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CLINICAL REVIEW

Sleep in Angelman syndrome: A review of evidence

Karen Spruyt [a, b, *], Wiebe Braam [c, d], Leopold MG. Curfs [a, e]

[a] Governor Kremers Center-Rett Expertise Center & MHeNs, Maastricht University, The Netherlands
[b] Department of Developmental and Behavioral Pediatrics, Shanghai Children's Medical Center Affiliated with Shanghai Jiaotong University School of Medicine, Shanghai, China
[c] 's Heeren Loo, Department Advisium, Wekerom, The Netherlands
[d] Governor Kremers Centre, Maastricht University, The Netherlands
[e] Department of Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands

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SUMMARY

Sleep problems are reported to be extremely prevalent in individuals with developmental disabilities. The consensus guidelines for Angelman syndrome (AS) consider abnormal sleep-wake cycles and diminished need for sleep as associated features. We report an integrative research review and a meta-analysis of studies with sleep as the primary aim of investigation in an AS sample.

14 studies met eligibility criteria with half of them being surveys. Thirteen of the 17 conceptually formed sleep disorder item-groups showed to be significant for individuals with AS. There is evidence that arousal during sleep, somnolence and possibly short sleep duration are the primary sleep problems in individuals with AS.

According to the results of this review and meta-analyses, there is clear evidence for sleep problems in individuals with AS. Individual effect sizes remain overall small, but nevertheless findings suggest disorders of arousal and sleepiness to be distinctive. In light of these findings, other sleep complaints in individuals with AS should be carefully examined. Consistent standards for research on sleep in individuals with AS are critical for new lines of investigation.

Introduction

Children exhibiting the features of severe developmental delay, jerky movements, seizures, and happy disposition were first described by Angelman [2]. In Angelman syndrome (AS), many characteristic features are due to deficient ubiquitin protein ligase 3a (UBE3A). That is, the gene for which UBE3A maps to chromosome 15q11-q13 is imprinted such that only the maternally inherited gene is expressed [OMIM#105830] [3]. AS is defined as a neurogenetic disorder with a prevalence of 1:10,000–20,000 worldwide. The main features are severe intellectual disability, speech impairment, ataxia, epilepsy, sleep disorder and a behavioral phenotype that reportedly includes happy disposition, attraction to or fascination with water and hyper-motoric behavior [4–6].

In the consensus guidelines [7,8] abnormal sleep-wake cycles and diminished need for sleep are considered associated features of AS [8]. Distinctive sleep problems or disorders are scarcely reported. On the one hand, abnormal encephalogram (EEG) patterns [6,9] were found to be sufficiently distinguishing to help identify AS at an early age. These patterns basically involve either characteristic rhythmic patterns (unrelated to epilepsy) or less specific epilepsy-related discharge activity. Based on these features a model of cortical and thalamo-cortical dysfunction has been proposed [6]. Unfortunately, the observed EEG rhythmic patterns, in part due to their transient nature, might be common in chromosomal disorders in general. Studies investigating sleep polysomnographic patterns [10] auxiliary suggested that the 2–3 c/s spike/waves complexes are typically poorly defined in individuals with AS. On the other hand, the related sleep problems to such EEG abnormalities remain poorly characterized. For instance, phone interviews with caregivers indicated that 72% of individuals with AS have 'sleep dysfunction' [11]. In the clinical review by Pelc et al. [12]: reduced

Abbreviations: AS, Angelman syndrome; BEDS, behavior evaluation of disorders of sleep; CI, 95% Confidence Interval; ES, effect size estimates; EEG, electro-encephalogram; GABA, gamma aminobutyric acid; REM, rapid eye movement; UBE3A, ubiquitin protein ligase 3a.

* Corresponding author. Maastricht University Medical Centre, PO Box 616, 6200 MD Maastricht, The Netherlands. Fax: +31 (0)43 3881870.
E-mail address: spruytsleep@gmail.com (K. Spruyt).

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sleep duration, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, reduced rapid eye movement (REM) sleep and periodic leg movements, were concluded as characteristic problems. Moreover, these sleep problems were reported to not interfere with daytime functioning [12]. Also, the sleep problems were summarized to diminish by late childhood [12] as in typically developing children, although this was not a collective finding [1,13].

Alternatively, in individuals with developmental disabilities sleep problems are reported to be extremely prevalent [14–16]. Their sleep problems however often have a multifactorial origin and a tendency to be chronic. The robust interplay between the genetic, neurobiological and epigenetic features of developmental disabilities possibly generates an overlap in sleep complaints. In fact, the most common sleep complaints in individuals with developmental disabilities are problems with initiating and maintaining sleep as well as irregular sleep [17,18]. As a result, the management of their sleep problems is chiefly focused on the complaints of initiating and maintaining sleep yet through a diversity of strategies [17,19–22]. Treatment was also found to mainly rely on subjective measures to identify and monitor problematic sleeping [17].

The high prevalence of sleep complaints and the few systematic studies of sleep that have been conducted in AS per Pelc et al. [12], underlines the need for a disability-specific understanding of the sleep problems. This may help the adaptation of sleep interventions to the specific needs of individuals with AS. The purpose of the present study is therefore to provide an integrative research review and quantitative summary of the literature on sleep in individuals with AS.

Methods

The review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Methods of searches, selection of studies, data extraction and quality assessment were specified a priori. Based on the following inclusion and exclusion criteria articles were searched, screened and selected.

In the first round, our electronic search strategy comprised the MeSH terms *"Angelman syndrome", "sleep", "polysomnography", "questionnaire", "actigraphy"* across PubMed and Web of science (e.g., see flowchart 1). Inclusion criteria were citing "sleep" either or not combined with "polysomnography", "questionnaire", "actigraphy". More specifically, sleep should be the primary aim of the study; for example, it should not involve copying of information or tables from other studies regarding sleep variables. Excluded were papers that did not primarily discuss AS (in contrast to Pelc et al. [12]), reviews in general and articles in non-English language. In the second round, reference lists of the retained articles and AS review articles were screened on *"AS in the title and whether their primary scope was sleep or sleep disorders in AS"*. Finally, articles retained for detailed analyses have "sleep" as the primary aim of the study in an AS sample. Studies up to February 1st 2016 were included.

'Sleep' was categorized into sleep quantity (duration or architecture), sleep quality (problems or disorders), regularity (bedtime schedule, circadian rhythm), sleepiness, sleep hygiene, sleep ecology and sleep treatment. The characteristics of each study were extracted and tabulated. Descriptive analyses will be presented. Statistical analyses were performed with Statistica version 10 (StatSoft, Inc. (2009), STATISTICA, Tulsa, OK).

Meta-analyses were performed with Comprehensive meta-analysis version 2.2.064 (Biostat, Englewood, NJ). Results reflect relative weight under the random effect model (unless reported otherwise). The effect size estimates (ES) for each outcome variable of interest are illustrated in the forest plots (the size of the symbol expresses the weight) and are printed in tables. Heterogeneity (I-squared, or how comparable studies in the meta-analysis are) and statistical significance were reported to describe the variance between studies. The z-value or test for overall effect indicates whether the individual ES is significantly different from zero. That is, in meta-analysis the null hypothesis is that all of the separate null hypotheses are true.

Firstly, items of the questionnaires across studies were conceptually grouped and their ES were calculated when possible (ES: pooled event rate). Secondly, a meta-analysis was performed on the available subscale data (ES: standardized difference in means ± standard error). Lastly, we wanted to pursue a meta-analysis of objective sleep data, but given the limited amount of objective data available we pooled when possible the study results from diary, logs, actigraphy and polysomnography (ES: pooled means ± standard error).

Results

Descriptive analysis

Study sample

The selection process is shown in Fig. 1. Based on the selection criteria 52 articles were selected. Following more in-depth examination 14 articles were retained for detailed review (e.g., see Table 1). Since the first study investigating sleep in AS in 1992, less than one study per year (0.64 ± 1.05 study per year with min. 0 to max. 3) had sleep as a primary aim in an AS sample. Half of the studies were performed in the USA [23–29] and 42.9% were performed in Europe (i.e., Italy [1,10,30], Netherlands [13,31] and UK [32]) and 1 study was done in Japan [33]. The sample size ranged from 1 to 339 individuals with AS (on average 62.35 ± 110.91) within the age-range of 2–44 years. Overall gender was nearly equally distributed, i.e., 49.4 ± 26.23% males.

Study methodology

Of the 14 studies, three were case(-series) reports, four were intervention studies, and seven were descriptive (e.g., see Table 2). Subjective sleep measures such as diaries, logs or questionnaires were applied in 78.6% the studies [1,13,23–28,31–33] of which six used a sleep questionnaire [1,13,25–28]. The sleep questionnaires used were: behavior evaluation of disorders of sleep (BEDS) [34], Simonds & Parraga questionnaire adapted by Wiggs and Stores [35,36], Bruni's sleep disturbance scale for children [37], and children's sleep habits questionnaire [38]. Polysomnography was used in 3 studies [10,29,30] of which two are from the same author (hence an overlap in the sample) and the latter being a case report. Two studies [24,28] used subjective and actigraphic recordings as sleep measures, one applied subjective recordings and polysomnography (i.e., clinical purpose) [23] and two studies [27,32] reported a combination of all three.

