Sleep in youth with autism spectrum disorders: systematic review and meta-analysis of subjective and objective studies

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ABSTRACT

Background Sleep problems are common and impairing in individuals with autism spectrum disorders (ASD). Evidence synthesis including both subjective (ie, measured with questionnaires) and objective (ie, quantified with neurophysiological tools) sleep alterations in youth with ASD is currently lacking.

Objective We conducted a systematic review and meta-analysis of subjective and objective studies sleep studies in youth with ASD.

Methods We searched the following electronic databases with no language, date or type of document restriction up to 23 May 2018: PubMed, PsycInfo, Embase+Embase Classic, Ovid Medline and Web of Knowledge. Random-effects models were used. Heterogeneity was assessed with Cochran's Q and I² statistics. Publication (small studies) bias was assessed with final plots and the Egger's test. Study quality was evaluated with the Newcastle Ottawa Scale. Analyses were conducted using Review Manager and Comprehensive Meta-Analysis.

Findings From a pool of 3359 non-duplicate potentially relevant references, 47 datasets were included in the meta-analyses. Subjective and objective sleep outcome measures were extracted from 37 and 15 studies, respectively. Only five studies were based on comorbidity free, medication-naïve participants. Compared with typically developing controls, youth with ASD significantly differed in 10/14 subjective parameters and in 7/14 objective sleep parameters. The average quality score in the Newcastle-Ottawa Scale was 5.9/9.

Discussion and clinical implications A number of subjective and, to a less extent, objective sleep alterations might characterise youth with ASD, but future studies should assess the impact of pharmacological treatment and psychiatric comorbidities.

BACKGROUND

Autism spectrum disorders (ASDs) encompass a wide range of neurodevelopmental conditions characterised by a deficit in social communication, together with restricted, repetitive and stereotyped behaviours, interests or activities.[1] Although not formally part of the diagnostic criteria,[1,2] sleep problems are frequently reported in individuals with ASD (eg, refs [3–5]) and contribute to their functional impairment. Sleep difficulties are associated with a significant amount of distress for the patients and their families[6] and negatively impact on cognitive abilities and self-regulation of disruptive behaviours during the daytime.[7–9]

In order to appropriately manage them, it is necessary to characterise the profile of sleep problems in children and adolescents with ASD. While a number of individual studies have been conducted, we are aware of only one meta-analysis that summarised the available body of evidence.[10] However, this meta-analysis was limited to objective sleep studies, that is, studies relying on actigraphic or polysomnographic measures. While these (in particular, polysomnography (PSG)) are considered rigorous measures of sleep, it is important to also consider sleep measures subjectively reported by patient and/or their parents via questionnaires, as they are arguably more 'ecological' and they reflect the subjective perception, which is important in the management process of the disorder. Furthermore, the meta-analysis by Elrod and Hood[10] was published in 2015 and, as such, an update is warranted.

OBJECTIVE

To conduct a systematic review and meta-analysis of subjective and objective studies of sleep in children and adolescents with ASD compared with typically developing controls.

STUDY SELECTION AND ANALYSIS

We followed the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group[11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12] The protocol of this systematic review was registered in PROSPERO (CRD42018100016).

Type of studies

We included case–control studies comparing children with ASD to typically developing individuals on subjective and/or objective sleep parameters.

Type of participants

We included studies on children/youth (≤20 years) diagnosed with ASD according to *Diagnostic and Statistical Manual III* (DSM III) to DSM 5 criteria or International Statistical Classification of Diseases, Ninth Revision (ICD-9) to ICD-10 criteria, or according to a clinical diagnosis of ASD, compared with typically developing participants. Definition of ASD based on cut-off on questionnaires targeting ASD symptoms was not considered rigorous and as such was exclusionary. Psychiatric comorbidities were not an exclusionary criterion.

Outcomes

Any subjective sleep parameters from any sleep questionnaire and/or any objective sleep parameters measured using PSG, actigraphy or multiple sleep latency test (MSLT), which were presented in at least two studies, were meta-analysed. We selected the following subjective parameters: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night awakenings, parasomnias, sleep-disordered breathing, daytime sleepiness, general sleep problems, sleep quality, sleep efficiency, sleep

onset latency (min), sleep duration (min) and restorative value of sleep (ie, feeling well rested after waking up). For PSG, we considered total sleep time, sleep onset latency, time spent in each sleep stage, rapid eye movement (REM) latency, sleep efficiency and wake time after sleep onset. As for actigraphic parameters, we selected: sleep onset latency, true sleep, assumed sleep time, actual wake time and sleep efficiency. For MSLT, we considered latency to falling asleep.

Search strategy/syntax
We searched the following electronic databases: PubMed (MEDLINE), Ovid databases (PsycInfo, Embase + Embase classic and Ovid MEDLINE) and Web of Knowledge Databases (Web of Science (Science Citation Index Expanded), biological abstracts, biosis, food science and technology abstracts), up to 23 May 2018 with no language/date/type of document restrictions. Further details on the search strategy/syntax, including search terms for each database, are reported in the online supplemental material 1. References of included studies and of reviews conducted on this topic were also hand-searched to find potential pertinent studies undetected with the electronic search strategy.

