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Sleep in adults with ADHD: Systematic review and meta-analysis of subjective and objective studies

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ABSTRACT

Sleep alterations associated with adulthood ADHD are poorly understood. Here, we conducted the first meta-analysis of sleep studies in adults with ADHD. Based on a pre-registered protocol (PROSPERO-CRD42017065407), we searched Pubmed, Ovid and Web of Knowledge databases through August 3rd, 2017, with no language or publication type restrictions, and contacted study authors for unpublished data/information. From a pool of 8812 references, we retained 13 studies. Random-effects models were performed and study quality was rated using the Newcastle-Ottawa Scale. Compared to adults without ADHD, those with ADHD significantly differed in seven out of nine subjective parameters (Standardized Mean Difference, SMD, ranging from 0.56 to 1.55) and two out of five actigraphic parameters [SMD (95% CI): sleep onset latency: 0.80 (0.46–1.14); sleep efficiency: −0.68 (−1.03, −0.34)]. No significant differences were detected for polysomnographic parameters. We conclude that, whereas subjectively reported sleep problems are significantly associated with ADHD in adults and should be systematically screened during the clinical interview, additional research is needed to understand if they are underpinned by objective sleep alterations.

1. Introduction

With a worldwide estimated prevalence of about 5% (Polanczyk et al., 2014), Attention-Deficit/Hyperactivity Disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood. Impairing symptoms of ADHD persist into adulthood in about 65% of cases (Faraone et al., 2006), with a pooled prevalence of adulthood ADHD around 2.5% (Simon et al., 2009).

1.1. Sleep in children with ADHD

It is well established that ADHD is frequently comorbid with other psychiatric disorders, including oppositional defiant disorder, conduct disorder, mood and anxiety disorders, and substance use disorders (Faraone et al., 2015). Among other conditions possibly associated with ADHD, in the past decade there has been a mounting interest for the relationship between ADHD and sleep disturbance (Cortese et al., 2013). Meta-analytic evidence (Cortese et al., 2009; Diaz-Roman et al., 2016; Sadeh et al., 2006) based on this increasing body of research shows that, compared to non ADHD controls, children with ADHD present with significantly more subjectively reported sleep problems and, to some extent, also objective sleep alterations, as measured by actigraphy or polysomnography (PSG). Of note, one meta-analysis (Cortese et al., 2009) found that such alterations were not accounted for by comorbid psychiatric conditions or by the pharmacological treatment of ADHD.

1.2. Sleep in adults with ADHD

By contrast, evidence on sleep alterations in adults with ADHD is mixed and has not been meta-analyzed yet. While some studies reported an association between ADHD and sleep onset latency, poor sleep efficiency, high nocturnal motor activity, and restless legs syndrome in adults (e.g., Bogdan and Reeves, 2016; Fargason et al., 2013; Philipsen et al., 2005), others failed to find significant difference in important objective sleep parameters such as sleep latency, number of

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sleep awakenings, and total time in bed (Kooij et al., 2001). The inconsistency among studies may be accounted for by possible confounding factors, such as, among others, different methods to diagnose ADHD and lack of a comparison group in some studies (e.g., Fisher et al., 2014; Langberg et al., 2016).

Given these mixed findings, a meta-analysis that takes into account possible confounding factors is timely to elucidate if and to which extent ADHD is significantly associated with subjectively reported and/or objectively measured sleep alterations, possibly replicating findings from children. Indeed, given developmental changes in sleep patterns and ADHD symptoms, it should not be assumed that sleep findings in children are necessarily identical to those in adults with ADHD.

The focus on sleep in individuals with ADHD is of relevance for the management of ADHD. Such problems can be a significant source of distress for the patients and their families (e.g., Hvolby et al., 2008; Owens et al., 2000; Owens et al., 2013). They may also worsen or mimic symptoms of ADHD (Dahl, 1996). Therefore, the appropriate assessment and treatment of sleep problems might improve the quality of life of individuals referred for ADHD assessment and reduce the severity as well as the impairment of ADHD. However, in order to appropriately manage sleep complaints in patients with ADHD, it is necessary to better characterize their profile and understand the specific sleep alterations underlying these complaints.

Here, we conducted the first systematic review with meta-analysis of studies reporting subjective or objective sleep parameters in adults with a diagnosis of ADHD according to standardized criteria for the diagnosis of ADHD. Give the exploratory nature of this meta-analysis, no *a priori* hypotheses were formulated.

2. Method

We followed the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). The protocol of this systematic review was registered in PROSPERO (CDR 42017065407). Data were extracted from the published reports (journal article) of the studies, or obtained by study authors. The PRISMA checklist is reported in the Supplemental material 1.

2.1. Types of studies

Case-control studies comparing subjective and/or objective sleep parameters in adults with and without ADHD were included.

2.2. Types of participants

2.2.1. Inclusion criteria

Studies on adults (≥18 years) with a diagnosis of ADHD established according to the *International Classification of Diseases* (ICD) (any version) or the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (any version) were eligible. Studies had also to include a comparison group of adults without ADHD.

2.2.2. Exclusion criteria

We excluded studies where participants presented with ADHD symptoms above a specific cut-off in ADHD scales, without meeting formal criteria for ADHD as per DSM or ICD criteria.

2.3. Outcomes

Any subjective sleep parameter from any sleep questionnaire (e.g., sleep onset latency, psychosomatic symptoms during sleep onset, sleep duration, night awakenings, sleep quality, sleep efficiency, restorative value of sleep (i.e., feeling rested after waking up), daytime sleepiness, general sleep problems) and/or any objective sleep parameter (e.g., actigraphy: sleep onset latency, true sleep, assumed sleep time, actual wake time, sleep efficiency; PSG: sleep onset latency, stage 1 sleep %, stage 2 sleep %, slow wave sleep %, REM %, REM latency, total sleep time, sleep efficiency, wake time %) were eligible. We included any parameter present in at least two studies.

2.4. Search strategy/syntax

The following electronic databases were searched until August 3rd, 2017, with no language/date/type of document restrictions: Pubmed (Medline), Ovid databases (PsycInfo, Embase + Embase classic, Ovid Medline), and Web of Knowledge databases (Web of science (Science Citation Index Expanded), Biological abstracts, Biosis, Food science and technology abstracts). Additional details on the search strategy/syntax, including search terms for each database, are reported in the Supplemental material 2. References of included studies were scanned to find any potential pertinent study detected with the electronic search.

2.5. Study selection

Retrieved references were independently screened and blindly double-coded for eligibility by two study authors. Any disagreement was resolved by a senior author. If needed, study authors were contacted to gather missing/additional information.

2.6. Study quality/bias assessment

Study quality was assessed using the Newcastle-Ottawa Scale for case control studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) focusing on the following items: case definition, representativeness of the cases, selection of controls, definition of controls, comparability of cases and controls on the basis of the design or analysis, ascertainment of exposure, non-response rate.

2.7. Data extraction and statistical analysis

Data extraction was performed blindly by two of the authors, and any discrepancy between the two was resolved by consensus with a third senior author. We contacted study authors when necessary. Data extracted from each study included: first author, publication year, country where the study was conducted, participants details (number, age, sex, medication use, ADHD subtypes, and comorbidities), sleep measures (mean, SD), and study key findings.