Study scope

Evaluating the general content of the study, the following results were found. Sleep quantity was part of the sleep aim in 71.4% of the studies and sleep quality in 64.3%. Reports on sleep regularity were done in 28.6%, and to a certain degree in 14.3% of the 14 studies included. Only one study reported on sleepiness and similarly for sleep hygiene. Sleep ecology was incorporated in 21.4% of the studies. Sleep treatment was part of the study in 42.9% of the 14 articles reviewed.

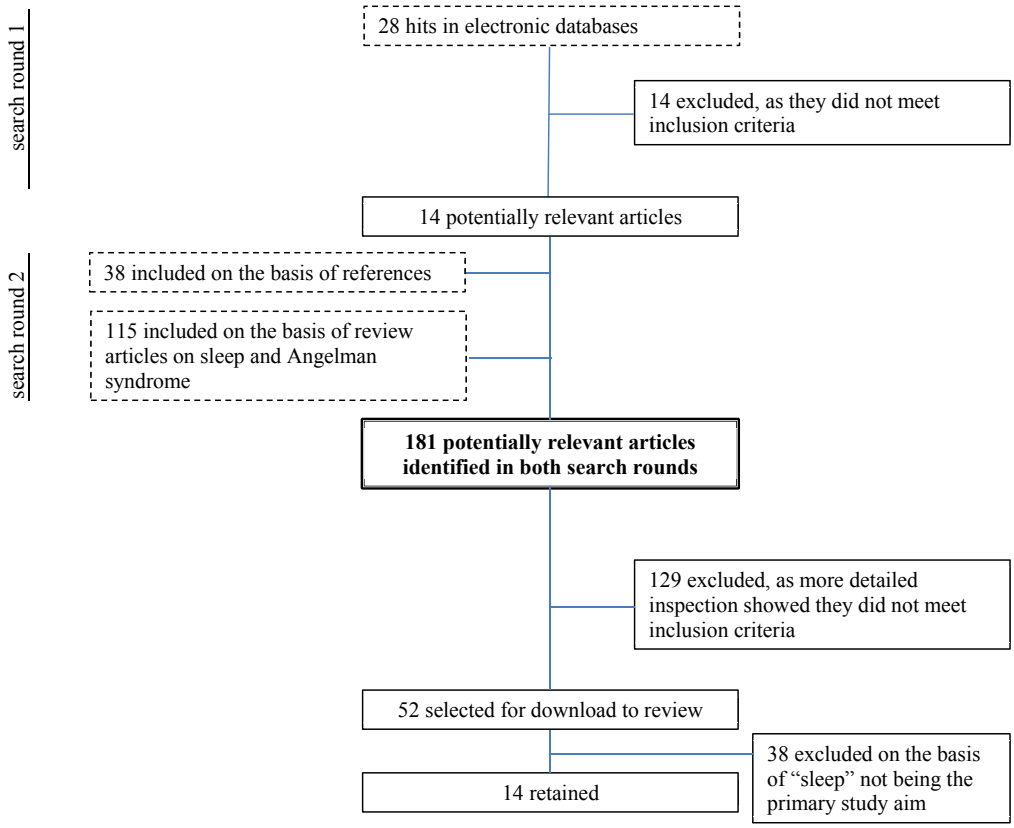


Fig. 1. Flow chart of literature search.

Table 1
All studies and their sleep category.

Authors	Year	Setting	Study design	Sleep measure	Sleep quantity	Sleep quality	Sleep regularity	Sleepiness	Sleep hygiene	Sleep ecology	Sleep treatment
Summers et al. [23]	1992	USA	Single case quasi-experimental interrupted time-series	Subjective (prior polysomnography)	x		(x)				x
Zhdanova et al. [24]	1992	USA	Intervention (AB design): effect of melatonin	Subjective Actigraphy	x		(x)				x
Bruni et al. [12]	2004	Italy	Comparative descriptive	Subjective	x	x		x			
Miano et al. [9]	2004	Italy	Comparative descriptive	Polysomnography	x						
Didden et al. [13]	2004	Netherlands	Descriptive	Subjective		x					
Miano et al. [30]	2005	Italy	Comparative descriptive	Polysomnography		x					
Walz et al. [25]	2005	USA	Descriptive	Subjective	x	x			x	x	
Anderson et al. [32]	2008	UK	Case series	Subjective Polysomnography Actigraphy	x	x	x				
Braam et al. [31]	2008	Netherlands	Randomized placebo-controlled	Subjective	x	x					x
Conant et al. [26]	2009	USA	Descriptive	Subjective	x					x	
Takaesu et al. [33]	2012	Japan	Case series intervention	Subjective			x				x
Goldman et al. [27]	2012	USA	Comparative descriptive	Subjective Polysomnography Actigraphy	x	x	x				
Allen et al. [28]	2013	USA	Intervention study: multiple baseline design across participants	Subjective Actigraphy	x	x	x			x	x
Jain et al. [29]	2014	USA	single-case intervention: effect melatonin	Polysomnography		x					x

AB design: the initial 'A' in this design refers to a baseline for each subject and 'B' stands for a treatment/measurement.

Risk of bias in included studies

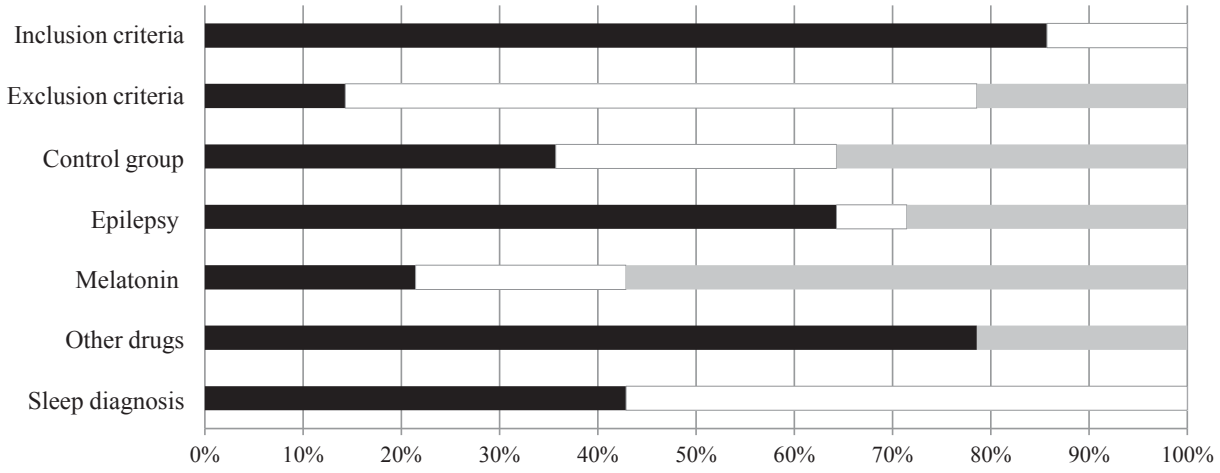
When evaluating the quality of studies [39] reviewed regarding a potential risk of bias, we screened the articles for study design, inclusion/exclusion criteria being clearly stated and measured, inclusion of control group, report of epilepsy/melatonin/other drug use and sleep diagnosis (e.g., see Fig. 2). The study design was in 42.9% mixed, 42.9% prospective and 14.3% retrospective. Only two studies [23,33] clearly stated a classification-based sleep diagnosis, the remainder mainly reported the complaints.

Table 2
Study characteristics and findings.