Screening and data extraction
Screening
Title and abstracts of all non-duplicated papers were independently screened by two of the authors (JZ and AD-R). Potential pertinent papers were retained and assessed for eligibility by screening the full text. A third senior author (SC) acted as arbitrator when disagreement in any screening stage. If needed, corresponding authors of retained studies were also contacted to request further information.

Data extraction
Data extraction was independently performed by two of the authors (JZ and AD-R), and any discrepancy between them was resolved by consensus. The following data were extracted from each study: first author and publication year, country where the study was conducted, study participants' details (number, percentage of males, mean age and SD, ASD diagnostic criteria, medication status and comorbidities), mean and SD for each outcome measure (subjective and/or objective sleep parameters) and nights recorded for sleep assessment.

Risk of bias assessment
Two authors (JZ and AD-R) independently assessed the methodological quality or risk of bias of included studies using the Newcastle-Ottawa Scale for case–control studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This scale includes the following domains: 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 and non-response rate. Disagreements between both authors were resolved by consensus.

Statistical analysis
Analyses were performed with Review Manager 5.3 (http://community. cochrane.org/tools/reviewproduction-tools/revman-5) and Comprehensive Meta-Analysis (http://www.meta-analysis.com/index.php). Random-effects models were used to compute standardised mean difference (SMD) for each sleep parameter, with 95% CI and the Hedges' correction[13] to avoid sample size bias. The inverse variance method and the Z statistic were used to calculate the pooled SMD and assess its statistical significance. Heterogeneity degree between studies was measured with Cochran's Q and I^2 statistics.[14] Publication bias were explored using the Egger's test and the funnel plots.[15] We also conducted a post hoc analysis including only studies based on comorbidity-free, medication-naïve participants.

FINDINGS
From a pool of 3359 non-duplicate potentially relevant references, 47 datasets (reported in 48 references) were included in our meta-analysis[5–8 16–56] (figure 1). The list of excluded reports (with reasons for exclusions) and included studies are provided in the online supplemental materials 2 and 3, respectively. Table 1 shows the main characteristics of the studies included in the meta-analysis. All studies were cross-sectional, and the average quality score in the Newcastle-Ottawa Scale was 5.9/9 (scores ranged from 3 to 8; online supplemental material 4).

Subjective outcome measures were extracted from 37 studies,[5–8 16–18 21 22 24 25 27–37 39 40 42–47 49–54 56] while objective outcome measures were obtained from 15 studies (eight studies using PSG,[20 25 26 29 32 37 44 53] six using actigraphy,[18 19 27 47 50 52] and one using both.[41]) Overall, the number of participants ranged from 75 to 5430 for studies reporting subjective sleep parameters and from 144 to 312 for sleep objective studies. Two studies[35 38] reported sleep data of two different samples, and we included both samples in the meta-analysis independently.

Subjective measures of sleep difficulties
Compared with control individuals, participants with ASD, showed significantly higher bedtime resistance (SMD = 1.00, 95% CI 0.67 to 1.33), sleep onset delay (0.98, 0.66 to 1.29), sleep anxiety (0.96, 0.61 to 1.32), night awakenings (0.72, 0.44 to 1.01), parasomnias (0.88, 0.60 to 1.15), sleep-disordered breathing (0.48, 0.28 to 0.67), daytime sleepiness (0.34, 0.16 to 0.52), sleep onset latency (in min) (0.81, 0.59 to 1.02), restorative value of sleep (0.13, -0.96 to 1.02) and general sleep problems (0.93, 0.67 to 1.20). They also showed lower sleep duration (−0.88, −1.18 to −0.57). In contrast, children with ASD did not significantly differ from control individuals in sleep quality, sleep efficiency or sleep duration in min (table 2 and the online supplemental material 5). As shown in table 2, the heterogeneity between studies was statistically significant for almost all subjective sleep parameters (I^2 ranged from 81% to 95%), except for sleep efficiency and sleep onset latency (in min). There was also evidence for publication bias for 5 out of 14 subjective sleep parameters: sleep duration (t = 2.19, p = 0.040), sleep anxiety (t = 2.69, p = 0.014), parasomnias (t = 3.30, p = 0.003), daytime sleepiness (t = 2.26, p = 0.032) and general sleep problems (t = 2.31, p = 0.028). The results of the Egger's test and the funnel plots are reported in table 2 and the online supplemental material 6, respectively.

