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Sleep, vigilance & disruptive behaviors

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Sleep, vigilance & disruptive behaviors

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Editorial: Sleep, vigilance & disruptive behaviors

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Editorial on the Research Topic
Sleep, vigilance & disruptive behaviors

The Frontiers in Psychiatry Research Theme of *Sleep, vigilance, and disruptive behaviors* has two aims: first, to promote the understanding of the connections between vigilance and disruptive daytime behavior in the context of sleep deprivation and, second, to explore how naturalistic observations and pattern recognition can play a role in furthering our understanding of these connections. The theme is devoted to the British neurologist Henry Head and German psychiatrist Heinrich Hoffmann. In 1923, Head defined vigilance as the ability of the body "to respond to an effective stimulus with a more or less appropriate reaction" (1). In 1845, Hoffmann, at that time still a general practitioner, depicted the connection of "vigilance" with disruptive behaviors of children and youth in a cartoon book entitled, "Struwwelpeter—Merry Tales and Funny Pictures" [(2, 3) and see Figure 1 for book cover]. In this book, each story describes a clinical condition and the multiple links to affected vigilance, which in consequence cause disruptive daytime behaviors. The narratives of "Fidgety Philip" (for attention deficit hyperactivity disorder, ADHD and/or restless legs syndrome, RLS), "John Head-in-Air" (attention deficit disorder paired with sensory processing dysfunctions), "Struwwelpeter" and "Conrad" (sensory processing dysfunctions paired with obsessive compulsive behaviors), "Augustus" (eating disorders), "Flying Robert" and "Harriet" (oppositional defiant disorder), "The Inky Boys" (mobbing and bullying in context with racism), and "Cruel Frederick" (oppositional defiant disorder) were originated from observations utilizing pattern recognition and are described in an easily understandable visual format of cartoons. Both impaired vigilance and disruptive behaviors mirror sleep disturbances. They can also be observed and are independent of cultural norms, enabling an exploratory screening approach to an individuals' wellbeing. Importantly, these