Authors, reference number	Sample size AS	Sample size other	Age AS (y)	Age other (y)	Gender AS (# male)	Gender other	Genetic etiology	Epilepsy AS	Sleep assessment	Sleep outcome	Sleep treatment	General conclusion	Conclusion regarding AS	Conclusion regarding other
Summers et al. [23]	1	NA	9	NA	1	NA	Interstitial deletion on chromosome 15 region q11q13		24 h recording system, whole interval recording	Hours slept at baseline, treatment, follow up	Behavioral and pharmacological	Increased night sleep and reduced day sleep	Sleep-wake schedule disorder [DSM III-R]	
Zhdanova et al. [24]	13	NA	2–10	NA	4	NA	12: typical 15 q 11–q 13 deletions; 1: paternal UPD 15 resulting from a 13; 15 Robertsonian translocation inherited along with a normal chromosome 15 from the father		Sleep diary Blood samples Actigraphy (a Pocket on the back of a cloth vest)	Total sleep period at baseline, treatment	Melatonin; 5 days on 0.3 mg dose administered 1/2–1 h before subject's habitual bedtime	Regularized and less interrupted sleep	A moderate increase in circulating melatonin levels significantly reduces motor activity during the sleep period	
Bruni et al. [1]	49: A:37; B:12	893 control, random selection from 3 schools in Rome	A: 2.3–14.8 B: 15.8–26.2	6.5–14.10	A: 20 B: 6	442	25: deletion of chromosome 15q11–13; 6: methylation imprinting mutation; 7: UBE3A mutations; 5: paternal UPD; 6: negative genetic testing	–	Sleep disturbance scale for children [37]	39 sleep complaints queried	NA	Sleep/wake rhythms fragmentation	4 genetic subtype similar	24 sleep complaints significantly different from control
Miano et al. [9]	15: A:9; B:6	Age-matched: 24 control (C:9 & D:15); 19 mental retardation (E:9 & F:10)	A: 3-5; B: 9–17	C: 3–8; D: 8–18; E: 4–9; F: 10–17	A:5 B:2	C:6 D:6 E:4 F:2	11: a deletion of Prader Willy syndrome/AS region with absence of the maternal allele; 1: paternal UPD; 1: mutation of the UBE3A gene; 2: excluded the presence of 15q deletion or imprinting region microdeletions, but impossible to exclude the presence of UBE3A mutations		Polysomnography	Sleep structure	NA	Signs of disturbed sleep: reduction of % rapid eye movement sleep; increase in stage 4 and slow-wave sleep		<8 years: no significant differences between subjects with AS and patients with mental retardation and epilepsy; >9 years: AS presented a number of stage shifts/hour higher than that found in patients with mental retardation and epilepsy
Didden et al. [13]	109	NA	2–44	NA	53	NA	78%: deletion; 11% disomy; 3%: trans-location inversion; 8%: not reported by parent; 15%: clinical history and features		Simonds & Parraga questionnaire adapted by Wiggs and Stores [35,36]	31 sleep complaints & Parental/Caregiver Behaviors and Reactions to Participant's Sleep Problem	NA	40% had a severe sleep problem: severe types of frequent night waking occurred most often (37%), followed by early waking (10%); only 2% showed severe settling problems	No association with neither individual-related variables nor parents' and caregivers' coping strategies	
Miano et al. [30]	10	15: mental retardation without epilepsy (A); 13: mental retardation with epilepsy (B)	2–16	A: 3-10; B: 3–9	5	A: 6; B: 8	6: a deletion of Prader Willy syndrome/AS region with absence of the maternal allele; 1: paternal UPD; 3: mutation of the UBE3A gene	3 febrile convulsions; 3 myoclonic epilepsy; 1 tonic–clonic generalized seizure; 1 absence epilepsy + myoclonic epilepsy; 2 no epilepsy and 4 taking valproic acid; 1 valproic acid + clobazam; 2 valproic acid + clonazepam; 1 valproic acid + diazepam	Polysomnography	Sleep respiratory; PLM index	NA	A high prevalence of sleep disordered breathing and periodic leg movements; an important causative role for epileptiform discharges and anti-epileptic drugs in the disruption of sleep continuity	% of rapid eye movement sleep was reduced	% of rapid eye movement sleep was reduced in B
Walz et al. [25]	339; 195 between 5 and 12 yrs	307 control	3–22	5–12	165		60%: maternal deletion of 15q11.2-q13; 16%: genetic workup negative; 7%: paternal UPD; 3% UBE3A mutation; 2% imprinting mutation; 1% other structural rearrangement; 11% unsure/did not answer question		BEDS [34]	28 sleep complaints	NA	A variety of sleep problems in almost 50%	Medium association between genetic subtype and sleep complaint (Cohen effect size)	Problems exceed those present the general population
Anderson et al. [32]	3 siblings	NA	28; 29; 32	NA	0	NA	deletion of maternal 15q11-q13		Sleep diary Actigraphy Polysomnography in 1 woman	2-week period detailing wake and sleep times and daily activities; circadian rhythm; apnea/hypopnea	NA	No evidence for an intrinsic CRSD; striking central and obstructive sleep apnea		NA

Braam et al. [31]	8	NA	5.7–20.11	NA	3	NA	6: deletion; 2: disomy		Saliva specimens; sleep diary	Lights out time; sleep onset time; sleep latency; sleep offset time; number of nights/ week with wakes; number of wakes/ night; duration of wakes; total sleep time	Placebo and 5 or 2.5 mg melatonin	Effective in decreasing sleep latency, advancing sleep onset, and increasing total sleep time	Melatonin levels after 4 weeks of treatment were extreme high, probably due to slow melatonin metabolisation by CYP1A2	Slow melatonin metabolisation is probable part of AS phenotype. Melatonin dose should be low.
Conant et al. [26]	290	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		Behavior Evaluation of Disorders of Sleep (BEDS) [34]	107 sleep complaints	NA	Similar to those of the previous study employing the BEDS [25]		
Takaesu et al. [33]	15	14 control	16.3 ± 7.3	13.4 ± 4.2	7	8	15q11–q13 deletions		Sleep logs Blood samples	Melatonin profile in AS patients with CRSD: irregular sleep-wake type, n = 4; free-running type n = 2; delayed sleep phase type, n = 2	In 6 a daily dose of 1 mg of melatonin between 18:00 and 19:00	Lower nighttime serum melatonin levels of AS	The nocturnal melatonin levels were comparably low both in AS patients with and without CRSD except for the cases with delayed sleep phase type, which showed normal but delayed peak melatonin level; treatment improved sleep	
Goldman et al. [27]	15	469 normative sample [38]	2–16	NA	6	NA	3: UPD; 1: imprinting center mutation; 1: an imprinting center mosaic genotype (this child had only questionnaire data).	–	AS: CSHQ [38] parent: ISI (Morin 1993), ESS (Johns 1991); PSI-SF (Abiden 1995); polysomnography (14 completed); 28 nights of actiwatch (10 with max. 7 days)	AS: 45 sleep complaints; parent: 5 insomnia questions; 8 sleepiness questions; 36 stress items	NA	Nocturnal awakenings and restless sleep; disrupted night-time sleep of the parents		
Allen et al. [28]	5	57 developmental delay without autism (A); 69: typically developing (B) (from Goodlin-Jones et al. (2008))	2–11	A: 45.7 ± 11.7; B: 40.9 ± 10.7	2	Not reported	Confirmed by genetic testing		Sleep diary; Actigraphy; Questionnaires: DBC-P, abbreviated CSHQ, Customer satisfaction questionnaire		Behavioral treatment package targeting the sleep environment, the sleep-wake schedule, and parent–child interactions during sleep times.	After treatment, the scores on the DBC-P showed a reduction in the incidence of non-sleep behavior problems; changes in disruptive bedtime behaviors and in sleep onset were		
Jain et al. [29]	1	NA	9	NA	1	NA			Polysomnography	Nighttime awakenings; pauses in breathing	Sustained-release melatonin: 3 mg 30 min prior to bedtime	A reduction in arousals and improvement in insomnia with sustained-release melatonin		

Abbreviations: AS: Angelman syndrome; BEDS: behavior evaluation of disorders of sleep; CRSD: circadian rhythm sleep disorders; CSHQ: children's sleep habits questionnaire; CYP1A2: cytochrome P450 Family 1 Subfamily A Member 2; DBC-P: developmental behavior checklist; DSM III-R: diagnostic and statistical manual of mental disorders, third edition, Revised; ESS: Epworth sleepiness scale; ISI: insomnia severity index; NA: not applicable; PLM: periodic leg movement; PSI-SF: parenting stress index short form; UBE3A: ubiquitin protein ligase 3a; UPD: uniparental disomy; %: percentage.



Black bar: Yes**; White bar:** No**; Grey bar:** unknown/not reported/not applicable

Fig. 2. Risk of bias (%).

Meta-analyses of sleep questionnaire items

The majority of the sleep disorder item-groups were significantly present in AS. Overall the ES ranged from small to large effects.

