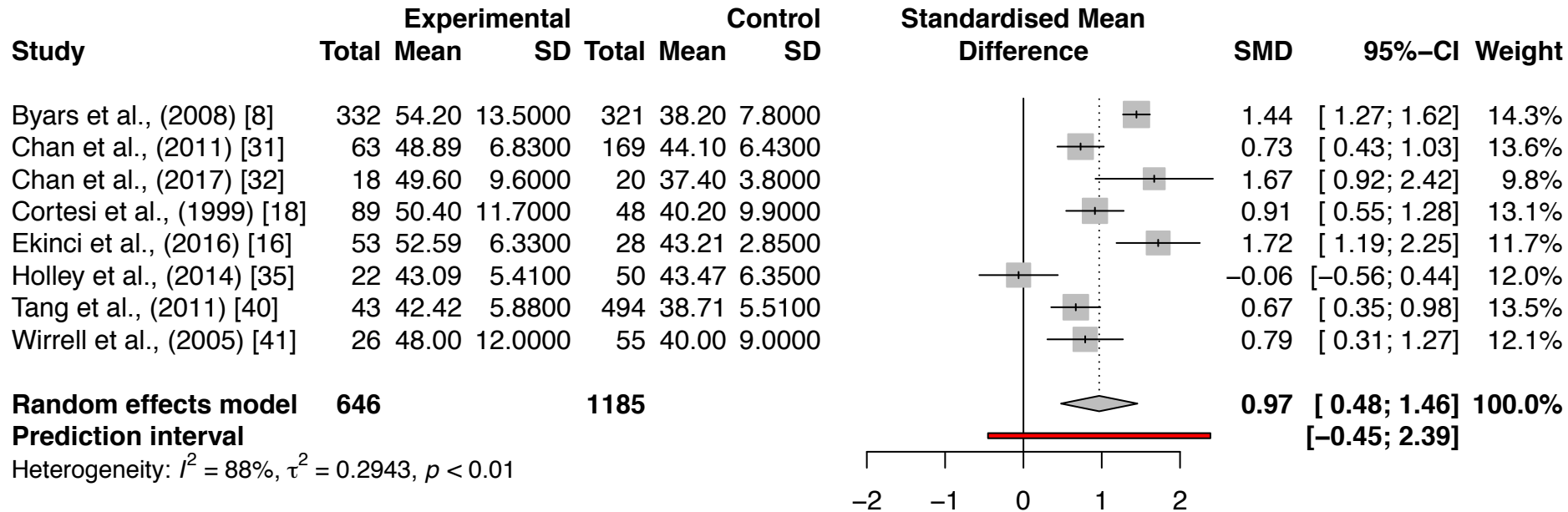
Holley <i>et al</i> , 2014 [35]	23	50	10	9.3	48	44	Childhood absence epilepsy, generalised tonic clonic seizures, focal seizures and not known	CSHQ Actigraphy	CSHQ total score and subscales Actigraphy	96% on AEDs	N/A	3	2	3	0.89
Maganti <i>et al</i> , 2005 [9]	11	8	13.4	14.3	45	50	5 Childhood absence, 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 2012 [38]	8	23	11.9	8.3	50	39	5 Idiopathic localisation related epilepsy 3 Symptomatic localisation related epilepsy	PSG	TST, SE(%), N1, N2, N3 and REM%	100% on AEDs	No	2	1	2	0.56
Shaheen <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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