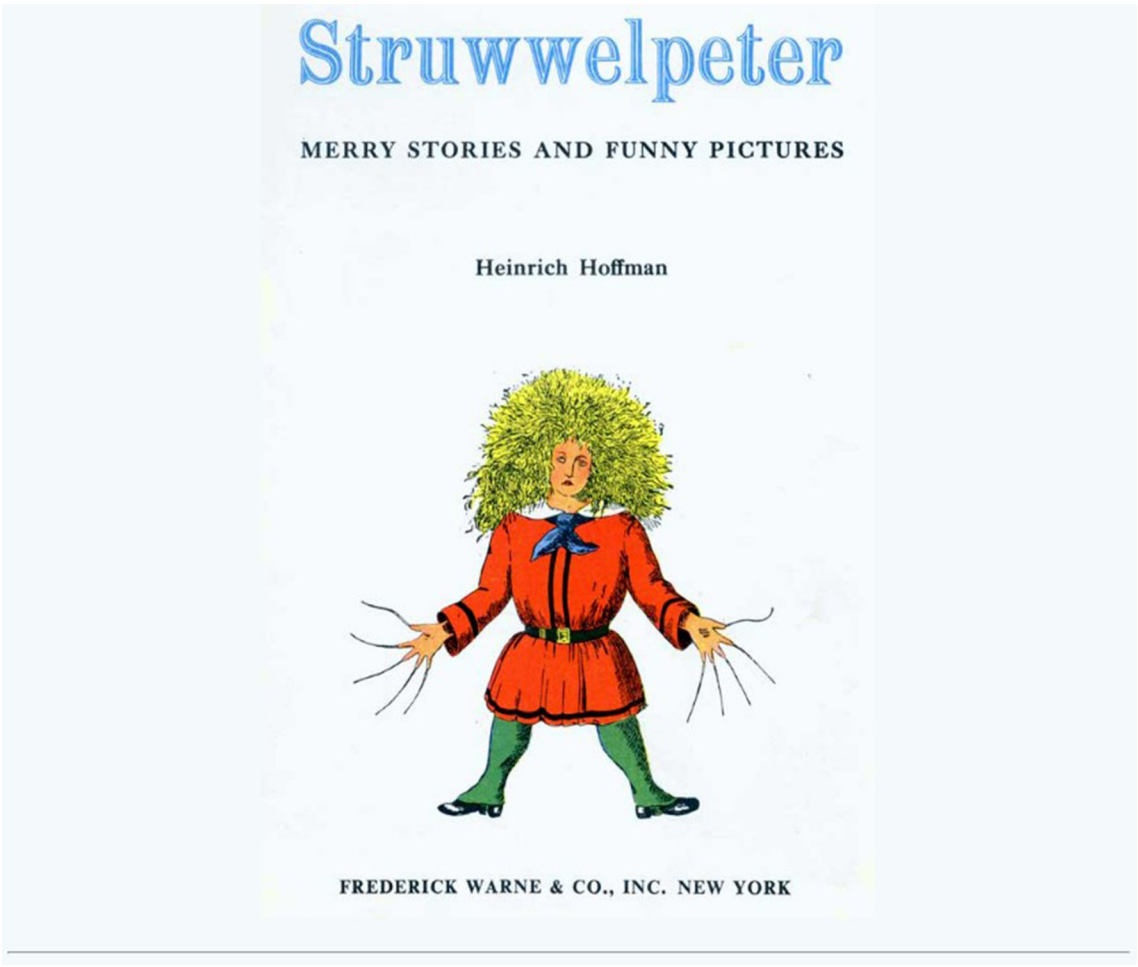

FIGURE 1
"Just look at him! there he stands, With his nasty hair and hands. See! his nails are never cut; They are grimed as black as soot; And the sloven, I declare, Never once has combed his hair; Anything to me is sweeter Than to see Shock-headed Peter." (3).

are commonly in conjunction with underlying and missed sleep problems, which have been culturally segregated and medicalised areas—usually investigated by daytime-focused sub-specialists, without acknowledging sleep disturbances. Indeed, naturalistic observations and their meaning are the foundation of clinical history taking, a practice commonly used in communication between clinicians and patients (including parents in the case of pediatric patients). A discourse to examine the validity of outsourcing such observable contextual concepts into lab settings without capturing and agreeing first on the observed patterns, their epistemic justification, and phenomenology is overdue. The Research Theme *Sleep, vigilance, and disruptive behaviors* is a Frontiers in Psychiatry eBook, consisting of 14 peer-reviewed articles and discussing a variety of topics such as sleep and how it affects daily functioning, the broadest definition of vigilance, and behaviors seen as disruptive in children and as challenging or worrisome in adults. All articles, whether they are reviews, case reports, or cohort studies, invite the readers to review the interconnections among the three topics *via* naturalistic observations and exploration from multiple perspectives.

Of the five review articles, the first one revisits the *concept of vigilance* as an indicator of sleep disturbances. Since the introduction of the vigilance concept by Head, many different aspects were analyzed; however, the underlying context for gathering insight into the interplay between sleep and daytime behaviors, reflecting both physical and cognitive performance, as well as sleep quality and quantity, was hardly ever investigated (Klösch et al.). Similarly, the second review article explores a *universal screening strategy for sleep health in the community*, utilizing social-ecological considerations, as the cultural context of the current (medicalised) approach does not acknowledge the myriad of presentations and possible root causes of sleep disturbances (Blunden et al.). The third review examines the functional links between *thermoregulation for maintaining thermoneutrality and sleep* in children with chronic health conditions as circadian patterns of sleep-wake are dependent on patterns of body temperature changes (McCabe et al.). The fourth review and meta-analysis investigates the efficacy of *eye masks and earplugs in intensive care units* as an intervention for promoting sleep health (Karimi et al.). The fifth review

investigates the root causes of most hypermotor restlessness, such as central iron deficiency and its exacerbation by vitamin D deficiency (Silvestri and Ipsiroglu). While the first two reviews focus on screening and how to integrate a sleep screening in a tier service model (Blunden et al.; Klösch et al.), the latter three reviews demonstrate how, with minimal consideration, sleep health can be promoted in the various facets of modern medicine and mirrors the need for a holistic approach to sleep and sleep health and how harmonization of first-line treatment options could improve sleep health (Karimi et al.; McCabe et al.; Silvestri and Ipsiroglu).