Random-effects models were used to compute effect size for each sleep variable. We calculated the standardized mean difference (SMD), with 95% confidence interval (CI), with the correction of Hedges (Hedges, 1981) to avoid bias due to sample size. The pooled SMD, and related 95% CI, was calculated through the inverse variance method, and its statistical significance was assessed by the Z statistic. I^2 (Higgins and Thompson, 2002) was calculated to quantify heterogeneity among studies. Finally, Egger's test (Egger et al., 1997) and funnel plots were used to evaluate publication bias. Analyses were performed using Review Manager 5.3 (http://community.cochrane.org/tools/review-production-tools/revman-5) and Comprehensive Meta-Analysis (https://www.meta-analysis.com/) software.

3. Results

3.1. Studies included in the meta-analysis

From a pool of 8812 non-duplicate potentially relevant references, 13 studies (Arns et al., 2014; Baird et al., 2012; Bioulac et al., 2016; Boonstra et al., 2007; Brevik et al., 2017; Frye et al., 2017; Kooij et al., 2001; Philipsen et al., 2005; Sobanski et al., 2008, 2016; Tonetti et al., 2017; Van Veen et al., 2010; Weibel et al., 2017) were retained for the

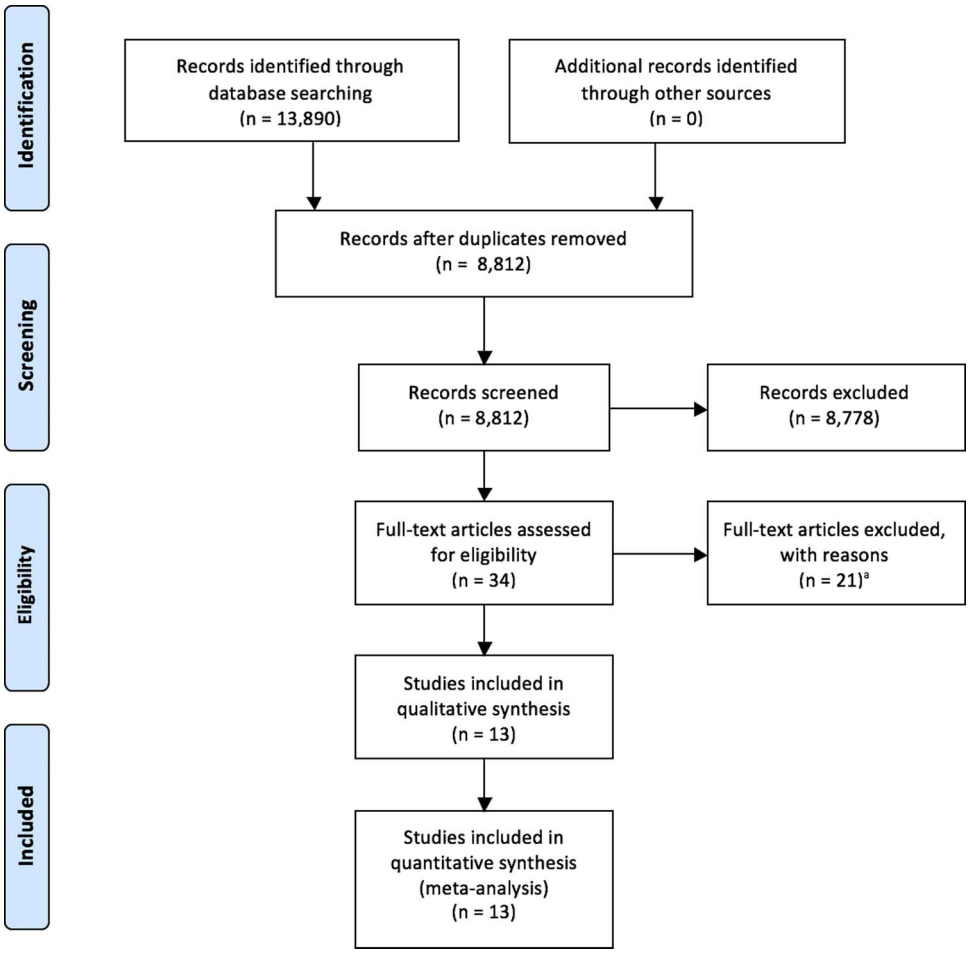

Fig. 1. Flow Diagram of Selection Process. [a]Reasons for the exclusion of these studies are listed in the Supplemental material 3.

meta-analysis. A detailed description of selection process is shown in the PRISMA flow diagram (Fig. 1). Reasons for the exclusion of studies assessed in full-text length are listed in Supplemental material 3. Results of study quality/bias assessment are shown in Supplemental material 4.

Table 1 reports the main characteristics of the included studies, which were all cross-sectional. Five studies (Bioulac et al., 2016; Boonstra et al., 2007; Philipsen et al., 2005; Sobanski et al., 2008, 2016) included both subjective and objective sleep measures, four reported only subjective measures (Arns et al., 2014; Brevik et al., 2017; Kooij et al., 2001; Weibel et al., 2017), in three studies (Baird et al., 2012; Tonetti et al., 2017; Van Veen et al., 2010) actigraphy was the only method employed for assessment, whereas one study (Frye et al., 2017) was based only on PSG.

As for medication status, one study (Boonstra et al., 2007) recruited ADHD medications naïve participants. Participants stopped medications before starting the assessment in five studies (Bioulac et al., 2016; Kooij et al., 2001; Philipsen et al., 2005; Sobanski et al., 2008; Van Veen et al., 2010), in other five studies participants were receiving pharmacological treatments during the assessment (Baird et al., 2012; Brevik et al., 2017; Frye et al., 2017; Tonetti et al., 2017; Weibel et al., 2017), and information on medication status was not available from two studies (Arns et al., 2014; Sobanski et al., 2016). Comorbidity rates with other psychiatric disorders were not reported in three studies (Arns et al., 2014; Boonstra et al., 2007; Sobanski et al., 2016), whereas all other studies recruited adults with comorbid psychiatric conditions, with the exception of one (Sobanski et al., 2008), focusing on participants without comorbidity.

The Rechtschaffen and Kales criteria (Rechtschafen & Kales, 1968) were applied as scoring rules in all studies in which PSG was used, except for one study (Bioulac et al., 2016) in which either those criteria or the criteria proposed by the American Academy of Sleep Medicine (Iber et al., 2007) were followed.

3.2. Subjective sleep parameters

Compared to adults without, those with ADHD presented with significantly longer sleep onset latency (SMD: 0.67, 95% CI: 0.41, 0.92, $p < 0.01$), significantly more psychosomatic symptoms during sleep onset (SMD: 0.64, 95% CI: 0.21, 1.07, $p = 0.04$), night awakenings (SMD: 0.56, 95% CI: 0.40, 0.73, $p < 0.01$), general sleep problems (SMD: 1.55, 95% CI: 0.72, 2.39, $p = 0.003$), significantly lower sleep quality (SMD: 0.69, 95% CI: 0.38, 0.99, $p < 0.01$), sleep efficiency (SMD: -0.55, 95% CI: -0.83, -0.27, $p = 0.01$), and significantly higher daytime sleepiness (SMD: 0.75, 95% CI: 0.29, 1.21, $p = 0.01$).