Objective parameters of sleep alterations
As reported in table 3, children with ASD significantly differed from control individuals in several objective parameters measuring sleep patterns using PSG. Specifically, children with ASD showed lower total sleep time (−0.90, −1.51 to −0.30), longer sleep onset latency (0.53, 0.21 to 0.86), higher time spent in stage 1 sleep (0.48, 0.06 to 0.90), lower time of REM sleep (−0.88, −1.56 to −0.21), lower sleep efficiency (−1.20, −1.98 to −0.41) and higher time awake after sleep onset (0.49, 0.11 to 0.87). However, no significant differences were observed between children with ASD and control individuals in stage 2 sleep, slow wave sleep and REM latency (table 3 and the online supplemental material 5). In relation to actigraphy, we found differences between both groups only in sleep onset latency (table 3 and the online supplemental material 5). Children with ASD displayed significantly longer sleep onset latency than control individuals (0.80, 0.55 to 1.05). Evidence of heterogeneity was found for almost all polysomnographic sleep parameters (I^2 ranged from 55% to 85%), with the exception of sleep onset latency and wake time but only for a single actigraphic sleep parameter (sleep efficiency, $I^2 = 62\%$). No evidence of publication bias was detected in the Egger's test (table 3) and the funnel plots (online supplemental material 6).
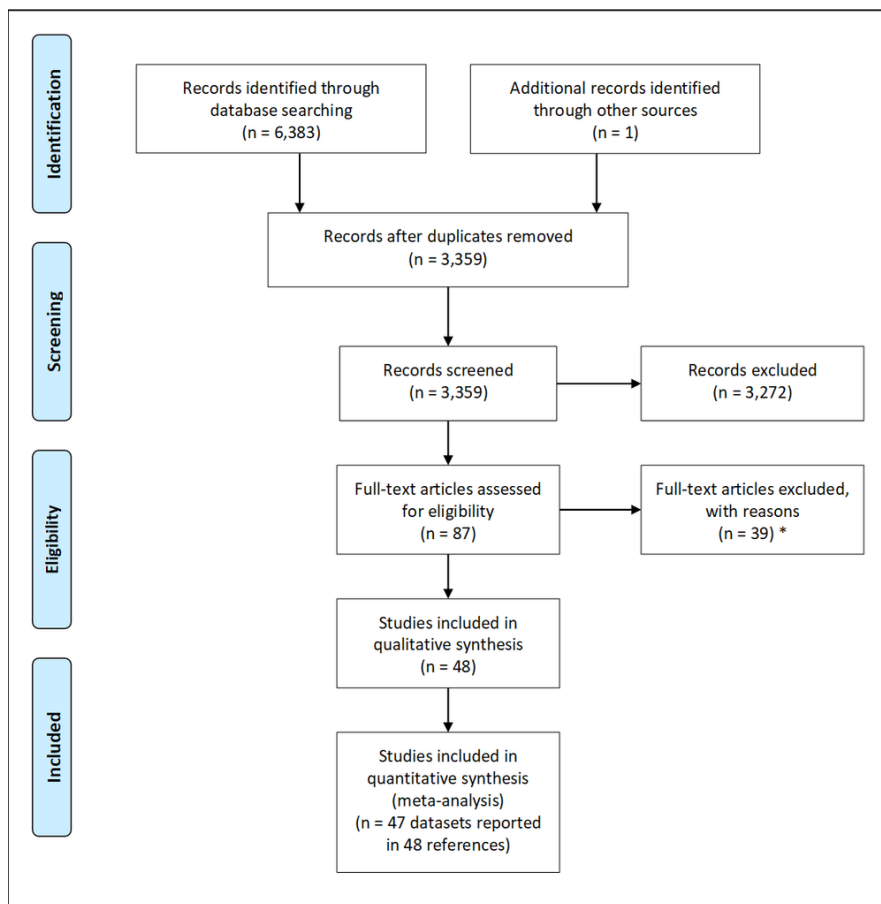
Figure 1 PRISMA flow chart. *Reasons for exclusion for each paper are reported in the online supplemental material 2. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Post hoc analysis

The post hoc analysis based on studies including only comorbidity-free and medication-naïve participants was limited to PSG studies as only two studies for subjective measures and one study for actigraphic measures, respectively, provided usable data. As shown in table 4 the post hoc analysis of PSG studies replicated the results of the main analysis (except for the parameter duration of sleep stage 1, which was not more significant between participants with ASD and controls).

CONCLUSIONS AND CLINICAL IMPLICATIONS

To our knowledge, this is the first meta-analysis including both subjective and objective measures of sleep in children with ASD. We found that, compared with typically developing children, those with ASD presented with a number of significant sleep impairments, quantified both by subjective and objective parameters.

Our results were in accordance with the findings of a previous meta-analysis in children with ASD,[10] in which these children also showed significantly lower total sleep time, increased sleep onset latency and worse sleep efficiency compared with typically developing children. However, these differences between groups observed during PSG were not consistent with actigraphy-defined measures since only sleep time or sleep efficiency statistically differed.

It should be noted that, although the previous meta-analysis by Elrod and Hood[10] pooled both PSG and actigraphy sleep outcomes together, their analyses of moderating factors revealed a significant impact of sleep assessment method on sleep efficiency. Specifically, their results suggested no difference in children with ASD and controls in actigraphic sleep efficiency, being this consistent with our results to a greater extent.