The second block consists of six articles investigating the associations between sleep and behavioral patterns, e.g., ADHD, utilizing big and small data. Vigilance regulation disturbances in the awake state play a key role in the development of mental health disorders. Hyperactivity in ADHD is an attempt to increase the low vigilance level *via* external stimulation to avoid drowsiness—this common hypothesis led to the *analysis of resting-state EEGs in children diagnosed with ADHD or depression* (Berger et al.). The study, using longitudinal "big" data from the National Korean Registry, suggests that addressing *underlying sleep disturbances rather than sleep duration* is the most important factor in predicting and preventing adjustment problems in young children. Furthermore, more attention should be paid to maternal depressive symptoms in preschooler years as much as during the postpartum period for better child adjustment outcomes (Cha). The next two studies utilized small data and a qualitative approach. While one study explores *disruptive behaviors of adolescents with Down syndrome* in a summer school setting, including the link to probable familial RLS, relieved by hours of physical activity, this qualitative study reveals that disruptive behaviors of children with intellectual disabilities have different connotations depending on guiding contextual frameworks (Chan et al.). Finally, yet importantly, in a qualitative study, *parental challenges in sourcing effective sleep solutions for their child with cerebral palsy* are explored. Sleep may be a low priority for parents or clinicians as other health problems take precedence (Petersen et al.). *The RLS prevalence in hospitalized psychiatric patients, a multicenter adult study from Germany and Switzerland,* rounds this picture. Clinically significant RLS had almost five times higher prevalence in psychiatric patients, and more than three-quarters were diagnosed with RLS for the first time, which necessitates for an RLS screening (Weber et al.). The brief research report on *patient characteristics and medication prescriptions in children with mental health and neurodevelopmental disorders referred to a Canadian sleep clinic* demonstrates that special attention to probable RLS-induced insomnia should be given as early as the triaging process at the community level (Ipsiroglu et al.). Note that RLS, even familial RLS, is an underestimated clinical sleep/wake-behavioral diagnosis, where there is no need for a sleep laboratory-based diagnostics—instead, relying solely on naturalistic observations and exploration, including structured history taking and blood work, steps which should become essential in assessments of insomnia [Silvestri and Ipsiroglu, (4)].

The third block analyses exposure to sleep/wake behaviors and timing, in relation to digital media. In a large study from the United Kingdom, the relationship between *smartphone addiction and sleep quality in young adults* was investigated demonstrating that 39% of young adults reported smartphone addiction. Smartphone addiction was associated with poor sleep, independent of the duration of usage, indicating that the length of time should not be used as a proxy for harmful usage (Sohn et al.). Data from South Germany, a region with high social-economic status, show that the actual *exposure to digital media may start already in 12-month-old infants*; a proportion of 10% of 1-year-old children was already regularly exposed to digital media (Durham et al.). Given the warnings of the American Academy of Pediatrics and national guidelines, which recommend no digital media use at all under the age of 18 months, the question could be around how this rate might fluctuate in varied regions with different social-economic statuses. Explorations for *understanding sleep-wake behaviors in late chronotype adolescents* show that with increasing lateness, the likelihood of experiencing poor sleep quality and mood disorders increases (Lang et al.). However, bedtime was not predicted by dim light melatonin onset (DLMO) indicating that the factors contributing to a late chronotype are multiple and complex. Understanding these contributing factors, and their relative importance across individuals, needs exploration. Again, this article proves our leitmotif that naturalistic observations and exploration will open up new perspectives to typical "disruptive" adolescent behaviors.

Reading these articles, as an editorial team, we have been thinking about critical issues in our field. Sleep is an important public health issue. However, the current emphasis is on clinical sleep medicine as a Western-centric urban sub-specialty, where we have not implemented a universal screening concept for sleep health, and the knowledge regarding pattern recognition (see Head's *vigilance concept* and Hoffman's *disruptive behaviors)* is often overlooked, or even unknown. Many partners in the community, such as public health nurses, occupational therapists, psychologists, general practitioners, internists, psychiatrists, and even pediatricians and child and adolescent psychiatrists, lack basic sleep health training and knowledge. Thus, we all unanimously agree to advocate for establishing sleep as a priority on the national public health agenda. We suggest *"HumanRight2Sleep"'* or *"ChildRight2Sleep"* as the communication motto for overcoming a checklist-based daytime focus, a *rights-based approach to sleep disturbances* may support us to review things from a patient rather than a professional sub-specialist perspective and move the agenda further.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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

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ORIGINAL RESEARCH
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The Association Between Smartphone Addiction and Sleep: A UK Cross-Sectional Study of Young Adults

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Background: In a large UK study we investigated the relationship between smartphone addiction and sleep quality in a young adult population.

Methods: We undertook a large UK cross-sectional observational study of 1,043 participants aged 18 to 30 between January 21st and February 30th 2019. Participants completed the Smartphone Addiction Scale Short Version, an adapted Pittsburgh Sleep Quality Score Index and reported smartphone use reduction strategies using both in-person ($n = 968$) and online ($n = 75$) questionnaires. A crude and adjusted logistic regression was fitted to assess risk factors for smartphone addiction, and the association between smartphone addiction and poor sleep.