However, adults with and without ADHD did not significantly differ in sleep duration and restorative value of sleep (Table 2, Fig. 2). Heterogeneity, as indicated by I^2, ranging from low to high, was as follows: 0% (night awakenings, psychosomatic symptoms during sleep onset, and sleep efficiency), 37% (sleep quality), 54% (sleep onset latency), 70% (sleep duration), 83% (general sleep problems), 86% (daytime sleepiness), 90% (restorative value of sleep). Egger's tests were not significant for any outcome (Table 2).

3.3. Objective sleep parameters

Considering actigraphic values, adults with ADHD showed a significantly higher sleep onset latency (SMD = 0.80, 95%

Table 1
Characteristics of studies included in the meta-analysis.

First author (year)	Country	*N* (males)[a]	Mean age (SD)	Control group[b]	Subtype	Medication	Comorbidity	Sleep measure	Nights recorded	Main results found
Arns (2014)	The Netherlands	ADHD = 19 (non-reported); Control = 28 (13)	ADHD = 34.1 (11.33); Control = 34.1 (9.72)	Healthy controls	Non-reported	Non-reported	Non-reported	PSQI	–	↑ PSQI ↑ Sleep latency ↓ Sleep duration
Baird (2012)	UK	ADHD = 13 (8); Control = 19 (12)	ADHD = 31.3 (11.7); Control = 32.3 (13.3)	Healthy controls	Non-reported	4 (3 stimulants, 1 atomoxetine)	1 depression, 4 anxiety, 7 none	Actigraphy	≥5	↓ Actual sleep time ↓ Sleep efficiency
Bioulac et al. (2016)	France	ADHD = 39 (18); Control = 18 (8)	ADHD = 36.2 (9.0); Control = 37.2 (10.1)	Healthy controls	12 inattentive, 27 combined	No (72 h before evaluation)	20 anxiety (past or present)	ESS, MWT, PSG	1	↑ ESS ↓ Sleep latency (MWT)
Boonstra (2007)	The Netherlands	ADHD = 33 (16); Control = 39 (18)	ADHD = 37.9 (10.3); Control = 37.8 (9.5)	Healthy controls	32 combined, 1 hyperactive-impulsive,	No (naïve)	Non-reported	Actigraphy, sleep/activity log	7	↑ Sleep latency ↑ Difficulty initiating sleep ↓ Sleep quality ↓ Sleep efficiency
Brevik (2017)	Norway	ADHD = 268 (108); Control = 202 (75)	ADHD = 38.1 (11.4); Control = 36.5 (8.0)	Without ADHD	54 inattentive, 6 hyperactive-impulsive, 75 combined, 133 non-reported	69 methylphenidate, 12 amphetamines, 3 atomoxetine, 7 combined, 36 none, 136 non-reported	Anxiety (177 ADHD, 34 controls), bipolar (32 ADHD, 1 control), dyslexia (121 ADHD, 14 controls), alcohol problems (35 ADHD, 2 controls), problems with other drugs (36 ADHD, 1 control)	BIS	–	↑ Total score and subscores
Frye (2017)	USA	ADHD = 32 (21); Control = 103 (47)	ADHD = 19.26 (0.84); Control = 19.62 (1.31)	Without ADHD	Non-reported	30 ADHD (21 psycotropic and 9 other), and 20 controls (8 psycotropic and 12 other)	Multiple both groups (including obstructive sleep apnea)	PSG	1	Non-available[c]
Kooij (2001)	The Netherlands	ADHD = 8 (5); Control = 8 (4)	ADHD = 29.4 (8.2); Control = 33.1 (7.2)	Healthy controls	1 inattentive, 7 combined	No (8 weeks before evaluation)	1 major depressive disorder, 2 various	Sleep log Actigraphy[d]	–	↓ Sleep quality Higher nocturnal activity
Philips (2005	Germany	ADHD = 20 (11); Control = 20 (11)	ADHD = 33.45 (8.94); Control = 33.34 (8.81)	Healthy controls	20 combined	No (2 weeks before evaluation)	3 restless legs	PSG, PSQI, another sleep questionnaire	2	↓ Sleep quality ↓ Restorative value of sleep ↓Psychosomatic symptoms during sleep onset
Sobanski (2008)[e]	Germany	ADHD = 24 (16); Control = 24 (non-reported)	ADHD = 36.2 (8.9); Control = Non-reported	Healthy controls	3 inattentive, 21 combined	No (4 weeks before evaluation)	No	PSG, two questionnaires	2	↑ Sleep onset latency (subjective) ↓ Sleep efficiency ↑ N. awakenings ↑ Wake time ↓ REM sleep
Sobanski (2016)	Germany	ADHD = 27 (19); Control = 182 (69)	ADHD = 34.2 (9.0); Control = 30.8 (12.2)	Without ADHD	Non-reported	Non-reported	Non-reported	ESS, MSLT	–	↑ ESS
Tonett (2017)	Italy	ADHD = 18 (11); Control = 37 (21)	ADHD = 39.61 (12.01); Control = 37 (11.74)	Without ADHD	3 inattentive, 15 combined	15 at least one medication (including methylphenidate, valproate and trazodone)	15 at least one psychiatric comorbidity	Actigraphy	7	↑ Time in bed ↑ Sleep onset latency ↑ Mean activity score ↑ wake time ↓ Sleep efficiency
Van Veen (2010)	The Netherlands	ADHD = 40 (21); Control = 24 (12)	ADHD = 18-55 years; Control = 29.1 (7.9)	Healthy controls	6 inattentive, 34 combined	No (1 month before evaluation)	Non-reported	Actigraphy Dim Light[f] Melatonin Onset (DLMO)	7	↑ Sleep onset latency ↓ Sleep efficiency Higher delay of circadian sleep phase
Weibe (2017)	Switzerland	ADHD = 129 (72); Control = 65 (19)	ADHD = 35.68 (11.94);	Healthy controls	Non-reported		62 history of major depressive episode, 20 anxious disorder		–	

(*continued on next page*)

Table 1 (*continued*)

First author (year)	Country	*N* (males)[a]	Mean age (SD)	Control group[b]	Subtype	Medication	Comorbidity	Sleep measure	Nights recorded	Main results found
			Control = 28.98 (9.38)			17 stimulants, 33 antidepressants, 13 sedatives		PSQI, ISI, ESS, STOP-Bang questionnaire		↑ PSQI (total score and every sub-score except for sleep duration) ↑ ISI ↑ Probability of obstructive sleep apnea (STOP-Bang questionnaire)

Abbreviations: ADHD = attention deficit hyperactivity disorder, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, MWT = Maintenance of Wakefulness Test, PSG = PSG, BIS = Bergen Insomnia Scale, MSLT = Multiple Sleep Latency Test, ISI = Insomnia Severity.

[a] If sleep data were available from a total sample (including participants with and without sleep disorders) we included these data as a whole.

[b] Healthy controls did not have any psychiatric disorder, whereas controls without ADHD were participants that could have any other psychiatric disorder different from ADHD.

[c] Main results found in this study are not available because we only included in our meta-analysis a subsample of participants from the total sample of the study (participants over 18 and without excluding sleep disorders). Data are part of the Penn State Child Cohort (PSCC), and were provided by the authors on request.

[d] Kooij et al. (2001) included actigraphic measures not reported in the other retained studies, as such, these were not meta-analyzed.