More specifically, the conceptually grouped nightmares, night terrors and fearful dreams items (e.g., see Fig. 3A), based on four questionnaire studies [1,13,25,26] including 20 items (i.e., 16 similar ones) showed a moderate degree of heterogeneity. This could be ascribed to the items themselves and the answer format (e.g., Bruni et al. [1] including once or twice per week) as well as the sample characteristics. Despite the small ES, this item group being suggestive of 'waking up during the night' showed to be distinctive. In two studies [1,13] eight items queried movements during sleep (e.g., see Fig. 3B). Also here the degree of heterogeneity was large. Apart from the item/answer format discrepancies and the sample characteristics, the timing of occurrence during the sleep period might be influential in the effect size estimation. Furthermore, the item "nocturnal hyperkinesias" [1] is the least specific item yielding a larger ES. Of the three questionnaires applied in the four studies [1,13,25,26], seven items (i.e., four similar ones) queried fear (e.g., see Fig. 3C), and alike the previous items heterogeneity was large. The item 'anxiety/fear when falling asleep" [1] showed the largest ES. Two studies [1,13] questioned bedtime problems (i.e., four items) (e.g., see Fig. 3D), however each of the items queried bedtime problems almost uniquely, resulting in a high degree of heterogeneity. In addition to the methodological differences between the two studies, the heterogeneity might thus be ascribed to the disparity between the ES of "particular bedtime routine" [13] being the largest and the ES of "reluctant to go to sleep" being the smallest [13]. Yet, despite the large individual ES, bedtime problems were not significantly more present in AS. The combined ES for nighttime urination (e.g., see Fig. 3E) was also not significant and highly heterogeneous. It was based on three questionnaires [1,13,25] with four items of which two items were similar. Excluding the item 'getting up to use the bathroom" [1] which contrasts the bed-wetting items did not alter the result (ES = 0.453, 95%CI: 0.181 to 0.755, z-value = −0.284, p-value = 0.777; I-squared = 96.43%, p-value < 0.0001). Potentially the different age-ranges across the studies, in addition to their methodological differences, might explain this result.

The four survey studies [1,13,25,26] involving three questionnaires and 11 items (i.e., six similar items) querying sleep disordered breathing (e.g., see Fig. 3F) were also found highly heterogeneous due to item characteristics and samples. Excluding the item "breathes through mouth rather than nose" [13], which has the largest ES, decreased the heterogeneity (ES = 0.053, 95%CI: 0.027 to 0.101, z-value = −8.203, p-value < 0.0001; I-squared = 88.14%, p-value < 0.0001). Also regarding the combined ES for bruxism, based on three questionnaire studies [1,13,25] including four items (i.e., three similar ones) (e.g., see Fig. 3G), there was significant evidence of heterogeneity. This could again be ascribed to the methodological differences, and with the exclusion of the item "bites tongue" [13] increasing the ES (ES = 0.123, 95%CI: 0.054 to 0.255, z-value = 4.316, p-value < 0.0001; I-squared = 83.82%, p-value = 0.002).

From the BEDS [34] questionnaire in two studies [25,26] nine items (i.e., eight similar ones) involving the sensitivity to the environment resulted in a high heterogeneity (e.g., see Fig. 3H; fixed effect model) that could be ascribed to the diversity of the items themselves. Exclusion of the item "is awakened by loud noises" [25,26] resulted in a decrease of the heterogeneity (ES = 0.073, 95%CI: 0.061 to 0.087, z-value = −9.777, p-value < 0.0001; I-squared = 87.09%, p-value < 0.0001). The combined ES for napping, based on two questionnaires and three items (i.e., two similar ones) from three studies [13,25,26] (e.g., see Fig. 3I) showed that methodological differences may account for the large heterogeneity. Whilst the combined ES for somnolence, based on three questionnaires and seven items (i.e., two similar ones) from four studies [1,13,25,26] (e.g., see Fig. 3J), showed no significant evidence of heterogeneity, the ES remained small.

Three survey studies [1,25,26] involving two questionnaires and four items (i.e., two similar items) showed a non-significant combined ES (e.g., see Fig. 3K) for difficulty falling asleep, which was found to be heterogeneous likely due to methodological differences. In contrast to others, the studies by Bruni et al. [1] and Didden et al. [13] questioned nighttime sweating; i.e., three items (e.g., see Fig. 3L). There was no evidence of heterogeneity but ES remained very small. The combined ES for

difficulties when waking up, based on three questionnaires and 11 items (i.e., eight similar ones) from four studies [1,13,25,26] (e.g., see Fig. 3M) showed heterogeneity. This high amount of heterogeneity could be ascribed to the methodological diversity of the studies included, and specifically to the type of behavior assessed when waking up. Characteristic for the syndrome might be the large ES for the items "wakes up in a good mood" and "wakes up rested" by Didden et al. [13]. For sleepwalking a significant combined ES was found (e.g., see Fig. 3N). This was based on the homogeneous set of items across three survey studies [1,13,26] or three questionnaires. Only Bruni et al. [1] reported a low prevalence which might be ascribed to the cut-off applied; i.e., including the occurrence of sleepwalking as once or twice per week.

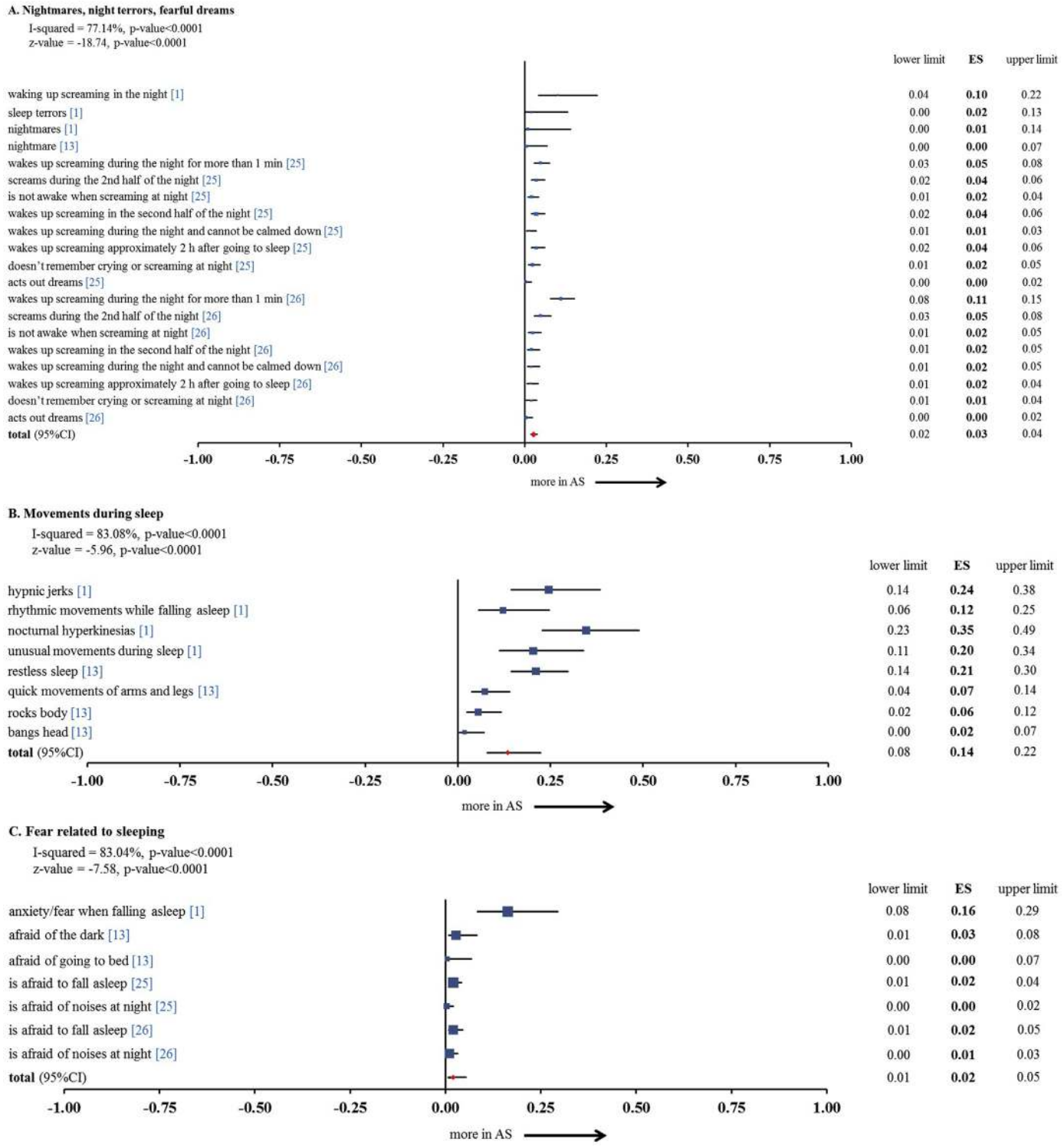


Fig. 3. Meta-analysis on the conceptually grouped sleep disorder items. Printed are item [reference number]. Positive values indicate presence in individuals with AS. Negative values indicate absence in individuals with AS. Size of the symbol indicates relative weight under random effects (unless specified otherwise please see text).