Our work adds meta-analytic evidence to the Elrod and Hood study,[10] extending to subjective measures of sleep disturbances in ASD. Our results stress further that children with ASD displayed a considerable burden of sleep problems. These children seemed to experience greater bedtime resistance, sleep anxiety, sleep-disordered breathing and parasomnias, as well as longer sleep onset latency and higher daytime sleepiness. However, there was less consistency about total sleep time, depending on how it was estimated (ie, with a score in a sleep questionnaire or a length in min). Finally, despite children with ASD showed significantly higher scores in general sleep problems than typically developing children, they did not differ in terms of subjectively reported sleep quality and sleep efficiency, although the limited number of included subjective studies reporting sleep quality (n=3) and sleep efficiency (n=2) suggest that this conclusion should be considered with caution.

Our results based on subjective measures were generally not consistent with those obtained with objective parameters. For instance, children with ASD and control individuals did not significantly differ in terms of sleep duration based on parents' report. By contrast, children with ASD showed a significantly lower total sleep time compared with typically developing children according to PSG measures. This is not surprising and reflects the well-known mismatch between subjective and objective measures.[57] Indeed, discrepancies between subjective and objective sleep measures have been reported in earlier studies in both children with ASD (eg, refs [18 41]) and children with other neurodevelopmental disorders (eg, refs [58 59]). For example, objective measures were usually taken on one or two nights, while subjective measures reflected the perception of the parent over several nights. Taking into account the advantages and limitations of both subjective and objective sleep measures, rather

Table 1 Descriptive table of the studies included in the meta-analysis

First author (year)	Country	ASD group			Control group			Co-occurrent drugs	Comorbidities	Main sleep measures	Nights recorded (PSG/ACT)
		Diagnosis	n (% male)	Age (years)	Type	n (% male)	Age				
Aathira[16] (2017)	India	DSM-IV	71 (80.28)	5.3±1.8	TD	65 (61.54)	5.7±1.6	22 psychotropic medication, 11 antiepileptics	11 children with ASD had epilepsy	CSHQ	NA
Al-Farsi[17] (2018)	Oman	DSM-IV-TR	122 (82.8)	3–14	TD	90 (64)	3–14	NS	NS	CSHQ	NA
Allik[18] (2006)*	Sweden	ICD-10	32 (87.5)	10.80±1.25	TD	32 (87.5)	10.9±1.3	0	0	ACT, other subjective	7
Baker[19] (2013)	Australia	Clinical diagnosis	27 (81.48)	15.5±1.3	TD	27 (81.48)	15.5±1.1	12 ASD (including antidepressants, psychostimulants, sleeping agents, antiacne treatments, the contraceptive pill, antipsychotics and anti-inflammatories) and 2 TD (antiacne medication and thyroxine)	NS	ACT, other subjective	7
Bruni[20] (2007)	Italy	ICD-10 and DSM-IV	18 (88.89)	12.26±2.50	TD	12 (58.33)	12.6±3.7	0	0	PSG	2
Chou[21] (2012)	China	DSM-IV	110 (87.3)	7.6±2.4	TD	110 (87.3)	7.9±2.0	NS	NS	Other subjective	NA
Cotton[22] (2006)*	Australia	Clinical diagnosis	37 (75.7)	7.09±2.49	TD	55 (58.2)	8.88±3.95	NS	NS	Other subjective	NA
Cotton[23] (2010)*	Australia	Clinical diagnosis	34 (73.53)	7.2±2.5	TD	33 (69.70)	8.2±3.2	NS	NS	Other subjective	NA
Couturier[24] (2005)	Canada	DSM-IV	23 (95.7)	9.4±2.0	TD	23 (95.7)	9.5±2.0	75% ASD (56% stimulants, antipsychotics, and antidepressants, and 12.9% others)	NS	CSHQ	NA
Elia[25] (1991)	Italy	DSM-III-R	4 (100)	13.3 (10.5–15)	TD	5 (100)	13.0 (9–17)	NS	0	PSG	3
Elia[26] (2000)	Italy	DSM-IV	17 (100)	10.36±3.79	TD	5 (100)	9.22±2.02	0	0	PSG	2
Fletcher[27] (2017)	Australia	DSM-IV-TR	21 (81.0)	106.67±26.82 months	TD	29 (48.3)	102.10±17.07 months	ASD group: three melatonin, two stimulant, two SSRI, one atomoxetine	NS	ACT and CSHQ	14
Giannotti[28] (2008)*	Italy	DSM-IV-TR	104 (86.54)	2.3–7.10	TD	162 (62)	2.2–7.11	0	19.44% epilepsy (ASD group)	CSHQ	NA
Giannotti[29] (2011)*	Italy	DSM-IV-TR	40 (77.5)	5.32±3.12	TD	12 (75)	5.8±2.4	0	0	PSG	2
Guler[30] (2016)	Turkey	DSM-5	60 (73.3)	7.10±1.50	TD	60 (65)	6.93±1.59	NS	NS	CSHQ	NA
Han[31] (2017)	China	DSM-5	212 (85.4)	6.0±2.7	TD	334 (81.4)	5.9±2.6	NS	0	CSHQ	NA
Harder[32] (2016)*	USA	Clinical diagnosis	21 (100)	7.8±1.8	TD	23 (78.26)	8.0±1.9	0	0	PSG	1
Henderson[33] (2011)	USA	Clinical diagnosis	58 (86.2)	9.0±2.09	TD	57 (52.6)	8.25±1.98	NS	NS	Other subjective	NA
Hirata[7] (2016)	Japan	DSM-5	193 (80.83)	4.45±1.24	Community group	965 (80.83)	4.51±1.15	0	0	Other subjective	NA
Hodge[5] (2014)*	USA	DSM-IV-TR (questionnaire)	108 (83.33)	7.33±3.18	TD	108 (83.33)	7.71±3.13	NS	NS	CSHQ	NA

