ADVANCES IN CHILDHOOD SLEEP ASSESSMENT: TOOLS FOR SPECIFIC POPULATIONS

EDITED BY: Catherine Mary Hill, Carmen M. Schroder and Karen Spruyt
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ADVANCES IN CHILDHOOD SLEEP ASSESSMENT: TOOLS FOR SPECIFIC POPULATIONS

Topic Editors:
Catherine Mary Hill, University of Southampton, United Kingdom
Carmen M. Schroder, Hôpitaux Universitaires de Strasbourg, France
Karen Spruyt, Institut National de la Santé et de la Recherche Médicale (INSERM), France

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EDITORIAL
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Editorial: Advances in Childhood Sleep Assessment: Tools for Specific Populations

Catherine Mary Hill[1], *Carmen M. Schroder*[2] *and Karen Spruyt*[3]*

[1] University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [2] Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [3] Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

Keywords: tool, child, sleep, questionnaire, developmental disability

Editorial on the Research Topic

Advances in Childhood Sleep Assessment: Tools for Specific Populations

In 2014 the Research Topic "Advances in Childhood Sleep Assessment: The Tool" was launched as a response to the publications "Development of pediatric sleep questionnaires as diagnostic or epidemiological tools: a brief review of dos and don'ts" (1) and "Pediatric Sleep Questionnaires as Diagnostic or Epidemiological Tools: A Review of Currently Available Instruments" (2). The field of pediatric sleep has greatly evolved since then and a real boost in new technologies and approaches is noted. This Special Issue demonstrates this boost with the publication of 14 studies dedicated to: children with neurodevelopmental conditions (autism spectrum disorder, Down syndrome, Angelman syndrome, Fragile X syndrome, bipolar disorder, $n = 5$), children with sleep disorders ($n = 3$), tools assessing sleep ($n = 3$), and three review papers on tools.

Sleep problems in children with developmental disabilities are reported to be common, yet their measurement is to this day challenging. In autism spectrum disorder, the validity of one brand of actigraphic measurement compared to polysomnography, the gold standard, was investigated by Yavuz-Kodat et al.. Authors concluded an acceptable clinical agreement between both tools to measure problematic sleeping in children with autism spectrum disorder. Similarly, the challenge to find an alternative to the gold standard is shown by Grantham-Hill et al.. Namely, in line with an increased demand to publish also negative results to improve science, the authors concluded that the psychometric properties of the screening questionnaire for obstructive sleep apnea in youth with Down syndrome were mediocre. This struggle for adequate tools is further demonstrated by multi-method approaches, which provide a broad range of sleep information but simultaneously are time and labor intensive, in an already challenged setting. A successful multi-method approach, reported by Trickett et al., assessing sleep quality and timing in children with Angelman syndrome demonstrated significant intra- and inter-individual variability. Such variability should inform us that assessment of and intervention for problematic sleeping in children with developmental disabilities needs a tailored approach. As in Dueck et al., multi-method approaches also show us what is feasible and what is not. In a Fragile X cohort, this study moreover focusses on sleep environment, biomarkers, and circadian rhythm data obtaining an all-round assessment, yet with necessary individual modifications during data collection. Lastly, Lopes et al. applying questionnaire and diary during each mood episode in youth with bipolar disorder showed that sleep complaints often occur during manic or depressive episodes, but equally well in both episodes. This study further highlighted that sleep problems may contribute to the maintenance of psychopathological symptomatology. Each of these aforementioned studies highlight the complexity associated with the measurement of sleep in youth with developmental disabilities but also the immense discrepancy between the need given the high prevalence and clinical demand vs. the scientific solution per the study limitations listed.

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Mehmet Y. Agargün, Yuzuncu Yil University, Turkey

***Correspondence:**
Karen Spruyt
spruytsleep@gmail.com

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Systematic reviews appraising such diverse tools and assessment methodologies that fully capture problematic sleep behavior in children with developmental disabilities are therefore strongly encouraged. In this Special Issue, two narrative reviews and a systematic review are published. Bioulac et al. comprehensively discuss the subjective and objective methods to assess excessive daytime sleepiness in children with attention deficit hyperactivity disorder. Stubbs and Walters focus on questionnaires to assess pediatric restless legs syndrome, concluding that more studies are needed to validate a single question as well as existing adult versions of restless legs syndrome scales. Finally, in a systematic review, Sen and Spruyt take a broader scope discussing all available sleep questionnaires. That is, the original review of sleep questionnaires from 2011, which has led to the Special Issues on sleep tools supportively hosted by Frontiers, was updated to 2020 providing the pediatric sleep field a benchmark toward subjective sleep assessment. Nonetheless, each of the reviews emphasize that there is room for improvement in the development and psychometric evaluation of tools.

In typically developing children aged 8–9 years, Mazza et al. showed that self-report of sleep-wake patterns through use of a diary might be a means to obtain complementary subjective information. A more objective measure is local forehead and abdomen skin temperature, as Bach et al. reported from data collected in 6–12 year olds. This study offers a non-invasive measure of the sleep-wake cycle discussing the best and fewest number of sites for temperature measures. This proxy assessment of sleep via body temperature regulation in particular is potentially neglected in children with developmental disabilities. Smith et al. went one-step further in the discussion concerning accelerometery compared to the gold standard. Authors highlighted the interrelation of the device placement and the selected algorithm, demonstrating discrepancies in sensitivity and specificity toward sleep timing, quantity, and quality metrics.

The search for non-invasive methods and optimal bio-algorithms to assess sleep is progressively noted in the field, and also in this Special Issue. Measuring sleep disorders specifically was discussed in three papers. In the continued search to optimally appraise sleep disordered breathing Yanney et al. concluded that pulse transit time is more sensitive but less specific than oximetry. Galbraith et al. focused on annotating videos to assess chronic insomnia in children surviving brain tumors. That nocturnal behaviors in a naturalistic setting can be informative toward the diagnostic process is similarly explored by Gall et al.. Here, authors examined automatic 3D video analysis of children exhibiting rhythmic movement disorders to overcome laborious manual scoring of videos. Both studies address a clear need for standards in objective quantification of sleep behavior beyond the gold standard polysomnography or the widely used actigraphy, principally investigating sleep in the familiar sleep environment of a child.

We are thankful to the participating authors, the Frontiers team and its editors for contributions to a topic that warrants extra scientific attention. Special Issues like this provide a unique portal to publish papers on sleep methodology. Combined, the studies included indicate that we are embarking on a new era of sleep assessment in children with neurodevelopmental disorders. Indeed, the gold standard might not be the "holy grail" when assessing children with neurodevelopmental conditions. For these children, polysomnography is inherently challenging due to multiple electrode placement, an unfamiliar setting and unaccustomed procedures. Each child needs a personalized and resource intensive approach to successfully examine sleep through such standardized techniques. Furthermore, polysomnography is not the best tool for some sleep disorders which may be better assessed in the home setting using different technologies. Resource limitation also drives creative solutions to diagnosis and is necessary to meet the demand for sleep disorder diagnosis which in most countries significantly outstrips health service capacity. At such tipping points in the development of a specialist field, a creative process of trial and error is critical to advance practice. That is why hosting and contributing both positive and negative findings in Special Issues like this one are essential to advance the frontiers of sleep assessment in children.

AUTHOR CONTRIBUTIONS

KS drafted, CH and CS edited the editorial. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Validity of Actigraphy Compared to Polysomnography for Sleep Assessment in Children With Autism Spectrum Disorder

Enise Yavuz-Kodat[1], Eve Reynaud[1], Marie-Maude Geoffray[2,3], Nadège Limousin[4], Patricia Franco[5], Patrice Bourgin[1,6] and Carmen M. Schroder[1,6,7]*

[1] Centre National de la Recherche Scientifique, Université de Strasbourg, Institut des Neurosciences Cellulaires et Intégratives, Strasbourg, France, [2] Department of Child and Adolescent Neurodevelopmental Psychiatry, Le Vinatier Hospital, Bron, France, [3] Health Services and Performance Research (HESPER), Claude Bernard University Lyon 1, Lyon, France, [4] Department of Neurology and Clinical Neurophysiology, University Hospital Bretonneau, Tours, France, [5] Lyon Neuroscience Research Center U1028/UMR 5292, Claude Bernard University Lyon 1, Lyon, France, [6] Sleep Disorders Center, International Research Center for ChronoSomnology, Strasbourg University Hospitals, Strasbourg, France, [7] Department of Child and Adolescent Psychiatry, Strasbourg University Hospitals & University of Strasbourg Medical School, Strasbourg, France

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Edited by:
Giuseppe Plazzi,
University of Bologna, Italy

Reviewed by:
Hiroshi Kadotani,
Shiga University of Medical Science, Japan
Oliviero Bruni,
Sapienza University of Rome, Italy

***Correspondence:**
Eve Reynaud
ereynaud@unistra.fr

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Actigraphy (ACT) is a non-invasive objective assessment tool for the study of sleep–wake rhythms. It is of particular interest in children with autism spectrum disorder (ASD), as sleep disorders are highly prevalent and have a significant impact on both cognitive and behavioral functions. As polysomnography (PSG), the gold standard for the assessment of sleep, is difficult to perform in children with ASD, ACT has become a tool of choice but has not yet been validated against PSG using state-of-the-art methodology. The main objective of this study was to assess, for the first time, the validity of ACT compared to PSG for the measurement of sleep in children with ASD. During the same night of hospitalization, PSG and ACT were conducted in 26 children (6 girls and 20 boys; mean age 5.4 years ± 1.6) diagnosed with ASD according to DSM-5 criteria and standardized diagnostic scales. Sleep parameters were total sleep time (TST), sleep latency (SL), wake after sleep onset (WASO), and sleep efficiency (SE). To compare PSG and ACT, we conducted sleep parameter agreement analyses including: intraclass correlation coefficient (ICC), Bland-Altman plots, and equivalence tests. The comparison also included an epoch-by-epoch (EBE) agreement analysis to determine sensitivity (ability to detect sleep) and specificity (ability to detect wake). According to equivalence tests, the difference between ACT and PSG measures was clinically acceptable for TST (<30 min, $p < 0.01$), SL (<15 min, $p < 0.001$), and SE (10%, $p < 0.01$), but not for WASO (<15 min, $p = 0.13$). There was a good agreement between methods for SL (ICC = 0.79) and TST (ICC = 0.85) and a moderate agreement for WASO (ICC = 0.73) and SE (ICC = 0.68). The EBE agreement analysis revealed a high sensitivity (0.94 ± 0.06) and moderate specificity (0.5 ± 0.2). Since sleep disorders are one of the most common comorbidities within the ASD population and are highly prevalent, it is essential to validate objective tools of assessment. To our knowledge, our study is the first to validate ACT compared to PSG,

using a state-of-the-art methodology, in children with ASD. The results suggest ACT to be a valid method to evaluate sleep within this population, with a good reliability for most sleep parameters.

Keywords: autism, autism spectrum disorder, actigraphy, actimetry, polysomnography, PSG, validation, sleep

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities. Symptoms are present from early childhood and significantly affect daily functioning (1). ASD is four times more common in males than in females, and its worldwide reported prevalence approaches 1% of the population (2–4). Comorbidities are very common in ASD. Indeed, over 70% of individuals diagnosed with ASD have concurrent somatic or psychiatric conditions (5, 6). Sleep disorders are among the most common associated disorders in this population, with prevalence rates ranging from 50 to 80% (7, 8).

Studies based on parent-reported sleep problems have shown that the most common complaints are related to bedtime resistance, sleep initiation, nighttime awakening, and shortened sleep time (9). In accordance with these findings, studies using objective measurements of sleep quality parameters have revealed that children with ASD, compared to typically developing children (TD), display increased sleep onset latency, decreased sleep efficiency, as well as an increased number and duration of night wakings (10, 11). Research also provides support for the idea that sleep disturbances are strongly associated with daytime functioning in children with ASD. In a recent study, Mazurek and Sohl (12) showed that sleep disturbances significantly account for behavioral dysregulation, notably inattention, impulsivity, irritability, and physical aggression (12). They also showed that night wakings have the most consistently strong association with daytime behavior problems. Other authors found that sleep disturbances are significantly correlated with both internalizing and externalizing symptoms in children with ASD, using the Pediatric Behavior Scale (13). Studies have further suggested that ASD children who experience sleep problems have also cognitive impairment. For example, decreased sleep duration in children with ASD was correlated with nonverbal communication deficits (14), lower overall intelligence, adaptive functioning, and socialization skills (15, 16).

Finally, it is well characterized that sleep disturbances worsen quality of life of both children with ASD and their families (17, 18). Levin and Scher reported that sleep problems contributed significantly to maternal stress (19).

If not treated early, sleep disorders persist from infancy to adolescence (20). Thus, it is essential to address sleep problems in children with ASD, in order to favorably impact not only nocturnal symptoms, but also their daily functioning as well as overall quality of life of these children with ASD and those of their caregivers.

In order to efficiently design sleep interventions and overall medical care, it is essential to assess sleep quality parameters in children with ASD. Polysomnography (PSG) is the gold standard for sleep quality assessment but, aside from the cost involved and its limited availability, it can be challenging and often impossible to conduct PSG in this population (21). Indeed, polysomnographic recording may be compromised because many children with ASD present sensory abnormalities, and thus may not tolerate electrodes on their scalp or face (11). As an alternative, actigraphy (ACT) has been used as a non-invasive, objective, and cost-effective assessment tool for the study of rest-activity cycles as a proxy to sleep–wake rhythms. It has become a tool of choice to assess sleep quality in children with ASD. However, to the best of our knowledge, no study has yet investigated the validity of ACT compared to PSG for the measurement of sleep in children with ASD.

The aim of this study was to compare the agreement of actigraphy (MotionWare 8®—CamNtech MotionWare 1.1.20) with gold standard polysomnography in children diagnosed with ASD.

MATERIALS AND METHODS

Participants

Participants were recruited as part of a French multicenter clinical research program (university hospitals of Strasbourg, Lyon, and Tours), examining the role of sleep disorders and circadian rhythm disorders in children with ASD.

The study complied with the principles of the Declaration of Helsinki (1989) and standards of good clinical practices. All procedures have been approved by the regional French Institutional Review Board (Comité de Protection des Personnes "Est IV", 11/04/2012, 1 place de l'hôpital 67091, Strasbourg). Written, signed, and informed consent was obtained prior to participation from the parents of participants, and assent was obtained from the child when possible.

Inclusion criteria were a diagnosis of ASD using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV-R/5 criteria (1). All children underwent an initial diagnostic evaluation including the Autism Diagnostic Observation Scale [ADOS (22)], and the Autism Diagnostic Interview-Revised [ADI-R (23)] which was completed with parents. All participants met diagnostic criteria for ASD using the ADOS cutoff and met criteria on all domains of the ADI-R. The ADOS and ADI are gold standard measures for the diagnosis of ASD and were administered by certified practitioners. Furthermore, children had to be on stable medication 2 months before the inclusion and during the assessment periods.

Exclusion criteria were secondary ASD (e.g., associated with fragile X syndrome, Rett syndrome, Down syndrome, Bourneville tuberous sclerosis, Von Recklinghausen's disease, cytomegalovirus encephalitis, congenital rubella syndrome, and phenylketonuria). Patients with epilepsy, comorbid severe physical disability, or severe allergy were also excluded from the study. Participants were not allowed to have had transmeridian travels over two time zones or more, 3 months before the assessments.

Twenty-nine children with ASD were included into this study and underwent a night of polysomnography assessment as part of the overall research protocol, while wearing concomitantly an actigraphy wrist watch.

Measures

Sleep quality parameters used in this study were: TST, SL, WASO, and SE; TST was defined as the time between sleep onset and sleep offset minus the time of WASO, and SL was defined as the time between bedtime and sleep onset. WASO was defined as the number of minutes scored as wake between sleep onset and sleep offset. SE was defined as the ratio of TST to the time in bed (i.e., time from bedtime to get up time). We defined "bedtime" as the moment when the child is in bed, ready to sleep, and "get up time" as the moment when the child is getting up.

Actigraphy

Children wore an actigraph (the MotionWare 8®—CamNtech MotionWare 1.1.20) on their non-dominant wrist or on the left wrist by default if the child was not lateralized yet. The actigraph is an electronic device containing a piezo-electric accelerometer that measures the intensity, the amount, and the duration of physical movement in all directions. The actigraph activity is measured in counts defined as the amplitude of the signal produced by the accelerometer in the actigraph, with the number of counts being proportional to the intensity of the movement. The accelerometer samples the amplitude of the movement 32 times per second. The peak of intensity is defined for each second as the highest amplitude within the 32 records, and peak intensity values are summed into an epoch of 1 min.

Actigraphy data were scored automatically for sleep/wake using the Actiwatch Activity and Sleep Analysis 7® software algorithm, version 7.23. We used four different sensitivity-threshold settings: automatic, low, medium, and high. The low sensitivity-threshold is defined as a threshold level of 80 counts, i.e., an activity score of 80 counts or more during one epoch is necessary for that epoch to be scored as wake. The medium sensitivity threshold corresponds to a threshold level of 40 counts, the high sensitivity threshold to a threshold level of 20 counts, and the automatic sensitivity threshold to a variable threshold level derived from the subject's individual activity level. The low sensitivity-threshold setting of actigraphy showed the best fit for the comparison of actigraphy-derived sleep parameters to PSG and was thus reported here (for all other settings, please refer to **Supplementary Data**).

While activity counts were recorded in 1-min epochs, they were converted into 30-s epochs for the epoch-by-epoch analyses, as done in previous studies (24, 25), in order to allow for comparison with PSG data. The conversion has been done using the provided feature in the actigraphy reading software (MotionWare 8®), which consists in dividing a 1-min epoch of wake in two 30-s epochs of wake and similarly so for the sleep epochs.

Polysomnography

Polysomnography was conducted with Compumedics Siesta 802a (Compumedics, Abbotsford, Australia). We collected the following channels for sleep staging: 13 electroencephalogram (EEG) channels (FP1, FP2, F3, F4, C3, Cz, C4, T3, T4, M1(A1), M2(A2), O1, O2), bilateral electrodes for electrooculogram (E2, E1) and submental electromyogram (Chin2–Chin1), and electrocardiograms (ECG+, ECG-) and sensors to monitor airflow. Raw data were digitalized at a sampling rate of 1,024 Hz, and a notch filter of 50 Hz was applied. PSG studies were manually double scored by two independent raters using Compumedics Profusion PSG V4.1 version 445 Software following the American Academy of Sleep Medicine (AASM) guidelines for sleep staging in 30-s epochs (26).

Data Analyses

The comparison of polysomnography- and actigraphy-derived sleep parameters was based on a single concurrent night of recording and included two sets of comparisons as primary analyses: 1) the agreement analysis of the four sleep parameters: TST, SOL, WASO, and SE, and 2) an epoch-by-epoch agreement analysis. For secondary analyses, we compared the ACT sensitivity-threshold settings for each sleep parameter and epoch-by-epoch variables, as reported in the **Supplementary Data**. All analyses were restricted to nighttime sleep–wake patterns.

All statistical analyses were performed using R Statistics Software Version 3.4.3.

Sleep Parameter Agreement Analyses

For the sleep parameter analysis, we performed a state-of-the-art agreement analysis method (27) using ICC, Bland-Altman plots, and Yuen two one-sided paired equivalence test (28).

The ICC is an index that, contrary to Pearson correlation, assesses not only how well correlated the two techniques are but also if they are equal. ICC ranges from 0 (no agreement) to 1 (perfect agreement). An ICC < 0.5 indicates poor agreement, 0.5 < ICC > 0.75 indicates moderate agreement, 0.75 < ICC > 0.9 indicates good agreement, and ICC > 0.90 indicates perfect agreement (29).

Bland-Altman plots are a graphical method that allows to visually examine the degree of agreement between two techniques. In this method, the differences between PSG and ACT (i.e., SL according to actigraphy minus SL according to PSG) are plotted against their averages. The plot includes one value for each subject, a reference line (equal to zero, representing perfect agreement between PSG and ACT), the mean of the differences between the two techniques (representing the mean bias), and limits of agreement (which are defined as a deviation from the mean superior to two standard deviations).

Finally, the Yuen two one-sided paired tests for equivalence allow to conclude if two techniques are *clinically* equivalent within a pre-set range of acceptability. In equivalence tests, the null and alternative hypotheses are reversed compared to usual tests (e.g., Student t-test). The null hypothesis of an equivalence test states that there is a difference between conditions, whereas the alternate hypothesis states that there is no difference (28). This test is necessary in order to attest a true clinical equivalence between two tests, when the null hypothesis is rejected (p-value < 0.05). In our study, the ranges were set to ±30 min for TST, ±15 min for SL, and ±15 min for WASO. We set two ranges for SE, a conservative one to ±5%, and an extended one to ±10%.

Epoch-by-Epoch Agreement Analysis

Each epoch, comprised of 30 s of recording, was coded as a binary score (W = wakefulness and S = sleep) for both ACT and PSG.

PSG being the gold standard, coding by this method was defined as the accurate state. As detailed in **Table 1**, epochs where ACT accurately identified sleep or wake were respectively called true sleep (TS) and true wake (TW). Conversely, epochs where ACT misidentified sleep for wake were called false wake (FW), and those where ACT misidentified wake for sleep were called false sleep (FS).

Epoch-by-epoch analysis consisted in calculating accuracy, sensitivity, and specificity for all of the sensitivity settings (automatic, high, medium, and low). Accuracy was defined as the number of epochs that ACT correctly classified into sleep or wake (as defined by PSG) divided by the total number of epochs: *(TS + TW)/(TS + TW + FS + FW)*. Sensitivity was calculated as the number of epochs where ACT correctly identified sleep, divided by the number of epochs scored as sleep by PSG: *TS/(TS+FW)*. Specificity was defined as the number of epochs correctly identified as wake by ACT, divided by the number of epochs scored as wake by PSG: *TW/(TW+FS)*. Sensitivity answers the question, "What percentage of PSG sleep epochs are detected by ACT?", and specificity answers to the question "What percentage of PSG wake epochs are detected by ACT?" (30).

We also computed the predicted value for sleep (PVS), which is the percentage of epochs scored as sleep by ACT that were also scored as sleep by PSG: *TS/(TS+FS)*, and the predicted value for wakefulness (PVW), which is the percentage of epochs scored as wake by ACT that were also scored as wake by PSG: *TW/(TW+FW)* (31). PVS answers the question, "Within epochs identified as sleep by ACT what is the percentage of PSG sleep?," and PVW answers the question "Within epochs identified as wake by ACT, what is the percentage of PSG wake?"

TABLE 1 | Definition of epoch qualification for the epoch-to-epoch agreement analysis.

		PSG	
		Sleep	**Wake**
ACT	Sleep	True sleep (TS)	False sleep (FS)
	Wake	False wake (FW)	True wake (TW)

We also calculated the Cohen's kappa coefficient value (k) for all sensitivity settings of the actigraph. The k coefficient is an indicator that reflects the percentage of scoring agreement between two techniques (PSG and ACT) which is not due to chance (32). We considered a kappa coefficient of 0–0.2 as slight agreement, 0.2–0.4 as fair agreement, 0.4–0.6 as moderate agreement, 0.6–0.8 as substantial agreement, and 0.8–1.0 almost perfect agreement (33).

ACT Sensitivity-Threshold Setting Analysis

ANOVA was used to compare the sleep parameters according to the sensitivity-threshold settings of actigraphy (automatic, high, medium, and low) and also to compare sensitivity, specificity, PVS, PVW, and kappa of the epoch-by-epoch agreement analysis, for each sensitivity settings.

In order to make pairwise comparisons of all ACT sensitivity-threshold settings for each sleep parameter, we computed a *post hoc* test, the Tukey's range test.

RESULTS

Study Participants

Among the 29 subjects who initiated the combined recording of actigraphy and PSG, one participant had incomplete data because he pulled the PSG electrodes off during the night, one participant did not tolerate the actigraph, and for one participant, a technical issue with the actigraph compromised the data. Overall, 26 participants completed the concurrent PSG and ACT recordings and were included in the final analysis. The sample included 20 boys and six girls, with a mean age of 5.36 ± 1.57 years and an age range [2.94–8.1] years.

As seen in **Table 2**, most of the children exhibited a developmental delay in adaptive behaviors with delays ranging from [0.58–5.92] years.

Actigraphy Sensitivity-Threshold Setting

The low sensitivity-threshold setting of actigraphy showed the best fit for the comparison of actigraphy-derived sleep parameters to PSG and was thus reported here. Results for other settings (low, medium, high, automatic) can be found in **Supplementary Data**.

TABLE 2 | Descriptive characteristics of the study participants.

Population description (N=26)	**% (N)**	**Mean (SD)**	**Range**
Demographic characteristics			
Gender (boys)	77% (20)		
Chronological age (years)		5.36 (1.57)	[2.94–8.10]
VABS subscale equivalent age			
Daily living skills (years)		2.66 (1.19)	[1.25–5.00]
Communication (years)		2.32 (1.34)	[0.75–5.83]
Motor skills (years)		3.21 (1.45)	[1.67–5.92]
Socialization (years)		1.98 (1.03)	[0.58–4.00]

VABS, Vineland Adaptive Behavior Scales (34).

Sleep Parameter Agreement Analyses

Intraclass Correlation Coefficient

ICC highlighted a good correlation between PSG and ACT for SL and TST, and a moderate agreement for WASO and SE (**Table 3**).

Bland-Altman Plots

As a reminder (see the section *Sleep Parameters Agreement Analyses*), in this method, the differences between the two techniques (i.e., SL according to actigraphy minus SL according to PSG) are plotted against their averages. Differences are expressed as PSG - actigraphy, so a negative value indicates actigrahy overestimated the sleep parameter, whereas a positive value indicates actigraphy underestimated the sleep parameter.

The Bland-Altman plots revealed that, for almost all participants, the differences between ACT and PSG fall between the [-2SD; + 2SD] limits of agreement (**Figure 1**). In average, ACT underestimates SL (mean difference = 6.06 min) and WASO (mean difference = 7.57 min) and overestimates TST (mean difference = -25.09 min) and SE (mean difference = -3.58%).

TABLE 3 | Intraclass correlations between actigraphy and polysomnography.

Sleep parameters	ICC
SL	0.795
WASO	0.731
TST	0.850
SE	0.689

ICC ranges from 0 (no agreement) to 1 (perfect agreement). ICC < 0.5 indicates poor agreement, 0.5 < ICC > 0.75 indicates moderate agreement, 0.75 < ICC > 0.9 indicates good agreement, and ICC > 0.90 indicates perfect agreement (29). ICC, Intraclass correlation coefficient; SL, sleep latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency.

Equivalence Tests

The equivalence tests allow to conclude if the two techniques are *clinically* equivalent within a pre-set range of acceptability, and a p-value inferior to 0.05 indicating equivalence (as detailed in the section *Sleep Parameter Agreement Analysis*). A clinical equivalence between ACT and PSG was observed within the pre-set range of acceptability for SL ($p < 0.001$) and TST ($p<0.01$) (**Figure 2**). SE was equivalent in the two methods when using the less conservative range of acceptability of 10% ($p < 0.01$) but not when using the conservative range of 5% ($p = 0.25$). WASO measured by ACT was not equivalent to PSG ($p = 0.13$).

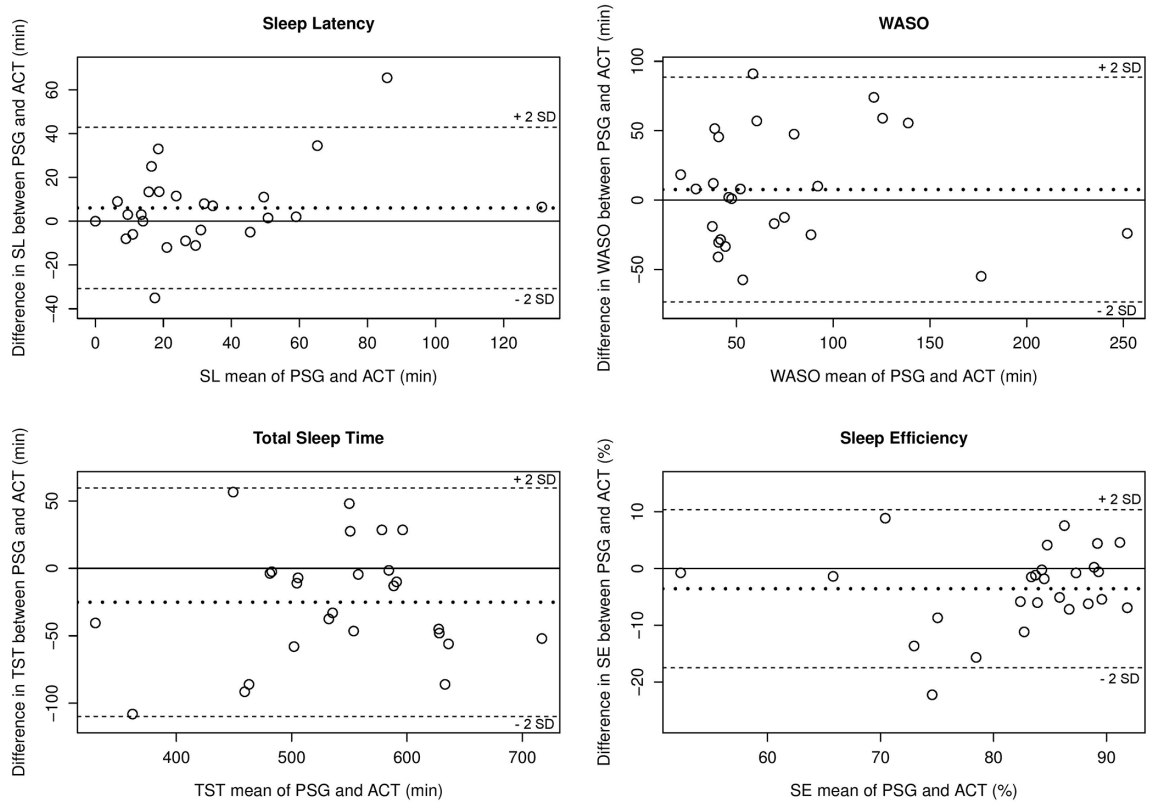

FIGURE 1 | Bland-Altman plots (35) for the comparison of PSG and ACT for each sleep parameter. The mean of each sleep parameter with the two techniques is represented in the *x*-axis and differences (i.e., mean biases) for each sleep parameter between the two techniques are represented in the *y*-axis. Each subject is represented by a dot. The continuous line which passes through zero, representing perfect agreement between PSG and ACT, is the reference line. The bold dotted line represents the mean difference of the study sample (i.e., mean bias) for each sleep parameter with the two techniques. Differences are expressed as PSG—actigraphy, so a negative value indicates actigraphy overestimated the sleep parameter, whereas a positive value indicates actigraphy underestimated the sleep parameter. SL, sleep latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency.

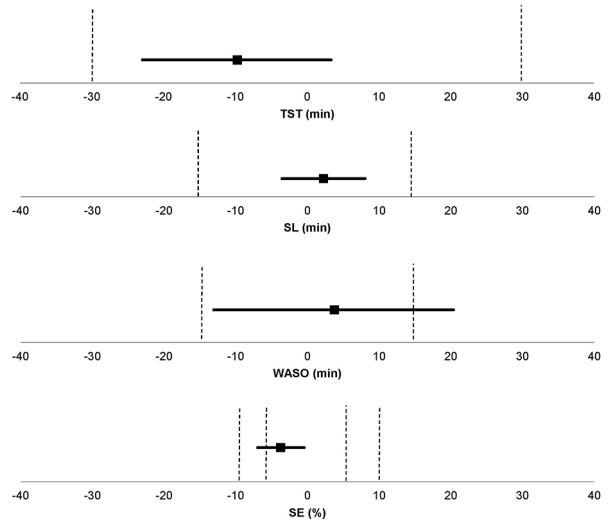

FIGURE 2 | Equivalence tests (28) between PSG and ACT for each sleep parameter. The pre-set ranges of acceptability (represented by the dashed lines) were set to ± 30 min for TST, ± 15 min for SL and WASO, and ± 5% and ± 10% for SE. SL, sleep latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency.

Epoch-by-Epoch Agreement Analysis

Sensitivity, specificity, accuracy, PVS, PVW values, and Cohen's kappa coefficient of epoch-by-epoch comparisons between ACT and PSG are shown in **Table 4**. ACT showed high sensitivity and moderate specificity in classifying epochs into sleep or wake. The accuracy between ACT and PSG was high, and the kappa values showed substantial agreement. PVS was high, whereas PVW was moderate.

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the validity of actigraphy for the assessment of sleep in children with ASD, compared to polysomnography, the gold standard. The comparison of PSG and ACT included two sets of state-of-the-art comparisons and analyses: the agreement analysis of the four sleep parameters and an epoch-by-epoch agreement analysis.

TABLE 4 | Epoch-by-epoch agreement analysis between ACT and PSG.

Epoch-by-epoch agreement indicators	(Mean ± SD)
Sensitivity	0.939 ± 0.057
Specificity	0.511 ± 0.201
Accuracy	0.868 ± 0.077
PVS	0.901 ± 0.076
PVW	0.640 ± 0.166
Kappa	0.735 ± 0.154

Agreement indicators are defined in the methods section (Epoch-by-Epoch Agreement Analysis). Kappa coefficient between 0–0,2 = slight agreement; 0,2–0,4 = fair agreement; 0,4–0,6 = moderate agreement; 0,6–0,8 = substantial agreement; 0,8–1,0= almost perfect agreement (33). PVS, predicted value for sleep; PVW, predicted value for wakefulness.

Sleep parameter agreement analyses revealed, on the basis of ICC, a good agreement between PSG and ACT for the assessment of SL and TST, and a moderate agreement for WASO and SE. Similarly, we observed a clinically satisfactory equivalence for the measurement of SL and TST but not for WASO between ACT and PSG, within the pre-set range of acceptable deviation. SE was significantly equivalent in the two methods when using the less conservative range of acceptability of 10% ($p < 0.01$) but not when using the conservative range of 5% ($p = 0.25$). The Bland-Altman plots revealed that, for almost all participants, the differences between ACT and PSG fell between [-2SD; +2SD] limits of agreement, and there were no visible trends indicating that ACT performed differently with respect to SL, TST, WASO, or SE values.

Epoch-by-epoch agreement analyses showed high sensitivity, PVS and accuracy, substantial kappa, but moderate PVW and specificity. These results indicate that ACT has a high ability to identify TS, but lower ability to detect TW. According to Sadeh's recommendation, one should look for a specificity higher than 0.60, in the epoch-by-epoch ACT/PSG comparisons (36). In our study, we found a moderate specificity of 0.51 with the low sensitivity-threshold setting. With the medium and high sensitivity-threshold settings (results in **Supplementary, Table S3**), we obtained better specificity (respectively, 0.617 ± 0.193 and 0.699 ± 0.18), but all other indicators were lower (specificity and PVW) or equivalent (accuracy, kappa, and PVS), and above all, sleep parameters (TST, WASO, and SE) were less accurate with those settings (results in **Supplementary, Table S3**).

To date, most studies which have investigated the validity of actigraphy, by comparing it to polysomnography, were conducted in healthy young adults (25, 32, 37). However, actigraphy is a particularly useful tool in pediatric research and thus widely employed, even though some devices have not been validated yet in this population. Actigraphy has been validated in the TD pediatric population, e.g., in infants and young children (38–40) and also in adolescents (41). Although results of previous studies may be misleading as different devices and scoring algorithms do not perform equally across age groups (24), the agreement indicators of the present study were within the range of those reported in the literature ([0.88–0.93] for the sensitivity, [0.46–0.77] for the specificity, and [0.84–0.9] for the accuracy) (24, 42). Thus, our results are consistent with what has been reported in the TD pediatric population: actigraphy correctly identifies sleep periods (as denoted by the high sensitivity) but is less accurate in identifying WASO (as denoted by the low specificity). Despite the growing interest in actigraphy research, validation studies in children are still lacking. This is of particular importance as children display different sleep behaviors than adults with children displaying more movements during sleep than adults. Validation studies should take into consideration these differences and examine sleep across different developmental age groups.

Within the pediatric population, there are children for whom sleep disorders are much more prevalent. Indeed, up to 80% of young children with ASD have sleep disorders (43–45) compared to about 25% of TD children (46). These disturbances among the ASD population are three to four

times more common and have been related to daytime symptomatology (12–15), hence the importance of measuring sleep in this population.

The vast majority of sleep studies in the ASD population have focused on subjective assessment of sleep (i.e., parent-reported sleep questionnaires or sleep diaries) because of the difficulties performing more objective assessments (e.g., actigraphy, polysomnography). Indeed, in 2015, according to Elrod and Hood's meta-analysis (7), there were only 10 studies that examined sleep objectively using PSG (11, 47, 48) and/or ACT (49–51). The PSG sleep parameters observed in our study were similar to those described by Buckley et al. (52), who included 60 ASD children aged 2.24–13.1 years. In the present study, compared to theirs, were reported, respectively: a SL of 35.2 min (±33.2) against 39.4 min (±33.2), a WASO of 77.2 min (±56) against 73.5 min (±72.2), and a SE of 80.3% (±10.1) against 80.2% (±12.7). In average, TST was 47 min higher in our sample compared to Buckley et al. (52), but the SD were very large on this measure for both studies (respectively, 91 and 126 min). For actigraphy, results are too device and setting-dependent to allow a direct comparison between studies. For example, in the current literature, reported WASO range from 18 to 88 min (50, 51) (for details see Methodology and **Supplementary Data**). As many children with ASD present sensory abnormalities, and thus may not tolerate electrodes on their scalp or face, PSG recording may be compromised. Actigraphy has become more and more popular as an alternative, non-invasive, objective, and cost-effective assessment tool for the study of rest-activity cycles as a proxy to sleep–wake rhythms. It has become a tool of choice for the assessment of sleep quality in children with ASD but has not been validated yet in this population. Our study provides, for the first time, the mandatory evidence for the validity of actigraphy compared to PSG for these assessments in children with ASD, providing thus the basis for improved medical care of sleep disorders in these children. It is essential to validate sleep measures in other specific pediatric populations, as results found in the TD children cannot be extrapolated to them.

As reported by Meltzer et al. (53), it is common to find validation-type studies using inadequate methodology and relying only on correlation analyses, or alternatively focusing more on sensitivity than specificity, leading to deceptive results. To address this, we used multiple comparison and performed recommended agreement analysis methods (27, 28). We also compared both clinical sleep parameters and recorded epochs, to report sensitivity and specificity. Moreover, in the literature, results regarding actigraphy-derived sleep quality parameters in children with ASD are contradictory (10, 50). This may be due to variable wake sensitivity threshold that many studies do not report. Thus, we compared several sensitivity-threshold settings.

A particular strength of the present study is that we included ASD children across the spectrum, with and without associated intellectual disability ranging from low to high severity (with respect to DSM-5). This allows to generalize our results to the overall population of ASD children and not only to high functioning ASD children, as is often the case. In our study, we find the same male predominance in ASD population [i.e., six girls and 20 boys (54)]. Our study sample was young, with a mean age of 5.36 years. It is important to study sleep quality in children and detect sleep difficulties as early as possible, especially since untreated sleep difficulties maintain with time and become chronic.

Despite these strengths, there are also some limitations to this study. The main limitation is the relatively small sample size of 26 subjects and high interindividual variability, which may both reduce statistical power, especially regarding equivalence tests. However, the sample size was above the average sample size of previous studies examining the validity of actigraphy against polysomnography reported by Meltzer et al. (53), which was of 18 (range [8–45] participants). Also, the interindividual variability of the present study is similar to that reported in previous studies (11, 14, 55) and did not refrain from finding that actigraphy is a valid method to assess sleep quality parameters in children with ASD, compared to polysomnography. Furthermore, we have included children within the broad spectrum of ASD and did not only focus on a homogeneous group of high functioning children with ASD, thus reflecting a more representative population of children with ASD and sleep disturbances such as those seen in sleep clinics—which is a strength of this study. We also compared only a single night of actigraphy to concurrent PSG recording while it is recommended to collect five to seven nights of recording across devices (56). This can be explained by the fact that it is not feasible to carry-out seven consecutive days of polysomnography in children with ASD, because of sensory abnormalities or associated behavior disturbances. Lastly, it should be noted that the data sampling over the actigraph recording was set to 1-min epochs and retrospectively converted to 30-s epochs by the software to allow comparison with the PSG epoch settings, as done by previous studies (24, 25). Although this has little influence on the comparison of general sleep parameters, it can lead to a small artificial reduction of epoch-by-epoch agreement indicators, including specificity and sensitivity. For a better comparability between PSG and ACT epochs, future studies should insure automated synchrony in timing and epoch lengths.

In addition to these limitations, it is important for researchers and clinicians to understand that sleep/wake scoring depends on specific devices, algorithms, and sensitivity thresholds. The default mode of an actigraph may be valid in one specific population but not in another. For scoring purposes, a daily diary and/or event marker use, when possible, is necessary in order to accurately identify sleep periods.

CONCLUSION

To our knowledge, our study is the first to validate actigraphy as a method to assess sleep quality parameters compared to polysomnography, using a particularly sound state-of-the-art methodology, in a young population of children with ASD. The results suggest actigraphy to be a valid method to evaluate sleep within a particularly vulnerable population, with a high sensibility and a good reliability for most sleep parameters, including TST and sleep onset latency. With the increasing number of research studies using actigraphy, it is important to have multiple validation studies for each device and each developmental age, across healthy and clinical samples. This study confirms ACT as

the objective alternative to assess sleep quality in children with ASD and can provide reliable information to clinicians when investigating sleep to improve quality of life.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the regional French Institutional Review Board with written informed consent from parents of participants and assent was obtained from the child when possible. All parents of subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the regional French Institutional Review Board (CPP Est IV 11/04/2012).

AUTHOR CONTRIBUTIONS

EY-K collected the data, conducted the actigraphy and polysomnography data processing, and wrote the manuscript. ER planned and performed the analyses and contributed to manuscript revision. M-MG collected part of the data and assisted with manuscript review and revisions. NL collected part of the actigraphy and polysomnography data and assisted with manuscript review and revisions. PF collected part of the actigraphy and polysomnography data and assisted with manuscript review and revisions. PB assisted with the study design and the funding and contributed to manuscript review and revisions. CS designed the study, secured funding, collected the data, assisted with data interpretation and critique, as well as contributed to manuscript review and revisions. All authors are responsible for the reported research and have reviewed and approved the final manuscript as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00551/full#supplementary-material

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A Novel Approach to Assess Sleep-Related Rhythmic Movement Disorder in Children Using Automatic 3D Analysis

Markus Gall[1], Bernhard Kohn[1], Christoph Wiesmeyr[1], Rachel M. van Sluijs[2,3], Elisabeth Wilhelm[2], Quincy Rondei[2], Lukas Jäger[2], Peter Achermann[3,4,5], Hans-Peter Landolt[3,4], Oskar G. Jenni[3,6], Robert Riener[2,3,7], Heinrich Garn[1] and Catherine M. Hill[8]*

[1] Sensing and Vision Solutions, AIT Austrian Institute of Technology GmbH, Vienna, Austria, [2] Sensory-Motor Systems Lab, ETH Zurich, Zurich, Switzerland, [3] Sleep & Health Zurich, University Center of Competence, University of Zurich, Zurich, Switzerland, [4] Institute for Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland, [5] The KEY Institute for Brain Mind Research, Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry, Zurich, Switzerland, [6] Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland, [7] Faculty of Medicine, University of Zurich, Zurich, Switzerland, [8] Division of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

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***Correspondence:**
Markus Gall
Markus.Gall@ait.ac.at

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Background: Unlike other episodic sleep disorders in childhood, there are no agreed severity indices for rhythmic movement disorder. While movements can be characterized in detail by polysomnography, in our experience most children inhibit rhythmic movement during polysomnography. Actigraphy and home video allow assessment in the child's own environment, but both have limitations. Standard actigraphy analysis algorithms fail to differentiate rhythmic movements from other movements. Manual annotation of 2D video is time consuming. We aimed to develop a sensitive, reliable method to detect and quantify rhythmic movements using marker free and automatic 3D video analysis.

Method: Patients with rhythmic movement disorder (n = 6, 4 male) between age 5 and 14 years (M: 9.0 years, SD: 4.2 years) spent three nights in the sleep laboratory as part of a feasibility study (https://clinicaltrials.gov/ct2/show/NCT03528096). 2D and 3D video data recorded during the adaptation and baseline nights were analyzed. One ceiling-mounted camera captured 3D depth images, while another recorded 2D video. We developed algorithms to analyze the characteristics of rhythmic movements and built a classifier to distinguish between rhythmic and non-rhythmic movements based on 3D video data alone. Data from 3D automated analysis were compared to manual 2D video annotations to assess algorithm performance. Novel indices were developed, specifically the rhythmic movement index, frequency index, and duration index, to better characterize severity of rhythmic movement disorder in children.

Result: Automatic 3D video analysis demonstrated high levels of agreement with the manual approach indicated by a Cohen's kappa >0.9 and F1-score >0.9. We also demonstrated how rhythmic movement assessment can be improved using newly introduced indices illustrated with plots for ease of visualization.

Conclusion: 3D video technology is widely available and can be readily integrated into sleep laboratory settings. Our automatic 3D video analysis algorithm yields reliable quantitative information about rhythmic movements, reducing the burden of manual scoring. Furthermore, we propose novel rhythmic movement disorder severity indices that offer a means to standardize measurement of this disorder in both clinical and research practice. The significance of the results is limited due to the nature of a feasibility study and its small number of samples. A larger follow up study is needed to confirm presented results.

Keywords: 3D video, automated, rhythmic movement disorder, contactless, Jacinto capita nocturna, diagnostic tool, sleep

INTRODUCTION

Rhythmic movement disorder (RMD) is a poorly understood sleep-related movement disorder defined by the International Classification of Sleep Disorders (ICSD-III) (1) as repetitive, stereotyped rhythmic movements (RMs) of large muscle groups in the frequency range 0.5–2 Hz (1), (2). The predominant forms are head-banging, body-rocking, and head-rolling (3). Typically, RMD starts in infancy with a maximum prevalence rate of 2.87% as confirmed by our recent community-based study of 1,447 infants and toddlers (4).

A diagnosis of RMD is only made when there are clinical consequence of nocturnal movements, specifically significant sleep disturbance, impaired daytime functioning, or physical injury (1). While RMD may cause local trauma and hair loss (5), reports of more serious injuries are rare (6). RMD can have social consequences; it may cause embarrassment (6, 7) and noise from head-banging or movements of the bed may disturb other household members (8). Importantly however, RMD can significantly affect sleep quality. Limited studies report poor concentration, difficult behavior, as well as impaired memory and decision making capabilities in children with this condition (9, 10).

The American Academy of Sleep Medicine (AASM) provides rules for scoring RMs using polysomnography. An episode of RMs consists of at least four movements, occurring with a frequency range from 0.5 Hz to 2.0 Hz and electromyography (EMG) should be at least twice the baseline amplitude (11). Guidance on assessment of severity is not provided. This contrasts with other childhood sleep disorders, for example, sleep disordered breathing, where decades of research in large populations of children have refined diagnostic criteria, allowing associations to be made between a measure of severity, the apnea/hypopnea index (AHI), and meaningful outcomes (12). This is a critical omission for RMD as objective measures are essential to improve diagnosis, monitor treatment outcomes, and standardize research. Thus, an important next step in progressing our understanding of this disorder is an agreed measure of severity and a standardized and objective method to quantify movements.

Furthermore, our clinical experience shows that many children fail to exhibit their typical RMs when constrained by sensors in a sleep laboratory environment (3). Stepanova et al. (13) also noted that polysomnography underestimates RMs compared to parental report. Thus, in children with suspected RMD, polysomnography is primarily used to exclude other disorders that cause movements during sleep such as epilepsy and periodic leg movements and, where rhythmic movements are seen, to confirm the clinical diagnosis.

Another technology, actigraphy, successfully quantifies movement amplitude and sleep quality but fails to distinguish RMs from other high amplitude movements (14). Manual observation and annotation of standard two-dimensional (2D) videosomnography (overnight video alone) is another method to assess RMD with the advantage that children can be assessed over multiple nights in their home bedroom environment unconstrained by sensors. While simple digital film images of movements can confirm a clinical diagnosis, quantification of the timing, duration, and episodic nature of movements require time-consuming and intensive analysis. Despite these limitations, videosomnography is a promising area for future research (15). One approach to address these limitations is 3D video (3). Recent research has demonstrated the utility of contactless 3D video for the detection of abnormal chest wall movements in central sleep apnea syndrome (16) and limb movements in periodic limb movement (PLM) disorder (17). Using 3D has the advantage to also include the depth axis, not accessible using 2D video analyses alone.

In summary, standards for objective quantification and characterization of RMs are not well established and standard technologies are imperfect. We aimed to address these limitations by evaluating a novel automated 3D assessment algorithm to quantify RMs. Furthermore, we aimed to develop novel indexes to quantify RMD severity as a basis for future international standards of assessment in this poorly understood disorder.

MATERIAL AND METHODS

Setting

Data were collected as part of a feasibility study (https://clinicaltrials.gov/ct2/show/NCT03528096) of sensory stimulation therapy in children with RMD (18, 19). Assessments were made in the University of Zurich, sleep laboratory, Switzerland. The study was approved by the ethics committees in both the UK (National Research Ethics Committee and Health Research Authority - IRAS 234505) and the Cantonal Ethics Committee of Zurich (KEK 2017-01880) alongside approvals from Swissmedic (2017-MD-0035). Parents of participating children signed informed consent, and children signed informed assent.

Children were aged 5 to 18 years with a clinical diagnosis of RMD confirmed by a somnologist (CMH). Children were

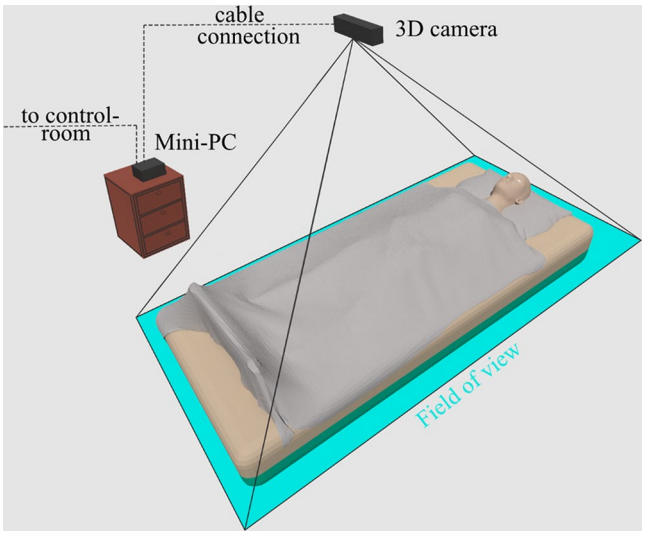

FIGURE 1 | Sleep laboratory setup. The participant was placed in a bed with a 3D camera (Kinect v2) mounted on the ceiling. The camera was directed towards the participant with the field of view covering the bed area. The recorded video was transmitted to a fan-less mini-PC located in the same room. This PC further transmitted the data to a notebook located in the control room.

excluded if they were sensitive to motion sickness based on self-report. Parent report of RMD semiology, history of injury, influence on sleep, and daytime functioning were recorded.

Sleep Laboratory Setup

Rooms were equipped with hardware, as illustrated in **Figure 1**.

The participants slept one night in a standard bed (adaptation night) and another one in a bed that can rock gently (Somnomat) (18, 19) but was stationary for the measurement (baseline night). In both nights, Sheets were of average thickness. The feasibility study included a third night (intervention night) where the bed was rocking. However, this night was excluded from our 3D analysis since bed induced movements could not be distinguished from actual RMs reliably yet.

We used a time-of-flight sensor (Microsoft Kinect One V2) (20) as 3D camera mounted at the ceiling approximately 1.3 m above the bed to record 2D gray scale and 3D video. The time-of-flight principle measures the distance between the sensor and an object, based on the time it takes the infrared light from emission until its return to the sensor, after being reflected by an object. As a result, each pixel of the obtained 3D images holds the value of the distance to the nearest object detected. Further detail on the camera is available in the appendix section 9.1. The area of interest was set to the edges of the bed and thus created a depth map of the bed and participant. The sensor was mounted with a magnetic clip and additionally secured using a safety strap. A frame rate of 30 frames *per* second was used with radiation intensity compliant with current safety standards (21) for optical radiation.

The obtained 3D and 2D videos were transmitted to the control room using a fan-less mini-PC. A notebook equipped with sufficient storage capacity saved the data for further processing. Synchronization was automatically achieved between manual 2D and automatic 3D annotations using manually set, clear markers such as lights on/off.

Definition of RMs and the Ground Truth

AASM recommendations for scoring an episode of RM, based on muscle activity recordings using electromyography sensors (22), were adapted to fit the method of visual scoring of 2D video:

- RM frequency was defined to be in the range of 0.5–2.0 Hz.
- The minimum number of movements required to define an episode of RMs was 4.

To define discrete episodes, the authors determined an additional criterion: if no movement occurred during a period of time equivalent to two RMs, the episode was scored as complete and any further movements immediately following this interval were defined as a new episode.

Scoring was performed manually by RS and EW. Episodes of RMs, and periods without movements, or with general non-RM, were annotated using start and duration entries. Movements were annotated while simultaneously monitoring experimental nights and offline revised to their best knowledge. This manual scoring approach formed the ground truth for 3D algorithm performance measure.

3D Algorithm

The 3D algorithm was an automated processing pipeline with the aim to detect movements and classify these into RMs and non-RMs based on raw 3D image input (**Figure 2**).

Firstly, obtained 3D images were pre-processed by subsampling and noise reduction using different filter operations (**Figure 2A**). Next, the motion map indicated the temporal depth change around the current frame for each pixel (**Figure 2B**) by approximating the first derivative relative to the noise.

From the motion map, the 3D signal was derived as a 1D value representing the movement activity for each frame (**Figure 2C**). The higher the values of the pixels indicating movement, the higher the resulting 3D signal. Thus, the 3D signal depended on the number of included pixels and their motion response. Next, peaks of the 3D signal were categorized in actual movements or peaks induced by noise. We used two thresholds to identify real movements: one to define start and stop of a potential movement separating floor noise from peaks, and the other identified real movements and ignored noise induced peaks. Threshold calibration was performed for each room individually.

In a next step, the annotated movements were classified into RMs and non-RMs. As RMs occur rhythmically, 3D signals of annotated movements was analyzed using fast Fourier transform (FFT) with the goal of finding characteristics separating the classes in the frequency domain. FFT used a window of 3 s to achieve a resolution of 0.33 Hz according to the time–frequency uncertainty. We used an overlap of 50% and zero padding, resulting in segments of 1.5 s. Due to padding, possible inaccuracies may be induced at the first and the last segment of a movement, as detected by our algorithm; therefore, we excluded these segments from the

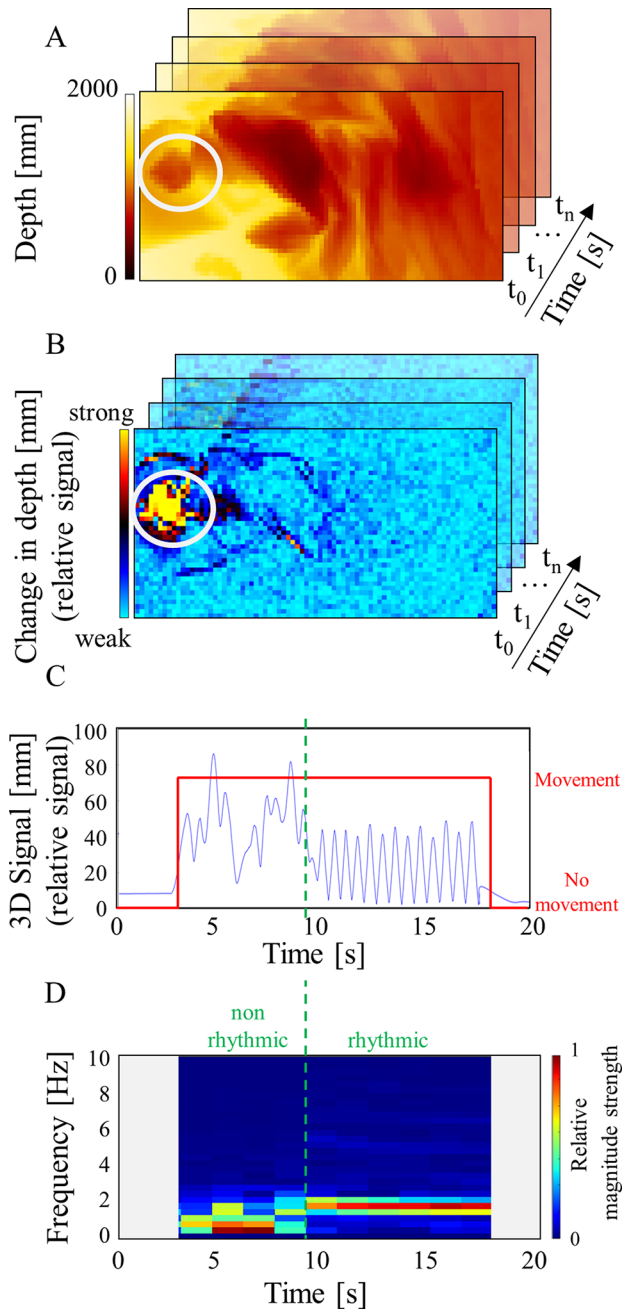

FIGURE 2 | 3D algorithm processing pipeline. The chosen example shows a child lying in a bed where the head is indicated in **(A** and **B)** by the white circle. **(A)** The pre-processed depth image stores the distance between camera and bed for each pixel in color coded millimeters. The example shows a person lying in bed covered with a blanket. A white circle highlights the participant's head. **(B)** The motion map indicates movement. Here, a movement augmentation in the head region is present (yellow area). **(C)** The 3D signal (blue) shows a deflection for this time interval and a movement is annotated (red) where the 3D signal is augmented. Represented is a movement sequence where the first part reflects the participant changing from a lying position to a RM position on all fours followed by RMs. **(D)** The FFT spectrogram shows the frequencies over time. Relative strength of the magnitude is indicated by the colorbar. The RM part shows a narrower frequency band around 2Hz (right of green line). In contrast, the transitional movement shows a blurred spectrum (left of green line).

analyses. RM segments showed a narrow (~2 Hz) frequency band, with the mean frequency representing the participant's movement frequency (**Figure 2D**). We also detected an absence of frequency components in the range below this peak. In contrast, general movements presented a blurred spectrum suggesting an overlay of many frequencies. From this information, features from the frequency domain were engineered with the aim of identifying spectral characteristics of RMs distinct from those of non-RMs. The best features for separation and their thresholds were identified using Cross-Validation and Random Decision Forests (23). The final implementation used the three best features for classification: the power of the lower frequencies (0–0.67 Hz) best separated the two movement types followed by the frequency with the highest power and the frequency with the second highest power.

As noted in 2.2, when annotating the ground truth, termination of a RM episode was originally defined as a cessation of movement lasting for at least the duration of two movement cycles. In practice, for a 2 Hz movement frequency, this is equivalent to only 1 s. As it was not possible to count movements with sufficient precision to apply the same rule for 3D annotations, we introduced a revised threshold minimum pause duration that was independent of movement frequency. Specifically, a minimum pause duration of 10 s was based on both pragmatic and clinical considerations. Evaluation of this 10 s rule resulted in F1-score and Cohen's kappa with highest agreement when applied to the 3D and the manual method (**Figure 3**). This finding suggested that the previously defined rule was too sensitive to apply when annotating manually. The new 10 s rule was also applied to manual annotations.

Algorithm Evaluation

Comparison of automatic 3D and manual 2D approaches used the following standard classification features: false positive rate, true positive rate, Cohen's kappa or F1-score, and comparison of indices such as number of RM episodes or episode duration.

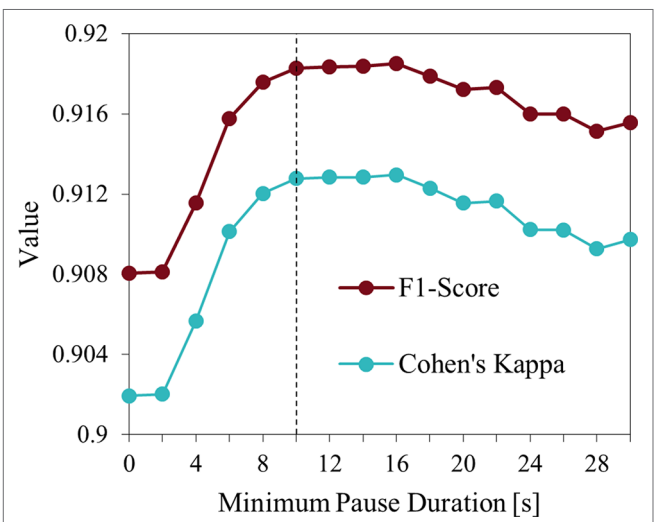

FIGURE 3 | Minimum pause duration influence on evaluation measures. Indicated are the F1-score and Cohen's kappa for different values of the minimum pause duration applied to 3D video and visual-manual method. Durations >10 s do not result in further improvements.

Even though many single events were recorded, due to the low number of recorded nights and participants, we chose not to include measures of statistical significance in our results.

Severity Measures for RMD

Clinically relevant indexes of movement severity were defined as follows:

1) Total duration of rhythmic episodes based on time in bed (s)
2) Total duration of non-rhythmic episodes based on time in bed (s)
3) Number of RM episodes based on time in bed (count)
4) Mean duration of RM episodes (s)
5) Rhythmic movement index (RM index)* (episodes/h of time in bed)
6) Duration index* (% of time in bed occupied by RMs)
7) Frequency index*(Hz)

Furthermore, we developed graphical plots to map these indices to time of night:

1) RM time of night distribution plot
2) Fragmentation plot*
3) Duration distribution plot*
4) Frequency distribution plot*

Measures/plots marked with an asterisk (*) are novel and aim to improve objective RMD assessment. They are based on indices used to characterize other sleep disorders like the PLM index or AHI (22, 24) both calculated as numbers of events *per* hour of sleep.

To maximize detection of RMs, we purposively excluded neurophysiological measures of the sleep-wake state, so our calculations such as the RM index were based on time in bed. The RM index (Equation 1) therefore reflects how often the night is disrupted by RM episodes and includes RMs after lights out before sleep onset.

$$RM\,index = \frac{number\,of\,RMs(episodes)}{time\,in\,bed(h)} \quad (1)$$

The fragmentation plot illustrates the distribution of time between consecutive RM episodes. It is based on the concept of the inter-movement-interval (imi) histogram as used in PLM research (25).

The RM index and plot alone may not be sufficient to describe RMD severity. In RMs, the effort and amplitude of movements is independent of the number of episodes. However, the duration of the episodes provides an indication of severity. For example, 40 × 2 s duration RM episodes would generate the same RM index as 40 × 3-minute episodes if the episodes start at the same times. Clearly, the second example expends more movement effort due to longer episode duration. Therefore measurements that reflect this difference in severity are essential for RMD diagnosis. To address this dimension, we introduced the duration index (Equation 2) calculated as the ratio of RM time to total time in bed.

$$duration\,index = \frac{RM\,time(h)}{time\,in\,bed(h)} \quad (2)$$

The corresponding duration distribution plot provides additional information. With these novel indices, RM severity was characterized through combining variables of sleep fragmentation and duration.

To provide further characterization of RM episodes, we propose the frequency index. This index provides more detailed insight on effort, thereby being a valuable extension of the duration index. The duration index already indicates how much time is spent in RMs but does not capture the mechanical effort in terms of how often the individual actually moved during this time. Slow RMs require less physical effort than faster ones since a change of movement direction occurs much less often. The frequency index reflects this movement effort by calculating the mean RM frequency (Equation 3 with k, the total number of episodes, and $\dot{f}$, the mean frequency of the recording's n-th RM episode).

$$frequency\,index = \frac{\sum_{n=1}^{k} \dot{f}_n}{k} \quad (3)$$

Furthermore, the frequency distribution plot indicates time of the night when specific frequencies occurred. Thus, the somnologist can observe how RM frequency, and thus effort, changes over the night. Automatic 3D with its ability to rapidly process complex data offers significant advantages over cumbersome manual 2D video scoring to generate such frequency-based data.

In summary, we propose three new indices for harmonized RMD assessment. The RM index reports how often a night is disturbed by RM episodes; the duration index gives an indication on how much effort is involved in RMD episodes, and finally, the frequency index provides data on the mean frequency of RMs.

RESULTS

Six children with sleep-related RMD between age 5 and 14 years (M_{age}: 9.0 years, SD: 4.2 years) were recruited in the UK, of whom two were female and four male. Recorded movement semiologies included head banging, head rolling, body rocking, and body rolling. One participant did not exhibit RMs during the study despite video documentation of movements in the home environment.

Table 1 compares scoring results for automatic 3D video versus visual-manual 2D analysis. Records of individual results are shown in **Table S1** of the Appendix section. As expected, most of the segments in each record were classified as negative. Therefore, the resulting true negative rate and accuracy were higher or equal to 99%. Segments of incorrect episode classification comprise a small proportion compared to the number of true episode classifications. A good performance is indicated by an F1-Score of 0.918 calculated from the Positive Predictive Value of 0.912 and the True Positive Rate of 0.924. Some records show even higher values. What also stands out in the table is the value of Cohen's kappa of ~0.9 stating almost perfect agreement of the two methods, according to Landis and Koch (26).

Table 2 shows the evaluation results on RMD measures. Presented are the mean values over all recordings. Results for

TABLE 1 | Classification results of the automatic 3D video method versus manual approach across 12 nights of data.

Performance metric	Value
Number of true negative segments*	148,669
Number of false positive segments*	894
Number of false negative segments*	762
Number of true positive segments*	9,281
Number of segments classified as RM by ground truth*	10,043
Number of segments classified as non-RM by ground truth*	149,563
True positive rate**	0.924
True negative rate**	0.994
False negative rate**	0.076
False positive rate**	0.006
Positive predictive value**	0.912
Accuracy**	0.990
F1-score**	0.918
Cohen's kappa**	0.913

(*) Values were derived as sum of all individual records. (**) Values were calculated with classification scores marked with (*).

TABLE 2 | Evaluation results for automatic 3D video analysis and visual-manual 2D annotations separately.

	3D	Manual
RM duration (h)	0.71	0.70
Non-RM duration (h)	10.37	10.38
Number of episodes	28.92	9.17
Mean episode duration (s)	73.85	205.79
RM index (episodes/h)	2.60	0.77
Duration index (%)	6.04	5.93
Frequency index (Hz)	1.08	
Bed time (h)	11.08	11.08
Total time (h)	132.99	132.99

Presented are the mean RMD measures over all recordings.

individual participants are given in **Table S1** of the appendix section. The most interesting aspect of **Table 2** is the RM duration. While automatic 3D video scoring finds a mean duration of 0.71 h *per* participant, the manual 2D approach shows a mean duration of 0.70 h *per* patient, a difference of 36 s. The average number of episodes detected by 3D is 28.92 *per* time in bed, while the manual approach detects only 9.17 on average. Since the mean duration is nearly the same but number of detected episodes differs, the results show that 3D tends to discriminate discrete episodes more sensitive. Episodes detected with the manual approach have a mean duration of 205.70 s, which is more than double of that detected by 3D analysis. Our newly introduced indices reflect these findings well: The average duration index is equal for both methods with a value of 0.06. The RM index is augmented for 3D with a value of 2.60 compared to 0.77 for the manual approach.

In addition to the numeric scores, RM episodes can be plotted graphically using our novel indices.

First, **Figure 4** shows the distribution of RMs over the night as the accumulated sum of all recordings. The y-axis shows the counts of RMs occurring in time intervals of 30 min. The figure shows that RMs are more likely to occur at the beginning of the night and then augment at the beginning of the second half of the night. From this data, we can also see that automatic 3D and manual 2D annotations highly agree.

Figure 5 shows the RM episode durations for automatic 3D and manual 2D approaches. Interestingly we observed that the majority of events had a duration of less than 1 min. Importantly, 3D detected more episodes of shorter duration.

Analysis on duration distribution over the night shows that durations largely vary over most periods of the night (**Figure 6**). During sleep onset, RMs show longer durations, while results show that following periods are of shorter duration. Periods 1-2 and 2-3 include only one movement each for the manual data. With the start of the second half of the night, movement durations augment whereby movements in the last period again diminish to medium durations.

The fragmentation plot, **Figure 7**, reflects the time interval between consecutive RM episodes from the start of the movement to the start of the subsequent one and indicates sleep quality. The episode duration plot and the higher number of 3D detected episodes predict the findings

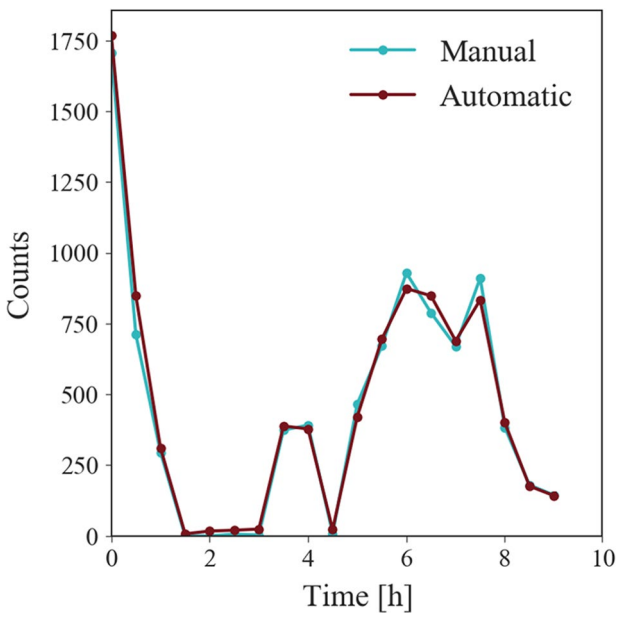

FIGURE 4 | RM time of night distribution plot for all recordings. Each data point shows how many RM episodes occur over all recordings in time intervals of 30 min. RMs occur predominantly in the beginning of the night and the start of the second half of the night. Automatic 3D finds high agreement with data obtained by manual annotations.

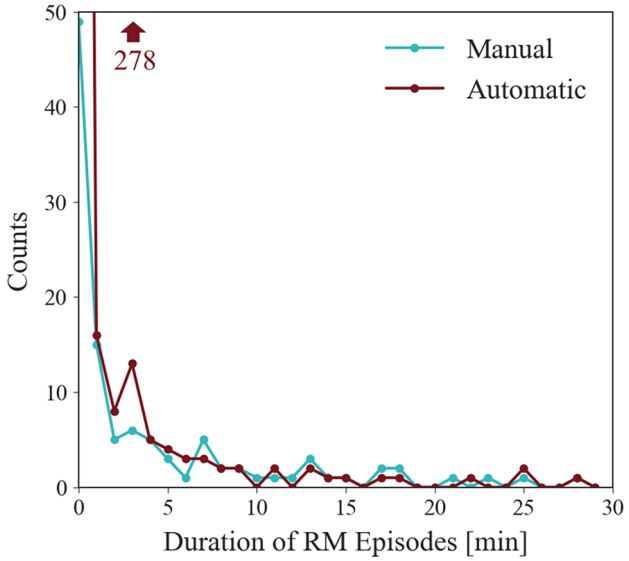

FIGURE 5 | Duration distribution plot for all recordings. Represented is the count of detected RMs with a duration between intervals of 1 min. Noticeable is the high count of durations between 0 and 1 min. The data point for automatic 3D in this first interval exceeds the plot window, but its value is indicated by the arrow.

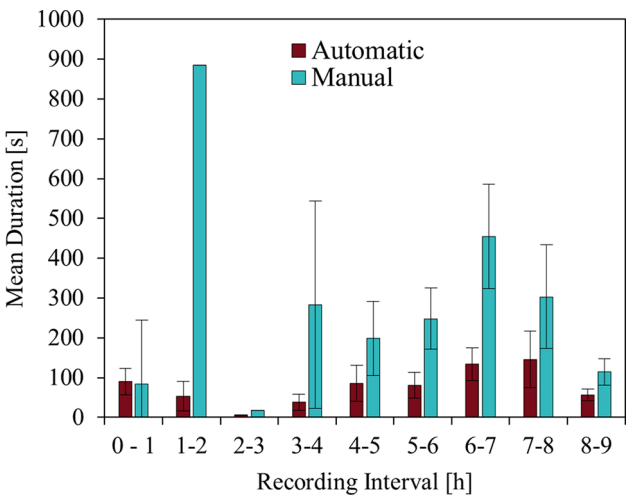

FIGURE 6 | RM duration distribution overnight. The plot shows the mean duration of RMs per hour of the recorded nights for the automatic 3D and manual 2D method. Error bars indicate the standard error of the mean. RM durations indicate high variety for each of the periods. Periods 1-2 and 2-3 include only a single RM each for the manual data, where the standard deviations equal zero.

of the fragmentation plot, namely, that 3D reports a higher fragmentation than manual annotation, also supported by the higher RM index.

Table 3 compares three individual participants' records using the proposed RMD indices, illustrating how this allows rapid comparison between cases and illustrates the spectrum of severity of RMD. We chose these three examples since they best represent the spectrum of severity.

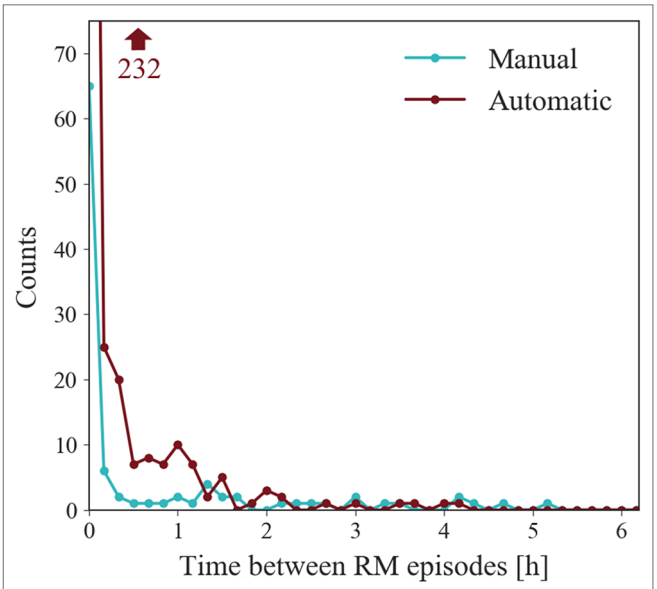

FIGURE 7 | Fragmentation plot of all records. Illustrates the distribution of time elapsed between onset of consecutive RMs presented with a convenience interval width of 10 min. 3D reports higher fragmentation than the manual approach as the majority of time periods are less than 10 min. This data point lies outside of the plot window, but its value is indicated by the arrow.