[e] In Sobanski et al. (2016): The participants assessed by MSLT were not the same than those who completed the ESS questionnaire; only participants who completed the ESS appear on this table, because it was the only variable of this study included in the meta-analysis.

[f] In Van Veen et al. (2010): DLMO was also measured but this was not meta-analyzed since it was not reported in any other study. In this study, severe comorbidities were an exclusion criterion, but the study did not exclude mild disorders.

CI = 0.46–1.14, $p < 0.001$) and a significantly lower sleep efficiency (SMD = −0.68, 95% CI = −1.03, −0.34, $p = 0.001$) compared to non ADHD controls (Table 3, Fig. 3). Heterogeneity, as indicated by I^2, ranging from high to low, was as follows: 28% (sleep onset latency), 33% (actual wake time and sleep efficiency), 74% (assumed sleep time), 78% (true sleep). Egger's tests for any outcome were not significant (Table 3).

No statistically significant differences between participants with ADHD and controls were found in any sleep parameter assessed by means of PSG (Table 3, Fig. 4). Heterogeneity, as indicated by I^2, ranging from high to low, was as follows: 0% (total sleep time, stage 1 sleep, stage 2 sleep), 13% (REM latency), 44% (wake time), 56% (sleep efficiency), 60% (sleep onset latency), 79% (REM percentage). Egger's tests were not significant for any outcome, except for a marginally significant value for slow wave sleep % (Table 3).

3.4. Bias/Quality of the included studies

A detailed description of the assessment of each item of the Newcastle-Ottawa scale for each included study is reported in Supplemental material 4. The average score was 5.5 (maximum possible score: 9) and scores ranged from 4 to 7. In most instances, downgrading was due to selected (convenience) samples (as opposed to representative samples) and lack of matching/adjustment for possible confounders, such as psychiatric comorbidities, between individuals with and without ADHD.

3.5. Publication bias

Funnel plots are reported in Supplemental material 5. In line with the results of the Egger's test, overall they showed no evidence of publication bias.

4. Discussion

This is the first meta-analysis of subjective and objective sleep studies in adults with ADHD. Whereas, compared to non ADHD controls, adults with ADHD presented with significant differences in the majority of the subjective parameters retained in our meta-analysis, they differed from controls only in two actigraphic parameters (sleep onset latency and sleep efficiency) and in none of the polysomnographic measures.

Our results are overall consistent with previous meta-analytic findings in children/adolescents. More specifically, regarding subjective findings, significantly increased sleep onset latency, daytime sleepiness, higher number of night awakenings in adults with compared to those without ADHD, as well as a lack of significant difference in sleep duration between the two groups, are similar to the findings from a previous meta-analysis in children/adolescents (Cortese et al., 2009). The items "Restorative value of sleep", "Psychosomatic symptoms during sleep onset", "General sleep problems", "Sleep quality", and "Sleep efficiency" can not be compared between the present meta-analysis and the Cortese et al. one because they were not assessed in the previous meta-analysis in children/adolescents. Additionally, significantly longer sleep onset latency measured via actigraphy was detected both in the present meta-analysis and in the previous one in children/adolescents. By contrast, significantly lower sleep efficiency and longer stage 1 sleep at the PSG, reported, respectively, in two meta-analyses in children/adolescents (Cortese et al., 2009; Diaz-Roman et al., 2016), were not replicated in the present meta-analysis, albeit findings in children/adolescents were close to non-significance (sleep efficiency in children/adolescents in the Cortese et al. meta-analysis: SMD: 0.25, 95% CI: 0.03–0.47; stage 1% in the Diaz-Roman et al. meta-analysis: SMD: 0.32, 95% CI: 0.08–0.55). As such, it is possible that the addition of future studies would make our results even more similar to those reported in children/adolescents. Unfortunately, there were no sufficient data to assess other polysomnographic parameters that were

Table 2
Subjective sleep parameters.

Sleep parameter (k)						Heterogeneity			Egger's test	
	ADHD (n)	Control (n)	SMD (95% CI)[a]	Z	p	χ^2	p	I^2	t	p
Night awakenings (4)	333	273	0.56 (0.40, 0.73)	6.72	< 0.00001	1.71	0.64	0	1.31	0.32
Sleep duration (3)	154	113	−0.16 (−0.70, 0.37)	0.60	0.55	6.74	0.03	70	0.55	0.68
Daytime sleepiness (4)	449	467	0.75 (0.29, 1.21)	3.22	0.001	21.61	< 0.0001	86	0.37	0.74
Sleep onset latency (7)	487	386	0.67 (0.41, 0.92)	5.14	< 0.00001	13.14	0.04	54	0.73	0.50
Restorative value of sleep (4)	345	285	0.41 (−0.28, 1.11)	1.16	0.25	29.00	< 0.00001	90	0.83	0.50
Psychosomatic symptoms during sleep onset (2)	44	44	0.64 (0.21, 1.07)	2.91	0.004	0.23	0.63	0	–	–
General sleep problems (3)	154	113	1.55 (0.72, 2.39)	3.64	0.0003	12.03	0.002	83	9.15	0.07
Sleep quality (5)	200	156	0.69 (0.38, 0.99)	4.42	< 0.00001	6.35	0.17	37	0.37	0.73
Sleep efficiency (2)	135	85	−0.55 (−0.83, −0.27)	2.54	0.01	3.77	0.05	73	–	–

Abbreviations: *k* = number of studies, ADHD = attention deficit hyperactivity disorder, SMD = pooled standardized mean difference, CI = confidence interval, *Z* = test for overall standardized mean difference, X^2 = heterogeneity test, I^2 = heterogeneity index (%).

[a] A negative SMD indicates that this sleep parameter was higher in the control group, except for the parameters of restorative value of sleep and sleep quality. A positive SMD in these sleep parameters indicates that participants with ADHD had a lower restorative value of sleep or a lower sleep quality than controls.

identified as significantly different between children with and without ADHD in a previous meta-analysis, namely apnea-hypopnea index and time to fall asleep at the multiple sleep latency test (MSLT) (Cortese et al., 2009). Another factor that may explain why findings in children were not replicated in the present meta-analysis is the presence of possible developmental effects. Since, to our knowledge these have not been assessed in methodologically sound research, future longitudinal studies measuring sleep prospectively in childhood and adulthood would contribute to clarify this issue.