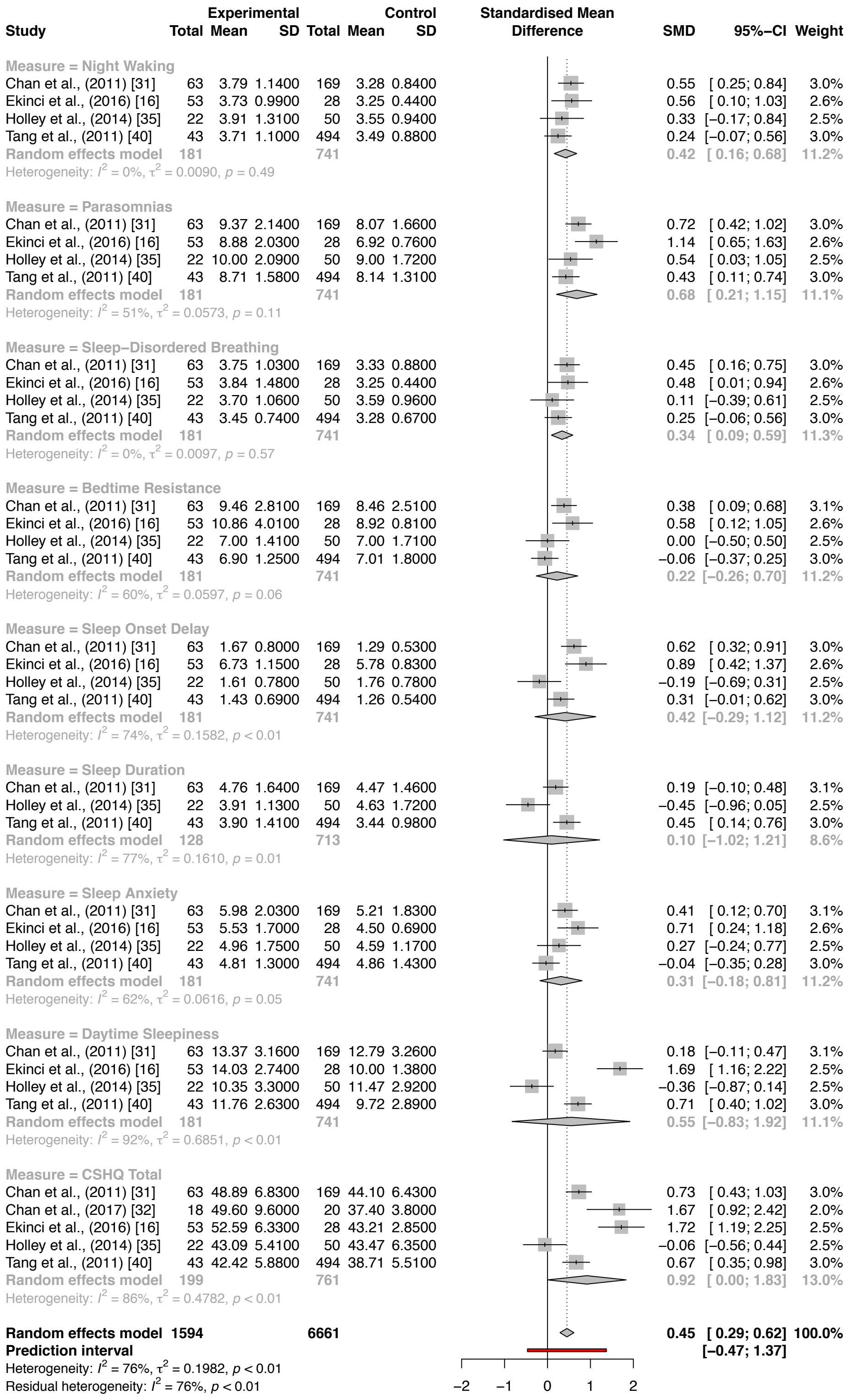
Abbreviations: AEDs= Anti-epileptic drugs, CSHQ= Children's sleep habits questionnaire, EEG= Electroencephalography, PDSS= Paediatric daytime sleepiness scale, PSG= Polysomnography, PSQ= Paediatric sleep questionnaire, REM= Rapid eye movement, SBQ= Sleep behaviour questionnaire, SE= Sleep efficiency,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