TABLE 3 | Proposed indices on recordings showing different manifestations of RM symptoms.

Case	Duration index (%)	Rhythmic movement index (episodes/h)	Frequency index (Hz)
A	0.08	0.59	0.87
B	15.88	2.41	1.05
C	5.88	2.16	0.97

Chosen recordings were obtained during adoption nights.

RM distribution across the night (**Figure 8**), generated by both automatic 3D and manual 2D annotations for the cases, graphically represents both the duration index and RM index reported in **Table 3**. Case A has a duration index close to zero, suggesting relatively mild RMD as shown in the plot. Additionally, the RM index is very low. The frequency index does not add any value in this case since the duration and number of RM episodes are low. Case B illustrates greater severity. This is again reflected in the indices in **Table 3**, where the duration index indicates that 15.88% of the total night is spent in RMs. The RM index of 2.41 indicates that each hour of the night is disturbed more than twice by an RM episode. Finally, case C shows an intermediate severity. Again, the proposed indices reflect this estimation perfectly. Note how the frequency index yields additional useful information: Not only does participant B have RMs for a longer period of the night and shows more sleep fragmentation but also the higher frequency of movements denotes greater effort engaged in RMs across the night.

In addition to the measures already described, **Figure 9** shows an example of frequency analyses from the 3D data of one individual. The figure is similar to the RM episode distribution

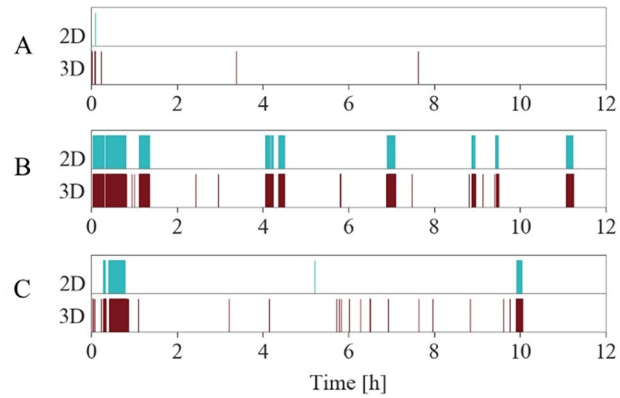

FIGURE 8 | RM time of night distribution plots according to **Table 3**. The three examples show automatic 3D annotations (lower, red) and manual 2D annotations (upper, cyan) over time. RM annotations are indicated with a colored rectangle. Periods without annotations stay blank. Case A only shows few RMs in the beginning of the night, hardly recognizable on the full night scaled plot. Case B exhibits the most severe form of RMD, while case C exhibits mild symptoms compared to B.

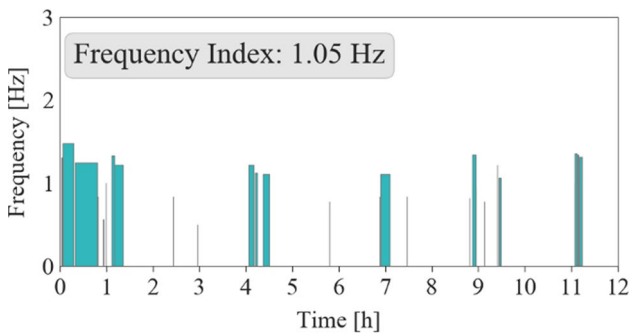

FIGURE 9 | Frequency distribution plot of an individual record (Case B). The mean frequency of an episode is plotted over the time in hours. For this case, frequency remains relatively stable over the night.

plot where episodes are plotted over time. In contrast, the y-axis represents the mean frequency for each episode, illustrating relative stability of movement frequency across the night.

DISCUSSION

Benefits of Automatic 3D Analysis

The objective of this work was to develop and evaluate an automated method to quantify RMs using a contactless 3D video approach. Furthermore, we aimed to define useful indices to quantify RMD severity to provide information for the development of future international scoring standards.

Obvious improvements were introduced by replacing manual analysis of 2D videos by automatic and marker free 3D video analysis. Annotating 2D videos manually is time-consuming and monotonous to perform, and measures such as movement frequency are difficult to determine. In practice, annotating several hours of data cannot be performed with the same reliability and speed as computerized approaches.

This work also set out to propose new measures to better characterize severity of RMD in the same way that the apnea-hypopnea-index or the periodic limb movement index is used to describe severity of sleep apnea and PLM disorder, respectively. Based on this concept, we introduced the RM index, reflecting how often the time in bed is disrupted by RM episodes. This index is in analogous to the periodic leg movement index and makes use of the same formula. However, established frequency count indices fail to capture the proportion of the time occupied by RMs, so a measure of episode duration was also developed: Longer periods of movement expend greater effort and result in more sleep disruption. Graphical plots of RM distribution through the night, frequency changes, duration, and fragmentation add value by helping to objectively quantify RMD through the sleep period. Better understanding of RMD severity using objective and reproducible quantitative parameters has the potential to support clinical diagnosis and determine at what threshold RMs become a disorder. The ICSD III criterion D refers to disturbance of sleep, but precisely what threshold of sleep fragmentation or duration of RM is important has yet to be determined. Such quantitative measures would facilitate the study of the relationship between RMD severity and impact on health, cognitive, behavioral, and quality of life measures. They also provide a means of measuring treatment outcomes in both clinical practice and treatment trials.

Automatic detection of RMs also creates the possibility for real time intervention treatment, whereby the automated 3D system triggers the onset/offset of connected devices. A number of authors have suggested treatment approaches that include, for example, aversion or stimulus substitution approaches (5, 27, 28), which rely on a response to initiation of movement. For example, the Somnomat rocking bed, which formed part of this feasibility study (19), could be activated in response to the patient's RMs.

Differences Between Automatic 3D and Manual 2D Analysis Methods

The most notable difference between automatic 3D and visual-manual 2D analysis was in RM episode counts. 3D was more sensitive in discriminating episodes than 2D, as short movement pauses may be overlooked by manual scoring. Our experience suggested merit in defining discrete episodes of RMs with a minimum inter-movement duration of 10 s. This criterion was simpler to operationalize rather than a movement frequency-based criterion (defined for manual annotations as equal to or greater than the duration of two RMs), which will differ between individuals. This definition might even improve interrater variability in manual scoring. However, it should be recognized that this 10 second criterion was generated pragmatically for the purposes of this study and should be tested in future studies.

The automatic approach classified some movements as RMs that were not identified by manual scorers. False positive detections occurred when 3D detected a general movement having rhythmic

elements. Similarly, RMs with a slow general movement in parallel resulted in some false negative scoring. In these cases, Fourier analysis yielded a frequency spectrum that appeared similar to that of a general non-RM. However, falsely classified movements were rare compared to the number of correctly classified ones. From a practical clinical and research stand point, automated analysis with the level of accuracy generated by our data offers significant advantages over manual scoring and, importantly, the contactless nature of the measurement device allows also RMs to be assessed without inhibiting movements.

Limitations of This Study

The study included only six participants analyzed over two nights. One participant did not show RMs during any of the two nights. The methodologies should be replicated in future datasets. Intra- and inter-scorer variability is not available because annotations were revised by the same scorer.

CONCLUSION

We present a novel approach to characterize RMD in children using contactless automatic 3D video assessment. This method not only turned out to be fast and highly reliable but also matched the results of manual scoring to a high degree. Three novel indices are proposed: the duration index, the RM index, and the frequency index, that offer a clinically relevant multi-dimensional quantification of RM severity and lay the foundation for a systematic approach to assessment of this poorly understood sleep disorder. This novel use of readily available 3D technology offers a practical measurement approach that could be used in the laboratory or home environment. In conclusion, automatic 3D has the potential to become a valid method to assess RMD severity in children and to enable comparable and reproducible quantification of RM episodes.

DATA AVAILABILITY STATEMENT

The datasets for this study will not be made publicly available because 3D and 2D video data shows participant identifying information.

ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki. The UK National Research Ethics Committee and Health Research Authority (IRAS 234505), the Cantonal Ethics Committee of Zurich (KEK 2017-01880) and Swissmedic (2017-MD-0035) approved the study. Informed consent was obtained from the responsible adults and subjects gave informed assent.

AUTHOR CONTRIBUTIONS

MG, RS, EW, QR, LJ, PA, RR, and CH conceived, planned, and carried out the study and measurements. MG, RS, H-PL, OJ, HG, and CH supervised the project. MG, BK, and CW designed the computational framework and algorithms. MG and HG analyzed the data. MG wrote the manuscript with support from BK, CW, RS, HG, and CH. All authors provided feedback and helped shape the research and critically reviewed the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00709/full#supplementary-material

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BRIEF RESEARCH REPORT
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Video Analysis of Parent–Child Interactions in Behavioral Sleep Disorders: Development of a Scoring Algorithm

Lorna Galbraith[1], *Kim Bull*[1] *and Catherine M. Hill*[1,2]*

[1] *Faculty of Medicine, University of Southampton, Southampton, United Kingdom,* [2] *Children's Sleep Disorder Service, Southampton Children's Hospital, Southampton, United Kingdom*

Introduction: Behavioral sleep disorders, including chronic insomnia (CI), are generally assessed by subjective parent interview. However, evidence suggests that parental report of children's overnight behaviors is unreliable, perhaps due to recall bias or confusion due to sleep deprivation. Video technology has been used clinically to capture complex behavioral disorders in children during the day. However, there is no standardized means of analyzing child and parent behavior at bedtime or during the night. We aimed to create an algorithm for this purpose.

Methods: Child brain tumor survivors (a population previously shown to have a high prevalence of CI) were screened for difficulties initiating and maintaining sleep using sub-scales from the Sleep Disturbance Scale for Children. Those who screened positive (n = 3) then completed a detailed parent interview to confirm a clinical diagnosis of CI. One night of home video footage was obtained from initial settling period to morning waking (SOMNOmedics camera). Footage was imported into BORIS© software and a coding system for parent and child behavior was developed over multiple iterations until agreeable inter-rater reliability (>70%) was achieved between two independent coders.

Results: The final coding categories were: 1) time domains, 2) physical environment, 3) child global status, 4) location, 5) activity, and 6) physical interaction. This achieved 74% inter-reliability in its last iteration.

Discussion: A statistically acceptable behavior scoring algorithm was achieved. With further development, this tool could be applied clinically to investigate behavioral insomnia and in research to provide more objective outcome measurement.

Keywords: sleep, tool, child, insomnia, behavior

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Irma Rukhadze,
UCLA David Geffen School of Medicine, United States

***Correspondence:**
Catherine M. Hill
c.m.hill@soton.ac.uk

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INTRODUCTION

Chronic insomnia (CI) is the commonest childhood sleep disorder (1). According to the Third Edition of the International Classification of Sleep Disorders (ICSD-3), a diagnosis of CI requires 1) difficulty initiating and/or maintaining sleep, 2) adequate opportunity to do so, and 3) subsequent daytime dysfunction. The symptoms must occur at least three times per week and have been present

for at least 3 months (2). CI leads to insufficient sleep which can be detrimental to a child's behaviour (3), cognitive function (4), and brain development (5).

The commonest CI in childhood is behavioral insomnia. There are two core sub-types.

1. Sleep onset association disorder, where the child requires specific "associations," for example a parent/carer present in the room or environmental factors such as music or light, to fall asleep. (From here on "parent" will refer to any carer with involvement in the bedtime routine). With these associations, the child settles to sleep easily but following natural night wakings struggles to resettle to sleep without the same conditions they have associated with bedtime. Typically, the child then signals for a parent by crying or leaving the room (6), this is interpreted as a troublesome night waking.
2. Limit setting sub-type, where the child makes repeated requests to the parent in an attempt to delay his/her bedtime, that is, "curtain calls". This is accommodated by the parent, who fails to enforce sufficient boundaries (6).

Where elements of both sleep onset association insomnia and limit setting insomnia are present, the term "combined type insomnia" (6) is used.

The standard diagnostic assessment of CI is through a clinical history, which has some limitations. First, while parental recall of their child's *sleep schedule* (i.e., sleep onset and duration) has been shown to correlate with objective measures (actigraphy), overnight *sleep quality* [the child's overnight activity including number of night wakings (7)] is less reliably reported (8, 9). Parents are only able to report activity of which they are aware. If the child does not disturb the parent, these wakings may be overlooked9. While the child's own account is relevant, many children with CI may not have the developmental skills to provide an accurate history. Furthermore, parental recall may be restricted by their own memory of events, which may be impaired when tired, particularly after repeated awakenings (9). On occasions the sleep problems may be exaggerated, thus misleading any intervention put in place by the clinician (10).

An important etiological factor in the development of CI is parent behavior. This is usually communicated by self-report so is dependent on the parent's awareness of his or her own actions. Additionally, parents have been shown to sometimes be untruthful when asked to give a self-report of their parenting due to social desirability bias. For example, they may tell clinicians that their child is up-to-date with their vaccines when they are not (11). An objective measure of both child sleep and parent-child interaction would therefore be of value.

Actigraphy is the commonest objective measure of sleep in the child's home environment. It detects overnight activity by measuring limb movement *via* a wrist-worn device (12). However, it does not detect wakeful stillness, therefore its validity as an objective measure in insomnia patients is limited (13).

Direct observation of parent behavior is more accurate than parent self-report (14, 15). However, the presence of an observer influences both child and parent behavior, and it is costly and impractical in most clinical settings. Home video somnography (HVSG) is a simple technique using an infra-red camera setup in the child's bedroom that measures sleep and captures information about the child's usual sleep ecology (sleep setting and parent behaviors) without the need for body worn sensors. HVSG was pioneered in the 1970s by Anders and colleagues (16–18) to assess developmental changes in infant sleep. In these original studies basic sleep states were scored (awake, active sleep, quiet sleep). VSG has been since used across multiple applications, principally to assess episodic movement disorders (19) in sleep. The advent of smartphone cameras and low cost motion sensitive night cameras has brought this application into every household, and increasingly, parents and clinicians are exploiting this technology in the clinic to report sleep-related symptoms (20).

However, the use of HVSG for behavioral analysis at bedtime and during the night is new. Only one case study has been published to date using HVSG to observe and code parent and child behavior in CI (21). The authors used a basic coding system to analyze the child's sleep quantitatively. Only one coder assessed the footage, therefore no inter-rater reliability was calculated. There are a number of established coding systems for daytime parent-child interactions (22–24) designed for specific situations, such as to measure infant soothing and distress (22), or to code parent and child interactions over a short duration, such as the Iowa Family Interaction Rating Scale (23). A recent study investigated the scoring of motion detection video recording to measure sleep disturbance in three children aged 3 to 5 years with autism spectrum disorder (25). This study found that there was 100% agreement between two observers who scored night wakings and sleep disturbance (within a five second interval of each other) using the video footage. The authors acknowledged that this technology could be applied to monitor parent-child interactions which might contribute to problematic sleep behavior.

We have previously reported that sleep problems are prevalent in survivors of childhood brain tumors (26). In a clinical population of brain tumor survivors, 37/55 (67%) of participants aged 3 to 27 years were at risk of having a sleep disorder based on validated questionnaires (Children's Sleep Habits Questionnaire, Pittsburgh Sleep Quality Index, and the Epworth Sleepiness Scale). The study indicated that the commonest sleep disorder experienced in this population was likely to be CI, independent of both the type of treatment received and the tumor's location in the brain. We therefore hypothesized that CI in brain tumor survivors had a behavioral etiology. However after some preliminary research, we found that there was no standardized method to analyze sleep-related behavior. Therefore, for this study, we selected childhood brain tumor survivors, a population we knew were likely to have a high proportion of behavioral sleep disorders, to produce and test a tool to analyze sleep behaviors.

We aimed: a) to develop a reliable (i.e. reproducible), practical parent-child behavior scoring tool for use with an overnight home video recording of the child's bedtime and overnight activity and b) to compare parent-report of child sleep with HVSG objective measures.

METHODS

Ethical approval was obtained from the Health Research Authority and South Central—Hampshire A Research Ethics

Committee and research governance approval from University Hospital Southampton NHS Foundation Trust.

Materials

Children were screened for eligibility using the Disorders of Initiating and Maintaining Sleep subscale of the Sleep Disturbance Scale for Children (SDSC). This consists of 7 questions rated on a 5-point Likert scale pertaining to the previous 6 months with a maximum score of 35. If the child scored 16 or more they were eligible for further assessment.

Equipment used for HVSG was the SOMNOmedics infrared camera with SOMNOwatch actigraphy. This is a portable camera designed to capture activity in low light conditions along with audio recording. The data are downloaded to DOMINO Light™ software that synchronizes actigraphy data with video footage, allowing the coder to rapidly locate periods of movement. However, this software only allows basic marking of the video in real time and had limitations for the analysis of multi-layered aspects of sleep ecology.

An alternative software, BORIS© (Behavior Observation Research Interactive Software), was identified. This was developed by researchers at the University of Turin to document animal behavior. BORIS© offers the requisite features for this study, namely, it was intuitive to use and allowed the coder to classify behaviors as *state* events, which are ongoing (e.g. when the child is asleep), or *point* events which happen at a single point in time (e.g. time at sleep onset).

Data Source

Eligible potential children (aged 3 to 12 years who had completed brain tumor treatment at least six months previously) were pre-screened for CI using the SDSC questionnaire. Three children who were at risk of CI were recruited.

Recruited children underwent one night of HVSG at home. Recording was programmed to begin prior to the start of their normal bedtime routine, and the parent was instructed to stop the recording when the child woke up in the morning. Families were instructed to carry out their normal bedtime routine, therefore the camera captured all interactions happening in the bedroom during the bedtime routine and during the night.

The day following the overnight recording, parents were interviewed by the researcher LG (Lorna Galbraith) using a structured clinical interview (Southampton Children's Hospital Sleep Service). This interview was audio-recorded, and the recording was used to confirm or reject a clinical diagnosis of CI and to obtain the caregiver's self-report of overnight activity.

Coding System Development

Crano's principles of coding system development were employed (27). This specifies that the following options are considered: a) a categorical or a rating system (in this case a categorical system was more appropriate to incorporate a wide range of behaviors), b) an intensive or extensive system (an intensive approach was initially selected to analyze interactions in detail), and c) a non-inferential or inferential system, the latter meaning that the coder must consider the function of a person's action as well as the action itself (27). A partially inferential approach was adopted, to reflect the fact that the emotional tone of any behavior was important to the outcome (sleep onset) rather than the action itself. For example, a parent can soothe their child during the bedtime routine by singing a lullaby gently; however, if the singing is loud and stimulating, this will not help to settle the child. The authors applied their expertise in sleep medicine (Dr Catherine Hill - CH) and psychology of childhood brain tumor survivors (Dr Kim Bull [KB]) to the development of the parent-child interaction coding system. A draft version of a coding algorithm was developed using the following headings: 1) sleep schedule variables, 2) events during the bedtime routine, 3) events after lights out, 4) events after a night waking, and 5) parent-child interactions. Parent-child interactions were further dichotomized as either sleep-promoting or sleep-hindering, as determined by the coder. Physical and verbal behaviors were separated. The full list of codes from this first draft of the coding system can be seen in **Table 1**.

The coding system was then tested using the video data from the overnight footage. LG coded 10-min segments of video data with high levels of parent-child interaction using BORIS©. CH independently coded these segments. Any disagreements were discussed, and the coding system was modified accordingly. During this process a coding system manual was constructed. This iterative process was repeated multiple times until all observed behaviors were accounted for and defined in a coding manual.

Reliability of the Coding System

The coding system was then tested for inter-rater reliability (IRR). LG and CH each independently coded a 20-min segment of video during a bedtime routine. A modified percentage agreement was used to calculate IRR by adding up the number of codes with exact agreement between the two coders, within a time frame margin of five seconds, and dividing by the total number of codes. The percentage agreement statistic was selected since it is straight-forward to calculate, given the relative complexity of the multi-layer coding system, and is intuitive to interpret; 0% agreement means complete disagreement, whilst 100% means total agreement. An inter-rater percentage agreement of 70% has been reported to be sufficient for complex systems (28). Alternative statistics for IRR were considered, such as Cohen's kappa, but this can be easily skewed if certain behaviors are more frequently coded than others (29), which we predicted would be the case. Additionally, Cohen's kappa is used to exclude agreement which would have occurred by chance—since the draft coding system was relatively complex, with 46 different behaviors, chance agreement was deemed unlikely. Percentage agreement was therefore calculated for the coding system.

Comparison of VSG Data to Parental Report

Once reliability of the coding system was considered to be acceptable, LG coded the video footage in full using BORIS©,

TABLE 1 | Initial draft of the Overnight Parent-Child Interaction Coding System. The first iteration of the coding system, constructed by the research team based on the clinical expertise of an experienced pediatric sleep consultant.

Category	Event
Sleep schedule	Bedtime routine (S)
	Lights out (P)
	Sleep (P)
	Night waking (P)
	Wake time (P)
	Physical contact brief (P)
	Parent present not engaging (S)
	Sleep onset (P)
Bedtime routine	Reading (S)
	Singing (S)
	Playing (S)
	Electronics (S)
	Physical contact extended (S)
After lights out	Self soothes (P)
	Signals (P)
	Activity (S)
	Leaves room (P)
Night waking	Self soothes (P)
	Signals (P)
	Activity (S)
	Leaves room (P)
	Drinks (S)
	Movement arousal (S)
Parent positive commentary	Positive statement (P)
	Offers reward (P)
	Praise (P)
	Reassure (P)
	Calm response (P)
	Authoritative statement (P)
Parent negative commentary	Raises voice (P)
Parent positive behavior	Authoritative action (P)
	No response (P)
	Parent ignoring child (P)
Parent negative behavior	Fulfills curtain call (P)
	Parent engaging w/child (S)
	Soothing behavior (S)
Child positive commentary	Child agrees (P)
Child negative commentary	Settling environment (P)
	Settling process (P)
	Anxious comment (P)
Disagrees (P)	
Child positive behavior	Positive behavior change (P)
Child negative behavior	Non-compliant behavior (S)
	Physical resistance (P)
	Tantrum (S)
	Curtain call (P)

P, point event; S, state event. A point event is a brief event occurring in a single moment; a state event is a prolonged behavior with a marked start and end point.

including the bedtime routines and any night wakings. The coded data were compared to parental interview to assess the accuracy of parental self-report of the child's sleep schedule (i.e. time at sleep onset and morning waking) and the child's sleep quality (i.e. number of night wakings and night waking duration).

Following the analysis of the video, each participating family was contacted to discuss any findings of the overnight study, and if the child was found to have a significant sleep problem, the family were offered an appointment with the Southampton Children's Hospital Sleep Service.

RESULTS

Participants

Three children aged between 3 and 8 years, who were deemed to be at risk of CI following screening, were recruited. Demographic data can be seen in **Table 2**, though this has been abridged to protect participant anonymity. Parental interview confirmed a clinical diagnosis of CI in participant 1, however participants 2 and 3 did not meet the diagnostic criteria for CI.

The Overnight Parent-Child Interaction Coding System

Thirty-six hours of overnight footage were produced during data collection, of which nearly 3 h involved parent-child interaction. These video data were used to develop and test the reliability of the coding system.

The final coding system is depicted in **Table 3**. It comprises twenty-six codes divided into six categories. These categories were as follows:

1) *Time domains.* This allows the observer to record "sleep schedule" variables of the child's sleep, i.e., sleep onset and morning waking, as well as the timing of the settling routine and the time at "lights out" (i.e. when the settling routine finishes).
2) *Physical environment.* The observer can record changes in the bedroom environment, such as loud sounds or changes in light which might be disruptive to the settling process.
3) *Child global status.* These codes relate to the child's sleep/wake status, including any night wakings.
4) *Location*. The observer can record whether the subject (parent or child) is in or out of the bed and their position (e.g. sitting, lying). This was included because frequent changes of the child's position may indicate that the bedtime routine is not having the desired settling effect. Additionally, presence of the parent in the room when the child falls asleep may be indicative of a sleep onset association.
5) *Activity*. The observer can record various activities occurring in the bedroom (e.g. reading, playing a game, singing), and indicate whether the behavior is "soothing" or "non-soothing" based on the child's reaction to the activity (i.e. whether they settle or become excited/agitated).
6) *Physical interaction*. The observers can record either brief or extended close physical contact. This is significant as physical contact could be a beneficial soothing aspect of a bedtime routine, however it could also be contributing to a detrimental sleep onset association.

Reliability of the Coding System

Overall inter-rater percentage agreement the final version of the coding system was 74% which is above the guideline threshold of 70% (28). 100% agreement was achieved for the categories "time domains" and "child global status," in line with Lesser's 2019 study, which found percentage agreement

TABLE 2 | – Participant demographics.

Participant number	Age (years)	Years since end of treatment	Co-morbidities	SDSC[2] screening score (/35)
1	8.28	6.43	Hydrocephalus, hormone deficiency, epilepsy, developmental delay	24
2	7.49	1.94	Hormone deficiency	16
3	3.94	2.21	Hydrocephalus, hormone deficiency, facial palsy, hearing loss, developmental delay	18

SDSC, Sleep Disturbance Scale for Children. A score of 16 or more indicates an increased risk of a Disorder of Initiating or Maintaining Sleep. All children were above this threshold.

between two observers for sleep onset, sleep offset, and night wakings to be 100%. "Location" and "activity" had a lower but acceptable percentage agreement (80% and 74% respectively), though on most occasions when the two coders "disagreed" in these categories it was because the timestamps of their observations were more than 5 s apart. There was 0% agreement for "physical interaction" due to the coders disagreeing on the start and end time of the behavior, since the view of the parent and child was partially obstructed by bedding. Agreement for "physical environment" could not be assessed using the final coding system because there were no changes in the physical environment during the segment of video.

Accuracy of Parental Report

Parental interview was compared with objective coded data from the overnight video study relating to timing of sleep and number of night wakings (**Table 4**). Sleep schedule (sleep onset and sleep offset time) was reasonably accurately reported, but the number and duration of night wakings (determinants of the child's sleep quality) were consistently under-reported. This was generally because the child self-soothed quietly without signaling for the parental attention.

Additionally, we noted that parents tended to omit information about the child's bedtime routine and overnight behavior. For example, when asked about the physical environment of the child's bedroom, one parent described it as quiet and with dim lighting. However, on observation, the main bedroom light was turned on and off several times, family members walked in and out of the room, and a mobile phone in the room started ringing loudly during the settling process. The child was visibly distracted by these events which disrupted the otherwise soothing atmosphere in the bedroom.

There were examples of a mismatch between parent report and HVSG observation in all three cases, particularly in regards to parent or child behavior. A parent whose child did not have CI reported that the child signaled whenever he woke up in the night and that she had to be present in the room in order for him to fall asleep. However, following coding of the child's overnight footage, it was observed that the child was able to self-soothe on multiple occasions following night waking without the presence of the parent.

For all participants, a graphical visual summary of the bedtime and overnight activity was generated using BORIS© (**Supplementary Figures 1** and **2**).

TABLE 3 | Final version of the Overnight Parent-Child Interaction Coding System. The final iteration of the coding system used to analyze parent and child behaviors at bedtime and during the night.

Category	Event	Modifier
Time domains	Settling routine (S)	
	"Lights out" (P)	
	Sleep onset (P)	
	Morning waking (P)	
Physical environment	Noise intrusion (S)	
	Music (S)	
	Bright lighting (S)	
Child global state	Sleep (S)	
	Night waking (S)	
	Movement arousal (S)	
Location	In bed (S)	*Position:* • Lying • Sitting • Standing • On all fours • Crouching • Mobile
	Out of bed (S)	
Activity	Laughing (P)	*Helpful to sleep?* • Soothing • Non-soothing • Neutral
	Reading (S)	
	Singing (S)	
	Playing (S)	
	Eating (S)	
	Drinking (S)	
	Verbalization (S)	
	Rocking (S)	
	Tidying/housekeeping (S)	
Personal care (S)		
	Electronics (S)	
	Self-stimulating (S)	
Physical interaction	Brief close physical contact (P)	
	Extended close physical contact (S)	

P, point event, S, state event. A point event is a brief event occurring in a single moment; a state event is a prolonged behavior with a marked start and end point.

DISCUSSION

CI is the most common sleep disorder experienced by children, yet diagnosis is guided by subjective parental report. Despite parent-child interactions at bedtime being key to the etiology of CI, there is no accepted method to assess these interactions objectively. This study aimed to develop a new tool to objectively assess overnight interactions between children and their parents,

TABLE 4 | Parent report vs. objective measurement of child's sleep schedule and sleep quality. Sleep schedule was accurately reported by parents; however, report of child's sleep quality was poorly reported. All parents under-reported the frequency and duration of night wakings.

	Variable	Participant 1		Participant 2		Participant 3	
		Reported	Observed	Reported	Observed	Reported	Observed
Sleep schedule	Sleep onset time	20:30	20:37	20:30	20:15	21:30	21:04
	Sleep offset time	06:30	06:10	07:00	06:15	06:10	06:10
Sleep quality	Number of night wakings	4	12	0	2	0	1
	Total duration of night wakings (min)	12.0	26.0	0	1.8	0	3.1

which could assist in the identification of behaviors contributing to recurring CI. We have created a reliable and reproducible coding system, the Overnight Parent-Child Interaction Coding (OPIC) System, to fulfill this purpose.

The OPIC system demonstrated acceptable reliability. This is particularly significant considering there were 26 behaviors accounted for in the final version of the coding system. The poor percentage agreement for two of the coding categories ("physical environment" and "physical interaction") can be partially explained by the infrequent use of these codes in the segment of video used to test reliability. Reliability should be tested again using different footage samples. Nevertheless, the reliability of the coding system is a promising starting point for future development.

We have shown that this coding system can be applied to three separate overnight videos involving complex, lengthy bedtime routines, and nighttime interactions. The coding system has been used to support parental interview as an investigative tool both in children with CI and without CI and yields additional data to parental report. Applying the coding system to these videos has exposed aspects of the bedtime routine, such as changes in the physical environment, which parents did not disclose during the interview. For example, family members entering and leaving the room and the main light being turned on and off. The parents may have omitted these details from the interview due to recall error, though the clinical interview was undertaken the following day to minimize this risk. It is also possible that parents were selective in their disclosure, either due to an awareness that the behavioral dynamic was inappropriate or because they did not believe it to be relevant for the interviewer. The significant mismatch between one parental account of an idealized settling environment, despite the observed reality which was noisy and at times chaotic is interesting and may reflect social desirability bias (11).

The comparison between parental report and observation of the child's sleep schedule and sleep quality in this small sample supports previous reports that parents are poor historians in terms of their child's sleep quality (8, 9). This finding is significant because problems with *maintaining* sleep are of equal importance as *initiating* sleep in the diagnostic criteria for CI. Therefore, if parents are unable to accurately report their child's ability to maintain sleep, an alternative investigation to parental interview to support a diagnosis is warranted.

In practice, HVSG and coding of parent-child interactions could be used to aid clinical management. CI is treated using behavioral intervention, with the clinician providing advice based on reported child and parent behaviors (30). This usually involves removing problematic sleep onset associations and advice on sleep hygiene (31). However, it seems likely that advice given by the clinician could be improved if the clinician had objective evidence of the nature of parent-child interactions during the bedtime routine. This could facilitate a more targeted family-centered management plan. This plan could be enhanced by focusing on specific examples of problematic and/or constructive parent-child interactions, which could be replayed from HVSG footage. Video feedback has been used in psychological interventions to effectively guide parents with child behavior management (32–35) and has been shown to improve child attachment security (34), parent mental health status (32), and parent self efficacy (36) [confidence in their own ability to succeed (37)] in comparison to simple verbal feedback.

Following behavior coding using BORIS©, the software was used to create a graphical output of all codes recorded during an observation. This displayed all activity which occurred in the bedroom, including child and parent activity and changes in physical environment. This graph could also provide a visual educational tool for the families of children with CI to demonstrate a complex and excessively long bedtime routine, compared to an appropriate graphical representation of a brief but soothing bedtime routine (see **Supplementary Figures 1** and **2**).

While the OPIC system demonstrated acceptable reliability, further development and testing is warranted as the current version has some limitations. Firstly, coding was time-consuming (the viewing of segments, at times, required up to four times the duration of the whole video to enable scoring where significant interactions between the parent and child took place). This limits its application in clinical practice. To overcome this limitation the OPIC system could be further simplified to focus on core behaviors of interest. Alternatively, the clinician could code shorter segments of the video rather than the entire bedtime routine. For example, 1 min for every 5 min of video. This would take less time than coding the whole bedtime routine and would still enable video feedback, including examples of undesirable interactions.

Another limitation of this study was the approach to IRR testing. Only two coders tested the coding system, both of whom were involved in its development, and were therefore familiar with the coding system. To develop the coding system further

and enable its validation as an investigative tool, it should undergo testing by a larger group of independent coders.

In the future, HVSG combined with objective coding systems based on OPIC could be a promising supplement to actigraphy as an objective assessment of children's sleep. HVSG could also offer advantages over actigraphy for a subsample of children with sensory processing difficulties, such as those with autism spectrum disorder, who might not tolerate a wrist-worn device (38).

A systematic approach to quantifying child and parent behavior in CI would offer an objective outcome measurement tool for CI interventions. The effectiveness of behavioral interventions in childhood CI has only been tested previously using sleep diaries (39), questionnaires (40–42), and actigraphy (39, 40, 42). Robust objective assessment of behavioral interventions in childhood CI could provide a more reliable insight into the outcome of these interventions, since researchers could directly observe the extent to which the management plan has been implemented by parents.

To conclude, the OPIC system, when applied to home videosomnography, offers the potential for personalized interventions in the clinical management of behavioral insomnia and an objective outcome measurement in clinical research. The paradigm of sleep scoring and video observation is core to mainstream sleep diagnostics and the OPIC system applies similar approaches to a behavioral setting. Software could be adapted within conventional commercial sleep systems to accommodate such an approach.

DATA AVAILABILITY STATEMENT

The raw coding data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher. The video data for this manuscript are not publicly available because this would breach the terms of our ethical approval for this study. Requests to access the datasets should be directed to Dr Catherine Hill, c.m.hill@soton.ac.uk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Health Research Authority and South Central – Hampshire A Research Ethics Committee (reference 18/SC/0012) University Hospital Southampton NHS Foundation Trust (reference CHI0913). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The study was designed by LG, KB, and CH. Recruitment and data collection was completed by LG. Iterative development of the coding system and the coding of video to calculate inter-rater reliability were done by LG and CH. Data analysis was completed by LG.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00861/full#supplementary-material

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Multi-Method Assessment of Sleep in Children With Angelman Syndrome: A Case–Controlled Study

Jayne Trickett[1,2], Chris Oliver[1], Mary Heald[1,3], Hayley Denyer[1,4], Andrew Surtees[1,3], Emma Clarkson[1,5], Paul Gringras[6] and Caroline Richards[1]*

[1] Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, United Kingdom, [2] Department of Health Sciences, College of Life Sciences, University of Leicester, Leicester, United Kingdom, [3] Forward Thinking Birmingham, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom, [4] Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, [5] The Huntercombe Group, Worcestershire, United Kingdom, [6] Evelina London Children's Sleep Medicine Department Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

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***Correspondence:**
Jayne Trickett
Jkt12@leicester.ac.uk

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Objectives: To assess sleep quality and timing in children with Angelman syndrome (AS) with sleep problems using questionnaires and actigraphy and contrast sleep parameters to those of typically developing (TD) children matched for age and sex.

Methods: Week-long actigraphy assessments were undertaken with children with AS (n = 20) with parent-reported sleep difficulties and compared with age and sex matched TD controls. The presence of severe sleep problems was assessed using the modified Simonds and Parraga sleep questionnaire. Sleep hygiene was measured using the Family Inventory of Sleep Habits.

Results: Actigraphy and parent-completed sleep diary data indicated that children with AS had significantly earlier bedtimes ($p = .003$, Cohen $d = .47$) and poorer sleep efficiency (78%, $p = .04$, $d = .33$) than TD children (84%). No significant differences in total sleep time, sleep onset latency or wake after sleep onset were found between the two groups. The expected relationship between later bedtimes and increasing age found for the TD group ($p < .001$, $\beta.78$) was not evidenced for the AS group ($p = .09$, $\beta.39$). Considerable inter-individual and night to night variation in actigraphy assessed total sleep time and wake after sleep onset was found for children with AS compared to TD children. Parent report indicated that a greater proportion of children with AS had severe night waking problems compared to TD children (81 versus 5%). No significant differences in sleep hygiene and excessive daytime sleepiness were found between the two groups ($p > .05$).

Conclusions: This study reports the largest objective dataset of sleep quality parameters in children with AS. Sleep quality in this group was characterised by poor efficiency and significant intra- and inter-individual variability that warrants further investigation. This variability should inform assessment and intervention for sleep in children with AS, as averages of total sleep, even across a 7 day period may not capture the difficulties with night waking highlighted by parental questionnaire report.

Keywords: sleep, actigraphy, Angelman syndrome, intellectual disability, case–control

INTRODUCTION

Angelman syndrome (AS) is caused by lack of expression of the *UBE3A* gene on the maternal 15q11–13 chromosome, arising from various genetic mechanisms (1). These mechanisms include a 5–7 Mb *De Novo* interstitial deletion of the maternal 15q11.2–Q13 region for approximately 75% of individuals, Paternal Uniparental Disomy (UPD) (1–2%), an Imprinting Defect (1–3%), and mutation in the *UBE3A* gene (10%) (2).

Several physical and behavioural features are consistently associated with AS, which include severe developmental delay, ataxic gait, frequent smiling/laughing, repetitive arm movements and limited or absent speech (3). Other characteristics present in over 80% of individuals include microcephaly, seizures, and abnormal EEG (3). Sleep disturbances, including insomnia and general sleep disorders or difficulties, are widely reported in AS (4). A systematic review of studies investigating sleep disturbances in children with genetic syndromes reports prevalence rates of sleep disturbances in children with AS of between 48% and 70% (5). Sleep disturbance in AS may occur downstream from impaired *UBE3A* expression resulting in the dysfunction of GABA receptors (6, 7). A number of studies have suggested that individuals with AS do experience circadian rhythm disorders (8) evidenced by a shift in melatonin offset timings relative to TD children and children with epilepsy (9). However, whether individuals with AS secrete a smaller volume of endogenous melatonin than peers is unclear (8, 9). More specifically, Takaesu et al. (8) identified 53% of their sample of 15 individuals with AS to have a circadian rhythm disorder, including an irregular sleep–wake cycle disorder (26.7%), non-24-h sleep–wake cycle (13.3%), and delayed sleep phase disorder (13.3%). Impaired circadian rhythm implicating the activity of E6-AP encoded by the affected *UBE3A* gene specific to AS has been hypothesized (10). Thus, in the investigation of sleep disturbance in AS, there is a need to characterize the specific sleep disturbances experienced by children with AS using validated questionnaires and objective measures and evaluate sleep phase, given possible circadian rhythm disorders.

Specific problems relating to sleep reported in children with AS include increased sleep onset latency, bedtime resistance, anxiety, rhythmic movements whilst falling asleep, nocturnal wakings, sleep disordered breathing and daytime sleepiness (6). Prevalence rates for night waking range from 60 to 100%, with a decrease in waking observed with increasing age (11). Variability in reported prevalence rates may be due to different definitions of night waking used across studies. When quantifying the severity of night waking as three or more times a week and lasting over several minutes, the prevalence was 46% of children with AS (mean age 8.64 years) (12).

Little is known about the impact of sleep disturbance on children with AS. Daytime sleepiness according to single items on questionnaires is reported for only between 8 and 24% of children (6, 13–15) and represents a small effect size (.10) in a meta-analysis (16). This raises questions as to whether children with AS have a reduced need for sleep and whether shortened total sleep time negatively impacts upon children's daytime functioning. Whilst the behavioural impact of shortened sleep duration has not been studied in children with AS, children with severe intellectual disabilities with sleep problems have a greater severity of challenging behaviour (17). The reduced total sleep time may be due to increased sleep onset latency, reported for between 32% and 91% of individuals (6, 13, 18), in combination with reduced sleep efficiency due to night wakings (7, 19). The range of definitions for night waking and the inclusion of young adults in some of these studies limit the conclusions that can be drawn from these data. Therefore, there is a need to identify how poor sleep in AS is characterised using objectively assessed total sleep time, sleep onset latency, and duration of night waking using a clearly defined age range of children with a parent-reported sleep problem compared to a control group of TD children.

Few studies have used objective measures to provide detailed descriptions of sleep quality in children with AS; one used polysomnography (20) and two studies employed actigraphy with samples of ≤13 children (19, 21). Actigraphy assessment over a minimum of 7 days for 10 children with AS aged 2 to 16 years, showed means for children's total sleep time of 406 min (SD 55), wake after sleep onset 114 min (SD 33), and sleep onset latency of 41 min (SD 23) (19). The authors commented upon the extended night waking; however it is important to compare actigraphy assessed night waking to that of TD children, in order to draw conclusions about the severity of impaired sleep in children with AS. A larger actigraphy study of children with AS is needed to overcome the limitations of the existing literature.

As sleep in childhood is sensitive to developmental maturation, it is also important to assess sleep quality and timing in atypical populations compared to an age-matched sample of TD children which is lacking in previous studies. The advantage of actigraphy assessment of sleep is that it is unobtrusive and sleep timing and quality can be monitored across multiple nights, unlike one night polysomnography. This would enable night to night variation, hereafter referred to as intra-individual variation, in sleep quality to be assessed. The assessment of this sleep parameter is important, as greater intra-individual variation in sleep offset timing is associated with more externalising, inattentive and aggressive behaviour in TD pre-school children (22). Aggression is frequently reported in individuals with AS (73% prevalence) (23), therefore identifying correlates of challenging behaviour in this group would elucidate the hypothesis that poor long-term sleep quality due to sleep variability does impact upon daytime functioning in children with AS.

In addition to the comparison of sleep quality and timing of sleep in children with AS who have a parent reported sleep disturbance compared to that of age-matched TD children, the cross-sectional associations with age in children with AS need to be compared against those of TD children. TD children in this study provide a benchmark for typical sleep quality for a child without AS of the same age. Currently, the profile of sleep problems across the developmental trajectory of AS is unclear. Retrospective caregiver report from adolescents and adults with AS indicate that sleep quality and daytime sleepiness improved for 65% of the sample (24). In adulthood, only 56% of a sample of 53 individuals slept for 8 h or more according to caregiver report (25). Other cross-sectional studies using age as a correlate or comparing between arbitrary age groups have suggested that sleep difficulties persist with age (15, 6). However, these studies did not compare age associations with sleep outcomes relative to an

age-matched control group. Actigraphy assessments paired with sleep diaries would enable sleep timing to be correlated with age.

The aims of this study are to: 1) describe the profile and variability of sleep quality and quantity in children with AS with a reported sleep problem across a week long assessment, 2) compare symptoms of sleep disturbance, specifically sleep disordered breathing, excessive daytime sleepiness and the role of sleep hygiene in children with AS, to those shown by TD children, and 3) determine the association between age and total sleep time and bedtime for each group and compare across groups.

MATERIALS AND METHODS

Participants

Twenty-two children with AS with a parent reported sleep disturbance were recruited from Angelman UK (Angelman syndrome UK support group) and from an existing database of families at the Cerebra Centre for Neurodevelopmental Disorders. Whilst no statistically significant differences in sleep disturbance severity between the genotypes of AS are reported (26, 27, 6) there are differences in rates of seizures and motor impairments between the AS genotypes (28). Therefore, to cater for known differences between the groups, only children with the UBE3A deletion subtype of AS were included. Two children did not tolerate the Actiwatch for the required four nights and their data were excluded from the study. Typically developing (TD) children were age-matched to each child with AS and were recruited through social media and through family and friends of staff at the Cerebra Centre for Neurodevelopmental Disorders. The mean age of children with AS was 9.4 years (SD 3.7) (see **Table 1**). Neither age, nor sex differed significantly between the groups. No difference in maternal education (X^2 = 2.42, p = .658) or family income was found between the two groups (X^2 = 6.78, p = .342). Medications used by children with AS are presented in **Table S1**.

Procedure

Consent was obtained from parents of participants. The study received favourable ethical review from the University of

TABLE 1 | Demographic characteristics.

		AS	TD	T/X²	P value
Age mean (SD)		9.43 (3.72)	9.62 (3.71)	T = .155,	.879
Males n (%)		8 (40.0)	9 (45.0)	X² = .102,	.749
Adaptive Behavior Composite score VABS standard score mean (SD)		43.95 (9.17)	–	–	–
Able to walk unaided n (%)[a]		7 (37)	20 (100)	18.25	<.001
Ever experienced tonic–clonic seizures		9 (45)	–	–	–
Ever experienced absence seizures		20 (100)	–	–	–
Ever experienced clonic seizures		4 (20)	–	–	–
Ever experienced myoclonic seizures		7 (35)	–	–	–
Ever experienced tonic seizures		2 (10)	–	–	–
Ever experienced atonic seizures		9 (45)	–	–	–
Ever experienced focal seizures		6 (30)	–	–	–
Ever experienced unknown classification of seizures (e.g. epileptic spasms)		3 (15)	–	–	–
Medically refractory epilepsy[b]		3 (20)	–	–	–
Using medication to aid sleep n (%)[c]		13 (65.0)	–	–	–
Medication helpful to aid sleep[d]		10 (76.9)	–	–	–
Maternal education[e]	Fewer than 5 GCSE's or O Level's (grades A–C), NVQ 1 or, BTEC First Diploma	2 (10.0)	0	X² = 2.42	.658
	5 or more GCSE's or O Level's (grades A–C), NVQ 2, or equivalent	2 (10.0)	2 (10.5)		
	3 or more "A" Levels, NVQ 3, BTEC National, or equivalent	1 (5.0)	1 (5.3)		
	Polytechnic/university degree, NVQ 4, or equivalent	11 (55.0)	10 (52.6)		
	Masters/doctoral degree, NVQ 5, or equivalent	4 (20.0)	6 (31.6)		
Family income[f]	Less than £15,000	2 (10.5)	0	6.78	.342
	£15,001 to £25,000	2 (10.5)	4 (21.1)		
	£25,001–£35,000	2 (10.5)	1(5.3)		
	£35,001–£45,000	4 (21.1)	2 (10.5)		
	£45,001–£55,000	2 (10.5)	6 (31.6)		
	£55,001–£65,000	3 (15.8)	1 (5.3)		
	£65,001 or more	4 (21.1)	5 (26.3)		

[a]*One missing response AS group.*

[b]*Defined as defined as inadequate seizure control despite appropriate medical therapy with at least 2 Anti-epilepsy drugs in maximally tolerated doses for 18 months–2 years, or adequate seizure control with unacceptable drug-related side effects (29) 5 missing responses.*

[c]*One parent indicated that clobazam administered in the evening was helpful to aid sleep. Included this response in using medication to aid sleep. Clobazam was administered to three other children in the absence of other medication to aid sleep. As no comment of its efficacy for sleep was reported, these three children were excluded from the total.*

[d]*One missing response AS group.*

[e]*One missing response TD group.*

[f]*One missing response AS group, 1 missing response TD group.*

Birmingham. Families were instructed that their child should wear an actigraph for seven nights of continuous wear where possible. For children with AS a researcher visited the family to set up video equipment to record night-time sleep behaviours (see 30) and instruct on sleep diary completion and operation of the event marker on the actigraph. A comparable training video was sent to parents of children in the TD group. Parents completed a questionnaire pack and this was returned by post or the pack was collected in person by the researcher. The Vineland Adaptive Behavior Scales-2 (31) was completed either over the phone or in person with the family of children with AS. The measures and recruitment of TD children in this study replicate those used in study of sleep in children with Smith–Magenis syndrome (32).

Measures

A questionnaire was completed by parents to collect information about children's medication use, epilepsy, maternal education and family income. Adaptive ability in the AS group was assessed using the Vineland Adaptive Behavior Scales-2 Interview. A standardised behaviour composite score for the sample was reported. No measure of ability was used in the TD group; chronological age was assumed to be commensurate with developmental age as no statements of additional learning needs were indicated.

Symptoms of Sleep Disturbance and Sleep Hygiene Questionnaires

Severe sleep disturbance was assessed using the Modified Simonds and Parraga sleep questionnaire (33, 34) which has been validated for use with individuals aged 2 to 16 with an autism spectrum disorder (34). The presence of severe night waking, settling problems and early morning wakings were derived from this questionnaire based on the frequency (many times a week or daily) and intensity of the problems (e.g. night waking—takes over a few minutes to fall back to sleep; settling—takes over an hour to fall asleep).

The sleep-related breathing disorders screening questionnaire is a 22-item informant report measure from the Pediatric Sleep Questionnaire used to assess risk for sleep-related breathing disorders, which includes children with obstructive sleep apnoea and upper airway resistance syndrome (35). The 22 items relate to sleepiness, behaviour, snoring, and breathing subscales and sleep-related breathing disorder subscale. Items from the snoring subscale only were reported as other subscales require the child to be able to communicate their internal state.

Excessive daytime sleepiness was assessed using the modified Epworth Sleepiness Scale (MESS; 35). Parents/carers rate the likelihood of their child falling asleep in eight different situations (0 to 3), with higher scores indicating a greater likelihood. The questionnaire is based on the Epworth Sleepiness Scale (ESS) for adults. The ESS has good reliability and validity (36). The MESS has been used previously with children with intellectual disabilities and neurodevelopmental disorders (37). As the majority of children with AS are nonverbal, the question referring to 'sitting and talking to someone' was modified by the authors to include 'sitting and talking to or interacting with someone.' Seven out of the eight questions used in the MESS in the present study are similar to those used in a validation study of the ESS for Children and Adolescents (38) with individuals aged 12–18 years, which showed strong test-retest reliability and high internal reliability (39). In the present study a cut off score of >10 was used to identify children at risk of excessive daytime sleepiness.

Sleep hygiene was assessed using the Family Inventory of Sleep Habits (FISH; 40) developed from a sample of children with autism spectrum disorder. Items are scored on a five-point Likert scale, with higher scores indicating better sleep habits. The test-retest reliability of the measure with children with autism spectrum disorder is .83, and in the TD population is .59. The FISH also has good external validity with measures of childhood sleep (40).

Actigraphy

Sleep quality was assessed using the Actiwatch 2, manufactured by Philips Respironics. This accelerometer's sampling rate is 32 Hz and 30 s epochs were used. Sleep onset and offset were defined as the clock times at the start of the first of 10 min scored as sleep (after lights out time) and the end of the last 10 min scored as sleep respectively. Wake After Sleep Onset (WASO) was detected according to the device's medium sensitivity (40 counts per epoch). All other parameters were calculated according to default Actiware version 6.0.7's settings, as these settings were found to have the greatest concordance with polysmonography (41). Compared to polysomnography, these settings have high sensitivity to detect sleep (.94) and specificity to detect waking (.69) in school-aged children (42)[1]. Parents were asked to press an event marker button at the child's bedtime. Fifteen children with AS wore the Actiwatch on their ankle and five wore it on their wrist. Alternative actigraphy placement; a pocket in a cloth vest, has been used in another actigraphy study of children with AS (21). All TD children wore the Actiwatch on their wrist.

As an adjunct to actigraphy data, parents completed a paper sleep diary on behalf of their child to include bedtime (time child got into bed), time lights turned off, whether the event marker used to indicate bedtime and wake time was pressed at the correct time in the evening and morning, estimated time taken to fall asleep, wake up time in the morning and time got out of bed. Other important data for actigraphy data cleaning were collected, to include the timings and nature of any sedentary periods of activity after 6 pm, timings of any daytime naps, and the timings of periods when the Actiwatch was removed.

Data were cleaned to ensure that artefacts were removed and that the start of the intentional rest interval- bedtime was identified using a combination of the event marker, sleep diary, and the automatically calculated rest interval. This avoided relying solely on the software automatically calculated sleep intervals, which have poorer concordance with polysomnography (43, 44). Parental reporting of early morning final wake time may be inaccurate; therefore, sleep offset used the end of the autoscored rest interval. Intervals were extended to capture the entire sleep

[1]Meltzer et al. (42) used 1 min epochs in comparison with polysomnography.

period if an additional 20 min after the end of the autoscored rest period but before the sleep diary indicated wake up time were coded as sleep by the software. Inter-rater reliability for 20% of the lights out time data in the AS group was excellent (45): intra-class coefficient: 97 (CI: 94–99).

Analysis

Analyses were conducted using SPSS version 25. As some data were non-normally distributed, Mann–Whitney U and Wilcoxon Signed Ranks tests were used to compare actigraphy and questionnaire data between the AS and TD groups. Chi-squared analyses were used to compare categorical outcomes between groups. Linear regressions were used to explore the association between age and total sleep time and lights out time in both groups. To assess the degree of inter-individual variability in sleep, the SD of the total sleep time/wake after sleep onset of the group was divided by the group mean of the sleep parameter. Intra-individual variability was calculated by dividing the child's SD in total sleep time/wake after sleep onset from the assessment period by the mean of the child's sleep parameter from the assessment period. Effect size was calculated using Cohen R = $Z \div \sqrt{N}$.

RESULTS

Describing Sleep Quality and Quantity

The results shown in **Table 2** demonstrate that children with AS had significantly earlier lights out times and poorer sleep efficiency than TD children. Differences in WASO also demonstrated a trend towards greater WASO in the AS group compared to the TD group, but the difference between the two groups was not statistically significant. No difference in sleep quality actigraphy parameters were found between children with AS who did or did not take sleep medication (see **Table S2**). When comparing the difference in actigraphy parameters between children in the AS group who did not receive melatonin (n = 9) and the TD group, there were no significant differences on any of the actigraphy parameters ($p > .05$), except earlier average lights out time for the AS group (AS group median 20:01, interquartile range 19:25–20:15, U = 35.0, p = .008). The same pattern of differences was found between children with AS who did receive melatonin (n = 11) and children in the TD group (average lights out time AS group median 20:04, interquartile range 19:32–20:33, U = 55.5, p = .023). No difference in the ratio of weekday versus weekend nights was found between the two groups. Furthermore, no difference between the average of total sleep time on weekday nights and weekend nights was found for children with AS (Z = -.859, p = .391) and TD children (Z = -.224, p = .823). Seven children with AS (age range: 4.0–13.21 years) had a nap on at least one of the days during the assessment period compared with three TD children (age range: 5.63–15.75 years). In the AS group, individual nap periods ranged from 5 to 240 min. In the TD group, individual nap periods ranged from 20 to 100 min.

According to the minimum recommended sleep time guidelines (46) seven children with AS and one TD child met the recommendations for their age group ($X^2 = 5.63$, 1, p = .018). See **Table 3** for distributions by age group.

TABLE 2 | Grand median and interquartile ranges of actigraphy sleep and daily activity parameters across the assessment period and average duration of daytime naps in children with AS and TD children.

	AS	TD	Between-group comparisons		
			Mann–Whitney U/X^2	*P*	Cohen's R
Nights of actigraphy Median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–7.0)	169.5	.386	.14
Ratio weekday/weekend nights Median (IQR)	.27 (.25–.29)	.29 (.25–.32)	155.5	.210	.20
Lights out time h:min Median (IQR)	20:02 (19:30–20:19)	20:52 (20:25–21:37)	90.50	.003*	.47
Sleep offset h:min Median (IQR)	7:03 (5:58–7:41)	7:01 (6:29–7:23)	173.50	.473	.11
Sleep onset latency min Median (IQR)	19.32 (7.12–35.72)	15.42 (10.45–27.78)	197.50	.946	.01
Wake After Sleep Onset min Median (IQR)	76.39 (42.44–122.65)	56.67 (45.52–61.78)	129.0	.055	.30
Sleep efficiency (%) Median (IQR)	77.86 (71.95–85.69)	83.81 (81.67–85.67)	124.0	.040*	.33
Total sleep time min Median (IQR)	480.0 (459.83–548.0)	497.5 (479.5–525.88)	183.5	.655	.07
Total sleep time weeknight mins Median (IQR)	472.10 (446.34–538.06)	500.69 (475.90–528.43)	177.0	.534	.08
Total sleep time weekend min Median (IQR)	491.0 (459.56–572.56)	497.25 (479.94–542.13)	180.5	.598	.10
Average duration of diurnal nap across assessment period for children who napped min Mean (SD)	31.08 (44.73)	7.86 (5.58)	–	–	–
Average timing of diurnal nap h:min Mean (SD)	15:59 (2:08)	16:18 (4:06)	–	–	–

$p < .05$. Average duration of diurnal nap = total nap duration across assessment period according to sleep diary divided by number of nights of actigraphy data

TABLE 3 | Proportions of children with AS and TD children meeting recommended minimum total sleep.

	AS	TD
	n (%)	n (%)
Children aged 4–5 years average TST ≥ 10 h	2 (40)	0
Children aged 6–12 years average TST ≥ 9 h	1 (10)	1 (9)
Children aged 13–15 years average TST ≥ 8 h	4 (80)	0

Inter and Intra-Individual Variability in Total Sleep Time and Night Waking

Children with AS had greater variation in night to night (intra-individual variation) total sleep time and wake after sleep onset compared to TD children. Children with AS also had greater variation between individuals (inter-individual variation) in total sleep time and wake after sleep onset compared to TD children (see **Table 4**).

Sleep Hygiene, Symptoms of Sleep Disordered Breathing, and Excessive Daytime Sleepiness

The proportion of children with excessive daytime sleepiness did not differ between the two groups AS (n = 2 10.5%) and TD (0%), X^2 = 2.22, p = .136. Children with AS did not have lower scores on the FISH measure of sleep hygiene compared to TD children. Children with AS were more likely to snore more than half of the time compared to TD children, but no other differences in sleep disordered breathing symptoms were observed (see **Table 5**).

TABLE 4 | Coefficient of variance statistics for total sleep time and wake after sleep onset between children and within an individual child's assessment period in children with AS and TD children.

	AS	TD
Inter-individual coefficient of variance TST (%)	12	8
Inter-individual coefficient of variance WASO (%)	60	24
Intra-individual coefficient of variance TST (%)	15	10
Intra-individual coefficient of variance WASO (%)	53	24

Associations Between Age and Total Sleep Time and Lights Out Time for Children With Angelman Syndrome and Typically Developing Children

The lights out time for children with AS did not significantly vary with age [R^2 = .15, F (1, 18) = 3.21, p = .09, β.39] compared to the association with later bedtimes for TD children with increasing age [R^2 = .61, F (1, 18), 28.43 p < .001, β.78] (see **Figure 1A**). Total sleep in children with AS also did not significantly decrease with age [R^2 < .01, F (1, 18) = .07, p = .799, β -.06] unlike the association observed in the TD group [R^2 = .59, F (1, 18) = 25.57, p < .001, β -.77] (see **Figure 1B**). When the regressions were repeated separately for weekend averages (see **Figure 1C**) and weeknight averages (see **Figure 1D**), a decrease in total sleep time only associated with increasing age in on weeknights in the TD group [R^2 = .63, F (1, 18) = 30.16, p < .001, β.79].

DISCUSSION

This is the largest actigraphy study of children with AS to date and the first to report wide inter and intra-individual variability in total sleep time and night waking in children with AS. As anticipated given the sample of children with AS with a parent reported sleep problem, 81% of children with AS had severe night waking problems according to a validated questionnaire. The data show that children with AS with parent-reported sleep problems had significantly earlier lights out times and poorer sleep efficiency than TD children and that a minority of children with AS napped during the day. No significant differences in total sleep time, wake after sleep onset and sleep offset time were found compared to TD children. Children with AS did not have an excess of daytime sleepiness compared to TD children, but were more likely to snore more than half the time (24 versus 0% of children) and, significantly, no difference in sleep hygiene practices were found between the two groups. Cross-sectional associations between lights out time, total sleep time and age indicated that increasing age is not associated with later bedtimes and decreased total sleep time in the AS group, unlike the relationship found for the TD group. The use of an age-matched TD contrast group in the first case–controlled actigraphy study of

TABLE 5 | Scores on questionnaire measures of sleep hygiene, likelihood of dozing during daytime activities, sleep-related breathing disorders, and sleep disturbance for TD and AS groups.

	AS n	AS	TD n	TD	U statistic/X^2	P value
Median sleep hygiene score on FISH† (IQR)	18	50.50 (46.75–56.50)	19	51.0 (47.0–54.0)	157.0	.670
Median pediatric Epworth sleepiness scale score † (IQR)	19	1.0 (0–6.0)	20	2.0 (1.0–3.0)	175.0	.669
Number (%) of children with severe settling problems	18	2 (11.1)	20	0	2.35	.126
Number (%) of children with severe night waking problems	16	13 (81.3)	20	1 (5.0)	21.75	< .001
Number (%) of children with severe early morning waking problems	19	4 (21.1)	20	1 (5.0)	2.25	.134
Always snores	16	0 (0)[a]	20	0 (0)	–	–
Snores more than half the time	17	4 (23.5)	19	0 (0)	5.03	.025
Snores loudly	16	1 (6.7)[a]	20	0 (0)	1.37	.241
Has heavy or loud breathing	17	7 (43.8)[a]	20	3 (15.0)	3.66	.056
Has trouble breathing, or struggles to breathe	16	1 (6.7)[a]	20	0 (100)	1.37	.241

[a]*One parent reported "don't know".*

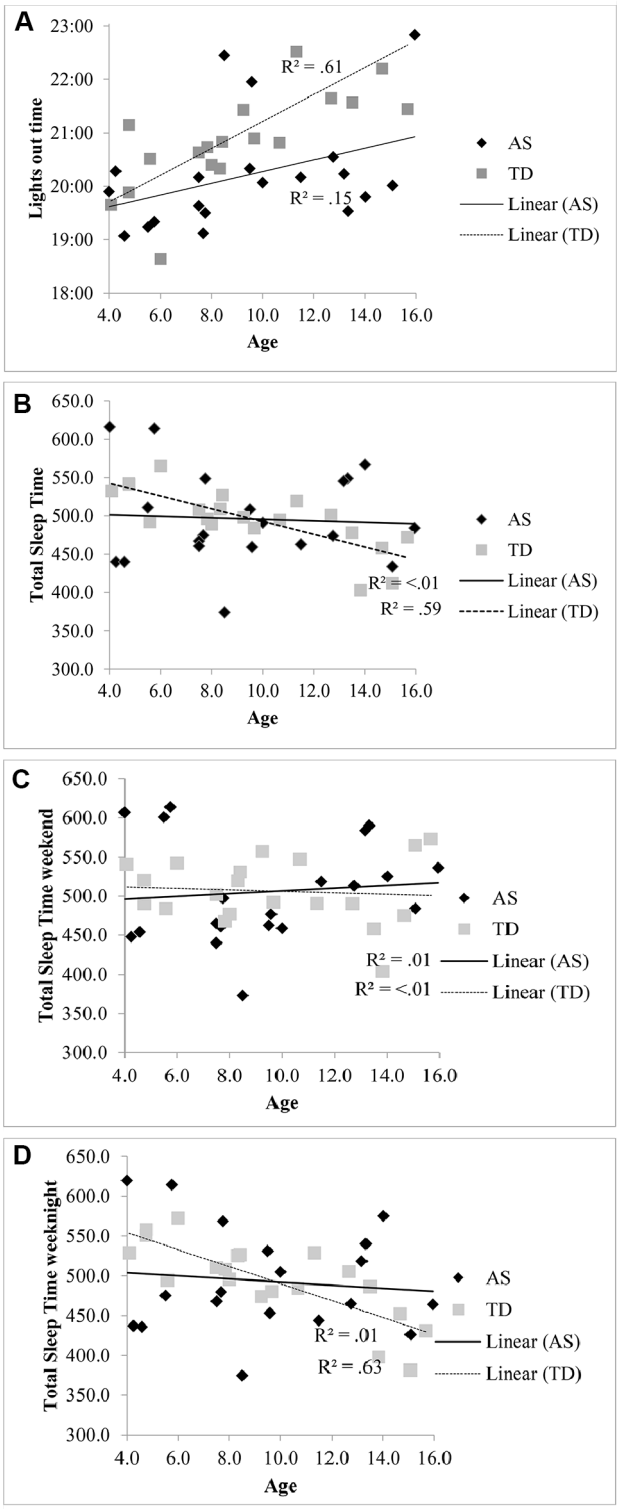

FIGURE 1 | (A) Relationship between lights out time and age in children with AS and TD children. **(B)** Relationship between total sleep time and age in children with AS and TD children. **(C)** Relationship between total sleep time at the weekend and age in children with AS and TD children. **(D)** Relationship between total sleep time on weeknights and age in children with AS and TD children.

children with AS has enabled the benchmarking of impairment in sleep quality and differences in sleep timing.

These findings contrast from previous studies which indicate that individuals with AS have reduced total sleep time (see 19, 47). Our findings show that more children with AS sleep on average for the minimum recommended time than TD children. Given the inclusion criterion of children with AS with a parent-reported sleep disturbance, should the reported total sleep time be shorter in the wider AS population, we would have expected to have replicated this finding. It is possible that the TD group over-represented children with poor sleep quality, as in another study the average actigraphy assessed total sleep time in a large sample of children aged 9–11 years in the United Kingdom (48) met the minimum criteria advised by the American Academy of Sleep Medicine for this age group (45). The lack of relationship between age and bedtime in the AS group in contrast to the TD group is relevant to this finding. It has been suggested that it is environmental factors, as opposed to biological mechanisms, that may be responsible for the reduction in total sleep time with age in TD children (49, 50), as the decrease in total sleep time with age was only found on school days in one meta-analysis (47) and in the present study. This finding suggests that it may not be the case that the required sleep duration for TD children decreases, but that environmental constraints such as additional activities in the evening result in later bedtimes, as observed in **Figure 1A**, which reduces the time in bed and subsequent sleep period. Children with AS may not have the same demands on their time in the evening for extra-curricular and social activities, as their adaptive ability does not increase in line with their TD peers. Given the lack of difference in sleep onset latency between the groups, it would suggest that bedtimes in children with AS are aligned with their circadian phase. However, further research using melatonin assays to assess the timing of endogenous melatonin secretion onset is needed to explore whether children with AS have a circadian phase shift, as risk for circadian rhythm disorders has been identified in a small sample of individuals with AS (8). Further research is also needed both within TD and AS populations to investigate the hypothesised biological mechanisms of phase shift with age.

Despite the lack of difference between children with AS and TD children in total sleep time and wake after sleep onset, it is important to note that all parents of children with AS who participated in this study considered their child to have a sleep problem, and 81% had severe night waking problems according to a questionnaire definition. It is possible that heightened levels of night waking reported by parents in the AS group are due, in part, to greater self-soothing skills in the TD group, such that the TD children wake their parents less frequently and therefore night waking is under reported by parents of TD children. Additionally, it is possible that as children with AS are likely to have limited self-soothing skills due to their low adaptive ability, night wakings are extended as parents need to enter the child's room which may be more stimulating and hinder the child's ability to fall back to sleep quickly. Night waking duration varied substantially both between children with AS and from one night to another. This variability warrants further exploration. It is possible that the variance in night waking may be associated with nocturnal seizure frequency, however we do not have nightly reports on seizure frequency and duration to test this hypothesis. This has implications for

assessment, namely that the severity of night waking using the average from children in one study cannot be generalised across children with AS. It is more important to assess sleep quality in children individually, and to evaluate night waking duration on multiple nights and consider the pattern of variation in sleep quality for each child. The detrimental impact of caring for a child with disturbed sleep cannot be underestimated, as parents of children with AS cite the impact of the impact of their child's sleep problems on their own ability to function as a concern (51).

According to parental report of sleep disordered breathing symptoms, children with AS were more likely to snore more than half the time compared to TD children, although no child always snored. Preliminary evidence from a sleep questionnaire suggests that children with AS may be at risk of sleep disordered breathing compared to TD children (12), and habitual snoring reported for 24% of the AS sample is higher than the 9% reported for community samples using the same definition (52). However, these data were drawn from a small sample (n = 17), so caution is needed to generalise this finding to the wider AS population. However, given these rates of reported habitual snoring objective cardiorespiratory sleep studies should be performed with low threshold of clinical suspicion in this vulnerable group. Children with AS were not more likely to experience excessive daytime sleepiness according to the MESS. This finding does support previous literature demonstrating low prevalence of daytime sleepiness among individuals with AS (6, 13–15). The lack of excessive daytime sleepiness in both groups could reflect the lack of difference in average total sleep time between the groups. No differences in sleep hygiene practices were found between the two groups, therefore poorer sleep efficiency cannot be attributed to a distracting or uncomfortable bedroom environment or routines, particularly with regard to providing children with attention during the night. This is encouraging as children with AS are effective in obtaining social attention from adults (53). This suggests that whilst sleep hygiene needs to be examined on a case by case basis for each family, interventions for sleep in children with AS may not need to focus particularly on parent-child interactions at night, despite the strong motivation for social interaction observed in children with AS. However, it should be acknowledged that parents of children with AS may have had a different interpretation of brief interactions. Therefore, the role of parent-child interactions during night wakings needs to be explored using video footage and objective coding of interaction length and social approaches.

Limitations

There are some limitations to the design of this study, predominantly the wrist placement of the Actiwatch for TD children and ankle placement for the majority of children with AS. A review suggests that whilst further research is needed, data obtained *via* ankle placement do not differ to those obtained *via* wrist placement (54). Due to children with AS's limited receptive language, it was difficult to encourage children to wear the Actiwatch on their wrist and explain the value of wearing the watch. The Actiwatch was more often tolerated on the ankle when it was out of sight. On balance, it was felt that the statistical power obtained by including a greater number of children with a rare genetic syndrome in the study outweighed the risk of extraneous variance between the groups due to differential placement of the Actiwatch, however, it is possible that ankle placement may have underestimated wake after sleep onset if children had more limited leg movements compared to arm movements during the night. Whilst still the largest actigraphy sample of children with AS to date, the small sample size does limit the generalisation of these findings to other children with the deletion subtype of AS. Whilst polysomnography is often considered the 'gold standard' method of objectively assessing sleep, children with AS may struggle to tolerate wearing the equipment. Additionally, polysomnography can fail to capture habitual sleep/wake patterns in an ecologically valid sleep environment. Therefore, actigraphy was used to assess sleep in this population. Of note is that whilst we did not find differences in actigraphy parameters between children who were and were not administered medication to aid sleep, the cause of sleep disturbance in these two subgroups may be different.

Whilst it is informative to compare the cross-sectional relationships between sleep quantity and timing and age between children with AS and TD children, these data do not account for individual differences in children's trajectories over time. Given the wide inter and intra-individual variation in total sleep time, it is important to approach these data with caution. A longitudinal study is required to confirm the difference in sleep quantity and timing with age in children with AS when interpersonal variation is accounted for. A longitudinal study could also identify the age at which sleep quality in children with AS diverges from the trajectory seen in TD children. We were unable to measure daytime melatonin in children with AS as the actigraphy and sleep diary data collection were facilitated by parents at home to maximise participation and also to ensure that data were ecologically valid. This does limit the discussion of the mechanisms that underpin interpersonal variation in sleep duration and quality among children with AS, as melatonin profiles in children with AS are disturbed (9). The measurement of endogenous melatonin should be a priority for future studies.

Conclusions

This study generated the largest objective dataset of sleep quality parameters in children with AS. Sleep quality was characterised by a high degree of variability, both among children with AS with parent-reported sleep disturbance, and between nights for each individual child. This variability needs to inform further assessments of and interventions for sleep in children with AS, as averages of total sleep, even across a seven night period do not capture the difficulties with night waking highlighted by parental questionnaire report. No change in total sleep time with age unlike that found in TD children on weekday nights was hypothesised to be accounted for by the lack of environmental and social constraints on children with AS.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available due to small numbers of participants with a rare syndrome. Data may be identifiable.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Birmingham. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JT contributed to the design of the study, data collection, data analysis, and manuscript writing. CO contributed to the design of the study, supervision of the project, and manuscript editing. MH contributed to the design of the study and manuscript editing. HD contributed to data collection, data cleaning, and manuscript editing. AS contributed to data collection and manuscript editing. EC contributed to data collection and manuscript editing. PG contributed to the design of the study and manuscript editing. CR contributed to the study design, supervision of the project, and manuscript editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00874/full#supplementary-material

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ActiGraph GT3X+ and Actical Wrist and Hip Worn Accelerometers for Sleep and Wake Indices in Young Children Using an Automated Algorithm: Validation With Polysomnography

Claire Smith[1], *Barbara Galland*[1], *Rachael Taylor*[2] *and Kim Meredith-Jones*[2]*

[1] Department of Women's and Children's Health, University of Otago, Dunedin, New Zealand, [2] Department of Medicine, University of Otago, Dunedin, New Zealand

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***Correspondence:**
Kim Meredith-Jones
kim.meredith-jones@otago.ac.nz

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Objectives: Our count-scaled algorithm automatically scores sleep across 24 hours to process sleep timing, quantity, and quality. The aim of this study was to validate the algorithm against overnight PSG in children to determine the best site placement for sleep.

Methods: 28 children (5–8 years) with no history of sleep disturbance wore two types of accelerometers (ActiGraph GT3X+ and Actical) at two sites (left hip, non-dominant wrist) for 24-h. Data were processed using the count-scaled algorithm. PSG data were collected using an in-home Type 2 device. PSG-actigraphy epoch sensitivity (sleep agreement) and specificity (wake agreement) were determined and sleep outcomes compared for timing (onset and offset), quantity [sleep period time (SPT) and total sleep time (TST)], and quality metrics [sleep efficiency and waking after sleep onset (WASO)].