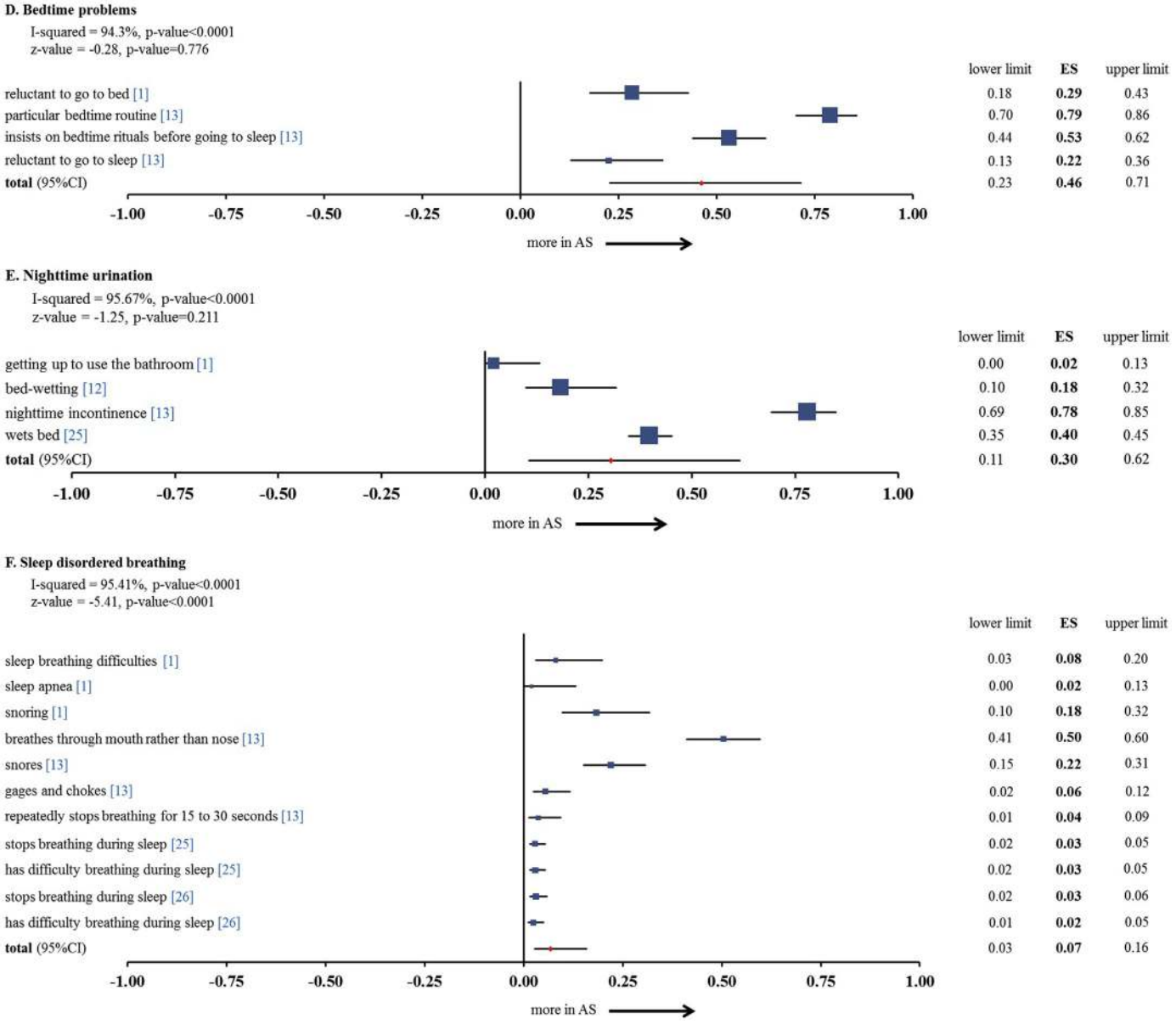


Fig. 3. (*continued*).

The four survey studies [1,13,25,26], involving three questionnaires and six items (i.e., two similar items; non-medical) showed a significant combined ES for non-medical sleep aids (e.g., transitional object) (e.g., see Fig. 3O) but it was found to be highly heterogeneous likely due to item and sample characteristics. The ES ranged from small to moderate effect. Additionally, three survey studies [1,13,25] involving three questionnaires and four items (i.e., medical) showed a significant combined yet small ES (e.g., see Fig. 3O) for medical sleep aids (e.g., drugs) without heterogeneity between studies.

The combined ES for sleep duration, based on three questionnaires and six items (i.e., two similar ones) from three studies [1,25,26] (e.g., see Fig. 3P) was not significant (hence similar to control) but there was significant evidence of heterogeneity. This very high amount of heterogeneity could be ascribed to the methodological diversity of the studies included, and specifically to the cut-offs applied. Excluding the item "how many hours does your child nap during the day" [26] resulted in a similar non-significant ES (ES = 0.545, 95%CI: 0.181 to 0.866, z-value = 0.208, p-value = 0.835; I-squared = 99.11%, p-value < 0.0001). Conversely, two studies [25,26] queried sleep duration in comparison to peers with two items of which the combined ES was suggestive of sleeping less than peers. Of note, the two items used are at the extreme of each other resulting in a high degree of heterogeneity (e.g., see Fig. 3Q; fixed effect model).

The individual ES of items that were not conceptually grouped can be found in Table 3. Awakenings and poor sleep quality stick out, whereas appearing more active than other children was not distinctive.

Questionnaire subscales

The subscale sleep disordered breathing was shared by the survey studies; i.e., Bruni et al. [1], Goldman et al. [27], Walz et al. [25]. The combined ES for this subscale (note, Walz et al. [25]

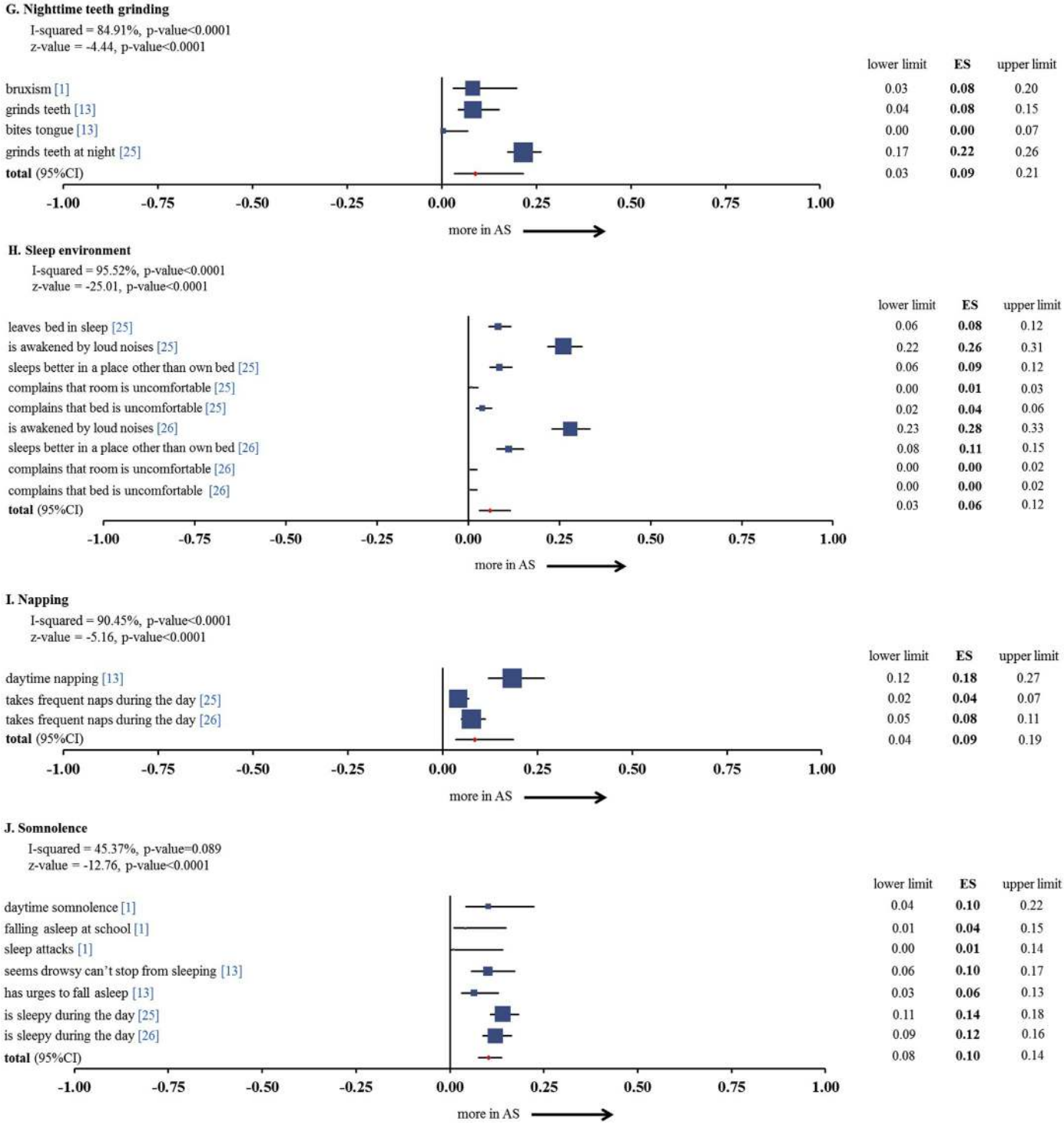


Fig. 3. (*continued*).