It is not surprising that findings from this meta-analysis were different for subjective *vs.* objective parameters, as these relate to different measures/constructs. Overall, our findings might be interpreted according to the "sleep-state misperception" phenomenon, described in patients with primary or psychophysiological insomnia, who, despite subjective complaints of sleep problems, do not present with any significant alteration in polysomnographic parameters (Perlis et al., 1997). However, this hypothesis R1needs to be further tested and does not seem completely plausible to explain our findings. Indeed, we did find significant differences between adults with and without ADHD in two objective, actigraphic parameters, namely sleep onset latency and sleep efficiency, which were, respectively, increased and decreased in individuals with compared to those without ADHD. Furthermore, the fact that we did not detect any significant difference in any of the assessed polysomnographic parameters does not imply that there are no significant differences in polysomnographic parameters between adults with and without ADHD. First, we included only outcomes for which at least two studies provided data. As such, as mentioned, we could not meta-analyze apnea-hypopnea index and time to fall asleep at the multiple latency test, that were reported as significantly different between children with and without ADHD in a previous meta-analysis (Cortese et al., 2009). Second, whereas the majority of the studies on polysomnographic measures in individuals with ADHD included only the standard parameters of sleep macroarchitecture, assessing sleep microarchitecture may provide useful insights. For instance, in one study in children with ADHD, although no significant differences were found between patients with ADHD and controls in sleep macroarchitecture parameters, significant differences did emerge when considering cyclic alternating pattern (Miano et al., 2006). Third, it has been shown that sleep patterns in individuals with ADHD are underpinned by a high degree of night-to-night variability (Gruber et al., 2000). Whereas such variability is usually reflected in subjective questionnaires, it may not be detected in a few nights of PSG. Of note, as shown in Table 1, the majority of the PSG studies included in the present meta-analysis lasted more than one night. Therefore, whereas the first night effect is unlikely (only 2 of the retained studies lasted one night), the short length of the retained studies might have been not ideal to capture the night-to-night-variability associated with sleep patterns in ADHD.

Two additional factors that need to be taken into account when interpreting findings on sleep parameters in individuals with ADHD are: 1) the presence of psychiatric comorbidities and: 2) the medication status of the participants. As for comorbidities, it has been reported that psychiatric disorders may have opposite effects on PSG parameters. For instance, depressive disorder has been associated with a decrease delta power (Riemann et al., 2001), contrary to what has been found in individuals with personality disorders (e.g., Philipsen et al., 2005). Considering that only one study (Sobanski et al., 2008) recruited individuals with ADHD without comorbidities, it is possible that the presence of comorbidities in the other studies impacted on the pooled estimates in a way that was not possible to assess in this meta-analysis, since data were not presented separately, in each study, for subjects with and without comorbidities. Of note, whereas, as shown in Table 1, some of the studies recruited non ADHD controls, others compared individuals with ADHD to healthy controls, so that the presence of comorbidities was not properly controlled for in all the included studies. This may have influenced the pooled estimates of the present meta-analysis. As for the medication status, although the effects of ADHD medications on the subjective and objective sleep parameters is far from being clear (Cortese et al., 2009; Stein et al., 2012), there is evidence that these medications may negatively impact on at least some sleep parameters and lead to subjectively reported sleep onset delay. In a number of studies included in this meta-analysis (Table 1), ADHD medications were stopped one or more days before the sleep assessment. This might contribute to explain the discrepancy between positive results for subjective sleep parameters (reflecting the participants' perception of their sleep patterns not necessarily limited to the nights without treatment) and negative findings for objective sleep measures during the nights with no pharmacological treatment.

The variability in terms of comorbidities and medication status across studies may contribute to explain the high heterogeneity values, indicated by the I^2 statistics, which was detected for a number of outcomes. In our view, on the one hand, heterogeneity in medication status and comorbidity is not an issue when one seeks to characterize the subjective sleep complaints of individual with ADHD, because indeed such heterogeneity characterizes patients in the daily practice. On the other hand, in order to understand the mechanisms underlying the subjective sleep complaints, it is desirable to reduce such heterogeneity and assess groups of participants as homogeneous as possible.

The results of our systematic review/meta-analysis should be considered in the light of its strengths and limitations. As for the strengths, we pre-registered the protocol in a publicly available repository (PROSPERO), reducing the risk of reporting bias. Furthermore, we endeavored to perform a comprehensive and systematic search in several databases, with no restrictions in terms of language or document type,

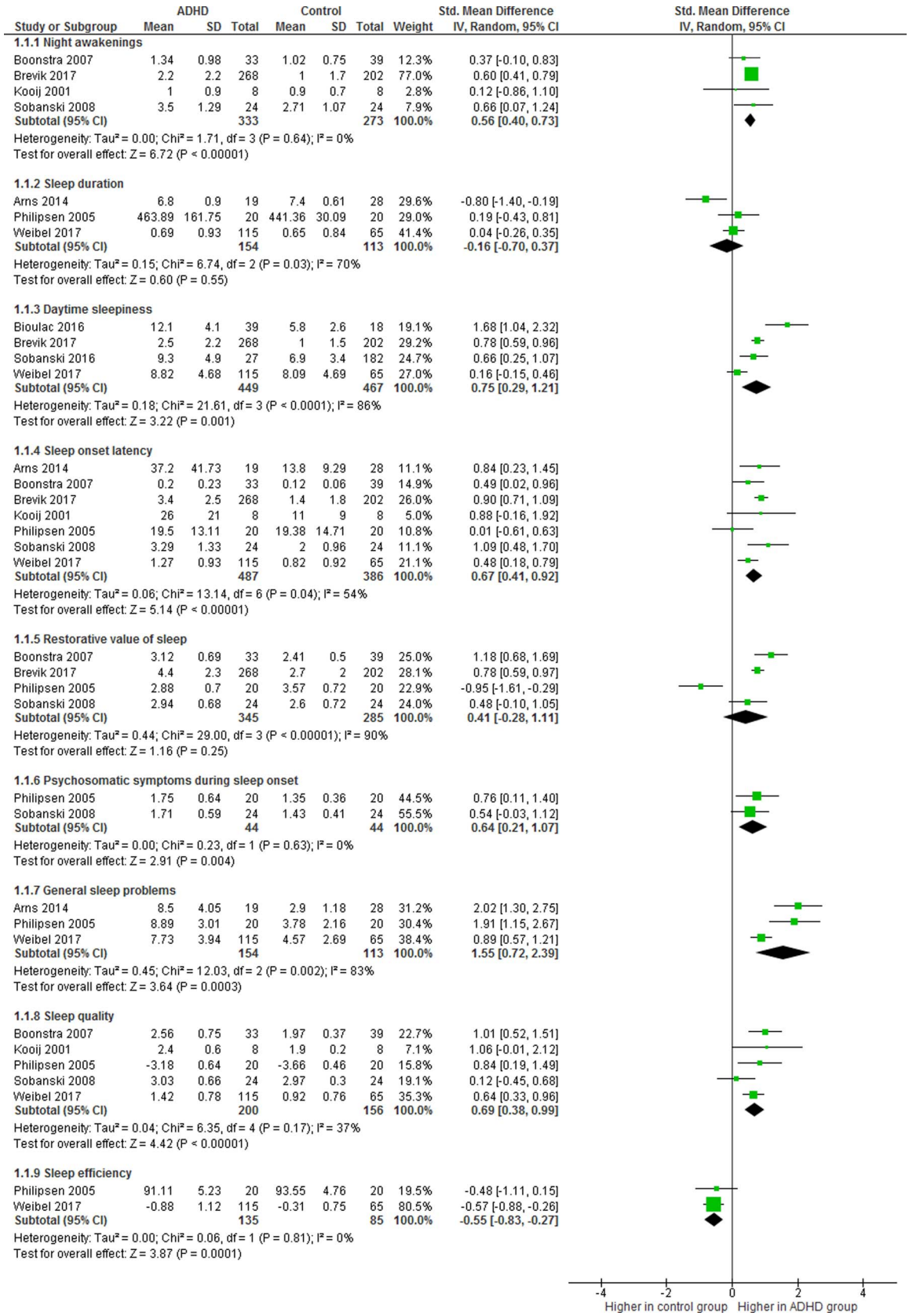

Fig. 2. Forest Plot of the Standardized Mean Differences (SMD) Obtained for Subjective Sleep Parameters. IV, inverse variance method; Random, random-effects model; CI, confidence interval; Chi^2, heterogeneity test; df, degrees of freedom; I^2, heterogeneity index; Z, test for overall standardized mean difference; ADHD, attention deficit hyperactivity disorder.