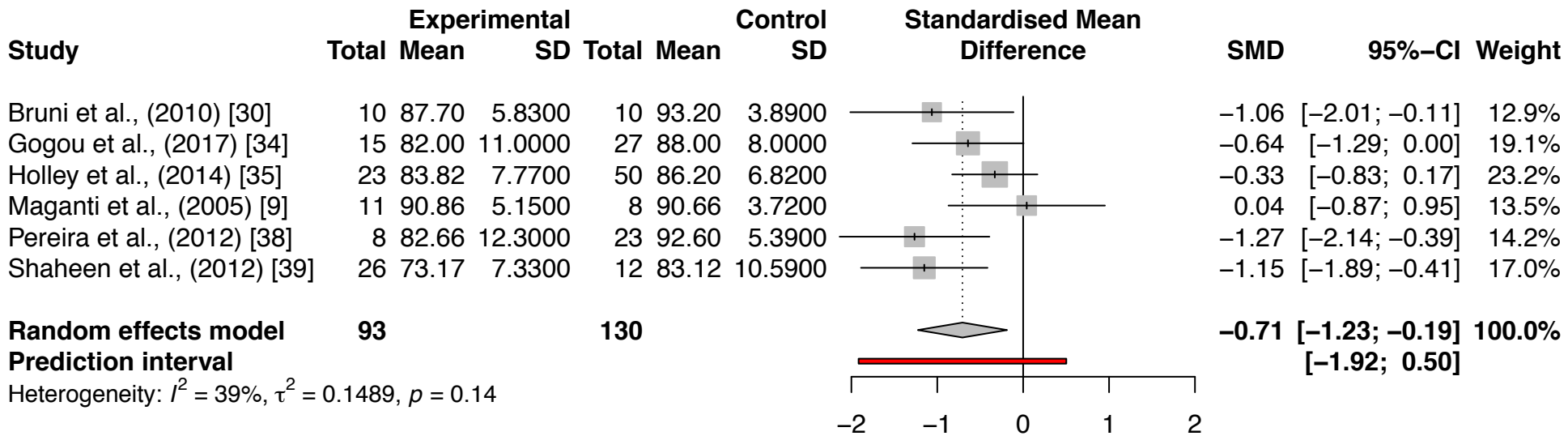
Figure



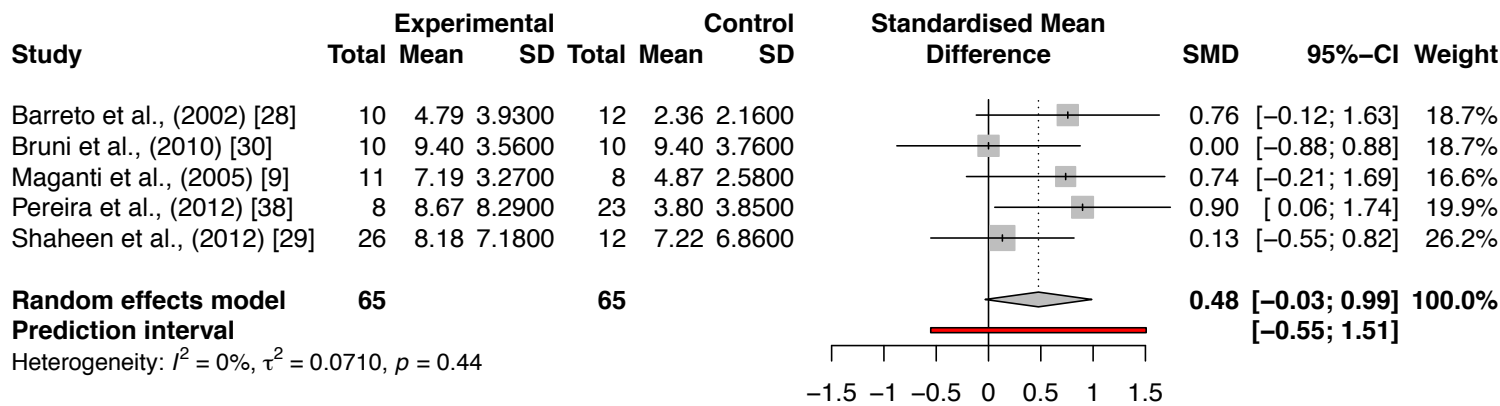




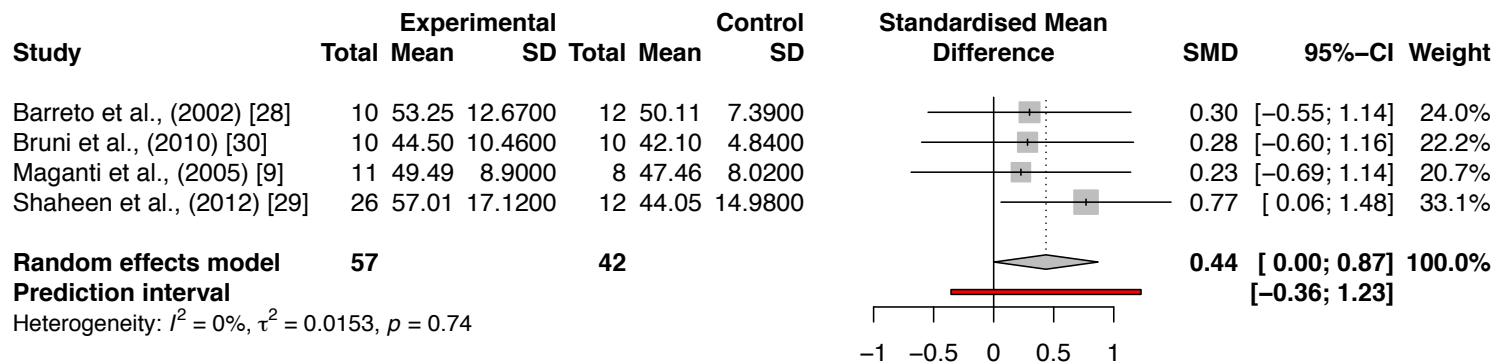