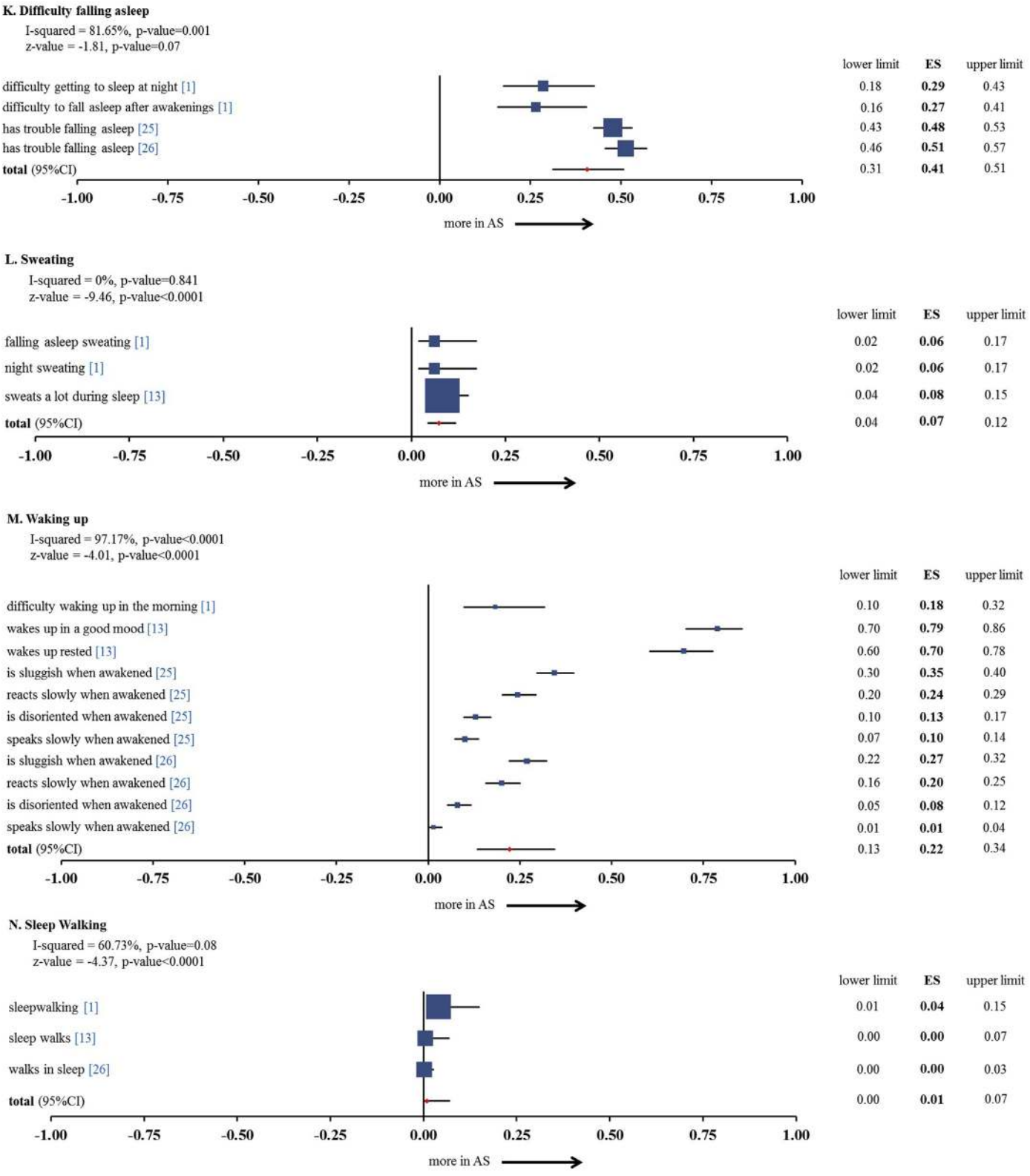


Fig. 3. (*continued*).

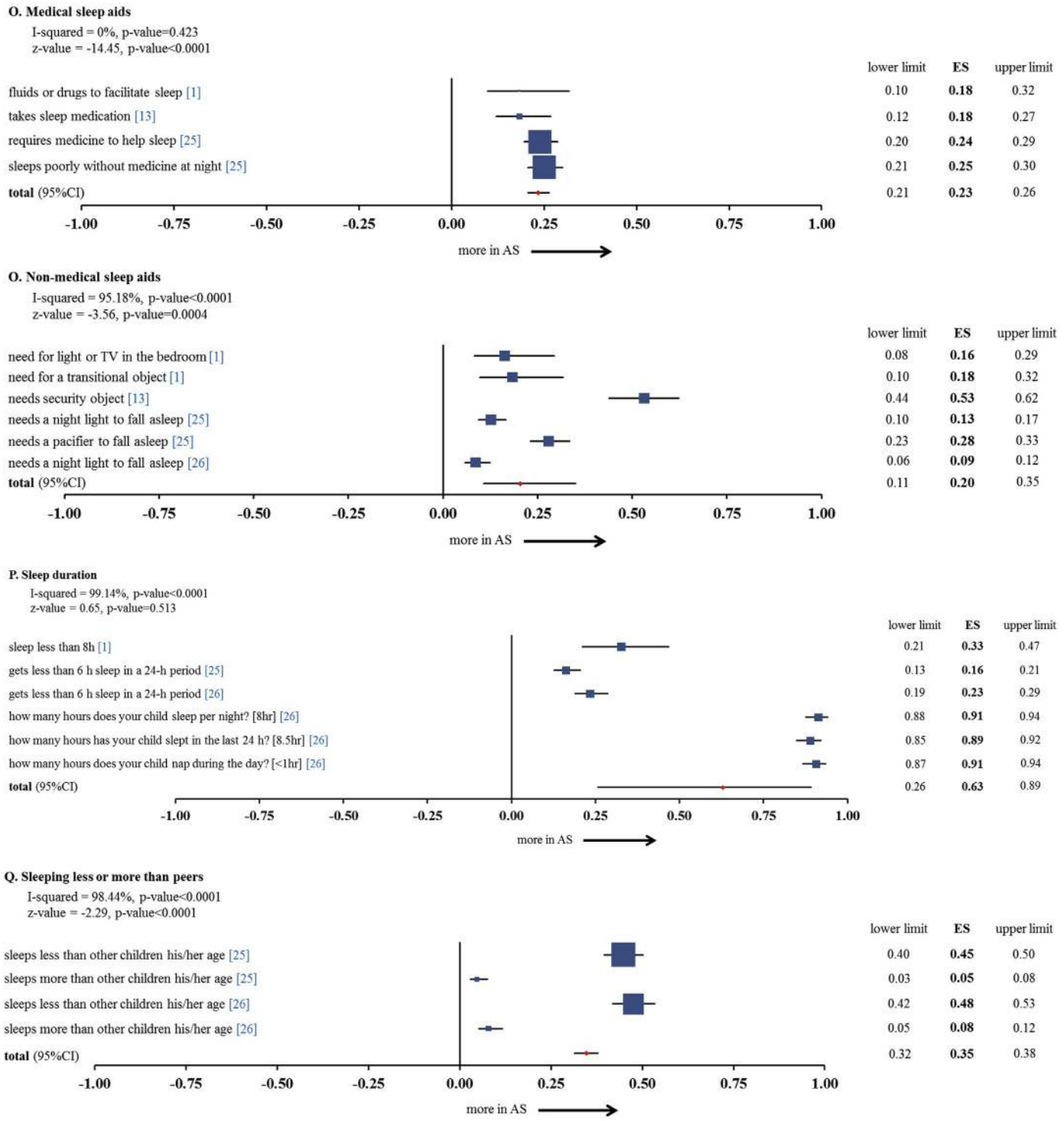


Fig. 3. (*continued*).

included bruxism) were 1.093 ± 0.246 (95%CI: 0.610 to 1.575, z-value = 4.439, p-value < 0.0001). There was significant evidence of heterogeneity (I-squared = 86.5%, p-value = 0.001). For these survey studies also the Total subscale score was available resulting in a combined ES of 2.676 ± 1.185 (95%CI: 0.354 to 4.998, z-value = 2.259, p-value = 0.024; I-squared = 99.389, p-value < 0.0001). Note: the total subscale for Walz et al. [25] was manually calculated. In spite of the different answer scales used across the studies (e.g., 1 to 5 Likert-scale) this average remains low, i.e., a low frequency can be expected.

Of note, Allen et al. [28] had a graphical display of the sleep questionnaire results and Goldman et al. [27] reported only the subscale scores, and therefore both studies could not be fully incorporated in these meta-analyses.

Table 3
The remaining questionnaire items.