Table 3
Objective sleep parameters.

Sleep parameter (*k*)						Heterogeneity			Egger's test	
	ADHD (*n*)	Control (*n*)	SMD (95% CI)[a]	*Z*	*p*	χ^2	*p*	I^2	t	*p*
PSG										
Total sleep time (3)	91	141	0.11 (−0.18, 0.40)	0.76	0.45	1.76	0.41	0	1.59	0.36
Sleep onset latency (4)	115	165	−0.13 (−0.55, 0.29)	0.61	0.54	7.45	0.06	60	0.03	0.98
Stage 1 sleep % (4)	115	165	0.16 (−0.10, 0.42)	1.23	0.22	2.74	0.43	0	0.15	0.89
Stage 2 sleep % (4)	115	165	−0.19 (−0.44, 0.07)	1.44	0.15	0.51	0.92	0	0.64	0.59
Slow wave sleep % (4)	115	165	0.02 (−0.24, 0.27)	0.13	0.90	0.50	0.92	0	4.64	0.04
REM % (4)	115	165	−0.01 (−0.59, 0.58)	0.02	0.99	14.30	0.003	79	1.15	0.37
REM latency (2)	44	44	−0.15 (−0.60, 0.30)	0.64	0.52	1.15	0.28	13	–	–
Sleep efficiency (4)	115	165	−0.08 (−0.48, 0.32)	0.39	0.70	6.83	0.08	56	0.02	0.99
Wake time % (3)	91	141	0.19 (−0.21, 0.60)	0.94	0.35	3.59	0.17	44	0.01	0.99
Actigraphy										
Sleep onset latency (4)	103	119	0.80 (0.46, 1.14)	4.63	< 0.00001	4.19	0.24	28	0.06	0.96
True sleep (4)	103	119	−0.14 (−0.74, 0.46)	0.45	0.65	13.59	0.004	78	0.94	0.45
Assumed sleep time (2)	46	58	−0.55 (−1.42, 0.32)	1.24	0.22	3.92	0.05	74	–	–
Actual wake time (3)	64	95	0.40 (−0.01, 0.80)	1.92	0.05	2.99	0.22	33	0.75	0.59
Sleep efficiency (4)	103	119	−0.68 (−1.03, −0.34)	3.87	0.0001	4.46	0.22	33	1.49	0.27

Abbreviations: *k* = number of studies, ADHD = attention deficit hyperactivity disorder, SMD = pooled standardized mean difference, CI = confidence interval, *Z* = test for overall standardized mean difference, X^2 = heterogeneity test, I^2 = heterogeneity index (%).

[a] A negative SMD indicates that this sleep parameter was higher in the control group.

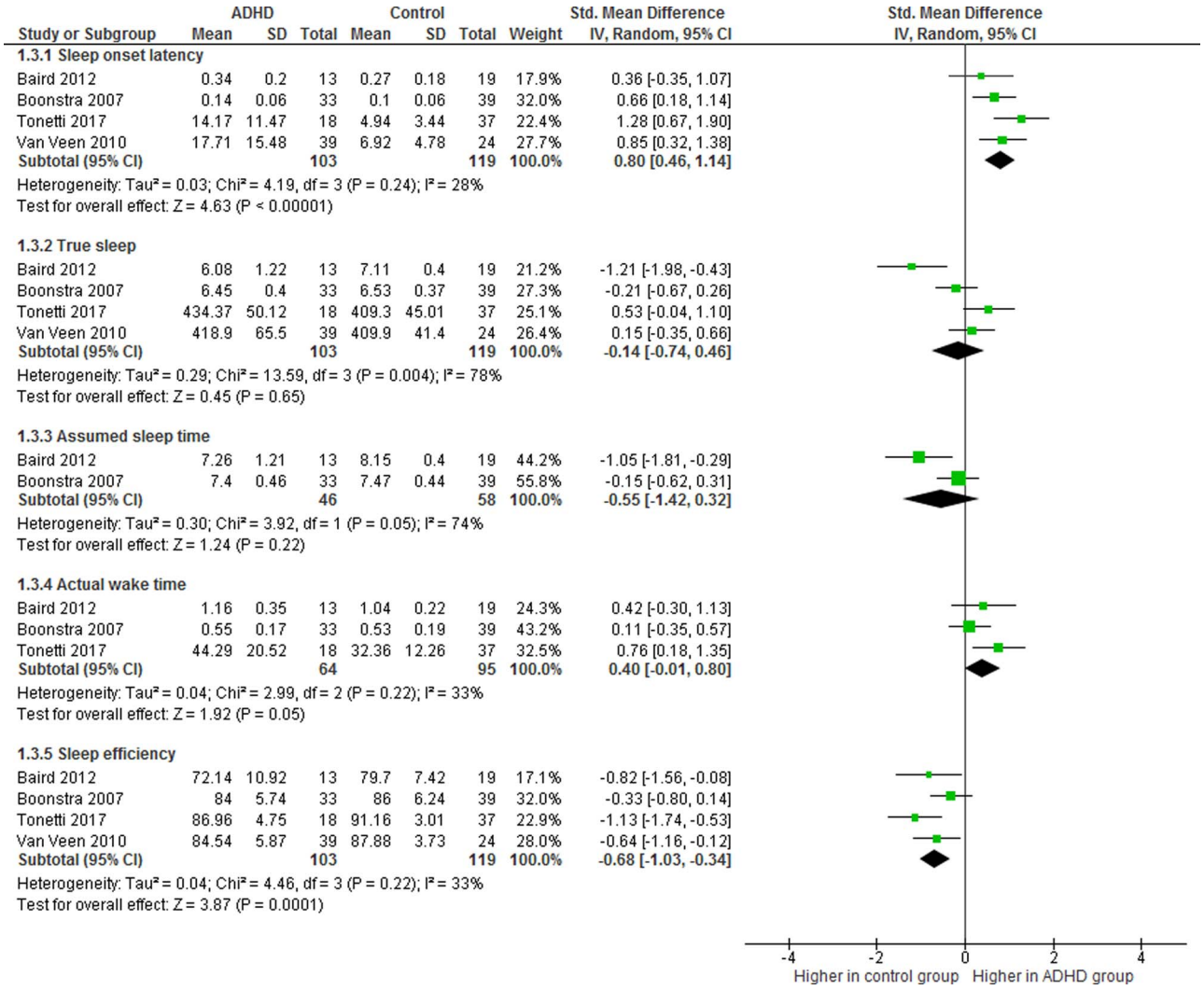

Fig. 3. Forest Plot of the Standardized Mean Differences (SMD) Obtained for Sleep Parameters Measured With Actigraphy. IV, inverse variance method; Random, random-effects model; CI, confidence interval; Chi^2, heterogeneity test; df, degrees of freedom; I^2, heterogeneity index; Z, test for overall standardized mean difference; ADHD, attention deficit hyperactivity disorder.