Results: Overall, sensitivities were high (89.1% to 99.5%) and specificities low (21.1% to 45.7%). Sleep offset was accurately measured by actigraphy, regardless of brand or placement site. By contrast, sleep onset agreed with PSG using hip-positioned but not wrist-positioned devices (difference ActiGraph : PSG 21 min, $P < .001$; Actical : PSG 14 min, $P < .001$). The ActiGraph at the wrist accurately detected WASO and sleep efficiency, but under (–34 min, $P < .001$) and overestimated (5.8%, $P < .001$) these at the hip. The Actical under- and over-estimated these variables respectively at both sites. Results for TST varied ranging from significant differences to PSG of –26 to 21 min (ActiGraph wrist and hip respectively) and 9 min (ns) to 59 min for Actical (wrist and hip respectively).

Conclusion: Overall the count-scaled algorithm produced high sensitivity at the expense of low specificity in comparison with PSG. A best site placement for estimates of *all* sleep variables could not be determined, but overall the results suggested ActiGraph GT3X+ at the hip may be superior for sleep timing and quantity metrics, whereas the wrist may be superior for sleep quality metrics. Both devices placed at the hip performed well for sleep

timing but not for sleep quality. Differences are likely linked to freedom of movement of the wrist *vs* the trunk (hip) during overnight sleep.

Keywords: actigraph, accelerometer, sleep, physical activity, 24-h, Polysomnography, children

INTRODUCTION

Short sleep duration, timing, poor quality, and high variability are characteristics of children's sleep that are increasingly recognized as being associated with a wide range of adverse health outcomes including an increased risk of obesity (1). Accurate measurement of these sleep behaviors can be achieved using objective tools that estimate sleep and wake with sensors that measure body movement in terms of acceleration. These accelerometers are placed within small watch sized devices known as actigraphs (2). Accelerometer sensors are also used to estimate intensity of physical activity by processing movement into relevant components (sedentary, light, moderate, or vigorous physical activity) (3).

While sleep researchers traditionally refer to these devices as actigraphy devices, and physical activity researchers as accelerometers, they work on the same principle of using accelerometer sensors to detect motion. Devices used to measure physical activity are typically placed on the hip, whereas those used to measure sleep are usually placed on the wrist. These conventional practices stem from earlier validation studies when accelerometry sensors were uni-axial (sense movement in one direction only), so the sensors in physical activity devices were usually placed at the hip to be more sensitive to vertical acceleration associated with walking/running (4). Omnidirectional accelerometers are most sensitive in one plane, generally the vertical, but are also sensitive to movement in other directions, with the output being a composite of the signals. In contrast, triaxial accelerometers consist of three orthogonal accelerometer units that measure acceleration in each of the three planes separately, providing an output for each plane, as well as a composite measure (4).

The advantages of actigraphy/accelerometry are the relatively low cost and the unobtrusive nature of the device compared to laboratory or in-home PSG systems, making it an ideal tool for large-scale studies. However, most research to date has examined sleep and physical activity in isolation, requiring participants to either wear the device during the day to measure physical activity or just at night to measure sleep. Neither provide accurate estimation of sleep or physical activity given that participants do not put the device on as soon as they wake, and often take them off well before they go to bed (5). In order to improve compliance and wear time for both sleep and physical activity, protocols now recommend participants wear accelerometers over 24-h (6).

Estimating sleep from actigraphy requires computer algorithms to classify sleep and wake based on the assumption that the presence of movement indicates wakefulness and the absence of movement indicates sleep. Typically, algorithms vary by the population studied, device worn, and the site placement they were developed for (wrist or hip), but most work in a similar fashion: to define each minute of recorded activity as either a sleep or wake epoch by weighting the activity scores of the surrounding minutes. Various commercially available algorithms for assessing sleep are available (7), although the Sadeh algorithm (8) which has been validated in children and adolescents against the gold-standard for measuring sleep; polysomnography (PSG) (2, 8) is most commonly used in children. The major limitation of these algorithms is poor accuracy in detecting wake after sleep onset when subjects may be lying awake, but motionless, leading to overestimates of sleep (9). Conversely, when a person has very restless sleep, in the case of some sleep disorders, actigraphy can underestimate sleep (10). In addition, most sleep algorithms were developed for devices worn at the wrist and only a limited number of studies in adults (11–16) have demonstrated the accuracy of these algorithms compared to PSG when worn at the hip. To our knowledge, there are no studies that compare actigraphs worn at the hip to PSG in children.

We recently developed a count-scaled algorithm that automatically scores sleep and physical activity across a 24-h wear protocol (5). This count-scaled algorithm (17) uses a scaling process to standardize counts across the entire recording before epoch allocation, potentially giving the algorithm flexibility to apply to different accelerometers where count outputs differ due to different sensor sensitivities, or device placements.

To date we have validated the algorithm in infants during daytime napping and have shown accuracy rates of 85–86% against PSG (17). We have also reported agreements with parental diary data for overnight and 24-h sleep parameters in children from 6 months to 5 years (18). The current study extends this research for the measurement of nocturnal sleep in older children. The aims of this study are to: 1) validate the count-scaled algorithm against overnight PSG in children aged 5 to 8 years using two devices; the omnidirectional Actical and the triaxial ActiGraph GTX3+, 2) to compare different site placements (wrist *vs* hip) to determine the best placement site for measuring sleep, and 3) to compare the count-scaled automated algorithm to the most common algorithm used in child actigraphy, the Sadeh algorithm.

METHODS

Subjects and Data Collection

Children were recruited from the general Dunedin (New Zealand) population by convenience sampling using a community newspaper, flyers on notice boards, and word of mouth. Children were aged 5 to 8 years at the time of

recruitment. Ethical approval for the research was obtained from the University of Otago Human Ethics Committee (H15/025).

Demographic and Anthropometric Data

Information was collected on participant's age, sex, date of birth, and ethnicity using New Zealand census questions (19). The participants address was used to determine area based socio-economic status using the New Zealand Deprivation Index (NZDep Index, 2013) (20). At the first visit, height (cm) and weight (kg) were measured using standard techniques. Body mass index z-scores for age were calculated and cut-offs for overweight and obesity made according to WHO reference data (21).

Sleep Disturbances Scale for Children (SDSC)

To assess children for sleep disturbance, parents completed the Sleep Disturbances Scale for Children (SDSC) (22). The SDSC is a 27-item validated inventory rated on a 5-point Likert-type scale that investigates the occurrence of sleep disorders over the last 6 months in children aged 6–16 years. The instrument's purpose is to categorize sleep disorders in children. As well as giving an overall score the instrument uses six subdomains: disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep–wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis. The sum of scores provides a total sleep score with a possible range from 26 to 130 (higher numerical values reflect a higher frequency of occurrence of symptoms). Higher scores indicate greater sleep difficulties, with total scores ≥56 signifying the presence of a clinically meaningful sleep disturbance.

Actigraphs

Children wore four accelerometers [two Actical (Philips Respironics Inc., Murrysville PA, USA) and two ActiGraph GT3X+ (ActiGraph, Pensacola, USA) accelerometers] on the right side of the hip and non-dominant wrist for approximately 36 h (**Figure 1**), including two overnight periods. All devices were initialized using 15 s epochs, and processed with the normal frequency filter (Actigraphs). The Actigraphs were initialized using Actilife (V 6.11.9), and the Acticals using Actical Version 3.0.The same computer was used to program the accelerometers and the PSG recording device and times were synchronized.

FIGURE 1 | Site placements for wrist and waist worn ActiGraph GT3X+ and Actical accelerometers.

Actigraphy Processing

Data were downloaded as.csv files and processed using the count-scaled algorithm developed in MATLAB (MathWorks, Natick, MA, USA) or the Sadeh algorithm (23) in ActiLife (ActiGraph, Pensacola, FL, USA). The count-scaled algorithm, described in greater detail elsewhere (5, 17) uses only the vertical axes outputs and scales each recording period for each participant relative to the mean value of all epochs that have non-zero counts. The algorithm is initiated using a "time flag" of 7:30 pm for sleep onset (night time sleep) and 6:00 am for sleep offset (morning wake). These flags were determined from the average bedtime and wake times that accurately reflected those for the age of our dataset, but can be modified for any age group or individual. To detect sleep and wake states, a weighted sum of the activity in the current minute, the preceding 4 min and the following 2 min is computed and then compared with the sleep–wake threshold of 1 (< 1 = sleep). The algorithm detects wake "events" as the last minute of 15 continuous minutes of sleep followed by 5 min of awake and sleep "events" as the start of 15 continuous minutes of sleep preceded by 5 min of awake. To detect the bedtime sleep "event" the algorithm first moves 3 h forward to detect the first sleep onset event. If sleep is not detected in the 3 h it moves 2 h backwards to identify the last sleep onset event. If a sleep event is not detected within the 3 h after or 2 h before the chosen bedtime, the chosen bedtime (e.g. 7:30 pm) is used. To detect sleep offset the algorithm performs in a similar way, but attempts to detect a wake time rather than a sleep time. All files in this study were processed using the automated mode, but the program does include an option for visual determination of sleep onset and offset as applied previously in other studies where sleep timing is not so predictable. The Sadeh algorithm is the most commonly used algorithm for sleep–wake scoring in children (24). The algorithm is: where SI is the sleep indicator of the current epoch (if SI ≥0, the current epoch is classified as sleep); μ is the mean activity on a 11-min window centered on the current epoch; σ is the standard deviation of activity for the last 6 min; LogAct is the natural logarithm of the

activity of the current epoch increased by 1 and nat is the number of epochs that satisfy the criterion 50 ≤ epoch activity <100 in an 11-min window centered on the current epoch (23). As we used the Sadeh algorithm embedded within the ActiLife software which cannot be used to analyze Actical devices, we were only able to compare data from the Actigraphs.

Home-Based Polysomnography

Overnight PSG was conducted on the second night of the accelerometer wear protocol and data were recorded using a Type 2 ambulatory sleep device (Embletta® MPR with ST+ Proxy; Natus Medical, CA, USA) within participant's homes at a sampling rate of 500 Hz and using guidelines of the American Academy of Sleep Medicine (25). The researcher began the PSG set up approximately 1 h before bedtime. The PSG included right and left electro-oculograms, four electroencephalograms (C4/M1, C3/M2, O2/M1, O1/M2), left and right submental electromyogram, thoracic and abdominal respiratory effort and ECG. Oxygen saturation was measured with pulse oximetry. Data were downloaded and analyzed using RemLogic software (Version 3.4, Embla Systems, Broomfield, CO, USA). Data were scored in 30-s epochs using AASM sleep staging criteria (Berry et al.). Sleep onset was considered the first epoch of sleep after lights out and sleep offset the last epoch of sleep. The study PSGs were scored visually by one author (CS) with a 94.3% inter-scorer reliability for sleep/wake on 12,317 against epochs scored by a second author (BG).

Epoch-By-Epoch Comparison

The PSG and count-scaled actigraphy data were extracted epoch-by-epoch and aligned. To allow for comparison to the count-scaled algorithm the PSG 30 s epoch lengths were separated into two 15 s epochs. Depending on their agreement with PSG, each epoch was categorized as True Sleep, False Sleep, True Wake, or False Wake. Epoch concordance was calculated in terms of sensitivity (% sleep agreement), specificity (% wake agreement), and accuracy (% sleep and wake agreement). Because overnight recordings consist of many more sleep epochs than wake epochs (in a healthy subject, at least 85% of the epochs would correspond to "sleep" (26), to provide equal weights to this categorical data, a prevalence-adjusted bias-adjusted kappa (PABAK) was computed to counteract this (27). The interpretation of PABAK is the same as for kappa i.e. the Landis and Koch scale (28) is used to interpret the level of agreement where coefficients ≤0 indicate poor agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–1.00, almost perfect agreement. We did not analyze the Sadeh algorithm epoch-by as the algorithm uses 1-min epoch lengths compared the count-scaled algorithm which uses 15-s. We have however provided comparisons between the count-scaled algorithm and Sadeh algorithm for all summary sleep outcomes.

Sleep Outcomes

Sleep outcome variables were calculated from the PSG recordings and from the accelerometers located at both the wrist and hip, using the count-scaled algorithm and Sadeh algorithms as described above. The PSG and actigraphy data were analyzed separately by different researchers. Standard sleep variables were calculated for the period between sleep onset and sleep offset. Relevant sleep variables defined below included those related to dimensions of: a) sleep timing; sleep onset and sleep offset, b) sleep quantity; Sleep Period Time (SPT) and Total Sleep Time (TST), and c) sleep quality; sleep efficiency and waking after sleep onset (WASO). **Figure 2** gives a schematic of these variables extracted for both actigraphy and PSG.

- Sleep Onset: clock time of first consecutive minutes scored as evening sleep
- Sleep Offset: clock time of first consecutive minutes scored as morning wake
- Sleep Period Time (SPT): the elapsed time between sleep onset and sleep offset
- Wake after Sleep Onset (WASO): number of minutes scored as awake between sleep onset and offset
- Total Sleep Time (TST): represents true sleep time and is calculated as SPT minus WASO
- Sleep Efficiency: the percent of time asleep between sleep onset and offset and thus excludes sleep latency

Sleep outcomes were compared to PSG using paired t-tests for normally distributed data and Wilcoxon sign-rank test, for WASO, which was not normally distributed.

Bland Altman

Bland Altman plots were used to examine the limits of agreement between sleep outcome variables of total sleep time and sleep efficiency measured by actigraphy devices against those measured by the gold-standard PSG. The Bland-Altman plot shows the difference between two measures on one axis against the average of two measures on the other axis (29). Upper (UALM) and lower limits (LALM) of agreement are calculated as the mean difference ± 1.96 × standard deviation. The limits of agreement are a measure of precision and show the range of values expected for 95% of individuals.

Power Calculation

The sample size was powered to detect differences in our primary outcome variable which was mean total sleep time between PSG and accelerometry. Based on a mean (SD) for total sleep time by accelerometry of 660 (38) minutes in children aged 3–7 years (30), our study has 90% power at the 5% level of significance to detect a difference between methods of 30 min with 22 participants. This sample size also allows us to detect correlations between the two methods of at least r = 0.6.

RESULTS

Study Participants

Twenty-eight participants with more than 5 h of PSG data were included in the epoch-by-epoch analyses and 23 participants with complete overnight PSG and congruent actigraphy were included in the comparison of sleep outcomes. **Table 1** provides

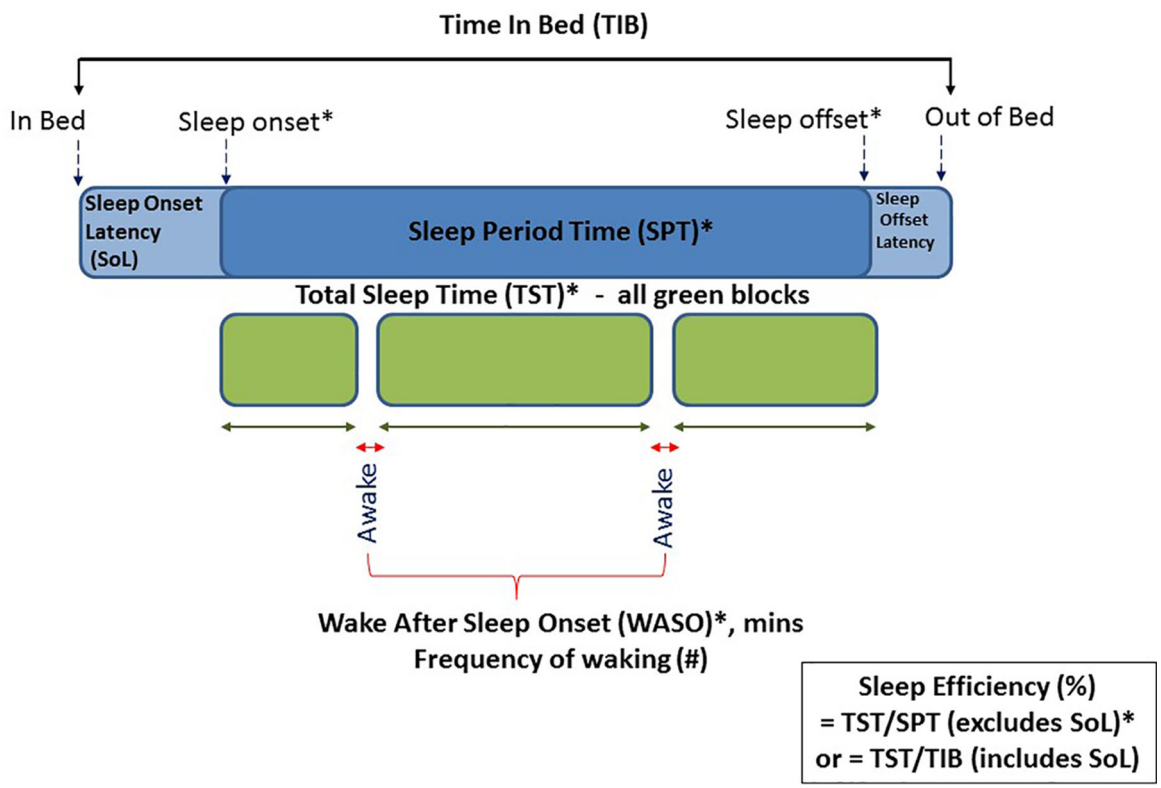

FIGURE 2 | Schematic diagram of actigraphy and PSG data extracted across the night of sleep. Those marked with an asterisk were variables included in this validation study.

a description of the participants. The mean age of participants was 7.2 years (SD 1.2), 17 (61%) were boys, the majority (n = 22, 79%) were of European ethnicity, and 14 (50%) resided in areas of low deprivation (NZDepIndex levels 1–3), 5 (18%) in areas of medium deprivation (levels 4–7), and 9 (32%) in areas of high deprivation (levels 8–10). Twenty five percent of participants were categorized as overweight and 4% as obese. The total SDSC score for all participants was within the normal (non-clinical) range with a mean (SD) score of 37.0 (5.7) and range, 26 to 52.

Sleep and Wake Epoch-By-Epoch Comparison

Table 2 shows the sensitivity (epochs correctly identified as sleep), specificity (epochs correctly identified as wake) and accuracy (both sleep and wake epochs correctly identified) for the two accelerometers placed at the hip, and at the wrist. Mean values of overall accuracy were within a narrow range, from 86.0% (Actical at the wrist) to 90.2% (ActiGraph at the hip). Sensitivities achieved were also within a narrow range [95.7% (wrist positioned ActiGraph) to 99.5% (hip positioned Actical)]. Specificities however were more variable with the wrist positioned ActiGraph being highest 62.0%, with only 21.1% being achieved for the hip-positioned Actical. Epoch-by-epoch agreements using PABAK ranged from 0.74 (Actical hip) to 0.81 (ActiGraph wrist) with both devices showing moderate to substantial agreement overall and slightly higher agreement compared to PSG at the wrist than at the hip.

Sleep Outcome Variables

Bivariate Correlations

Bivariate correlations for all sleep outcome variables according to PSG, actigraphy devices (ActiGraph GT3X+ and Actical) and placements (hip and wrist) are given in **Supplementary Tables S1**–**S5**. Sleep timing variables (onset and offset) were positively correlated (all significant excluding the wrist Actical), and sleep duration variables (TST and SPT) were significantly and positively correlated across all five matrices. Sleep quality variables of WASO and sleep efficiency were significantly negatively correlated. Other correlations were: sleep onset was significantly and negatively correlated with SPT and TST in all five matrices, whereas sleep offset correlated positively with SPT and TST i.e. the later the children went to sleep, the shorter their sleep was, and the later they woke up (sleep offset) the longer their sleep was in terms of both amount of sleep (TST) and opportunity for sleep (SPT). WASO significantly and negatively correlated with TST for the ActiGraph (both placements) and the Actical wrist i.e. the more waking between sleep onset and offset, the less total sleep. Although this trend was apparent within the

TABLE 1 | Demographic and health characteristics of participants (n = 28).

	n	%
Boys	17	61
Age (years)		
5	3	11
6	11	39
7	8	21
8	8	29
Ethnic group		
NZ Māori	2	7
European	22	79
Asian	4	14
Deprivation		
Low (1–3)	14	50
Med (4–6)	5	18
High (7–10)	9	32
BMI category		
Normal weight	20	71
Overweight	7	25
Obese	1	4
Sleep problem		
A small problem	1	4
Not a problem at all	27	96
Family position		
Middle	5	18
Oldest	12	43
Only	1	4
Youngest	10	36
< 15	7	25
15–30	10	36
30–45	5	18
45–60	5	18
> 60	1	4

BMI, body mass index.

PSG data, this was not significant. The hip placed Actical showed no relationship between TST and WASO.

ActiGraph GT3X+ *Vs* PSG

Table 3 shows sleep and wake outcomes measured using the ActiGraph compared to PSG for the wrist and hip-positioned devices. Sleep onset recorded on the ActiGraph was significantly later (21 min) than PSG for the wrist positioned device, but not the hip, whereas sleep offset times were similar to PSG for both placements (hip 0:00 (0:26) min; wrist −0:05 (0:13) min). Consequently, the wrist placed device underestimated SPT (equating to the difference between onset and offset) by 27 min compared to PSG, whereas no significant differences were observed for the hip placement.

WASO measured using the ActiGraph at the wrist was not significantly different to PSG-derived WASO, whereas the hip positioned device underestimated WASO by 34 min. This impacted sleep efficiency such that hip placed devices overestimated efficiency by a median of 4.6%, whereas sleep efficiency derived from wrist worn devices was comparable to PSG. Since TST (the actual sleep time between onset and offset) uses all these metrics, the wrist device underestimated TST by 26 min, and the hip device overestimated TST by 21 min.

Hip *Vs* Wrist

The final column in **Table 3** shows P-values for the comparison of sleep outcomes for hip versus wrist placed devices. Sleep onset was significantly later measured by the wrist compared to the hip with no difference in sleep offset. There was no evidence of a difference for WASO or SPT between the wrist and the hip, however TST was significantly shorter for the hip. SE (%) was also significantly lower at the wrist (92.5%) compared to the hip (98%).

Count-Scaled *Vs* Sadeh

Supplementary Tables S6 and **S7** show the comparison of the hip and wrist Actigraphs using the Sadeh algorithm compared to the count-scaled algorithm. At the hip, the only significant differences in performance (measured by difference to PSG) of the count-scaled algorithm compared to the Sadeh were for WASO (count-scaled underestimated WASO compared to the Sadeh; P = 0.029) and sleep efficiency (overestimated; P = 0.023), whereas all other metrics were comparable i.e. no significant differences encountered between the count-scaled and Sadeh performance for sleep onset, sleep offset, TST, or SPT. However at the wrist, the count-scaled algorithm performed better than the Sadeh on WASO and sleep efficiency (both differences P < .001) whereas all other metrics were comparable.

Actical *Vs* PSG

Table 4 compares Actical-derived sleep measures compared to PSG for the wrist and hip positioned devices. Like the ActiGraph sleep onset using the Actical wrist positioned device was significantly later (14 min) than PSG, whereas the hip positioned device was comparable to PSG [−0:03 (0:13)]. Sleep offset time again was similar to PSG using both placements, as was SPT.

Both placements underestimated WASO (hip 45 min; wrist 24 min), resulting in an overestimation of sleep efficiency (hip

TABLE 2 | Sensitivity, specificity, and accuracy of epoch-by-epoch comparisons with PSG of the two accelerometers placed at the hip and the wrist.

Device	Placement	n[a]	Accuracy	Sensitivity	Specificity	PABAK (95% CI)
			% (95% CI)	% (95% CI)	% (95% CI)	
ActiGraph GT3X+	Hip	28	88.2 (84.1, 91.3)	97.2 (96.1, 98.0)	41.6 (30.9, 53.2)	0.76 (0.75, 0.77)
ActiGraph GT3X+	Wrist	28	90.2 (86.3, 93.1)	95.7 (94.5, 96.4)	62.0 (47.0, 74.9)	0.81 (0.80, 0.81)
Actical	Hip	28	86.7 (82.7, 90.0)	99.5 (92.2, 99.6)	21.1 (15.3, 28.3)	0.74 (0.73, 0.74)
Actical	Wrist	27	86.0 (76.2, 92.2)	98.0 (97.3, 98.6)	45.7 (34.2, 57.3)	0.79 (0.65, 0.66)

[a]*Participants with >5 h PSG and congruent actigraphy. PABAK, Prevalence-Adjusted Bias-Adjusted Kappa.*
≤0 indicate poor agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–1.00, almost perfect agreement.

TABLE 3 | Comparison of Actigraph GT3X measured sleep outcomes to PSG and comparison of wrist and hip positioned devices.

Sleep variable	Tool	Placement	n	Mean (SD)	Mean Δ (95% CI) Act-PSG	*P* PSG-Act	*P* Hip *vs* wrist
Sleep onset (hh:min)	PSG	PSG	23	20:37 (0:38)			
	Actigraph GT3X	Hip	23	20:44 (0:43)	0:06 (–7, 20)	.328	
		Wrist	23	20:58 (0:33)	0:21 (13, 31)	**<.001**	**.022**
Sleep offset (hh:min)	PSG		23	6:50 (0:38)			
	Actigraph GT3X	Hip	23	6:49 (0:43)	0:00 (–11, 11)	.898	
		Wrist	23	6:45 (0:39)	–0:05 (–11, 1)	.086	.357
SPT[iii] (min)	PSG		23	613 (43)			
	Actigraph GT3X	Hip	23	606 (40)	–7 (–22, 7)	.296	
		Wrist	23	586 (34)	–27 (–37, –16)	**<.001**	**.004**
WASO[iv] median (IQR)	PSG		23	48 (19)			
(min)	Actigraph GT3X	Hip	23	12 (0, 41)	–34 (–14 to –9)	**<.001**	
		Wrist	23	48 (10, 78)	–7 (–36 to 19)	.784	**.001**
Sleep efficiency[v] (%)	PSG		23	92.2 (91 to 93)			
Median (IQR)	Actigraph GT3X	Hip	23	98.0 (93 to 100)	5.8 (1.8 to 7.2)	**<.001**	
		Wrist	23	92.5 (86.5 to 98.1)	1.3 (–4.2 to 5.6)	.717	**.001**
Total sleep time[vi] (min)	PSG		23	563 (46)			
	Actigraph GT3X	Hip	23	584 (64)	21 (1, 41)	**.043**	
		Wrist	23	538 (64)	–26 (–49, –3)	**.027**	**<.001**

[i]*Comparison to PSG using paired t-tests (WASO compared using Wilcoxon rank sum test).*
[ii]*Comparison of hip and wrist measured sleep outcomes using paired t-tests (WASO compared using Wilcoxon rank sum test).*
Wilcoxon Rank Sum tests used to compare actigraphy to PSG.
[iii]*SPT is the time between sleep onset and offset.*
[iv]*WASO is the minutes of wake between sleep onset and sleep offset.*
[v]*Sleep efficiency = [(total sleep time–WASO)/sleep duration]×100.*
[vi]*Total sleep time is the time between sleep onset and offset with WASO removed.*
Bolded text indicates p < 0.05.

TABLE 4 | Comparison of Actical measured sleep outcomes to PSG and comparison of wrist and hip positioned devices.

Sleep variable	Tool	Placement	n	Mean (SD)	Mean Δ (SD) Act-PSG	*P* PSG-Act	*P* Hip *vs* wrist
Sleep onset (hh:min)	PSG		23	20:37 (0:38)			
	Actical	Hip	23	20:34 (0:53)	–0:03 (–18, 11)	.652	
		Wrist	22	20:54 (0:44)	0:14 (7, 22)	**<.001**	**.015**
Sleep offset (hh:min)	PSG		23	6:50 (0:38)			
	Actical	Hip	23	7:04 (0:50)	0:14 (–2, 31)	.084	
		Wrist	22	6:50 (0:51)	–0:01 (–16, 13)	.876	.119
SPT[iii] (min)	PSG		23	613 (43)			
	Actical	Hip	23	631 (47)	18 (–4, 40)	.110	
		Wrist	22	597 (55)	–15 (–32, 2)	.075	**.005**
WASO[iv] median (IQR)	PSG		23	48 (38 to 58)			
(min)	Actical	Hip	23	0 (0 to 7)	–45 (–58 to –21)	**<.001**	
		Wrist	22	17 (0 to 32)	–24 (–45 to –9)	**.003**	.121
Sleep efficiency[v] median (IQR)	PSG		23	92.2 (90.0 to 92.7)			
(%)	Actical	Hip	23	99.9 (98.9 to 100)	7.6 (4.4 to 10.0)	**<.001**	
		Wrist	22	97.0 (90.4, 99.8)	4.3 (–1.9 to 7.0)	**.011**	.084
Total sleep time[vi] (min)	PSG		23	563 (46)			
	Actical	Hip	23	622 (50)	59 (35, 83)	**<.001**	
		Wrist	22	571 (45)	9 (–14, 32)	.420	**.003**

[i]*Comparison to PSG using paired t-tests (WASO compared using Wilcoxon rank sum test).*
[ii]*Comparison of hip and wrist measured sleep outcomes using paired t-tests (WASO compared using Wilcoxon rank sum test).*
Wilcoxon Rank Sum tests used to compare actigraphy to PSG.
[iii]*SPT is the time between sleep onset and offset.*
[iv]*WASO is the minutes of wake between sleep onset and sleep offset.*
[v]*Sleep efficiency = [(total sleep time–WASO)/sleep duration]×100.*
[vi]*Total sleep time is the time between sleep onset and offset with WASO removed.*
Bolded text indicates p < 0.05.

7.6%; wrist 4.3%). In calculating the SPT, these differences amounted to the hip positioned device overestimating SPT by 59 min, whereas the wrist device produced values comparable to PSG.

Hip *Vs* Wrist

The final column in **Table 4** shows P-values for the comparison of sleep outcomes for hip versus wrist placed Actical devices. The Actical device produced fewer sleep variable outcome differences

between wrist and hip positions than the Actigraph GT3X+ (**Table 4**).

Sleep onset was significantly later measured at the wrist compared to the hip with no evidence of a difference for sleep offset. SPT and TST were shorter measured at the wrist. There was no evidence of a difference between the wrist and hip for WASO but the results showed a tendency for SE (%) to be lower at the wrist (97% *vs* 99%, P < 0.084).

Bland-Altman Plots

Figure 3 displays Bland-Altman plots for the differences in TST for each device at the hip and wrist positions using the count-scaled algorithm against the gold standard PSG-derived measures. The plots illustrate a systematic positive bias (mean difference lines for each device were above zero) for TST estimated from the count-scaled algorithm for the ActiGraph and Actical positioned at the hip. The mean difference for the wrist positioned ActiGraph device was below zero indicating a systematic negative bias (underestimation) of TST measured using this device/placement. For the Actical at the wrist, the mean difference was closer to the line of identity (mean = 9 min) indicating less bias. The limits of agreement for all were large indicating a wide dispersal of differences with no trends apparent.

Figure 4 shows the Bland-Altman plots for sleep efficiency. The hip positioned ActiGraph and Actical positively overestimated sleep efficiency. There was less bias in sleep efficiency measured by the wrist ActiGraph (mean of −0.6% i.e. close to zero) and wrist (mean overestimation of 3%). All plots illustrate a trend for a larger positive difference as mean sleep efficiency increases i.e. the higher the sleep efficiency, the larger the discrepancies between PSG and actigraphy.

DISCUSSION

Our study demonstrates that overall, sleep variables estimated using the count-scaled algorithm and measured using both the ActiGraph and the Actical whether placed at the wrist or hip have high sensitivity for detecting sleep (96–99%) but poorer wake specificity (21–62%) in comparison with PSG. These findings are in agreement with a review of previous validation studies in children where one in five studies returned sensitivities above 80%, and more than half returned sensitivities below 60% (7). The level of accuracy must be considered within the context of the automated count-scaled algorithm, developed specifically for large-scaled studies. It does not rely on the concurrent

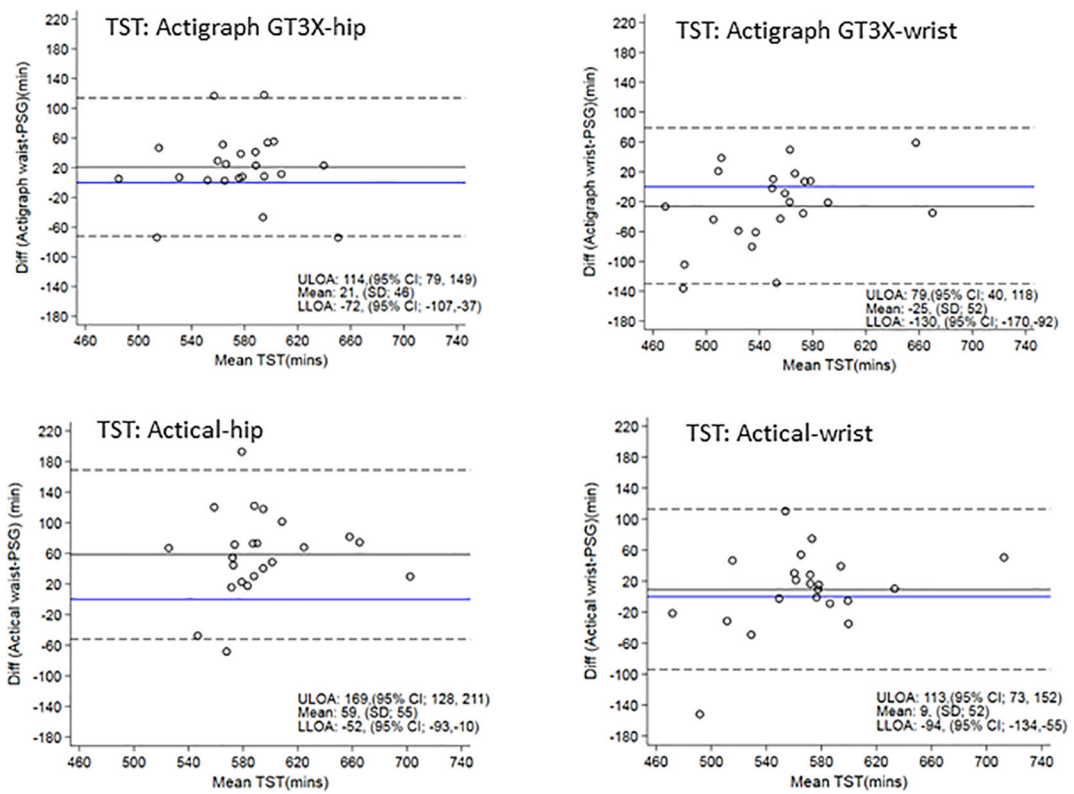

FIGURE 3 | Bland Altman plots of TST differences between actigraphy and PSG are on the y-axis and means are on the x-axis. Perfect agreement is shown by the blue line crossing zero on the y-axis. Mean differences are represented by black solid lines and the upper and lower levels of agreement by dashed lines. ULOA, Upper Limit of Agreement; LLOA, Lower Limit of Agreement; TST, Total Sleep Time.

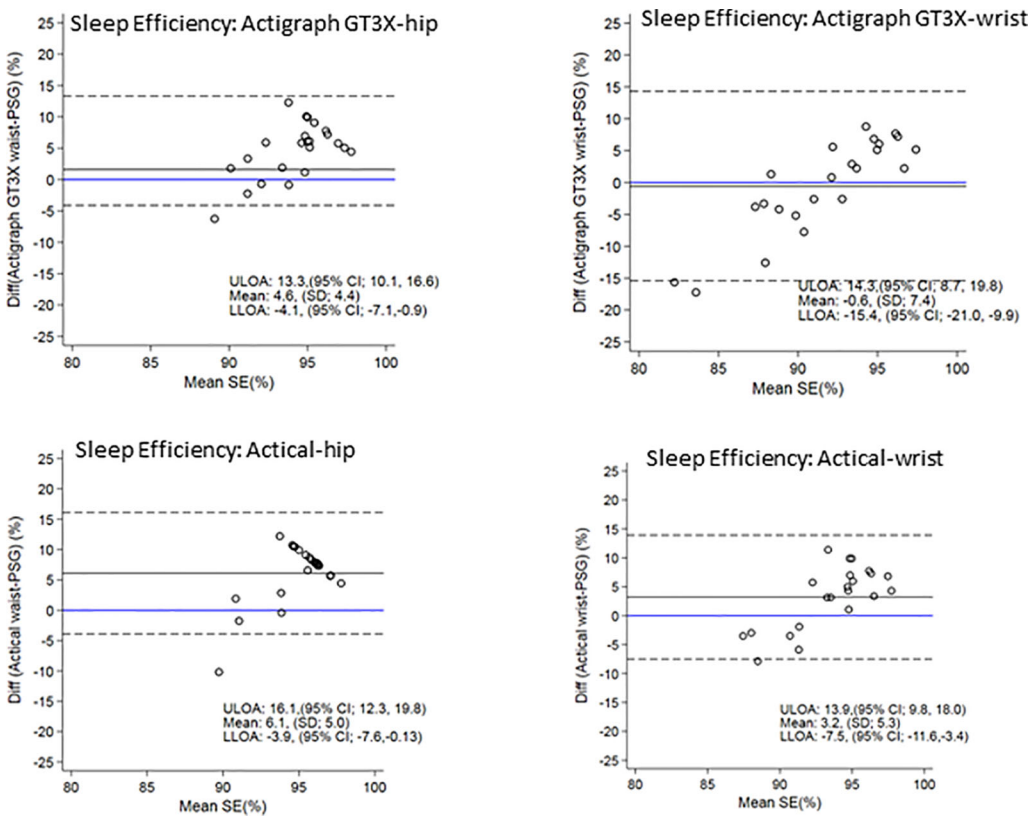

FIGURE 4 | Bland Altman plots of TST differences between Acticals and PSG are on the y-axis and means are on the x-axis. Perfect agreement is shown by the blue line crossing zero on the y-axis. Mean differences are represented by black solid lines and the upper and lower levels of agreement by dashed lines. ULOA, Upper Limit of Agreement; LLOA, Lower Limit of Agreement; TST, Total Sleep Time.

collection of a sleep diary data which may have improved the sleep–wake agreement. However this has to be balanced against the time consuming nature of entering diary data for researchers handling large datasets.

Some differences were observed in relation to various sleep outcomes. Overall, sleep offset time estimates were very close to PSG (regardless of device or positioning) and compared well against the Sadeh algorithm, reflecting the preciseness of using our automated count-scaled algorithm to detect this metric in these actigraphy devices. This is perhaps not surprising given that young children are likely to produce bodily movements at both areas of device placement i.e. the trunk and limbs upon waking. The wrist placement for both devices produced later sleep onset than hip placement, the latter producing no differences in sleep onset time when compared against the gold standard PSG. These differences in sleep onset outcomes related to placement may reflect what happens when settling to sleep; a person's trunk lies still, but the hands are still free to move, delaying the accuracy of the device at the wrist to detect the first identified period of sleep onset. Our actigraphy rules in processing required 15 min of sleep (epochs indicative of no or little movement) to be preceded by at least 5 min of awake (epochs indicative of movement) before marking sleep onset. The trunk can be assumed to be motionless during settling to sleep (if the person does not change position), and therefore a hip positioned device may detect sleep earlier than the wrist, and closer to the true sleep onset time.

The ActiGraph placed at the wrist was superior to the hip in terms of detecting waking after sleep onset and sleep efficiency in comparison with PSG. Taken together, and with the findings related to sleep timing above, our results suggest that researchers interested in sleep timing and sleep duration (sleep period time in this instance) would gain more accurate estimates using the hip placed ActiGraph at the expense of waking after sleep onset and sleep efficiency (sleep quality variables) that appear more reliably estimated at the wrist, and vice versa. It seems likely that the hands move more freely than the trunk during sleep and thus a wrist placement detects sleep disturbances more effectively. Hip placement may favor compositional data analysts who currently include all waking after sleep onset events as part of the sleep component of the 24-h day.

Overall, the Actical device placed at the hip measured sleep timing and duration (sleep period time) well. By contrast, metrics of sleep quality were relatively poor for this device at either placement site, underestimating WASO, and in keeping with the bivariate correlations, overestimating sleep efficiency (median 4.3% at wrist and 7.6% at the hip). Interestingly, at the wrist, this 4.3%

overestimation of sleep efficiency is identical to previous estimates of sleep efficiency derived from a PSG validation study of 30 adolescents (mean age 17.6 years) using the exact same device and placement (31). Given that few studies have determined the accuracy of hip accelerometers to PSG for measuring sleep in children, this is an important finding and highlights the potential usefulness of the count-scaled algorithm for detecting sleep period time in large cohorts i.e. without the addition of sleep diaries.

The metric of total sleep time (TST) representing the true amount of time the child sleeps, reflects a combination of waking after sleep onset and the length of the sleep period (SPT) i.e. increased waking reduces TST but a longer sleep period time increases TST as reflected within the bivariate correlations. The device/placement that produced values closest to PSG-measured TST was the Actical placed at the wrist; however this was a function of both an underestimation of WASO and a shorter (albeit not significant) sleep period time. In the previous adolescent validation study of the wrist Actical (31), TST was underestimated by 31 min, although they did not provide data for either WASO or SPT to understand what was driving this. In the current study, all other device/placements produced TST values that were significantly different to PSG-derived values.

PSG validation studies of the ActiGraph published for both children and adults do not include WASO metrics for this device (16, 24). In part this may be due to algorithms within the proprietary software for analyzing ActiGraph sleep data. For children at least, awakenings are defined as one or more consecutive epochs (60 s) having count levels that indicate movement. Our experience is that this produces very high waking frequencies. Most actigraphy rules for children include 5 min or more of consecutive awakenings to define waking after sleep onset (32). The current program includes options to manually adjust sleep periods and sleep scoring rules. WASO is a critical metric in the sleep field with children's night wakings being the most common sleep issue reported by parents (33). We suggest it is critical that software developers consider these shortcomings in future developments of proprietary software for 24-h accelerometry data.

All files in this dataset were analyzed using a count-scaled algorithm in automatic mode using time flags for the program to identify sleep onset and offset. This allows for hundreds of files to be analyzed at once, a major advantage for the processing of data from large-scale studies without the need for sleep diaries (5). In addition, the algorithm produces 24-h physical activity estimates that can be processed using user-defined cut-points for sedentary, and moderate to vigorous physical activity (34). Another automated sleep/wake algorithm has also been developed for a hip worn ActiGraph in children ActiGraph (35). The algorithm showed precise agreement with visual detection for sleep onset and offset, but has not yet been validated against gold-standard polysomnography. Despite referral in the paper to the algorithm detecting WASO (35), the data were not included, and therefore the precision of this variable against visual detection is unable to be ascertained.

This study cannot tell us which is the best placement to measure all activities across 24-h, as this requires validation of 24-h physical activity and sedentary behavior in concert with sleep. In moving forward, the ActiGraph is the one of the most widely used devices for measuring all behaviors of interest (36, 37). Our results do however suggest that for measuring sleep, different sleep dimensions will be impacted by placement site of the ActiGraph. Measuring variables such as sleep efficiency and waking after sleep onset are critical for measuring objective sleep quality, and therefore advances in this area for actigraphy are paramount given the move toward the importance of considering all sleep dimensions in regard to sleep health (38). Traditionally sleep quantity has been the key metric related to sleep health outcomes for children (1), probably related to its ease of measurement particularly in questionnaire or diary data, but there are now sleep quality recommendations for all age groups based on actigraphy and PSG data (39), and sleep timing and variability recommendations are a work in progress (40). All mean actigraphy values for sleep efficiency were in the recommended range for school-aged children i.e. ≥85% (39). For WASO, median durations measured by three of the four actigraph device–site combinations were in the appropriate (≤20 min) or uncertain recommendation ranges (21–40 min) for school-aged children; the Actical hip placement (WASO = 45 min) was just inside the inappropriate range recommendation i.e. 41 to 61+ min. Tracking of sleep architecture, including time spent in REM or NonREM sleep stages is not possible with accelerometry, as this requires the measurement of brain activity, eye movements, and muscle tension. Recent advances in consumer sleep trackers provide estimates of REM sleep, depth of sleep, and awake episodes across the night by including measures of heart rate alongside an accelerometer. The accuracy of these devices has not however been established.

Although debate remains regarding the best device placement for actigraphy, a review by Migueles et al. (41) suggests the hip site may produce more accurate estimates of physical activity (41), particularly with features from triaxial raw accelerometer signals that have narrowed the gap between physical activity energy expenditure estimates from wrist worn *vs* hip worn-devices (42, 43). A previous study in children using the ActiGraph devices for 24-h physical activity measures over 7 days found a higher compliance for wrist-worn versus hip-worn devices in 9–10 year-old children (44). Migueles et al. (41) also recommend different algorithms for estimating sleep-related behaviors for children and adolescents when devices are placed on the hip and the wrist; specifically the Tudor-Locke algorithm (45) for the hip and the Sadeh (46) for the wrist. For the hip, we suggest this would only apply for research concerned with when sleep onset and offset, as few sleep metrics are actually reported within the Tudor-Locke algorithm (45). Furthermore, this algorithm has not been validated against polysomnography.

The narrow age range of this study together with the exclusion of participants with sleep disturbance can be considered both a strength and a limitation. For validation purposes, this gave us a more homogenous sample to create greater precision in our estimates within the available sample size. Furthermore, keeping the age range narrow also reduces variability in sleep timing and duration, and excluding

participants with sleep disturbance also reduces variability in other sleep quality metrics as well. However limitations are inherent in not knowing how well our algorithm performs across different age groups, or in those with significant sleep disturbance. In addition, the algorithm does not include sleep latency in the automated outputs, but if a sleep diary or event marker is used to mark time in bed, then sleep latency can be easily calculated. These points could be addressed in future research. Furthermore, it must also be noted that although relatively small mean differences were observed between the count-scaled algorithm and PSG for most sleep outcomes, when assessing TST, individual biases were still present as indicated by the wide limits of agreement (Actigraph hip/wrist range −130 to 114 min; Actical hip/wrist range −94 to 169 min).

In conclusion, the count-scaled algorithm (used in the fully automated mode) demonstrated good accuracy for detecting sleep–wake epochs and precision in estimating some sleep outcome variables in children using data from two actigraphy devices. While we could not achieve our aim to determine a single best site placement for precise estimates of *all* sleep variables, our findings suggest that, for the ActiGraph at least, the hip may be superior for sleep quantity metrics, whereas the wrist may be superior for sleep quality metrics. The Actical device was precise at detecting sleep timing regardless of placement, but at the expense of sleep quality metrics. Additional research is needed to validate sleep algorithms for wrist and the hip-worn accelerometers across all age groups, and reporting of all sleep metrics is paramount to be able to understand the intricacies and importance of device placement. Furthermore, research is needed to validate these and other devices for the assessment of 24-h movement behaviors, that is, sleep, sedentary behavior, and physical activity.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Otago Human Ethics Committee (H15/025). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CS and KM-J are the Principle Investigators of the overall project. RT and KM-J conceived the idea for this study. CS and KM-J conducted the research. CS undertook all the data collection, PSG designed and undertook the statistical analyses. KM-J undertook all the accelerometry analyses. BG wrote the first and subsequent drafts of the manuscript and all authors critically revised the manuscript for important intellectual content. KM-J had primary responsibility for final content. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00958/full#supplementary-material

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Sleep and Daytime Complaints During Manic and Depressive Episodes in Children and Adolescents With Bipolar Disorder

Maria Cecilia Lopes, Miguel Angelo Boarati and Lee Fu-I*

Child and Adolescent Affective Disorder Program (PRATA), Department and Institute of Psychiatry at University of Sao Paulo Medical School, Sao Paulo, Brazil

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***Correspondence:**
Maria Cecilia Lopes
cissa.lopes@gmail.com

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Introduction: Depressive and manic episodes of bipolar disorder can interact with sleep complaints, followed by a worsened psychiatric condition. The aim of this study was to examine the interaction of sleep disorders with bipolar disorder in youths during depressive and manic episodes.

Methods: The target population was children and adolescents drawn from the Children and Adolescents Affective Disorder Program. Clinical assessment for current psychiatric diagnosis was done by direct clinical interview, Diagnostic Interview for Children and Adolescents (DSM-IV), and best-estimated clinical consensus. We applied sleep questionnaires from which we obtained sleep and daytime complaints during manic and depressive episodes. All statistical tests of significance were done using 2-tailed tests with $\alpha = 0.05$.

Results: Participants in this study comprised 29 children (age = 10 ± 3 years, boys = 23) and 43 adolescents (age = 15 ± 2.4 years, boys = 30). Sleep complaints were observed in 66.4% of participants during manic episodes and 52.3% during depressive episodes. 37.9% of patients had sleep complaints in both episodes. Time in bed was longer during depressive episodes than manic episodes ($p = 0.01$). We found a high prevalence of nocturnal enuresis in depressive episodes in children and adolescents, which was statistically significant compared with manic episodes ($p < 0.05$). Unrested sleep was higher in adolescents in both episodes, and it was statistically significant during manic episodes ($p < 0.05$).

Conclusion: According to our analyses, the minority of patients had sleep complaints in both episodes. Our data showed that nocturnal enuresis occurred more frequently during depressive than manic episodes. Further research is necessary to understand the implications of these data.

Keywords: sleep, nocturnal enuresis, bipolar disorder, children, adolescents

INTRODUCTION

Sleep complaints are frequently described in bipolar disorder (BD). The adverse consequences of poor sleep on mood, motivation, and cognitive changes have been associated with negative functional consequences in individuals with BD (1–5). Sleep disturbance may contribute to a relapse in BD as a prodromal symptom, or warning signal that can appear before an episode of depression or mania (6–8).

Jackson et al. (2003) (9) reported that the majority of patients with BD (over 80%) were able to identify early symptoms, with sleep disturbance being the most common prodrome of mania and the sixth most common prodrome of depression. Some authors have described a monoaminergic syndrome that can explain both pathophysiology in depression and sleep complaint with noradrenergic hyperactivity; in relation to this syndrome, "withdrawal-induced cholinergic overdrive and the cholinergic-monoaminergic system" are the two most investigated and supported models (10). Sleep disturbance may contribute to maintenance of symptoms and impairment followed by poor memory for the positive domains or events in their lives (11). However, there are few data about sleep and symptomatic daytime behaviors in childhood BD. The aim of this study was to describe the presence of sleep and daytime complaints in children and adolescents with bipolar disorder.

METHODS

The target population was children and adolescents drawn from the Children and Adolescents Affective Disorder Program at the Institute of Psychiatry of the University of São Paulo, Brazil, from May 2008 to December 2010. The inclusion criteria: to be enrolled in this study, patients should fulfill DSM-IV (12) criteria for BD type I, II, and NOS, in the Affective Disorder Program at the Institute of Psychiatry of the University of São Paulo, Brazil, from May 2008 to December 2010. Our study sample comprised 72 children and adolescents, of both genders, aged 06 to 18. The clinical assessment for current psychiatric diagnosis was done by direct clinical interview by two senior psychiatrists (LFI and MB) applying the Diagnostic Interview for Children and Adolescents-DSM-IV version, and best-estimated clinical consensus.

The sleep patterns were obtained in the application of sleep scale by a group of psychologists with a senior sleep physician (MCL), and by the psychiatric clinical interview using structure scales to analyze sleep patterns comparing depressive and mania episodes. Our protocol applied sleep questionnaires according to the Bruni scale (1996) (13) from which we obtained information about their sleep and daytime complaints, during manic and depressive episodes. There were the monthly support in the BD treatment. The sleep analyses were made after the diagnosis was done. The sleep state in each mood episode was defined and the sleep questions were also scored according to the intensity of the each symptom in a rate from 1 to 5: 5 Always (daily); 4 Often (3 or 5 times per week), 3 Sometimes (once or twice per week), 2 Occasionally (once or twice per month or less), 1 Never. Our sample were patients in undergoing treatment using different medications. All statistical tests of significance were done using 2-tailed tests with $\alpha = 0.05$.

Standard Protocol Approvals, Registrations, Patient Consents

Written informed consent was signed by the parents after the approval by the Ethics Committee of the institution. The study was approved by the Ethics Committee of the Clinical Hospital of the University of São Paulo, according to the Declaration of Helsinki.

RESULTS

The participants in this study comprised 29 children (age = 10 ± 3 years old, boys = 23) and 43 adolescents (age = 15 ± 2.4 years old, boys = 30). Sleep complaints were observed in 78% of participants during manic episodes and 80.1% during depressive episode; 37.9% of participants had sleep complaints in both episodes.

The characteristics of the BD was described in the: **Table 1**. The occurrence of sleep complaints were observed and we found differences between manic versus depressive episodes in youth with BD (see **Table 2**). Interesting, we did not find differences in the distribution of sleep complaints according the subtype of BD: I, II, and also NOS. Time in bed was longer during depressive episodes than in manic episodes. Nocturnal enuresis occurred more frequently in depressive episode than in manic episodes (see **Table 2**). We found 18 youth BP patients with nocturnal enuresis. We compared the presence of nocturnal enuresis when these patients were in depressive and mania episode and we found that the presence was higher in patients when they were in depressive episode (Qui Square test, $p < 0.001$). Also, we observed the presence of nocturnal enuresis was higher in prepubertal children compared the adolescent group (Qui Square test, $p = 0.009$).

Also, daytime energy after a sleep disturbance was higher during both episodes (two tailed test, $p < 0.01$). We found no association between the medication action and the complaints of

TABLE 1 | Demographic and clinical characteristics of total sample of children and adolescents with bipolar disorder and sleep complaints (n = 72).[a]

Clinical variables	%
Children n = 29	10 ± 3.0
Adolescents n = 43	15 ± 2.4
Age of 1st episode (y.o.)	7.0 ± 3.4
Gender (Male)	73.6
Family History of PD	97
School impairment	41
Past psychiatric history	18
Type of BD	
BD type 1	80
BD type 2	7
BD type–NOS	13

[a]*y.o., years old; PD, psychiatric disorder; BD, bipolar disorder; BD type–NOS, Bipolar Disorder Not Otherwise Specified.*

TABLE 2 | Comparison of sleep complaints during depressive episode and manic episode in children and adolescents with bipolar disorder (n = 72).[a]

Sleep complaints	Depressive episode	Manic episode	p value
Clinical variable	**%**	**%**	
Sleep structure	80.2	78.6	0.812
Initial insomnia	44.4	38.9	0.503
Hypersomnia	37.5	45.8	0.312
Terminal insomnia	79.1	72.2	0.334
Decreased need for sleep	16.1	66.7	<0.001*
Night awakening	44.4	44.4	1
Reverse night with day	3.6	1.4	0.002
Restless sleep	75.0	63.8	0.145*
Nocturnal enuresis	22.2	1.4	<0.001[b,]**
Restless sleep			
Sudden limb movements	56.9	65.2	0.307
Repetitive limb movements	29.1	36.1	0.370
Restless sudden movements	69.4	72.2	0.711
Sleepwalking	20.8	15.3	0.391
Talk during sleeping	51.4	50.0	0.867
Teeth grinding	36.1	37.5	0.862
Night terrors	34.7	33.3	0.860
Nightmares	43.1	44.4	0.875
Recurrent isolated sleep paralysis	15.3	15.3	1

[a,]*Sleep complaints were obtained by psychiatric clinical interview using structure scales to analyze sleep patterns comparing depressive and mania episodes. ns, non significant.*
[b,]***Qui Square test, p < 0.01.*

nocturnal enuresis in our patients. There was only difference between prepubertal and adolescent group in the unrested sleep that was higher in adolescents in both episodes, and particularly significant during manic episodes (two tailed test, p = 0.048). We did not find difference between genders. Interesting, we found an increase in the reverse night with day during depressive episode, and a higher expression in the decreased need for sleep need parameter in mania episode (see **Table 2**).

DISCUSSION

This is the first study to analyze the sleep complaints in two phases of BD in children and adolescents. We found differences in each patient, according to the nature of the episode (manic or depressive). Our patients also showed a high level of sleep complaints during manic and depressive episodes. Interestingly, the minority of patients had sleep complaints in both episodes. This finding may be associated with a parental misperception.

Sleep disturbance is often misdiagnosed and unsuspected in adults with refractory depression (14). The refractory depression can be found due to resistance to the treatment, and due to non-adherence to treatment, also a failure to detect an underlying medical comorbidity (15). The decreasing sleep duration, later sleep timing preference, longer sleep latency, increasing nighttime awakenings, and greater sleepiness over follow-up were associated with increasing severity the five psychiatric symptom outcomes over follow-up mania, depression, mood lability, anxiety, inattention/externalizing) (16). Moreover, the manifestations of activity patterns outside of acute episodes add to the accumulating evidence that dysregulation of patterns of activity may constitute a potential biomarker for BD (17). We hypothesized that the presence of interaction between daytime complaints associated with sleep complaints may increase some symptomatic behaviors in these patients, such as agitation, irritability, or others.

There wasn´t equal distribution between subtypes of bipolar disorder in children, and this fact may influence some symptoms in our sample, however the distribution of sleep complaints according the subtype of BD: I, II, and also NOS wasn´t different. Probably sleep can help more in the follow up, and to be considered a biomarker needs more studies, despite the fact that the sleep alterations frequently appear long before the onset of BD, and appear to be related specifically to the polarity of the index episode. The underlying of neurobiology and genetics of bipolar disorder are limited by a heterogeneous clinical phenotype. We would hypothesize that the symptom of each bipolar endophenotypes might be based on the sensitivity to sleep deprivation. The detection and treatment of sleep alterations in special high risk populations may help achieving an earlier detection of the illness (18). In fact, Hernandez et al. (19) in 2017 showed in an elegant study in a sample of 83 patients that sleep disturbances, severe mood instability, bad temper, anxiety symptoms, and aggression were among the most common signs of psychopathology reported in children diagnosed with BD before puberty.

Sleep loss may be one warning signal that can appear before an episode of depression or mania, and it may contribute to a relapse in BD as a prodromal symptom. There is an increase in sleep complaints in children who have been exposed to tragic stress (20). The prevalence of nocturnal enuresis has been reported to be higher children exposed to acute stress (20). Patients with nocturnal enuresis have been associated with sleep instability (21), and it may be a sign of vulnerability or depression. The relationship between sleep and nocturnal enuresis in children and adolescents with BD may be a marker of sleep instability in these patients. Also, unaffected child and adolescent offspring of bipolar parents may have a decrease in the need that may represent an endophenotype of BD in youth (22). In same direction, the sleep complaints in our sample were part of the episode, that were included in the bipolar disorder symptoms. The medications may cause nocturnal enuresis, however in our study as sleep complaints were present only during mood episodes and not in the stable mood, and the restless sleep can be biomarker of mood state.

There is a need to understand the longitudinal processes of the mood disorders, particularly in the early diagnosis in youth. The refractory condition is a common complaint, and there is a role of sleep disorders that was described by McCall et al., in 2019 (14). Youth with bipolar I disorder and a comorbid nightmare disorder appear to be at heightened suicide risk (23), and sleep complaints have been associated with suicidal behavior in youth patients with major depression (24). Our study was developed in a longitudinal setting within the same cohort, and the data should be followed by studies with the longitudinal cohort. There were differences in the polysomnogram studies that showed sleep changes in the expression of REM density in

pediatric mood disorders versus attention deficit disorder, and this data can help in the differential diagnosis of the youth patients (25, 26). There is need to evaluate the subjective sleep complaints together with objective analyses. Another limitation of our study was that the protocol did not include the score of Bruni scale (13).

In this study, we tried to develop the sleep phenotype in bipolar disorder, and we used binary analyses that can be less "predictive" but more associative of symptoms. However, the relationship between sleep and daytime complaints in children and adolescents with BD is still unclear. In order to detect mood change in BD, may be necessary to repeat them multiple times or even in both episodes (manic and depressive). Further studies are necessaries to understand the implications of these findings.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Sao Paulo. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ML made all data analyses and discussion. MB was the expert in the clinical interview. LF-I designed the project, arranged for data collection and data tabulation. She also reviewed the analysis, results and discussion.

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Excessive Daytime Sleepiness Measurements in Children With Attention Deficit Hyperactivity Disorder

Stéphanie Bioulac[1,2,3]*, *Jacques Taillard*[2,3], *Pierre Philip*[1,2,3] and *Patricia Sagaspe*[1,3]

[1] CHU Pellegrin, Clinique du Sommeil, Bordeaux, France, [2] Université de Bordeaux, Sommeil, Attention et Neuropsychiatrie, USR 3413, Bordeaux, France, [3] CNRS, SANPSY, USR 3413, Bordeaux, France

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood. It is a heterogeneous disorder in terms of clinical presentation that is probably due to the frequent occurrence of comorbidity. Children with ADHD more frequently report sleep disorders (notably delayed sleep phase syndrome) and excessive daytime sleepiness (EDS) than typically developing children. The aim of this article is to propose a narrative review of the assessment of EDS in the context of ADHD with first a summary of the subjective and objective tools used to measure it. Secondly, perspectives in terms of electroencephalogram (EEG) markers and neurofeedback are proposed. Then, possibilities for new kinds of evaluation are discussed (virtual reality, ecological momentary assessment, etc.). Lastly, we discuss specific clinical situations with EDS in the context of ADHD as links with narcolepsy, the comorbidity with other psychiatric disorders, and the context of sluggish cognitive tempo.

Keywords: attention deficit hyperactivity disorder (ADHD), Children, excessive daytime sleepiness (EDS), assessment, neuropsychological markers

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***Correspondence:**
Stéphanie Bioulac
stephanie.bioulac@chu-bordeaux.fr

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood with a worldwide estimated prevalence of about 5% (1). It is characterized by inappropriate levels of inattention, impulsivity, and hyperactivity (2). Follow-up studies have documented the persistence of ADHD into adulthood in 50% to 65% of cases (3).

Sleep disorders have been extensively investigated in patients with ADHD, and their prevalence is reported to be in the range of 25–55% (4–6). Children with ADHD commonly exhibit additional mental health and neurodevelopmental comorbidities (7). Taurines R (8) introduces the notion of "developmental comorbidity" to highlight the importance of considering the age- and development-dependent occurrence of comorbidity in this disorder. Concerning the chronological order of occurrence, he posits that psychiatric conditions may be present before the appearance of first definite ADHD symptoms ("pre-comorbidity," such as temperament factors, sleep disturbance, autism spectrum disorders, and atopic eczema). This work underlines the importance of sleep in the context of ADHD.

The most dominant sleep disturbance observed in patients with ADHD is delayed sleep phase syndrome (DSPS) associated with difficulties in falling asleep, difficulties in awakening, and/or excessive daytime sleepiness (EDS), characterized by difficulties in maintaining adequate alertness for daily activities with sleep occurring unintentionally or at inappropriate times almost daily.

Children with ADHD report EDS and more sleep problems than typically developing children (9). Other studies confirmed this subjective EDS (10–12) and notably described insufficient sleep on school days and during weekends and a higher level of EDS (13). Contrary to subjective data, there is significantly less evidence supporting group differences in objective measures of sleepiness (major findings in **Table 1**). Moreover, both meta-analyses of Cortese in 2006 and 2009 (9, 19) demonstrated that children with ADHD showed a tendency to be sleepier than controls during the daytime but without reaching pathological levels. Thus, while all these data point to the existence of objective EDS, the nature of this EDS remains to be determined. It might be a primary disorder or the consequence of other sleep disorders. Indeed, most studies with objective measures using the maintenance sleep latency test (MSLT) excluded patients with primary sleep disorders. An exception is the study by Prihodova (17), where 10 patients presented sleep-disordered breathing and 9 had periodic limb movements (PLMD) when asleep. Furthermore, the methodology used for the MSLT differed from one study to another (see **Table 1**). The mean age of the patients must also be taken into account, with younger patients in the work by Lecendreux (15) and older ones in the study by Golan (16). Indeed, a decrease in mean sleep latency with Tanner stages has been reported in healthy subjects. Moreover, even though patients were free of treatment and had stopped treatment at least 2 days before the test, there may have been an "after-effect" on sleepiness assessment. Since ADHD is a heterogeneous disorder, identification of its phenotypes would allow better understanding of its clinical diversity. Sleep and EDS are dimensions that may be involved in specific phenotypes.

The aim of this article is to propose a narrative review of the assessment of EDS in the context of ADHD with first a summary of the subjective and objective tools used to measure it. Secondly, perspectives in terms of electroencephalogram (EEG) markers and neurofeedback are proposed. Then, possibilities for new kinds of evaluation are discussed [virtual reality, ecological momentary assessment (EMA), etc.]. Lastly, we discuss specific clinical situations with EDS in the context of ADHD as links with narcolepsy, the comorbidity with other psychiatric disorders, and the context of sluggish cognitive tempo (SCT).

TABLE 1 | Major findings of MSLT in studies with ADHD children compared to control children.

Authors	Population	MSLT	Results
Palm et al. (14)	10 children with DAMP (deficit in attention, motor control, and perception) 18 control children 6–12 years	4X 30 min 10 am, 12 am, 2 pm, and 4 pm	Mean sleep latency DAMP vs. controls: 24.8 vs. 26.5 min (NS)
Lecendreux et al. (15)	26 ADHD children (*DSM IV*) 21 control children 5–10 years Medication free	4X 20 min 10 am, 12 am, 2 pm, and 4 pm	Mean sleep latency ADHD vs. controls: 16.7+/–5.4 min vs. 18.9+/– 3 (NS) Significant differences between groups for MSLT at 10 am, 12 am, and 2 pm
Golan et al. (16)	32 ADHD children (*DSM IV*), mean age: 12.4+/–4.6 years 29 control children, mean age: 12.0+/–3.6 years Medication free	5X 30 min 8 am, 10 am, 12 am, 2 am, and 4 pm	Mean sleep latency ADHD vs. controls: 21.9+/–2.6 min vs. 27.9+/– 1.85 min ($p < .005$) Significant differences between groups for MSLT at 8 am, 10 am, 2 am, and 4 pm
Prihodova et al. (17)	26 ADHD children (*DSM IV*) 26 control children 6–12 years Medication free	5X 20 min 10 am, 12 am, 2 am, 4 pm, and 6 pm	Mean sleep latency ADHD vs. controls: 16.1+/–3.4 min vs. 17.1+/– 2.4 min (NS) No significant difference between groups for MSLT
Wiebe et al. (18)	26 ADHD children (*DSM IV*) 56 control children 7–11 years	4X 20 min 10 am, 12 am, 2 pm, and 4 pm	Mean sleep latency ADHD vs. controls: 18.4+/–2.2 min vs. 17.5+/– 3.5 min (NS) No significant difference between groups for MSLT

MSLT, maintenance sleep latency test; DSM IV, Diagnostic and Statistical Manual of Mental Disorders version IV; ADHD, attention deficit hyperactivity disorder; NS, not significant.

METHODS

We used the following search strategy. We considered papers examining the assessment of EDS in ADHD children. Only data published in English were included. We conducted a narrative review using the PubMed database up to June 2019 with the following keywords combination: "ADHD children" and ("sleepiness" or "excessive daytime sleepiness" or "hypoarousal") and "assessment". For perspectives, the search in PubMed used the following keywords: "ADHD children" and ("sleepiness" or "excessive daytime sleepiness" or "hypoarousal" or "EEG" or "arousal" or "vigilance") or "neurofeedback".

ASSESSMENT OF SLEEPINESS IN CHILDREN

Clinical Assessment

The clinical expression of EDS in children is very variable and differs from that exhibited by adults. Sleepiness can occur intermittently, often during passive activities such as reading and watching TV. At first, sleepy children may exhibit inattention, hyperactivity, or behavioral problems. This clinical presentation may mimic a patient with ADHD, which raises the issue of the differential diagnosis.

Clinical History

A clinical detailed history is crucial for the initial evaluation of a child with EDS (20, 21). First, the sleep history should include a review of the child's wake/sleep schedule on weekdays, weekends, and during summer. It is important to report the child's sleep

habits and estimate his/her sleep quantity (total daily 24 h sleep time with naps), which may be compared and interpreted with the norms for age and overall level development (21). Secondly, the clinical presentation frequently provides enough data to suggest a sleep disorder. Symptoms should be screened for sleep-disordered breathing, circadian disorder, PLMD, narcolepsy symptoms, and medical causes of EDS (21). Finally, a detailed sleep diary recording at least 2 weeks of the child's wake/sleep schedule confirms the information provided by the parents and the child. It is also important to probe the use of caffeine or other stimulants, and whether the child is taking a sedative. Sedentary habits such as watching TV, playing video games, and/or excessive snacking must be explored.

In the event of ADHD, it is important to explore the clinical history of the sleep symptoms and compare it with the prescription of stimulants. In fact, stimulants can induce insomnia but also can improve sleep disorders in the context of ADHD. Moreover, in a subgroup of children with ADHD taking methylphenidate, EDS increased a few hours after taking it. The study by Cockcroft K (22) showed that children with ADHD treated by methylphenidate demonstrated significantly higher levels of subjectively EDS 6 h after taking their stimulants both in the morning and in the afternoon.

Physical Examination

The physical examination is often normal in children with EDS. This examination can provide indications on sleep disorders such as sleep-disordered breathing in children, as in those with adenoid facies.

Subjective Evaluation Tools

There is no specific questionnaire to assess sleepiness for children with ADHD. The questionnaires adapted for children can be used in patients with ADHD.

Self-Reported Sleepiness Questionnaires

Even if EDS is a frequent symptom in sleep disorders, validated tools in pediatric populations are lacking. Three clinical rating scales have been used to assess sleepiness specifically: the Stanford Sleepiness Scale (23), the Epworth Sleepiness Scale (ESS) (24), and the Pediatric Sleepiness Scale (11). The recent review by Benmedjahed (25) on the evaluation of sleepiness in children concluded that the ESS (24) or ESS versions modified for pediatric populations was the most frequently used measure of EDS. The ESS is the most commonly used measure of EDS. The eight questions assess sleep propensity in eight different daily-life activities. This questionnaire was validated in a population of adults with narcolepsy (26). Various modified versions of the EES are currently in use in pediatric populations with situations adapted to children. Melendres et al. (27) proposed a modified ESS (two items modified from the adult version to be more applicable to children), and Johns (28) proposed another modified version of this scale for children and adolescents called the ESS-CHAD. Scores range from 0 to 32. A score > 10 indicates the need for further evaluation.

The Pediatric Daytime Sleepiness Scale (PDSS) is a validated measure for assessing daytime sleepiness in children. It was developed to assess EDS in young school-age populations. It is an eight-item questionnaire evaluating subjective experiences of daytime sleepiness (items are scored from 0 to 4). Scores range from 0 to 32 (normal score <15, cutoff for sleepiness >20).

The Teacher's Daytime Sleepiness Questionnaire (TSDQ) (29) is a teacher-reported measure. It is a six-item questionnaire rated on a three-point scale.

Self-Reported Sleep Questionnaires for Children

There are other questionnaires that assess sleep in children. In these questionnaires, some questions concern sleepiness. The most frequently used questionnaires are the following: the Sleep Disturbances Scale for children (30) (with the subscale excessive somnolence), the Sleep Disorder Inventory for children and adolescents (31), the Cleveland Adolescent Sleepiness Questionnaire (32), the Children's Sleep Habits Questionnaire, and the Pediatric Sleep Questionnaire (PSQ) (12). The reviews by Moreira GA (33) and Benmedjahed (25) confirm the dearth of available validated measures for assessing EDS in pediatric populations.

Objective Measures

Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) is the recommended test to assess objective sleepiness both adults and children (32). This test assesses the time it takes to fall asleep (objective by the first epoch scored as sleep) during the daytime. The MSLT instructs the subject to fall asleep (protocol defined in AASM Practice Parameters for Clinical Use of MSLT, 2005) (34) while lying in bed in a dark and quiet room for five 20 min periods spaced at 2 h intervals. It is technically feasible and provides clear results in developmentally normal children aged 5 years and older (35–37), which showed that average MSLT sleep latency of 10 min or less is statistically significant for healthy children 5–16 years of age on bedtime and rise time schedules that allow at least 10 h of sleep per night.

As stated in these guidelines (36): "The MSLT, preceded by nocturnal PSG, is indicated in children suspected of having hypersomnia from causes other than narcolepsy to assess excessive sleepiness and to aid in differentiation from narcolepsy" (option level). Indeed, normative data indicate that children who were prepubertal or at early pubertal stages were less likely to fall asleep during the MSLT than older adolescents. These data suggest that the standard protocol may underestimate mild degrees of sleepiness (36). Thus, some researchers have modified the standard protocol by using 30 min nap opportunities instead of 20 min for prepubertal children, but more research is needed to confirm the impact of this increased time for nap opportunities (38, 39). In children with narcolepsy, the standard MSLT protocol appears adapted. The recent work from Pizza (40) exhibited that a mean sleep latency ≤8.2 min at the MSLT are valid and reliable markers for pediatric NT1 diagnosis. Nevertheless, no normative data for sleep latency have been found in the preschool population in whom daytime napping is customary.

Actigraphy

Actigraphy monitors rest/activity cycle by integrating the occurrence and degree of arm movement activity over time. It

provides information about daytime activity, night/sleep activity (sleep patterns estimated by scoring algorithms) and activity circadian rhythm. This information can be useful in assessing sleep problems in adolescents with ADHD, especially to determine sufficient and insufficient sleep duration or stability or variability in sleep/wake patterns (41, 42). Martin-Martinez (43) propose a novel methodology for the automatic diagnosis of the combined type of ADHD based on nonlinear signal processing of actigraphy by combining a feature from the 24 h analysis, with features from the first part of sleep and the afternoon activity interval. Actigraphy cannot measure daytime sleepiness. The AASM recommendations suggest using actigraphy to assess pediatric patients with circadian rhythm sleep/wake disorder, to monitor total sleep time prior to testing with MSLT in pediatric patients with suspected central disorders of hypersomnolence and to estimate total sleep time in "adult" patients with suspected insufficient sleep syndrome. As it has been shown that children, especially boys, move during sleep more often than adults, actigraphy should be used with caution with the understanding that actigraphy has both strengths (multiday assessment, ability to detect sleep) and limitations (overestimation of wake during the sleep period) (44).

PERSPECTIVES IN TERMS OF EVALUATION OF SLEEPINESS WITH EEG CHARACTERISTICS AND RELATED TREATMENT

EEG Characteristics

Sleepiness can be evaluated objectively by power density of waking EEG. The sleepier the subject, the more alpha (8–12 Hz) (45) and/or theta (4–8 Hz) (45, 46) EEG activity with eyes open will be evident, thus giving objective information about sleepiness. The evolution of theta/alpha power (6.25–9 Hz) of waking EEG across the 24 h day reflects the sleep homeostatic process (evolution of sleep pressure during 24 h) (47).