Items	ES	95% CI	z-value	p-value
Bruni's sleep disturbance scale for children in Bruni et al. [1]				
Latency to sleep > 30 min	0.14	0.07 to 0.27	−4.39	0.00
Bedtime variations	0.20	0.11 to 0.34	−3.84	0.00
Drink stimulant beverages in the evening	0.10	0.04 to 0.22	−4.61	0.00
More than two awakenings per night	0.35	0.23 to 0.49	−2.11	0.04
Poor sleep quality	0.31	0.19 to 0.45	−2.64	0.01
Waking up to drink or eat in the night	0.08	0.03 to 0.20	−4.64	0.00
Pains of unknown origin during sleep	0.04	0.01 to 0.15	−4.37	0.00
Convulsions during sleep	0.01	0.00 to 0.14	−3.23	0.00
Sleep talking	0.01	0.00 to 0.14	−3.23	0.00
Variation of waking time	0.16	0.08 to 0.29	−4.23	0.00
Sleep paralysis	0.06	0.02 to 0.17	−4.58	0.00
Simonds & Parraga questionnaire adapted by Wiggs and Stores in Didden et al [13]				
Appears more active than other children	0.43	0.34 to 0.53	−1.43	0.15
Wakes in morning before 5 a.m. and stays awake	0.08	0.04 to 0.15	−6.92	0.00
Sleeps with head tipped right back	0.07	0.04 to 0.14	−6.90	0.00
Falls to the ground due to muscle weakness	0.06	0.02 to 0.12	−6.77	0.00
Behavior evaluation of disorders of sleep in Walz et al [25]				
Sleeps worse after eating certain foods/beverages	0.06	0.04 to 0.09	−12.01	0.00
Takes medicine during the day that makes him/her sleep worse	0.02	0.01 to 0.04	−9.75	0.00
Behavior evaluation of disorders of sleep in Conant et al [26]				
Takes medicine during the day that makes him/her sleep worse	0.02	0.01 to 0.04	−8.96	0.00

ES: effect size estimates; 95% CI: 95% confidence interval.
Note: z-value indicates whether the ES is significantly different from zero.

Meta-analysis of (semi-)objective sleep parameters

Each of the combined ES printed in Table 4 showed significant evidence of heterogeneity. Excluding the data obtained via logs and diaries [31,33] resulted in a significant and more homogeneous combined ES for: total sleep time (minutes) (ES = 427.65 ± 22.90, 95%CI: 382.77 to 472.53, z-value = 18.677, p-value < 0.0001; I-squared = 50.64%, p-value = 0.108), sleep onset latency (minutes) (ES = 58.07 ± 23.63, 95%CI: 11.76 to 104.38, z-value = 2.458, p-value = 0.014; I-squared = 66.69%, p-value = 0.083) and wake after sleep onset (minutes) (ES = 112.36 ± 7.23, 95%CI: 98.18 to 126.54, z-value = 15.534, p-value < 0.0001; I-squared = 0%, p-value < 0.0001). The combined ES for sleep efficiency (%) based on 4 studies [27,30,31,33] (e.g., see Table 4; note: Goldman et al. [27] was calculated from the data) was also affected by the methodological diversity of the studies included. Excluding the data obtained via logs [31] resulted in a significant yet homogeneous combined ES (ES = 66.75 ± 4.11, 95%CI: 58.69 to 74.8, z-value = 8.94, p-value < 0.0001; I-squared = 0%, p-value = 0.596). Noteworthy in Table 4 are the overall wide 95% CI.

Other sleep parameters were inconsistently reported. For example, only Miano et al. [30] reported the first REM latency of 228.9 ± 203.42 min, %REM sleep of 10.4 ± 6.45 and %slow wave sleep of 40.5 ± 21.35 (n = 10).

Meta-analysis of other characteristics

Insufficient data were available to pursue a meta-analysis of the pre-post intervention studies. This was also the case

Table 4
Meta-analysis of (semi-)objective sleep parameters.

Study	Sleep parameter	ES	95% CI	z-value	p-value
	Total Sleep Time (min.)	*490.27 ± 39.80*	*412.26 to 568.27*	*12.32*	*0.000*
Zhdanova et al. [24]	Actigraphy	554.7 ± 124.81	310.08 to 799.318	4.444	0.000
Miano et al. [30]	Polysomnography	391.3 ± 42.30	308.40 to 474.20	9.252	0.000
Anderson et al. [32]	Actigraphy	468 ± 25.98	417.08 to 518.92	18.01	0.000
Braam et al. [31]	Logs	608.00 ± 28.99	551.18 to 664.82	20.97	0.000
Goldman et al. [27]	Actigraphy	405.50 ± 14.15	377.77 to 433.23	28.66	0.000
Takaesu et al. [33]	Logs	549.60 ± 21.77	506.94 to 592.26	25.25	0.000
	Sleep Onset Latency (min.)	*54.32 ± 9.73*	*35.24 to 73.40*	*5.58*	*0.000*
Miano et al. [30]	Polysomnography	90.40 ± 27.99	35.54 to 145.26	3.23	0.000
Braam et al. [31]	Logs	60.00 ± 6.18	47.88 to 72.12	9.70	0.000
Goldman et al. [27]	Actigraphy	40.80 ± 6.02	29.01 to 52.59	6.78	0.000
	Wake After Sleep Onset (min.)	*87.31 ± 23.89*	*40.48 to 134.14*	*3.65*	*0.000*
Miano et al. [30]	Polysomnography	107.61 ± 14.27	79.645 to 135.58	7.54	0.000
Braam et al. [31]	Logs	39.5 ± 12.46	15.07 to 63.93	3.17	0.000
Goldman et al. [27]	Actigraphy	114 ± 8.39	97.55 to 130.45	13.59	0.000
	Sleep Efficiency (%)	*73.78 ± 7.79*	*58.52 to 89.04*	*9.48*	*0.000*
Miano et al. [30]	Polysomnography	61 ± 7.39	46.52 to 75.48	8.26	0.000
Braam et al. [31]	Logs	86.98 ± 2.04	82.98 to 90.98	42.64	0.000
Goldman et al. [27]	Actigraphy	78.04 ± 22.28	34.37 to 121.71	3.50	0.000
Takaesu et al. [33]	Logs	68.87 ± 5.07	58.93 to 78.81	13.58	0.000

ES: effect size estimates; 95% CI: 95% confidence interval; min.: minutes; %: percentage.
Note: z-value indicates whether the ES is significantly different from zero.

regarding several sample characteristics such as age, genetic etiology or epilepsy.

Discussion

This review demonstrates the importance of going beyond general statements about poor sleep in individuals with AS and to identify the specific complaints. A more detailed description of potential sleep phenotypes of AS is imperative since new medications and interventions to improve sleep in individuals with developmental disabilities are being developed [17,18,22]. In the context of this review, there is evidence that arousal during sleep, somnolence and possibly short sleep duration are the primary sleep problems in individuals with AS. In addition, medical aids along with sweating and poor sleep efficiency are relevant sleep issues.

The literature search

Using sleep as the primary aim, the literature search yielded 14 articles that identified gaps in knowledge and new avenues for future sleep research. The majority of these articles included a subjective assessment of sleep such as surveys [1,13,25–28]. The main objective of the 14 articles was examining sleep quantity and sleep quality (or sleep disorders) in a descriptive manner. Six articles focused on treatment; however, only one study had an AB-experimental design [24] and one study had a randomized placebo-controlled design [31]. Other articles described interventions in case(-series) including one study based on an interrupted time series design and a multiple baseline design [28].

Despite the inclusion criteria being clearly stated and measured in most of the articles, few studies included a control group. Only two studies reported a sleep diagnosis using a diagnostic classification system, i.e., sleep-wake schedule disorder [23] and circadian rhythm sleep disorders [33]. While melatonin is frequently given to treat sleep problems in individuals with developmental disabilities [19,40–42], in about 60% of the articles this fact remains unknown.

Overall, our findings emphasize the need for a more rigorous sleep research approach. Despite a slight increase in the number of studies applying subjective sleep assessment, since the descriptive review by Pelc et al. [12], no new polysomnographic studies in individuals with AS have been published. In summary, consistent standards for the study of sleep in individuals with AS are critical for the development of new lines of investigation.

The applied questionnaires

Among the 14 studies, four questionnaires were used: behavior evaluation of disorders of sleep [34], Simonds & Parraga questionnaire adapted by Wiggs and Stores [35,36], Bruni's sleep disturbance scale for children [37], and children's sleep habits questionnaire [38]. It is beyond the scope of the current review to discuss them in detail. Each questionnaire also involved some modifications of or additions to the original questionnaire towards individuals with developmental disabilities. On the one hand, such alterations may unfortunately affect the internal and external generalizability of the applied tools [43,44], hence affecting their findings. On the other hand, this finding correspondingly underlines the need for sleep tools suitable for populations with developmental disabilities such as AS. In short, the item and answer format across these four questionnaires potentially produced most of the heterogeneity found in the combined ES. The reported heterogeneity might also be in part ascribed to differences in the sample demographics such as age and presence of epilepsy.