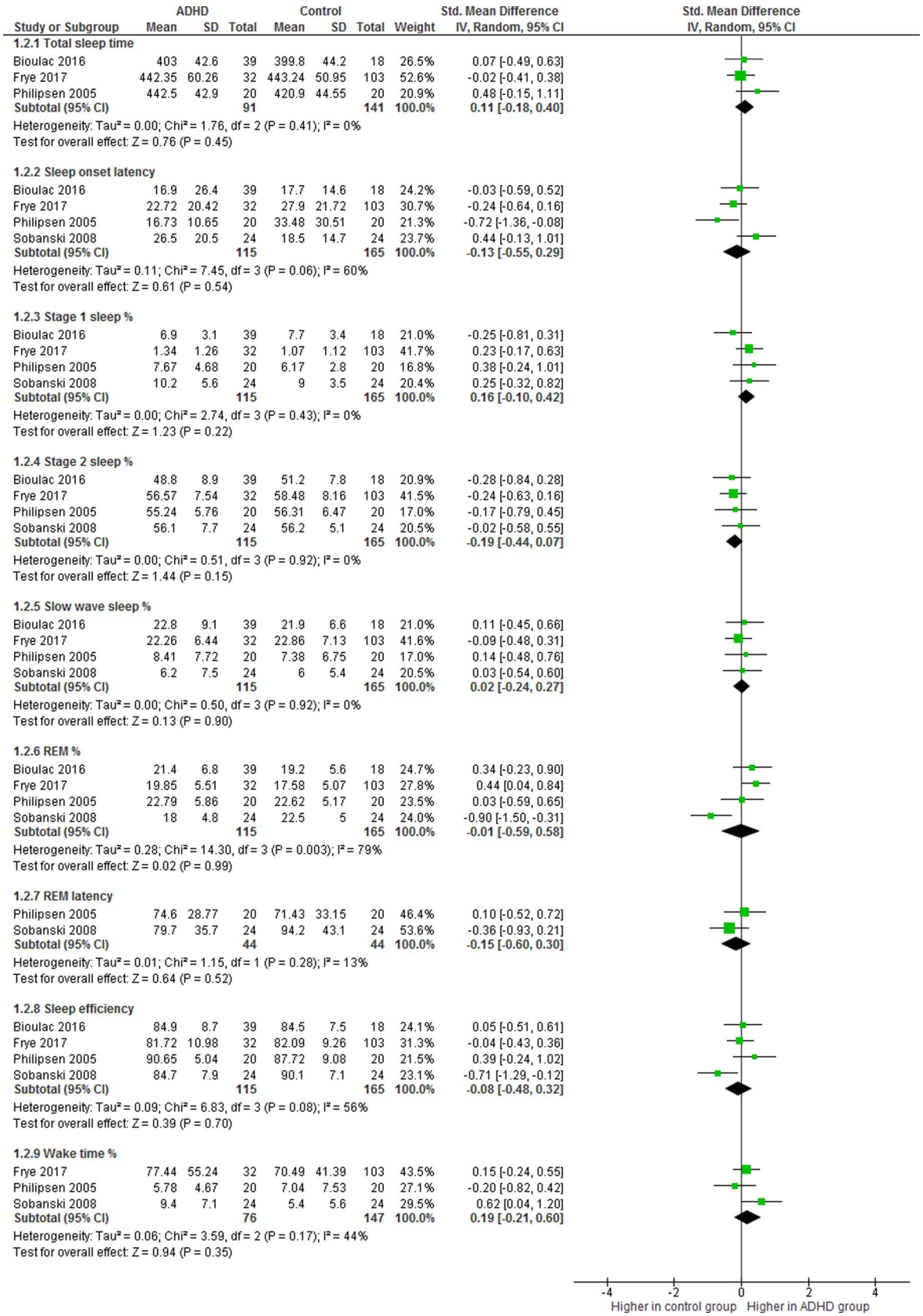

Fig. 4. Forest Plot of the Standardized Mean Differences (SMD) Obtained for Sleep Parameters Measured With PSG. IV, inverse variance method; Random, random-effects model; CI, confidence interval; Chi^2, heterogeneity test; df, degrees of freedom; I^2, heterogeneity index; Z, test for overall standardized mean difference; ADHD, attention deficit hyperactivity disorder.

and we gathered unpublished data from study authors. Additionally, we used a state-of-the-art tool, the Newcastle-Ottawa scale, to assess the quality of the retained studies. There are also a number of limitations that should be taken into account, which are mostly related to the individual studies that we included rather than to methodological issues with our systematic review/meta-analysis. First, for some outcomes, only a limited number of studies was available. Second, since we meta-analyzed data when outcomes were reported in at least two studies, some parameters could not be meta-analyzed. Third, as indicated by the I^2 values, for some outcomes, heterogeneity in the estimate was large. It is possible that the lack of adjustment for psychiatric comorbidities and the variable medication status in individual studies might have contributed to such heterogeneity. Furthermore, it should be noted that the presence of a formal sleep disorder was not exclusionary across all included studies, which may have increased heterogeneity of findings. Fourth, since individual studies did not present data separately in males and females, we could not assess possible gender effects. Finally, we could not assess the impact of ADHD presentation (or, as it used to be referred to in previous DSM editions, “subtype”) because data were not presented separately for each subtype in individual studies.

Future studies should address the limitations that we detected in available research reports, particularly in relation to the objective studies. More specifically, we deem it important for further objective studies to be conducted in more ecological settings (home recordings), over several nights, and to focus not only on sleep macroarchitecture, but also on sleep microarchitecture. Future studies should also focus on circadian rhythm alterations, which have been so far quiet neglected in the field. in fact, we could find only one study (van Veen et al., 2010) assessing the DLMO. Furthermore, future studies should be conducted in medication naïve samples of adults with and without ADHD matched for comorbid psychiatric disorders and other relevant demographic variables. Additionally, studies dosing melatonin levels and combining PSG with other imaging methods are welcome to gain insight into the pathophysiology of sleep disorders in this population.

Therefore, we hope that the present systematic review/meta-analysis will :1) highlight, from a clinical standpoint, the importance of a systematic screening of sleep complaints in adults referred for ADHD assessment, focusing in particular on the parameters that we detected as significantly different between adults with and without ADHD, namely sleep onset latency, psychosomatic symptoms during sleep onset, sleep quality and efficiency and daytime sleepiness; 2) from a research standpoint, help shaping the next generation of sleep research in ADHD, to better understand if and to which extent subjectively reported sleep complaints are underpinned by objective sleep alterations. This, in turn, will support the development of pathophysiologically based effective interventions strategies for sleep disturbances in adults with ADHD, thus reducing the burden of this disorder.

Declaration of conflicts of interest

Dr. Díaz-Román, Ms. Mitchell and Dr. Cortese declare no conflicts of interest.

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We acknowledge the authors of one of the studies included in the meta-analysis (Frye et al., 2017) for providing additional unpublished data/information.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.neubiorev.2018.02.014.