In children and adolescents with ADHD, the most dominant waking EEG features are increased power of slow waves and/or decreased power of fast waves recorded in resting state and over the fronto-central region in comparison with healthy children/adolescents [reviewed in (48–50)]. These EEG abnormalities could represent a cortical "slowing," characterized by an increase in theta band activity (4–7 Hz) and by an increase in delta band activity (0–4 Hz) coupled with a decrease in beta band activity (14–30 Hz) [reviewed in (48–50)]. In adults with ADHD, the cortical "slowing" was maintained and was characterized by an increase in theta band activity in comparison with healthy adults (50).

This increase in theta band activity can reflect sleepiness (51) and/or cortical hypoarousal (52–54) both in children/adolescents and adults with ADHD, thereby confirming the hypoarousal model described above (55, 56). However, using the skin conductance level (SCL) as an unusual marker of drowsiness, Barry (57) suggested that alpha activity is the major band associated with arousal and not theta or beta activity in patients with ADHD. Clarke et al. (58) demonstrated that a subgroup with excess beta activity was not hyperaroused (assessed by SCL) and that the theta-to-beta ratio (TBR) was not associated with arousal.

Other studies have investigated the TBR [ratio of theta band (4–7 Hz) power divided by beta band (13–30 Hz) power [reviewed by (48, 49)]. In children/adolescents with ADHD, this ratio is abnormally higher than in healthy subjects. The meta-analysis of Snyder (59) demonstrated that TBR is remarkably robust with an effect size of 3.08 and a sensitivity and specificity greater than 90%. In view of these results, the Food and Drug Administration (FDA) approved the Neuropsychiatric EEG-Based Assessment Aid (NEBA) System (using a single electrode recording from central-midline location (Cz) and a ground electrode at the frontal-midline location (Fz) with eyes closed to obtain the TBR) as a diagnostic biomarker of ADHD in 2013. Recent studies did not confirm elevated TBR in adults with ADHD (60, 61) and suggest that it is age-dependent (50).

The review by Newson (50), which identified 65 studies in children and adults with ADHD, showed that the results differ greatly depending on the EEG power used (relative or absolute) and the recording conditions used (eyes open or closed). Consistency and validation scores in children were better in the eyes-closed condition with than with eyes open. Moreover, the studies analyzed absolute or relative power band, but the mean effect size was better with relative band than with absolute band (62, 63). Bussalb et al. (63) proposed a standardized method for calculating the TBR.

The heterogeneity in the EEG characteristics of these children could be related especially with the heterogeneity of the clinical profiles of ADHD. Already in 1996, Chabot and Serfontein (64) demonstrated three different EEG profiles in children with ADHD: one with a generalized increase in theta/alpha activity, another with an increase in alpha activity, and a third small group with an increase in beta activity.

Clarke et al. (65) identified three subgroups: the cortical hypoarousal group with elevated theta waves and decreased beta waves was coupled with symptoms of delinquent behaviors, the maturational lag group with elevated slow-wave (delta and theta) activity and decreased alpha waves, and the hyperarousal group with excessive beta activity was coupled with markers of ritualistic obsessive behaviors. These three subgroups were replicated, and an additional group was subsequently added (increased alpha and beta band power) (66).

Loo et al. (67), in a large sample of children, identified five subgroups of children with ADHD according to their resting EEG characteristics. Those with elevated slow-wave activity (delta and theta band) had higher levels of externalizing behaviors and cognitive deficits. Latent subgroups with elevated alpha and beta power had higher levels of internalizing behaviors, emotion dysregulation, and intact cognitive functioning. They demonstrated that there was no resting EEG abnormality that specifically characterizes children with ADHD or without ADHD and that there are age and gender

differences in resting EEG characteristics (68). Boys with the combined subtype had higher theta power and lower alpha power than those with the inattentive type (68). Loo et al. (51) reported that the TBR was higher in the combined subtype than in the attentive subtype. Recently, Bussalb et al. (63) demonstrated two distinct subgroups in 363 children: one characterized by an elevated TBR and the other with a normal TBR.

The results analyzing resting state cortical activity in patients with ADHD are very heterogeneous, and the identification of distinct EEG subgroups is not consensual. Nevertheless, since EEG analysis is considered to be the gold standard to quantify sleepiness, evidence is accumulating of a subgroup of patients characterized by cortical hypoarousal.

In a different approach, the group of Hegerl (69, 70) using an automatic resting EEG classification of sleepiness [Vigilance Algorithm Leipzig software (VIGALL, seven EEG-vigilance stages)] demonstrated unstable arousal regulation in children and adults with ADHD. This arousal instability was characterized by a faster decline to the low EEG-vigilance stages and more fluctuations in their stages of vigilance, i.e., higher number of stage switches. A vigilant state instability [unstable vigilant state that fluctuates (71)] is observed in healthy sleep-deprived subjects: increasing sleep drive brings about escalating state instability in attention (the effort to recover and maintain attention increases), making neurobehavioral performance increasingly variable. This state instability could explain the higher sleepiness observed in patients with ADHD.

Despite years of research and the identification of clusters, quantitative EEG is not helpful in classifying ADHD patients and cannot be considered as a diagnostic biomarker for ADHD. However, the identification of EEG subgroups may help to optimize treatments (stimulant and non-stimulant treatment, neurofeedback, exercise, and dietary intervention) and/or measure the response to them. Indeed, stimulant treatment was more efficient in the hypoarousal subgroup [for review, see Kirkland (72)] or unstable alertness (70) and was not efficient in ADHD patients with a slowed individual alpha peak frequency (73).

Treatment With Neurofeedback

Neurofeedback training (NFT) analyzes EEG activity and transforms it into instant feedback (visual and/or auditory signal) received by the user. By learning, the user self-regulates the amplitude of specific EEG activity. Neurofeedback is considered a non-pharmacological treatment option for ADHD [for review, see van Doren (74)].

The efficacy of NFB for children with ADHD is controversial. Meta-analyses published in the past decade have been contradictory (i.e., 75–78). For some authors like Thibault (75), the mechanisms involved raise questions. They suggest that neurofeedback could be an especially powerful form of placebo intervention, a kind of "superplacebo." The most common NFT protocols in the treatment of ADHD are theta/beta training, and sensorimotor rhythm (SMR, increase activation at 12–15 Hz) and slow cortical potential (SCP) protocols. SCP neurofeedback has been compared to alpha-enhancement neurofeedback. Theta/beta training aims at reinforcing reductions in theta activity and increases in beta activity and could be more appropriate and efficient in the hypoarousal subgroup of patients with ADHD (76). SMR aims to decrease delta and beta activity. In light of the hyperarousal theory of insomnia, SMR reduces the symptoms of insomnia, especially the hyperarousal. SMR could be more appropriate and efficient in the hyperarousal subgroup of patients with ADHD. Bussalb et al. (63), who, in analyzing TBR, differentiated two distinct subgroups of ADHD patients, consider that neurofeedback should be divided into two subgroups: TBR downward and SMR upward. In all cases (diagnostic biomarker, prognostic biomarker, and/or biomarker of therapeutic response), more research is needed before EEG activity can be applied in clinical settings.

NEUROPSYCHOLOGICAL MARKERS: LINKS BETWEEN ATTENTION AND SLEEPINESS

Attentional Process and Arousal Level

Arousal and attention are heterogeneous processes that interact with each other (77).

On one hand, attention corresponds to the appropriate allocation of processing resources to relevant stimuli. Attention is sub-divided into: (a) attentional orientation (the simple direction of attention to a particular stimulus); (b) selective (or focused) attention (giving attentional priority to one stimulus instead of another); (c) divided attention (dividing attention between two or more different stimuli); and (d) sustained attention (attending to one stimulus over an increasing period of time). On the other hand, arousal can be defined as the state of physiological reactivity, ranging on a continuum from sleep to alert wakefulness. Sleepiness increases the probability of the transition from wakefulness to sleep.

The arousal level controlled by homeostatic sleep pressure and the waking systems has repercussions on the attentional system, which modulates cognitive components such as executive functioning. The fundamental biological rhythm of sleep/wakefulness controlling the level of arousal is essential for maintaining optimal brain functions. Normal sleep ensures alert wakefulness, which is essential for appropriate decision-making and optimal adaptation to the environment, and is beneficial for global cognition (78).

The level of arousal can have an impact on cognitive functioning, in particular on attention and executive functions, *via* the modulation of the level of vigilance. Vigilance is a state of high efficiency of the central nervous system and is considered in a behavioral perspective as sufficient preparedness to detect and respond to critical events that occur rarely, and which are difficult to discriminate in extremely monotonous situations (e.g., detection tasks) (79). Vigilance could be the behavioral correlate of physiological alertness.

Links With Executive Functions

This hypothesis echoes the model of attention proposed by Van Zomeren and Brouwer (80), which is widely used in

neuropsychology and distinguishes an "intensity" component (vigilance/alert) and a "selectivity" component (selective attention and divided). In this model, the alert component refers to the ability to respond quickly and appropriately to the demands of the environment. It can be linked with the mobilization of energy so that the nervous system responds better. Tonic alert corresponds to a general state of arousal, which varies during the day. Phasic alert relates to the voluntary capacity to rapidly increase the general level of attention to anticipate an expected event. This vigilance/alert component modulates attention, which is a prerequisite to any other cognitive function. Thus, the influence of arousal level on cognitive functioning operates through the influence of the intensity component on component selectivity. This vigilance/alert component *via* modulation of attention also impacts executive functions. Executive functions govern all cognitive functions necessary to control and execute complex non-routine activities (81). Executive functions are a set of processes involving flexibility, decision-making, inhibition, planning, coordination, and control of thoughts and actions. Their main function is to facilitate the adaptation of the subject to the requirements and sudden fluctuations of the environment, especially when faced with new situations for which the action routines are no longer sufficient. Impairment of executive functioning results in disturbances in the complex activities of daily living.

New Dimensional Tools to Assess the Impact of Sleepiness on Cognitive Functions

Impairments in sleep and alertness frequently occur in children with ADHD (19). Moreover, children and adolescents with ADHD often exhibit symptoms of inattention. Cognitive disorders affecting vigilance, attention, cognitive control, and executive functions are usually observed (82–85), leading to difficulties in performing complex daily life activities (86). Daily life is punctuated by a variety of complex activities related to different areas for children and adolescents (education, pedestrian safety), which all require adequate levels of alertness and attention.

Therefore, the clinical evaluation of sleepiness in ADHD could be achieved in the future by measuring the influence of arousal level on cognitive functioning (vigilance, attention, executive functions), including by measuring these functions when performing complex activities of daily living. The measurement of the level of sleepiness could be considered from a physiological to a psychological–behavioral sphere.

Neuropsychological assessment, notably involving vigilance, could be informative about the level of sleepiness. Calhoun, Fernandez-Mendoza, et al. (87) showed, in a large general population of young children, that parent-reported EDS was associated with impairment in cognitive and behavioral functioning. The Continuous Performance Test (CPT) is the most widely used task to assess vigilance, attention and impulsivity in children with ADHD (88). The KITAP (Attention Assessment Battery—Child Version) allows assessment of the attentional and executive performance of school-age children with validated standardized tests. The tests allow the evaluation of the "intensity" component of attention such as alertness and sustained attention, and the "selectivity" component such as selective attention and divided attention, as well as executive functions such as mental flexibility or inhibition.

An innovative approach could be to use the technology of virtual reality to determine the level of sleepiness as a function of cognitive alteration in ADHD children and adolescents immersed in the ecological tasks of everyday life. A study using a simulated driving task showed that not only the objective level of alertness but also inhibitory control deficits contribute independently to highway driving impairment in adults with ADHD (86). Virtual reality simulation is a technology that could allow the influence of arousal level on cognitive functioning (attention and executive functions) to be measured through vigilance and its impact on complex activities of daily life. In parallel, the monitoring of eyelid frequency and pupil diameter (eye-tracking system) or facial dynamic changes (89) could be promising (90).

Another innovative approach could be the use of EMA to evaluate daily and diurnal variations in sleepiness and repercussions on daily life such as in the emotional, cognitive, behavioral, social, and physical domains (91, 92) in ADHD.

EXCESSIVE DAYTIME SLEEPINESS IN CHILDREN WITH ADHD

The links between ADHD and sleep disorders remain unclear. While specific sleep disorders are a frequent comorbid condition associated with ADHD according to a categorical approach, they can also induce ADHD-like symptoms if considered dimensionally and are thought to be the consequence of EDS. Given the complexity of the interaction between ADHD and sleep, the team of Miano (93–95) identified five sleep phenotypes in ADHD: a sleep phenotype characterized by a hypo-arousal state "narcolepsy-like," another associated with delayed sleep onset latency, a phenotype related with sleep-disordered breathing, another associated with restless legs syndrome and/or PLMD, and a phenotype related to epilepsy/or EEG interictal discharges.

Links With Narcolepsy

Narcolepsy, which is characterized by EDS and abnormal REM sleep, is a chronic sleep disorder caused by a deficiency of hypocretin/orexin-producing neurons within the lateral hypothalamus (type 1 narcolepsy with cataplexy). In type 2 narcolepsy, where cataplexy is absent and orexin levels normal, the physiopathology is unknown. The "narcolepsy-like" phenotype (ADHD and hypersomnia) described by Miano could be part of a subtype of type 2 narcolepsy (96). A body of evidence reinforces the links between ADHD and narcolepsy, and ADHD symptoms are more frequent in children (97) or adults (98) with narcolepsy than in control subjects. A systematic review demonstrated that the prevalence of ADHD symptoms in narcolepsy was >30% (99).

In addition, adult narcoleptics present more childhood ADHD than controls (100, 101). Using MSLT or EEG features, some authors have hypothesized the existence of a dysfunction in arousal in the pathophysiology in ADHD (15, 65, 100). A physiopathological model for ADHD involves a deficit in arousal (hypo-arousal model). Children with ADHD have greater difficulty in falling asleep, awakening, and/or maintaining adequate daytime alertness than control children, and use hyperactivity as a strategy to stay awake and alert in order to counteract the tendency to fall asleep (55, 56).

Moreover, high levels of EDS and shorter REM latency are classically both potential signs of narcolepsy (102). In the study by Diaz-Roman (10), polysomnographic recordings showed that children with ADHD presented significantly greater general sleep problems than control subjects and shorter REM latency in the ADHD group. Nevertheless, other studies failed to find differences in REM latency between children with and without ADHD in polysomnography (PSG) (9, 103). A recent study found that serum orexin A levels were significantly lower in drug-naive children with ADHD, especially in the attention deficit dominant subgroup (104). As suggested by Cortese (105), orexin neurons located in the perifornical and dorsomedial hypothalamic areas (implicated in arousal) could be hypoactivated, while those located in the lateral hypothalamus (involved in reward processing, stimulating feeding, and other reward-seeking behaviors) could be overactivated in patients with ADHD.

Specific Clinical Situations

"Sluggish cognitive tempo" (SCT) is a behavioral construct characterized by a set of symptoms as sluggish, under-motivated, lethargic, slowed, and/or forgetful behavior (106, 107). This condition is strongly associated with ADHD (notably with the inattentive subtype), although the meta-analysis by Becker et al. (106) identified SCT symptoms that were distinguishable from ADHD inattentive symptoms. Some authors hypothesized that SCT symptoms are specifically related with sleep problems and EDS (106, 108, 109). SCT symptoms were found to overlap with EDS in patients with ADHD but were distinct from sleep problems. Objective assessments of EDS may help to better phenotype these subjects and to propose other therapeutic strategies, to the extent that this condition predicts non-response or poorer response to methylphenidate in children with ADHD (110). Pharmacological treatment such as wakefulness drugs might be more indicated in this subgroup of patients.

Comorbidity

Moreover, SCT is strongly associated with internalizing symptoms, especially depressive symptoms. It is important to evaluate sleep in the context of comorbidity (internalizing and externalizing disorders), as mentioned by Spruyt (111) and by Diaz-Roman (10). Comorbid conditions may also play a role in EDS in children. Diaz-Roman (10) found significant correlations between psychopathology and sleep measures with a significant correlation between scores on the Child Behavior Checklist (a questionnaire completed by the parents which evaluates internalizing and externalizing problems) and EDS and general sleep problems. This finding was in line with previous data supporting the link between sleep problems and children with ADHD with comorbid anxiety and depression (112), and with a study by Mulraney M et al. (113) who reported links between emotional problems and sleep disturbances in ADHD. When assessing sleep in children with ADHD, it is also necessary to evaluate other psychiatric comorbidities, notably internalizing problems such as depression and anxiety that seem to play a role in the expression of EDS in these children.

In conclusion, ADHD is a heterogeneous disorder in terms of its clinical presentation and underlying physiopathological mechanisms. EDS, a usual complaint in children with ADHD, seems to be a pertinent clinical dimension. Thus, the identification of a specific "sleepy ADHD" phenotype appears to be both a clinical and objective maker. The identification of EEG subgroups would help in defining various phenotypes and optimizing treatments. More studies are needed in children with ADHD to assess EDS. The interactions between EDS and the attentional process and executive functions should also be probed.

AUTHOR CONTRIBUTIONS

SB wrote sections *Introduction* and *Assessment of Sleepiness in Children* of the manuscript. JT wrote section *Perspectives in Terms of Evaluation of Sleepiness With EEG Characteristics and Related Treatment* of the manuscript. PS wrote section *Neuropsychological Markers: Links Between Attention and Sleepiness* of the manuscript. PP wrote the *Introduction* and did a rereading of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Pediatric Sleep Tools: An Updated Literature Review

Tabitha Sen[1] *and Karen Spruyt*[2*]

[1] School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia, [2] Lyon Neuroscience Research Center, INSERM U1028-CNRS UMR 5292, University Claude Bernard, School of Medicine, Lyon, France

Since a thorough review in 2011 by Spruyt, into the integral pitfalls of pediatric questionnaires in sleep, sleep researchers worldwide have further evaluated many existing tools. This systematic review aims to comprehensively evaluate and summarize the tools currently in circulation and provide recommendations for potential evolving avenues of pediatric sleep interest. 144 "tool"-studies (70 tools) have been published aiming at investigating sleep in primarily 6–18 years old per parental report. Although 27 new tools were discovered, most of the studies translated or evaluated the psychometric properties of existing tools. Some form of normative values has been established in 18 studies. More than half of the tools queried general sleep problems. Extra efforts in tool development are still needed for tools that assess children outside the 6-to-12-year-old age range, as well as for tools examining sleep-related aspects beyond sleep problems/disorders. Especially assessing the validity of tools has been pursued vis-à-vis fulfillment of psychometric criteria. While the Spruyt et al. review provided a rigorous step-by-step guide into the development and validation of such tools, a pattern of steps continue to be overlooked. As these instruments are potentially valuable in assisting in the development of a clinical diagnosis into pediatric sleep pathologies, it is required that while they are primary subjective measures, they behave as objective measures. More tools for specific populations (e.g., in terms of ages, developmental disabilities, and sleep pathologies) are still needed.

Keywords: sleep duration, sleep quality, sleep hygiene, questionnaire, child, review

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***Correspondence:**
Karen Spruyt
karen.spruyt@inserm.fr;
karen.spruyt@univ-lyon1.fr

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INTRODUCTION

There is significant power in the efficiency and cost-effective nature of questionnaires and surveys as contributors to aetiological discoveries of a wide range of medical disorders. These instruments however, do not always possess the objective nature of medically advised and established tools, e.g., polysomnography, and can become a hindrance to adequate diagnoses, particularly when neglecting recommendations of their development (1). Despite these problems, there has been considerable effort to transform the structure of health questionnaires, specifically in the field of pediatric sleep, to reflect a systematic approach of the highest concordance to medical diagnostic standards.

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention deficit hyperactivity disorder; ASDC, Association of Sleep Disorders Centers classification; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; ICSD, International Classification of Sleep Disorders; PSG, polysomnography; RLS, Restless Legs Syndrome; ROC, Receiver Operating Characteristic curve.

The systematic review by Spruyt et al. (2, 3) in 2011, publicly summarized the shortcomings of questionnaires and their developmental standards while advising a thorough procedure in which to follow to adequately evaluate or develop a tool.

Since this time, a variety of tools have been established, both adhering to and overlooking the recommended steps. More detailed information on the 11 steps can be found in Spruyt et al. (3). Briefly, *Step 1* is to reflect on the variable(s) of interest and targeted sample(s). *Step 2* is to consider the research question that the instrument will be used to address. Thus, the goal of this step is to reflect on whether the tool will be suitable to collect the type of data required to address your hypothesis. *Steps 3* (response format) and *Step 4* (items) build on the two preceding steps. They allow us to reflect not only on "which" questions and "which"' answers assesses the variable(s) of interest, but also on "how" a question is formulated and "how" it can be answered. The common goal of steps 1–4 is that we want the underlying "concepts" and/or "assumptions" contained in the questions, such as language (e.g., jargon), meaning and interpretation of the wording to be identically understood by all respondents. Getting as close as this ideal as possible will minimize errors of comprehension and completion. *Step 5* involves piloting of your drafted tools. Piloting also prevents disasters with the actual data collection. In fact, *Steps 2–5* should be an iterative process, meaning that we do them repeatedly, until a consensus has been reached among experts and/or respondents with descriptive statistics underpinning those decisions. Assessing the performance of individual test items, separately and as a whole, is *Step 6* (item analysis). There are two main approaches to item analysis: classical test theory and the item-response theory, either of which should be combined with missing data analysis. The next step is about identifying the underlying concepts of the tool (*Step 7* Structure) because only rarely is a questionnaire unidimensional. *Steps 8* and *9* are about assessing the reliability and validity, respectively. Reliability does not imply validity, although a tool cannot be considered valid if it is not reliable! Several statistical, or psychometric, tests allow us to assess a tool's reliability and validity (cfr. textbooks written on this topic). For instance, validation statistics of the tool may involve content validity, face validity, criterion validity, concurrent validity or predictive validity. *Step 10* is about verifying the stability, or robustness, of the aforementioned steps. It is the step in which you assess the significance, inference, and confidence (i.e., minimal measurement error) of your tool, using the sample(s) for which it was designed. *Step 11* involves standardization and norm development, allowing large-scale usage of your tool.

This review aims to conclude the trends associated with these questionnaires, and reinforce the importance of certain stages of tool development and highlight the direction of research that would be ideal to follow.

MATERIALS AND METHODS

To achieve consistency and retrieve relevant studies to the Spruyt (2, 3) review, the search terms(*) and databases were mirrored; *"Sleep" AND ("infant" OR "child" OR "adolescent") AND ("questionnaire," "instrument," "scale," "checklist," "assessment," "log," "diary," "record," "interview," "test," "measure").* The databases included PubMed, Web of Science (WOS), and EBSCOHOST (per PRISMA guidelines). Additional limitations to the search criteria were applied for date and age range of the respective study populations. Database-wide searches were conducted between 18th of April 2010 (Spruyt, 2011 publication date of search) and 1st of January 2020. Age categories listed in PubMed filters between 0 and 18 years were also applied to restrict the search to pediatric populations alone. Contrastingly, language criteria were not specified but post hoc constrained to English. Papers in other languages could not be evaluated by one of the authors, in case a consensus on the psychometric evaluation was needed. The search for relevant studies extended to authors in listserver groups PedSleep2.0 and the International Pediatric Sleep Association (IPSA) in order to achieve maximal inclusion. The refinement of these study characteristics ensured that the systematic review would evaluate relevant studies in pediatric tool development, adaptation, and validation. Final search count was sizeable (refer to **Figure 1**).

Full-text access was achieved through the literary database "Library Genesis" or author contact if necessary (see Acknowledgments). All flagged citations were then manually screened for relevant keywords in their respective titles, abstracts and methods to further refine studies relevant to the systematic review—these being 11 psychometric steps (2, 3) and 7 sleep categories (sleep quantity, sleep quality, sleep regularity, sleep hygiene, sleep ecology, and sleep treatment) (4). Consequently, independent studies were highlighted and screened, and each study's descriptive variables were extracted and collated. Any absence of indispensable information regarding the tools use was addressed through contact of authors.

Statistical Analysis

A total of 11 steps (2) and 7 sleep categories (4) were extracted and were statistically analyzed for frequency and descriptive assessment (refer to **Tables 1** and **2**). Any variables unmentioned or neglected were described as "empty," and tabulated as such in the forthcoming interpretations. Continuous variables will be described as mean values (± standard deviation) and categorical variables will be shown as absolute and relative values. Statistical analyses were performed with Statistica version 13 (StatSoft, Inc. (2009), STATISTICA, Tulsa, OK).

RESULTS

Studies Included

As described by **Figure 1**, the total number of studies generated from the database search was sizeable, at n=341. Key emphasis of a pediatric diagnostic tools' use, development or validation deemed it eligible for review, as well as the general translation and consequent adaptation of any pediatric questionnaire, survey, log, diary, etc. The titles and abstracts of each report

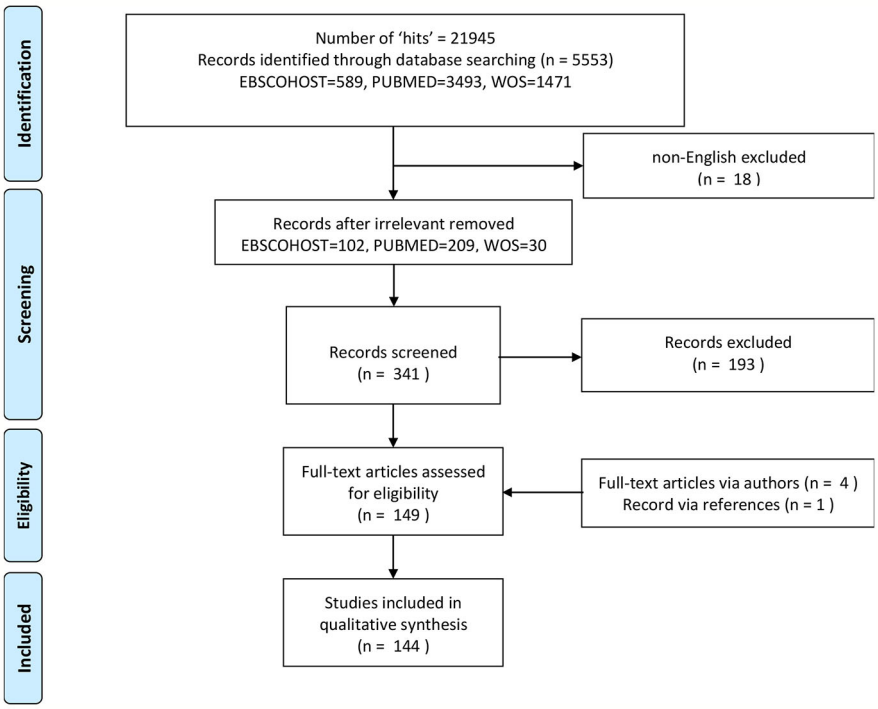

FIGURE 1 | Flowchart of studies included.

were screened accordingly, resulting in the omission of 193 articles and final inclusion of 144 articles. Exported abstracts were then assigned their respective full-text. Complete text access was not available for 14, while retrieved from either the literature database "Library Genesis" or *via* author permission (n=4, see Acknowledgments), leaving 144 or 70 tools eligible for review based on the search conducted.

A more thorough examination of methodological processes was then executed to reveal categories to which each article was suitably assigned for ease of future assessment (refer to **Table 1**); "*New Development (N)*," "*Psychometric Analysis (P)*," and "*Translation (T)/Adaptation (A)*," or a combination thereof. Each paper was assigned to the appropriate criteria; "*Development*" if the report's main purpose was to produce an unprecedented tool, "*Psychometric Analysis*" if the explicit objective was to assess the reliability and validity of said tool, and "*Translation and/or Adaptation*" for all studies that in any way translated or altered a tool to suit a specific population, culture, and/or nation. Overall (**Table 2**), 36.8% of the studies aimed to merely psychometrically evaluate a pediatric sleep tool, while 9% additionally translated it. 24.3% of the studies aimed to independently translate while 4.2% additionally adapted their tool. As for lone adaptations, there were 4.2% of studies that performed this, while 18.8% created an entirely new tool. 1.4% of the studies conducted both a new tool development and translation and alike, 0.7% of studies adapted their new tool to particular population, culture, or other.

Study Characteristics

The structural organization and publication features of each study are detailed in **Table 1**. In the **Appendix** are the acronyms for each tool reviewed. Since the 2011 Spruyt review on pediatric diagnostic and epidemiological tools, approximately 144 "tool"-studies have been published. The focus into pediatric tool evaluation peaked in 2014 where 16.7% of all studies were conducted, closely followed by 2017 (13.9%), and 2016 and 2019, each at 13.2% as well as 2015 at 12.5%. As for the remaining years of this decade, between 2010 and 2014, 2018 , the percentage of total studies published ranged from 0.7%–9.7% (n=1–10) per year. Over a third of the total studies were published in Europe (38.9%), followed by North America (25%), Asia (18.1%), Middle East (2.8%), South America (7.6%), Australia and Oceania (6.3%), and the United Kingdom (1.4%).

Across all 144 studies evaluated, it was evident that sleep tools were predominantly developed and evaluated for a combination of children and adolescents between the ages of 6–18 years (27.1%), followed closely by tools for adolescents 13–18 years at 22.2% and children 6–12 years alone at 16.7%. Only 10 studies covered the 0–18 years age range, and one did not define its range (82). Meanwhile, only 5.6% of all the studies assessed tools for preschool-aged children (2–5 years) alone and 1.4% for infants (0–23 months) alone. As for the studies remaining, a combination of age ranges was investigated with the most predominant combination being both preschool children and children (ages of 2–12 years) at 8.3% of the total studies. The

TABLE 1 | Basic information of studies evaluated.

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
AIS (5)	Chung	2011	Hong Kong, China	1,516	12–19	8	three-point Likert	self	in the last month	no	1,2,4,5,6,7,8,9
setting : three schools with different levels of academic achievement											
ASHS (6)	Storfer-Isser	2013	Boston, USA	514	16–19	32	six-point ordinal	self	in the past month	no	1,2,6,7,8,9,10
setting : Cleveland Children's Sleep and Health Study, a longitudinal, community-based urban cohort study											
ASHS (7)	de Bruin	2014	Amsterdam, Netherlands	186 normal and 112 insomnia	12–19	28	six-point rating	self	in the past month	yes	1,2,8,9
setting : a community sample of adolescents and a sample of adolescents with insomnia (registered through a website)											
ASHS (8)	Chehri	2017	Basel, Switzerland	1,013	12–19	24	six-point rating	self	in the past month	no	1,2,4,6,7,8,9,10
setting : classroom – individual											
ASHS (9)	Lin	2018	Qazvin, Iran	389	14–18	24	six-point rating	self	in the past month	no	1,2,4,5,6,7,8,9,10
setting : classroom – individual											
ASQ (10)	Arroll	2011	Auckland, New Zealand	36	>15	30	mixed	self	mixed	yes	1,2,3,4,5,6,9
setting : primary care patients											
ASWS (11)	Sufrinko	2015	north Carolina, USA	467	12–18	10		self		no	1,2,6,7,8,9,10
setting : classroom – individual											
ASWS (12)	Essner	2015	Seattle, USA	491	12–18	28	six-point Likert	self	previous month	no	1,2,7,8,9
setting : data were pooled from five research studies with heterogeneous samples of adolescents with nondisease-related chronic pain, sickle cell disease, traumatic brain injury, or depressive disorders, as well as adolescents who were otherwise healthy, from three sites in the Northwest and Midwestern United States.											
BEARS (13)	Bastida-Pozuelo	2016	Murcia, Spain	60	2–16	7	yes/no	parent		no	1,2,4,6,9
setting : first time visit at National Spanish Health Service's mental healthcare centre											
BEDS (14)	Esbensen	2017	Ohio, USA	30	6–17	28	five-point Likert	parent	in last 6 months	no	1,2,6,8,9
setting : take-home questionnaires and sleep diary											
BISQ (15)	Casanello	2018	Barcelona, Spain	87	3–30 months	14	mixed	parent		yes	1,2,4,5,6,8,9
setting : clinic based (self-report and follow-up interview)											
BRIAN-K (16)	Berny	2018	Porto Alegre, RS, Brazil	373	7–8	17	three-point Likert	parent	in the last 15 days	yes	1,2,3,4,5,6,7,8,9
setting : classroom – individual											

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
CAS-15 (17)	Goldstein	2012	New York, USA	100	2–12	15	mixed	clinician		yes	all steps except 10
setting : children referred to the pediatric otolaryngology outpatient offices for evaluation of snoring and suspected sleep disordered breathing											
CBCL (18)	Becker	2015	Cincinnati, OH, USA	383	6–18	7 sleep items	three-point Likert	parent/self		no	1,2,6,8,9
setting : referred patients to tertiary-care pediatric hospital											
CCTQ (19)	Dursun	2015	Erzurum, Turkey	101	9–18	27	mixed	parent	on work and free days	no	1,2,6,8,9
setting : sample from clinical (outpatient psychiatry) and community settings											
CCTQ (20)	Ishihara	2014	Tokyo, Japan	346	3–6	27	mixed	parent	on work and free days	no	1,2,6,8,9
setting : mailed to parents *via* kindergartens											
CCTQ (21)	Yeung	2019	Hong Kong, China	555	7–11	27	mixed	parent		no	1,2,3,4,5,6,8,9
setting : five primary schools in the Hong Kong SAR											
CRSP (22)	Cordts	2016	Kansas, USA	155	9.82	62		self		no	1,2,6,7,9,10
setting : take-home questionnaire/classroom group											
CRSP (23)	Meltzer	2013	Denver, Colorado, USA	456	8–12	60	mixed	self	mixed	yes	1,2,4,8,9,10
setting: primary care pediatricians' offices, an outpatient pediatric sleep clinic, community flyers and advertisements, two independent Australian schools, two different pediatric sleep laboratories, and outpatient clinics or inpatient units of a children's hospital for oncology patients											
CRSP (24)	Meltzer	2014	Denver, Colorado, USA	570	13–18	76	mixed	self	mixed	no	1,2,4,7,8,9,10
setting: from several studies: pediatric sleep clinics at two separate children's hospitals, outpatient clinics and inpatient units of a children's hospital for oncology patients, two independent Australian schools, an Internet based sample of adolescents, including those with asthma (categorized in clinic group) and those without asthma (categorized in community group)											
CRSP (25)	Steur	2019	Amsterdam, Netherlands	n= 619 general n=34 clinic	7–12	26 (total score on 23)	three-point	self	one week	no (English items listed)	1,4,7,8,9,10,11
setting : online data collection in cooperation with the Taylor Nelson Sofres Netherlands Institute for Public Opinion, an outpatient sleep clinic											
CRSP-S (26)	Meltzer	2012	Denver, Colorado, USA	388	8–12	5	5-point rating	self		no	1,2,6,7,8,9,10
setting : primary care pediatrician's offices: the Sleep Clinic at the Children's Hospital of Philadelphia (CHOP), through community flyers and advertisements in the Delaware Valley, through two independent schools in Adelaide, South Australia, while waiting for an overnight polysomnography at CHOP or the Children's Hospital of Alabama, or during outpatient clinic visits or on the inpatient unit at St. Jude Children's Research Hospital											
CSAQ (27)	Chuang	2016	Taichung, Taiwan	362	8–9	44	four-point Likert	parent		no	all steps except 11
setting : elementary school											
CSHQ (28)	Markovich	2015	Halifax, Canada	30	6–12	45 (33 scored question)	three-point Likert	parent	in the previous week	no	1,2,8,9
setting : data were collected from two larger studies											
CSHQ (29)	Dias	2018	Braga, Portugal	299	2 weeks–12 months	48	four-point Likert	parent	mixed	yes	1,2,4,5,6,7,8,9
setting : women were contacted at the third trimester of pregnancy; send by email											
CSHQ (30)	Ren	2013	Beijing, China	912	6–12	33	three-point Likert	parent		no	1,2,6,7

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
setting : Parent meeting at primary and elementary students in Shenzhen											
CSHQ (31)	Liu	2014	Chengdu, China	3,324	3–6	33	three-point Likert	parent	a typical week	no	1,2,6,7,8,9,10
setting : 21 mainland Chinese cities; take-home questionnaire											
CSHQ (32)	Tan	2018	Shanghai, China	171	4–5	33	three-point and four-point Likert	parent		no	1,2,6,7,8,9,10
setting : distributed at the schools; take-home questionnaire											
CSHQ (33)	Waumans	2010	Amsterdam Netherlands	1,502	5–12	33	four-point Likert	parent		no	1,2,4,5,6,7,8,10
setting : primary schools and daycare centers											
CSHQ (34)	Steur	2017	Amsterdam Netherlands	201	2–3	33	three-point Likert	parent	1-week	no	1,2,4,6,7,8,10,11
setting : online questionnaire *via* a Dutch market research agency											
CSHQ (35)	Mavroudi	2018	Thessaloniki, Greece	112	6–14	45	four-point Likert	parent	a "common" recent week	no	1,2,8,9
setting : patients were ascertained sensitive to a variety of aeroallergens											
CSHQ (36)	Johnson	2016	Florida USA	310 (177+34+99)	2–10	33	a 1–3 rating + yes/no	parent		no	1,2,6,7,8
setting : enrolled from three study sites : 24-week, multisite randomized controlled trial of parent training (PT) versus parent education; an 8-week randomized trial of a PT program; Autism Speaks Autism Treatment Network											
CSHQ (37)	Sneddon	2013	Vancouver, BC, Canada	105	2–5	33	three-point Likert	mother		no	1,2,6,7,8,9
setting : early intervention programs, outpatient mental health clinics; general community											
CSHQ (short) (38)	Masakazu	2017	Tokyo, Japan	178; 432; 330	6–12	19	three-point rating	parent	a typical recent week	no	1,2,3,4,5,6,8,9,10
setting : different collection times/settings: elementary school; pediatric psychiatric hospital; community											
CSHQ (39)	Schlarb	2010	Tübingen, Germany	298;45	4–10	48	three-point + yes/no	parent		no	1,2,4,6,7,8,9
setting : community sample *via* schools, clinical sample											
CSHQ (40)	Silva	2014	Lisbon, Portugal	315	2–10	33	three-point rating	parent	a recent more typical week	no	1,2,4,5,6,7,8,9
setting : community sample											
CSHQ (41)	Lucas-de la Cruz	2016	Cuenca, Spain	286	4–7	33	three-point rating	parent		no	1,2,4,6,7,8,9
setting : cross-over cluster randomized trial from 21 schools											
CSHQ (42)	Fallahzadeh	2015	Kashan, Iran	300	5–10	33	three-point rating	parent		no	1,2,4,5,6,7,8,9
setting : public and private schools											

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
CSHQ (43)	Loureiro	2013	Lisbon, Portugal	574	7–12	26	three-point Likert	parent		no	1,2,4,5,6,8,9
setting : community and clinical samples											
CSHQ (short) (44)	Bonuck	2017	Boston, Masacheusettes	151;218	4–10; 24–66 months	23		parent		no	1,2,6,9
setting : clinic sample data (two datatest were reused for this study: Owens (1997/8) and Goodlin-Jones (2003-5), respectively)											
CSHQ (14)	Esbensen	2017	Cincinnati, OH, USA	30	6–17	33	three-point Likert	parent		no	1,2,6,8,9
setting: community-based study in children with Down syndrome											
CSM (45)	Jankowski	2015	Warsaw, Poland	952	13–46	13	mixed	self		yes	1,2,4,6,8,9
setting : residents from Warsaw and Mielec districts											
CSRQ (46)	Dewald	2012	Amsterdam Netherlands	166; 236	12.2–16.5; 13.3–18.9	20	ordinal response categories ranging from 1 to 3	self	previous 2 weeks	no	1,2,4,6,7,8,10
setting : five high schools in and around Amsterdam and from five high schools in Adelaide and Outer Adelaide											
CSRQ (47)	Dewald-Kaufmann	2018	Amsterdam Netherlands	298		20	ordinal response categories ranging from 1 to 3	self	previous 2 weeks	no	1,2,9,11
setting : participants were recruited from high schools around Amsterdam; referred to the Centre for Sleep–Wake Disorders and Chronobiology of Hospital Gelderse Vallei in Ede, the Netherlands; adolescents who received cognitive behavioural therapy for their sleep onset and maintenance problems (see de Bruin et al)											
CSWS (48)	LeBourgeois	2016	Boulder, CO, USA	161; 485; 751; 55;85	2–8 (different across studies)	25 (different across studies)	four-point (different across studies)	parent		no	all steps except 11
setting : 5 studies with independent samples (different across studies)											
DBAS (49)	Lang	2017	Basel, Switzerland	864	17.9	16	10-point Likert	self		no	1,2,4,6,7,8,9,10
setting : students in vocational education and training; in a classroom setting											
DBAS (50)	Blunden	2012	Queensland Australia	134	11–14	10	mixed	self		no	1,2,3,4,5,6,7,8,9
setting : From sleep education intervention											
ESS (51)	Krishnamoorthy	2019	Puducherry, India	789	10–19	8	four-point Likert	self		no	all steps
setting : villages of rural Puducherry, a union territory in South India											
ESS (52)	Crabtree	2019	Memphis, Tennessee	66	6–20	8	four-point Likert	self	in various everyday situations	no	1,2,8,9,11
setting : children and young adults (ages 6 to 20 years) were assessed by the M-ESS after surgical resection, if performed, and before proton therapy											
ESS-CHAD (53)	Janssen	2017	Victoria, Australia	297	12–18	8	four-point Likert	self	thinking of the last two weeks	no	1,2,6,7,8,9,10
setting : Part of a broader research project; schools in regional Victoria (qualtrics survey)											

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
FoSI (54)	Brown	2019	Washington, DC, USA	147	14–18	11	five-point Likert	self	last month	no	1,2,6,7,8,9,10
setting : two school-based health centers in the Washington Metropolitan Area											
I SLEEPY (55)	Kadmon	2014	Ontairo, Canada	150	3–18	8	yes/no	parent/self		yes	1,2,4,5,6,9
setting : referred for evaluation at a pediatric sleep clinic											
IF SLEEPY (55)	Kadmon	2014	Ontairo, Canada	150	3–18	8	yes/no	parent/self		yes	1,2,4,5,6,9
setting : referred for evaluation at a pediatric sleep clinic											
I'M SLEEPY (55)	Kadmon	2014	Ontairo, Canada	150	3–18	8	yes/no	parent/self		yes	1,2,4,5,6,9
setting : referred for evaluation at a pediatric sleep clinic											
ISI (5)	Chung	2011	Hong Kong, China	1,516	12–19	8	five-point Likert	self	in last 2 weeks	no	1,2,4,5,6,7,8,9
setting : three schools with different levels of academic achievement											
ISI (56)	Kanstrup	2014	Solna, Sweden	154	10–18	5	five-point rating	self	past 2 weeks	no	1,2,4,6,8,9
setting : patients with chronic pain referred to a tertiary pain clinic upon first visit											
ISI (57)	Gerber	2016	Basel, Switzerland	1,475 adolescents, 862 university students and 533 adults	11–16	7	eight-point Likert	self		yes	1,2,4,6,7,8,9,10
setting : 3 cross-sectional studies; *via* schools											
JSQ (58)	Kuwada	2018	Osaka, Japan	4,369; 100	6–12	38	mixed (6 point intensity rating)	parent		no	1,2,7,8,9,10,11
setting : 17 elementary schools; 2 pediatric sleep clinic											
JSQ (preschool) (59)	Shimizu	2014	Osaka, Japan	2,998;102	2–6	39	six-point Likert	parent		no	1,2,4,6,7,8,9,11
setting : private kindergarten, nursery school, and recipients of regular physical examinations at the age of 3 years; two pediatric sleep clinics											
LSTCHQ (60)	Garmy	2012	Lund, Sweden	116 child respondents; 44 parent respondents	6–13	11	mixed	parent/self		yes	1,2,4,5,8,9
setting : school-based distriution											
MCTQ (61)	Roenneberg	2003	Basel, Switzerland	500 (142 being <21years)	6–18	~9*	seven-point rating; mixed	self	free/work days	yes	1,2,5,6
setting : distributed in Germany and Switzerland in high schools, universities, and the general population. This paper was added because of its relevance despite being outside the timeframe of the current review											
MEQ (62)	Cavallera	2015	Milan, Italy	292	11–15	17		self		no	1,2,4,5,7,8,9
setting : convenience school-based samples											
(r)MEQ (63)	Danielsson	2019	Uppsala, Sweden	671	16–26	5		self		no	1,2,6,7,8,9
setting : selected randomly from the Swedish Population Register											
aMEQ (64)	Rodrigues	2016	Aveiro district, Portugal	300	12–14	19	mixed	self		no	1,2,4,5,6,8,9,11

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
setting: 80% public and 20% private schools from the district of Aveiro											
aMEQ-R (65)	Rodrigues	2019	Aveiro district, Portugal	n1=300 (same 2016) n2= 217	12–14	10	mixed	self		no	1,2,4,5,6,8,9,11
setting: several schools of the Aveiro district											
MESC (66)	Diaz-Morales	2015	Madrid, Spain	5,387	10–16			self		no	1,2,4,6,7,8,9,10
setting: public high schools in Madrid and the surrounding area											
MESSi (67)	Demirhan	2019	Sakarya, Turkey	1,076	14–47	15	five-point Likert	self		yes	1,4,5,7,8,9,10
setting: high school and university students											
MESSi (68)	Weidenauer	2019	Tuebingen, Germany	215	11–17	15	five-point Likert	self		yes	1,6,8,9,10
setting: three different gymnasia (highest stratification level of school teaching) in SW Germany, Baden-Wuerttemberg											
My Sleep and I (69)	Rebelo-Pinto	2014	Lisbon, Portugal	654	10–15	27	five-point Likert	self		no	1,2,3,4,7,8,9,10
setting: schools in Portugal part of project Sleep More to Read Better											
My children's sleep' (69)	Rebelo-Pinto	2014	Lisbon, Portugal	612	21–68	27	five-point Likert	parent		no	1,2,3,4,7,8,9,10
setting: schools in Portugal part of project Sleep More to Read Better											
NARQoL-21 (70)	Chaplin	2017	Gothenburg, Sweden	158	8–13; 15–17	21	five-point Likert	self		no	all steps
setting : patient and control group											
NSD (71)	Yoshihara	2011	Tochigi, Japan	40	6 months–6 years	2		parent	diary	yes	1,2,3,4,5,6
setting : take home diary											
NSS (72)	Ouyang	2019	Beijing, China	n=53 pediatric n= 69 adult	>8 years	15				no	1, 2, 7, 8, 9
setting : sleep lab											
OSA Screening Questionnaire (73)	Sanders	2015	Southampton, UK		infancy to 6 years	33		parent	over a week	yes	1,2,3,4,5,6,9
setting : *via* a local Down syndrome parent support group											
OSA-18 Questionnaire (74)	Huang	2015	Hsinchu, Taiwan	163	6–12	18	seven-point ordinal	parent	past 4 weeks	yes (English)	1,2,4,7,8,9,10
setting : *via* schools											
OSA-18 Questionnaire (75)	Kang	2014	Taipei, Taiwan	109	2–18	18	seven-point ordinal	parent		yes	1,2,4,6,8,9
setting : recruited from the respiratory, pediatric, psychiatric, and otolaryngologic clinics											
OSA-18 Questionnaire (76)	Bannink	2011	Rotterdam, Netherlands	119 patients; 162 (child);459 parent	2–18	18; OSA-12 in children, OSA-18 in parents	seven-point ordinal	parent/self		yes	1,2,4,6,8,9

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
setting : patients with syndromic craniosynostosis; convenience sample of parents											
OSA-18 Questionnaire (77)	Mousailidis	2014	Athens, Greece	141	3–18	18	seven-point ordinal	parent		yes	1,2,4,6,8,9
setting : children who were referred for overnight polysomnography at the Sleep Disorders Laboratory											
OSA-18 Questionnaire (78)	Fernandes	2013	Guimarães, Portugal	51	2–12	18	seven-point ordinal	parent	past 4 weeks	yes (English)	1,2,4,5,6,8,9
setting : sleep clinic											
OSA-18 Questionnaire (79)	Chiner	2016	Alicante, Spain	60	2–14	18	seven-point ordinal	parent	4 weeks	yes	1,2,4,6,7,8,9
setting : children with suspected apnea-hypopnea syndrome were studied with polysomnography											
OSA-5 Questionnaire (short) (80)	Soh	2018	Melbourne, Australia	366 and 123	2–17.9	5	four-point Likert	parent	past 4 weeks	yes	all steps except 11
setting: Melbourne Children's Sleep Centre for polysomnography											
OSD-6 QoL Questionnaire (81)	Lachanas	2014	Larissa, Greece	91	3–15	6	seven-point ordinal	parent		yes (Greek and English)	1,2,4,5,6,8,9
setting : children undergoing polysomnography											
oSDB and AT (82)	Links	2017	Baltimore, USA	32		39	three-point rating	parent		yes	1,2,4,6,8,9
setting : online Questionnaire											
OSPQ (83)	Biggs	2012	Adelaide, Australia	1,904	5–10	26	four-point Likert	parent	last typical school week	no	1,2,4,5,6,7,8,10,11
setting : *via* 32 elementary schools in Adelaide											
PADSS (84)	Arnulf	2014	Paris, France	73; 98	>15	17		self		no	1,2,3,4,5,6,7,8,9
setting : patients with sleepwalking or sleep terror referred to the sleep disorder unit; controls											
PDSS (85)	Felden	2015	Curitiba, Brazil	90	10–17	8	five-point Likert	self		yes	1,2,4,5,8,9
setting : two private schools											
PDSS (86)	Komada	2016	Tokyo, Japan	492	11–16	8		self		no	1,2,4,5,6,7,8,9
setting : one elementary school, one junior high school and one high school, located in suburbs of Japan											
PDSS (87)	Bektas	2015	Izmir, Turkey	522	5–11	8	four-point Likert	self		no	1,2,4,5,6,7,8,9,10
setting : students were in grade 5-11											
PDSS (88)	Ferrari Junior	2018	Florianópolis, SC, Brazil	773	14–19	8	five-point Likert	self		no	1,7,8,9,10
setting : state schools of Paranaguá, Paraná											
PDSS (89)	Randler	2019	Petrozavodsk, Russia	n1= 285 n2= 267 n3= 204	7–12	8	five-point Likert	self		yes	1,2,4,5,6,7,8,9,10
setting : Schools from six different settlements located in North-Western Russia (Murmansk region) participated in the study during our framework project "Sleep Health in Russian Arctic"											

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
Pediatric Sleep CGIs (90)	Malow	2016	Nashville, USA	20	5.3	14	seven-point rating	parent		yes (link)	1,2,4,5,6,9
setting : participants in a 12-week randomized trial of iron supplementation in children with autism spectrum disorders											
PedsQL (fatigue scale) (91)	Al-Gamal	2017	Amman, Jordan	70	5–18	18	three- and five-point Likert	self		no	1,2,4,5,6,8,9
setting : oncology outpatient clinic											
PedsQL (fatigue scale) (92)	Qimeng	2016	Guangzhou, China	125	2–4	18	five-point Likert	parent		no	1,2,4,5,6,7,8,9
setting : diagnosed to have acute leukemia for 1 month at the least											
PedsQL(fatigue scale) (93)	Nascimento	2014	São Paolo, Brazil	216; 42 children (8–12 years), 68 teenagers (13–18 years), and 106 caregivers (parents or guardians)	8–18	18	five-point Likert	parent/self		no	1,2,4,6,7,8,9,10
setting : oncology inpatient and outpatient pediatric clinics											
PISI (94)	Byars	2017	Cincinnati, OH, USA	462	4–10	6	six-point Likert	parent		yes	1,2,4,6,7,8,9,10
setting : behavioral sleep medicine evaluation clinic											
PNSSS (95)	Whiteside-Mansell	2017	Little Rock, Arkansas, USA	72	1 week to 28 weeks	14	four-point scale	professional		no	1,2,8
setting : a naturalistic study of participants enrolled in two home visitation support programs											
PosaST (96)	Pires	2018	Porte Alegre, Brazil	60	3–9	6	five-point rating	self		yes	1,2,4,5,8,9
setting : children undergoing polysomnography											
PPPS (97)	Finimundi	2012	Porto Alegre, Brasil	144	10–17	mixed	five-point rating	self		no	1,2,9
setting : adolescent students attending elementary school in two public schools in the state of Rio Grande do Sul (municipalities of Esteio and Farroupilha – great Porto Alegre, and Serra Gaúcha											
P-RLS-SS (98)	Arbuckle	2010	Cheshire, United Kingdom	cognitive debriefing interviews with 21 of the same children/ adolescents and 15 of their parents	6–17	26 morning and 28 evening items	Wong and Baker pain faces scale	parent/self		no	1,2,4,5,6
setting : four pediatric sleep disorders specialists											
PROMIS (99)	van Kooten	2016	Amsterdam, Netherlands	6 experts, 24 adolescents and 7 parents	12–18	27 (PROMIS-SD), 16 (PROMIS-SRI)	through Computerized AdaPOINTive Testing	self/parent/ expert		no	1,2,9
setting : distributed to the adolescents in the classroom											
PROMIS (100)	van Kooten	2018	Amsterdam, Netherlands	1,046	11–19	27 (PROMIS-Sleep		Self		no	1,2,6,7,9,10

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
						Disturbance), 16 (PROMIS-Sleep-Related Impairment)					
setting : online; schools from all educational levels and from different regions of the Netherlands											
PROMIS (101)	Forrest	2018	Philadelphia, PA, USA	1,104 children (8–17 years old) and 1,477 parents of children 5–17 years old	5–17	43; the final item banks included 15 items for Sleep Disturbance and 13 for Sleep-Related Impairment	frequency-based (1: never, 2: almost never, 3: sometimes, 4: almost always, 5: always)	self/parent	7-day	yes	1,2,6,7,8,9,10
setting : a convenience sample of children and parents recruited from a pediatric sleep clinic											
PROMIS (102)	Bevans	2019	Philadelphia, PA, USA	8 expert sleep clinician-researchers, 64 children ages 8–17 years, and 54 parents of children ages 5–17 years	children ages 8–17 and parents of children ages 5–17.	The final item pool contains 43 child-report items and 49 parent-report items	five-point Likert	Self/Parent	In the past 7 days	yes	1,2,3,4,5,6,9
setting : A preliminary child sleep health conceptual framework was generated based on the two PROMIS Adult Sleep Health item banks. Thereafter, the framework was refined based on expert and child and parent interviews											
PSIS (103)	Smith	2014	Texas, USA	155	3–5	12	five-point Likert	parent		no	1,2,6,8,9
setting : identified using a commercial mailing list and print advertisements distributed throughout local schools, daycares, community centers, and health care providers											
PSQ (104)	Ishman	2016	Ohio, USA	45	16.7	22	yes/no/don't know	parent		no	1,2,6,8
setting : teen-longitudinal assessment of bariatric surgery (Teen-LABS) participants at high-risk for obstructive sleep apnea											
PSQ (105)	Yüksel	2011	Manisa, Turkey	111	2–18	22	yes/no and I don't know	parent		no	1,2,4,5,6,8,9
setting : pediatric allergy and pulmonology outpatient department											
PSQ (106)	Bertran	2015	Santiago, Chile	83	0–15	22	yes/no/don't know	parent		no	1,2,6,7
setting: habitually snoring children referred for polysomnography											
PSQ (107)	Hasniah	2012	Kuala Lumpur, Malaysia	192;554	6–10	22	"yes=1," "No=0," and "Don't know=Missing"	parent		no	1,2,4,5,6,8,9
setting : part of the national epidemiological study of the prevalence of sleep-disordered breathing in Malaysian school children											
PSQ (108)	Chan	2012	Hong Kong, China	102	2–18	22	yes/no/don't know	parent		no	1,2,9,11

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
setting : underwent overnight sleep polysomnography studies for suspected OSA in the sleep laboratory											
PSQ (109)	Ehsan	2017	Cincinatti, USA	160	2–18	22	yes/no/don't know	parent		no	1,2,6,9
setting : using an existing clinical database encompassing all children referred to the Cincinnati Children's Hospital Sleep Center for polysomnography											
PSQ (110)	Li	2018	Beijing, China	9,198	3.0–14.4	22	yes/no/don't know	parent		no	1,2,6,7,8,9
setting : 11 kindergartens, 7 primary schools and 8 middle schools from 7 districts of Beijing, China											
PSQ (111)	Longlalerng	2018	Chiang Mai, Thailand	62	7–18	22	yes/no/don't know	parent		no	1,2,4,5,8,9
setting : clinic based retrieval classified as overweight or obese according to the International Obesity Task Force and diagnosed with obstructive sleep apnea											
PSQ (112)	Raman	2016	Ohio, USA	636	4–25.5	36		parent		yes	1,2,4
setting : patients scheduled for a sleep study											
PSQ (113)	Certal	2015	Porto, Portugal	180	4–12	22	yes/no	self		yes	1,2,4,5,6,8,9
setting : *via* schools north Portugal											
PSQ (114)	Jordan	2019	Paris, France	201	2–17	22	"yes," "no" or "don't know,"	parent		yes	1,2,4,5,6,7,8,9,10
setting : admitted to the Odontology Center of the Rothschild Hospital (Assistance Publique e Hopitaux de Paris)											
PSQI (115)	Passos	2017	Pernambuco, Brazil	309	10–19	19	0–3 rating	self		no	1,2,4,5,6,7,8,9,10
setting : subjects who engaged in amateur sports practice											
PSQI (116)	Raniti	2018	Melbourne, Australia	889	12.08–18.92	18	four-point Likert scale	self	1 month	no	1,7,8,9,10
setting : 14 Australian secondary schools											
RLS (117)	Schomöller	2019	Potsdam, Germany	33 (11 RLS)	6–12 and 13–18	12	mixed	self/parent		yes	1,2,3,4,6,8,9
setting : with the support of medical somnologists, who recruited pediatric patients from their practice or sleep laboratories, newsletter announcements in the Restless Legs Association journal, and *via* local selfhelp groups.											
SDIS (118)	Graef	2019	Cincinnati, Ohio	392	2.5–18.99	SDIS-C, 41 items, 2.5–10 years; SDIS-A, 46 items, 11–18 years	seven-point Likert scale	parent		no	1,9
setting : Youth with insomnia, of whom 392 underwent clinically indicated diagnostic PSG within ± 6 months of SDIS screening											
SDPC (119)	Daniel	2016	Philadelphia, USA	20;6	3–12	41	0–4 rating	parent	Interview modelling	no	1,2,4,6,9
setting : parents of children with acute lymphoblastic leukemia and medical providers											
SDSC (120)	Huang	2014	Guangzhou, China	3,525	5–16	26	five-point scale	parent	six months	no	1,2,4,5,6,7,8,9,10,11
setting : selected from five primary schools in Shenyang											

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
SDSC (121)	Putois	2017	Sierre, Switzerland	447	4–16	25	five-point scale	parent	six months	yes	1,2,4,5,6,7,8,9,10,11
setting: schools; pediatric sleep clinic											
SDSC (122)	Saffari	2014	Isfahan, Iran	100	6–15	26	five-point scale	parent	six months	no	1,2,4,5,6,8,9
setting: primary and secondary schools in Isfahan City, Iran											
SDSC (14)	Esbensen	2017	Cincinnati, OH, USA	30	6–17	26	five-point scale	parent	6 months	no	1,2,6,8,9
setting: part of a larger community-based study down syndrome sample											
SDSC (123)	Cordts	2019	Portland, OR, USA	69	3–17	26	five-point Likert	parent	6 months	no	1,6,8,9
setting: longitudinal pediatric neurocritical care programs at two tertiary academic medical centers within 3 months of hospital discharge											
SDSC (124)	Mancini	2019	Western Australia, Australia	307	4–17	26	five-point Likert	parent	6 months	no	1,2,10
setting: recruited *via* the Complex Attention and Hyperactivity Disorders Service (CAHDS), in Perth, Western Australia											
SDSC* (125)	Moo-Estrella	2018	Yucatán, Mexico	838	8–13	25	number of days : 0 = 0 days, 1 = 1–2 days, 2 = 3–4 days, 3 = 5–6 days, and 4 = 7 days.	self	during the last week	no	1,2,3,4,5,6,7,8,9
setting : between the third and sixth grades of elementary school, recruited by convenience sampling											
SHI (126)	Ozdemir	2015	Konya, Turkey	106 patients with major depression; 200 volunteers recruited from community sample	16–60	13	Always, Frequently, Sometimes, Rarely, Never	self		no	1,2,6,7,8,9,10
setting : university based retrieval											
SHIP (127)	Rabner	2017	Boston, USA	1,078	7–17	15	three-point Likert	parent/self		no	1,2,6,8,9
setting: parents and children each completed questionnaires individually within 1 week prior to the child's multidisciplinary headache clinic evaluation											
Sleep Bruxism (128)	Restrepo	2017	Medellın, Colombia	37	8–12	1	yes/no	parent	5-day diary	yes (English)	1,2,4
setting : recruited from the clinics at Universidad CES											
SNAKE (129)	Blankenburg	2013	Datteln, Germany	224	<10	54	1–4 rating (mixed)	parent		yes (English)	all steps
setting : children with severe psychomotor impairment; questionnaire-based, multicenter, cross-sectional survey											
SQI (5)	Chung	2011	Hong Kong, China		12–19	8	three-point Likert	self	In past 3 months	no	1,2,4,5,6,7,8,9,10
setting: three schools with different levels of academic achievement											
SQ–SP (130)	Maas	2011	Maastricht, Netherlands	345	1–66	45	seven-point Likert	parent	last three months	yes	1,2,6,7,8,9,10,

(Continued)

TABLE 1 | Continued

Tool acronym	First author	Year	Place of origin	Sample size	Age (years)	Number of questions	Scale	Respondent	Timeframe	Reference has questionnaire	Steps fulfilled
setting: individuals who consulted the sleep clinic for individuals with ID; individuals from a control group who attended a special day care center, special school or adult activity center for individuals with ID; participants of two published studies Maas et al., 2008, 2009); individuals who consulted a psychiatric clinic for children and adolescents with ID											
SQS-SVQ (131)	Önder	2016	Sakarya, Turkey	1,198	11–15	15*		self		yes	1,2,4,7,8,9,10
setting: an instrument adaptation study with different groups											
SRSQ (132)	van Maanen	2014	AmsterdamNetherlands	951;166;236;144;66	14.7 (mean)	9	three-point ordinal	self	previous 2 weeks	no	1,2,6,8,9
setting : various samples from the general and clinical populations; online and paper and pencil											
SSR (133)	Orgilés	2013	Alicante, Spain	1,228	8–12	26	three-point	self		yes	1,2,4,6,7,8,9,10
setting : 9 urban and suburban schools; per 20 in group											
SSR (43)	Loureiro	2013	Lisbon, Portugal	306	7–12	26	three-point	self		no	1,2,4,5,6,8,9
setting : community and clinical samples											
SSSQ (134)	Yamakita	2014	Koshu, Japan	58	9–12	Please note your bedtime and wake time on both weekdays and weekends		self	log	no	1,2,8,9
setting : a typical elementary school in Koshu City											
STBUR (135)	Tait	2013	Michigan, USA	337	2–14	5	yes/no, and don't know	parent		yes	1,2,3,4,6,7
setting : parents of children scheduled for surgery											
STQ (136)	Tremaine	2010	Adelaide, Australia	65	11–16	18	time	self		no	1,2,9
setting : 3 different private (independent) schools in South Australia											
The Children's Sleep Comic (137)	Schwerdtle	2012	Landau, Germany	201	5–10	37	tick in applicable square	self		no (examples)	1,2,4,9
setting : three primary schools in Germany (group)											
The Children's Sleep Comic (138)	Schwerdtle	2015	Würzburg, Germany	176;393	5–11	20	tick in applicable square	parent/self		no (examples)	1,2,3,4,6,8,9,11
setting : three primary schools in Germany (group)											
TuCASA (139)	Leite	2015	São Paolo, Brazil	62	4–11	13		parent		yes	1,2,4,8,9
setting : sleep-disordered breathing diagnosed by polysomnography and controls											
YSIS (140)	Liu	2019	Shandong Province, China	11,626	15.0 ±1.5	8	five-point Likert	self	past month	yes	1,2,4,5,6,7,8,9,10,11
setting : Shandong Adolescent Behavior and Health Cohort, five middle and three high schools in three counties of Shandong Province, China											

Steps: 1: purpose; 2: research question; 3: response format; 4: generate items; 5: pilot; 6: item-analysis, nonresponse; 7: structure; 8 reliability; 9: validity; 10: confirmatory analyses; 11: standardize and develop norms

TABLE 2 | Overview of psychometric analyses performed.