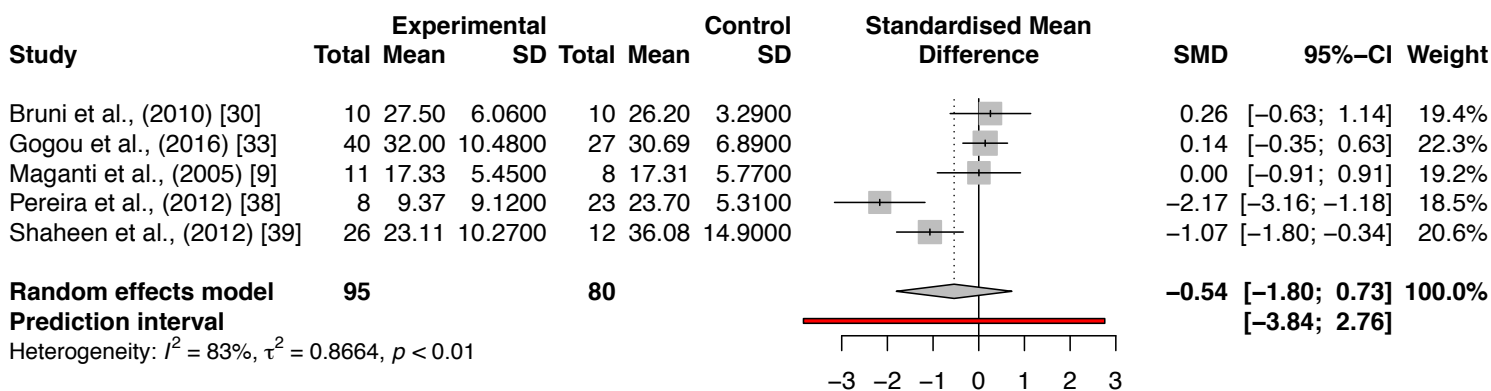
1. N1%



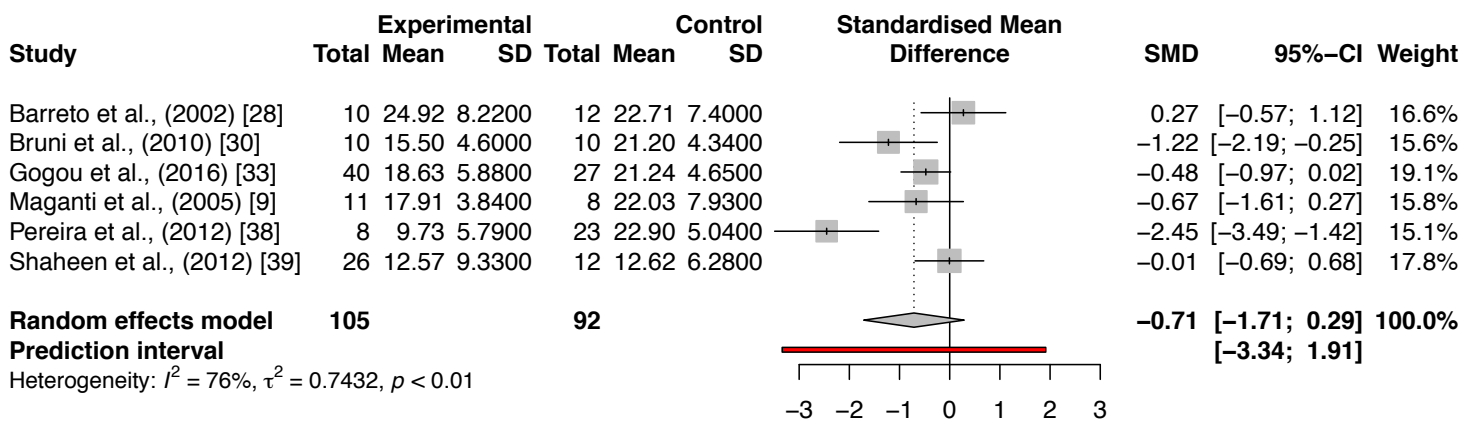
2. N2%



3. N3%



4. REM%



Figure