Continued

Systematic review

Table 1 Continued

First author (year)	Country	ASD group Diagnosis	ASD group n (% male)	ASD group Age (years)	Control group Type	Control group n (% male)	Age	Co-occurrent drugs	Comorbidities	Main sleep measures	Nights recorded (PSG/ACT)
Hoffman[34] (2006)*	USA	DSM-IV-TR	106 (84)	8.2±2.69	TD	168 (55)	8.62±3.28	NS	ASD group: 14 seizure disorders, 15 ADHD, 6 cerebral palsy	CSHQ	NA
Inamura[35] (1984) (1)†	Japan	ICD-9 (modified version)	11 (-)		TD	16 (-)	NS	NS	NS	Other subjective	NA
Inamura (1984) (2)†	Japan	ICD-9 (modified version)	19/20 (-)		TD	17/18 (-)	NS	NS	NS	Other subjective	NA
Kelmanson[8] (2018)	Russia	DSM-5 (questionnaire)	18 (100)	5	TD	54 (100)	5	NS	NS	CSHQ	NA
Kheirouri[36] (2016)	Iran	DSM-IV-TR	35 (68.6)	8.1±4.0	TD	31 (58.1)	7.3±2.6	97.1 ASD	0	CSHQ	NA
Lambert[37] (2016)*	Canada	DSM-IV	11 (NS)	10.27±2.24	TD	13 (NS)	10.23±2.01	1 ASD (methylphenidate)	0	PSG, CSHQ and other subjective	2
Levin[7] (2016)	Israel	DSM-IV	34 (73.5)	3.28±0.43	TD	31 (48.4)	3.02±0.48	NS	0	CSHQ	NA
Li[38] (2012) (1)†	China	DSM-IV	49 (-)	4.7±0.7	TD	49 (-)	4.5±0.9	NS	NS	CSHQ	NA
Li[38] (2012) (2)†	China	DSM-IV	35 (-)	9.0±2.0	TD	42 (-)	8.3±1.8	NS	NS	CSHQ	NA
Lopez-Wagner[39] (2008)*	USA	DSM-IV-TR	106 (84)	8.2±2.69	TD	168 (55)	8.62±3.28	NS	ASD group: 14 seizure disorders, 15 ADHD, 6 cerebral palsy	CSHQ	NA
Malow[40] (2009)*	USA	Clinical diagnosis	93 (90)	5.7±2.1	TD	64 (59)	6.8±2.2	13% ASD and 5% TD (including atomoxetine, benadryl, citralopram, clonidine, dexmethylphenidate, divalproex sodium, fluoxetine, guanfacine, melatonin, methylphenidate, oxycarbmazapine, risperidone and sertraline)	0	CSHQ	NA
Maski[41] (2015)	USA	Clinical diagnosis	22 (86)	11.3±2.1	TD	20 (90)	12.3±2.1	31.8% ASD (three stimulants, two antidepressants, one guanfacine±antidepressant, one mood stabiliser±antidepressant)	0	PSG, ACT and CSHQ	1 PSG/7 ACT
Matsuoka[42] (2014)	Japan	DSM-IV-TR	31 (93.55)	6–12	TD	372 (48.9)	9.4±4.5	Antiallergics, antipsychotics, antiepileptics, methylphenidate (exact percentage for ASD group is not reported)	Two TD had epilepsy, ASD no reported	CSHQ	NA
May[43] (2015)	Australia	DSM-IV-TR	46 (52.17)	9.84±1.89	TD	38 (63.16)	9.04±1.62	7 ASD (including serotonin-specific reuptake inhibitors, stimulants, risperidone and melatonin)	NS	CSHQ	NA
Miano[44] (2007)	Italy	DSM-IV	16 (100)	9.4±2.33	TD	18 (50)	10.2±2.93	0	0	PSG	2
Mutluer[45] (2016)	Turkey	DSM-5	64 (79.69)	11.66±3.8	TD	53 (75.47)	11.75±0.85	0	0	Other subjective	NA
Paavonen[46] (2008)	Finland	DSM-IV and ICD-10	52 (76.9)	10.1±3.4	TD	61 (47.5)	10.0±1.9	0	NS	Other subjective	NA