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
AIS (5)	P		quality	structure	test-retest; internal	convergent/ discriminant		yes; a total score ≥7		original AIS developed per ICD-10	DSM-IV-TR diagnosis of insomnia by interview
ASHS (6)	P	yes	regularity, hygiene, ecology,	structure	internal	convergent/ discriminant	confirmatory				
ASHS (7)	P	yes	regularity, hygiene, ecology,		test-retest, internal	construct; convergent/ discriminant					insomnia per DSM-IV-TR
ASHS (8)	PT (Farsi)	yes	regularity, hygiene, ecology	structure	test-retest, internal	convergent/ discriminant	confirmatory				
ASHS (9)	PT (Persian)	yes	regularity, hygiene, ecology	structure	test-retest, internal	content; construct	confirmatory				
ASQ (10)	N		quality, sleepiness			face				ICSD	
ASWS (11)	P	yes	quantity, hygiene	structure	internal	content; construct	confirmatory				
ASWS (12)	P	yes	quantity, hygiene	structure	internal	construct					
BEARS (13)	PT (Spanish)	yes	quantity, quality, sleepiness			criterion					ICD-10 diagnoses assigned to these children, prior to the commencement of the parent group intervention were: F90, F98.2, F93.3, F80.1, F93.0, Z62
BEDS (14)	A	yes	quantity, quality, hygiene, ecology		test-retest; internal	construct; convergent/ discriminant					Down syndrome
BISQ (15)	T (Spanish)	yes	quantity, hygiene		test-retest; interrater/ observer	content; construct					
BRIAN-K (16)	N		regularity, hygiene,	structure	internal	content; construct					
CAS-15 (17)	P		quality	structure	test-retest; internal; interrater/ observer	construct; criterion; convergent/ discriminant		yes; a score ≥32			
CBCL (18)	P	yes	quantity, quality, sleepiness		test-retest	convergent/ discriminant					patients were diagnosed with sleep disorders according to ICSD-2
CCTQ (19)	T (Turkish)		quantity, regularity		internal	content					

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
CCTQ (20)	P		quantity, regularity		test-retest; internal	criterion					
CCTQ (21)	PT (Chinese)		quantity, regularity		test-retest. internal	content; construct					
CRSP (22)	P		quantity, quality, sleepiness, hygiene	structure		content; construct	confirmatory				
CRSP (23)	N		quantity, quality, sleepiness, hygiene		internal	construct; criterion; convergent/ discriminant					
CRSP (24)	P		quantity, quality, sleepiness, hygiene	structure	test-retest; internal	construct; criterion; convergent/ discriminant	confirmatory				
CRSP (25)	PT		quantity, quality, sleepiness, hygiene	structure	internal	convergent/ discriminant	confirmatory		mean (SD)/n(%)		
CRSP-S (26)	P		sleepiness	structure	test-retest; internal	construct; convergent/ discriminant	confirmatory				
CSAQ (27)	N		quantity, quality, sleepiness	structure	test-retest; internal; interrater/ observer	content; construct; convergent/ discriminant					
CSHQ (28)	P		quantity, quality, regularity, sleepiness, hygiene, ecology		test-retest	construct; criterion				original was designed to identify sleep problems based on ICSD-1	
CSHQ (29)	AT (Portuguese)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	convergent/ discriminant				original was designed to identify sleep problems based on ICSD-1	
CSHQ (30)	P		quantity, quality, regularity, sleepiness, hygiene, ecology	structure						original was designed to identify sleep problems based on ICSD-1	
CSHQ (31)	P		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	content; construct	confirmatory			original was designed to identify sleep problems based on ICSD-1	
CSHQ (32)	P		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	internal	content; construct	confirmatory			original was designed to identify sleep problems based on ICSD-1	

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
CSHQ (33)	T (Dutch)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal; interrater/ observer		confirmatory			original was designed to identify sleep problems based on ICSD-1	
CSHQ (34)	T (Dutch)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	internal		confirmatory		a mean total CSHQ score of 41.9±5.6	original was designed to identify sleep problems based on ICSD-1	
CSHQ (35)	A		quantity, quality, regularity, sleepiness, hygiene, ecology		internal	convergent/ discriminant				original was designed to identify sleep problems based on ICSD-1	allergic rhinitis
CSHQ (36)	A		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	internal					original was designed to identify sleep problems based on ICSD-1	autism spectrum disorder
CSHQ (37)	P		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	internal	criterion				original was designed to identify sleep problems based on ICSD-1	
CSHQ (short) (38)	A		quantity, quality, regularity, sleepiness, hygiene, ecology		internal	convergent/ discriminant	confirmatory	yes; a total CSHQ score of ≥ 24		original was designed to identify sleep problems based on ICSD-1	clinical samples diagnoses based on the DSM-IV: pervasive developmental disorders, attention-deficit and disruptive behavior disorders, anxiety disorders; depressive disorders, and others and also without psychiatric disorder
CSHQ (39)	PT (German)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	content		yes; per subscale provided		original was designed to identify sleep problems based on ICSD-1	sleep disorders per ICSD II
CSHQ (40)	T (Portuguese)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	face				original was designed to identify sleep problems based on ICSD-1	
CSHQ (41)	PT (Spanish)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	face; content; construct				original was designed to identify sleep problems based on ICSD-1	

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
CSHQ (42)	T (Persian)		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	face; content; construct; convergent/ discriminant				original was designed to identify sleep problems based on ICSD-1	
CSHQ (43)	T (Portuguese)		quantity, quality, regularity, sleepiness, hygiene, ecology		test-retest; internal	content		yes; a cutoff total score of 44		original was designed to identify sleep problems based on ICSD-1	ICSD II for Sleep Related Breathing Disorder, Parasomnia, Behavioral Sleep Disorder
CSHQ (short) (44)	A		quantity, quality, regularity, sleepiness, hygiene, ecology			convergent/ discriminant		yes; a cutoff total score of 30		original was designed to identify sleep problems based on ICSD-1	
CSHQ (14)	P		quantity, quality, regularity, sleepiness, hygiene, ecology		internal	construct; convergent/ discriminant				original was designed to identify sleep problems based on ICSD-1	Down syndrome
CSM (45)	T (Polish)		regularity, sleepiness		internal	content; construct		accumulated percentile distribution			
CSRQ (46)	T (English)	yes	quantity, regularity, sleepiness	structure	internal		confirmatory				
CSRQ (47)	P		quantity, regularity, sleepiness			criterion		yes; ≥35; optimal sensitivity : 27.5; optimal specificity: 50.5			
CSWS (48)	P	yes	quantity, regularity	structure	test-retest; internal	content; construct	confirmatory				children with Sleep-Onset Association Problems per ICSD
DBAS (49)	T (German)		quantity, quality, regularity	structure	internal	content	confirmatory				
DBAS (50)	P		quantity, quality, regularity	structure	test-retest; internal	content					
ESS (51)	PT (Tamil)	yes	sleepiness	structure	internal	face; content; construct	confirmatory		>11 = excessive daytime sleepiness; 11-14 = moderate and >15 = high		
ESS (52)	P	yes	sleepiness		internal	convergent/ discriminant		yes. cutoff score of 6			
ESS-CHAD (53)	P	yes	sleepiness	structure	test-retest; internal	construct; criterion					
FoSI (54)	PA		quality	structure	internal	convergent/ discriminant	confirmatory				

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
I SLEEPY (55)	N		quality, sleepiness			criterion		yes; those endorsing three or more symptoms or complaints on the questionnaires			
IF SLEEPY (55)	N		quality, sleepiness			criterion		yes; those endorsing three or more symptoms or complaints on the questionnaires			
I'M SLEEPY (55)	N		quality, sleepiness			criterion		yes; those endorsing three or more symptoms or complaints on the questionnaires			
ISI (5)	P		quality	structure	test-retest; internal	criterion; convergent/ discriminant		yes; a total score ≥9		partially diagnostic criteria of insomnia in DSM-IV	DSM-IV-TR diagnosis of insomnia by interview
ISI (56)	T (Swedish)		quality		internal	criterion				partially diagnostic criteria of insomnia in DSM-IV	chronic pain
ISI (57)	T (German)		quality	structure	internal	convergent/ discriminant	confirmatory			partially diagnostic criteria of insomnia in DSM-IV	
JSQ (58)	P		quantity, quality, regularity, sleepiness, hygiene	structure	internal	content	confirmatory	yes; 80 for total score	standardized T scores by age and gender; 50.00 ± 10.00		
JSQ (preschool) (59)	P		quantity, quality, regularity, sleepiness, hygiene	structure	internal	face; criterion		yes; cutoff 84	standardized T scores by age and gender; 50.00 ± 10.00		
LSTCHQ (60)	N		quantity, regularity, sleepiness, hygiene, ecology		test-retest	face; content; construct					
MCTQ (61)	N	no, therefore added here	regularity								

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
MEQ (62)	T (Italian)		regularity, sleepiness	structure	internal	content					
MEQ (63)	P		regularity, sleepiness	structure	internal	convergent/ discriminant					
aMEQ (64)	PT (European Portuguese)		regularity, sleepiness		internal	face; content			mean ± 1SD, percentiles 10 and 90, and the less restrictive percentiles 20/80; cut-points for the males and females		
aMEQ-R (65)	PA		regularity, sleepiness		internal	content; criterion; convergent/ discriminant			aMEQ (≤45 and ≥60); aMEQ-R (≤23 and ≥33)		
MESC (66)	P	yes	regularity, sleepiness	structure	internal	convergent/ discriminant	confirmatory				
MESSi (67)	PT (Turkish)		regularity, sleepiness	structure	internal	face; content; convergent/ discriminant	confirmatory				
MESSi (68)	P		regularity, sleepiness		internal	convergent/ discriminant	confirmatory				
My Sleep and I (69)	P		quantity, hygiene, ecology	structure	internal	convergent/ discriminant	confirmatory				
My children's sleep (69)	P		quantity, hygiene, ecology	structure	internal	convergent/ discriminant	confirmatory				
NARQoL-21 (70)	NT (English)		quality, sleepiness	structure	test-retest; internal;	content; construct; convergent/ discriminant	confirmatory	yes; a NARQoL-21 score below 42			diagnostic criteria for narcolepsy according to ICSD-3
NSD (71)	NA		quality								Asthma per Global Initiative for Asthma classification
NSS (72)	AT (Chinese)		sleepiness	structure	internal	face; content; convergent/ discriminant					ICSD-3 criteria
OSA Screening Questionnaire (73)	N		quality			face; content					Down syndrome
OSA-18 Questionnaire (74)	T (Chinese)		quality	structure	test-retest; internal	construct; convergent/ discriminant	confirmatory	yes; cutoff scores ranging from 55 to 66			OSA per ICSD 2

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
OSA-18 Questionnaire (75)	T (Chinese)		quality		test-retest; internal	construct; criterion					
OSA-18 Questionnaire (76)	T (Dutch)		quality		test-retest; internal	convergent/ discriminant					craniosynostosis
OSA-18 Questionnaire (77)	T (Greek)		quality		test-retest; internal	criterion					
OSA-18 Questionnaire (78)	T (Portuguese)		quality		internal	convergent/ discriminant					
OSA-18 Questionnaire (79)	T (Spanish)		quality	structure	test-retest; internal; interrater/ observer	construct; convergent/ discriminant					
OSA-5 Questionnaire (short) (80)	A		quality	structure	internal	content	confirmatory				
OSD-6 QoL Questionnaire (81)	T (Greek)	yes	quality		test-retest; internal	criterion					
oSDB and AT (82)	N		quality, treatment		internal	face; content; construct; criterion					
OSPQ (83)	N		quality, regularity, sleepiness	structure	test-retest; internal	face	confirmatory		the cutoffs for the 95th percentile (T-score of 70) by sex and age		
PADSS (84)	N		quality	structure	test-retest; internal	face; construct		yes; cutoff for the overall scale was located at 13/14			sleepwalking or sleep terror per ICSD
PDSS (85)	T (Brazilian Portuguese)		quantity, regularity, sleepiness		test-retest; internal	content					
PDSS (86)	T (Japanese)		quantity, regularity, sleepiness	structure	test-retest; internal	content					
PDSS (87)	T (Turkish)		quantity, regularity, sleepiness	structure	internal	content; construct	confirmatory				
PDSS (88)	P		quantity, regularity, sleepiness		internal	construct	confirmatory				
PDSS (89)	PAT (Russian)		quantity, regularity, sleepiness	structure	test-retest; internal	face; content	confirmatory				
Pediatric Sleep CGIs (90)	N		quantity, hygiene, ecology			convergent/ discriminant				elements of insomnia as defined by the ICSD	Autism Spectrum Disorders

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
PedsQL(fatigue scale) (91)	AT (Arabic)		sleepiness		internal	content; construct; convergent/ discriminant					cancer
PedsQL (fatigue scale) (92)	AT (Chinese)		sleepiness	structure	internal	content; construct; criterion	confirmatory				acute leukemia
PedsQL(fatigue scale) (93)	PT (Brazilian Portuguese)		sleepiness	structure	internal	construct; convergent/ discriminant	confirmatory				cancer
PISI (94)	P		quality	structure	test-retest; internal	content; construct; convergent/ discriminant	confirmatory			items per group consensus regarding the following ICSD-II general insomnia criteria	
PNSSS (95)	P		ecology		interrater					assess five of the AAP recommendations related to sleep practices	
PosaST (96)	T (Brazilian Portuguese)		quality		internal	criterion		yes; using the cumulative score ≥2.72 of the original scale			
PPPS (97)	P		quantity; regularity, sleepiness, hygiene		internal						
P-RLS-SS (98)	N		quality			face; content					including also ADHD subgroup per DSM-IV criteria
PROMIS (99)	P		quality, regularity, sleepiness		internal	face; content					
PROMIS (100)	P		quality, regularity, sleepiness	structure		content	confirmatory				
PROMIS (101)	P		quality, regularity, sleepiness	structure	internal	content; construct	confirmatory				
PROMIS (102)	PA		quality, regularity, sleepiness			content					
PSIS (103)	P		quality, regularity		internal	content; construct					child psychopathology and functioning per DSM-IV-TR
PSQ (104)	P		quality		internal						obese adolescents undergoing bariatric surgery
PSQ (105)	T (Turkish)		quality		internal	content; construct				items similar DSM-IV	
PSQ (106)	T (Spanish)		quality	structure				yes; cutoff score >0.33			

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
PSQ (107)	T (Malay)		quality		test-retest; internal	face; content					
PSQ (108)	P		quality			criterion		yes; original 0.33 and AHI>1.5			
PSQ (109)	P		quality			face; content		yes; cutoff of 0.72–0.76.			asthma per ICD 9
PSQ (110)	PT (Chinese)		quality	structure	test-retest	content; construct					
PSQ (111)	T (Thai)		quality		test-retest; internal	face; content		yes; a cutoff of >0.33			
PSQ (112)	P		quality					yes; a cutoff value of seven points			
PSQ (113)	PT (Portuguese)	yes	quality		test-retest; internal	face; content					
PSQ (114)	PT	yes	quantity, quality, regularity	structure	test-retest; internal	face; construct	confirmatory				
PSQI (115)	T (Brazilian Portuguese)	yes	quantity, quality, regularity	structure	test-retest; internal	content	confirmatory				
PSQI (116)	P	yes	quantity, quality, regularity	structure	internal	content; convergent/ discriminant	confirmatory				
RLS (117)	NP		quality		test-retest; internal	face; content			calculated RLS index (difference in score between 14 day time points); one control subject had a higher index value (14) than two RLS-diagnosed (10 and 13)	criteria for children established by the International Restless Legs Syndrome study group	
SDIS (118)	P	yes	quantity, quality, sleepiness			convergent/ discriminant					insomnia per ICSD-2 or ICSD-3
SDPC (119)	P		quantity, quality, sleepiness			content					cancer
SDSC (120)	T (Chinese)	yes	quantity, quality, sleepiness	structure	internal	construct	confirmatory			original SDSC fits ASDC	
SDSC (121)	T (French)	yes	quantity, quality, sleepiness	structure	test-retest; internal; interrater/ observer	construct; convergent/ discriminant	confirmatory		T-score >70	original SDSC fits ASDC	

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
SDSC (122)	T (Persian)	yes	quantity, quality, sleepiness		internal	construct; convergent/ discriminant				original SDSC fits ASDC	
SDSC (14)	P	yes	quantity, quality, sleepiness		internal	construct; convergent/ discriminant				original SDSC fits ASDC	Down syndrome
SDSC (123)	P	yes	quantity, quality, sleepiness		internal	construct; convergent/ discriminant				original SDSC fits ASDC	neurocritical care acquired brain injury
SDSC (124)	P	yes	quantity, quality, sleepiness				confirmatory				ADHD
SDSC* (125)	N		quantity, quality, regularity, sleepiness	structure	internal	content				ICSD 2 as reference	
SHI (126)	T (Turkish)		quantity, quality, sleepiness	structure	test-retest; internal	construct	confirmatory				major depressive disorder per DSM-IV criteria
SHIP (127)	N		quantity, regularity, sleepiness		internal	content; construct; criterion; convergent/ discriminant					chronic headache per International Headache Classification
Sleep Bruxism (128)	N		quality								
SNAKE (129)	N		quantity, quality, regularity, sleepiness, hygiene, ecology	structure	test-retest; internal	construct; convergent/ discriminant	confirmatory		T-score and percentage rank for raw score per factor	per ICSD-2	severe psychomotor impairment
SQI (5)	P		quality	structure	internal	convergent/ discriminant		yes; total score ≥5			DSM-IV-TR diagnosis of insomnia by interview
SQ–SP (130)	P	yes	quantity, quality, sleepiness,	structure	test-retest; internal	construct; convergent/ discriminant	confirmatory				individuals with intellectual disability
SQS-SVQ (131)	AT (Turkish)		quantity, regularity, ecology	structure	test-retest; internal	criterion	confirmatory			sleep quality items comparable to DSM IV insomnia criteria	
SRSQ (132)	N		quantity, quality, regularity, sleepiness		test-retest; internal	content		yes; a cutoff of 17.3			
SSR (133)	T (Spanish)		quality, regularity, sleepiness	structure	internal	construct; convergent/ discriminant	confirmatory			original items per ICSD	

(Continued)

TABLE 2 | Continued

Tool acronym	NPTA	in Spruyt et al	Sleep categories	Factor analysis	Reliability analyses	Validity analyses	Confirmatory analysis	ROC	Normative values or cutoffs	Clinical classification	Specific population
SSR (43)	T (Portuguese)		quality, regularity, sleepiness		internal	content				original items per ICSD	
SSSQ (134) **STBUR** (135)	N N		quantity, regularity quality	structure	test-retest	criterion		yes; 10.40 (1.37–218.3) for 5 items			
STQ (136)	P		quantity, regularity			convergent/ discriminant					
The Children's Sleep Comic (137)	N		quantity, quality, regularity, sleepiness, hygiene			content; construct				ICSD-2	
The Children's Sleep Comic (138)	P		quantity, quality, regularity, sleepiness, hygiene		internal	content; convergent/ discriminant		yes; a total intensity of sleep problem score of 9	stanine value (5±2), percentile rank and relative frequency for the raw intensity of sleep problem score	ICSD-2	
TuCASA (139)	AT (Portuguese)	yes	quality		internal	content; convergent/ discriminant					
YSIS (140)	NT (English)		quality	structure	test-retest; internal	face; content; construct; convergent/ discriminant	confirmatory	yes: Normal :< 22 (< 70th percentile); Mild insomnia : 22 (70th percentile)–25; Moderate insomnia/ clinical insomnia : 26 (85th percentile)–29; Severe insomnia/ clinical insomnia :≥ 30 (95th percentile		based on ICSD-3 [12] and DSM-V [13] diagnostic criteria	

lesser frequent combinations of age ranges for which tools were assessed in these studies, ranged from 0.7–7.6% per combination.

As for the sample size, this ranged between 20 and 11,626 children inclusive of adult (6–13) participants across all publications, where 15.6% of all studies used a sample size >1,000 participants large (**Table 2**). Of these study samples, approximately 46.5% of respondents were parents, 41% were self-report, and 11.1% either a combination of experts, children, mothers, and parents. For two, the respondent is primarily a professional (17, 95).

Sleep Categories

As exemplified in **Table 2**, the overall focus of these studies was overwhelmingly directed at tools measuring the quality of sleep or identification of sleep pathologies in all pediatric age classifications (68.1%), followed by the levels of sleepiness (55.6%) and duration of sleep (48.6%). Various secondary coobjectives of these studies were to investigate tools measuring the sleep regularity (46.5%) and sleep hygiene practices (29.2%). Rarely but in existence, was the singular assessment of sleep ecology and treatment around sleep pathologies at a frequency of 21.5% and 0.7%, respectively. About 19 studies (13.2%) queried simultaneously nearly all categories (except treatment).

The 11 Steps

Regarding the psychometric evaluation step-by-step guide proposed by Spruyt (2, 3), less than half the required 11 steps (chiefly 1, 2, 6, 8, and 9 were done) were fulfilled across all studies. Steps 3 and 10 were often not reported (i.e., 84.7% and 63.2%, respectively). Three studies reported all steps (2.1%), three only lack step 11 (2.1%), and four (2.8%) only lack steps 10 and 11. The most common combination of steps (7.7%) reported are 1, 2, and 4 joined with 5, 6, 7, 8, 9 or 5, 6, 8, 9 or 6, 7, 8, 9, 10. After a decade, only 18 papers (12.5%) reported some form of norms. An in-depth description of the steps fulfilled is described in the categorically-divided (per purpose, see Methods) results below.

Tools Newly Developed

According to our search criteria, a total of 27 novel pediatric sleep tools were developed between 2010 and 2020 (refer to **Table 2** and shaded). Of these, approximately eight were published in Europe (29.6%), eight in North America (29.6%), four in Asia (14.8%), three in South America (11.1%), two in Australia and Oceania (7.4%), and two in the United Kingdom (7.4%). The majority were developed for child-adolescent age ranges (66.7%), while one for preschool children (2–5 years) and one for all three aforementioned ages (2–18 years). All newly developed tools possessed a multipurpose objective, most of which assessed sleep quality (77.8%), followed by the assessment of sleepiness (51.9%) and sleep regularity (41.7%) and sleep quantity (41.7%), while more rarely assessing hygiene (25%), ecology (12.5%), and treatment (4.2%).

In addition, three tools being newly created are an English translation of the NARQoL-21 (70) and YSIS (140), and also an adaptation, the nighttime sleep diary (NSD) (71). The latter being a diary adapted to monitor nighttime fluctuations in young children with asthma.

Only two tools were developed according to the 11 aforementioned steps required for psychometric validation of a tool; the NARQoL-21 (70) and SNAKE (129) (refer to **Table 2**). One other tool, OSPQ (83) also developed normative scores for widespread usage while fulfilling most steps but steps 3 and 9. Whereas the CSAQ (27) fulfilled all steps except step 11, and the BRIAN-K (16), PADSS (84), and SDSC* (125) except steps 10 and 11. The outstanding tools were mostly absent of steps 5, 7, 8, 9, and 10. For the newly developed diary, NSD (71) steps 1–6 were fulfilled.

Almost half of the tools queried general sleep problems (41.7%). Twenty-five percent aimed at surveying sleep disordered breathing. While others such as sleep bruxism (128), PADSS (84), P-RLS-SS (98), RLS (117), NARQoL-21 (70), YSIS (140), and NSD (71) focused on a specific sleep problem (16.7%). Tools aimed at investigating sleep complaints in children with (developmental) disabilities are besides NSD (71), the OSA Screening Questionnaire (73), Pediatric Sleep CGIs (90), SHIP (127), and SNAKE (129).

Tools Translated

In total, 35 out of the total 144 studies primarily aimed to translate an existing tool alone (refer to **Table 2**). Namely, 17 tools have been translated: BISQ (15), CCTQ (19), CSHQ (29, 33, 34, 40–43), CSM (45), CSRQ (46), DBAS (49), ISI (56, 57), MEQ (62), OSA-18 (74–79), OSD-6 (81), PDSS (85–87), PosaST (96), PSQ (105–107, 110, 111, 113), PSQI (115), SDSC (120–122), SHI (126), and SSR (43, 133). The most frequently translated tools were: OSA-18 (17.1%), CSHQ (14.3%), and PSQ (11.4%). The most common translation was to Portuguese (n=4), Spanish (n=4), and Turkish (n=4), followed by Brazilian Portuguese (n=3), Chinese (n=3), and Dutch (n=3). Less often, tools were translated to German, Persian, and Greek as well as English, Italian, Polish, Swedish, Japanese, French, Malay, and Thai. Again, primarily tools for child/adolescent age ranges as parental reports have been translated. Of these, the main categorical foci, and often overlapping, were sleep quality (77.1%), quantity (48.6%), and sleepiness (48.6%).

When ranked from most to least prevalent step, apart from steps 1 and 2, we found: step 8 (97.1%), step 4 (91.4%), step 9 (88.6%), step 6 (85.7%), step 5 (57.1%), step 7 (51.4%), and step 10 (34.3%) being performed across the studies. The CSHQ (34) and SDSC (120, 121) included norm development (step 11). Step 3 is missing in all translations. Only the translation of the SDSC fulfilled nearly all steps with (121) missing step 3 and (120) missing steps 3 and 9. Receiver Operator Curve (ROC) analyses were performed in five : OSA-15 (74), PosaST (96), PSQ (106, 111), and CSHQ (43).

Tools Adapted

Moreover, six studies (see **Table 2**) specifically aimed to adapt a tool from a preexisting one, most notably the Children's Sleep Habits Questionnaire (CSHQ) (66.7%), among these a shortened version and infant adaptation, along with the BEDS (14) (16.7%) adapted toward children with Down syndrome, and the OSA-18 Questionnaire (16.7%), which was also shortened [toward OSA-5 (80)] to suit the sample of interest. Although the number of items

may have changed, no substantial changes to the answer categories could be noted. Only 33.3% reported steps 3, 4, 5, 7, 10 yet steps 6, 8, 9 were analyzed in 83.3%. None developed norms. In two studies (38, 44) ROC analyses were pursued for the CSHQ.

Tools Adapted and Translated

Six studies adapted and also translated existing tools (see **Table 2**): CSHQ (29), PedsQL (91, 92), SQS-SVQ (131), TuCASA (139), and NSS (72). The CSQH and TuCASA were adapted and translated to Portuguese, the PedsQL to Arabic and Chinese, while SQS-SVQ to Turkish and NSS to Chinese. The adaptations involved an infant version of CSHQ and child-sample for NSS, the PedsQL to children with cancer and acute leukemia, and the TuCasa was adapted toward children of low socioeconomic status. Regarding the SQS-SVQ it was modified based on personal communication with the authors of the original version. That is, four items were added.

For these tools Steps 3 and 11 were not performed, while Steps 8 and 9 were performed in all. About half (50%) did steps 5, 6, and more than half step 7 (66.7%) and less than half did step 10. Some aspects of step 4 were inconsistently applied across 83.3% of the studies (e.g., expert perspective).

Tools Psychometrically Evaluated

Approximately 53 studies were published that focused solely on psychometric evaluation of questionnaires between 2010 and 2020 (refer to **Table 2**). Of these, commonly investigated were CSHQ (11.3%), CRSP, and PSQ (each 7.5%), followed by SDSC and PROMIS (each 5.7%). The greatest number were printed in 2014 (15.1%), as well as 2018 and 2019 (each 13.2%) and 2015, 2016, 2017 (each 11.3%), and a lesser number of instruments were evaluated in the other years. In terms of location, the majority were published in North America (43.4%) followed by Europe (22.6%) and Asia (18.9%), Australia and Oceania (11.3%), and the South America (3.8%). Especially tools for adolescent age ranges (34%) were psychometrically evaluated, followed by child-adolescent age range (22.6%). 9.4% involved tools for preschoolers (2–5 years) and 15.1% are for child (6–12 years) alone. The remainder are combinations: preschooler child (3.8%), preschool to adolescent (9.4%), and all (0–18 years; 3.8%).

Ranked on sleep category, the tools examined: 64.2% sleep quality; 58.5% sleep quantity; 47.2% sleep regularity; 58.5% sleepiness; 35.8% sleep hygiene, 20.8% sleep ecology but none for treatment. Among all 53-instrument validations, none adhered to all eleven recommended steps of tool evaluation. Besides steps 1 and 2, especially steps 9 (90.6%) and 8 (75.5%), 6 (64.2%) have been reported upon psychometrically evaluating tools, and less common have been steps 7 (54.7%), 10 (41.5%), and 4 (34%). Least common in psychometric screening were steps 5 (13.2%), 3 (13.2%), and again 11 (15.1%). ROC analyses were performed in 11 studies (20.8%): ESS (52), AIS and SQI (5), JSQ (58, 59), PSQ (108, 109, 112), CAS-15 (17), CSRQ (47), and Comics (138). Almost fulfilling all steps were: CAS-15 (Goldstein et al., 2012) and Comics (137, 138).

Tools Psychometrically Evaluated and Adaptations

Three tools underwent evaluation but were simultaneously modified: FoSI was adapted for adolescents (54), and a reduced itemset was suggested for aMEQ-R (65) and PROMIS (102).

Tools Psychometrically Evaluated and Translated

In addition to the 53 instruments validated, there were 13 studies flagged that additionally translated their respective tools (refer to **Table 2**); the ASHS to Persian, the BEARS to Spanish, CCTQ to Chinese, the CSHQ to German and Spanish, the ESS to Tamil, the MEQ to European Portuguese, the MESSi to Turkish, the PSQ to Chinese, Portuguese and French, and the PedsQL to Brazilian Portuguese. Step 9 was performed in all studies, closely followed by steps 4, 6, and 8 (93.3% each). Step 7 (69.2%) and 5 (53.8%) and 10 (46.2% each) were not as frequently pursued. Again, steps 3 and 11 (15.4%) were nearly absent in the psychometric evaluation. Of these, the ESS (51) underwent all steps.

Tools Psychometrically Evaluated, Translated With Adaptations

The Russian version of the PDSS (89) did not report step 3, but executed to a certain extent all the steps to psychometrically evaluate a translated tool to its population. Based on the advice of the area specialist and the focus group of children questions #3 (Trouble getting out of bed in the morning), 4 (Fall asleep/ drowsy during class), 7 (Fall back to sleep after being awakened), and 8 (Usually alert during the day (reverse coded)) were modified for better understanding.

Some Extra Remarks

Translations of Tools

Although the studies reported here are English papers, popular translations are Chinese, Portuguese, Spanish, and Turkish. The CSHQ, PSQ, and OSA-18 were the most frequently translated tools.

Tools With Norm Scores

Psychometric studies of particular interest are those that developed normative values or clinical/community cutoff scores for widespread usage, of which there were overall 18. Norms have been developed for CAS-15 (17), ESS (51, 52), JSQ (58, 59), SDSC (120, 121), CSHQ and CRSP (25, 34), CSRQ (47), MEQ (64, 65), NARQoL-21 (70), OSPQ (83), PSQ (108), SNAKE (129), Comic (138), and YSIS (140) (refer to **Table 2**).

The CAS-15, PSQ, CSRQ, and ESS studies provided "normative" ROC cutoff scores, with the Krishnamoorthy et al. (51) providing cutoffs for moderate and high excessive sleepiness.

Population-based norms were developed for preschoolers and school-aged children of JSQ. Average T-scores for all as well as for boys/girls in age bands of 2–3, 4, 5–6 years separately are available for each subscale: restless legs syndrome, sensory; obstructive sleep apnea syndrome; morning symptoms; parasomnias; insomnia or circadian rhythm disorders; daytime excessive sleepiness; daytime behaviors; sleep habit; insufficient

sleep; and restless legs syndrome, motor. For school-aged median T-scores are available for 1st–2nd, 3rd–4th,5th–6th grade per the following subscales: restless legs syndrome, sleep disordered breathing, morning symptoms, nighttime awakenings, insomnia, excessive daytime sleepiness, daytime behavior, sleep habit, and irregular/delayed sleep phase.

Regarding the SDSC, French (France and French speaking Switzerland) as well as Chinese T-scores are available. The Chinese study reports average T-scores per the subscales sleep–wake transition disorders; disorders of initiating and maintaining sleep; disorders of excessive somnolence; disorders of arousal; sleep hyperhidrosis; and sleep breathing disorders. Whereas the French study copied the approach of the original report, i.e., tabulated the full T-score range from 31 to 100 including marks for clinical ranges.

The CSHQ study aimed to validate the Dutch version of the tool for toddlers while developing norms due to the current inaccessibility of the CSHQ in this age group. Norm values were decidedly the mean total score in the sample population and while the factor-structure was unsupported, the normative score developed was still representative of the presence and severity of sleep problems in 25% of toddlers. Authors report the mean total score for lower/higher socioeconomic status, 2 and 3 year olds, girls and boys, yes/no problem sleepers. The authors similarly provided means and standard deviations for the 23 items of the CRSP.

The MEQ studies are comparable providing means and standard deviations as well as percentiles. Also percentiles are reported in the YSIS study.

For the NARQoL-21 a comparison was made with a validated health-related quality of life tool, and a cutoff of <42 was deemed as sensitive and specific, supplementary available are cutoff scores for differentiating between optimal and suboptimal quality of life.

T-scores for subscales by gender and age (5–7 and 8–10 years old) are provided for OSPQ: sleep routine, bedtime anxiety, morning tiredness, night arousals, sleep disordered breathing and restless sleep.

For SNAKE a t-distribution was generated for Disturbances going to sleep, Disturbances remaining asleep, Arousal disorders, Daytime sleepiness, and Conduct disorders for children in ages between 1 and 25 years old. For the Children's Sleep Comic (ages 5 to 11) stanines were generated for the raw intensity of sleep problem score.

Tools With ROC Analyses

Twenty-eight (19.4%) studies reported ROC findings. This was primarily done for (refer to **Table 2**) CSHQ (n=4) and PSQ (n=5). That is, in 20% the ROC was calculated given clinical versus control/community samples, while in 48% of the papers a PSG parameter was used (e.g., apnea-hypopnea index, obstructive index). Another criterion was used in 32% of the cases (e.g., validated questionnaire, parental report, or optimal cutoff from original paper).

Papers With Questionnaires Available

In **Table 1**, the studies (32.6%) that printed or made available their questionnaire in supplementary files or appendix are shown.

Use of Classification Systems

Primarily the ICSD classification system was used to generate/mimic items for the following new tools: the Pediatric Sleep CGIs (90), RLS (117), SDSC* (125), SNAKE (129), the Children's Sleep Comic (137), and YSIS (140). When tools were psychometrically evaluated and/or translated/modified such as the CSHQ or the SDSC the classification system upon which their original items were generated remains.

Tools Used in Specific Populations

The SNAKE has been specifically developed for children with psychomotor disabilities, and hence serves as a good example of tool development. Whereas the vast majority of studies involved tools that are modifications or compilations, as well as a psychometric evaluation of the tool utility in an "atypical" population.

DISCUSSION

Since the 2011 Spruyt (2, 3) review, it has been encouraged that further psychometric validation is pursued for all questionnaires to develop a broader and more reliable range of tools. While "*tools do not need to be perfect or even psychometrically exceptional, they need to counterpart clinical decision-making and reduce errors of judgment when screening for poor sleep,*" suggested Spruyt (personal communication). This is done through the descriptive, iterative process of a tool protocol and often requires all steps of psychometric evaluation. Without this we have observed that tools rely on minor aspects of their psychometric validity for (clinical) application when this is often fallacious and nonspecific to the study population. Following the systematic review however, a dramatic increase in tool translations and adaptations has been observed which is to be irrefutably applauded. Nonetheless, it is important to develop standardized tests that are culture-free and fair in order to identify sleep issues across the board based on an unbiased testing process.

Twenty-seven new tools have been developed, while most of the papers published reported translations/adaptations or a psychometric evaluation of an existing tool. More than half of the tools queried general sleep problems. Irrespective of the infrequency of tools developed in categories like sleep ecology and treatment, there is an emerging need for further research into these areas given the environmental impact of technology on pediatric sleep in the 21st century (141, 142).

The two new tools that underwent all 11 steps aimed at investigating sleep problems either in terms of a quality of life tool for narcoleptics (NARQoL-21) (70) or as a sleep disorder tool for children with severe psychomotor impairment (SNAKE) (129). Several other tools accomplished nearly all steps (see Tables: OSPQ, CSAQ, BRIAN-K, PADSS, SDSC*, NSD, and YSIS).

Since the 2011 review, tools for specific populations (e.g., in terms of ages, developmental disabilities, sleep pathologies) are still needed. Epidemiological tools assessing sleep in adolescents specifically have received some focus, where they were second in

publication frequency. This dramatic influx of relevant research can be a result of the rising sleep-reduction epidemic in teenage populations influenced by biological, psychological and sociocultural factors. In addition, the investigation into the effects of sleep hygiene and ecology (143), which are heavily influenced by sociocultural phenomena, have slowly presented themselves across children and adolescents (6–18 years). With the introduction of technology at the forefront of childhood influence (144, 145), pediatric sleep habits and consequently quality is slowly gaining traction where studies flagged here are acknowledging the underlying weight of sleep hygiene on sleep quality and sleep quantity. Although at present, these tools are still demanding attention for further psychometric validation. An urgent call for tools with adequate psychometric properties is concluded in several recent reviews (146–148).

Especially assessing the factor structure of tools toward construct validation has been pursued, while other steps continue to be overlooked. Similarly, general tools to screen for sleep pathologies remain preponderant since the 2011 review. Alternatively, a file-drawer problem can be expected. Combined with the difficulty of finding a suitable journal to publish a tool validation study, this may lead to a skewed scientific literature toward commonly published and used tools. This is potentially echoed in atypical populations as seen by the influx of psychometric evaluations of existing tools. Undoubtedly, more studies are needed in an era where sleep is rapidly gaining public interest, and the need for a scientifically sound answer on the consequences of a "poor sleep" endemic is pressing.

Several tools pop out for diverse reasons. The first tool of note is the JSQ (58, 59) validated for Japanese children investigating sleep in a large population-based sample flagged by our search and developing normative values for this tool at a 99% confidence interval. This tool is notable in that given its statistical validity and reliability in a large population sample, the plausibility of this being mirrored in other cultures is possible. Important to note however, is that sleeping habits in Japanese children may vary greatly to those in western countries. Therefore, the changes in sociocultural sleep habits when adapting for other populations should be considered. Secondly, SNAKE the sleep questionnaire for children with severe psychomotor impairment underwent all 11 steps and was uniquely developed (hence not modified) for a specific population. More alike are needed (149). Thirdly, PADSS, and BRIAN-K both newly developed tools drew our attention because they examine arousal level and biological rhythm. Although the PADSS may need some further validation studies toward diagnosing, monitoring, and assessing the effects of treatment in arousal disorders in childhood particularly, it addresses the need for more specialized tools. Whereas the BRAIN-K being a modification of an adult version may benefit from additional psychometric evaluations beyond the current age range. Also, the FoSI, measuring fear, being based on the adult version assessing fear in a rural trauma-exposed sample (150) warrants further psychometric scrutiny. In contrast to others, the RLS (117) proposes a difference in scores between two time points 14 days apart to identify RLS-related symptoms. Lastly, addressing the need for tools allowing the child to express themselves regarding sleep is the Children's Sleep Comic, being an adapted version of the unpublished German questionnaire "Freiburger Kinderschlafcomic" and providing pictures for items and responses. Hence, pinpointing to the "un"published tools in the field and a welcomed child's perspective regarding inquiring about sleep in an alternative way.

Adhering to the words of Spruyt, that instruments should be enhancing clinical decision-making and significantly reducing errors of judgment, the study by Soh et al. identified, developed, and abbreviated the OSA-5 questionnaire after recognising preexisting faults in the original 18-item version. It was identified that the OSA-18 was initially designed as a disease-specific quality of life tool that does not predict obstructive sleep apnea (OSA) symptoms consistent with the gold-standard PSG. Recently Patel et al. (151) scrutinized the accuracy of such clinical scoring tools. Additionally, the study by Soh et al. (80) acknowledged that there exists a lack of parental understanding of some items and their wording in the original instrument. As a result, the OSA-18 was abbreviated to 11-items and then to 5- so that ultimately it would "*perform better as a screening tool for use in triage and referral planning.*" Our review also revealed other tools addressing this sleep problem: I'm sleepy (55). While OSA is increasingly relevant in pediatric epidemiology due to the rise in obesity, parental knowledge of the condition and consequent treatment options is imperative. A recent 2017 study regarding the development of a questionnaire informing parents of this treatment was designed by Links et al. (82). The tool aims to alleviate parental conflict around the choice for or against this treatment in children and is a first in its approach as a questionnaire focusing on medical treatment decision making. Like the objectives of OSA-5, this tool is notable in that it aims to *"improve the quality and impact of patient and family decisions about OSA diagnosis and treatment"* (82). As part of the personalized/precision medicine era, the CAS-15 (17) and PROMIS-papers pop out. The CAS-15 is one of the few tools where the respondent is the professional. The PROMIS, although presented as a potential screening/diagnostic tool, recently underwent several psychometric evaluations. It involves an item bank of Patient Reported Outcomes Measurement, or better it is intended to measure the subject's "view" of their health status (e.g. sleep). Although these patients reported outcome measures (PROM) adhere to the same psychometric characteristics as diagnostic/screening tools, the scope of a PROM is very different. Namely, PROMs allow the efficacy of a clinical "intervention" to be measured from the patients' perspective. Unfortunately, these specific instruments have not undergone all steps, accordingly, they would benefit from further validation and possible cultural/linguistic adaptation to achieve a more widespread use in the future.

As for the majority of tools that lack the detailed mention above, there is need for comment on the gradually increasing recognition for disease-specific instruments or instruments for specific populations. Alternatively, measuring the severity of sleep conditions over the frequency is still much needed. It was observed by Spruyt that nearly all questionnaires up until the 2010 search, focused on the frequency of sleep problems,

however since then, several tools have aimed to increase the specificity and sensitivity of sleep tools to the severity of common pediatric illnesses and specific age groups associated with them e.g. Down syndrome, Narcolepsy (148), infancy, etc. This specificity of condition severity and age may help to refine treatment measures and streamline clinical interventions.

Additionally, in contrast to our review in 2011, the studies reported here are English papers, although popular translations are Chinese, Portuguese, Spanish, and Turkish. That is, between 2010 and 2020 especially the CSHQ, PSQ, and OSA-18 were translated. This is likely an approximation due to the exclusion of non-English papers and of dissertations etc. In 2011, we observed that the development or modification of tools may not always evolve into a scientific paper.

Vis-à-vis fulfillment of psychometric criteria, preliminary and confirmative factor analysis methods have been included in the scope of, and completed in either partially or completely, most the studies which was lacking prior. Primarily construct and content validity *via* factor structure or item correlation, and Cronbach alpha statistics are noticed. Standardized scoring and item generation however, is still ill-managed as a requirement and is an important step in developing a diagnostic tool or adapting/translating an existing one. Nonetheless, generally, it can be said that much of the studies into tool-psychometrics deserve recognition for endeavoring to adhere to steps 1 through 11. But the overarching suggestion thus far, is to more thoroughly fulfill the facets of validation; i.e. content, convergence, discriminative, and criterion-related validity (steps 8 and 9), pilot questionnaires in the event of an adaptive change made (step 5), examine the underlying factors to ensure (uni) dimensional structure of a said tool (steps 7 and 10) and develop norms alongside cutoff scores (step 11). Furthermore, although several tools mimic classification systems a more thorough psychometric scrutiny thereof is still needed. As a consequence, to date, the vast majority of tools reflect an appraisal of the frequency of a sleep complaint.

Several limitations should be noted. We post hoc limited our flagged studies to only English language given that they reach the broader scientific community. Furthermore, several of the tools included are not 100% sleep tools (e.g. health related). In addition, our way of presenting being "New Development (N)," "Psychometric Analysis (P)," and "Translation (T)/Adaptation (A)," or a combination thereof, involved overlaps in descriptive analyses. Contrary to the original paper by Spruyt, this one did not apply searches in Dissertations and Theses, Google Scholar (Web crawling), ebooks and conference Sleep abstract books, and as a consequence might not be an exhaustive list of tools. Alternatively, studies involving app's did "hit" our search terms yet were not retained during further screening toward our aims. Lastly, given that this is a systematic review we didn't pursue a quality assessment of study designs investigating sleep tools. Nevertheless, in Spruyt et al. (2) each of the necessary steps are stipulated.

Recommendations

It is recommended that future tools further the investigation into sleep hygiene, ecology [see (143)] and schedules of pediatric populations as this is becoming a highly relevant field of research upon the introduction of technology into sleeping habits and routines. The increasing prevalence of sleep deprivation in children (152–155) requires in depth discovery as to what damage or lack thereof is being done as a result of a 21st century society.

In addition to this, it is suggested that pediatric tools should be further introduced and adapted or validated for reporting by children older than 8 years of age. Since there is evidence to suggest that children as young as eight years can report information critical to their own health, it is recommended that a large proportion of questionnaires be designed for children in this age category as well as parents (1). Conjunctional use of these however, is advised to develop any diagnosis.

Although several tools listed mimic classification systems, or were psychometrically evaluated in samples that underwent clinical diagnoses upon a classification system, there is still room for improvement. Combined with primarily convenience samples such as clinical referrals and lack of details on (at risk of being poor) sampling techniques, the internal and external validity of studies might be seriously jeopardized.

Sensitivity and specificity are key in differencing screening versus diagnostic tools. Yet also, the sample on which this difference is determined plays a key role, where the diagnostic tools chiefly aims at subjects believed to have the problem. Thus, screening tests are chosen toward high sensitivity while diagnostic tests are chosen toward high specificity (true negatives).

Lastly, caution is warranted upon a general positive score regarding reliability and validity assessment, and readers are advised to remain critical concerning the statistical techniques applied in the individual studies. Several recommendations for future tool development or evaluation have been listed in **Box 1**.

BOX 1 | Research agenda: a need for

- Tools assessing sleep ecology, sleep routines/hygiene, regularity, treatment
- Psychometric evaluation of apps
- Tools for daytime sleep
- Tools per sleep pathology
- Tools for specific populations
- Tools sensitive and specific regards classification systems
- Tools adept to developmental changes
- Tools differentiating between school days and nonschool days
- Tools as a PROM, Patient-Reported Outcome Measures
- A venue to publish psychometric evaluations of tools
- Methodologic scrutiny regarding sampling (patient/population), statistical techniques, the aim(s), and type of study
- Availability of the tools published, especially translations
- Equal attention to all 11 steps; e.g. step 3 such as answer but also time format
- Replication studies
- Self-reporting tools for school-aged children
- Question and/or Response formats beyond frequency
- Sleep duration not being a categorical answer
- Caution regarding "child"-modifications of adult tools or applications beyond the intended age range
- Culture-free or fair tools
- Reviews and meta-analyses on criterion validity of subjective tools

Tool development and evaluation, as mentioned in the past is time and labor-intensive (2). In short, scientific copycats (i.e. replication studies) are needed!

AUTHOR CONTRIBUTIONS

TS performed first search, extracted data, and wrote the first draft during her internship. Her work was updated, verified and finalized by KS.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Tool acronym	Tool
AIS	Athens Insomnia Scale
ASHS	Adolescent Sleep Hygiene Scale
ASQ	Auckland Sleep Questionnaire
ASWS	adolescent sleep wake scale
BEARS	Bedtime problems (B) Excessive daytime sleepiness (E), Awakenings During the night (A) Regularity of sleep (R) and Snoring (S)
BEDS	Behavioral Evaluation of Disorders of Sleep
BISQ	Brief Infant Sleep Questionnaire
BRIAN-K	Biological Rhythm Interview of Assessment in Neuropsychiatry – Kids
CAS-15	Clinical Assessment Score-15
CBCL	Child Behavior Checklist sleep items
CCTQ	Children's ChronoType Questionnaire
CRSP	Children's Report of Sleep Patterns
CRSP-S	Children's Report of Sleep Patterns – Sleepiness Scale
CSAQ	Children's Sleep Assessment Questionnaire
CSHQ	Children's Sleep Habits Questionnaire
CSM	Composite Scale of Morningness
CSRQ	Chronic Sleep Reduction Questionnaire
CSWS	Children's Sleep-Wake Scale
DBAS	dysfunctional beliefs and attitudes about sleep scale
ESS-CHAD	Epworth Sleepiness Scale for Children and Adolescents
FoSI	Fear of Sleep Inventory
I SLEEPY	I SLEEPY, short pediatric sleep apnea questionnaire
IF SLEEPY	IF SLEEPY, short pediatric sleep apnea questionnaire
I'M SLEEPY	I'M SLEEPY, short pediatric sleep apnea questionnaire
ISI	Insomnia Severity Index
JSQ	Japanese Sleep Questionnaire
LSTCHQ	Sleep Length and Television and Computer Habits of Swedish School-Age Children
MCTQ	Munich ChronoType Questionnaire
MEQ	Morningness-Eveningness Questionnaire
aMEQ-R	reduced Morningness-Eveningness Questionnaire
MESC	Morningness–Eveningness Scale for Children
MESSi	Morningness–Eveningness Stability Scale improved
My Sleep and I	
My children's sleep	
NARQoL-21	narcolepsy-specific HrQoL self-report questionnaire
NSD	nighttime sleep diary
NSS	Narcolepsy Severity Scale (Chinese)
OSA Screening Questionnaire	Obstructive Sleep Apnea Screening Questionnaire
OSA-18 Questionnaire	Obstructive Sleep Apnea Questionnaire
OSD-6 QoLQuestionnaire	obstructive-sleep-disorders-6-survey
oSDB and AT	Obstructive Sleep-Disordered Breathing and Adenotonsillectomy Knowledge Scale for Parents
OSPQ	omnibus sleep problems questionnaire
PADSS	Paris Arousal Disorders Severity Scale
PDSS	Pediatric Daytime Sleepiness Scale
Pediatric Sleep CGIs	Pediatric Sleep Clinical Global Impressions Scale
PedsQL	Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale
PISI	Pediatric Insomnia Severity Index
PNSSS	Parent Newborn Sleep Safety Survey
PosaST	pediatricobstructive sleep apnea screening tool
PPPS	Puberty and Phase Preference Scale (also cited as Morningness Eveningness Scale)
P-RLS-SS	Pediatric Restless Legs Syndrome Severity Scale
PROMIS	Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment item banks
PSIS	Parent-Child Sleep Interactions Scale
PSQ	Pediatric Sleep Questionnaire
PSQI	Pittsburgh Sleep Quality Index
RLS	Restless legs syndrome
SDIS	Sleep Disorders Inventory for Students
SDPC	Sleep Disturbances in Pediatric Cancer
SDSC	Sleep Disturbance Scale for Children
SDSC*	Sleep Disturbances Scale for School-age Children
SHI	Sleep Hygiene Index
SHIP	Sleep Hygiene Inventory for Pediatrics
Sleep Bruxism	parental-reported sleep bruxism
SNAKE	a questionnaire on sleep disturbances in children with severe psychomotor impairment (Schlaffragebogen für Kinder mit Neurologischen und Anderen Komplexen Erkrankungen)
SQI	Sleep Quality Index
SQ–SP	Sleep Questionnaire developed by Simonds and Parraga
SQS-SVQ	sleep quality scale and sleep variables questionnaire
SRSQ	Sleep Reduction Screening Questionnaire
SSR	Sleep Self-Report
SSSQ	simple self-report sleep questionnaire
STBUR	(Snoring, Trouble Breathing, Un-Refreshed questionnaire
STQ	Sleep Timing Questionnaire
The Children's Sleep Comic	
TuCASA	Tucson Children's Assessment of Sleep Apnea Study
YSIS	Youth Self–Rating Insomnia Scale

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Psychometric Properties and Predictive Value of a Screening Questionnaire for Obstructive Sleep Apnea in Young Children With Down Syndrome

Sarah Grantham-Hill[1], Hazel J. Evans[1,2], Catherine Tuffrey[3], Emma Sanders[1], Heather E. Elphick[4], Paul Gringras[5], Ruth N. Kingshott[4], Jane Martin[6], Janine Reynolds[4], Anna Joyce[7], Catherine M. Hill[1,2*†] and Karen Spruyt[8†]*

[1] Faculty of Medicine, School of Clinical and Experimental Sciences, University of Southampton, Southampton, United Kingdom, [2] Department of Sleep Medicine, Southampton Children's Hospital, Southampton, United Kingdom, [3] Department of Community Child Health, Solent NHS Trust, Portsmouth, United Kingdom, [4] Department of Respiratory and Sleep Medicine, Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom, [5] Department of Sleep Medicine, Evelina London Children's Hospital, Guys St Thomas's NHS Trust, London, United Kingdom, [6] Southampton Centre for Biomedical Research, University Hospital Southampton NHS Trust, Southampton, United Kingdom, [7] School of Psychotherapy & Psychology, Faculty of Humanities, Arts and Social Sciences, Regent's University London, London, United Kingdom, [8] Laboratoire de Physiologie intégrée du système d'éveil CRNL- INSERM U1028-CNRS UMR 5292, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France

Study Objectives: Obstructive sleep apnea (OSA) is common in children with Down syndrome (DS) and is associated with adverse health and cognitive outcomes. Daytime clinical assessment is poorly predictive of OSA, so regular screening with sleep studies is recommended. However, sleep studies are costly and not available to all children worldwide. We aimed to evaluate the psychometric properties and predictive value of a newly developed screening questionnaire for OSA in this population.

Methods: 202 children aged 6 months to 6th birthday with DS were recruited, of whom 188 completed cardio-respiratory sleep studies to generate an obstructive apnea hypopnea index (OAHI). Parents completed the 14-item Down syndrome OSA screening questionnaire. Responses were screened, a factor analysis undertaken, internal consistency calculated and receiver operator characteristic (ROC) curves drawn to generate an area under the curve (AUC) to assess criterion related validity.

Results: Of 188 children who completed cardiorespiratory sleep studies; parents completed the screening questionnaire for 186. Of this study population 15.4% had moderate to severe OSA defined by an OAHI of ≥5/h. Sixty-three (33.9%) participants were excluded due to "unsure" responses or where questions were not answered. Using the remaining 123 questionnaires a four-factor solution was found, with the 1st factor representing breathing related symptoms, explaining a high proportion of the variance. Internal consistency was acceptable with a Cronbach alpha of 0.87. ROC curves for the

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Massachusetts General Hospital and Harvard Medical School,
United States

***Correspondence:**
Sarah Grantham-Hill
sarah.grantham-hill@nhs.net
Catherine M. Hill
C.M.Hill@soton.ac.uk

†These authors share last authorship

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total score generated an AUC statistic of 0.497 and for the breathing subscale an AUC of 0.603 for moderate to severe OSA.

Conclusion: A well designed questionnaire with good psychometric properties had limited predictive value to screen for moderate to severe OSA in young children with DS. The use of a screening questionnaire is not recommended. Screening for OSA in this population requires objective sleep study measures.

Keywords: Down syndrome, trisomy 21, screening, obstructive sleep apnea/apnea, psychometric properties

INTRODUCTION

Down syndrome (DS) is the commonest chromosomal abnormality affecting approximately 1:1,200 live births worldwide (1). Children with DS are at increased risk of obstructive sleep apnea (OSA) a condition characterized by repetitive partial (hypopnea) or complete (apnea) airway collapse in sleep, despite continued respiratory effort. OSA is estimated to affect 75%, of this population compared to 1.2% of typically developing (TD) children (2, 3). Risk factors are multifactorial including syndrome-specific characteristics such as hypotonia, macroglossia, craniofacial structure, and obesity, exacerbated by adenotonsillar hypertrophy in early childhood (4).

OSA causes nocturnal hypoxia and fragmented sleep with adverse health consequence that have been extensively studied in TD children including: hypertension (systemic and pulmonary) (5), cognitive deficits (impaired attention and executive function) leading to impaired learning and school performance (6), as well as reduced quality of life (7), and increased health care utilization (8). Similar findings are emerging in children with DS who arguably may be more at risk due to their limited cognitive reserve and underlying cardiovascular disease (9). Indeed, Breslin et al.. studied 38 school-aged children with DS and reported that co-occurring OSA was associated with a nine point reduction in verbal IQ and reduced cognitive flexibility (10). We have also recently reported that OSA predicts deficits in parent-reported executive function behaviors in very young children with Down syndrome (11). It has further been hypothesized that OSA in DS may be a risk factor for the development of Alzheimer's disease (12). Prompt identification and treatment of OSA in DS is therefore an important goal.

Multiple studies have reported poor correlation between parental report of OSA symptoms and polysomnography (PSG) results (the gold standard for the diagnosis of OSA) (13, 14). This may be due to a lack of awareness of nocturnal symptoms or the presence of silent apnea which is difficult for parents to detect. Children with DS referred for PSG have more severe disease than TD children, suggesting that milder symptoms are overlooked or attributed to unmodifiable symptoms of DS.

Given the increased burden of disease and challenges in diagnosis in this population, the American Academy of Pediatrics recommends routine screening with PSG by the age of 4 years (15). There is evidence of limited compliance with these guidelines with one study reporting that only 47.7% of children had undergone a PSG (16). In the UK, screening is recommended annually from infancy to 3–5 years of age in DS, using a minimum of pulse oximetry (17). If there is any abnormality detected on pulse oximetry, or clinical suspicion of a false negative oximetry result, then further assessment with, as a minimum, cardiorespiratory polygraphy studies is recommended (17). We have published recommended oximetry screening thresholds that can be used to determine the need for further diagnostic evaluation in this population (18). This screening method has a high reported sensitivity (92%) with a specificity (63%) with one night of domiciliary Masimo pulse oximetry. While oximetry is a screening tool that is, on the whole, well tolerated, it has resource implications (19). Other groups have researched alternative screening methods, including urinary biomarkers, 3D photogrammetry, and combined measures including cephalometry and multiple clinical variables (20–22). All of these approaches have limitations of time and cost and therefore a screening questionnaire is an appealing alternate approach.

Screening questionnaires are used in clinical practice to identify sleep problems in TD children. There has been increasing work looking at the utility of these questionnaires in the DS population. Ebsensen et al.. studied the convergent validity of three questionnaires, the Behavioral Evaluation of Disorders of Sleep (BEDS), Children's Sleep Habits Questionnaire (CSHQ), and Sleep Disturbances Scale for Children (SDSC) in a group of 30 children with DS aged 6–17 years. All three questionnaires have sub-scales relating to sleep disordered breathing and were previously validated (23–25). There were strong correlations between these sub-scales but, in the absence of an objective measure of OSA in this study, no conclusions could be drawn about the sub-scales' ability to predict OSA (26). OSA screening questionnaires have been designed for TD children. The Pediatric Sleep Questionnaire (PSQ) had initial reported sensitivities and specificity of 0.85 and 0.87 respectively to predict moderate to severe OSA in TD children at 2–18 years (27, 28), however concerns have been raised about its specificity within TD populations. Sproson et al.. reported specificity of only 0.17 for an OAHI ≥5/h in a young UK population (29). It may have further limitations in the DS population as it includes questions that relate to child behavior and growth that may be due to underlying features of their DS, as opposed to co-occurring OSA. Cielo et al.. encountered this difficulty when testing the PSQ in children with cranio-facial abnormalities where sensitivity and specificity were only 0.57 and 0.48 respectively to predict moderate to severe OSA (30).

Furthermore, Pabery et al.. reported an even lower sensitivity of 0.37 for the PSQ to predict moderate to severe OSA in 35 children with Down syndrome aged 2–16 years (31).

We have previously reported the methodology used to design a 14-item OSA screening questionnaire intended for children with DS aged up to 6 years (32, 33). Specifically, we used a content validity process to design a questionnaire specific to children with DS incorporating expertise from health care professional and parents into the design process. Details of this process are outlined elsewhere (28, 29). The present study aimed to evaluate the psychometric properties and predictive value of this questionnaire when tested in a population of young children with DS.

MATERIALS AND METHODS

Participants

Children with a confirmed diagnosis of DS between the ages of 6 months to 6th birthday were recruited to one of three research centers in the UK at Southampton, Sheffield, and The Evelina London Children's hospitals. Children were excluded if they had undergone a cardiorespiratory sleep study in the preceding 3 months, were receiving home oxygen therapy or non-invasive ventilation. Children were recruited through multiple approaches as previously described (19).

Measures

Demographics and Medical History

Parent/caregivers provided information on their child's age, gender, relevant past medical history (use of prophylactic asthma treatment, upper airway surgery, epilepsy, congenital cardiac condition, home oxygen use and whether born prematurely under 37 weeks gestation) and socio-demographic characteristics including parental education levels and smoking status. Children were weighed and measured and a body mass index calculated.

Questionnaire

The DS OSA questionnaire, developed by Sanders et al. (32), comprises 14 items rated on a five point Likert scale: never (never in the past 6 months), Rarely (less than one night a week), Occasionally (1–3 nights a week), almost always (4–6 nights a week), always (every night). An additional "unsure" response was allowed for each item. The questionnaire was designed to be completed by the child's primary caregiver. Details of the questions can be found in **Tables 1** and **4**.

Domiciliary Cardiorespiratory Polygraphy

OSA was assessed using the SOMNOtouch device (SOMNOmedics, Germany) comprising chest and abdominal respiratory inductance plethysmography (RIP) bands, internal pulse oximetry, nasal pressure flow with snore sensor, body position sensor, and actigraphy. We have previously reported our positive experience of domiciliary studies in this population (34). A sleep log recorded sleep onset, night waking's, and morning wake up times.

TABLE 1 | Number of missing and unsure data items as per question response (N=186).

Question number	Missing data items [frequency (%)]	Unsure data items [frequency (%)]
1. How often does your child snore when they do not have a cold?	0 (0.0%)	4 (2.2%)
2. How often can you hear your child snoring from outside the bedroom?	0 (0.0%)	6 (3.2%)
3. How often does your child struggle to breath while asleep?	1 (0.5%)	22 (11.8%)
4. How often does your child's breathing go quiet and then he/she gasp?	0 (0.0%)	21 (11.3%)
5. When your child is asleep, how often do you touch/nudge your child to make them breathe again?	0 (0.0%)	11 (5.9%)
6. How often does your child sleep in unusual positions?	1 (0.5%)	1 (0.5%)
7. How often does your child have restless sleep?	2 (1.0%)	5 (2.7%)
8. How often does your child sweat while asleep?	1 (0.5%)	10 (5.4%)
9. How often does your child wake up during the night? (more than children of a similar age)?	1 (0.5%)	5 (2.7%)
10. How often does you child have difficulty waking up in the morning, even after getting plenty of sleep?	1 (0.5%)	1 (0.5%)
11. How often is your child grumpy first thing in the morning?	1 (0.5%)	2 (1.1%)
12. How often does your child tend to breathe during their mouth during the day?	0 (0.0%)	41 (22.0%)
13. How often is your child unusually sleepy during the day?	0 (0.0%)	8 (4.3%)
14. How often does your child appear more hyperactive or fidgety than children of a similar age?	0 (0.0%)	13 (7.0%)

Studies were scored by an experienced technologist (RNK), using Domino Light software (SOMNOmedics, Germany). Details of scoring criteria and quality assessment of studies have been published (19). Sleep and wake were estimated using parental sleep log and integrated actigraphy. As per AASM scoring criteria, where two or more signals were of poor quality, data were excluded. Respiratory events were scored according to standard pediatric scoring criteria for adapted sensors (35). Where nasal flow signal was lost an "undefined apnea" was scored, where RIP sum indicated paradoxical breathing in the presence of a minimum three percent oxyhemoglobin desaturation for at least two breaths. The obstructive apnea/hypopnea index (OAHI) was calculated by summing obstructive apnea, hypopnea, mixed and undefined apnea indices during the total sleep time. OSA was diagnosed if OAHI was ≥ 5/h representing both a meaningful threshold for clinical intervention and reflecting the sensitivity of domiciliary cardiorespiratory polygraphy in children (6).

Procedure

The study was approved by the UK National Research Ethics Committee (reference 13/SC/0106). Parents provided informed consent for their child to participate. Procedures for the full study are published (18).

Statistical Analysis

Analyses were performed using SPSS (IBM SPSS, version 22.00, Chicago, IL, USA). Questionnaire data were checked for entry error and 10% were double entered at random to check for data integrity.

Responses were initially screened for missing and unsure responses. Items at this point were considered for ongoing inclusion in further analysis. As principle component analysis and reliability analysis require continuous data entry, 63 participants who had given an "unsure" response or had failed to respond to any item were excluded.

Demographics, past medical history and OAHI were compared between the excluded and included participants using either the chi-squared test or paired T tests to detect significant differences between the groups.

Question responses were split into positive or negative responses based on clinical significance. For example, in question 1 "how often does your child snore when they do not have a cold" a negative response was counted as "never, rarely, and occasionally" and a positive response as "almost always and always." Demographics and past medical history of participants were compared for these dichotomized responses using a chi-squared test or paired T-test to identify any bias in response.

A principal component analysis was conducted to identify structure within the questionnaire and to determine the relationship of its underlying dimensions. A Kaiser-Meyer-Olkin (KMO) adequacy of sample measure was performed (36). To be an adequate sample a value of 0.5 is required. Factors were initially extracted using an Eigen-value greater than one. To aid extraction, scree plots and an approach with fixed number of factors were used. An orthogonal varimax rotation aids interpreting the factors to produce defined subscales. Factors were interpreted and assigned meaning by the authors SG-H, KS, and CH. Stability of the factors were checked by performing a split half method and ensuring similar results were achieved to those for the group as a whole. Cronbach alpha, a measure of internal consistency, was checked for the scale as a whole. Internal consistency of the subscales was then measured using a split half method.

Receiver operator characteristic (ROC) curves were generated for both the total score of the questionnaire and the underlying subscales as predicators of OSA status. Questionnaire responses were scored from 1 to 5, where 1=never and 5=always. Area under the curve (AUC) statistics were generated: An AUC of 0.5 indicates no predictive power and an AUC of 1 indicates perfect predictive power.

The study aimed to choose a point on the curve which maximized sensitivity over specificity to identify the maximal number of true positives based on the concept that the questionnaire would act as an initial screening tool rather than a diagnostic tool. This value would be out of total maximum possible points scored from the questionnaire.

RESULTS

Two hundred two participants enrolled in the study, of whom 186 had both a completed DS OSA questionnaire and a calculated OAHI. Participant flow through the study is shown in **Figure 1**.

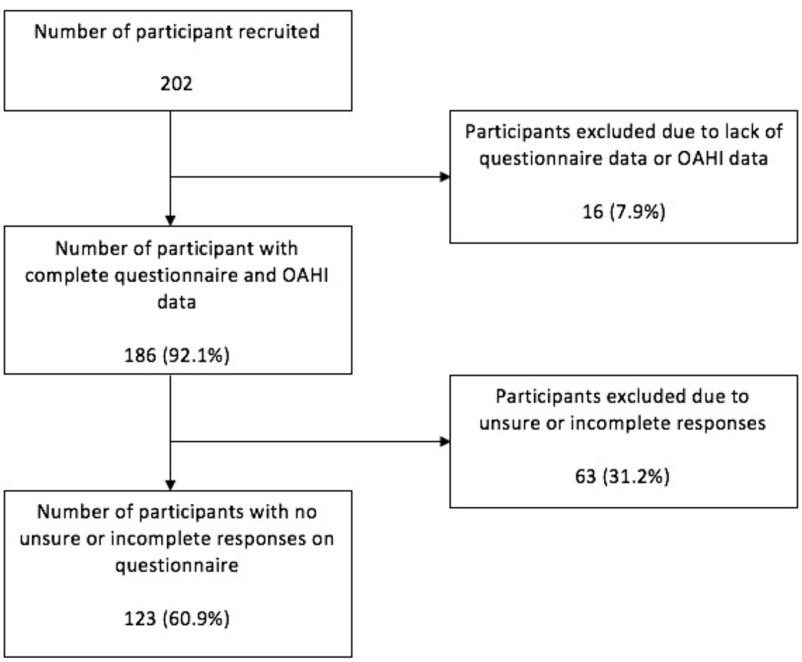

FIGURE 1 | Participant flow throughout the study.

Missing and Unsure Data Items

The number of unsure and missing data items among this sample of 186 are shown in **Table 1**. Twenty-two percent of all parents completing the questionnaire answered "unsure" to question 12 "how often does your child tend to breathe through their mouth during the day." It was therefore felt to be a poor question and excluded from further analysis.

Sixty-three (33.9%) parents answered randomly "unsure," or data were missing, for one or more other question and these questionnaires were excluded from data analysis leaving a sample of 123 (66.1%) fully completed questionnaires for the final analysis.

Demographic and Clinical Characteristics

Demographics of the final sample are shown in **Table 2**. There were no significant differences in child's age, gender, body mass index (BMI) category, relevant past medial history, parental socio-demographic features, or study center between the 123 (66.1%) participants included in the final analysis and 63 (33.9%) that were excluded. Significant difference in responses to questions are shown in **Table 3A** for when comparing "unsure response" to an alternative response and **Table 3B** when comparing dichotomized positive and negative responses to individual questions. Where significant differences in clinical or demographic characteristics were identified these were discussed by lead authors. It was agreed that these did not represent any systemic bias. No question items were rejected on the basis of these findings.

Psychometric Properties

A principle component analysis was conducted on 13 items with an orthogonal rotation (varimax). The Kaiser-Mayer-Olkin (KMO) measure verified the sampling adequacy for the analysis with a KMO =0.843, additionally all individual KMO values were above the acceptable limit.

Initial analysis extracted three factors with Eigen-values greater than 1. This explained 61.7% of the variance, however

TABLE 2 | Demographic and respiratory event differences for the included and excluded groups.

Item		Whole group (n=186)	Included (n=123)	Excluded (N=63)	P value
Gender	Male:female	99:87	65:58	34:29	0.504
Age in months (mean)		36.16 (SD 20.6) (range 6–71)	34.87 (SD 20.3) (range: 6–71)	38.68 (SD 21.1) (range 6–71)	0.659
BM1 > 95th centile [restricted to those aged ≥ 2 years, (N=129]		24 (18.6%)	13 (16.8%)	11 (21.2%)	0.069
Previous upper airway surgery		33 (17.7%)	22 (17.8%)	11 (17.5%)	0.560
Parent 1 educational level	One GCSE at C level	29 (15.6%)	20 (16.3%)	9 (14.3%)	0.393
	A-level	23 (12.4%)	16 (13%)	7 (11.1%)	
	HND	35 (18.8%)	24 (18.5%)	11 (17.5%)	
	Degree	74 (39.8%)	50 (40.7%)	24 (38.1%)	
Parent 2 educational level	One GCSE at C level	22 (11.8%)	14 (11.4%)	8 (12.7%)	0.693
	A-level	23 (12.4%)	13 (10.6%)	10 (15.9%)	
	HND	29 (15.6%)	23 (18.7%)	6 (9.5%)	
	Degree	72 (38.7%)	48 (39%)	24 (38.1%)	
Respiratory event category	OAI > 1/h	44 (22.4%)	27 (22.0%)	17 (27%)	0.469
	OAHI≥2/h	81 (43.5%)	57 (46.3%)	24 (38.1%)	0.283
	OAHI≥5/h	26 (14%)	19 (15.4%)	7 (11.1%)	0.284
	OAHI≥10/h	14 (7.5%)	10 (8.1%)	4 (6.3%)	0.455

Further clarification of educational level: 1. GCSE at level C: has passed examinations conducted at the age of 16 years, 2. A-levels: has obtained examination results at the age of 18 years, 3. HND: post-18 year higher education achievement taken as alternative to a degree for more vocational subjects, 4. Degree: successful completion of a university course.

TABLE 3A | Responses to question items where proportion answering unknown varied significantly according to demographic and clinical characteristics of the sample (n=186).

Question item	Demographic or clinical characteristic		Number (%) or mean (SD) by item response		P value
			Response "unknown"	All other responses	
3. *How often can you hear your child struggle to breathe while asleep?*	History of upper airway surgery	Yes	0 (0%)	29 (17.8%)	0.018
		No	22 (100%)	134 (82.2%)	
	Age (months)		42 (4.5%)	35 (1.6%)	0.032
4. *How often does your child's breathing go quiet and then he/she gasps?*	BMI		17.87 (1.5)	16.82 (1.3)	0.03
13. *How often is your child unusually sleepy during the day?*	Smokers in the home	Yes	4 (50%)	17 (9.6%)	0.06
		No	4 (50%)	161 (90.4%)	
14. *How often does your child appear more hyperactive of fidgety than children of a similar age?*	Smokers in the home	Yes	4 (30.8%)	17 (9.8%)	0.036
		No	9 (69.2%)	156 (90.2%)	

Percentages are calculated out of respondents to the questions.

TABLE 3B | Demographic and clinical characteristics of the sample that differed significantly in respondents answering positively *versus* negatively to specific questions.

Question item	Demographic or clinical characteristic	Number (%) or mean (SD) by item response			P value
			Less positive response (Category 1)	More positive response (Category 2)	
1. *How often does your child snore when they do not have a cold?*	Presence of wheeze	Yes	51 (42.5%)	37 (59.6%)	0.014
		No	69 (57.5%)	24 (38.8%)	
		Not known	0 (0%)	1 (1.6%)	
	Use of prophylactic asthma treatment*	Yes	13 (10.9%)	12 (19.5%)	0.045
		No	40 (33.3%)	27 (43.4%)	
		Not applicable	67 (55.8%)	23 (37.1%)	
	Parental education level**	Unknown	5 (4.4%) 13 (10.9%)	0 (0%) 7 (11.3%)	0.001
	Parent 1	No examinations	3 (2.7%) 2 (1.7%)	5 (8.1%) 6 (9.7%)	0.002
	Parent 2	GCSE less than a D	5 (4.4%) 4 (3.4%)	5 (8.1%) 6 (9.7%)	
		GCSE more than a C	12 (10%) 11 (9.2%)	16 (25.2%) 11 (17.7%)	
		A levels	13 (10.9%) 13 (10.9%)	10 (16.2%) 10 (16.1%)	
		HND	21 (17.6%) 19 (16%)	14 (22.8%) 10 (16.1%)	
		Degree	60 (50%) 57 (47.9%)	12 (19.6%) 12 (19.3%)	
2. *How often can you hear your child snoring from outside the bedroom?*	Presence of wheeze	Yes	62 (43.4%)	24 (64.9%)	0.02
		No	81 (56.6%)	12 (32.4%)	
		Unsure	0 (0%)	1 (2.7%)	
	Parental education levels	Unknown	5 (3.5%) 15 (10.6%)	0 (0%) 4 (10.8%)	0.001
	Parent 1	No examinations	6 (4.2%) 6 (4.2%)	2 (5.4%) 3 (8.1%)	0.002
	Parent 2	GCSE less than a D	7 (4.9%) 8 (5.6%)	2 (5.4%) 2 (5.4%)	
		GCSE more than a C	16 (11.3%) 13 (9.2%)	12 (32.4%) 8 (21.6%)	
		A levels	17 (11.9%) 15 (10.6%)	6 (16.2%) 8 (21.6%)	
		HND	22 (15.5%) 21 (14.8%)	12 (32.4%) 8 (21.6%)	
		Degree	69 (48.7%) 64 (45.%)	3 (8.2%) 4 (10.8%)	
3. *How often can you hear your child struggle to breath while asleep?*	Presence of wheeze	Yes	40 (39.6%)	42 (67.7%)	0.001
		No	60 (59.5%)	20 (32.3%)	
		Unsure	1 (0.9%)	0 (0%)	
	Use of prophylactic asthma treatment	Yes	10 (9.9%)	15 (24.2%)	0.001
		No	32 (31.7%)	28 (45.2%)	
		Unapplicable	59 (58.4%)	19 (30.6%)	
	Parent 1 education	Unknown	4 (4%)	0 (0%)	0.001
		No examinations	1 (1%)	5 (8.1%)	
		GCSE less than a D	2 (2%)	6 (9.6%)	
		GCSE more than a C	13 (13%)	13 (21%)	
		A levels	11 (11%)	10 (16.1%)	
		HND	19 (19%)	14 (22.6%)	
		Degree	50 (50%)	14 (22.6%)	
4. *How often does your child's breathing go quiet and then he/she gasps?*	Parental education level	Unknown	4 (5.3%) 8 (10.4%)	1 (1.1%) 10 (11.6%)	0.001
	Parent 1	No examinations	1 (1.3%) 1 (1.3%)	6 (6.9%) 7 (8%)	0.003
	Parent 2	GCSE less than a D	4 (5.3%) 3 (3.9%)	4 (4.6%) 4 (4.6%)	
		GCSE more than a C	6 (7.8%) 7 (9.1%)	20 (23%) 14 (16.1%)	
		A levels	10 (13%) 5 (6.5%)	11 (12.6%) 15 (17.2%)	
		HND	11 (14.3%) 11 (14.3%)	22 (25.3%) 16 (18.4%)	
		Degree	41 (53%) 42 (54.5%)	23 (26.5%) 21 (24.1%)	
5. *When your child is asleep how often do you nudge/touch them to make them breath again?*	Smokers in the house (0.03)	Yes	9 (6.7%)	10 (24.4%)	0.003
		No	125 (93.3%)	31 (75.6%)	
	Parental education	Unknown	5 (3.8%) 12 (9%)	0 (0%) 7 (17%)	0.001
		No examinations	5 (3.8%) 4 (3%)	3 (7.3%) 5 (12%)	0.001
		GCSE less than a D	7 (5.3%) 8 (6%)	2 (4.9%) 2 (4.9%)	
		GCSE more than a C	12 (9%) 11 (8.3%)	14 (34.1%) 9 (22%)	
		A levels	15 (11.3%) 15 (11.3%)	8 (19.5%) 6 (14.6%)	
		HND	25 (18.8%) 20 (15%)	7 (17.1%) 8 (20%)	
		Degree	64 (48.%) 63 (47.4%)	7 (17.1%) 4 (9.5%)	
7. *How often does your child have restless sleep?*	Use of prophylactic asthma treatment	Yes	2 (4.%)	23 (17.7%)	0.018
		No	16 (32.7%)	51 (39%)	
		Not applicable	31 (63.3%)	56 (43.3%)	
	BMI category	Normal	0 (0%)	4 (4.1%)	0.022
		Underweight	13 (65%)	79 (81.4%)	
		Overweight	4 (20%)	2 (2.1%)	
		Obese	3 (15%)	12 (12.4%)	

(Continued)

TABLE 3B | Continued

Question item	Demographic or clinical characteristic		Number (%) or mean (SD) by item response		P value
			Less positive response (Category 1)	More positive response (Category 2)	
8. *How often does your child sweat while asleep?*	Presence of smokers	Yes	5 (25%)	97 (62.6%)	0.002
		No	15 (75%)	58 (37.4%)	
	Presence of wheeze	Yes	43 (42.2%)	43 (58.9%)	0.025
		No	59 (57.8%)	29 (39.7%)	
		Not applicable	0 (0%)	1 (1.4%)	
	Parent 1 education level	Unknown	4 (3.9%)	1 (1.4%)	0.028
		No examinations	3 (2.9%)	6 (8.3%)	
		GCSE less than a D	3 (2.9%)	6 (8.3%)	
		GCSE more than a C	12 (11.8%)	15 (20.8%)	
		A levels	14 (13.7%)	8 (11.1%)	
		HND	16 (15.7%)	16 (22.2%)	
		Degree	50 (49.1%)	20 (27.9%)	
10. *How often does your child have difficulty waking up in the morning, even after getting plenty of sleep?*	Parent 2 education level	Unknown	11 (13.5%)	9 (30%)	0.003
		No examinations	6 (7.4%)	3 (10%)	
		GCSE less than a D	8 (9.9%)	2 (6.7%)	
		GCSE more than a C	18 (22.2%)	2 (6.7%)	
		A levels	16 (19.8%)	7 (23.3%)	
		HND	22 (27.2%)	7 (23.3%)	

Further clarification of educational level: 1. GCSE at level C: has passed examinations conducted at the age of 16 years, 2. A-levels: has obtained examination results at the age of 18 years, 3. HND: post-18 year higher education achievement taken as alternative to a degree for more vocational subjects, 4. Degree: successful completion of a university course

**For asthma treatment, this was only recorded for children who reported a history of wheeze*

***For parental education the first parent is shown in black and second parent in gray.*

most of the variance was accounted for by the first factor (41.3%). The screen plot showed inflexion both at the second factor and the 4th, with the 3rd and 4th factor contributing a similar amount of the total variance. To interpret the factors further it was forced to produce either a two, three, or four factor solution. These were reviewed by the authors and it was felt that a four-factor solution was the most appropriate and meanings were assigned to each factor, generating subscales where factor 1 represented breathing and physical related symptoms; factor 2 represented night time behavior; factor 3 represented morning behavior; and factor 4 represented the impact of poor sleep on the next day's behavior. Items were considered to load on to a factor if they had a value of greater than 0.3 and substantially load if they had value greater than 0.7. If items loaded onto multiple factors they were assigned to the factor in which they had the highest loading. If they had similar loading, as was the case with item 5 (when your child is asleep, how often do you touch/nudge your child to make them breathe again), they were assigned to the factor which clinically matched the best item. Loading of the factors determined the subscale structure of the questionnaire which is shown in **Table 4**.

Reliability

A split half method was used to examine the internal consistency of the individual subscales. Spearman Brown coefficients were 0.8 for subscale 1, 0.79 for subscale 2, 0.75 for subscale 3, and 0.5 for subscale 4. An acceptable reliability was therefore achieved in subscales 1–3 but not subscale 4.

The reliability for the scale, as a whole, was assessed using Cronbach alpha which gave a value of 0.87

TABLE 4 | Structure of the questionaire.

Breathing Subscale
How often does your child snore when they do not have a cold?
How often can you hear your child snoring from outside the bedroom?
How often can you hear your child struggle to breathe while asleep?
How often does your child's breathing go quiet and then he, she gasp?
How often does your child sweat while asleep?
Night time behavior subscales
How often does your child have restless sleep?
How often does your child wake up during the night (compare to a child of a similar age)
How often does your child sleep in unusual position?
Morning behavior subscale
How often does your child have difficulty waking up in the morning even after getting plenty of sleep?
How often is your child grumpy first thing in the morning?
Impact of poor sleep on next day behavior subscale
How often is your child unusually sleepy during the day?
How often does your child appear more hyperactive or fidgety than children of a similar age?

Receiver Operator Characteristic Analysis

The mean and standard deviation for the total score and subscale scores are shown in **Table 5**.

The AUC for the total questionnaire score was 0.497 (95% CI 0.352–0.642) for on OAHI > 5/h, and 0.569 (0.360–0.778) for an OAHI > 10/h. The breathing subscale gave an AUC of 0.542 (0.407–0.677) for an OAHI> 5/h, and 0.603 (0.409–0.796) for an OAHI> 10/h. AUC values for other subscales are shown in **Table 6**. ROC analysis was additionally performed for the other

TABLE 5 | Questionaire total score and subscales scores.

	Mean score (SD)
Total score	33.3 (10)
Breathing subscale	14.1 (5.6)
Night-time behavior subscale	10.7 (3.8)
Morning behavior subscale	3.5 (1.7)
Impact of poor sleep on the next day behavior subscale	5.1 (2.02)

TABLE 6 | Area under the curve values for total score of the questionnaire and subscales for obstructive apnea hypopnea index (OAHI).