References

Arns, M., Feddema, I., Kenemans, J.L., 2014. Differential effects of theta/beta and SMR neurofeedback in ADHD on sleep onset latency. Front. Hum. Neurosci. 8, 1019.
Baird, A.L., Coogan, A.N., Siddiqui, A., Donev, R.M., Thome, J., 2012. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. Mol. Psychiatry 17, 988–995.
Bioulac, S., Sagaspe, P., Micoulaud-Franchi, J.A., Altena, E., Taillard, J., Schroder, C., et al., 2016. Objective level of alertness and inhibitory control predict highway driving impairment in adults with ADHD. J. Atten. Disord. http://dx.doi.org/10.1177/1087054716633751.
Bogdan, A.R., Reeves, K.W., 2016. Sleep duration in relation to attention deficit hyperactivity disorder in American adults. Behav. Sleep Med. 1–11.
Boonstra, A.M., Kooij, J.J., Oosterlaan, J., Sergeant, J.A., Buitelaar, J.K., Van Someren, E.J., 2007. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 30, 433–442.
Brevik, E.J., Lundervold, A.J., Halmoy, A., Posserud, M.B., Instanes, J.T., Bjorvatn, B., et al., 2017. Prevalence and clinical correlates of insomnia in adults with attention-deficit hyperactivity disorder. Acta Psychiatr. Scand. 136, 220–227.
Cortese, S., Brown, T.E., Corkum, P., Gruber, R., O’Brien, L.M., Stein, M., et al., 2013. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 52, 784–796.
Cortese, S., Faraone, S.V., Konofal, E., Lecendreux, M., 2009. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J. Am. Acad. Child Adolesc. Psychiatry 48, 894–908.
Dahl, R.E., 1996. The impact of inadequate sleep on children’s daytime cognitive function. Semin. Pediatr. Neurol. 3, 44–50.
Diaz-Roman, A., Hita-Yanez, E., Buela-Casal, G., 2016. Sleep characteristics in children with attention deficit hyperactivity disorder: systematic review and meta-analyses. J. Clin. Sleep Med. 12, 747–756.
Egger, M., Davey, S.G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J.A., et al., 2015. Attention-deficit/hyperactivity disorder. Nat. Rev. Dis. Primers 1, 15020.
Faraone, S.V., Biederman, J., Mick, E., 2006. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol. Med. 36, 159–165.
Fargason, R.E., Hollar, A.F., White, S., Gamble, K.L., 2013. Adults with ADHD-without insomnia history have subclinical sleep disturbance but not circadian delay: an ADHD phenotype? J. Atten. Disord. 17, 583–588.
Fisher, B.C., Garges, D.M., Yoon, S.Y., Maguire, K., Zipay, D., Gambino, M., et al., 2014. Sex differences and the interaction of age and sleep issues in neuropsychological testing performance across the lifespan in an ADD/ADHD sample from the years 1989 to 2009. Psychol. Rep. 114, 404–438.
Frye, S., Fernandez-Mendoza, J., Calhoun, S., Vgontzas, A., Liao, D., Bixler, E., 2017. Role of periodic limb movements during sleep in adolescents with attention deficit hyperactivity disorder: differential association with internalizing vs. externalizing behaviors. Sleep 40 (Suppl. 1), 347.
Gruber, R., Sadeh, A., Raviv, A., 2000. Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 39, 495–501.
Hedges, L., 1981. Distribution theory for Glass’s estimator of effect size and related estimators. J. Educ. Stat. 6 (2), 107–128.
Higgins, J., Thompson, S., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Hvolby, A., Jorgensen, J., Bilenberg, N., 2008. Actigraphic and parental reports of sleep difficulties in children with attention-deficit/hyperactivity disorder. Arch. Pediatr. Adolesc. Med. 162, 323–329.
Iber, C., Ancoli- Israel, S., Chesson, A., 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications, 1st ed. .
Kooij, J.J., Middelkoop, H.A., van, G.K., Buitelaar, J.K., 2001. The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case-control study. J. Clin. Psychiatry 62, 952–956.
Langberg, J.M., Dvorsky, M.R., Becker, S.P., Molitor, S.J., 2016. School maladjustment and external locus of control predict the daytime sleepiness of college students with ADHD. J. Atten. Disord. 20, 792–801.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339 b2700.
Miano, S., Donfrancesco, R., Bruni, O., Ferri, R., Galiffa, S., Pagani, J., et al., 2006. NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. Sleep 29, 797–803.
Owens, J.A., Maxim, R., Nobile, C., McGuinn, M., Msall, M., 2000. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. Arch. Pediatr. Adolesc. Med. 154, 549–555.
Owens, J., Sangal, R.B., Sutton, V.K., Bakken, R., Allen, A.J., Kelsey, D., 2013. Subjective and objective measures of sleep in children with attention-deficit/hyperactivity disorder. J. Atten. Disord. 17 (Oct. (7)), 550–564.
Perlis, M.L., Giles, D.E., Mendelson, W.B., Bootzin, R.R., Wyatt, J.K., 1997. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J. Sleep Res. 6, 179–188.
Philipsen, A., Feige, B., Hesslinger, B., Ebert, D., Carl, C., Hornyak, M., et al., 2005. Sleep in adults with attention-deficit/hyperactivity disorder: a controlled

polysomnographic study including spectral analysis of the sleep EEG. Sleep 28, 877–884.
Polanczyk, G.V., Willcutt, E.G., Salum, G.A., Kieling, C., Rohde, L.A., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int. J. Epidemiol. 43 (April (2)), 434–442.
Rechtschafen, A., Kales, A., 1968. A Manual Standardized Terminology, Techniques and Scoring System and Sleep Stages of Human Subjects. UCLA Brain Information Service ed., Los Angeles.
Riemann, D., Berger, M., Voderholzer, U., 2001. Sleep and depression–results from psychobiological studies: an overview. Biol. Psychol. 57, 67–103.
Sadeh, A., Pergamin, L., Bar-Haim, Y., 2006. Sleep in children with attention-deficit hyperactivity disorder: a meta-analysis of polysomnographic studies. Sleep Med. Rev. 10, 381–398.
Simon, V., Czobor, P., Balint, S., Meszaros, A., Bitter, I., 2009. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br. J. Psychiatry 194, 204–211.
Sobanski, E., Alm, B., Hennig, O., Riemann, D., Feige, B., Schredl, M., 2016. Daytime sleepiness in adults with ADHD: a pilot trial with a multiple sleep latency test. J. Atten. Disord. 20, 1023–1029.
Sobanski, E., Schredl, M., Kettler, N., Alm, B., 2008. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep 31, 375–381.
Stein, M.A., Weiss, M., Hlavaty, L., 2012. ADHD treatments, sleep, and sleep problems: complex associations. Neurotherapeutics 9, 509–517.
Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of observational studies in epidemiology (MOOSE) group. JAMA 283, 2008–2012.
Tonetti, L., Conca, A., Giupponi, G., Natale, V., 2017. Circadian pattern of motor activity in adults with attention-deficit/hyperactivity disorder. Chronobiol. Int. 34, 802–807.
Van Veen, M.M., Kooij, J.J., Boonstra, A.M., Gordijn, M.C., Van Someren, E.J., 2010. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol. Psychiatry 67, 1091–1096.
Weibel, S., Jermann, F., Weiner, L., Nicastro, R., Ardu, S., Pham, E., et al., 2017. Insomnia in adult attention-deficit/hyperactivity disorder: A comparison with borderline personality disorder population in a clinical setting and control participants. Compr. Psychiatry 76, 119–128.