Continued

Table 1 Continued

First author (year)	Country	ASD group			Control group			Co-occurrent drugs	Comorbidities	Main sleep measures	Nights recorded (PSG/ACT)
		Diagnosis	n (% male)	Age (years)	Type	n (% male)	Age				
Pace[47] (2016)	France	DSM-5	19 (NS)	10.7±1.2	TD	19 (NS)	9.9±1.6	0	0	ACT	7
Park[48] (2012)	Korea	DSM-IV-R	166 (87.3)	7.49±3.05	TD (siblings)	111 (47.7)	7.94±3.50	NS	0	Other subjective	NA
Patzold[49] (1998)*	Australia	DSM-III and DSM-III-R	38 (81.58)	7.79±2.63	Some with developmental disabilities	36 (80.56)	8.42±2.58	45% ASD (antipsychotics and over-the-counter medications), 20% TD (anticonvulsants and asthma medications)	NS	Other subjective	NA
Phung[50] (2017)	USA	Clinical diagnosis	19 (84.2)	16.88±2.50	Neurotypical adolescents	10 (60)	15.73±2.00	NS	NS	ACT, other subjective	7
Richdale[51] (1995)	Australia	DSM-III and DSM-III-R	12 (50)	9.12±4.99	Non-ASD	35 (57.14)	7.33±2.61	NS	Two ASD had epilepsy, four TD were asthmatic, one had allergy, one had both	Other subjective	NA
Souders[52] (2009)	USA	DSM-IV-TR (checklist)	59 (81.4)	7.53±1.92	TD	40 (65)	7.09±2.09	56.7% ASD (15 melatonin, 3 catapres, 4 risperidone, 2 aripiprazole, 1 hydroxyzine, 1 fluoxetine)	0	ACT and CSHQ	10
Tessier[53] (2015)*	Canada	DSM-IV-TR	13 (100)	10.23±2.08	TD	13 (100)	10.23±2.0	0	0	PSG	2
Tzischinsky[54] (2018)	Israel	DSM-5	69 (81.16)	4.94±1.23	TD	62 (66.13)	4.82±1.15	22 ASD (including melatonin, risperdal, ritalin and neuleptil)	NS	CSHQ	NA
van der Heijden[55] (2018)	Netherlands	DSM-IV	68 (89.7)	9.6±1.9	TD	243 (51.9)	8.7±2.1	NS	ASD: 16 ADHD, 7 other	Other subjective	NA
Yang[56] (2018)	China	DSM-IV	169 (85.80)	5.23±2.0	TD	172 (84.88)	5.29±1.58	NS	NS	CSHQ	NA

*The following studies presented some overlapped participants: (1) Allik 2006, Allik 2006 and Allik 2008; (2) Cotton 2006, Cotton 2010 and Patzold 1998; (3) Giannotti 2008 and Giannotti 2011; (4) Harder 2016, and Malow 2009; (5) Hodge 2014 and Hodge 2013; (6) Hoffman 2006 and Lopez-Wagner 2008; and (7) Lambert 2016 and Tessier 2015. Studies reported in this table are those studies from which data for meta-analysis were extracted.

†Numbers 1 and 2 within parenthesis denote two different samples were reported in studies.

ACT, actigraphy; ADHD, attention-deficit/hyperactive disorder; ASD, autism spectrum disorder; DSM-III, *Diagnostic and Statistical Manual III*; DSM-III-R, *Diagnostic and Statistical Manual III*, revised; DSM-IV, *Diagnostic and Statistical Manual IV*; DSM-IV-TR, *Diagnostic and Statistical Manual IV*, text revision; DSM-V, *Diagnostic and Statistical Manual V*; ICD-9, International Statistical Classification of Diseases, Ninth Revision; ICD-10, International Statistical Classification of Diseases, Tenth Revision; NA, not applicable; NS, not specified; PSG, polysomnography; SSRI, selective serotonin reuptake inhibitor; TD, typically development children.

Table 2 Summary of the results of the meta-analysis with subjective sleep parameters