	OAHI≥5 (95% CI and standard error)	OAHI≥10 (95% CI and standard error)
Total questionnaire score	0.497 (0.352–0.642) SE: 0.074	0.569 (0.360–0.778) SE: 0.107
Breathing and physical related symptoms subscale	0.542 (0.407–0.677) SE: 0.069	0.603 (0.409–0.796) SE 0.099
Night time behavior subscale	0.307 (0.234–0.506) SE: 0.070	0.442 (0.233–0.651) SE 0.107
Morning behavior subscale	0.501 (0.354–0.647) SE: 0.075	0.596 (0.403–0.790) SE: 0.099
Impact of poor sleep on the next day behavior subscale	0.618 (0.48–0.755) SE: 0.070	0.663 (0.490–0.836) SE: 0.088

subscales and is shown in **Table 6**. Furthermore, the group was stratified by gender, age, and previous ear, nose, and throat (ENT) surgery for the total score and breathing subscale. No AUC greater than 0.7 was achieved.

It was possible that some meaningful data were lost from over-stringent removal of questionnaires with unsure responses. Therefore, factor analysis was repeated including these questionnaires and replacing unsure responses with a mean imputation method. There was no change in the factors extracted. Next, including this complete data set, ROC curve analysis was repeated. The AUC for the total score to predict OAHI > 5/h was 0.515. Further analyses were not performed.

Predictive Value

Based on ROC curve analysis to maximize sensitivity an optimal total questionnaire score cut off score of 19.5 (out of a total of 65) was generated. This identified 18/19 of the true positives (sensitivity of 94.7%) and 6/104 of true negatives (specificity of 1.9%). The positive predictive value was 0.14 and negative predictive value was 0.86. This is illustrated in **Figure 2**, which highlights the failure of the questionnaire to screen out children with OAHI ≥ 5/h. The predictive value of the questionnaire did not improve when the 22 children with a past history of upper airway surgery were removed from the sample. In practice,

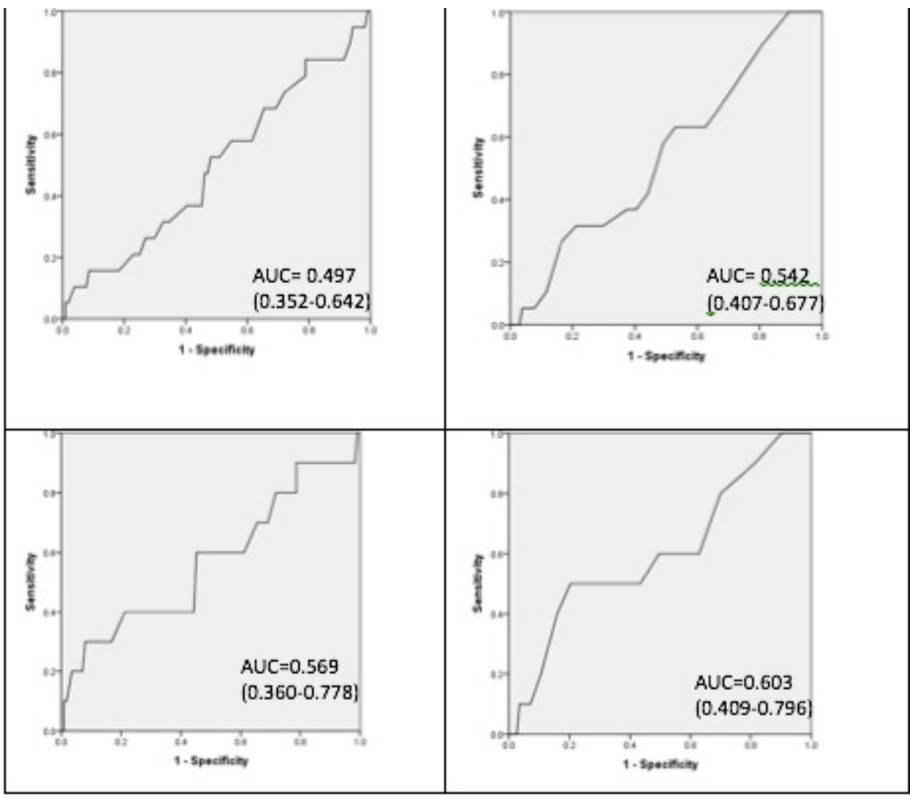

FIGURE 2 | Receiver operating characteristic curves. From left to right. Top left obstructive apnea hypopnea index (OAHI)≥5/h and whole questionnaire score. Top right OAHI > 5/h and breathing subscale. Bottom left OAHI≥10/h and whole questionnaire score. Bottom right OAHI≥10/h and breathing subscale.

therefore, for every 100 children screened, 94 would screen positive and require confirmatory diagnostics.

DISCUSSION

We have demonstrated that the DS OSA questionnaire has poor positive predictive value for clinically relevant OSA in young children with DS, despite robust psychometric properties. This supports previous findings that parental report in children with DS is a poor predictor of OSA (14, 37–39).

Similarly, the literature indicates that health professionals struggle to diagnose OSA based on clinical findings in DS patients, even when supported by questionnaire items (13, 29, 40). Recent data from the UK support our findings by demonstrating that the PSQ questionnaire, which has established high sensitivity in TD children, performs very poorly in this group (31).

Other groups have combined simple objective measures, such as BMI, with questionnaire data and medical history to improve prediction of OSA. Skotko et al. developed a tool to identify OSA in the Down syndrome population using data from 130 patients aged 3–24 years (22). The model had 300 rules and 101 variables, including questions from the CSHQ and sleep-related breathing disorder subscale of the PSQ questionnaires, patients' past medical history, physical examination, and BMI. This model had a negative predictive value of 90% and positive predictive value of 25% for an AHI ≥5/h. While this shows promise it has yet to be validated in another data set. Furthermore, given the large number of variables required for analysis, it may not be a simple tool to introduce into routine clinical practice unless technological aids are also established (22).

Development of the DS OSA questionnaire closely followed recommended methodology (33). The failure of this questionnaire to be a useful screen for OSA, despite a structured design process and good psychometric properties, reminds researchers of the importance of objective screening measures for OSA in clinical practice. It also serves to remind clinicians about the importance of only using questionnaire tools that have been robustly validated in the relevant population.

A key limitation of the questionnaire was the inclusion of the unsure response item. The aim was to prevent respondents giving false response to questions. It also allowed us to identify questions which could potentially lack clarity. This did, however, result in the exclusion of 33.9% of the sample. Given that there were no significant demographic or clinical differences between the final sample and the excluded group it is unlikely that this led to any systematic bias. Furthermore, using mean imputation methods to replace these questions did not change the factor structure of the questionnaire.

A further limitation of our data was the use of cardiorespiratory polygraphy rather than gold standard polysomnography to generate the OAHI. Cardiorespiratory studies tend to underestimate the OAHI as this technique cannot detect hypopneas associated with arousal. Use of cardiorespiratory studies in our study was a pragmatic choice reflecting typical UK practice. Furthermore, recent data in children indicate that this technology predicts OSA (defined by OAHI ≥ 5.6/h from polysomnography) with a sensitivity of 90.9% (95% CI, 79.6–100%) and a specificity of 94.1% (95% CI, 80–100%) (41). For this reason, we selected an OAHI of >5/h as a threshold to define OSA resulting in a prevalence rate of OSA in the sample of only 15%.

An additional limitation was that measurements for height and weight were only taken once by trained research nurses. A single measure may have led to inaccuracy.

Higher prevalence rates of OSA have been reported in large sample of individuals with DS. However, prevalence rates are influenced by age, sampling strategy, and the threshold used to define OSA. For example, Maris et al. reported OSA in 66.4% of 122 children with DS aged 0–18 years (based on a threshold of OAHI of >2/h) (42). However, 57% of these children were clinically referred with concerns about apnea. In contrast Skoto et al. reported lower rates of 44.4% in 56 children aged 3–5 years randomly selected from a DS follow-up program at Boston Children's Hospital (based on a threshold of OAHI of >2/h) (22). Due to the lack of state funded healthcare in the USA it is possible that children with access to regular care were from wealthier families. In the same way, however, social class can influence clinical research participants. Indeed in our study 42% of children had a parent who was a graduate suggesting a similar class bias in both studies (43). Our study population had a narrow age range (0.5–6 years), were largely community recruited and we used a threshold OAHI of > 5/h to reflect the sensitivity of cardiorespiratory polygraphy for the present analysis. Using a threshold of OAHI >2/h in our sample prevalence rates of OSA are 46.3%, almost identical to the Skoto figures, although there are difference as noted above in the population recruited. Also of note 17.8% of the final sample of 123 children had previously had adenotonsillectomy, potentially reducing their OAHI.

While in principle the low numbers with OSA as defined in this study may have reduced our ability to explore the validity of the questionnaire, as illustrated by **Figure 3**, there were no differences in responses between those with and without OSA.

The research field attests to a motivation of clinicians and researchers to offer a simpler screening alternative to cardiorespiratory or polysomnographic evaluation of OSA for children with DS. This motivation is understandable as sleep studies are expensive and may be poorly tolerated by children with learning disabilities. Alternative screening methods have been researched to offer a non-invasive alternative to polysomnography. Esbensen et al. investigated the potential of actigraphy to identify OSA in 27 children aged 5–17 years with DS. Actigraphy correlated with PSG for the total sleep time, wake after sleep onset, and sleep efficiency but not a clinical diagnosis of OSA (44). Elsharkawi et al. reported that a combination of four urinary biomarkers had a positive predictive value of 90% and negative predictive value of 68% to predict OSA at an AHI≥1/h (21). These techniques are expensive, not widely available and the authors noted that further studies were required in larger populations before this approach could be recommended as a screening tool. Imaging techniques have been studied. Three-dimensional photogrammetric measurements have been

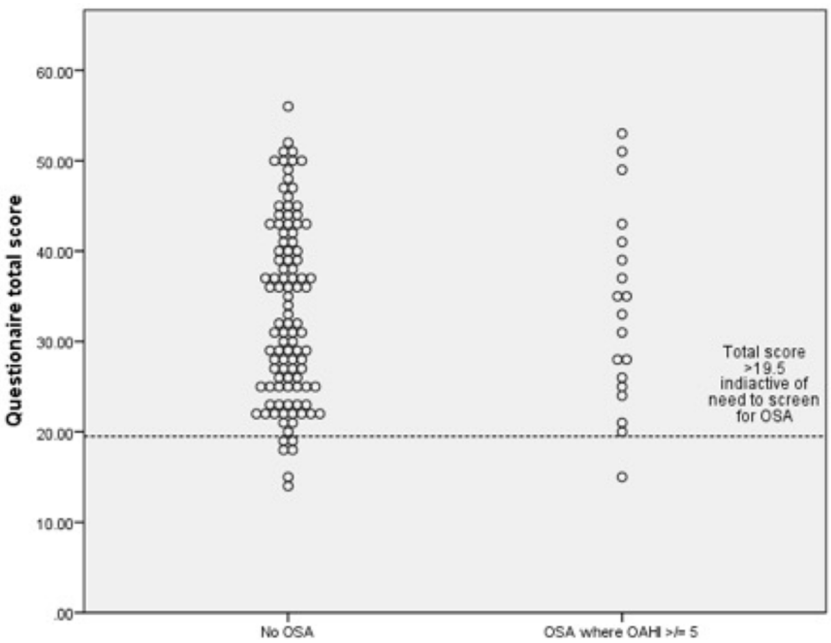

FIGURE 3 | Dot plots for obstructive apnea hypopnea index (OAHI) for (n-123) for children with and without obstructive sleep apnea (OSA) with a questionnaire score cut off of 19.5.

compared in DS children with and without OSA and with no differences established (20). Similarly, cephalometry was not found to usefully contribute to prediction of OAHI in a study of 130 children and young adults with DS (22). UK Royal College of Paediatrics and Child Health currently recommends screening children with DS annually for OSA from infancy to 5 years with a minimum of pulse oximetry (19). There has previously been little evidence to support this technique in this population but we have recently demonstrated a high sensitivity (92%) and specificity (63%) of one night of domiciliary Masimo pulse oximetry to predict OSA diagnosed by cardiorespiratory polygraphy (18).

CONCLUSION

A carefully constructed questionnaire with good content validity lacks criterion validity to make it a useful tool in clinical practice. This is in keeping with the literature that parental report and clinical evaluation in routine practice are poor predictors of OSA in DS. As such, objective screening methods should be adopted and our previous findings suggest that domiciliary pulse oximetry could offer an acceptable first-line screening approach, halving the number of children requiring more detailed sleep studies.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UK National Research Ethics Committee (reference 13/SC/0106). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CH and HJE conceived the idea for the study. CH, HEE, CT, and ES designed the questionnaire. CH, HJE, HEE, RK, JM, JR, AJ, and PG were involved in the recruitment of the subjects, conducting the questionnaire and PSG. SG-H, CH, and KS were involved in data analysis, data interpretation, and authoring the manuscript.

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REVIEW
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Tools for the Assessment of Pediatric Restless Legs Syndrome

Pamela Hamilton Stubbs[1*] *and Arthur S. Walters*[2]

[1] *Dr. Hamilton-Stubbs Sleep and Total Wellness Institute, LLC., Richmond, VA, United States,* [2] *Sleep Division, Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN, United States*

Background: There are only a few of the questionnaires for the diagnosis, severity and quality of life of adult Restless Legs Syndrome (RLS) that have been utilized in children. Even fewer of these types of instruments have been developed specifically for Pediatric RLS.

Methods: This article is a review of instruments used in adult RLS, their applicability to children and of instruments specifically developed for childhood RLS.

Results: A single question for the diagnosis of RLS has been validated for adults and utilized in one epidemiology study of adolescents with RLS. The Pediatric Emory RLS questionnaire has been developed as a diagnostic instrument for childhood RLS, utilized in two studies of RLS in children, but not yet validated. The IRLS (International Restless Legs Scale), the CGI (Clinical Global Impression), and the RLS-6, which have been validated for determining adult RLS severity, were administered without difficulty in one therapeutic study of adolescent RLS. In addition, the IRLS has also been utilized in another 5 studies of childhood and adolescent RLS. The pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) has been developed for use in children but not yet validated. A modification of the P-RLS-SS based upon rating the severity of the 4 diagnostic criteria for RLS has been developed for children but not yet validated. There are no Quality of Life scales developed for Pediatric RLS. However, 3 separate studies utilized the general Peds Quality of Life Inventory (PedsQL) in RLS children and adolescents and one of these studies also employed the general Sleep Behavior Questionnaire (SBQ) and yet another of these studies also employed the Pediatric Symptom checklist (PSC).

Discussion: There is a need for the development and validation of instruments specific to Pediatric RLS. Meanwhile, we recommend the use of the Pediatric RLS instruments that have been developed and we recommend use of the adult scales in adolescent RLS where language barriers are not a problem. If adult scales are used in younger children, we recommend that they be administered in conjunction with an ongoing discussion between the parent and the child during the scale administration.

Keywords: restless legs syndrome (RLS), diagnosis, severity, quality of life, sleep, pediatric, childhood, adolescence

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Edited by:
Karen Spruyt,
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Lunliya Thampratankul,
Mahidol University, Thailand

****Correspondence:***
Pamela Hamilton Stubbs
phamiltonstubbs@drhamiltonstubbs.com

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INTRODUCTION

Restless legs is a common disorder in adults and children. Approximately 25% of adults with RLS report symptoms onset between the ages of 10–20 years. Restless legs syndrome is known to adversely affect quality of life. The full impact of RLS upon children is unknown. Children with RLS have an increased incidence of co-morbid conditions such as attention deficit disorder, iron deficiency anemia, and parasomnias (1–4).

There are only a few of the questionnaires for the diagnosis, severity, and quality of life of adult restless legs syndrome (RLS) that have utilized in children. Even fewer of these types of instruments have been developed specifically for pediatric RLS. This article is a review of instruments used in adult RLS, their applicability to children and of instruments specifically developed for childhood RLS.

The American Academy of Sleep Medicine through the International Classification of Sleep Disorders 3 (ICSD3), the American Psychiatry Association through the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5), and International Restless Legs Syndrome Study Group (IRLSSG) have each developed separate diagnostic criteria for RLS (1–4). The three sets of criteria have minor differences. However, all three sets of criteria require the presence of the same five essential features (1–4).

1. Urge to move the legs usually due to abnormal sensations
2. The worsening or onset of symptoms associated with rest or inactivity
3. Temporary relief or partial relief of symptoms by movement, walking, or stretching
4. Symptoms are more severe later in the day, in the evening or night
5. Mimics of RLS such as leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping are to be excluded. Mimics are those disorders that meet all or almost all of the primary criteria for RLS but are not RLS.

In addition, and most importantly for the diagnosis of definite childhood RLS, all three sets of criteria indicate that the diagnosis of childhood RLS requires that the children must be able to describe the RLS symptoms in their own words.

Frequency of symptoms and duration are not included in all three sets of criteria. The IRLSSG divides duration into chronic persistent (at least two times per week for the past year) and intermittent (less than two times per week for the past year with at least five lifetime episodes). The DSM-5 requires a frequency of three times per week for at least 3 months. The ICSD-3 does not specify frequency or duration. Unlike the DSM-5 criteria the IRLSSG and ICSD3 criteria allow the diagnosis of milder and intermittent forms of RLS (**Table 1**) (1–4).

In 2013 the executive committee of the IRLSSG appointed a task force to update pediatric RLS diagnostic criteria (4). Simplified pediatric criteria were developed with specific recommendations for application in pediatric populations. The updated pediatric RLS diagnostic criteria are expected to improve clinical practice and facilitate research (1–4). For the purpose of this review, we used the IRLSSG consensus diagnostic criteria for RLS (2–4). The Pediatric RLS Severity Scale (P-RLS-SS) also developed through a subcommittee of the IRLSSG in conjunction with industry is a self-administered survey of symptoms and assessment of impact of RLS upon four domains (5).

The International Restless Legs Syndrome Study Group Consensus Diagnostic Criteria for Restless Legs Syndrome

1. A desire to move one or both legs that may or may not be accompanied by or caused by discomfort and unpleasant sensations in the legs.
2. Periods of rest or inactivity precipitate or worsen the desire to move the legs and associated unpleasant sensations.
3. Symptoms are reduced or completely eliminated by movement or symptoms are reduced or eliminated for the duration of movement.
4. Symptoms are more severe or limited to evening or night.
5. Symptoms cannot be solely caused by another medical or behavioral condition.

TABLE 1 | Criteria for restless legs syndrome (RLS) by different organizations.

Feature	IRLSSG	ICSD-3	DSM-5
5 essential features	Same	Same	Same
Frequency	Chronic persistent or Intermittent*	NA	3 times per week
Duration	Persistent or intermittent over 1 year	NA	3 months
Clinical significance	Can cause impairment but impairment is not required	Requires impairment with exception of genetic and epidemiological studies	Requires impairment
Waivers	Frequency and duration may be waivered in childhood, pregnancy, and drug induced RLS	Impairment requirement can be waived in genetic and epidemiological studies	NA
Recognizes drug induced RLS	Yes	Yes	No
RLS mimics must be excluded	Yes	Yes	Yes
Children/adolescents must describe symptoms in own words	Required	Required	Required

See full definition of chronic persistent and intermittent in text.

Specifier for Clinical Significance of Restless Legs Syndrome in Adults

Social, occupational, educational, or other important areas of functioning are adversely affected by the impact of RLS on sleep, energy/vitality, daily activities, behavior, cognition, or mood (2).

Diagnosis of Restless Legs Syndrome in Children

To promote accuracy, consistency in diagnosis, in 2013 the pediatric diagnostic criteria were updated and are the same as diagnostic criteria for adults with special considerations (2, 4):

1. The child must report RLS symptoms in his or her own words.
2. The diagnostician should be aware of the vocabulary children and adolescents may use to describe symptoms.
3. Application of RLS diagnostic criteria are determined by language and cognitive development and not age.
4. It is not known if the adult specifiers for clinical course apply to pediatric RLS.
5. As in adults, a significant impact on sleep, mood cognition, and function is found. Impairment is manifest more often in behavioral and educational domains.
6. Simplified and updated research criteria for probable and possible pediatric RLS are available.
7. Periodic limb movement disorder may precede the diagnosis of RLS in some cases.

Specifiers for Clinical Course of Restless Legs Syndrome in Adults and Children

A. Chronic-persistent RLS: without treatment, symptoms occur a minimum average of twice per week for 1 year
B. Intermittent RLS: without treatment symptoms are present on average <2/week for the past year and there is a history of at least five lifetime events

The diagnosis of RLS is based on the medical evaluation. A structured validated assessment tool can aid an accurate clinical diagnosis and facilitates research in assessment and diagnosis of RLS (2–4).

METHOD

A literature search was completed to identify screening tools used to diagnose RLS, rate the severity of RLS symptoms, and tools to evaluate the impact of RLS upon quality of life. Each tool was reviewed for applicable use in the evaluation of RLS in pediatric populations.

Results

Assessment tools were assigned to one of four categories:

1. Diagnostic tools
2. Severity scales
3. Quality of life scales
4. Quality of life instruments specific to sleep

A summary of the results and applicability to children is provided in **Table 2**.

RESULTS

Diagnostic Tools for Adult Restless Legs Syndrome

Cambridge-Hopkins Diagnostic Questionnaire

The Cambridge-Hopkins diagnostic questionnaire (CH-RLSq) is a self-administered questionnaire developed for large scale epidemiological studies (6). It does not require a diagnostician to be present. Questions cover the essential diagnostic criteria and the two most common RLS mimickers, leg cramps, and positional leg discomfort. The instrument allows patients to be categorized into one of three groups: has RLS, does not have RLS, and probable RLS.

The CH-RLSq is a validated patient completed questionnaire capable of identifying patients likely to have RLS. The scale was validated against the Hening telephone diagnostic interview (HTDI) (see below) which served as the "gold standard." The CH-RLSq has a sensitivity of 87.2% and specificity of 94.4%. The

TABLE 2 | Summary of assessment tools for restless legs syndrome.

Assessment tool	Validated in adults	Utilized in children
Cambridge-Hopkins Diagnostic Questionnaire (CH-RLSq)	Yes	No
Hening telephone diagnostic interview (HTDI)	Yes	No
RLS Diagnostic Index	Yes	No
Single question for RLS	Yes	Yes
The RLS-Expanded Questionnaire	Yes	No
The AIIMS RLS questionnaire for Indian patients (ARQIP).	Yes	No
Pediatric Emory RLS diagnostic questionnaire	No	Yes
The RLSQ	No	Yes
International Restless Legs Scale (IRLS)	Yes	Yes
Self-administered version of the International Restless Legs Syndrome study group severity rating scale (sIRLS).	Yes	No
Clinical Global Impressions Rating Scales (CGI)	Yes	Yes
RLS-6 scale of restless legs syndrome/Willis-Ekbom disease	Yes	Yes
Johns Hopkins Restless Legs Severity Scale (JHRLSS)	Yes	No
Augmentation Severity Rating Scale (ASRS)	Yes	No
Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS)	No	Yes
Rating the four RLS diagnostic criteria	No	Yes
Kohnen RLS quality of life instrument	Yes	No
The RLS Quality of Life Questionnaire—Abetz	Yes	No
The Restless Legs Syndrome Quality of Life Instrument (RLS-QLI)	Yes	No
The post-sleep questionnaire for RLS (PSQ)	Yes	No
The RLS next day impact questionnaire	Yes	No
The subjective post-sleep diary (SPSD) for RLS	Yes	No

Note from the authors: There are no assessment tools validated in pediatric populations.

positive predictive value is 85.5% but researchers state the high positive predictive value may be secondary to the high risk of RLS within the test population who were blood donors. The researchers estimate a positive predictive value of 63.4% in a general population (6).

The CH-RLSq is used to screen populations for RLS. If positive the HTDI can be used to confirm RLS. However, the CH-RLSq can also be used as a stand-alone assessment tool. To our knowledge the CH-RLq has not been applied as a stand-alone questionnaire in children.

Hening Telephone Diagnostic Interview

The Hening telephone diagnostic interview (HTDI) consists of questions based on the diagnostic criteria for RLS established by the IRLSSG as well as questions to exclude leg cramps (7). It is not a patient completed instrument. It was developed for the diagnostician to complete during a telephone interview with the patient but has been used during face to face interviews. The HTDI allows the diagnostician to place the patient into one of three categories: definite RLS, probable RLS, or does not have RLS. The updated version of the HDTI includes questions to help differentiate positional leg discomfort, another common RLS mimic. The revised version, to the best of our knowledge, remains to be validated.

The "gold standard" for diagnosing RLS is the clinical interview. The HTDI was validated by having patients undergo dual interviews by clinical experts in RLS. The rate of agreement between dual clinicians was 93–96%. The HTDI has a specificity of 91%, a sensitivity of 90%, a positive predictive value of 86–89%, and a negative predictive value of 94% (7).

The HTDI was developed for telephone interviews. In our opinion the HTDI would be a reliable tool for telemedicine interviews. The current IRLSSG guidelines require children to describe symptoms in their own words. The HTDI does not include descriptive language used by young children and to our knowledge the HTDI has not been applied to children.

Restless Legs Syndrome Diagnostic Index

This was developed to take into account other non-essential features of RLS that, if taken into account, might improve the diagnostic accuracy of an interview for RLS (8). There are 10 items and 5 address the essential features of RLS and 5 the non-essential features. These non-essential but frequently found features include sleep disturbance, a positive family history of RLS, the bettering of RLS symptoms with dopaminergic therapy, and the presence of periodic limb movements in sleep (PLMS) on an overnight sleep study as well as whether the RLS can be explained by a co-morbid medical condition (8). The RLS-DI has been validated in adults against the diagnosis of two independent sleep experts but to our knowledge this instrument has not been used in children. In adults the sensitivity was 93%, specificity was 98.9%, positive predictive value 98.8%, negative predictive value 93.9%, and 96.1% of the subjects could be identified correctly.

Single Question for Restless Legs Syndrome

The single question incorporates the NIH criteria for RLS: "when you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?" (9). The single question has been validated in adults against an in-person interview by two clinicians and has been used in at least once epidemiology study of RLS in adolescents (10). The single question shows a sensitivity of 100%, specificity of 96.8%, positive predictive value of 89.6%, and negative predictive value of 100%.

The Restless Legs Syndrome-Expanded Questionnaire

In this study the authors developed two questionnaires for the diagnosis of RLS and validated them both against an in person examination by two RLS experts which served as the gold standard (11). The first questionnaire was based upon the four diagnostic criteria for RLS and the second questionnaire was also based upon the four diagnostic criteria but added additional questions to eliminate mimics such as leg cramps as well as questions regarding sleep disturbance and other demographic information. To our knowledge the RLS-Expanded Questionnaire has not been applied as a stand-alone questionnaire for children. In adults the RLS-Expanded Questionnaire has a sensitivity of 81% and a specificity of 73%.

The All India Institute of Medical Sciences Restless Legs Syndrome Questionnaire for Indian Patients

The All India Institute of Medical Sciences (AIIMS) RLS questionnaire for Indian patients (ARQIP) is an expanded physician administered detailed questionnaire developed to uncover salient features required to diagnose RLS (12). All IRLSSG diagnostic criteria plus additional socio-cultural questions appear on the ARQIP. Socio-cultural questions were added to address aspects specific to Hindi culture, the use of culture specific terminology to describe symptoms, and the factors that alleviate symptoms. The questionnaire was developed in English and translated to Hindi.

The ARQIP was compared to the four diagnostic criteria for RLS. The evaluation procedure used two different examiners to administer one questionnaire, either the ARQIP or the four diagnostic criteria for RLS. Questionnaires were administered by face to face interview or telephone interview. All patients were given a final evaluation by an RLS expert who diagnosed each patient as having RLS or "no-RLS" which was considered the "gold standard" for the diagnosis. The ARQIP was was found to have greater sensitivity (100 *vs.* 73%), specificity (44 *vs.* 32.7%), negative predictive value (100 *vs.* 36.4%), and positive predictive value (79 *vs.* 70%) than the IRLSSG criteria administered alone (12). The ARQIP has been used to study RLS in adults (12). We did not find pediatric studies that used the ARQIP.

Diagnostic Tools Specific to Pediatric Restless Legs Syndrome

Pediatric Emory Restless Legs Syndrome Diagnostic Questionnaire

The pediatric Emory RLS diagnostic questionnaire is based on National Institute of Health consensus guidelines for pediatric RLS diagnostic criteria and questions adapted from the

Cambridge-Hopkins diagnostic questionnaire (CH-RLSq), the RLS-Expanded Questionnaire and the Phenotypic Presentation of Restless Legs Syndrome Questionnaire (13). Questions are modified for use in pediatric populations.

The questionnaire consists of two sets of similar questions developed for two different age groups: 8–12 years old and 13–18 years old. For children less than 13 years of age, the questionnaire is completed by the parent or primary caretaker in the presence of the child. For the younger children there are 47 questions. For the older children there are 46 questions. The first five questions of the instrument are screening questions.

1. The presence of growing pains
2. Difficulties sitting or lying still
3. An urge or strong need to move the legs due to uncomfortable feelings or sensations
4. A recurrent need to move the legs while sitting or lying down
5. History of leg rubbing or massage to relieve sensations

If any screening question is answered affirmatively, a series of age-specific questionnaires to evaluate details of the discomfort or sensations follow. The questionnaire addresses medications, RLS mimics, and quality of sleep. Both questionnaires provide front and back human images where the affected body part can be shaded. Questions 34–47 for children 8–12 years of age and questions 33–46 for adolescents focus on sleep disturbance. Both sets of questionnaires provide instructions for the classification of definite RLS, probable RLS, and the presence of sleep disturbance.

The pediatric Emory RLS diagnostic questionnaire has been used in a study to evaluate pediatric patients with chronic kidney disease (13) and in a separate study in children with nephrotic syndrome (14). The authors later noted one limitation of the pediatric Emory RLS diagnostic questionnaire is that the questionnaire has not been fully validated. The scale is published in its entirely as an appendix to the aforementioned article on pediatric RLS in chronic kidney disease (13).

The Restless Legs Syndrome Questionnaire

The RLSQ is a parent report questionnaire developed for the identification of pediatric RLS by a triangulation process of literature review, parent interviews, and a children's focus group (15). The final questionnaire has 11 items. The authors state that the questionnaire has been validated and is reliable with an internal consistency of 65% and repeat measure reliability rho = 0.58. However, the details of the validation process were not stated in the article and the scale itself was not published with the original article.

Severity Scales for Adult Restless Legs Syndrome

International Restless Legs Scale

The IRLS is a 10-question scale administered to the patient by an examiner but the patient does the severity rating. The examiner is available to answer any questions the patient has about the items (16). Severity is rated on each question as follows: 0= no symptoms, 1–mild, 2–moderate, 3–severe, and 4–very severe for a total score of 0–40. The IRLS has a severity subscale and an impact on quality of life subscale. The IRLS was originally validated correlating the total score to the Clinical Global Impression (CGI) (r = 0.74) and Patient Global Impression (r = 0.82) and readily distinguished patients from controls (16). The IRLS has been employed in at least two therapeutic studies in adolescents with RLS 13–18 years of age (17) or children with RLS aged 5–12 years (18), in two quality of life studies of children and adolescents aged 7–18 (19) and 12–20 (20), respectively, and in a study of the prevalence of RLS in children and adolescents with allergic rhinitis aged 8–18 years (21) and another study of the prevalence of RLS in children and adolescents with celiac disease aged 11–18 years (22). In one of these studies it is carefully explained that the scale was administered after a thorough discussion of symptoms and daytime function with the children and their parents (19). However, it is to be emphasized that the adult scale has not been validated in children or adolescents and if it is to be administered in these groups, we would recommend that it be done with the cautions above. The IRLS is the most utilized of the severity scales and is employed in most academic and pharmaceutically based studies of RLS therapy. The scale is copyrighted by the International Restless Legs Syndrome Study Group (IRLSSG) with the Mapi Research Trust as the official licensor and distributor. For use contact https://eprovide.mapi-trust.org/. For individual clinical or research use the scale is available at a nominal cost. The scale has undergone minor revisions since its original validation for better readability and the recommendation that the scale be rated for symptoms over the past 1 week rather than the past 2 weeks. Please contact Mapi for the latest version.

Self-Administered Version of the International Restless Legs Syndrome Study Group Severity Rating Scale

The first version of the IRLS (see above) was validated under conditions where the examiner had to be present with the patient in order to clarify any misunderstandings the patient might have about the questions that comprise the scale. The second version of the scale (sIRLS) was validated under conditions where the patient did not have to have the examiner present or available (23). The validation study which compared both types of administration indicated that the sIRLS was reliably answered when administered without the presence of the examiner and could theoretically be employed in mass mailings that would reach much larger numbers of patients. The correlation between the IRLS and the sIRLS was 0.94. This scale has not been applied to children but, by extension, the successful use of the IRLS in adolescents would be expected to be true for the sIRLS as well. The scale is copyrighted by the International Restless Legs Syndrome Study Group (IRLSSG) with the Mapi Research Trust as the official licensor and distributor. For use contact https://eprovide.mapi-trust.org/. For individual clinical or research use the scale is available at a nominal cost.

Clinical Global Impressions Rating Scales

Clinical Global Impressions of change are a standard tool used in severity assessment for many conditions and is not specific to restless legs syndrome. The CGI can be administered to the patient to get the patient's impression of the severity of their condition or it can be administered by the treating physician to get the treating physician's impression of the severity of the patient's condition. It has been employed in a study specific to adolescents with RLS in at least one instance (17). It is the most frequently employed tool to accompany the IRLS in therapeutic trails of medications for RLS.

Restless Legs Syndrome-6 Scale of Restless Legs Syndrome/Willis-Ekbom Disease

The RLS-6 has six items rated from 0 to 10 where the symptoms are rated over the past week (24). The items include severity of RLS at falling asleep, during the night, during the day when sitting or lying, and during the day when active. Another item probes daytime sleepiness and yet another asks how satisfied patients were with their sleep over the last seven nights. The scale has been validated in adults against the IRLS (see above) which served as the gold standard and has been employed in at least one therapeutic study of RLS in adolescents (17). The correlation coefficients of the RLS-6 items ranged from 0.35 to 0.67 with the IRLS total score. The European Restless Legs Syndrome Study Group (EURLSSG) owns intellectual property rights over the RLS-6 with Mapi Research Trust assigned for the management of instrument license and permission to use. For use please consult the Mapi Research Trust website http://www.proqolid.org. For individual clinicians and investigators the scale is available at a nominal fee.

Johns Hopkins Restless Legs Severity Scale

This consists of a single question that rates the usual time of day for onset of RLS for at least 50% of days (25). The symptoms are rated: 0= no symptoms; 1 = bedtime symptoms after or within an hour of going to bed; 2= evening and bedtime symptoms starting at or after 6:00 PM; 3 =day and night symptoms starting before 6:00 PM. The scale has been validated in adults against polysomnographic parameters such as periodic leg movements of sleep (R = 0.45, P=0.01) and sleep efficiency (R=0.60; P < .01) but to our knowledge has not been employed in children.

Augmentation Severity Rating Scale

In restless legs syndrome treatment with dopaminergic agonists may dramatically improve symptoms at night but may have a side effect of pushing the symptoms into the daytime (26). A generalized paradoxical worsening of RLS symptoms with, for example, spread to other body parts beyond the legs may also occur. This phenomenon is called Augmentation and the Augmentation Severity Rating Scale (ASRS) was designed to measure this phenomenon (26). The scale has three items evaluated over the previous week. The first item asks the time of day the symptoms began over the past week; the second item asks how quickly symptoms developed when sitting at various times of the day in the past week; the third item asks what body parts were involved over the past week. The instrument has been validated in adults against the independent opinion of two clinical experts and the correlation between the worst ASRS total score and expert rating was 0.72. To our knowledge the ASRS has not been employed in children.

Severity Scales Specific for Pediatric Restless Legs Syndrome

Pediatric Restless Legs Syndrome Severity Scale

The Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) is a Likert-type 41 item questionnaire based upon interviews of children and adolescents 6–17 years of age conducted at multiple centers (5). The P-RLS-SS was developed using concept elicitation interviews; generation of questions based on conceptual frameworks for measuring symptoms and impact of RLS; cognitive debriefing interviews of children and parents and qualitative analysis of the data using ATLAS.ti software and grounded-theory methods.

Development of the P-RLS was supervised by an advisory board of P-RLS experts and developers of the adult RLS Severity Scale. The P-RLS-SS measures symptoms commonly associated with RLS and the impact of RLS upon four domains: sleep, awake activities, emotions, and tiredness. A separate complementary parent questionnaires allows parents to provide observations regarding mood changes and information the child may not be aware of, such as sleeping in unusual positions.

The P-RLS-SS is a self-administered assessment tool recommended for children at least 9 years of age. Due to limited cognitive and reading abilities, younger children may need assistance completing the P-RLS-SS. The separate complementary parent questionnaire should be completed.

The next phase in development of the P-RLS-SS is the validation study. As developed, the plan is to field test the scale in order to determine the appropriateness of the questions and then to come up with a pared down final version of the scale with perhaps the addition of altered or additional questions as part of the validation procedure. The P-RLS-SS is the property of the International Restless Legs Syndrome Study Group (IRLSSG) and the IRLSSG web site can be consulted regarding its use http://www.irlssg.org.

Rating the Four Restless Legs Syndrome Diagnostic Criteria in Children

In one study in a modification of the P-RLS-SS the four primary criteria for the diagnosis of RLS were rated from least severe to most severe on a 0–4 scale in children 5–18 years of age as the sole measure of severity (27). The 5th criterion, the exclusion of mimics, was part of the questionnaire as was the necessity for the child to be able to describe the symptoms in their own words. However. these items were not given a numerical score. A score of at least one on each of the four primary items and an affirmative answer on the mimics question and the child volubility question was necessary before the scale could be administered. In other words, the child had to meet the criteria for definite RLS before the symptoms could be rated. Severity thus ranges from 4 to 16. This approach has the advantage that it is short and easy to administer and the questionnaire serves both

as a diagnostic tool and a severity rating tool. The disadvantage of the tool is that the four criteria are taken directly from material written for physicians and thus might not be understandable to either adults or children unless an examiner is personally present to verbally explain the questions to the subjects. It is also assumed that for very young children that the parent needs to be present to help with the responses. This approach holds promise but has also not yet been validated (27).

Quality of Life Scales for Adult Restless Legs Syndrome

General Restless Legs Syndrome Quality of Life Scales

Kohen Restless Legs Syndrome Quality of Life Instrument

The questionnaire consists of 12 items that explore four different realms: firstly—consequences of RLS symptoms on sleep, activities of daily living, mood, and social interactions; secondly, everyday life, tiredness, and mood: thirdly pain and side effects of RLS medications; fourthly, behaviors to cope with RLS (28). A 6 point Likert scale is used to determine the severity for each question. The questionnaire has been validated recently in adults and the Kohnen RLS QOL index correlates well with the IRLS which also contains quality of life elements (r= 0.68), and to the Clinical Global Impression (r = 0.42), and to varying degrees to four of the RLS-6 domains (r = 0.33 to 0.57). To our knowledge the Kohnen RLS QOL instrument has not been utilized in children. The European Restless Legs Syndrome Study Group (EURLSSG) owns intellectual property rights over the Kohnen RLS-Qol with the Mapi Research Trust assigned the management of the instrument licenses and permission to use. For use please contact the Mapi Research Trust at e-mail Pro-information@mapi-trust.org or through website https://eprovide.mapi-trust.org/about/about-proqolid. The scale is available at a nominal cost to individual clinicians or investigators.

The Restless Legs Syndrome Quality of Life Questionnaire —Abetz

In this scale there are 18 administered questions including impact of RLS on the domains of daily life, emotional well-being, social life, and work life (29). Higher scores indicated higher quality of life. The scale has been validated in adults by comparison to the SF-36 and a modified version of the IRLS (IRLS—patient version or IRLS-PV). There was better correlation of the RLS QOL Questionnaire—Abetz with the SF-36 mental component summary (MCS) scale (r=0.5, P < .0001) than with the physical component summary (PCS) scale which was not significant. The RLS QOL Questionnaire—Abetz summary score was able to distinguish between those patients rated as mild, moderate or severe on the IRLS-PV (F= 52.22, P <0.0001). To our knowledge the RLS QOL questionnaire—Abetz has not been utilized in children.

The Restless Legs Syndrome Quality of Life Instrument

This is a self-administered scale with 17 questions (30). The 17 questions were analyzed by factor analysis and four factors were identified: Daily function, social function, sleep quality, and emotional well-being. The instrument has been validated in adults against related scales of the SF-36 (r=0.47 to 0.60) and related items of the IRLS (r= −0.45 to −0.77), but to our knowledge has not been utilized in children. The RLS-quality of life instrument (QLI) is owned and maintained by the Restless Legs Syndrome Foundation (RLSF), a nation-wide support group for RLS patients and their families. Permission to use the instrument, free of charge, must be sought from the RLSF http://www.rls.org/research.

Restless Legs Syndrome Quality of Life Instruments Specific to Sleep

The Post-Sleep Questionnaire for Restless Legs Syndrome

This is a self-completed scale and tests five areas of interest over the last week: quality of sleep overall, ability to function in the day, frequency of RLS symptoms in the night, and RLS-related sleep disturbances and latency (31). The scale employs a Likert scale except for one open-ended question about the number of nights per week the patient has had RLS symptoms. Lower post-sleep questionnaire (PSQ) scores indicate worse sleep. The scale has been validated in adults against the IRLS, RLSQOL-Abetz, the Profiles of Moods States (POMS), and the Medical Outcomes Study (MOS)-Sleep Scale ($p < 0.007$ each) and also validated against the investigator and subject rated clinical global impression (CGI) ($p < 0.0001$). To our knowledge the PSQ has not been employed in children.

The Restless Legs Syndrome-Next Day Impact Questionnaire

There are 14 questions to determine the impact of RLS-related sleep loss on daily functioning (32). The questionnaire is designed to rate only a single day "today." It is self-administered at night and the patients are asked to fill out the items based upon their recollection of the previous 12 h. The questions are rated on an 11 point scale with higher numbers indicating more daytime dysfunction from RLS-related sleep loss. The scale probes impairments in alertness, concentration, and mood. The questionnaire has demonstrated content validity in adults through interviews with RLS patients and development by RLS and measurement experts but it has not to our knowledge been employed in children.

The Subjective Post-Sleep Diary for Restless Legs Syndrome

This diary was developed to be answered after a single night of sleep in RLS patients in order to assess their nocturnal sleep the night before (33). The diary consists of 12 items that the patient answers, e.g., recall of the time that they went to bed, time they awakened for the final time, how long it took them to fall asleep initially, how long they were awake in the middle of the night, and how much of the time spent awake was estimated to be due to RLS symptoms. The degree to which sleep was restful and the quality of sleep are both rated on a 0–10 scale with higher scores representing better sleep. Eight items from the diary were each correlated with the total score of the IRLS, the patient global impression, and with

five individual sleep constructs from the Medical Outcomes Study (MOS) sleep scale. The correlations varied greatly but were generally moderate to high. To our knowledge the subjective post-sleep diary (SPSD) has not been employed in children.

General Quality of Life Scales Applied to Pediatric Restless Legs Syndrome

In our literature search we did not find any studies utilizing quality of life scales that were specifically designed for pediatric RLS and to our knowledge none of the validated quality of life scales for adult RLS have been used in children or adolescents. However, three separate studies utilized the general Peds Quality of Life Inventory (PedsQL) in RLS children and adolescents (19, 20, 34). The PedsQL has 23 items on a self-report scale for children 2–18 years of age that utilizes four subscales: 1) physical functioning; 2) emotional functioning; 3) social functioning; and 4) school functioning (19, 20, 34). In one of these studies sleep quality was evaluated by another general measure the 26 item Sleep Behavior Questionnaire (34). Each item was rated 1 (never) up to 5 (always) according to how often the specific sleep symptom occurred over the past 6 weeks with higher scores indicating more sleep problems and reduced sleep quality. Scores could range between 26 and 130. In another of these studies the Pediatric Symptoms Checklist (PSC) was used as a general measure of Quality of Life (19). In the study parents of the participants where asked to respond to 35 questions rating their child's level of psychosocial problems. Responses to each question were made where never occurs = 0 points, occurs sometimes = 1 point, and occurs frequently = 2 points. The total score was then calculated.

DISCUSSION

This article is a review of tools for assessment of adult RLS, their applicability to children and of assessment tools specifically developed for childhood RLS.

Diagnosis

Diagnostic criteria provide standards for research and clinical practice. Criteria for RLS in children have been developed and follow the adult criteria. A diagnosis of definite RLS requires children to describe symptoms in their own words. A single question for the diagnosis of RLS has been validated for adults and utilized in one epidemiology study of adolescents with RLS (10). The pediatric Emory RLS questionnaire has been developed as a diagnostic instrument for childhood RLS, has been utilized in two studies, but has yet to be validated (13, 14). A parental questionnaire, the RLSQ has been validated for the diagnosis of pediatric RLS but the full scale has not been published to our knowledge (15).

Severity

The IRLS (International Restless Legs Scale), the CGI (Clinical Global Impression), and the RLS-6 all of which have been validated for determining RLS severity in adults were administered without difficulty in one therapeutic study of adolescent RLS (17). In addition, the IRLS has also been utilized in another five studies of childhood and adolescent RLS (18–22). However, it is to be emphasized that the adult version of the IRLS has not been validated in children or adolescents. The pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) has been developed for use in children but has not been validated (5). A modification of the P-RLS-SS based upon rating the severity of the four diagnostic criteria for RLS has been developed for children but not yet validated (27).

Quality of Life and Sleep Scales

We could find no instances where validated adult scales for RLS quality of life or sleep had been utilized in children and we could find no Quality of Life Scales or sleep scales specifically developed for RLS children. However, three separate studies utilized the general Peds Quality of Life Inventory (PedsQL) in RLS children and adolescents (19, 20, 34) and one of these studies also employed the general Sleep Behavior Questionnaire (SBQ) as an additional measure of quality of life (34) Yet another of these studies also employed the pediatric symptom checklist (PSC) as another general measure of quality of life in children with RLS (19).

Summary

There is a need for the development and validation of RLS diagnostic instruments, severity scales and quality of life instruments that are specific to children. In the interim, the adult scales have been utilized successfully in adolescent RLS where language barriers are not a problem. If adult scales are to be used in younger children we recommend that the methodology employed by Furudate be employed, i.e., that the scale be administered "after a thorough discussion of symptoms and daytime functioning with the participants and their parents (19)." Based upon our clinical experience we would go further and suggest that this process occur not only after a discussion with the children and their parents but during the administration of the scale as well so that the process be as interactive as possible such that misunderstandings do not arise. Having the child and parent decide upon a joint response would be a further recommendation.

AUTHOR CONTRIBUTIONS

Both the authors PS and AW contributed equally to conceptualization and writing of the manuscript.

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Observational Study of Pulse Transit Time in Children With Sleep Disordered Breathing

Michael P. Yanney[1], Andrew P. Prayle[2,3], Nicola J. Rowbotham[2], Miguel Kurc[1], Sean Tilbrook[1] and Nabeel Ali[1]*

[1] Sherwood Forest Hospitals Foundation Trust, Mansfield, United Kingdom, [2] Division of Child Health, Obstetrics and Gynaecology, Queens Medical Centre, Nottingham University Hospitals, Nottingham, United Kingdom, [3] NIHR Nottingham Biomedical Research Centre, Queens Medical Centre, Nottingham University Hospitals, Nottingham, United Kingdom

Background: Pulse transit time (PTT) is a non-invasive measure of arousals and respiratory effort for which we aim to identify threshold values that detect sleep disordered breathing (SDB) in children. We also compare the sensitivity and specificity of oximetry with the findings of a multi-channel study.

Methods: We performed a cross-sectional observational study of 521 children with SDB admitted for multi-channel sleep studies (pulse oximetry, ECG, video, sound, movement, PTT) in a secondary care centre. PTT data was available in 368 children. Studies were categorised as normal; primary snoring; upper airway resistance syndrome (UARS); obstructive sleep apnoea (OSA), and "abnormal other." Receiver operator characteristic curves were constructed for different PTT (Respiratory swing; Arousal index) thresholds using a random sample of 50% of children studied (training set); calculated thresholds of interest were validated against the other 50% (test set). Study findings were compared with oximetry categories (normal, inconclusive, abnormal) using data (mean and minimum oxygen saturations; oxygen desaturations > 4%) obtained during the study.

Results: Respiratory swing of 17.92 ms identified SDB (OSA/UARS) with sensitivity: 0.80 (C.I. 0.62–0.90) and specificity 0.79 (C.I. 0.49–0.87). PTT arousal index of 16.06/ hour identified SDB (OSA/UARS) with sensitivity: 0.85 (95% C.I. 0.67–0.92) and specificity 0.37 (95% C.I. 0.17–0.48). Oximetry identified SDB (OSA) with sensitivity: 0.38 (C.I. 0.31–0.46) and specificity 0.98 (C.I. 0.97–1.00).

Conclusions: PTT is more sensitive but less specific than oximetry at detecting SDB in children. The additional use of video and sound enabled detection of SDB in twice as many children as oximetry alone.

Keywords: pulse transit time, sleep disordered breathing, upper airway resistance syndrome, oximetry, sensitivity and specificity, children, video, sound

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****Correspondence:***
Michael P. Yanney
michael.yanney@nhs.net

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INTRODUCTION

Obstructive sleep disordered breathing (SDB) is a syndrome of upper airway dysfunction characterized by snoring and/or increased respiratory effort during sleep (1–3). It includes a spectrum of disorders: primary snoring (PS); upper airway resistance syndrome (UARS), obstructive hypoventilation, and obstructive sleep apnoea (OSA) (2, 3). There is strong evidence of

adverse neurocognitive, behavioral and cardiovascular outcomes in children with SDB, underlining the importance of diagnosis and management (4–7). The mechanisms behind these adverse outcomes are also being elucidated (8).

History and examination are poor at discriminating between children with OSA and PS and unreliable for determining which children require treatment (9, 10). Polysomnography (PSG) is the gold standard test for diagnosis but availability is limited (2, 11). Polygraphy is a less invasive alternative to PSG but also remains the domain of tertiary centers. Oximetry is widely used in both secondary and tertiary care centers and has been shown to have good specificity for detecting OSA in children but is much less sensitive. A study by Brouillette et al. suggests the sensitivity of oximetry may be about 50% when compared to PSG, but more recent studies have shown a much improved sensitivity using newer artificial intelligence techniques (12–14). Brouillette et al. defined a desaturation as a decrease in SaO_2 by 4% or more from baseline and a positive oximetry study as having three or more desaturation clusters with at least three desaturations < 90%. A cluster of desaturations was defined as five or more in a 10–30 min period; periods of artifact and wakefulness (based on heart rate variability criteria) were excluded from analysis. There is currently much interest in less invasive sleep study modalities or indices that can detect SDB with accuracy. A recent trend for some UK Clinical Care Commissioning Groups to refuse to fund adenotonsillectomies for SDB, unless the diagnosis has been confirmed with a sleep study, has also increased the importance of diagnostic accuracy (15).

We report the findings of using a limited multi-channel sleep system incorporating electrocardiogram (ECG), oximetry, video, sound, and pulse transit time (PTT) in a secondary care center. The VISI-sleep system was compared directly with PSG in a validation study by van Someren et al. in which 10 children aged 0.2–6.4 years were evaluated with both the Visilab system (oximetry, sound, video, and movement) and a conventional polysomnographic system (Oxcams), incorporating pulse oximetry, ECG, nasal airflow (thermistors), chest and abdominal movement (impedance), and video (16). There were just two discrepancies in the final diagnosis between the two systems. One child deemed to have a normal study with the Visilab system had mild obstruction identified with PSG. Another child deemed to have obstruction with the Visilab system was shown to have mixed apnoea with PSG. The authors also demonstrated good interobserver reliability in 17 sleep studies evaluated independently by two clinicians ($k = 0.52$). They concluded that the Visilab video system is easy to use and robust providing its limitations are understood.

The utility of PTT for detecting subcortical arousals in children with SDB is known, but values considered significant have not been established (17). We have evaluated two PTT indices (PTT arousals index; PTT respiratory swing) in children with suspected SDB to ascertain values that might be predictive of OSA. As a secondary objective, we have also assessed the sensitivity and specificity with which oximetry detects SDB compared with a multi-channel study. Our aim is to determine the value of the use of video and sound in addition to oximetry.

METHODS

We performed a cross sectional observational study of 581 children (<18 years of age) referred consecutively to a UK secondary care center for multi-channel sleep studies between February 2016 and November 2018. Children were referred predominantly for symptoms of SDB by otolaryngologists, pediatricians or general practitioners. Sleep studies were performed with two Stowood Scientific Instruments VISI-3 sleep systems incorporating ECG, video, sound, movement, pulse transit time and oximetry data (**Figure 1**). The VISI-3 sleep system utilizes Masimo technology for obtaining oximetry data with 2–4 s averaging times. Oximetry was measured with probes attached to either a finger or toe. Video was recorded with a Sony EVI-D90P infra-red camera. Children with symptoms of SDB who were unable or unwilling to undergo inpatient multi-channel studies had home oximetry studies instead. The data of these children were not included in the study.

PTT is measured from the mid-point of the R wave of the QRS sequence obtained by electrocardiography (ECG) to a pulse waveform value obtained from an oximeter and measured at 50% of the maximum point of the plethysmography curve (**Figure 2**). A rise in mean arterial pressure (MAP) causes the pulse wave to travel faster and PTT to shorten; conversely a lower MAP causes PTT to lengthen. PTT is therefore an estimate of the time taken for the pulse pressure wave to travel from the aortic valve to the periphery and is inversely correlated to blood pressure (BP) changes (18). PTT can identify changes in inspiratory effort as a result of BP fluctuations induced by negative pleural pressure swings.

PTT is measured in milliseconds and is calculated with VISI-3 software; PTT2 was calculated by applying a 17 point averaging (∼3.5 s) to the recorded raw channel PTT data. A PTT arousal was calculated as a drop in PTT2 >= 15 ms within 5–45 s as long as the PTT2 value was in the valid range of 150–500 ms. The PTT arousal index (PTT-AI) was calculated as the number of PTT arousals/ hour over the duration of the study. The average respiratory swing was analyzed using a derived PTT channel which had been interpolated for 1 s and then a three sample moving window average applied. The respiratory swing is the average size of respiratory rise from an inspiratory trough to expiratory peak and is measured in milliseconds.

Exclusions

The PTT and oximetry traces were assessed for artifact by a sleep physiologist prior to reporting. Oximetry artifact associated with movement or low perfusion was excluded; PTT artifact resulting from either plethysmography or ECG signal dropout was also excluded. PTT artifact was identified as rapid spikes in excess of 50 ms; typically >100 ms (**Figure 3**). Children with <4 h artifact free oximetry data were excluded from the study and children with < 3 h artifact free PTT data were excluded from the PTT analysis. We also excluded children categorized as "abnormal other" whose sleep study findings were due to causes unrelated

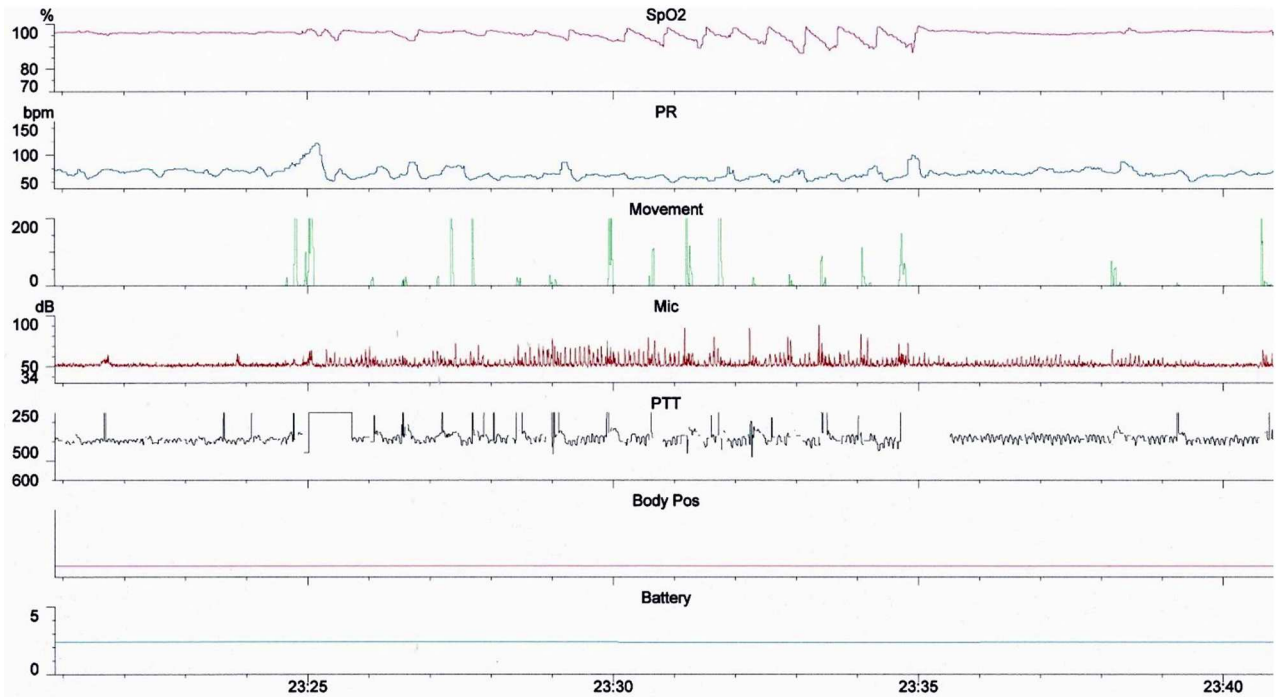

FIGURE 1 | Example of a 20 min epoch of the multi-channel study montage.

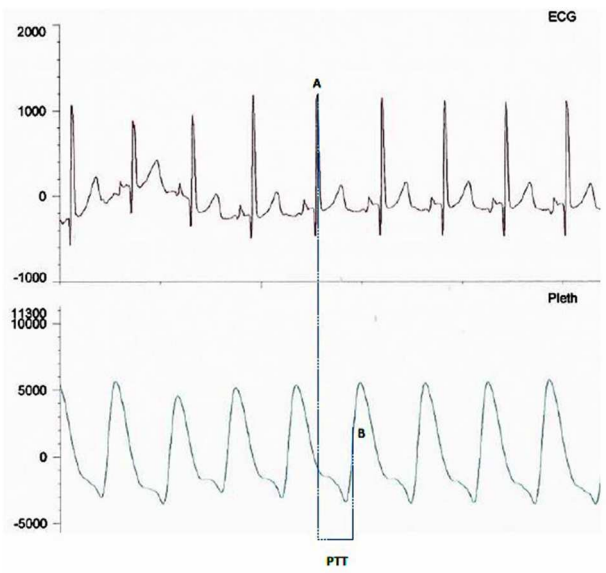

FIGURE 2 | Image showing PTT measurement between mid-point of the R wave **(A)** on the ECG trace and mid-point of the up slope **(B)** on the plethysmography curve.

to OSA, such as central apnoeas, chronic lung disease, a lower respiratory tract infection, or an exacerbation of asthma.

Sleep study categories were determined by a clinician (MY) using oximetry, video and sound criteria listed below. The oximetry, heart rate, sound and movement traces were used to identify sections of video that needed closer inspection. The video was assessed for evidence of obstructive episodes (defined below). Following assessment of the oximetry data, sleep study montage and video, the reporting clinician assigned one of the following five categories: normal; primary snoring; upper airway resistance syndrome; obstructive sleep apnoea or abnormal other. The reporting clinician remained blind to the PTT values until after the sleep study categories had been determined. Oximetry categories (**Table 1**) are based on those used by Sheffield Children's Hospital sleep service for perioperative risk stratification of children being considered for adenotonsillectomy. These categories are currently used in our hospital to guide management in children who have home oximetry and are the basis for determining which children might benefit from surgery and whether they are suitable for surgery in a secondary care center (12, 19–22).

Sleep Study Category Definitions

- **Normal**: No snoring or obstructed breathing evident on video and normal or inconclusive oximetry (**Table 1**)
- **Primary snoring**: Snoring but < 3 witnessed obstructive episodes on video and normal or inconclusive oximetry
- **Upper airway resistance syndrome**: Video and sound evidence of 3 or more discrete periods of obstructed breathing, associated arousals and normal or inconclusive oximetry
- **Obstructive sleep apnoea**: Video and sound evidence of obstructed breathing, associated arousals and abnormal oximetry

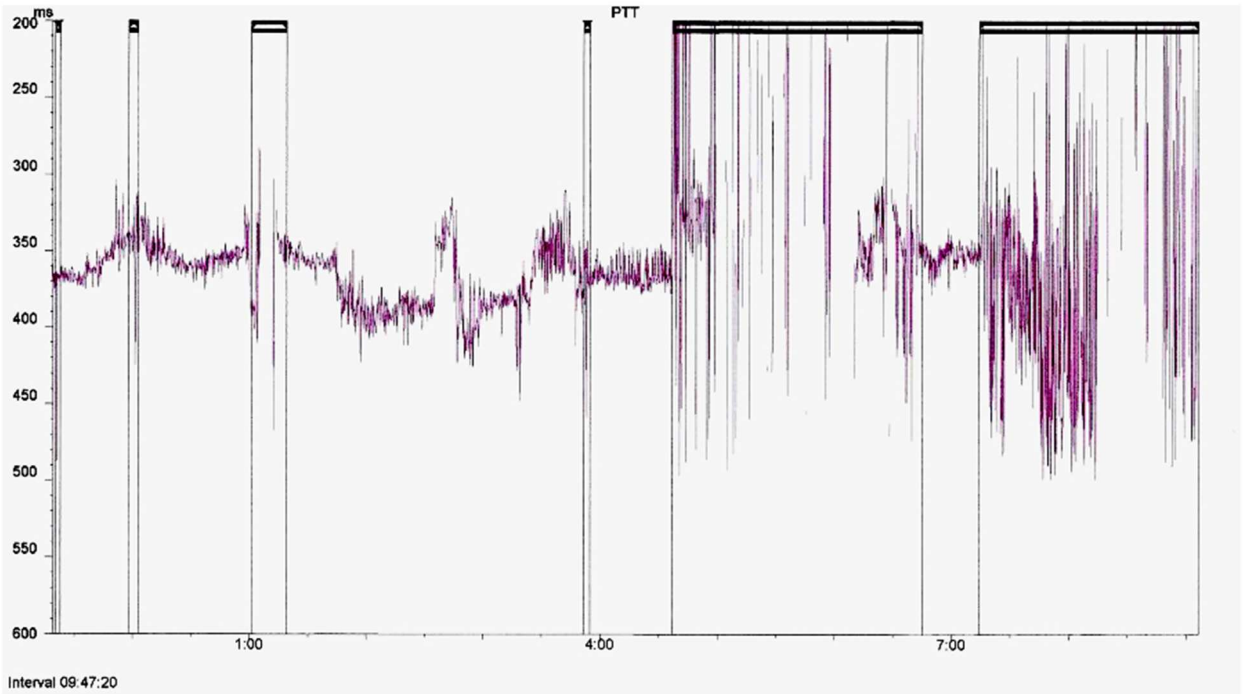

FIGURE 3 | Example of a full study PTT montage with artifact highlighted for exclusion from analysis.

TABLE 1 | Oximetry risk criteria for OSA.

	Normal	Inconclusive			Abnormal, low risk	Abnormal, high risk
Baseline	>94% and	94% or			<94% or	<94% or
Desaturation Index (>4% dip from baseline)	<4/h and	>4/h and	or	<4/h and	>4/h and	>4/h and
Minimum saturation	>90%	>90%		80–90%	80–90%	<80%

- **Abnormal other**: Abnormal oximetry findings without any video evidence of obstruction.

Other Definitions

- **Obstructive episodes** were identified on video as periods when there was a pause in snoring but continued respiratory effort, followed by an airway opening noise and an arousal.
- **An arousal** was identified if there was movement associated with an obstructive episode and a corresponding pulse rate rise.

Weight was measured with SECA (Hamburg, Germany) electronic chair scales or SECA baby scales. Height was measured with a SECA wall mounted stadiometer or a Dunmow Rollameter (Harlow Healthcare, UK).

The sleep study categories, oximetry indices, pulse transit time indices, growth measures, age, sex and referring clinician were recorded prospectively in a database maintained for audit and service evaluation purposes. The following oximetry indices were recorded: mean saturation, minimum saturation, dip index defined as >4% drop in baseline saturation/ hour and lasting for > 5 s but <180 s, mean heart rate and standard deviation, oximetry categories (normal; inconclusive; abnormal low risk; abnormal high risk) and duration of artifact free oximetry data. The PTT respiratory swing, PTT arousal index (number of PTT arousals/ hour) and duration of artifact free PTT data were also recorded.

Data Analysis

Receiver Operator Characteristic Curves (ROC) were calculated for PTT respiratory swing and PTT arousal index, using a random sample of 50% of the data (the training set). Cut offs were identified in the training set which had 90% sensitivity, 90% specificity, and a third cut off which maximized the arithmetic sum of sensitivity and specificity. To evaluate the performance of these thresholds in a second sample, they were validated against the other 50% (the test set), calculating the sensitivity and specificity for these thresholds. Data comparing sleep study outcomes based on oximetry findings or multi-channel study categories are presented in **Table 2**. Children classified as "Abnormal other" following multi-channel studies are not included in the table. We have calculated the sensitivity and specificity with which oximetry identified SDB compared to the multi-channel study. Data were analyzed with R (version

TABLE 2 | Sleep study categories compared with oximetry findings.

Oximetry categories	Number of children	Video findings	
		Normal or primary snoring	UARS or OSA
Normal	196	153	43
Inconclusive	249	180	69
Abnormal	76	6	70

3.4) using the packages dplyr, beeswarm, and pROC (23–25). Confidence intervals were calculated with the inbuilt command in the pROC package using the bootstrap method to calculate the sensitivity and specificity. For the arithmetic sum, we added together the sensitivity and the specificity for each threshold of PTT-AI or PTT respiratory swing. We then used the maximum one as the best threshold; chosen to minimize mis-diagnosis (26). Z scores for weight and BMI were calculated using WHO growth standard and the package hgdb (27).

A retrospective evaluation of 176 children with SDB referred for sleep studies informed our PTT sample size estimate although a formal calculation was not done (28). We analyzed, all available data for the 32 month period from February 2016 to November 2018 resulting in a final sample size of 368 children for the PTT analysis (190 children in the training dataset).

Ethical Considerations

The Research and Development department at Sherwood Forest Hospitals Foundation Trust was approached before commencing data collection. They confirmed that ethical approval was not required for the analysis of anonymised sleep study data which involved no change to usual care (29).

RESULTS

Figure 4 is a flow diagram of children assessed for the study. Oximetry and video data were available for 521 children (300 male; 221 female) and used for the oximetry sensitivity analysis. The data of 368 children (208 male; 160 female) were used for PTT analysis. The mean duration of oximetry data was 8.8 h (4.1–12) and the mean duration of PTT data was 5.1 h (3.0–10.5).

Table 2 shows the oximetry categories compared with the multi-channel study diagnoses. Use of a multi-channel study resulted in the detection of OSA or UARS in 182 children. Oximetry was abnormal in 76 children, 70 of whom had OSA. Oximetry was inconclusive or normal in 445 children, 112 of whom were diagnosed with UARS. Oximetry identified SDB (OSA) with a sensitivity of 0.38 (C.I. 0.31–0.46) and specificity 0.98 (C.I. 0.97–1.00); by definition, UARS cannot be identified with oximetry. Almost half (48%) of oximetry measurements ($n = 249$) were categorized as inconclusive.

The age range of children included in the PTT analysis was as follows: five children were < 1 year; 188 were aged 1–4 years; 127 were 5–8 years; 33 were 9–12 years; and 15 were 13–17 years. The mean age of children with OSA was 5.22 years; standard deviation (SD) 3.73. For those with UARS, mean age was 5.45 (SD 2.69); for children with primary snoring, mean age was 5.8 (SD 3.3); and for those with a normal study, mean age was 5.4 (SD 3.2). **Figure 5** shows scatter plots of age, weight z-scores, and body mass index z-scores demonstrating no significant differences in the baseline characteristics for any of the diagnostic categories.

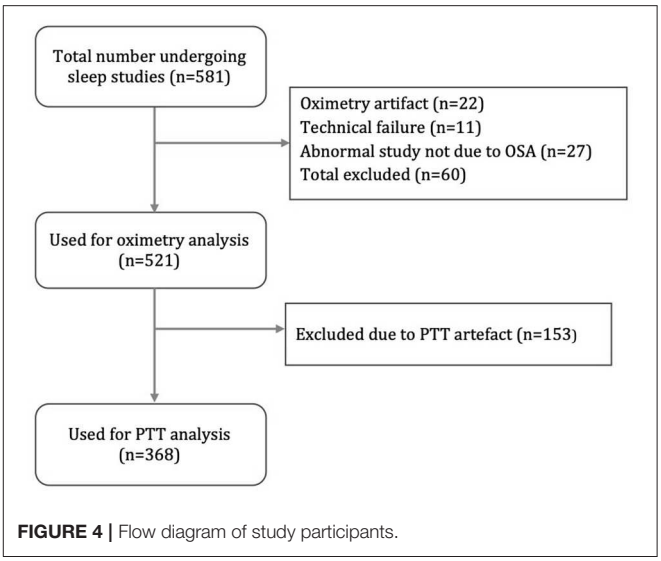

FIGURE 4 | Flow diagram of study participants.

Figure 6 shows scatter plots of the PTT respiratory swing and PTT arousal index according to diagnostic categories showing higher respiratory swing values in the groups with UARS and OSA compared to those with a normal study or primary snoring. **Figure 7** shows ROC curves of PTT respiratory swing (training and test datasets) and shows that a value of 17.92 ms maximized the sensitivity and specificity of detecting UARS or OSA, with a sensitivity of 0.80 (95% C.I. 0.62–0.90) and specificity of 0.79 (95% C.I. 0.49–0.87). Other thresholds of sensitivity and specificity are shown in **Tables 3**, **4**. We replicated the ROC curves with the testing set and found a PTT respiratory swing of 17.91 ms detects UARS or OSA with a sensitivity of 0.75 and specificity of 0.72.

Figure 8 shows a ROC curve of the PTT arousal index demonstrating poor specificity for detecting UARS or OSA. A value of 16.06/ hour identified children with UARS or OSA with a sensitivity of 0.85 (95% C.I. 0.67–0.92) and specificity of 0.37 (95% C.I. 0.17–0.48). Other training data PTT thresholds with sensitivity, specificity and confidence intervals are shown in **Tables 5**, **6**. **Table 7** shows the number of children with PTT respiratory swing values above and below the 17.92 ms threshold within the combined diagnostic categories (UARS/ OSA and snoring/ normal) in both the training and test datasets.

There were 177 children with normal or inconclusive oximetry who had PTT data available for analysis; 121 had a normal study or primary snoring using multi-channel criteria and 96 of 121 had a PTT respiratory swing below 17.92 ms. In the subgroup of children with normal or inconclusive oximetry, there were 56 with a diagnosis of UARS, 43 of whom had PTT respiratory swing values above 17.92 ms. Thus, when oximetry was inconclusive, PTT respiratory swing gave useful information on the presence or absence of UARS (χ^2 test $p < 0.001$).

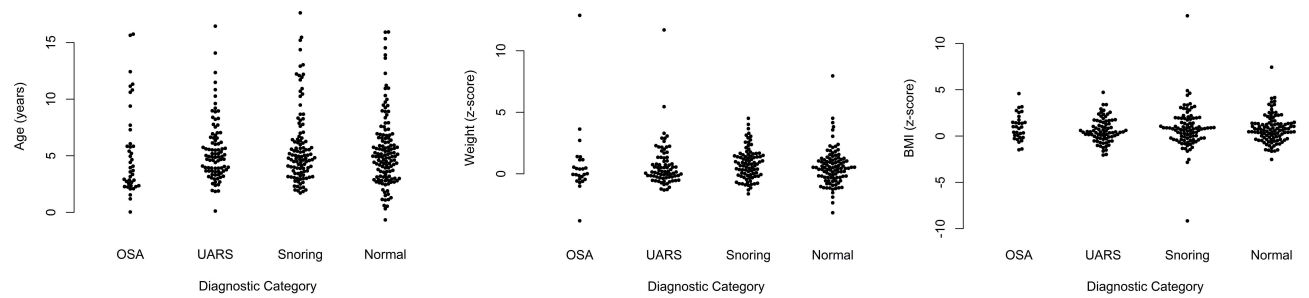

FIGURE 5 | Scatter plots of age, weight z-scores and BMI z-scores according to diagnosis.

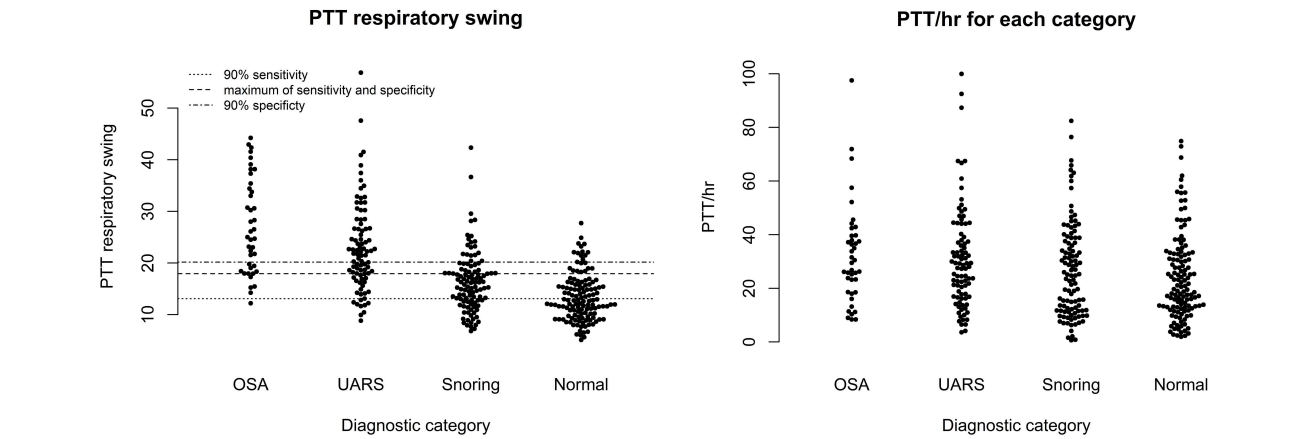

FIGURE 6 | Scatter plots of PTT respiratory swing and PTT arousal index.