The sleep disorders

Thirteen of the 17 conceptually formed sleep disorder item-groups showed to be significant for individuals with AS. More specifically, the most distinguishing finding was disorders of arousal, such as nightmares, night terrors and fearful dreams. This finding concurs with the general complaint of nighttime disruptive behaviors and fragmented sleep, or awakenings after sleep onset reported in the literature. It is however in contrast to the consensus guidelines [7,8] which proposes disorders related to the timing and duration of sleep. Despite the low individual ES, the combined ES of nightmares, night terrors and fearful dreams appear highly distinctive. 'Wakes up screaming during the night for more than 1 min' [26] or 'wakes up screaming during the night' [1] being partial arousals during sleep are examples of sleep behaviors manifesting disorders of normal arousal mechanisms. The obstacle herein is likely how these arousal/awakening problems are queried and how they are perceived by the respondent.

Our result concerning the presence of daytime sleepiness corresponds with this finding of disorders of arousal. Sleepiness was not inferred by Pelc et al. [12] in their review of sleep problems in AS. Possibly the influence of epilepsy and multi-drug treatment within this population needs to be accounted for when discussing this finding. Indeed, Conant et al. [26] pinpointed to the higher degree of sleep problems when using anti-convulsant drugs and Miano et al. [30] underlined the role of epilepsy in exacerbating the sleep problems. Alternatively, our finding concerning the use of medical sleep aids may further complement this clinical picture of disturbed arousal mechanisms.

In fact, our results identifying problems with partial arousals and somnolence, are also in line with the findings of intervention studies [24,29,31,33]. Several of these studies focused on melatonin. Exogenous melatonin is known to be used to correct circadian rhythm sleep disorders. Intervention studies suggest low endogenous melatonin levels in individuals with AS. Yet conversely, some individuals lose response to their melatonin treatment whilst high levels of melatonin remain present during the day [45].

Altogether, the cluster of 'arousal disorders – sleepiness – sleep aids' distinctively found in this meta-analysis may have the appearance of circadian-rhythm abnormalities, commonly reported as problems with the timing and duration of sleep.

Other sleep complaints that were also significant in our analysis may actually overshadow these arousal-sleepiness problems. Several examples of sleep complaints that may obscure the distinctive feature of an arousal-sleepiness problem, are: sleep hyperhidrosis, which may co-occur with an awakening. Or with regard to the sensitivity to the environment, especially the complaint of 'is awakened by loud noises' [25,26] is prominent. A similar misperception may occur regarding fear and nighttime movements. Previously we highlighted that disorders of arousal, sleep-wake transition disorders and disorders of initiating and maintaining sleep may appear alike from the viewpoint of the parent or caregiver [46]. In other words, the applied methodology may further hinder the discovery of disability-specific sleep problems within and across studies such as in individuals with AS.

Our meta-analysis consequently highlights that the 'nighttime' behavior exhibited by the individual with AS might be misperceived. This warrants adept sleep assessment. Bruni et al. [1] as a matter of fact demonstrated this aspect when reporting the

'unreported' sleep problems in individuals with AS. For example, they reported on enuresis, bruxism, somnambulism and snoring. Alternatively, Stores et al. [47] stressed that origins of a sleep problem may lie in the syndrome itself, the child's circumstances, or reflect comorbidity. In the context of potential misperception is the large individual ES of 'particular bedtime routine' [13] remarkable and suggestive for the need of more in-depth querying of sleep complaints. Likewise is the finding on sleep disordered breathing, which is predominantly ascribed to epilepsy by Miano et al. [30].

In sum, our finding of arousal difficulties pooled with the other significant sleep disorder item-groups, may support the thalamocortical dysfunction model [6] with its two characteristic patterns; that is, one related and one not related to epilepsy. A dysfunction thought to be resulting from dysregulation of synaptic GABAergic neurotransmission.

The actigraphic and polysomnographic recording of sleep

Findings showed problems with total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency, however short sleep duration and poor sleep efficiency were the most prominent findings. Based on questionnaires this finding was especially demonstrated by sleeping less or more than peers, but not in other formats. That is, primarily arbitrary cut-offs regarding numbers of hours slept have been applied.

Given that only 'one' study applied the polysomnography, our results need to be interpreted with caution. Furthermore, objective sleep parameters were inconsistently reported which calls for standards for sleep research in individuals with atypical development. Of note, actigraphic recordings rely on the bedtime and wake-up time provided by the respondent/participant, and are therefore semi-objective.

Our findings based on semi-objective data suggest a sleep duration ranging from 6:87 to 9:47 h and a sleep efficiency ranging from 58.52% to 89.04%. Also, the possible influence of methodology and misperception of the sleep parameter such as sleep onset latency by actigraphy needs to be accounted for when interpreting the meta-results.

With respect to the abnormal sleep-wake cycles or circadian rhythm sleep problems, as depicted in the consensus guidelines, the heterogeneity of the sample in the study by Takaesu et al. [33] and Summers et al. [23] may portray the complexity of the issue. Such heterogeneity may bring to mind the overshadowing aspect of other sleep complaints; that is, reports might be ignoring the latent arousal-problems as found in our meta-analyses.

The developmental stage

The need for more rigorous sleep research is not only pertinent towards a disability-specific understanding of sleep problems or towards sleep-phenotyping of neurodevelopmental disorders. That is, Goldman et al. [27] showed that the problematic sleeping of the individual with AS was associated with poor parental sleep, daytime somnolence and higher parental stress. As a consequence, detailed sleep assessment of the individual with AS may benefit the entire family. This aligns with facts such as the historian usually being the parent on the one hand, and our finding of specific nighttime disruptive behaviors in individuals with AS on the other hand. Moreover, resolving the disability-specific sleep problem as it arises may help the individual with a disability not only in the short-term but possibly also long term. Regrettably most studies applied a cross-sectional study design, in spite of the early reports on characteristic age-related differences in EEG patterns of individuals with AS [9]. Longitudinal studies are indeed needed since Bruni et al. [1] reported no improvement of sleep complaints at post-pubertal age, whereas Miano et al. [10] reported sleep macrostructure differences compared to controls before and after the age of eight years.

Lastly, 'wakes up in a good mood' [13] showed to have one of the highest individual ES. This finding imperatively underscores the methodology, the perception and the clarification of sleep behaviors in individuals with developmental disabilities. None of the studies reviewed this highly specific characteristic of AS in relation to sleep-related mood disorders.

Limitations

Although this review and meta-analysis contributes to the existing literature on sleep in individuals with AS in important ways, several limitations should be acknowledged. A lack of detail in the employed study designs and samples may limit the interpretations (e.g., use of melatonin). Not only is this problematic in data synthesis, it also impacts the examination of interaction effects (e.g., age, gender, genetic etiology, epilepsy). Further limitations were evident within the evaluation of the quality of the reviewed studies; i.e., one AB-experimental intervention design and one randomized placebo-controlled design, several case(series) and mostly descriptive studies. Lastly, a median of four studies is preferred to pursue a meta-analysis for an outcome in a review [48]. Therefore results based on small number of data should be interpreted accordingly.

Conclusion

This review and meta-analysis confirms the presence of sleep problems in individuals with AS. Results demonstrated that disorders of arousal, sleepiness and the use of sleep aids are characteristic. Although few objective studies have been performed, data support shorter sleep duration and poorer sleep efficiency. Future studies need to excel former methodologies (i.e., adept sleep assessment) and more detailed sample descriptions/analysis in order to generate disability-specific sleep problems and treatments in individuals with AS.

Practice points

In individuals with AS

- arousal/awakenings during sleep and daytime somnolence are primary sleep complaints
- short sleep duration is possibly a typical complaint, although this was infrequently questioned/calculated based on the anchor-points of: bedtime, estimated sleep onset/offset latency and wake up time, or based on objective assessment
- a classification-based sleep diagnosis should be chosen because the inquiry of the sleep complaint(s) and the perception of the sleep problem(s) may not concur
- a disability-specific understanding of sleep complaints should therefore be adopted since 1) sleep complaints might have an multifactorial origin, 2) the sleep problem might be chronic and (un)related to the developmental stage of the individual

Research agenda

Findings in this population may direct future research by

- uniquely stimulating the research on sleep-related mood disorders in light of the contrast between the reported sleep complaints versus the "wakes up in a good mood" behavior found in individuals with AS, and the potential dysregulation of synaptic GABAergic neurotransmission
- emphasizing sleep health to be a primary objective of inquiry in individuals with atypical development
- stipulating a clear need for psychometrically sensitive and specific sleep tools for individuals with developmental disabilities
- challenging the guidelines (e.g., the assessment, the management, the scoring) for sleep studies in atypically developing individuals
- broadening the scope of assessment towards sleeplessness and sleepiness, as well as timing of sleep (or napping behavior) in individuals with developmental disabilities
- urging more detailed reporting of sample characteristics which may foster innovative assessment, management and treatment plans

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Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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