Sleep parameter	k	N	SMD (95% CI)	Z	P values	Heterogeneity Q	P values	I^2	Egger's test t	P values
Bedtime resistance	21	3589	1.00 (0.67 to 1.33)	5.98	<0.00001	362.85	<0.00001	94	2.00	0.059
Sleep onset delay	22	3636	0.98 (0.66 to 1.29)	6.03	<0.00001	362.72	<0.00001	94	2.09	0.049
Sleep duration	22	3376	−0.88 (−1.18 to 0.57)	5.69	<0.00001	304.14	<0.00001	93	2.19	0.040
Sleep anxiety	20	3312	0.96 (0.61 to 1.32)	5.30	<0.00001	375.97	<0.00001	95	2.69	0.014
Night awakenings*	20	3312	0.74 (0.44 to 1.04)	4.81	<0.00001	274.60	<0.00001	93	1.26	0.222
Parasomnias	22	4747	0.88 (0.60 to 1.15)	6.24	<0.00001	330.97	<0.00001	94	3.30	0.003
Sleep-disordered breathing	24	4129	0.48 (0.28 to 0.67)	4.80	<0.00001	181.14	<0.00001	87	1.06	0.299
Daytime sleepiness	28	5430	0.34 (0.16 to 0.52)	3.62	0.0003	226.25	<0.00001	88	2.26	0.032
General sleep problems	27	5291	0.93 (0.67 to 1.20)	6.97	<0.00001	409.23	<0.00001	94	2.31	0.028
Sleep quality	3	155	0.24 (−1.05 to 1.52)	0.36	0.72	27.38	<0.00001	93	0.41	0.752
Sleep efficiency	2	75	−0.28 (−1.07 to 0.51)	0.68	0.49	2.63	0.11	62		
Sleep onset latency (min)	6	787	0.81 (0.59 to 1.02)	7.33	<0.00001	7.82	0.17	36	0.94	0.198
Sleep duration (min)	6	766	−0.32 (−0.74 to 0.11)	1.47	0.14	31.78	<0.00001	84	0.08	0.939
Restorative value of sleep	2	91	0.13 (−0.96 to 1.23)	0.24	0.81	5.23	0.02	81		

*In order to reduce the heterogeneity between effect sizes, data already reported in similar measures were not included. This decision led to the exclusion of the data provided in two studies[23 51] for subjective night awakenings, as well as to the division of sleep duration and sleep onset delay in two distinct variables: sleep duration and sleep onset delay reported as a score in questionnaire or as a length (in min).

SMD, standardised mean difference.

than considering these two types of measures as exclusionary, we would suggest they should be seen as providing complementary information. Additionally, even within objective studies, there were some discrepancies among apparently similar parameters. Of note, sleep efficiency was significantly different between participants with and without ASD when measured with PSG but not when assessed via actigraphy. The different degree of ecological validity of PSG (usually implemented in a lab) and actigraphy (in the home environment) may contribute to explain these discrepancies.

Our findings could have been impacted by the presence of psychiatric comorbidities and the drug intake of the subjects included in our meta-analysis. For example, psychiatric comorbidities, including epilepsy and attention-deficit/hyperactive disorder (ADHD) were reported in at least 19% (7/37) of the studies included in our meta-analysis. Drug intake,

including stimulants and melatonin, was mentioned in 35% (13/37) of the studies included. In fact, the impact of psychiatric comorbidities on sleep has been consistently reported in research.[60 61] The effects of drug on sleep patterns were also well documented.[61] Thus, the high heterogeneity of the results among studies we observed (based on the results of the Egger's test and the funnel plot) may be related to participants' comorbid conditions or medication intake. Unfortunately, most of the studies taking account in our analysis did not provide this information, which could have been useful to perform a meta-regression to assess the impact of these possible confounders. Additionally, our post hoc analysis based on studies including only comorbidity-free and medication-naïve participants could only confirm the results of the main meta-analysis of PSG studies, as there were not enough studies for the analysis of subjective and actigraphic parameters.

Table 3 Summary of the results of the meta-analysis with objective sleep parameters

Sleep parameter	k	N	SMD (95% CI)	Z	P values	Heterogeneity Q	P values	I^2	Egger's test t	P values
Polysomnography										
Total sleep time	8	247	−0.90 (−1.51 to 0.30)	2.93	0.003	29.76	0.0001	76	0.35	0.734
Sleep onset latency	7	211	0.53 (0.21 to 0.86)	3.26	0.001	7.06	0.32	15	0.24	0.818
Stage 1 sleep	8	247	0.48 (0.06 to 0.90)	2.25	0.02	15.67	0.03	55	0.37	0.723
Stage 2 sleep	8	247	0.12 (−0.50 to 0.73)	0.37	0.71	33.06	<0.0001	79	1.15	0.292
Slow wave sleep	8	247	−0.15 (−0.83 to 0.53)	0.43	0.66	41.08	<0.00001	83	0.56	0.596
REM latency	7	211	−0.03 (−0.48 to 0.42)	0.13	0.90	13.79	0.03	56	0.42	0.689
REM	9	273	−0.88 (−1.56 to 0.21)	2.56	0.01	46.07	<0.00001	83	1.47	0.182
Sleep efficiency	7	238	−1.20 (−1.98 to 0.41)	2.99	0.003	40.31	<0.00001	85	1.76	0.138
Wake time	7	211	0.49 (0.11 to 0.87)	2.53	0.01	9.67	0.14	38	0.75	0.485
Actigraphy										
Sleep onset latency	5	276	0.80 (0.55 to 1.05)	6.23	<0.00001	2.49	0.65	0	0.36	0.745
True sleep	6	301	−0.04 (−0.37 to 0.29)	0.24	0.81	9.65	0.09	48	1.74	0.156
Assumed sleep time	2	144	−0.14 (−0.47 to 0.20)	0.80	0.42	0.05	0.83	0		
Actual wake time	4	237	0.12 (−0.14 to 0.38)	0.92	0.36	2.03	0.57	0	0.45	0.697
Sleep efficiency	6	312	−0.16 (−0.54 to 0.22)	0.82	0.41	13.20	0.02	62	0.91	0.416

SMD, standardised mean difference.