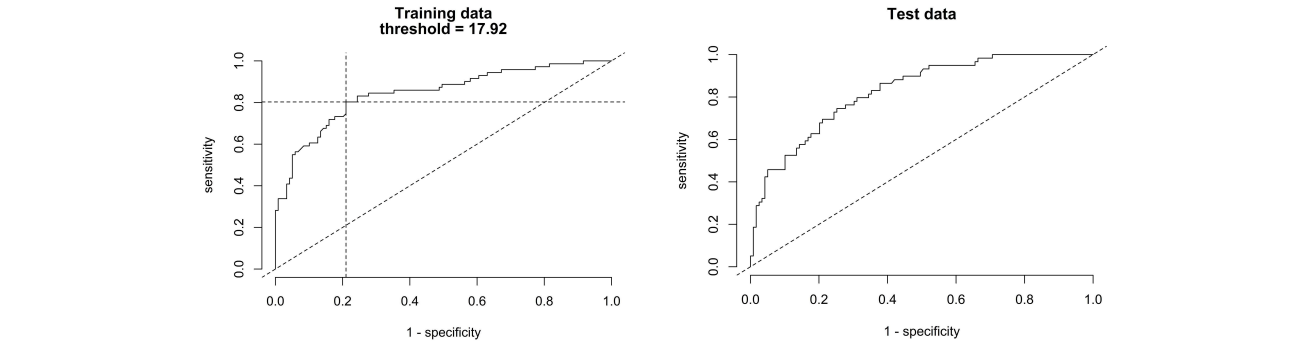

FIGURE 7 | ROC curves of PTT respiratory swing (training and test data) compared with a multi-channel study used to detect OSA or UARS.

DISCUSSION

This study is to our knowledge, the largest to evaluate PTT in children with SDB. A systematic review by Smith et al. evaluated 21 studies of the use of PTT in children. Most studies used PTT to screen for OSA whilst a few evaluated the use of PTT as a surrogate measure to track changes in blood pressure. The PTT arousal index (PTT-AI) is the most commonly studied PTT parameter and is a measure of the number of defined changes in PTT/ hour (17).

Pitson et al. have used "PTT swings" (Respiratory swing) in their evaluation of eight patients aged 13–68 years with OSA who were being started on nasal continual positive airway pressure (30). Their aim was to ascertain whether

TABLE 3 | 95% confidence intervals for PTT respiratory swing sensitivity at three thresholds (training data).

	2.5%	50%	97.5%
17.92 ms	0.62	0.77	0.90
13.07 ms	0.82	0.90	0.97
20.14 ms	0.46	0.61	0.76

TABLE 4 | 95% confidence intervals for PTT respiratory swing specificity at three thresholds (training data).

	2.5%	50%	97.5%
17.92 ms	0.49	0.77	0.87
13.07 ms	0.30	0.46	0.79
20.14 ms	0.81	0.91	0.97

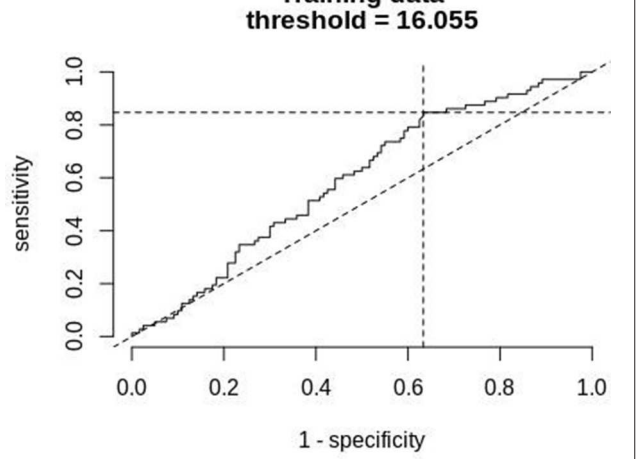

FIGURE 8 | ROC curve of PTT arousal index (training data) compared with a multi-channel study used to detect OSA or UARS.

respiratory oscillations in PTT could provide a useful measure of changes in respiratory effort in patients with sleep related breathing disorders. Patients were monitored with esophageal manometry, electroencephalograms (EEG), infra-red video, sound, oximetry and pulse rate. The authors found excellent correlation between the size of the swings in esophageal pressure and the size of the PTT swings (mean r=0.94), confirming its usefulness as a non-invasive measure of respiratory effort. Mehendale et al. also measured "PTT inspiratory effort" (Respiratory swing) in a study of 44 children with velopharyngeal incompetence, before and after a Sommerlad palate repair or a Hynes pharyngoplasty (31). Children were assessed for OSA with multi-channel cardiorespiratory studies and PTT inspiratory effort was used to assess changes in respiratory effort pre and post-operatively. The authors found a significant increase in PTT inspiratory effort ($p = 0.04$) in children undergoing a Hynes pharyngoplasty, suggesting increased upper airway resistance and respiratory effort. A significant

TABLE 5 | 95% confidence intervals for PTT arousal index sensitivity at the three thresholds of sensitivity (training data).

	2.5%	50%	97.5%
16.05/h	0.67	0.82	0.92
11.32/h	0.82	0.90	0.97
49.09/h	0.03	0.10	0.22

TABLE 6 | 95% confidence intervals for PTT arousal index specificity at the three thresholds (training data).

	2.5%	50%	97.5%
16.05/h	0.17	0.34	0.48
11.32/h	0.09	0.22	0.42
49.09/h	0.82	0.90	0.98

increase in the obstructive sleep apnea/hypopnea grading was also noted post-operatively ($p = 0.002$). The authors suggest that PTT inspiratory effort may have particular relevance in the identification of children with mild OSA and increased upper airway resistance resulting in increased inspiratory effort. Our findings are consistent with those of Mehendale et al.

A study by Katz et al. found PTT arousal index to be a more sensitive marker of cortical arousals than EEG and esophageal manometry (18). Griffon et al. also found PTT useful for discriminating between obstructive and central apnoeas but noted that about a third of apnoeas could not be scored due to artifact (32). We encountered similar problems with PTT artifact, leading to the exclusion of 26% of data. PTT is particularly prone to artifact due to the fact that it is computed from two physiological signals. Artifact occurs as a result of interference with the photoplethysmographic signal at the toe or finger or from loss of ECG signal due to disruption of chest wall leads with movement. Rapid eye movement (REM) sleep is particularly prone to PTT artifact due to significant variations in respiratory drive and rapid fluctuations in pulse rate and blood pressure affecting stability of the PTT signal. Obstructive events are most likely to occur during REM sleep and so a loss of stability in the PTT signal at this stage of the sleep cycle amplifies the impact of artifact.

Studies by Brietzke et al. and Bradley et al. have assessed the utility of PTT-AI to detect SDB in children using PSG as the gold standard (33, 34). Brietzke et al. studied 59 unselected symptomatic children routinely scheduled for PSG, 11 of whom had previously had an adenotonsillectomy and 15 who had a craniofacial syndrome (trisomy 21 and Apert syndrome) (34). The authors found that a PTT-AI cut off of 7.4 events/ hour identified SDB, defined as an Apnoea Hypopnea Index (AHI) > 3, with 93% sensitivity and 91% specificity. A PTT-AI cut off of 5.4 events/ hour identified SDB; defined as AHI > 1, with 81% sensitivity, and 76% specificity. The authors concluded that PTT-AI had excellent utility for detecting moderate or severe SDB but was not significantly better than oximetry at detecting

TABLE 7 | Number of children above and below PTT respiratory swing threshold in both training and test dataset.

	Training data			Test data			Overall total
	Above PTT swing threshold	Below PTT swing threshold	Total	Above PTT swing threshold	Below PTT swing threshold	Total	
UARS or OSA	57	14	71	44	15	59	130
Normal or snoring	24	95	119	33	86	119	238
Total	81	109	190	77	101	178	368

mild OSA. A similar study by Bradley et al. of 51 children aged 5–17 years with suspected SDB, found that a PTT-AI cut off of 11.36 events/ hour identified OSA (defined as AHI >3) with 94% sensitivity and 62% specificity. The same PTT-AI cut off identified OSA (defined as AHI >1) with a sensitivity of 66% and specificity of 67%. The authors showed that PTT-AI has validity for detecting moderate to severe OSA (AHI>3) but not mild OSA (33). In this study we found a poor association between PTT-AI and OSA or UARS, probably because about 60% of our cohort could be categorized as mild OSA (defined as UARS in this study). We observed that restless sleep may confound the ability of PTT-AI to detect SDB in our cohort. We did, however, find an association between PTT respiratory swing and OSA/UARS. There is emerging evidence that children with mild OSA (or UARS) have an increased risk of neurocognitive impairment, due to the effects of sleep fragmentation associated with frequent subcortical arousals in the absence of intermittent hypoxia (8, 35, 36). There is currently much interest in the identification of sleep study indices or biomarkers that can accurately identify children who would benefit from treatment (4). Further work is needed to ascertain whether PTT respiratory swing identifies children with mild SDB who are at risk of adverse neurocognitive outcome and who would benefit from adenotonsillectomy or treatment with nasal corticosteroids +/– leukotriene antagonists (37–40).

A potential limitation of this study is our use of SDB definitions (OSA, UARS, PS) based on multi-channel study criteria (oximetry, movement, video and sound) rather than PSG. The sleep system used (Stowood Scientific Instruments VISI−3 sleep system) records standard signals utilizing established and validated methods. For oximetry data, the sleep system utilizes Masimo technology which is validated in children and is favored due to its effectiveness at detecting and excluding motion artifact and because it has the option of a short averaging time (41, 42). PTT data was obtained with VISI software, using the same (or an upgraded version of) equipment as that used in several studies of PTT in children aged 1–18 years using PSG and/ or esophageal manometry as the comparator (16, 18, 30, 31, 33, 34, 43). A validation study by van Someren et al. of the Visilab system in a pediatric clinical setting, found the results comparable to those from PSG and with good interobserver reliability (16).

A study by Brouillette et al. showed that oximetry criteria for the diagnosis of OSA correlated with PSG findings with 98% specificity but 43% sensitivity (12). We found that abnormal oximetry correlated with multi-channel study findings of OSA with 98% specificity and 38% sensitivity; similar to the findings of Brouillette et al. using PSG as the comparator. The diagnosis of OSA in this study was based on both oximetry and video criteria making it likely that the findings are robust.

The oximetry criteria we have used to diagnose OSA have been validated in several studies (12, 19–22). We are therefore confident that children categorized as OSA in this study would correlate well with PSG given the known positive predictive value of oximetry and the additional video confirmation of the findings (12). We would also consider our definition of a normal study to be valid based on the absence of snoring, no obstructive events evident on video recording and no abnormal oximetry criteria. We acknowledge that our categories of UARS and PS need further validation. The strict definition of UARS requires esophageal manometry, an invasive technique which is not routinely used in the evaluation of children with SDB (18). The European Respiratory Society (ERS) task force statement defines UARS as follows: snoring, increased work of breathing, frequent arousals, but no recognizable obstructive events or gas exchange abnormalities (2). Our use of the term UARS is in line with these criteria apart from the identification of obstructive events on video. Based on the video evidence of obstructive episodes in children in this category, we presume that PSG will demonstrate some airflow obstruction, although it is uncertain if all witnessed obstructive events would meet the scoring criteria for apnoeas or hypopnoeas. We think it is likely that a number of children categorized as UARS would meet PSG criteria for mild OSA (Apnoea-Hypopnea Index 1–5). Our definition of UARS uses the same audio/video criteria as that used to confirm OSA; the main difference between the groups being the inconclusive or normal oximetry in those with UARS and abnormal oximetry in those with OSA.

The category of primary snoring is based on snoring being evident on sound recording with no (or minimal) evidence of obstructive events on video (2 or fewer events) and no abnormal oximetry criteria. The video criteria used to identify obstructive episodes have previously been described (44, 45). It is probable that some children in our categories of PS or UARS would be reclassified with PSG. We would argue however, that within the limitation of studies incorporating oximetry, video and sound, there is a need for distinction between the range of categories we have identified to aid clinical management decisions and particularly to identify children with OSA who are missed by the use of oximetry alone. It is possible that different labels could be used for the UARS category such as

"probable OSA" or "video diagnosed OSA." The use of the term UARS in clinical practice makes it possible to convey the essence of what clinicians need to know - that children with this diagnosis need more careful evaluation because some may benefit from surgery, whilst others could be managed with medical therapies (nasal corticosteroids +/− leukotriene antagonists) or watchful waiting. We note the striking similarities in PTT respiratory swing values in the categories of OSA and UARS (**Figure 6**) and the similar PTT respiratory swing values for children with PS or a normal study. We believe this observation provides some validity for our view that our categories of UARS and PS identify different entities within the SDB spectrum.

We sought to maintain consistency in our diagnosis of UARS by ensuring we identified three discrete clusters of obstructed breathing during the study period. This is based on oximetry criteria reported by Brouillette et al. recommending three or more clusters of desaturation episodes are identified for the diagnosis of OSA (12). We consider the UARS definition we have used to be pragmatic and potentially useful in health care settings with no access to PSG. Most children with SDB in the UK do not have access to PSG to confirm a diagnosis or to aid treatment decisions (46). Oximetry is the most widely used modality to identify SDB in children seen in UK secondary care centers but may only detect about 50% of affected children (12). We therefore surmise that many children with SDB and at risk of adverse neurocognitive outcomes remain undiagnosed. Furthermore, due to current trends in health care funding, these children may be unable to access necessary treatment (15).

We have demonstrated the feasibility of using a limited multi-channel sleep system in a secondary care center and have shown how the use of video and sound in addition to oximetry, increased the detection of SDB 2-fold compared to oximetry alone. It is our local experience that the findings from a multi-channel system are useful to Ear, Nose, and Throat (ENT) surgeons who are able to offer surgery and can expect to receive funding for children found to have UARS. Many are also managed with watchful waiting. However, if ENT surgeons only have a normal or inconclusive oximetry result on which to base management decisions, they are less likely to offer adenotonsillectomy in children with symptoms of SDB. This may be a direct result of the recent trend for Clinical Care Commissioning Groups to refuse funding for adenotonsillectomies in children with symptoms of SDB, who have no objective confirmation of OSA. This study also identifies the potential for PTT used in combination with oximetry to significantly improve the detection of SDB. This finding may have wide applicability but may be of particular interest to secondary care centers with no access to PSG.

We avoided bias by ensuring the PTT data analysis was done by a sleep physiologist and only reviewed by the reporting clinician after the sleep study categories had been determined. The reporting clinician was therefore blind to the PTT values whilst determining sleep study categories. The use of predetermined oximetry and video criteria for sleep study categories also minimized bias.

We envisage that PTT could be a useful addition to home multi-channel studies which are increasingly being evaluated for the benefits they afford over inpatient polygraphy or PSG. When given a choice, parents prefer home multi-channel studies to inpatient polygraphy or PSG for their convenience and because they facilitate better quality sleep; they also have potential cost benefits by avoiding an overnight hospital stay (47, 48). However, a significant challenge for home multi-channel studies is the problem of artifact. Our use of PTT monitoring in a hospital setting, where dislodged leads were resited during the night, still resulted in considerable artifact. This may be a limiting factor for PTT use in home multi-channel studies.

It is likely that oximetry obtained as part of inpatient multi-channel studies has reduced sensitivity for detecting SDB compared with home oximetry. Home studies potentially allow better quality sleep with more time in REM sleep, when SDB is mostly likely to occur.

The use of parental home video recordings has been shown to be a reliable screening tool for OSA and has good correlation with PSG findings (44). Parental home videos are currently being evaluated along with questionnaires to identify children who might be offered surgery for OSA without formal sleep studies.

This study demonstrates the potential for less invasive modalities to achieve a significant degree of accuracy in the detection of SDB. It will be important to validate the PTT findings with PSG or other treatment outcomes (i.e., neurocognitive).

CONCLUSIONS

We conclude that PTT respiratory swing can help identify SDB in children and is more sensitive but less specific than oximetry. We also found that the additional use of video and sound increased the detection of SDB 2-fold compared with oximetry alone. PTT used in combination with oximetry (+/– video and sound) could significantly improve the detection of SDB in health care settings with limited or no access to PSG.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MY was responsible for the original concept and design of the study, data collection, some data analysis and produced the first draft of the manuscript. AP and NR performed most of the data analysis. MK and ST were involved in data collection. NA contributed to the original concept and design of the study.

All authors contributed to the manuscript and approved the final version.

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PLAIN LANGUAGE SUMMARY

Pulse transit time (PTT) is a measurement calculated from the ECG and oximetry traces obtained during a sleep study, which has previously been shown to have the potential to help diagnose sleep disordered breathing (SDB). In this study we have identified threshold PTT values associated with SDB in children. Our findings suggest PTT is more sensitive but less specific than oximetry at detecting SDB. We also found that by combining video, sound and oximetry, we detected SDB in twice as many children as oximetry alone.

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Feasibility of a Complex Setting for Assessing Sleep and Circadian Rhythmicity in a Fragile X Cohort

Alexander Dueck[1], Olaf Reis[1], Manuela Bastian[2], Lucas van Treeck[1], Steffen Weirich[1], Frank Haessler[3], Andreas Fiedler[4], Michael Koelch[1] and Christoph Berger[1]*

[1] Department for Psychiatry, Neurology, Psychosomatics and Psychotherapy in Childhood and Adolescence, Rostock University Medical Center, Rostock, Germany, [2] Institute for Clinical Chemistry and Laboratory Medicine, Rostock University Medical Center, Rostock, Germany, [3] Department of Child and Adolescent Psychiatry, GGP Group, Rostock, Germany, [4] Department for Pediatric and Adolescent Medicine, Klinikum St. Marien, Amberg, Germany

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Karen Spruyt, Institut National de la Santé et de la Recherche Médicale (INSERM), France

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Marcel Smits, Independent researcher, Bennekom, Netherlands

***Correspondence:**
Alexander Dueck
alexander.dueck@med.uni-rostock.de

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Introduction: Sleep, circadian rhythms, (mental) health, and development are assumed to be intertwined. However, differentiated and reliable parameters of sleep and circadian rhythms are particularly difficult to assess for Fragile X (FXS) individuals. As those parameters need to be observed in complex settings, the feasibility of measurements for people with FXS was to be proven. Findings from this pilot study can inform further research and help to estimate sample sizes for future studies on FXS patients.

Methods and Sample: Nine individuals (male and female) with full mutation of the FMR1 gene were integrated in the study and underwent a complex measurement including actigraphy, sleep log, and 24-h saliva sampling in order to examine profiles of melatonin and cortisol, and a polysomnography.

Results: Seven actigraphy profiles, eight sleep logs, eight saliva profiles and seven polysomnographic data sets were collected. Complete data were analyzed for six individuals [mean age 14.87 years (SD 4.12), mean BMI 25.90 (SD 4.44)] were collected. No drop outs due to the constraints of the assessment were registered.

Discussion: All assessments and the setting in total were tolerated well by participants and caregivers. Procedures were adapted to individual needs of the participants.

Conclusion: All its components and the setting in total are absolutely feasible in the specific population of FXS individuals. Losses during consenting and recruiting have to be planned as well as high amounts of interindividual variances have to be taken into account.

Keywords: Fragile X, sleep, circadian rhythm, melatonin, polysomnography

INTRODUCTION

The Fragile X Syndrome (FXS) is a so-called rare disease (OMIM 300624)—being the most common form of inherited mental retardation (1, 2) with a worldwide prevalence of 1:4000 boys and 1:6000 girls at school age (3). It is caused by a trinucleotide expansion of CGG polymorphism which leads to a hypermethylation of the FMR1 gene on the X chromosome (4). With more than 200 CGG

repeats, the production of the Fragile X Mental Retardation Protein (FMRP) is absent (so-called full mutation). FMRP is involved in the regulation of protein synthesis and essential for typical brain development (5).

Sleep disturbances are common throughout different age groups of FXS patients (6–8). Parents report sleep problems in 32 up to 77% of children with FXS (6, 8), of which up to 64% are given some kind of sleep medication (7).

Despite the scope of the problem, we found only one study assessing sleep macroarchitecture objectively in FXS by using polysomnography. Miano et al. (9) examined a cohort of 14 FXS males who were observed for two nights in the sleep lab (9).

Different neuroendocrinologic parameters seem to be altered in FXS with respect to sleep and psychopathology. Interactions in symptomatology are controversially discussed (10–16). The role of melatonin in neuroprotection, cognitive, and learning disability has been discussed for FXS (17). In several studies, melatonin treatment in child and adolescent neuropsychiatry has been considered (17–20) and concrete recommendations for treatment were given (15–18, 20–22). For FXS however, we found only two studies directly assessing melatonin profiles (23, 24). Inhomogeneous results of both studies, however, can be explained by different samples (age), methods, and settings of assessment.

In sum, disturbances of sleep and circadian rhythms seem to common in FXS, but objective data is lacking. A major obstacle to obtain objective data might be the lessened compliance caused by cognitive and behavioral difficulties in FXS individuals (25). The aim of this study was to prove the feasibility of a complex multi-modal assessment of sleep and circadian rhythmicity considering the special needs of FXS individuals.

METHODS AND SAMPLE

The study design was approved by the ethics committee of Rostock University. Seventeen subjects with full mutation of the FMR1 gene were contacted by the treating physician and extensively informed about aims and setting of this study. After a meeting of subjects, caregivers (meaning parents and professional caregivers), and therapists, 12 subjects gave informed consent to participate after a time for consideration. Parents of one subject withdrew consent afterward and two participants did not show up for assessment. A sample of nine subjects was assessed (see flow chart in **Figure 1**) of which six complete data sets were gained. n = 7 PSGs, n = 8 sleep logs, n = 8 saliva profiles, n = 7 actigraphy data sets were collected. None of the participants got any kind of medical intervention or medication throughout the study.

Sleep Environment

Sleep environment was documented. Investigations were realized at our hospital (n = 1) or at home in two centers in North and South Germany. Subjects and families chose by themselves whether assessments should take place at our hospital or at home. As the equipment was mobile it could be used at any

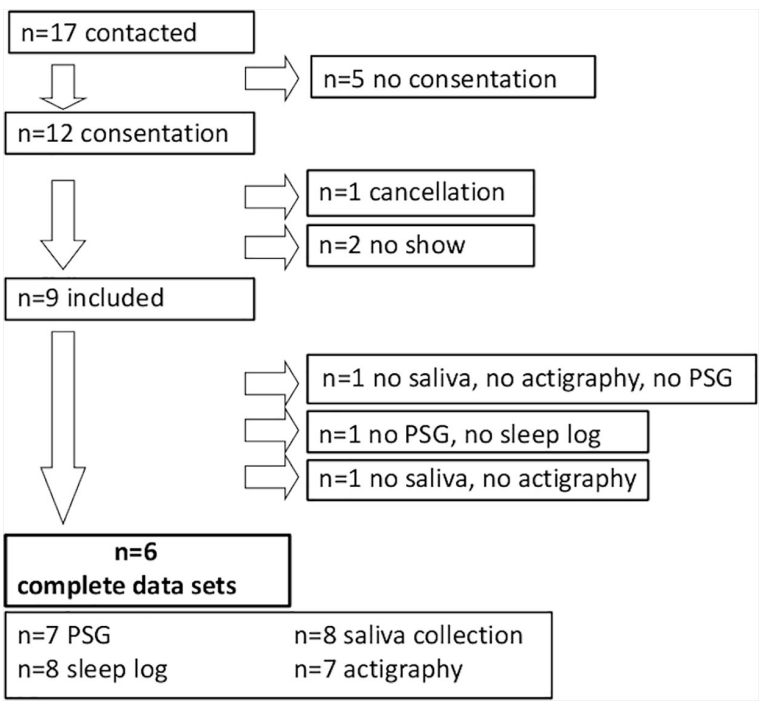

FIGURE 1 | Flowchart.

location. If participants were assessed at home a researcher visited them there.

Sleep Log

Sleep logs were kept for one week minimum and were filled out by caregivers. We asked for the time the subject went to bed, for bedtime routines, intake of medication, recuperation effects, sleep latency, WASO (wake after sleep onset) (number and time), time of sleep termination, and time of getting up. Global parameters of time in bed, total sleep time, variability of sleep duration, variability of sleep latency, variability of sleep onset, and variability of sleep termination were calculated.

Polysomnography

Prior the investigation, the PSG hardware was presented to the subjects. That included a head box dummy that a contact person or the participant himself could wear for some days, this way adapting to it. All PSGs were realized as one-night measurements. For polysomnography, we used the following electrodes and sensors: EEG: F3, F4, C3, C4, CZ (as reference), O1, O2, A1, A2, and FpZ (as ground), EOG one site, EMG: chin, tibialis anterior muscle right (TAR) and left (TAL), ECG, thoracic and abdominal belt, flow, and position sensor. The system used was the Somnoscreen plus© (SOMNOmedics GmbH, Randersacker, Germany). Data were collected and transferred *via* Bluetooth, with no electric wires between head box (located at participants chest), camera, or recording laptop being necessary. That gave participant the opportunity to move around without restrictions. Analyses were conducted by educated and experienced staff. Standard values were computed *via* the Domino© software (SOMNOmedics GmbH, Randersacker, Germany).

Saliva Samples

Sampling times were selected in relation to the current state of knowledge about endogenous melatonin secretion profile: 08:00 a.m., 12:00 a.m., 04:00 p.m., 06:00 p.m., 07:00 p.m., 08:00 p.m., 10:00 p.m., 00:00 p.m., 04:00 a.m., 08:00 a.m. Subjects were asked to refrain from eating or drinking at least 20 min before collection. Night samples were taken under dim light conditions while the subject stayed in bed. Light exposure prior and during sampling was measured by the light sensor of the actigraph (see **Figure 5**).

When sampling took place in the subject´s familiar environment, caregivers were extensively trained in the sampling method and were given a manual. If needed, they could contact the researcher 24/7. If it was regarded necessary participants were trained in spitting by a speech therapist before the assessment. Saliva samples were collected in a cup and then transferred to an Eppendorf tube. The samples were then stored in the domestic freezer until they were transferred to the laboratory cooled on dry ice. Melatonin was determined in saliva using a radioimmunoassay (Melatonin Saliva Direct RIA, DRG, Cat. RIA-5503) according to the manufacturer´s protocol. Samples (500 µl) were added with 25 µl of Enzyme. After 1 h of incubation, 50 µl Assay Buffer, 50 µl Adjustment Buffer, 25 µl ^{125}I Melatonin and 25 µl Melatonin Antiserum were added into the tubes. The probes were incubated for 20–24 h at room temperature. Precipitation reagent (1000 µl) was added. After vortexing, the probes were incubated for 20 min at 2–8°C and then centrifuged for 20 min at 3000 × g at 2–8°C. The supernatant was decanted and the tubes were dried for 2 min. Radiation was counted for 1 min in the Berthold Technologies LB2111 Multi Crystal Gamma Counter, combined with the data Station LBIS 501 software from Berthold technologies. Each series of measurement was performed with its own calibration curve. The calibration curve was determined by using a smoothed cubic spline. The limit of detection was 1.4 pg/ml.

The Cortisol levels were measured using ECLIA-Technology (cobas e411, Roche, Penzberg, Germany) and Immunoassay for the *in vitro* quantitative determination of cortisol in human saliva (Roche, Penzberg Germany, Cat. 06687733 190). The limit of detection was 1.5 nmol/l. Calibrations and control measurement were performed according to regulations of DAkkS.

Both hormones melatonin and cortisol were examined in each sample, with priority on melatonin if the amount of saliva was too small to detect both.

Actigraphy

The actigraph is a small, light-weight, wrist-worn monitor looking like a small watch. It includes an accelerometer (piezo element) and a light sensor to count motor activity and light exposure. Reading the data and charging the battery can be realized *via* USB. Participants were asked to wear the actigraph 24 h for at least 7 days (week and weekend) on the wrist of the non-dominant hand. The devices we used are waterproof, so they didn´t have to be removed while showering or bathing. Collected data was stored on a laptop and later transferred to a data base. Light exposure and movements were summarized and averaged for the period of 1 min. For our analysis, we enlarged the periods to 1 h. Interdaily stability and intradaily variability were computed directly from raw activity data according to the method used by Witting et al. (26). Both parameters are not dependent on *a priori* models of the data waveform (27). Interdaily stability scaled from 0 to 1 is a measure of consistency of circadian patterns (motor activity, light exposure) from one day to the next. It indicates the strength of coupling between a 24-h rhythm to an environmental zeitgeber. High intradaily variability is a measure for the hour-to-hour changes in activity and describes transitions between rest and activity. It also indicates nighttime activity or daytime resting.

Sleep scoring and awakening scoring was conducted with the Actiware© v5.59 software (Phillips Respironics GmbH, Hamburg, Germany). An epoch was considered as "awake" when the sum of activity counts for the eligible epoch and the two succeeding and preceeding neighbor epochs were higher than 40. The formula for the activity count sum calculation was:

activity count = epoch_{-2} *1/25 + epoch_{-1}*1/5 + epoch + epoch_{+1}*1/5 + epoch_{+2}*1/25. The sampling rate (epoch length) was 60 set for seconds. Movement data was collected over 7 successive days. As a movement detector the Motionwatch© 8 (CamnTech, Cambridge, UK) was used. The sampling rate (epoch length) was 60 set for seconds. Movement data was collected over 7 successive days.

TABLE 1 | Cohort: descriptive statistics.

Age (years)			BMI (kg/m^2)			Sex
Mean	SD	Range	Mean	SD	Range	1 f
14.87	4.12	8 to 20	25.9	4.44	18.08 to 31.64	5 m

SD, standard deviation; BMI, body mass index; kg, kilogram; m^2, square meters; f, female; m, male.

Statistics

Cosinor analysis is a well-established statistical method to describe circadian rhythms under the *a priori* assumption about the cosinus-like waveform of the activity data. A cosinor curve with a 24-h period was fitted to the collected data using the least-squares method. Various parameters, indicating the circadian rhythm, such as period, amplitude, acrophase, mesor and percent rhythmicity can be derived from the cosinor function itself (28).

RESULTS

Complete data sets were assessed for one female and five males with a mean age 14.87 years (SD 4.12, range 8 to 20 years) and an averaged BMI of 25.90 (SD 4.44, range 18.08 to 31.64) (see **Table 1**). In no case, the investigation was interrupted or cancelled during the assessment.

Sleep Environment

All six subjects slept in their own bed. Five had their own room, one shared the room with a sibling. For four subjects evening rituals or fix routines including bedding and pyjamas were observed. One participant did not show any sleep hygiene or evening routine and consumed media (TV and cell phone) in bed without parental regulation.

Sleep Log

The sleep log was filled out for all of the subjects. The recuperation effect of sleep (1 - very much, 2 - somewhat, 3 - middle, 4 - hardly, 5 - not at all) was reported as "very much" by five and with "middle" by one participant. No medication was reported for all participants. Three participants reported about taking naps during day time, ranging from 10 min up to 2 h.

For mean values of total sleep time, variability of sleep duration, sleep latency, variability of sleep latency, variability of sleep onset and variability of sleep termination see **Table 2**.

Polysomnography

Wearing the hardware and the investigation itself was tolerated well by all participants. The installation of all sensors takes a lot of time and can be experienced as stressful by the participants. Therefore, the time budget was planned with options for breaks and deflection, running between 1 and 2 h. A tablet or TV was used to distract participants during the time of installation. The dummy of the head box was received positively. Three subjects lost or removed the flow sensor throughout the night. No epileptic activity was determined in our group. For mean values and standard deviation see **Table 3**.

TABLE 2 | Sleep log data.

	FXS (n=6)	
	Mean	SD
Age	14.87	4.12
TST (h)	9.72	0.81
Variability of sleep duration (h)	0.77	0.71
Sleep latency (min)	8.69	6.57
Variability of sleep latency (min)	7.67	7.31
Number of night wake episodes	1.00	1.30
Total night awake period (min)	2.91	3.66
Variability of sleep onset (h)	0.35	0.19
Variability of sleep termination (h)	0.49	0.27

SD, standard deviation; FXS, fragile X syndrome; TST, total sleep time; h, hour; min, minute.

Saliva Samples

Sampling was tolerated well by all participants. During evening and night-time, the amount of saliva was somewhat reduced. In total, the data density was sufficient for melatonin, but less so for cortisol. Dim light melatonin onset (DLMO) can be defined as the period of time when melatonin concentration reaches 4 pg/ml or when concentration reaches doubled basal value. In our group, we found high melatonin values (above 4 pg/ml) but did not find an increase to doubled basal level in the group mean values (see **Figure 2A**). Surprisingly, we found the peak concentration around noon, with high values between the morning and afternoon, but not during the evening hours. As displayed in **Figures 2A, B** there levels vary a lot at all points of measurement, but especially in samples taken at 12:00 a.m. (mean 21.48 pg/ml, SD 39,49) and at 04:00 p.m. (mean 14.73 pg/ml, SD 22.57). Those results are mainly caused by the profile of subject number 6, as displayed in the individual 24 h melatonin trajectories (**Figure 2B**). Some participants show

TABLE 3 | PSG data.

	FXS (n = 6) (1)	
	Mean	SD
Age	14.87	4.12
TIB (min)	518.80	59.22
TST (min)	399.08	85.92
Sleep efficiency	78.63	19.95
Sleep latency	32.30	27.47
REM latency	179.17	79.24
SPT (min)	465.20	44.70
Awakening/h	0.68	0.46
WASO (% SPT)	18.78	23.30
REM (%)	14.43	2.63
N1 (%)	14.38	10.17
N2 (%)	46.12	3.20
N3 (%)	25.03	8.38

SD, standard deviation; FXS, fragile X syndrome; TIB, time in bed; REM, rapid eye movement (sleep state); TST, total sleep time; SPT, sleep period time; WASO, wake after sleep onset; N1, N2, N3, sleep states.

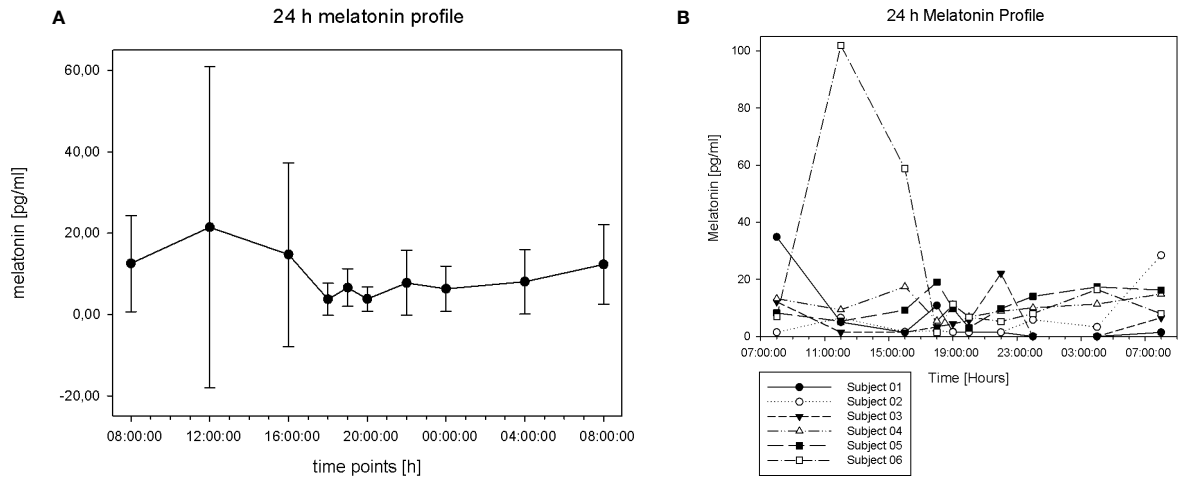

FIGURE 2 | (A) 24-h melatonin profile (mean and SD). **(B)** Individual 24-h melatonin curves.

individual peaks of concentration reaching the doubled basal level. Subject 1 peaks around 6:00 p.m., subject 3 around 10:00 p.m., subject 4 around 7:00 p.m., and subject 5 around 4:00 p.m. Subject 6 shows high values around noon with a following decrease in the afternoon and a second, but much smoother increase in the evening. Some individuals show peak concentration in the afternoon/evening time (subjects 1, 3, 4, 5, 6). Others have their peak in the morning (subjects 1, 2, 3) or show two peaks (subjects 1, 3, 6).

Figure 3 displays the amount of saliva for cortisol measurement. Unfortunately, the amount of data was not sufficient in our study to be analyzed *via* the cosinor fit method. This is mostly due to a lack of material in the samples taken. For three individuals samples were too small to be analyzed effectively.

In sum, patterns of hormone secretion during the day vary widely across individuals and time. A major problem occurred with the sampling of sufficient amounts of saliva for two targets.

Actigraphy

Wearing the actigraph was tolerated well by all of the subjects. Only two of the nine subjects included in the study did not want to wear an actigraph over the period of time. In both cases, there were concerns against the long duration of the investigation rather than the method itself.

To improve compliance in participants, the researcher or a close contact person also wore an actigraph (dummy) during investigation when considered appropriate. For group means and standard deviations of light exposure and movement per hour, see **Figure 4**. For calculated time in bed, total sleep time, sleep latency, sleep efficiency, and WASO; see **Table 4**.

The averages of interdaily stabilities for all participants were 0.35 (SD 0.28) for motor activity and 0.24 (SD 0.19) for light exposure. Intradaily variabilities were 0.61 (SD 0.14) for motor activity and 0.94 (SD 0.48) for light exposure.

Figure 5 displays motor activity and light exposure for a single participant for the day of saliva sampling. That way both parameters were controlled at times of sampling (vertical lines). **Figure 6** shows double plots of movement and light of two different FXS individuals over a time period of one week. In the plot on the left side variances of light exposure (light grey) and motor activity (black) are displayed. With this method the stability of daily routines (subjectively described by the sleep log) can be depicted objectively. All single cosinor fits reached the level of significance for light exposure and motor activity data (p 0,000) for the period of 24 h, averaged over for 7 days. For mean amplitude, mean mesor, percent rhythmicity of light exposure, and motor activity; see **Table 5**. Mean acrophase was around 02:00 p.m. for light exposure and 03:00 p.m. for motor activity.

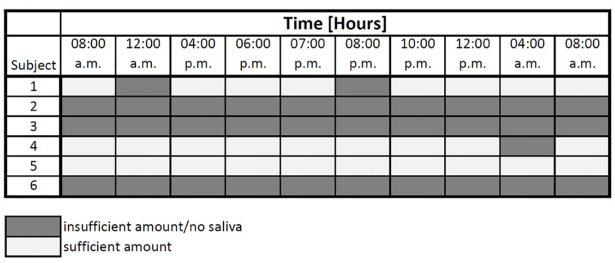

FIGURE 3 | Sufficiency of saliva for cortisol measurement.

DISCUSSION

A ratio of 12 participants consenting to nine participants included signals an attrition of about 33%. Thus, future studies should plan an oversampling of informed consents of about one third. Another third was lost during assessments (nine included/

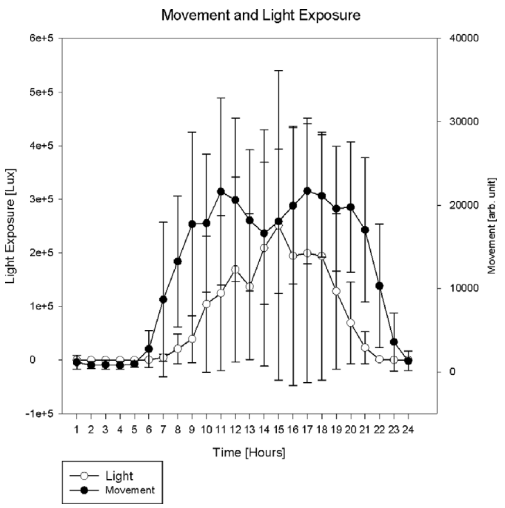

FIGURE 4 | . Actigraphy data: group mean and standard deviation of light exposure and movement.

TABLE 4 | Approximate sleep macro architecture based on actigraphy data.

	Mean	SD
TIB (min)	536.00	23.32
TST (min)	446.13	17.56
Sleep latency (min)	12.67	6.22
Sleep efficiency (%)	83.30	2.07
WASO (min)	64.75	8.92

SD, standard deviation; TIB, time in bed; REM, rapid eye movement (sleep state); TST, total sleep time; WASO, wake after sleep onset.

six complete data sets) with resisting to wear actiwatches for a whole week being the major reason for dropping out. However, no investigation was interrupted or cancelled during the assessment when certain individual adaptations were undertaken. In general, we regard it feasible to collect complex data on sleep and circadian rhythms in individuals with FXS. Feasibility should be explained in greater detail for different variables.

Sleep Environment

Nearly all subjects lived and slept in sleep supportive surroundings. There were families who strictly followed the same routines every day, including light exposure, eating, etc. For one girl, however, no sleep hygiene and routines were established.

Sleep Log

Naps were common for about one third of our participants (2 out of 6). In further studies, daily sleep routines need to be addressed along with the night sleep. The effect of sleep recuperation was assessed as very good to middle. Sleep log data represent the subjective opinion of caregivers about individual sleep (quality) which can be objectified by actigraphy. Differences in both parameters can indicate caregivers burden.

Polysomnography

In our study, seven out of nine participants underwent the PSG and tolerated it well. We successfully reduced rejection and burden, and enlarged compliance by 1) a dummy of the head box worn by the participant himself or by a close contact person for some time, 2) allowing the participant to use the tablet or watch TV during installation of the PSG electrodes, and 3) to move around freely. Compared to PSGs done at the lab, in-home investigations gave us the opportunity to observe daily routines and direct sleep environment of each individual. Thus, we decided to offer both settings to choose from. Miano et al. (9) conducted PSG under lab conditions and added one adaption night to reduce the first night effect (9). In order to minimize participants' burden, we decided to realize just one overnight measurement in our study. For children and adolescents, single-night PSG gave us also the opportunity to compare our data to normative values published by Scholle et al. (29) for a similar setting (29).

Despite seizures are common in FXS (30), we did not find any signs of it in our sample. The literature suggests rates of epilepsy in 10–20% and EEG anomalies in up to 74% of FXS-subjects (31). In order not to overlook signals indicating seizures, we decided to use a 10 channel EEG montage instead of the AASM recommended 3 channel derivation (32), which was well tolerated.

According to a study by (33), FXS individuals are at increased risk for obstructive sleep apnea syndrome (OSAS). In order to detect sleep disordered breathing, we decided to use a nasal probe with a pressure sensor (flow) and thoracic and abdominal belts. Belts were much better tolerated than the flow sensor.

Saliva Samples

We decided to let subjects spit into a sterile cup. This method was well tolerated and associated with low nighttime disturbance of the participants (see **Figure 5**). Both samples we compared our data with used radioimmunoassay (23, 24), as it was used in this study. Our data reveal a high amount of variance in levels of melatonin concentration at different time points (see **Figure 2**). Gould et al. did measure participants during a two days period doubling the amount

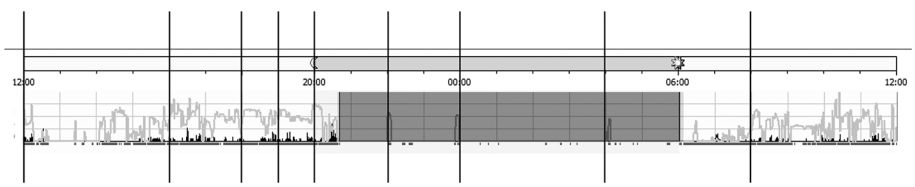

FIGURE 5 | Actigraphy data: control of saliva sampling for light exposure and motor activity.

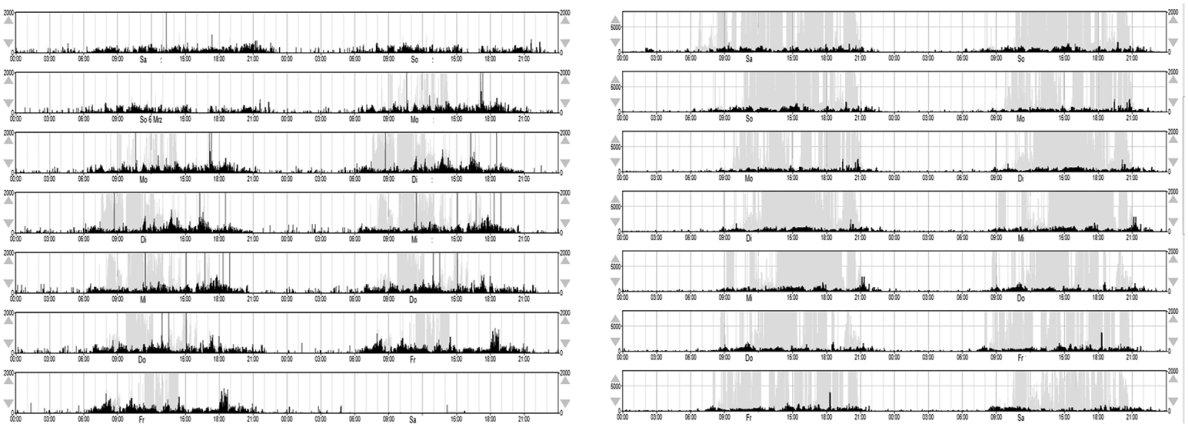

FIGURE 6 | Actigraphy data: double plots of two individuals.

TABLE 5 | Cosinor analysis of actigraphy data.

	Motor activity		Light exposure	
	Mean	**SD**	**Mean**	**SD**
Amplitude	11040.00	4837.71	116180.83	121024.06
Acrophase	14.48	1.48	13.82	1.65
Mesor	12273.33	5065.75	78037.00	80847.91
Percent Rhythm	74.62	15.63	65.69	16.40

SD, standard deviation.

of data per time point, but still found high amounts of variance within their data. For the melatonin peak with mean concentration of 169.87 pg/ml the SD was reported with 108.94 (24), which appears to be very similar to our findings.

In our cohort, we detected the melatonin peak concentration around noon (see **Figure 2A**). This contrasts the expected (physiological) profile with an increase of concentration during evening hours (DLMO) and high values during nighttime (34). High midday values in our study are associated with a high interindividual variance especially in the 12:00 a.m. and the 04:00 p.m. samples. The midday peak concentration is mainly caused by the oldest subject (20 years) in our group (subject 6, see **Figure 2B**) and is associated with extensive naps (2 h) every day (see sleep log section) in the afternoon. We found similarly high melatonin values during daytime in a 49-year-old woman, who did not take part in the complete setting. The high melatonin values around midday for two grown-up persons we suggest to be a hypothetic characteristic of adults with FXS. However, they might as well represent individual deviations. This question needs to be answered by further research. In contrast, O´Hare et al. (23) did not find any significant increase of serum melatonin levels during a 24-h period (sampling every 3 h) in an adult (mean age 59, range 47 to 69) FXS sample. The investigation took place in the hospital and melatonin examination was realized with blood drain *via* an intravenous cannula inserted at midday (23). Arguably, the lack of increase in O´Hare´s publication might be a result of the lab conditions. Gould et al. (24) investigated melatonin *via* in-home saliva sampling and described an increase of the melatonin level at 08:00 p.m. with a decrease at 08:00 a.m., a maximum peak at 02:00 a.m., and generally higher levels in their group of n = 13 FXS boys (mean age 8.04; SD 1.65; range 4.7 to 11.0 years) compared to the control group (24). The mean age in our group was very similar (14.87 years with just one 8 year old subject). Unfortunately, the amount of saliva from this young boy was not sufficient in the relevant samples (10:00 p.m., 00:00 p.m., 04:00 a.m. and second 08:00 a.m.) as it would be needed to compare the studies' data to our participant. However, the first 08:00 a.m. level (34.8 pg/ml) for the 8-year-old is much higher than the following ones (12:00 a.m.: 5.0 pg/ml) and all the levels during daytime. This refers to high levels during nighttime similar to Gould et al. (24).

The decrease of melatonin levels from childhood to adulthood in FXS might not only be a general progressive decrease with age (24). High concentrations in infants and prepubertal children (35), may suggest a drift in circadian profile of secretion. The finding of high melatonin values around midday in FXS adults under home conditions might be an important result and may have some potential for therapy. Treatments may include the organization of daytime structure and sleep interventions up to melatonin administration. To offer a nap might reduce "abnormal" and challenging behavior in some patients and increase quality of life—for the subject itself but also for the caring system. However, persistent high melatonin levels could be caused by food (36) or slow melatonin metabolism, itself perhaps caused by CYP1A2 gene polymorphism which might be associated with autism (37, 38). Both factors, food and CYP1A2 polymorphism and their interaction, should be addressed in further investigations.

FXS is often accompanied by psychiatric symptoms, such as ADHD-like behavior, ASD and challenging behavior (39) which often leads to pharmacological treatment (40). Gender differences in FXS´ psychopathology are well established. Females with FXS show more mood disorders than healthy controls. Males with FXS show more ADHD-like and

challenging behavior (41–43). ADHD itself is strongly associated with a disturbed circadian rhythmicity (44–46). The role of the HPA-Axis in FXS in general as well as in the psychopathology of the syndrome (ADHD, ASD, depressive symptoms, challenging behavior etc.) has often been described (10–14). However, the association of the cortisol level and the manifestation of autistic behavior is discussed controversially in this context (11, 13). Therefore, a sufficient examination of cortisol in saliva samples is recommended. Additional samples for the morning and early daytime should be taken to clarify these mechanisms. An extensive neuropsychiatric examination, including (mental) health, development, and caregivers burden should be useful. Cosinor analyses on hormone data should be useful to display the interplay of neuroendocrine and psychiatric aspects in FXS.

Actigraphy

The combination of saliva sampling with actimetry gives the researcher the opportunity to control time points and light conditions (see **Figure 5**). Constant light conditions during daytime, dim light and minimal movement during nighttime sampling become visible and controllable. As visible, the taking of samples did not disturb the night sleep. Constant routines, as indicated by sleep logs can be objectified by double plots for weeks, as shown in **Figure 6**.

In our sample, rhythmicity in the group is not very stable (IS < 0.5) and quite fragmented (IV > 0.9) for a period of one week. Instability of circadian rhythmicity and variability of sleep patterns, however, can be risk factors in family and caring systems.

In our small cohort single cosinor analyses were computed for each participant separately. For further analysis and correlation with other data, a groupwise cosinor analysis would be useful.

CONCLUSION

Polysomnography in our setting was well tolerated by participants and caregivers. It requires high efforts in time, logistic, and personal engagement. With a mobile system, overnight PSG investigations can be realized at the hospital or at home. Compliance can be enhanced by several measures tailored to the FXS population. In order to detect abnormal EEG-activity more than three electrodes should be used, which proved to be feasible. As the nasal probe was not tolerated by many of the participants, calculation of X-flow could be a useful and less invasive alternative to determine OSAS in FXS. PSG data will give us the opportunity to correlate objective sleep data with data on (mental) health and the subjects' and caregiver's burden. High variances, especially for hormone data, require large samples.

In-home, saliva collection proved to be a good method for this special group of participants. The best way to collect saliva from children with intellectual disability was to let the subjects spit into a sterile cup and then transfer saliva to an Eppendorf tube. Measuring hormones, melatonin, and cortisol from one saliva sample has led to comparatively poor data. However, the measurement of a full melatonin profile is essential for therapeutic considerations. For cortisol, additional saliva samples in the morning could be useful. To assess whether the melatonin peak at noon is a phenomenon typical for FXS in total the impact of age needs to be checked in a larger cohort of different ages. High melatonin concentration around midday in FXS (adults) might have important implications for treatment and daily life. Further investigations of melatonin profiles should include a sufficient amount of subjects in different age groups and address both food intake and CYP1A2 gene polymorphism. Actigraphy is a minimally invasive and well tolerated opportunity to measure circadian rhythmicity over a longer period of time. To find typical FXS patterns in sleep and circadian rhythmicity, an investigation within a big cohort and a comparison to a matched group (e.g., in sleep routines) would be necessary.

Therefore, the first author is in contact with the German Fragile X family support association Interessengemeinschaft Fragiles-X e.V. Germanys' biggest organization of affected people and their families, counting about 1000 FXS affected members, agreed to help to realize a bigger project. Extrapolating our results in recruitment, 500 to 550 individuals could be integrated and 300 to 350 complete data sets could be collected. An investigation with this number of participants all over Germany would be a logistic mammoth task, but would offer the opportunity to understand the structure of sleep problems. The optimal way to fully understand the role of sleep and circadian rhythms in the development of FXS of course, would be a longitudinal study over a time period of years.

In sum, disturbances of sleep and circadian rhythms are common in FXS. So are intellectual disability and psychiatric symptoms. Häßler et al. (47) point out the substantial burden of psychiatric and mental problems in patients with FXS of all age groups and recommend the initiation of an early psychiatric expert diagnosis with subsequent multimodal and multi-professional individualized management (47). There are indications for sleep and circadian rhythmicity playing an important role in this context. This study has proven the feasibility of a complex setting for the assessment of sleep and circadian rhythmicity considering the special needs of FXS individuals.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Rostock University Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed were part of data collection and/or publication.

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Conflict of Interest: FH was employed by the company GGP-Gruppe (Gesellschaft für Gesundheit und Pädagogik mbH), a corporation for health and education.

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Objective and Subjective Assessments of Sleep in Children: Comparison of Actigraphy, Sleep Diary Completed by Children and Parents' Estimation

Stéphanie Mazza[1]*, *Hélène Bastuji*[2,3] and *Amandine E. Rey*[2]

[1] HESPER Laboratory, Université Lyon 1, Université de Lyon, Lyon, France, [2] Central Integration of Pain, Lyon Neuroscience Research Center, Inserm U1028, Université Lyon 1, Université de Lyon, Lyon, France, [3] Unité d'Hypnologie, Service de Neurologie Fonctionnelle et d'Épileptologie, Hôpital Neurologique, Hospices Civils de Lyon, Bron, France

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Karen Spruyt,
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***Correspondence:**
Stéphanie Mazza
stephanie.mazza@univ-lyon1.fr

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In research and clinical contexts, parents' report and sleep diary filled in by parents are often used to characterize sleep-wake rhythms in children. The current study aimed to investigate children self-perception of their sleep, by comparing sleep diaries filled in by themselves, actigraphic sleep recordings, and parental subjective estimation. Eighty children aged 8–9 years wore actigraph wristwatches and completed sleep diaries for 7 days, while their parents completed a sleep-schedule questionnaire about their child' sleep. The level of agreement and correlation between sleep parameters derived from these three methods were measured. Sleep parameters were considered for the whole week and school days and weekends separately and a comparison between children with high and low sleep efficiency was carried out. Compared to actigraphy, children overestimated their sleep duration by 92 min and demonstrated significant difficulty to assess the amount of time they spent awake during the night. The estimations were better in children with high sleep efficiency compared to those with low sleep efficiency. Parents estimated that their children went to bed 36 min earlier and obtained 36.5 min more sleep than objective estimations with actigraphy. Children and parents' accuracy to estimate sleep parameters was different during school days and weekends, supporting the importance of analyzing separately school days and weekends when measuring sleep in children. Actigraphy and sleep diaries showed good agreement for bedtime and wake-up time, but not for SOL and WASO. A satisfactory agreement for TST was observed during school days only, but not during weekends. Even if parents provided more accurate sleep estimation than children, parents' report, and actigraphic data were weakly correlated and levels of agreement were insufficient. These results suggested that sleep diary completed by children provides interesting measures of self-perception, while actigraphy may provide additional information about nocturnal wake times. Sleep diary associated with actigraphy could be an interesting tool to evaluate parameters that could contribute to adjust subjective perception to objective sleep values.

Keywords: sleep diary, actigraphy, parents' report, school-based children, sleep measurements

INTRODUCTION

Twenty-five to 40% of healthy children and adolescents suffer from behavioral sleep problems affecting quality, timing or duration (1, 2). Insufficient quantity or quality of sleep predicts the development of health issues (3, 4), cognitive impairment and behavioral problems (5). Thus, the assessment of sleep-wake rhythms is valuable for the identification and management of sleep difficulties.

A variety of objective and subjective tools have been used to assess sleep-wake rhythms in children and adolescents, including polysomnography (PSG), actigraphy, sleep diary, and parental report questionnaires. These methods differ with respect to cost, duration, ease of use, level of intrusiveness, and type of data they provide. Laboratory-based PSG is deemed the "gold standard" for measuring objectively sleep parameters and architecture or for establishing the presence and severity of sleep disorders in children such as obstructive sleep apnea. However, PSG is a relatively expensive procedure that provides information about sleep for usually one or 2 nights, most of the time in an unfamiliar environment that can make PSG challenging and even frightening for children (6). Actigraphy is a non-invasive method to assess sleep-wake rhythms in the child's natural setting for extended periods of time, with a reasonable validity and reliability compared to PSG (7) or videosomnography (8). Actigraph is a wristwatch-like device containing an accelerometer providing a continuous monitoring of motor activity. This activity is translated to epochs of wake (activity) or sleep (inactivity) using a device-specific algorithm. Actigraphy recordings are often completed by a sleep diary filled by children's parents. Subjective tools, such as sleep diary and questionnaires, require minimum supervision and provide information related to personal perception of sleep. Sleep diary is a useful methodology to record information on sleep on a night-by-night basis (e.g., bedtime, sleep duration, sleep onset latency, night awakenings) and reflects a subjective global appraisal of each night sleep. Parental reports with questionnaires have often been used to evaluate children' sleep (9). This method can provide a detailed description of the child's sleep schedule, night awakenings and sleep-related behaviors such as bedtime resistance, parasomnia (e.g., sleepwalking and night terrors) and markers of sleep-disordered breathing (snoring, restless and disrupted sleep). Although simple questionnaires are suitable for screening and monitoring of a large population, sleep diaries are preferred for more detailed assessment of sleep-wake rhythms.

Beyond psychological factors (for instance depressive disorders), sleep quality itself influences the congruence between subjective and objective measures (10). Whereas good sleepers showed a more suitable perception of their sleep duration, the accuracy of patients with sleep-disorders varied widely (11, 12). Studies comparing objective and subjective assessments in large cohorts have found that adults overestimated their mean habitual sleep time by approximately 1-h when using sleep diary compared to PSG recording (13) or with questionnaires compared to actigraphy (14). In most studies investigating sleep in children, sleep diaries are filled in by parents. When parents have to estimate the sleep habits of their child, it has been shown that they tended to estimate with more accuracy sleep schedule variables than time awake in bed (sleep latency and night awakenings) (15). Moreover, the consistency of their reports decreased when the monitoring lasted a long time (16). Specifically, parents tend to report earlier bedtimes and later wake-up times in comparison with actigraphic measures, which average overestimation of sleep duration ranging from 30 to 113 min per night in different studies (17, 18). In adolescents, sleep parameters estimated with sleep diary and actigraphy measures are positively correlated especially during school days (19). They overestimated their sleep duration by approximately 1 h compared to actigraphy and underestimated their night awakenings (20). Short et al. (17) showed that between 13 to 17 years old, adolescents reported more accuracy than parents' reports; the latter overestimated sleep and underestimated bedtimes, suggesting that the use of adolescent reports should be preferred. There are few studies comparing sleep diary filled in by children and actigraphy. Most of them studied pre-adolescents or adolescents (17, 20–23). However, research on cognitive development, psychometric studies and longitudinal research indicate that children, as young as 8 years of age, can successfully provide valuable information about their own health when appropriate assessment methods are applied (24).

To our knowledge, this is the first study to investigate children's self-perception of their sleep, by comparing sleep diaries filled in by nonclinical children aged between 8 and 9, actigraphic sleep recordings, and parental subjective estimation during 7 days in a non-clinical population. Analyses were performed for the whole week and school days and weekends separately. To assess potential differences in sleep perception triggered by sleep quality, we compared children with high or low efficiency. We also evaluated the level of agreement and correlation between sleep parameters derived from these three measures.

METHODS

Participants

This study was part of a larger investigation examining the effects of a sleep education program on sleep, cognitive and academic performances in children. One hundred and thirty school-age children aged 8 to 9 years were recruited in five elementary schools. In the present study, the sample included the 100 children from the four schools where actigraphic measures were performed. Participants were instructed to wear an actigraph device, nights and days, during 7 consecutive days, and to complete a sleep diary each morning at school. Their parents had to fulfil a self-constructed Sleep-Schedule Time Questionnaire during the same period (see materials). The data analyzed for the current study corresponds to the baseline period of the larger study (before the sleep education program) and was collected during the fall to minimize potential seasonal effects. The protocol has been approved by the local Ethics Committee

(#IRB00010290-2016-08-03). Written informed consent was obtained from the parents and assent was obtained from the children prior to participation.

All participants had no history of psychiatric or neurological illness, developmental disorder or learning disability, according to parental reports. Sleep disorders were assessed using the Sleep Disturbance Scale for Children (25). Four children reached a pathological sub-score on the scale and were excluded from the analyses.

As five or more usable night recordings are recommended to obtain reliable measures of sleep for actigraphy in children (26), analyses were performed on actigraphic data with at least six usable nights including a minimum of one night during weekends (16% of the sample had only one night during weekend). Sleep diary and actigraphic recording were incomplete in 11 children and parents' report was missing for 9 children. Thus, a total 76 children (43 girls) aged 8–9 years ($M = 8.5$ years, $SD = 0.3$) with a complete set of data (sleep diary, actigraphic recording and parents' report) were included for analyses. Additional sample characteristics are presented in **Table 1**.

Measure

Objective Sleep Assessment: Actigraphy

Each child was invited to wear an actigraph (Actiwatch 2, Philips Respironics, Bend, OR, USA) on the non-dominant wrist for 1 week (5 school days and 2 weekends). This electronic wristwatch-like accelerometer measures the amount, duration and intensity of movements in free-living settings. Activity counts from the device were collected in 30-s sampling epochs and reflected the peak of acceleration detected and were used to determine sleep and wake intervals. Whether a particular epoch was scored as wake was determined by comparing activity counts for the epoch in question and those immediately surrounding it, to a threshold value (sensitivity threshold). If the total activity count was above the sensitivity threshold, the epoch was scored as wake, and if the total activity count was equal to or below the sensitivity threshold, the epoch was scored as sleep. For this study the sensitivity threshold was set to 40 counts by epoch (medium sensitivity) since this setting has been found to yield the least overestimation or underestimation of sleep or wakefulness for total sleep time and wake after sleep onset compared to PSG in children aged 9–11 years (27) and 6–12 years (28). The Actiwatch 2 devices are equipped with an event marker and a light sensor. At night, when children were in bed ready to fall asleep, they were told to use the event marker to designate their "bedtime". In the morning, when they woke up, they were instructed to mark the actigraph again. Sleep interval was marked manually for each record on the basis of event marker, activity, and light information. Sleep diary was used to know the timing of device removal. Actigraphic sleep data were analyzed in 30-sec epochs using Actiware Sleep software 6.0.9.

Sleep start and sleep end were determined automatically as the first and last 10 min period respectively in which no more than one epoch was scored as mobile. Automatic analyses were run to extract the following sleep parameters: (a) bedtime (clock time attempted to fall asleep), (b) wake-up time, (c) Total Sleep Time (TST - estimated amount of time scored as sleep, according to the Actiware-Sleep Algorithm), (d) Sleep Onset Latency (SOL - amount of time elapsing from bedtime to the first period of sleep), (e) Wake After Sleep Onset (WASO - number of minutes scored as wake-up time during sleep period). Analyses were performed on actigraphic data when at least six nights including at least one night during weekends were available.

TABLE 1 | Sample characteristics.

Variable	*N* or %
Age of children, mean (SD) [range]	8.5 (0.3) [7.9–9.3]
Sex, percentage	
F	56.6
M	43.4
Number of children per family, mean (SD) [range]	2.3 (0.7) [1–4]
Of which first born, percentage	31
Sleep Disturbance Scale in Children, mean (SD) [range]	
Insomnia	12.8 (4.1) [0–20]
Parasomnia	11.0 (3.3) [0–17]
Sleep related breathing disorders	7.3 (2.2) [0–11]
Circadian rhythms sleep-wake disorders	5.7 (2.2) [0–11]
Central disorders of hypersomnolence	3.3 (0.7) [0–5]
Birth order of child, mean (SD) [range]	1.7 (0.7) [1–3]
Number of electronic media devices at home (television, computers, consoles, tablets), mean (SD) [range]	3.8 (1.5) [1–8]
Children with their own cell phone, percentage	3.9
Children with an electronic media device in their bedroom, percentage	
No device	85.6
Consoles	11.8
Television	2.6
Computers	0.0

Children Self-Report Assessment: Sleep Diary

During 7 consecutive days, children completed a sleep diary each morning at 08:30 am. Instruction for filling in the diary was learned at school and children completed them under the teacher supervision during school days and alone during weekend. The sleep diary consisted in a daily record of sleep parameters. Each 24-h period was represented by a continuous line divided in boxes, one box corresponding to 1 h. Children were told to write the current date, then draw a down arrow to indicate their bedtime and a up arrow to indicate their wake-up time. Then, they shaded in the boxes corresponding to their assumed sleep period and leave boxes unshaded to show wake period during the day or the night. Children were asked to indicate, for each half hour, whether they were awake or asleep. The following parameters were extracted from the sleep diary: (a) bedtime (defined by the down arrow), (b) wake-up time (defined by the up arrow) (c) TST (colored part between time to bed and wake-up time, (d) SOL (uncolored part between time to bed and the beginning of TST), (e) WASO (uncolored part throughout the beginning and the end of TST), and (g) sleep quality, ease of waking and sleepiness scores.

Parents' Report: Sleep-Schedule Time Questionnaire

Bedtime, wake-up time and assumed TST were obtained through a self-constructed questionnaire. The questions were phrased as follows: "Last night, your child went to bed at _____" (bedtime), "This morning, you child woke up at _____" (wake-up time) and "Indicate the total sleep duration of your child last night: _____ (hours and minutes)" (total sleep time). Example entries of 8:00 pm, 06:00 am and 9 h 30 min were given on first row. No answer categories were presented for any question, and information was collected separately for school days and weekends. Sleep onset latency and time awake during the night were not obtained.

Statistical Analyses

All actigraphy and sleep diary data were visually reviewed by 2 trained assistants. To ensure a good agreement between the two raters, they were first trained by scoring 5 records collectively, then they individually scored 10 identical records to allow discussion of discrepancies. To assess the agreement of the two raters' observations, a Kendall coefficient was calculated for the 10 identical records. The overall agreement rate was 87%. Statistical analyses were performed using RStudio version 3.2.2 (29) and JAMOVI version 1.0 (30). Normality of distribution was tested using the Shapiro-Wilk test.

Sleep Parameters Analysis

Repeated measures ANOVAs were conducted on each sleep parameters with Measures (actigraphy vs. sleep diary vs. parents' report) as between-subjects factor and Study period (school days vs. weekends) as within-subjects factor. School days refer to Sunday to Friday nights and weekends refer to Friday and Saturday nights. The Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. P values were adjusted for multiple comparison tests through the Bonferroni correction. Values are given as mean ± SDs. The mean difference was calculated between actigraphic and subjective measures (sleep diary and questionnaire) with a 95% confidence interval. Effect size was estimated by using eta-squared or Cohen's d and was interpreted as small ($\eta^2 \leq 0.01$, $d \leq 0.3$), moderate ($\eta^2 \leq 0.08$, $d = 0.5$), or large ($\eta^2 \leq 0.25$, $d = 0.8$). The level of significance was set at $\alpha < 0.05$. To compare children with high and low sleep efficiency, the sample was divided according to the sleep efficiency calculated with actigraphy (ratio of TST divided by TIB for all days) using the median-split criterion and two-tailed student t-test were conducted between the two groups.

Sleep Parameters Agreements Analyses

Pearson correlations were performed to assess the potential extent of the association between sleep parameters for (1) actigraphy and sleep diary and (2) actigraphy and parents' report and (3) sleep diary and parents' report. Correlation coefficients are sometimes inadequate and can be misleading when assessing agreement between measurements, because they evaluate only the linear association of two sets of observations (a strong correlation does not imply that a good agreement exists between them). Bland Altman plots is a graphical approach to quantify agreement between two quantitative measurements by constructing limits of agreement (31). These statistical limits are calculated by using the mean and the standard deviation of the differences between two measurements. For good agreement, it is recommended that 95% of the data points should lie within +/- two standard deviations of the mean difference (32).

The difference for each subject between (1) actigraphy and sleep diary, (2) actigraphy and parents' report, and (3) sleep diary and parents' report for all days, school days and weekends were plotted against their averages. A reference line equal to zero represents perfect agreement between the two measures. The mean bias represents the mean difference between the two measures and limits of agreement are defined as a deviation from the mean to two standard deviations.

A classical test of variance for paired samples based on the bivariate normal distribution that compares the variance of the difference with the variance of the average was calculated according to the Pitman's test. A p-value > .05 suggested a significant difference in the variability between measurements.

RESULTS

Comparison of Sleep Parameters Assessed by the Different Measures

Mean (SD) of bedtime, wake-up time, total sleep time, sleep onset latency, and wake after sleep onset assessed by the 3 different measures are presented in **Table 2**.

ANOVA performed on bedtime showed significant main effects of Measures ($F_{1,75} = 62.8$, $p < .001$, $\eta^2 = .11$) and Study period ($F_{1,75} = 85.7$, $p < .001$, $\eta^2 = .38$), as well as a significant interaction ($F_{1,75} = 5.9$, $p = 004$, $\eta^2 = .01$). Bedtimes reported in sleep diary and parents' report significantly differed from actigraphy (all ps < .001, cohen's d > .74). Both children's and parents' estimations indicated significantly earlier bedtime compared to actigraphy (40.5 and 36.6 min, respectively; 95% CI are presented in **Table 2**). This misperception was found both during school days and weekends (all p values < .001, all d values > 50). A significant difference was found during weekends between sleep diaries and parents' reports, bedtime estimated in sleep diaries was 14.1 min earlier compared to parents' reports ($t_{75} = 32.5$, $p = .04$, $d = 0.21$) and therefore more distant from actigraphy measure.

When considering wake-up time, a significant main effect of Measures ($F_{1,75} = 27.2$, $p < .001$, $\eta^2 = .05$), Study period ($F_{1,75} = 101.0$, $p < .001$, $\eta^2 = .42$), and a significant interaction ($F_{1,75} = 7.7$, $p < .001$, $\eta^2 = .01$) were observed. Children reported in their sleep diary a wake-up time 16.6 min earlier than measured by actigraphy when considering all days ($t_{71} = 4.3$; $p < .001$, $d = .37$), whereas parents estimated wake-up time 9.7 min later than actigraphy measures ($t_{71} = -2.7$; $p = .02$, $d = -.23$). No significant difference was observed between the three measures during school days (all ps > .25). During weekends, wake-up time significantly differed between children's sleep diary and parents' reports (-39.6 min, $t_{71} = 7.9$, $p < .001$, $d = .66$). Children estimated waking up 24.3 min earlier compared to actigraphy measures during weekends ($t_{71} = 4.9$, $p < .001$,

TABLE 2 | Mean, SD and range for each sleep parameters according to actigraphy, sleep diary or parents' report during all days (the combination of school days and weekends), school days, and weekends.

	Actigraphy Mean (SD) [range] (*N* = 76)	Sleep diary Mean (SD) [range] (*N* = 76)	Parents' report Mean (SD) [range] (*N* = 76)
All days			
Bedtime (hrs:min)	21:44 (00:41) [20:35; 00:16]	21:02 (00:44) [20:00; 23:15]	21:05 (00:25) [20:00; 22:00]
Wake-up time (hrs:min)	07:40 (00:30) [06:05; 08:59]	07:23 (00:37) [06:00; 09:00]	07:48 (00:26) [07:00; 09:30]
TST (min)	528.3 (30.04 [411.6; 625.4]	620.8 (45.6) [498.8; 705.0]	564.7 (36.3) [390.0; 600.0]
SOL (min)	14.7 (11.24 [1.7; 47.1]	7.4 (18.6) [0.0; 92.5]	NA
WASO (min)	33.9 (10.5) [7.4; 62.3]	7.9 (19.0) [0.0; 105.0]	NA
School days			
Bedtime (hrs:min)	21:11 (00:40) [20:01; 23:28]	20:43 (00:39) [20:00; 23:00]	20:37 (00:31) [19:30; 22:00]
Wake-up time (hrs:min)	07:13 (00:24) [05:59; 08:08]	07:05 (00:28) [06:00: 08:15]	07:18 (00:29) [07:00; 09:30]
TST (min)	517.6 (45.2) [344.3; 655.3]	622.1 (42.3) [480.0; 693.8]	561.1 (43.4) [390.0; 600.0]
SOL (min)	13.4 (11.2) [0.3; 45.6]	8.9 (23.0) [0.0; 135.0]	NA
WASO (min)	33.6 (11.1) [8.0; 67.1]	7.9 (19.1) [0.0; 120.0]	NA
Weekends			
Bedtime (hrs:min)	22:17 (00:56) [20:53; 01:03]	21:22 (01:04) [20:00; 00:30]	21:36 (00:30) [20:30; 22:00]
Wake-up time (hrs:min)	08:06 (00:47) [06:12; 09:55]	07:42 (00:56 [06:00; 10:00]	08:20 (00:37) [07:00; 09:30]
TST (min)	537.9 (30.7) [437.7; 602.5]	619.4 (63.6) [420.0; 750.0]	568.3 (37.8) [390.0; 600.0]
SOL (min)	15.9 (15.2) [0.0; 62.8]	5.9 (17.2) [0.0; 90.0]	NA
WASO (min)	34.4 (13.8) [6.8; 76.5]	7.8 (22.5) [0.0; 200.0]	NA

TST, Total Sleep Time; SOL, Sleep Onset Latency; WASO, Wake After Sleep Onset; NA, Not Available.

d = .42). Conversely, parents' estimates were delayed by 16.1 min compared to actigraphy measures (t_{71} = -2.9, p = .02, d = -.24).