Table 4 Summary of the results of the post hoc analysis with polysomnographic parameters

Sleep parameter	k	N	SMD (95% CI)	Z	P values	Heterogeneity			Egger's test	
						Q	p	I^2	t	P values
Total sleep time	5	178	−1.12 (−1.57 to 0.66)	4.76	<0.00001	7.10	0.13	44	1.32	0.278
Sleep onset latency	5	178	0.56 (0.21 to 0.90)	3.12	0.002	4.68	0.32	15	0.95	0.413
Stage one sleep	5	178	0.20 (−0.11 to 0.52)	1.28	0.20	2.25	0.69	0	4.02	0.028
Stage two sleep	5	178	0.03 (−0.68 to 0.73)	0.07	0.94	18.55	0.001	78	0.35	0.747
Slow wave sleep	5	178	−0.17 (−1.14 to 0.80)	0.35	0.73	33.61	<0.00001	88	0.40	0.714
REM latency	5	178	0.01 (−0.57 to 0.58)	0.02	0.98	12.42	0.01	68	0.68	0.545
REM	6	204	−0.58 (−1.13 to 0.02)	2.04	0.04	16.49	0.006	70	0.04	0.972
Sleep efficiency	5	178	−0.90 (−1.38 to 0.42)	3.67	0.0002	8.14	0.09	51	0.44	0.689
Wake time	5	178	0.57 (0.10 to 1.04)	2.38	0.02	8.30	0.08	52	0.59	0.597

SMD, standardised mean difference.

In addition to the possible role of psychiatric comorbidities and medications, the causes of sleep impairments in children with ASD are likely to be complex and not mutually exclusive. Behavioural factors such as dysfunctional bedtime routines, exacerbated by comorbid anxiety or ADHD, may disrupt sleep, especially sleep onset delay. There is also an increasing body of evidence suggesting the contributing role of biological clock factors (mainly endocrine and genetic) that could be involved in dysregulation of day–night rhythm and sleep patterns in subjects with ASD (see review of ref [62]). For instance, ASD was associated with decreased urinary or blood melatonin level,[63] probably due to genetic and epigenetic abnormalities affecting the enzymes of the melatonin synthesis and degradation pathways.[64] Similarly, several studies suggested that BMAL1 (brain muscle ARNT [arylhydrocarbon receptor nuclear translocator]-like 1) or additional clock genes involved in the synchronisation of biological rhythms may be impaired in ASD. This may affect the ability of patients with ASD to anticipate and adapt their behaviours (including their sleep patterns) to environmental changes.[65]

The results of our systematic meta-analysis should be considered in the light of its strengths and limitations. As for the strengths, we preregistered the protocol in a publicly available repository (PROSPERO), reducing the risk of reporting bias. Furthermore, we endeavoured to perform a comprehensive and systematic search in several databases, with no restrictions in terms of language or document type, 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 were also a number of limitations that should be taken into account. First, statistical heterogeneity was significant for the majority of the included measures. Although this did not invalidate the results, it indicated that the pooled effect sizes could not appropriately summarise the results from all datasets. Second, while we endeavoured to perform a comprehensive search, there was evidence of publication bias for a number of measures, which suggested that a more transparent report of research findings in the field is needed. Third, as for the quality of individual studies, most of them were rated at overall medium quality or risk of bias using the Newcastle-Ottawa Scale, and main concerns were noted in relation to the comparability of groups and exposure-related items. The latter, along with the relatively sparse evidences available for some sleep parameters, calls for more studies assessing sleep impairments in children with ASD and by controlling the mentioned concerns.

Despite these caveats, we deem that our study provides meta-analytic evidence of objective and subjective sleep difficulties in patients with ASD. Clinicians managing children with ASD should systematically query about sleep alterations, during the first assessment and all along the follow-up. Subjective questionnaires such as the scale by Bruni et al[66] or Owens et al[67] can be used to screen sleep difficulties at the first assessment and at each follow-up visit with children with ASD. The extent to which these alterations are accounted for by comorbid disorders and/or the effect of pharmacotherapy should be better explored in future studies recruiting only medication-naïve and comorbidity-free participants, although our post hoc analysis suggest that objective differences inn sleep parameters are detected regardless the effect of comorbidities and medications. Additionally, further research needs to be performed to dissect the dysfunction of biological regulators in ASD. This may offer new promising avenues for early detection and therapeutic intervention in ASD.

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