There was a significant difference of TST for Measures ($F_{1,71}$ = 175.4, p < .001, η^2 = .42), but no significant difference for Study period (p = .12). A trend to significant interaction Measures x Study period was also found ($F_{1,71}$ = 2.5, p = .08, η^2 = .01). When considering all days, TST was overestimated by 92.4 min in sleep diary (t_{75} = -17.1, p < .001, d = -.1.5) and by 36.5 min in parents' report (t_{75} = -8.6, p < .001, d =-.73) compared to actigraphy. The difference between children's and parents' estimates was 56.0 min (t_{75} = -10.7, p < .001, d = -.91). Whereas actigraphy showed that TST significantly increased during weekends compared to school days (20.3 min, t_{71} = -2.6, p = .03, d = -.22), such difference was not observed in sleep diaries and parents' estimates (all ps = 1.0).

Comparison for WASO and SOL were conducted between actigraphy and sleep diary. Children significantly underestimated their WASO in sleep diaries by more than 25 min ($F_{1,71}$ = 163.4, p < .001, η^2 = .37), whatever the Study period (school days: t_{75} = 8.9, p < .001, d = .74; weekends: t_{75} = 9.2, p < .001, d = .77). A significant effect of Measures ($F_{1,71}$ = 14.8, p < .001, η^2 = .04) but no effect of Study Period (p = .87) nor interaction (p = .16) were observed for SOL. SOL estimated in sleep diary was 10.0 min smaller than SOL estimated with actigraphy during week-end (t_{75} = 3.1, p = .002, d = .31).

Sleep Estimation in "Poor" Versus "Good" Sleepers

Children were categorized as high efficiency sleepers (60.5% of girls) and low efficiency sleepers (52.6% of girls) based on a median split on the all days sleep efficiency measured with actigraphy and defined as 89.2% (low efficiency sleepers: 86.0 ± 3.3% vs high efficiency sleepers: 91.5 ± 1.6%, p < .001, d = 2.16). When children were grouped according to sleep efficiency levels, low efficiency sleepers showed a shorter TST (520.9 ± 30.7 min, range: 411.6-576.9) than high efficiency sleepers (535.8 ± 27.7 min, range: 481.7-625.4, t = 2.22, p = .03, d = .51). Low efficiency sleepers also had longer SOL and WASO (SOL: 20.1 ± 11.8, WASO: 37.9 ± 9.8) as compared to the highest efficiency sleepers (SOL: 8.7 ± 1.1, WASO: 29.7 ± 9.0, all p *values* < .001, d > .87). Interestingly, low efficiency sleepers went to bed earlier (21:34 ± 00:41) than the highest (21:53 ± 00:40, t = 2.0, p = .048, d = .46) while wake-up time remained no significantly different (p = .84).

When comparing the discrepancy between estimations from actigraphy and sleep diary, low efficiency sleepers showed a larger overestimation of their TST compared to children with a high sleep efficiency for all study periods (all days: 107.9 vs 76.5 min, t_{38} = 3.4, p = .001, d = .79; school days: 118.3 vs 88.0 min, t_{38} 2.3, p = .028, d = .53; weekends: 97.4 vs 65.1 min, t_{38} = 2.1, p = .036, d = .51). When school days and weekends were considered separately, the overestimation was even greater during the weekends as compared to school days (see **Table 3**). The discrepancy of WASO measured during school days was significantly different between the groups, indicating a larger underestimation in low efficiency sleepers compared to high efficiency sleepers (31.3 vs 19.6 min, t_{38} =-2.9, p = .025, d = -.54). There was no significant difference between the two groups regarding their bedtime, wake-up time and SOL estimations.

When comparing discrepancy between estimations from actigraphy and parents' report, all day measures suggested that parents of low efficiency sleepers presented with a larger overestimation of TST than parents of high efficiency sleepers (50.5 vs 24.0 min, t_{38} = 2.89, p < .005, d = .69). This overestimation mainly concerned TST during weekends (47.2 vs 13.8 min, t_{38} = 3.40, p = .001, d = .81), but not during school days (p = .16). None of the other comparisons reached statistical significance.

Agreement Between Measures

Actigraphy-Sleep Diary

Both bedtime and wake-up time showed low to high significant correlations between the two measures irrespective of the study period (r values between .26 and .77, see **Table 4**). The Bland-Altman plots revealed a satisfactory level of agreement for bedtime and wake-up time between these two measures for all

TABLE 3 | Mean discrepancy (and standard deviation) between measures (actigraphy estimations minus children or parents' estimations) for high efficiency and low efficiency sleepers according to the study period.

Discrepancy between actigraphy and sleep diary				Discrepancy between actigraphy and parents' report			
	High efficiency sleepers (*N = 38*)	Low efficiency sleepers (*N* = 38)	*p*		High efficiency sleepers (*N* = 38)	Low efficiency sleepers (*N* = 38)	*p*
All days				**All days**			
Bedtime (min)	40.9 (29.0)	40.0 (29.5)	.89	Bedtime (min)	40.8 (40.7)	32.2 (39.1)	.39
Wake-up time (min)	14.8 (32.8)	17.7 (38.9)	.74	Wake-up time (min)	-9.8 (28.7)	-9.9 (29.3)	.98
TST (min)	-76.5 (39.2)	-107.9 (40.2)	< .001***	TST (min)	-24.0 (42.3)	-50.5 (34.3)	.005**
SOL (min)	4.4 (15.3)	10.1 (23.7)	.24	SOL (min)	NA	NA	NA
WASO (min)	21.2 (24.0)	30.7 (18.5)	.065	WASO (min)	NA	NA	NA
School days				**School days**			
Bedtime (min)	29.0 (37.4)	26.5 (34.4)	.77	Bedtime (min)	39.3 (46.8)	28.6 (33.9)	.26
Wake-up time (min)	8.1 (28.0)	8.3 (35.4)	.98	Wake-up time (min)	-1.6 (36.8)	- 6.5 (31.6)	.54
TST (min)	-88.0 (59.4)	-118.3 (54.2)	.028*	TST (min)	-34.1 (57.2)	-53.8 (59.9)	.16
SOL (min)	3.2 (13.9)	6.0 (30.1)	.62	SOL (min)	NA	NA	NA
WASO (min)	19.6 (24.5)	31.3 (18.0)	.025*	WASO (min)	NA	NA	NA
Weekends				**Weekends**			
Bedtime (min)	52.9 (45.8)	53.4 (43.2)	.96	Bedtime (min)	42.4 (55.7)	35.7 (59.1)	.62
Wake-up time (min)	21.5 (50.3)	27.1 (60.0)	.67	SOL (min)	-18.8 (37.3)	-13.4 (50.5)	.60
TST (min)	-65.1 (50.0)	-97.4 (74.9)	.036*	WASO (min)	-13.8 (45.7)	-47.2 (35.8)	.001**
SOL (min)	5.6 (19.0)	14.2 (23.4)	.10	SOL (min)	NA	NA	NA
WASO (min)	22.8 (27.3)	30.2 (25.1)	.24	WASO (min)	NA	NA	NA

*TST, Total Sleep Time; SOL, Sleep Onset Latency; WASO, Wake After Sleep Onset; NA, Not Available. *p < .05, **p < .01; ***p < .001.*

the studied periods. For almost all participants, the difference between actigraphy and sleep diary fell between limits of agreement (see **Figure 1**) and bias remained constant for all bedtime and wake time means. The test of difference in variance did not show significant variability between the two measures (Pitman's test: all *p*s > .11; see **Table 5**).

We found a significant correlation between TST reported by actigraphy and sleep diary but only when measures were considered for all days (r = .43, p < .001). Bland-Altman plots revealed that almost all data were inside agreement limits, but the negative bias tended to increase with the increase of means for all days and weekend plots. Pitman test confirmed a significant difference (both *p*s < .001) in the variability between actigraphy and sleep diary for these two study periods (see **Figures 1A, C**). When measurements concerned the school days, a good agreement with no significant variability between the two

TABLE 4 | Correlation between sleep parameters assessed by actigraphy, sleep diary, and parents' report during all days, school days, and weekends.

		All days		School days		Weekends	
		Actigraphy	Sleep diary	Actigraphy	Sleep diary	Actigraphy	Sleep diary
Bedtime	**Actigraphy**		*r* = .772*** *p < .001*		*r* = .586*** *p < .001*		*r = 739*** *p < .001*
	Parents' report	*r* = .376*** *p < .001*	*r* = .466*** *p < .001*	*r* = .350*** *p = .002*	*r* = .408** *p < .001*	*r* = .231* *p = .046*	.262* *p = .028*
Wake-up time	**Actigraphy**		*r* = .447*** *p < .001*		*r* = .262* *p = .027*		.448*** *p < .001*
	Parents' report	*r* = .489*** *p < .001*	*r* = .507*** *p < .001*	*r* = .095 *p = .425*	*r* = .096 *p* = .419	*r* = .482*** *p < .001*	.585*** *p < .001*
TST	**Actigraphy**		*r* = .433*** *p < .001*		*r* = .105 *p* = .382		.179 *p = .135*
	Parents' report	*r* = .305** *p = .008*	*r* = .197 *p = .102*	*r* = .119 *p* = .321	*r* = .293* *p* = .016	*r* = .208 *p* = .075	.188 *p = .120*
SOL	**Actigraphy**		*r* = .175 *p = .144*		*r* = .209 *p* = .080		.114 *p* = .340
WASO	**Actigraphy**		*r* = -.009 *p = .939*		*r* = .018 *p* = .885		*r* = .011 *p* = .929

*TST, Total Sleep Time; SOL, Sleep Onset Latency; WASO, Wake After Sleep Onset. *p < .05, **p < .01; ***p < .001.*

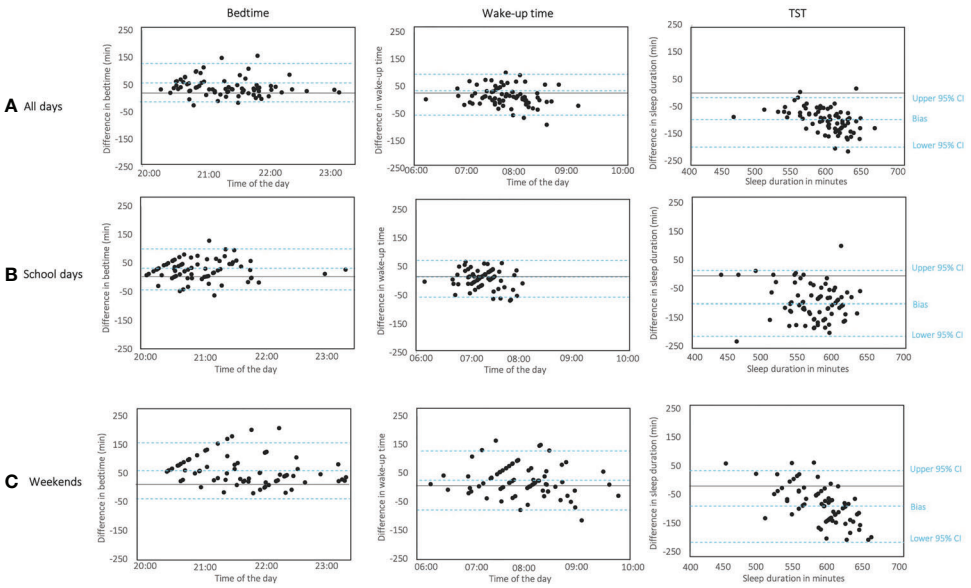

FIGURE 1 | Bland-Altman plots to assess the limits of agreement between actigraphy and sleep diary for bedtime (on the left), wake-up time (in the middle) and Total Sleep Time (TST, on the right) according to **(A)** all days, **(B)** school days, and **(C)** weekends. Each child's estimation is represented by a dot. Y-axis represents the difference between the two assessed measures being assessed; x-axis represents the average of the two methods. The horizontal line represents the bias; the two horizontal lines representing the 95% limits of agreement, which define the range in which 95% of the differences between methods are expected to fall and are calculated as the bias ± 1.96 standard deviation.

measures was found (Pitman's test $p = .57$), however the limits of agreement (-218; 11.2) and the difference obtained (-103 min) between the two measures were wide (see **Figure 1B**).

Agreement analyses for SOL only showed a satisfactory agreement between actigraphy and sleep diary for the weekend measures (Pitman's test $p = .19$), without any correlation between the two measures. No correlation or agreement were found for WASO parameters.

Actigraphy-Parents' Report

Significant correlations between the two methods were obtained regarding bedtimes and wake-up times (r values between .23 and .49), except for wake-up time during school days ($p = .43$). When all days and school days were considered, a significant agreement between actigraphy and parents' report was found for wake-up time (Pitman test $p = .32$ and $p = .14$, respectively) but not for weekends measures ($p = .024$). Regarding TST when all days were considered, parents' reports and actigraphy estimates showed a weak correlation ($r = .31$, $p = .008$) but no agreement (Pitman's test $p = .04$). A significant agreement was obtained for TST measured during school days; however, the two measures did not correlate ($p = .12$).

Sleep Diary—Parents' Report

Significant correlations between the two methods were found for bedtime (for all study periods, r values between .23 and .38, p values between .046 and < .001) despite no satisfactory agreement (Pitman's p between .070 and < .001). Wake-up time was significantly correlated between children and parents' estimations for all days ($r = .49$, $p < .001$) and weekends ($r = .48$, $p < .001$), but a satisfactory agreement was only observed during schooldays (Pitman's test $p = .80$). Regarding TST, the comparison between the two measures showed significant correlation for all days ($r = .31$, $p = .008$) and satisfactory agreement for all days and school days (Pitman's test $p = .76$ and $p = .81$ respectively).

DISCUSSION

This study builds on a vast literature on the validity of subjective sleep measures in pediatrics. We examined sleep parameters through 7-nights actigraphy measures, parents' reports, and sleep diaries and assessed agreement between these three measures. The originality of our study is that, unlike previous studies in which parents were requested to complete sleep diaries, sleep diaries were herein directly filled in by children.

Several studies exploring sleep of children by asking parents to complete sleep diaries showed an overestimation of sleep duration, inaccurate bedtime and time spent awake during the night compared to objectives measures (15, 21, 23, 33). Overestimation of sleep duration in the literature ranged from 30 to 113 min per night (18, 34) and might be explained by a difficulty to assess sleep latency and night waking in children who become more likely to maintain quiet wakefulness in bed (35, 36). In the present study, we observed a similar level of

TABLE 5 | Levels of agreement between the three measures for all sleep parameters during all days, school days, or weekends.

	ACTIGRAPHY vs. SLEEP DIARY				ACTIGRAPHY vs. PARENTS' REPORT				SLEEP DIARY vs. PARENTS' REPORT			
	Bias (95% IC)	Limits of agreement Lower; upper	Pitman's test		Bias (95% IC)	Limits of agreement Lower; upper	Pitman's test		Bias (95% IC)	Limits of agreement Lower; upper	Pitman's test	
			Variance (*r*)	*p* value			Variance (*r*)	*p* value			Variance (*r*)	*p* value
All days												
Bedtime (hrs:min)	40.5 (33.6; 97.4)	-16.4; 109.6	.11	.37	36.6 (27.4; 45.7)	-41.6; 114.7	.48	< .001***	3.2 (-12.6; 6.1)	-80.6; 74.2	.55	<.001***
Wake-up time (hrs: min)	16.3 (7.8; 24.8)	-53.8; 86.4	.07	.51	-9.7 (-16.4; -2.9)	-67.4; 48.0	.12	.32	-24.9 (-32.6; -17.2)	-88.6; 38.8	.27	.018*
TST (min)	-92.4 (-102.5; -82.4)	-175.7; -9.2	.43	<001***	-36.5 (-45.4; -29.9)	-114.5; 42.1	.21	.04*	56.0 (44.6; 67.4)	-48.4; 158.0	.04	.76
SOL (min)	7.3 (2.6; 12.0)	-32.0; 46.6	.48	<.001***	NA	NA	NA	NA	NA	NA	NA	NA
WASO (min)	26.0 (20.9; 31.2)	-16.7; 68.8	.55	.001***	NA	NA	NA	NA	NA	NA	NA	NA
School days												
Bedtime (hrs:min)	27.7 (19.3; 36.2)	-42.1; 97.6	02	.86	34.0 (24.6; 43.5)	-46.3; 114.4	.23	.046*	7.6 (-1.2; 16.5)	-67.2; 82.5	.22	.070
Wake-up time (hrs: min)	8.3 (0.8; 15.8)	-53.9; 70.4	.18	.12	-3.7 (-11.6; 4.2)	-70.5; 63.1	.17	.14	-12.0 (-20.9; -3.2)	-85.2; 61.2	.03	.80
TST (min)	-103.4 (-117.2; -89.6)	-218.0; 11.2	.07	.57	-43.5 (-57.5; -29.6)	-159.0; 71.9	.04	.73	57.8 (45.5; 70.1)	-40.9; 156.5	.02	.81
SOL (min)	4.6 (-0.9; 10.2)	-41.4; 50.6	.41	<.001***	NA	NA	NA	NA	NA	NA	NA	NA
WASO (min)	25.5 (20.3; 30.8)	-17.7; 68.8	.52	<.001***	NA	NA	NA	NA	NA	NA	NA	NA
Weekends												
Bedtime (hrs:min)	53.2 (42.7; 63.6)	-33.4; 139.8	.18	.11	39.1 (25.9; 52.2)	-72.8; 151.0	.56	<.001***	-14.1 (-29.2; 1.0)	-138.9; 110.8	.66	<.001***
Wake-up time (hrs: min)	24.3 (11.3; 37.4)	-83.6; 132.3	.17	.13	-16.1 (-26.6; -5.9)	-102.5; 70.3	.36	.024*	-39.6 (-50.5; -28.7)	-128.9; 49.7	.43	<.001***
TST (min)	-81.5 (-96.9; -66.0)	-209.7; 46.8	.63	<.001***	-29.6 (-39.7; -19.5)	-114.8; 55.6	.25	.029*	51.4 (35.2; 67.6)	-81.8; 184.6	.46	<.001***
SOL (min)	10.0 (4.8; 13.7)	-32.4; 52.3	.15	.19	NA	NA	NA	NA	NA	NA	NA	NA
WASO (min)	26.6 (20.3; 32.8)	-25.0; 78.1	.47	<.001***	NA	NA	NA	NA	NA	NA	NA	NA

Biases between measures are expressed as actigraphy minus sleep diary, actigraphy minus parents' report and sleep diary minus parent's report. Negative values indicate that the first measure overestimated the sleep parameter, whereas a positive value indicate that the first measure underestimated the sleep parameter. Levels of agreement for all comparisons during all days, school days and weekends for each sleep parameter are presented according to Bland-Altman analyses. Variance was determined by the Pitman's test of difference in variance between the two measures.

*TST, Total Sleep Time; SOL, Sleep Onset Latency; WASO, Wake After Sleep Onset; NA, Not Available; p values indicate the significance of Pitman's test; * p < .05, *** p < .001.*

discrepancy when children completed their own sleep diary. As their parents, children overestimated their sleep duration (92 min) and demonstrated significant difficulties to assess the amount of time they spent awake during the night by overestimating their sleep latency and wake after sleep onset (7 min and 26 min, respectively). One prior study used similar methodology in older children (11 to 12 years) to compare actigraphy and self-reported sleep parameters (20). Authors found that children self-report overestimated TST by 73 min, sleep onset by 21 min and WASO by 50 min. Several factors might explain such discrepancy between measures. As suggested by Lockley, Skene, and Arendt (37), even though these two methods attempt to measure sleep, they may measure different aspects of sleep since sleep diary relies on a subjective recollection of sleep, and actigraphy reports motor activity. Moreover, it is noteworthy that actigraphy as an objective measurement also has limitations, in particular with an overestimation of wake during sleep period (28, 38, 39) and sleep latency (40) when compared to the gold standard PSG recording.

In the present study, parents provided better estimation of sleep duration (+36 min) than children (+ 92 min) compared to actigraphy. When comparing self-report, parents' reports and PSG, Combs and colleagues (23) found that parents and children overestimated TST, sleep efficiency, and sleep latency compared to PSG. In contrast with our results, the differences between children and parents were less than 5 min and children provided a better estimation of TST than their parents. In this study children were older (age 9 to 17 years), and closer to those recorded by Short and colleagues (17) who previously showed that between 13 to 17 years old, adolescents' reports were more accurate than parents' reports. These results may suggest that sleep perception become more accurate with maturation.

On the basis of Bland-Altman tests, we observed that parents' report did not display a satisfactory agreement with actigraphy as in other studies (15, 18, 34). Only parents' perceptions of sleep duration and wake-up time were associated with sleep parameters as derived from actigraphy. However, actigraphy and sleep diaries completed by children regarding bedtime and wake-up time showed good agreement. The estimation of sleep duration during school days also showed satisfactory agreement, albeit to a lesser extent regarding the wide individual differences between the two measures. The current study further suggests that no agreement between actigraphy and children diaries was obtained for sleep onset latency or wake after sleep onset. Similar findings have been reported by Werner and colleagues (28) when actigraphy data were compared to diaries filled by parents. They found a satisfactory agreement regarding sleep start, sleep end, and sleep period, but not for nocturnal sleep and wake time. In accordance with previous studies, our results suggested that sleep diary completed by children or parents' report provide interesting measures of self-perception. However, because of their insufficient agreement for sleep duration and nocturnal wake time, actigraphy is a more appropriate choice when clinical or research assessment need accurate estimate of children's sleep.

Our results also suggested that school days and weekends should be analyzed separately. Children and parents' accuracy to estimate sleep parameters was different during these two periods. Total sleep time overestimation was greater for school days than weekends when children or parents' reports were compared to actigraphy. While actigraphy objectively reported a classical reduction of sleep duration during school days compared to weekends, parents and children estimated that sleep duration was similar between these two periods. As previously reported, when sleep parameters are considered for the entire week, parents tend to report earlier bedtimes and later wake-up times in comparison with actigraphic measures (17, 18). However, we found that wake-up time was better estimated by parents during school days than weekends. This result may be explained by a greater involvement in waking their child during school days compared to weekends, which allow them to be able to provide accurate wake time estimates. These results highlighted that sleep assessments lasting for a week are clinically important to apprehend sleep variation from school days to weekends, particularly if children "oversleep" on weekends to compensate for a lack of sleep (17, 41, 42). Averaging data from weekdays and weekends might wipe out those variation. Acebo and colleagues (26) and Short and colleagues (43) respectively suggested that actigraphy and sleep diary need at least five nights of recording to provide adequate stability for sleep parameters. Considering weekends assessment, two nights of sleep diaries have been shown to be insufficient to provide reliable estimation (43).

A number of factors may influence the measurement or perception of sleep parameters. Sleep quality itself has been shown to influence the congruence between subjective and objective measures (10). We found that discrepancy between objective and subjective measures was greater for children with lower sleep efficiency (< 89%). In this group, sleep time reported both by children in sleep diary and by their parents was overestimated in greater extent (> 30 min) compared to children with higher sleep efficiency. These children also underestimated their time spent awake during the night compared to those with higher sleep efficiency. Our results are in accordance with those reported by Van Den Berg and colleagues (44) in a cohort of elderly persons showing that subjects with poor sleep quality as measured by actigraphy consistently overestimated their sleep duration. Actigraphic measures of poor sleep quality such as shorter TST, lower sleep efficiency and longer SOL, were all associated with a higher diary estimates of TST than actigraphic measures. An earlier bedtime, later wake-up time, poor cognitive function and male gender were also associated with a higher level of disagreement. In children, inaccurate estimation of sleep indices might also arise from cognitive factors, such as the general level of cognitive functioning, the capacity to estimate time, the motivation to recall sleep parameters, or the ability to maintain in long term memory such information. Sleep diary filled by children associated with actigraphy could be an interesting tool to evaluate parameters that could contribute to adjust subjective perception to objective sleep values.

Our ability to define the study as a school project and the perfect consent rate we obtained (100%) discard consent or selection biases. Because feasibility of the sleep diary within the home environment and within the family schedules might affect compliance and increase variability between children (45), we have chosen to have sleep diaries filled-in upon the arrival at school, under teachers' supervision. Teachers' involvement every morning during this task might have contributed to improve data collection. However, we cannot rule out that results would have been the same if sleep diaries were completed at home.

This study presents limitations that need to be considered in interpreting the results. First, we included a non-clinical cohort of children for most of them middle-class Caucasian children, which may not allow findings to generalize to children suffering from sleep disorders or to samples characterized by greater demographic and socio-economic heterogeneity. Additionally, as mentioned two nights of weekend sleep diary entries may be insufficient to estimate valuable sleep indices because of the larger variance in weekend sleep patterns (43). Finally, the present study investigated the degree of convergence between

subjective measures and actigraphy which is known to present some limitation to estimate wake during sleep period. Subjective sleep assessments should be compared to the gold standard polysomnography in longitudinal studies to provide information about sleep perception evolution during life span.

CONCLUSION

The comparison between objective sleep measures, children self-reports and parents' report is useful to depict perception of children's sleep. The present study suggests that children aged between 8 and 9 are mature enough to complete a 7-day self-reporting of their sleep. Despite the classical indices of misperception, we found a good level of agreement between sleep-diary and actigraphy for bedtime and wake-up time, as for the total sleep time obtained during school days. Our results support the importance to analyze separately school days and weekends when we record sleep in children. Despite, the discrepancy found between subjective and objective measurements, the results of this study call for research on how the idealized parents and children perception of their sleep could be adjusted. Sleep diary associated with actigraphy could be an interesting tool to evaluate parameters that could contribute to reset subjective perception to objective sleep values.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité d'Ethique pour les Recherches Non Interventionnelles, Grenoble, France. Written informed consent to participate in this study was provided by the participants' legal guardian.

AUTHOR CONTRIBUTIONS

SM and AR developed the study concept. All authors contributed to the study design. Testing and data collection were performed by SM and AR. SM, HB, and AR performed the data analysis and interpretation. SM and AR drafted the manuscript. HB provided critical revisions. All authors approved the final version of the manuscript for submission.

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Skin Temperatures of Back or Neck Are Better Than Abdomen for Indication of Average Proximal Skin Temperature During Sleep of School-Aged Children

Véronique Bach[1]*, *Chris R. Abbiss*[2], *Jean-Pierre Libert*[1] and *Susan M. McCabe*[2]

[1] Peritox, UMR_I 01, University of Picardy Jules Verne, Amiens, France, [2] School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia

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***Correspondence:**
Véronique Bach
veronique.bach@u-picardie.fr

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Purpose: The tight association between sleep, body temperature regulation, and patterns of skin temperature change highlights the necessity for accurate and valid assessment of skin temperatures during sleep. With increased interest in this functional relationship in infants and children, it is important to identify where to best measure proximal skin temperature and whether it is possible to reduce the number of sites of measures, in order to limit the experimental effects in natural settings. Thus, the aim of this study was to determine the most suitable single skin temperature sites for representation of average proximal skin temperature during sleep of school aged children.

Methods: Statistical analyses were applied to skin temperature data of 22 children, aged 6 to 12 years, measured over four consecutive school nights in their home settings, to compare single site measures of abdomen, back, neck, forehead and subclavicular skin temperatures (local temperatures) with average proximal skin temperatures.

Results: Abdomen and forehead skin temperatures were significantly different (respectively higher and lower) to the other local proximal temperatures and to average proximal skin temperatures. Moreover, the time pattern of forehead temperature was very different from that of the other local temperatures.

Conclusions: Local forehead and abdomen skin temperatures are least suitable as single site representations of average proximal skin temperatures in school aged children when considering both the level and the time course pattern of the temperature across the night. Conversely, back and neck temperatures provide most fitting representation of average proximal skin temperatures.

Keywords: children, sleep, thermoregulation, skin temperature, home setting

INTRODUCTION

A close interaction between sleep and body temperature (T) has been shown to exist in animals and human neonates, children and adults. Two important consequences of this functional interaction are that sleep is regulated in phase with circadian body T regulation and that sleep disturbances are observed in association with thermoregulatory changes. Both sleep and thermoregulation are thought to be regulated by the preoptic area of the brain and anterior hypothalamus which further supports the functional interaction between these physiological processes [for a review, see (1)]. The association between sleep and T regulation highlights the necessity for accurate and valid assessment of body Ts within sleep research. Furthermore, the important effects of individuals' physiological characteristics (age, sex, health conditions, pathologies and medications), activity (daily occupation, type and timing of exercise, diet, bathing, use of screens, change in body position) and environment (seasons, ambient lighting, household T and humidity, bed microclimate) on their sleep and body T regulation, mean that body T assessment must be feasible and reliable in natural settings.

Human body T assessment is often divided into the "core" and the "shell". The core includes internal body organs such as muscles, lungs, heart, abdominal organs and brain and is typically measured *via* the rectum, esophagus or on the tympana. At rest, core body T remains relatively consistent between 36.5°C and 37.5°C. Conversely, the T of the peripheral shell (skin) is highly variable and heavily influenced by environmental conditions and mechanisms of heat gain and heat loss. Typically, metabolic heat produced within the core is transferred to the shell by internal conduction and by convection through blood flow. Blood flow is regulated differentially in each body region so that the skin T can differ drastically across regions. Areas with large arteries close to the skin surface (i.e. cheeks and the inguinal region) can be relatively hot (≥36.5°C), while limb skin T (i.e. ~33.5°C to 36.5°C at rest) and body extremities (<33.5°C at rest) can be much cooler.

In order to maintain body homeothermia, metabolic heat is lost to the environment through conduction, convection, radiation and evaporation and is modulated predominately by local skin blood flow and sweat rate. Heat exchange with the environment is dependent on the skin to environment T gradient. Cutaneous (skin) vasodilation and vasoconstriction play important roles in regulating skin blood flow to balance body heat loss and conservation. Distal body segments, and particularly the hands and feet, are characterized by many arterio-venous anastomoses [AVAs, shunts between arterioles and venules, which are innervated by the sympathetic constrictor neurons (2)] which adjust blood flow through the skin. Lyon et al. (3) have suggested that during development, the feet constitute the first body site to display vasoconstriction in term neonates. Early research (4) has shown that hand circulatory flow increases 44% when increased from 31°C to 35°C through water immersion. Changes in peripheral vasomotricity through AVAs can be assessed by the difference of skin Ts between the distal regions and proximal regions (assumed to devoid of AVAs), and are expressed as the distal-to-proximal skin T gradient (DPG**;** distal T minus proximal T). Therefore, even though core T provides fundamental thermal information to the hypothalamic regulating system, skin T plays a critical role in thermoregulation when ambient Ts varies [thermal transient (5)]. This is particularly true when considering the interaction between thermoregulatory processes and sleep-wake cycle regulation.

Sleep is regulated in phase with the circadian body T rhythm. From studies in adults, it has been shown that sleep onset usually occurs at or near the maximum rate of decline of core (rectal) T (6, 7). Conversely, morning awakening is associated with increases in core T. Magnussen [cited in (8)] suggested an autonomic (vegetative) sleep preparedness [starting around 100 min before sleep onset (8)] beginning with skin vasodilation. Behaviors before sleep and at bedtime facilitate vasodilation, mainly at the distal parts of the body. Distal skin vasodilation dissipates body heat and therefore leads to core T decrease, even when the person is clothed and covered. Thus, the patterns of distal (feet and hands, or wrist) skin T change are opposite to those of core T during the sleep-wake cycle (9–11). The patterns of proximal skin T change are intermediate, between the distal and the core T time patterns. Accordingly, during wake, the distal-to-proximal T gradient (DPG) is typically a negative value, with distal T lower than proximal T. The DPG increases (less negative, distal T rising toward proximal T) before sleep onset and during the first part of the night due to a more rapid increase in distal T than in proximal T. This leads to a "completely relaxed, one-compartment body" state [i.e. when DPG = 0°C, i.e., disappearance of the thermoregulatory shell (12)]. This is consistent with the observation that in preterm neonates homogenization between proximal and distal skin Ts was related to more rapid sleep onset (13). DPG can therefore be considered as a marker for skin thermal homogenization between the distal and the proximal regions of the body. Conversely, DPG decreases (more negative) towards wake and in the first part of the day (14). In this causal relationship, sleep is initiated as a consequence of the distal skin heat loss *per se* rather than of core T decrease (15), and skin T and the DPG might act as an input signal for the regulation of the sleep-wake cycle. Indeed, Kräuchi et al. (16) have demonstrated that the DPG is a better predictor of sleep onset than other measures, such as changes in core body T, melatonin level, heart rate, or subjective sleepiness rating. Subsequent studies have shown that the greater the DPG increase, the shorter the sleep onset latency (17, 18). Interestingly, alterations of body T pattern have been observed when sleep is compromised, in people with insomnia (19), narcolepsy (18) or children with bipolar disorder (20). Related to this, Boulant and Hardy (21) have shown that skin Ts modulate the firing rate of warm-sensitive neurons in the preoptic area and anterior hypothalamus, which are postulated

Abbreviations: AVA, arterio-venous anastomoses; BAT, brown adipose tissue; DPG, distal to proximal gradient; SD, standard deviation; SEM, standard error of the mean; H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, time (in hour) after reported bedtime; RB, reported bedtime; T, temperature; T3, T4, T4(R=L); Tw, average proximal temperatures; T_{abdo}, abdominal temperature; T_{clav}, clavicular temperature; T_{feet}, feet temperature; $T_{forehead}$, forehead temperature; $T_{left\ clav}$, left clavicular temperature; T_{neck}, neck temperature, $T_{right\ clav}$, right clavicular temperature.

as sleep-promoting signals. The neuronal activity of these warm-sensitive neurons increases at sleep onset and decreases prior to awakening and during wakefulness (22).

Studies performed on school-aged children sleeping in their natural settings showed that DPG [$T_{calf} - T_{subclavicular}$ (20), $T_{feet} - T_{subclavicular,\ abdomen}$ (23)] increased before and after sleep onset. Similar time patterns are also observed in preschool children (mean age: 4 years) (24), in 4 to 9 months old infants (25) and even in preterm neonates (13, 26). Although the usability of DPG to predict rate of sleep onset is reported as limited in infants (25) results show that, as in studies of adults, the larger the distal vasodilation, the more rapid the sleep onset (13). Also consistent with those shown in adults, the results of these studies of infants and children show that proximal and distal skin Ts do not share the same time patterns. Distal Ts have larger variation than proximal Ts, particularly in the initial hours from bedtime, leading up to and after sleep onset.

These results highlight the key role of skin Ts in the sleep wake-cycle, and point to the value of measuring skin Ts and DPG to complement polysomnography or actigraphy in sleep studies. Indeed, consideration of skin Ts goes beyond enhanced sleep assessment. It has been shown that it is possible to promote sleep initiation and maintenance with slight manipulations of distal and proximal skin Ts (producing changes that remain within the everyday circadian range) before and during sleep (27, 28). Experimentally induced peripheral vasodilation to enhance heat loss can be obtained with thermal manipulations (such as warm foot bath, use of hot water bottle) as well as non-thermal manipulations (e.g., lying down, closing eyes, active relaxation techniques) (for a review, see (29, 30). To the best of our knowledge, the use of deliberate slight thermal manipulation in order to improve sleep has never been studied in infants and children, despite its great interest. Notably, the relative importance of skin T (vs. core body T) in thermoregulation is understood to be even greater in infants and children than it is in adults, because of a higher density of skin thermoreceptors per surface unit and greater surface area (skin) to body mass (core) ratio [345 cm^2/kg in 9–11 years old boys vs. 263 cm^2/kg in young adults (31)] which enhance and accelerate the body heat exchange.

Reflecting the broad recognition of the importance of proximal and distal skin Ts in sleep research, various body sites have been used for measures of distal and proximal skin Ts (**Table 1**). To date, the majority of studies that have measured local **distal T** (sometimes called "peripheral") have measured T at the foot. Conversely, a considerable number of studies have also measured distal T at the hand, wrist or forearm. More rarely, distal T has been measured at the calf or on the leg. Average distal T (as opposed to local single distal T) is arithmetically averaged from various combinations of measures of T at distal regions.

Proximal skin T is more difficult to define. Proximal regions are most simply identified as those that are not distal, and proximal T usually refers to skin sites on the trunk (15). It has been identified that there are no or few AVAs in the skin of the chest (55), and the same is assumed for the rest of the trunk, with those regions accordingly considered not to play an important role in thermoregulatory heat exchanges (56). Some authors have included head regions [forehead (9, 41)] because no or few AVAs are observed on the forehead (55) but this is controversial (57). Moreover, regions supposed to have fewer AVAs are sometimes included in the proximal regions such as thigh (9) or forearm (15, 39), even though forearm is considered as distal region in other studies [**Table 1** (41)]. As for distal T, proximal T can be analyzed from a single site or as an average across several sites. Sites for single measurement typically include the trunk, including axilla, which is sometimes considered to be a reliable alternative of rectal T measure (58)), and abdomen, which is often chosen because of its special characteristics (position near the well irrigated liver, with non AVAs). In neonates under continuous monitoring of body T for the regulation of the incubator air T, abdominal T is often considered to be a good and non-invasive indicator of core T (3). More rarely, back is considered as a single site for proximal T, but in these studies T is measured on the mattress in the back region (51).

Average proximal T is obtained from various arithmetic averages of local proximal regions. The average values are calculated without (9) or with (16) weighting factors, which are roughly calculated according to each skin surface area over which the sensor is placed relative to the body surface area of the segment as a whole. It should be noted that this may differ for children and infants since proportions and skin surface area of each body segment change with development.

Given the vast possibilities for determining proximal or distal T measurement, **DPG (distal T minus proximal T)** may be calculated in different ways. Using single Ts, calculations have included proximal T which is not located on the trunk (forehead, flank, limbs) even though they have been shown to show similar time pattern as hands or feet T (13). Unique DPGs have been calculated between upper ($T_{ear\ lobe} - T_{mastoid}$), middle ($T_{hand} - T_{arm}$) and lower body ($T_{foot} - T_{leg}$) regions, and exhibit anti-correlated fluctuations in the hand-to-arm and foot-to-leg gradients (42). Most clear-cut formulas include trunk proximal T with $T_{foot} - T_{abdomen}$ more often used. The DPG can also be obtained from the difference between average distal and average proximal skin Ts, with a range of calculations reported.

It is clear that there are a range of possible sites and formulas for the measurement of proximal T and, to a lesser extent, distal T. Logically, it could be assumed that proximal T may be most accurately assessed as the average of multiple measures, from all over the proximal regions. That is, the more numerous the measurements, the more accurate the calculation of average proximal T. Indeed, some studies have calculated skin T from averages over 65 locations for a "full-body thermography" (59) or with skin infra-red thermography (60). Conversely, the use of multiple sites is at odds with practical considerations. This is of particular interest when considering measures in home settings, where the subject, relatives or caregivers are required to be accurate in their timing and placement of the sensors. As well as reducing participants' preparation time and reducing possible impact on their sleep, reducing the number of sensors reduces the risk of errors of sensor location.

TABLE 1 | Reported single and combined body sites for measures of distal skin T, proximal skin T and DPG.

Distal temperature		
Local distal temperature		
Foot	One foot, or average value of the right and left feet	(13, 23, 25, 32–36)
Hand	Measured variously at back of the hand(s), one or both middle fingers	(37, 38)
	On the fingertip	(39, 40)
	Thumb	(15)
Wrist		(11)
Forearm		(41)
Calf		(20)
Leg		(41)
Average distal T		
Combinations of measures of T at the hands (fingertip, finger, palm) or feet (instep, big toe)		(42)
Hands and feet		(18, 43–45)
Wrist and feet		(46)
Wrists and ankles		(47)
Extensive combination of ankles, calves, thighs, fingers, wrists and forearms		(48)
Proximal temperature		
Local proximal temperature		
Trunk	Subclavicular	(24, 45, 49)
	Sternum	(45, 46)
	Flank	(41)
	Axilla	(50)
	Abdomen	(25, 26, 37)
	Back	(51)
Average proximal temperature		
Pectoral and abdomen		(13)
Left and right subclavicular regions and sternum		(46)
Left and right subclavicular regions and sternum and thigh(s), abdomen, subclavicular region(s) and midthigh(s)		(18, 43–45, 52)
Subclavicular, sternal, back shoulders and spinal cross regions	Could be distinguished into back (shoulders and spinal cross) and front (subclavicular and sternum) regions.	(48)
DPG		
Using single Ts		
Proximal T not located on the trunk	Forehead and flank as proximal Ts and arm or leg as distal Ts,	(41)
	$T_{middle\ finger\ fingertip} - T_{forearm}$	(39)
	$T_{thumb} - T_{forearm}$	(15)
	Upper part of the body: $T_{ear\ lobe} - T_{mastoid}$ middle part of the body: $T_{hand} - T_{arm}$ lower part of the body: $T_{foot} - T_{leg}$	(42)
Proximal T located on the trunk	$T_{foot} - T_{torso}$	(53)
	$T_{foot} - T_{chest}$	(24)
	$T_{calf} - T_{subclavicular}$	(20)
	$T_{foot} - T_{abdomen}$	(3, 25)
Between average proximal and average distal temperatures	$T_{wrists\ and\ ankle} - T_{clavicular\ and\ sternal}$	(47)
	$T_{wrists\ and\ feet} - T_{subclavicular\ and\ sternal}$	(46)
	$T_{hands\ and\ feet} - T_{subclavicular,\ thigh,\ stomach\ and\ forehead}$	(14, 16, 54)
	$T_{hands,\ feet} - T_{subclavicular,\ thigh,\ abdomen}$	(44)
	$T_{ankles,\ calves,\ thighs,\ fingers,\ wrists\ and\ forearms} - T_{abdomen,\ subclavicular\ region\ and\ midthigh}$	(48, 52)
	$T_{ankles,\ calves,\ thighs,\ fingers,\ wrists\ and\ forearms} - T_{subclavicular,\ sternal,\ back\ shoulders\ and\ spinal\ cross\ regions}$	(48)

It may be practical to reduce the number of sensors used in infants and young children. Moreover, for those with behavioral or cognitive impairments, it would be safer to locate sensors at body sites where they are least likely to be tampered with or removed. With increased interest in the functional relationship between thermoregulation and sleep in infants and children, it is important to determine the accuracy of measures when fewer skin T sites are used with these populations. Morphological and thermoregulatory differences prevent extrapolation from results of studies of adults. Thus, the purpose of the present study was to compare single locations for measure of proximal T with that determined by average of proximal T sites. Special interest was

given to back T as the preferred site, for the abovementioned reasons, using sleep and skin T data of children aged 6 to 12 years.

METHODS

The present study is additional analysis of data which were collected as part of a study of reliability and patterns of skin T and sleep in 22 healthy school aged children, aged 6 to 12 years (mean, SD: 9 years 6 months ± 1 year 10 months), over four consecutive school nights in their home settings (23). Prior to participation, children provided written assent, and their parents provided written consent based on written information and verbal explanation of the requirements and possible risks associated with the study. The study was approved by Edith Cowan University Human Research Ethics Committee. Data collection was conducted in Perth Western Australia during the months of May to October (autumn to spring). The overnight bedroom Ts ranged from 15.6°C to 21.5°C (mean 18.5°C ± 1.4°C), bedroom humidity ranged from 49.2% to 75.4% (mean 63.8 ± 6.89%), and the bedroom ambient light ranged from 7.1 lux to 18.2 lux (mean 10.3 ± 2.7 lux). In addition to measures of sleep habits, perceptions of thermal comfort, core body T and ambient bedroom light and T the children's sleep was measured through use of actigraphy (Actigraph GT3X+ activity monitors, Actigraph, FL, USA) and parent log books [for full description, see (23)]. Their skin Ts were measured through use of Thermochron iButtons (DS1922L, Maxim/Dallas Semiconductor Corp., USA). The iButtons are specified to have accuracy of ±0.5°C in a range of 10°C to +65°C (www.maximintegrated.com). They have been found to provide valid measures of human skin Ts in natural settings (61). The iButtons were pre-set to record every 5 min, at high resolution (0.0625°C). Parents were instructed to place iButtons onto their child's skin 1 h before bedtime and to remove them on morning waking. Reflecting methods reported in other studies of human skin T (47, 62–64) the iButtons were attached to the children's skin using air-permeable adhesive skin tape (Fixomull, Beiersdorf, Hamburg, Germany). Eight skin sites were used, with iButtons attached at left and right feet (T_{feet}), abdomen (T_{abdo}), left and right subclaviculae (T_{clav} = averaged from $T_{right\ clav}$ and $T_{left\ clav}$), forehead ($T_{forehead}$), back of neck (T_{neck}), and central back area (T_{back}) (**Figure 1**). Notably, the study did not include measures of hand or finger. The decision to omit hand or finger T was based on safety considerations, to avoid risk of inadvertent ingestion of the small, battery sized sensors. The skin T data were formatted using Excel (Microsoft, 2016), in alignment with reported bedtimes for each child, each night. All skin Ts had high night to night reliability, as previously demonstrated (23).

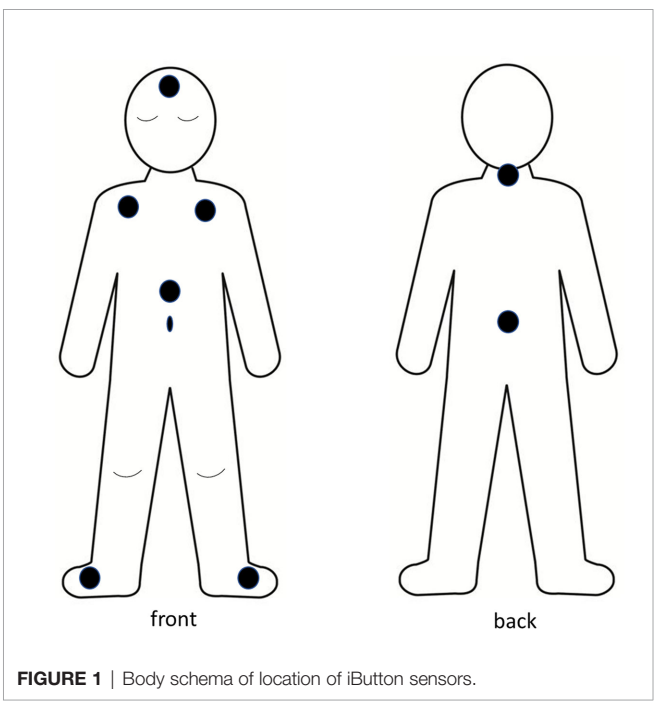


FIGURE 1 | Body schema of location of iButton sensors.

Data Analyses

For the current study, several formulas were used to calculate average proximal T, with different weighting coefficients. These reflect formulas most commonly used in published studies, and are shown as i) Formula 1, with a weighted formula (Tw) modified from Kräuchi et al. (14) using abdomen, right and left subclaviculae (averaged) and forehead Ts; ii) T4(R=L) Formula 2, using averaged values of left and right subclavicular Ts, abdominal T and back T; iii) T4 Formula 3, with the same local Ts, but attributing the same weighting factor for each of the 4 measures; and iv) T3 Formula 4, using a more typical formula for proximal Ts (right and left subclaviculae, abdomen) (23)

Formula 1 :

$$Tw = 0.45 \times T_{abdo} + 0.407 \times T_{clav} + 0.143 \times T_{forehead}$$

Formula 2 :

$$T4(R = L) = 0.33 \times T_{abdo} + 0.33 \times T_{clav} + 0.33 \times T_{back}$$

Formula 3 :

$$T4 = 0.25 \times T_{abdo} + 0.25 \times T_{right\ \ clav} + 0.25 \times T_{left\ \ clav} + 0.25 \times T_{back}$$

Formula 4 :

$$T3 = 0.33 \times T_{abdo} + 0.33 \times T_{right\ \ clav} + 0.33 \times T_{left\ \ clav}$$

In addition, distal to proximal gradients (DPGs) were calculated using each local proximal T: $T_{feet} - T_{local\ proximal}$.

Statistical Analyses

Normal data distribution was checked using a Kolmogorov-Smirnov test. Local proximal Ts (T_{abdo}, T_{clav}, T_{back}, T_{neck}, $T_{forehead}$), average proximal Ts (Tw, T4(R=L), T4 and T3) and variations of DPG (distal T - local proximal T) were compared using a two way repeated measures analysis of variance (Statview 5.0) to analyze the site and formula effects. Where significance

was observed posthoc analysis was performed using Posthoc test of Least Significant Difference (PLSD).

Each of the local proximal Ts (T_{abdo}, T_{clav}, T_{back}, T_{neck}, $T_{forehead}$) was compared to each of the average proximal Ts (Tw, T4(R=L), T4 and T3) by paired t-tests. This analysis was split or not into time of night and/or night.

Results are given as average values ± SEM. Significance was considered at $p < 0.05$.

RESULTS

Local Proximal Skin Temperatures

Significant time, site and interaction site x time effects were observed for local proximal skin T (**Figure 2**) (all $p < 0.001$). T_{abdo} was greater and $T_{forehead}$ lower than other Ts (always $p < 0.001$). T_{clav}, T_{back} and T_{neck} did not significantly differ from each other throughout the night. The significant site x time interaction ($p < 0.001$) reveals that the time course pattern may differ from one T to another, and that the differences between Ts are not kept constant throughout the night. Further analyses show two different patterns across the night (**Table 2**). T_{abdo}, T_{clav}, T_{back}, and T_{neck} significantly increased across each time point from reported bedtime until H2 and then decreased until H4. A final increase was then observed which began earlier for T_{abdo} (H6), later for T_{clav} (H7) and even later for T_{back} and T_{neck} (H9). Conversely, $T_{forehead}$ significantly decreased from reported bedtime to H3 and finally increased from H8 to the end of the night. As a result, T_{abdo} was initially significantly lower (0.53°C in average) than all the other Ts (at previous 60 min, and at RB) and thereafter was significantly higher than these Ts (from H1 to H10, +0.76°C, 0.75°C, 0.80°C when compared to T_{clav}, T_{back}, T_{neck}, 2.94°C when compared to $T_{forehead}$). In contrast, $T_{forehead}$ was on average 2°C lower than the other Ts. T_{back} was sometimes significantly higher (H3 and H4) or lower (previous 60 min, and during the last part of the night from H8 to H10) than T_{clav}. The greatest difference was observed at H3 (+0.37°C). During the last 3 h of the night, the difference between T_{back} and T_{clav} was 0.30°C, on average ($p < 0.04$). The other comparisons did not show any significant difference between T_{neck} on one hand and T_{clav} or T_{back} on the other.

Average Proximal Skin Temperatures

Significant effects were observed across time ($p < 0.001$), between each of the formula for proximal T ($p < 0.001$; **Figure 3**) and an interaction for time x formula ($p < 0.001$). Tw, which takes into account the lowest skin T of the forehead, was always significantly lower than the other averages of proximal T (in average −0.24°C, always, $p < 0.001$).

Comparisons between T4(R=L), T4 and T3 are sometimes significant or not according to the time. T4 and T4(R=L) values significantly differ across most time points (except at RB and H1) whereas exclusion or inclusion of the back T in the average (T4 or T4(R=L) vs. T3) led to significant differences during the last part of the night (from H5 to H10). These differences however remain lower than 0.16°C (between T4 and T3 at H9, $p < 0.001$).

Distal to Proximal Gradient

Distal to proximal gradients were calculated using the different local proximal T (T_{feet} – local proximal T; **Figure 4**). Consistent with the previous results on local proximal Ts, distal to proximal gradients exhibit significant time ($p < 0.001$), local proximal T ($p < 0.001$) and time x local proximal T ($p < 0.001$) effects. DPG calculated with the $T_{forehead}$ was also significantly different from DPG calculated from other local proximal sites (2.15°C in average). DPG calculated with T_{abdo} was also significantly different (except for the comparison with T_{back} at H1): the average difference with DPG calculated with T_{clav}, T_{back} and T_{neck} was 0.56°C). The other comparisons between the DPG calculated with T_{clav}, T_{back} and T_{neck} were mainly non-significant.

Local Proximal T as Indicator for Average Proximal Temperature

T_{abdo} was always significantly different from average proximal T, regardless of the average proximal T it was compared to (except comparison with Tw at RB). This was observed when split according to time (measured on hour to hour basis), i.e. 98% of the comparisons (**Table 3**), and in 84% (162/192 significant comparisons) when split according to time and night. During the 60 min before bedtime, and at RB, T_{abdo} was lower than the average values, whereas during the night, it was higher.

Similar conclusion can be drawn for **$T_{forehead}$** which was always significantly lower than the average values of proximal T (100% when split into time, and 100%=192/192 of the split into time and night).

T_{clav} exhibited intermediate results (77% and 55%=105/192) being at the beginning of the measurements higher than the average values and then lower.

T_{back} and **T_{neck}** showed the best results, with respectively only 58% and 31% (60/192) for T_{back} and 61% and 19% (36/192) for

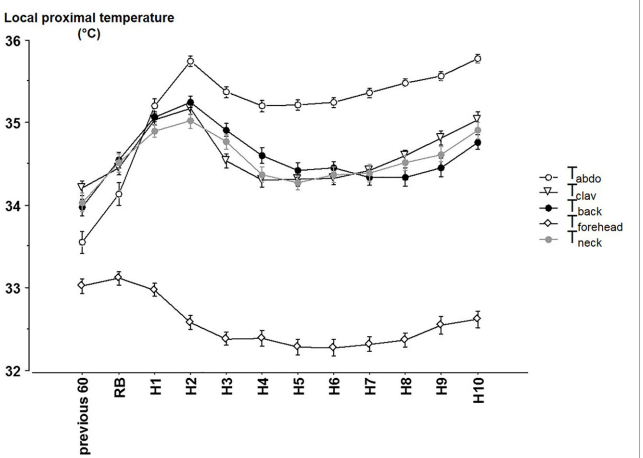


FIGURE 2 | The different local proximal skin temperatures (mean ± SEM) from 60 min before reported bedtime, at reported bedtime (RB) and at hourly timepoints after reported bedtime. abdo: abdominal Temperature, clav: average of the right and left clavicular temperatures. Previous 60 = during the 60 min before reported bedtime (RB), H1 to H10 hours in bed.

TABLE 2 | Comparisons of each local proximal skin temperature (T_{abdo}, T_{clav}, T_{back}, T_{neck}, $T_{forehead}$) from 1 h to the next one.

	previous 60 min vs RB	RB vs H1	H1 vs H2	H2 vs H3	H3 vs H4	H4 vs H5	H5 vs H6	H6 vs H7	H7 vs H8	H8 vs H9	H9 vs H10
T_{abdo}											
T_{clav}											
T_{back}											
T_{neck}											
$T_{forehead}$											

Previous 60 = during the 60 min before reported bedtime (RB), H1 to H10 hours in bed. Light grey indicates significant increase ($p < 0.05$), dark grey indicates significant decrease, white indicates NS comparisons.

T_{neck} of the comparisons being significantly different from the average proximal T. T_{back} showed a specific pattern with near-average proximal T values during the first part of the night (from H1 to H5) and deviation from these values during the second part of the night, indicating a specific pattern of T_{back} during this part of the night when compared with the other local proximal Ts.

DISCUSSION

The main purpose of the present study was to compare skin temperatures, measured at single proximal sites, with commonly used averages across multiple sites, to determine the most apt single site for representation of proximal T. A secondary aim was to examine the effect on calculations of average proximal T of including or excluding the specific local Ts. The main finding from this study was that that T_{back}, T_{neck} and to a lesser extent T_{clav} are more suitable indicators of average proximal T than T_{abdo}, or $T_{forehead}$. Additionally, we found that calculations which included $T_{forehead}$ for average proximal T were significantly lower

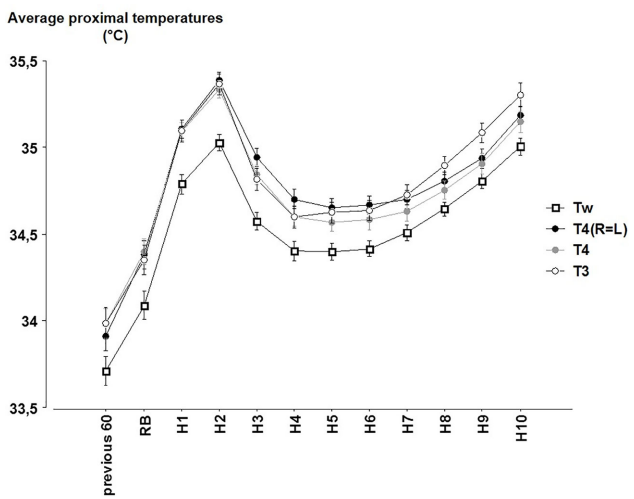


FIGURE 3 | The hourly averages of the different proximal temperatures (Tw = 0.45 T_{abdo} + 0.407 T_{clav} + 0.143 $T_{forehead}$; T4(R=L) = 0.33 T_{abdo} + 0.33 T_{clav} + 0.33 T_{back}; T4 = 0.25 T_{abdo} + 0.25 $T_{right\ clav}$ + 0.25 $T_{left\ clav}$ + 0.25 T_{back}; T3 = 0.33 T_{abdo} + 0.33 $T_{right\ clav}$ + 0.33 $T_{left\ clav}$) (mean ± SEM) according to the time (Previous 60 = during the 60 min before reported bedtime (RB). H1 to H10 hours in bed).

than the other formulas used for this measure. To our knowledge, this is the first study to identify T_{back} or T_{neck} as the most suitable single sites for representation of proximal T during sleep of school aged children, and to identify the significant effect of inclusion of $T_{forehead}$ in calculations of average proximal T.

Average or local proximal Ts usually follow a pattern similar to that of core T in adults exposed to constant routine (9) as well as during their sleep wake cycle, which differs to that of distal T (14). Differences in distal T may result from passive blood flow modification in proximal regions lacking AVAs when distal regions vasoconstrict or vasodilate (9). In our study, only $T_{forehead}$ is likely to have been consistent with core T pattern (not measured), while the pattern of other proximal Ts (local and averages) were similar to distal T (though of lower amplitude). Interestingly, Okamoto-Mizuno et al. (32) have observed that proximal T (chest) increased (as did distal T) in adults as well as in preschool infants around bedtime, but that age differences appeared after between infants (whose T_{chest} decreased though the night) and their mothers (whose T_{chest} remained almost constant until the end of the night). In contrast, in preterm neonates (26) as well as in 4 to 9 months old infants (25), T_{abdo} did not exhibit any notable change around sleep onset. Okamoto-Mizuno et al. (32) have suggested that these age differences may be explained by the fact that children, in contrast to adults, may rely more on proximal T than on distal T to lead core T decline during the sleep wake cycle. Such differences could result from vascular modifications: when exposed to hot environment, prepubertal boys were able to increase skin blood flow on the trunk (chest and back) (65) but also on the forehead (66) more than young men. In another study, these authors pointed out that cutaneous vascular conductance was larger on the forehead and the back (but not on the chest or the thigh) in boys than in young men (67). Finally, blood flow rate in the AVAs measured on the toe was also larger in 3 to 15 years old children compared to young or older adults (68). Interestingly, despite such differences regarding proximal T, DPG exhibits similar pattern between adults and infants, though of lower (more negative) value in children, indicating higher heterogeneity between the skin Ts when compared with adults (32).

There is currently no consensus in the literature on which local Ts should be taken into account to determine a proximal T, and to calculate DPG. Average proximal T is usually considered to be more reliable than its individual components as least when their rhythms are considered (9). However, for studies in natural

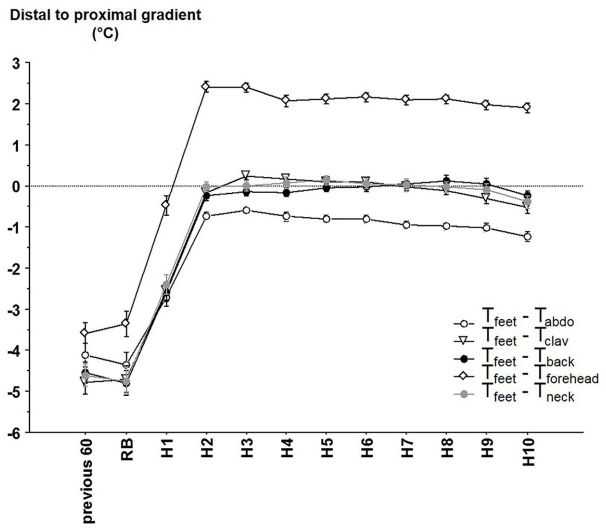


FIGURE 4 | The different distal-to-proximal skin temperature gradient (mean ± SEM) calculated between distal (i.e. feet) temperature and abdominal temperature (T_{abdo}), average right and left clavicular temperature (T_{clav}), back temperature (T_{back}), forehead temperature ($T_{forehead}$), neck temperature (T_{neck}) according to the time. Previous 60 = during the 60 min before reported bedtime (RB), H1 to H10 hours in bed.

settings, it would be of considerable practical advantage if a single site was determined as a sound indicator of average proximal T.

Average Proximal T

It has been demonstrated in adults that a set of 3 sensors that were positioned either on abdomen, subclavicular areas and mid thighs but were not on homologous regions (i.e. a right/left counterpart) can provide a reliable estimate of proximal T (43). We deducted from this that proximal T measured with at least 3 sites on the trunk (i.e. left and right clavicular regions, used as single Ts or as an average one, abdomen, back) could be our gold-standards. We also calculated Tw using area weighting coefficients for clavicular, abdomen, back and forehead (modified from 14), although calculating the average proximal T by the means of such weighting factors is controversial since it does not take into account the differential distribution and sensitivity of the skin thermodetectors over the skin surface area (69).

Our results confirm the notion that the location of the skin T, as well as the choice of the weighting coefficients, will significantly change the reckoning of average proximal T. Importantly, the impact of the $T_{forehead}$ in the average led to a −0.25°C difference with the other average proximal Ts (with a maximal gap of 0.37°C, which may be considered as moderately large). With exclusion of the $T_{forehead}$ value from the average proximal T (consistently with the arguments developed below), it is notable that the differences between the remaining average values (T3, T4 and T4(R=L)) are only pronounced during the last part of the night, because of the specific time pattern of local proximal Ts, especially of T_{back}. However, these differences remain at a low level (≤0.16°C), so that there is no important issue with respect to this choice.

Local Proximal Ts

To provide sound indication of proximal T, a local T candidate should fulfill several criteria regarding the level and the time pattern across the sleep-wake cycle.

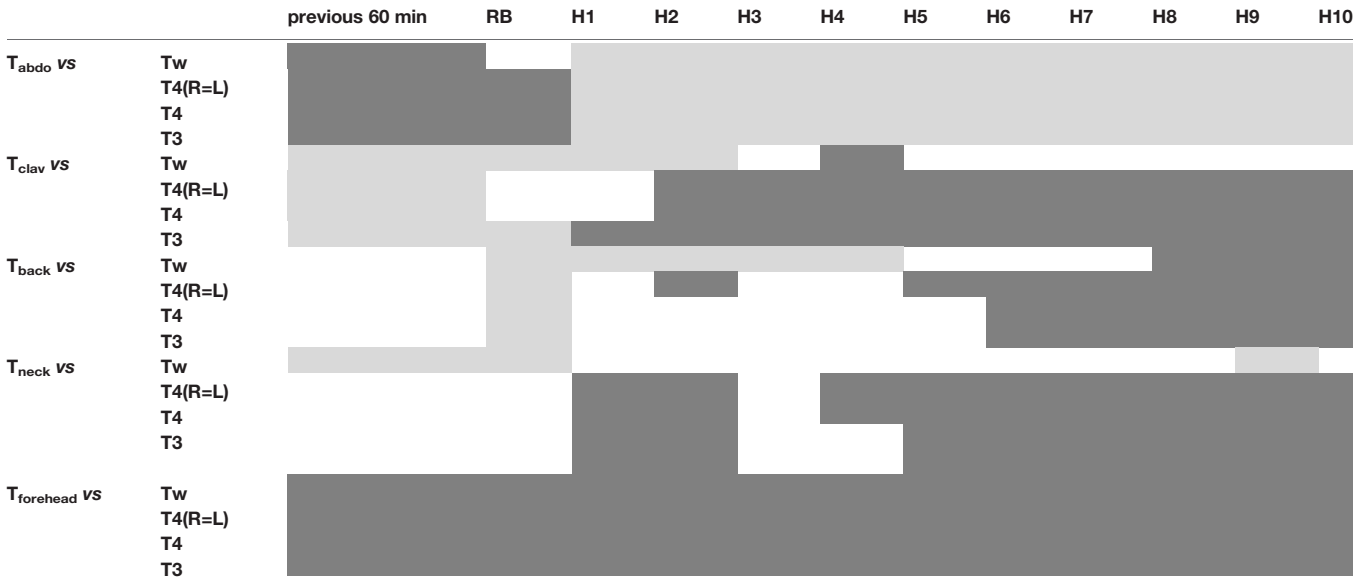
Abdominal T alone (25, 37) or included in an average formula (14, 16, 44, 48, 52, 54) has a clear preference in most studies of the literature for predicting proximal T and/or DPG. We observed that its time pattern is quite similar to other local proximal Ts, with a sharper increase between the 60 min period before recorded bedtime and H2 (+2.19°C). Part of this increase - as of the increases of the other local Ts that were measured under the bedding - is probably due to the attainment of a microclimate in the bed. Skin vasodilation around bedtime and sleep onset induces body heat losses that leads to core T decrease in naked as well as in covered subjects. For these latters, peripheral vasodilation allows the air T of the microclimate between the skin surface area and the covers to reach and remain constant at between 29 and 35°C (70, 71). The creation of an approximately thermoneutral microenvironment in the bed helps to protect the sleep stage structure (72). Interestingly bedding doesn't seem to change the time pattern which is maintained for covered feet and uncovered hands throughout a 24-h routine protocol (9). Unfortunately, we did not measure the T inside the bed. The increase of T_{abdo} was however greater than that of the other trunk Ts (+0.97°C for T_{clav} and +1.28°C for T_{back}) so that another phenomenon could intervene.

Comparisons with the different average proximal Ts pointed out that the level of T_{abdo} was always significantly lower (previous 60 min and RB, i.e. before sleep) or higher (from H1 to H10, i.e. probably during sleep; differences > 0.75°C) than the other local proximal Ts. In awake sitting adults, T_{abdo} was demonstrated to be higher than the other proximal Ts (subclavicular, thigh and forehead) (9). As a result, in our study DPG calculated with T_{abdo} was larger than those calculated with the other local proximal Ts (+0.56°C in average). This difference decreased during the last part of the night since the pattern for T_{abdo} was slightly different at the end of the night (beginning to increase at H6). Finally, T_{abdo} was always significantly different from all the average proximal Ts (whatever the formula), stressing the fact that T_{abdo} used alone cannot be considered as a good indicator of these averages assumed to be the gold standards, in contrast to the general belief. Longato et al. (43) have however reported that T_{abdo} should be integrated when calculating average proximal T, since the least accurate reconstruction for average proximal T occurred when the abdominal sensor was removed over the 5 sensors used.

$T_{forehead}$ and T_{neck}

The head plays a major role in thermoregulation, not only because of the large skin relative surface area (73), lower thermal insulation (74) and higher thermosensitivity (75, 76) but also because of the presence of numerous AVAs, at least in the areas irrigated by the angular and facial arteries (55). This irrigation could provide a selective refreshment of the

TABLE 3 | Results of the paired comparisons between each of the local proximal Ts (T_{abdo}, T_{clav}, T_{back}, T_{neck}, $T_{forehead}$) with each of the average proximal Ts (Tw, T4 (R=L), T4, T3).



Light grey indicates that local proximal T was higher than the average proximal T ($p < 0.05$), dark grey indicates that local proximal T was lower than the average proximal T, white indicates NS comparisons.

hypothalamus. We observed that the levels and the patterns for T_{neck} and $T_{forehead}$ were very different. Differences in the heat exchanges (the forehead is consistently uncovered, with low tissue insulation, more often exposed to air over the bed; the neck is probably not covered by sheets and covers but may perhaps be covered by long hair and/or isolated by supine sleeping) may at least partially account for this discrepancy. Differences in the vasomotor control, irrigation (temporal artery for the forehead and carotid artery for the neck) and the fact that the forehead is devoid of arteriovenous anastomoses (55) and countercurrent mechanisms may also be involved and could explain that previous studies have demonstrated that forehead T would accurately reflect core T (77). However, this remains controversial (78).

Kräuchi and Wirtz-Justice (9) found, in a constant routine protocol (awake sitting subjects over a 24-h protocol), that $T_{forehead}$ followed the same circadian pattern as T_{rectal}, but at a lower level (33.58 ± 0.21 vs 36.77 ± 0.07°C, respectively). Even though we did not measure continuously core T, we can assume that our results could be consistent with also a lower level (32.58 ± 0.03°C vs $T_{tympanic}$ = 36.44 ± 0.03°C).

The time pattern of $T_{forehead}$, in contrast to the other local proximal Ts, did not continue to increase after reported bedtime. $T_{forehead}$ was in correlation with ambient T of the bedroom (data not shown, see (23)), was on average 2°C below the other local Ts and was always significantly lower than all the average proximal Ts. These results suggest that $T_{forehead}$ is not a suitable as a local measure of proximal T, nor as a part of calculations for average proximal T.

In contrast to $T_{forehead}$, $\mathbf{T_{neck}}$ showed much narrower difference from the other local proximal Ts and was less often significantly different from the average proximal Ts (see **Table 3**), so that T_{neck} could be a good indicator of proximal T. T_{neck} has also been measured as an indicator of head T when using a cooling pillow in hot environment (79).

T_{back} and T_{clav}

Both $\mathbf{T_{back}}$ and $\mathbf{T_{clav}}$ follow a waveform similar to that of distal T (data not shown, see (23)) but of lower magnitude. As such, our results do not reflect the finding that T_{clav} in adults under constant routine shares the time pattern as core T (9). In contrast to the other local proximal T, $\mathbf{T_{back}}$ seems to fulfill all/most of the conditions to be a good indicator *per se* of average proximal T level, as well as patterns of change over time. Comparisons with average proximal Ts indicate that T_{back} and T_{neck} (see above) are good indicators of proximal Ts. This is also true, but to a lesser extent, for T_{clav}, as featured by more significant differences when compared to average proximal Ts. It must be noted however, that at the end of the night, these local Ts adopt specific time patterns, leading to slight but significant differences between each other and with average proximal Ts.

The impact of prone or supine sleeping position on back or ventral T measurements could not be analyzed in our study. In supine sleeping adults, fluctuation of Ts across the time were reduced on the back body regions compared to the ventral Ts (59). However, another study concluded that "skin-mattress T" (i.e. T measured on the back when sleeping supine) was a reliable measure of core T at least in normothermic neonates (58). Indeed, in such situations, sleeping supine almost suppresses the heat flow between the skin and the mattress (the T of which is almost equal to back T), as a result, T_{back} is directly correlated to core T variations.

Moreover, as far as T_{back} (midline of the back, approximatively T11-T12) and T_{neck} (midline of neck, below hairline) are considered, age differences should be considered: in human neonates, brown adipose tissue (BAT, 2–6% of body mass) is

located nearby the neck, in the interscapular region between the ribs and near the kidney. When exposed to cold environment, metabolic heat is produced in the BAT and its blood flow can increase up to one fourth of the cardiac input (80), maintaining a warm blood flow to the central nervous system and preventing brain cooling. As a result, the highest skin T is measured in the interscapular region, over the BAT [for a review, see (81)], and this T fell less than that of the other regional skin surface areas when the neonate is exposed to cool environment (82). Therefore, in this population, T measured nearby the BAT is rather an indicator of the increased activity of the BAT in response to cool challenge and/or of thermal-adaptive mechanisms when the challenge is prolonged (83).

Challenges and Limitations

It is important to measure and understand the relationship between skin Ts and sleep in people of all ages. Because of the impact of behavioral and environmental factors on thermoregulation and sleep, it is important that measures take place in people's natural settings. This creates challenges and limitations. The use of multiple sites for measures of skin T may enhance the reliability of data collection, by i) reducing risk of data loss due to inadvertent loss of iButtons and ii) accounting for the differences which may be observed across the night (due to body position change, displacement of bedcovers). However, use of multiple iButtons, with multiple skin sites, is likely to increase the risk of inaccurate placement of each iButton on the correct location. Furthermore, the time taken to apply iButtons to multiple sites may impact on the natural bedtime routines of individuals and families, and thus compromise the true nature of data collection in their home settings. It is important for researchers to understand the accuracy and reliability of single sites in comparison to multiple sites, so that the decision for each can be determined on true merit.

It is a limitation of this study that data are taken from just four school nights (Monday to Thursday). This was done to limit the variation between the children's daily activities, and also with concern regarding the possible burden of participation on the children and families. It meant, however, that the effects of weekend variations in activity were not accounted for. It is possible that, with confidence in the accuracy and reliability of use of fewer iButtons, researchers could reasonably ask participants to undertake more nights of data collection, and across different seasons, for more valid measures in natural settings and with everyday routines. An additional limitation is the fact that daytime wakefulness period was not considered, except for the 1-h long period before recorded bedtime. It would be of great interest to analyze whether T_{back} and T_{neck} are good indicators of proximal T also during the daytime/activity period.

CONCLUSIONS

There is an important relationship between sleep and body T, and both are affected by variation in individuals' activities and environments. It is fundamental, then, that body Ts are measured during sleep studies in natural settings as well as in sleep laboratories. With improved knowledge of body T rhythms across the sleep wake cycle of infants and children, there is exciting opportunity towards future studies where slight manipulations of skin body Ts and/or non-thermal (behavioral, environmental) parameters may improve sleep initiation and maintenance. In light of the major role of sleep in health and development, this is of particular interest for infants and children, particularly those with particular sleep disturbances, health conditions and developmental or neurological disorders. It is important that researchers have confidence in data collection which places minimal burden on participants, without compromising accuracy and reliability. Thus, practical considerations would favor the use of fewer thermal sensors in home-based studies. Our results show that T_{abdo} is not a suitable indicator of average proximal T: the level is too high (overestimation of the T) and the pattern is different during the night (so the error of this estimation is not the same across the night). Similar conclusion can be drawn for $T_{forehead}$, the pattern of which is more similar to that of core T. T_{back}, T_{neck} and to a lesser extent T_{clav} are more reliable indicators of average proximal T when used as single sites.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available due to ethical requirements and the level of consent given by participants. Requests to access the datasets should be directed to [CA, c.abbiss@ecu.edu.au].

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Edith Cowan University Human Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SM and CA conceived the study. SM collected the data. VB and SM analyzed the data. All authors contributed to the article and approved the submitted version.

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