Results: One thousand seventy one questionnaires were returned, of which 1,043 participants were included, with median age 21.1 [interquartile range (IQR) 19–22]. Seven hundred and sixty three (73.2%) were female, and 406 reported smartphone addiction (38.9%). A large proportion of participants disclosed poor sleep (61.6%), and in those with smartphone addiction, 68.7% had poor sleep quality, compared to 57.1% of those without. Smartphone addiction was associated with poor sleep (aOR = 1.41, 95%CI: 1.06–1.87, $p = 0.018$).

Conclusions: Using a validated instrument, 39% young adults reported smartphone addiction. Smartphone addiction was associated with poor sleep, independent of duration of usage, indicating that length of time should not be used as a proxy for harmful usage.

Keywords: smartphone addiction, sleep, smartphone harm reduction strategies, screen time, young adults, behavioral addiction

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INTRODUCTION

Smartphone use has become ubiquitous over the past decade. This has been accompanied by growing concerns around excessive and potentially harmful use (1). There are emerging reports of problematic behavior patterns in relation to smartphone use which mirror those of addiction (2). Although smartphone addiction is not formally recognized as a clinical diagnosis, it is a subject of active research. Validated instruments have been developed to characterize problematic

smartphone use in terms of recognized dimensions of behavioral addiction with scores above which the research subject is considered to report smartphone addiction (3, 4). Research subjects reporting smartphone addiction describe a decreased interest in face-to-face relationships, use despite knowledge of the negative consequences, impaired control over and pre-occupation with their devices, and anxiety when their phones are inaccessible; these are not unlike the symptom domains of substance use disorders or other behavioral addictions (2, 5–7). Studies have highlighted associations of smartphone addiction with reduced productivity and with lower academic attainment (8, 9), demonstrating the negative functional impact on young people's lives and future prospects. Indirect harms resulting from smartphone addiction include propensity for accidents, for example through use whilst driving, and potential contribution to the obesity crisis by facilitating sedentary lifestyles (10, 11). Although at an early stage, there is also some neuroimaging evidence of volume and activity parallels between smartphone addiction and other addictions (12).

Studies to date have used the length of smartphone usage (measured as the total daily length of smartphone use) as an exposure indicative of problematic usage (13). However, while it is true that heavy use is seen in people with any addiction, it is also true that this is not sufficient for an addiction to be present, reflected in the ICD-11 criteria for gaming and gambling disorders (6) and in proposed diagnostic criteria for smartphone addiction (7). For an addiction to be present, subjective distress and functional impairment must also be present – in the case of smartphone addiction, neglect of other meaningful activities, pre-occupation with the phone, distress when access to the phone is not possible, and continued use despite evidence of harm. Measuring duration of use is an inexact proxy for addiction, as some people may experience the features of addiction with lower duration of use while others may use their phone in an adaptive way for long periods of time (for example, answering work emails during a long commute) but be able to put the phone down without distress and attend to appropriate activities such as communicating with family members, or going to bed on time (14).

It is important to note that smartphone addiction has several terms of reference including "nomophobia," "problematic smartphone use," and "smartphone dependence." There is also a lack of consensus around whether putative "smartphone addiction" represents a distinct clinical identity and meets the criteria to be formally considered a behavioral addiction (15, 16). Furthermore, it remains unclear whether this dependence is on the smartphone itself or on the apps available through the device; whether the phone itself is like a substance of abuse or more like the needle through which addictive apps are delivered (14). There are similar patterns of behavior associated with specific applications (e.g., Facebook addiction, Instagram addiction) that are being investigated in their own right, and it is possible that certain types of phone use (e.g., social media use) may have more addictive implications than others (e.g., calling, texting), as the former involves display and expectation of approval through the creation, sharing, and viewing of content, while the latter replicates face-to-face relationships in terms of one-to-one communication (17, 18). Nevertheless, there is evidence of the existence of a behavioral phenotype that resembles addiction. The physical harms highlighted above, as well as emerging associations with psychiatric symptoms such anxiety and depressed mood indicate a pressing need to further investigate this growing phenomenon (19).

While the negative effects of screen time on sleep have been previously reported, smartphones are portable, hand-held devices that have much higher potential of interrupting sleep quality or quantity (20). Problematic smartphone use has been consistently linked to poor sleep in previous studies (4, 21), and smartphone overuse has been associated with daytime tiredness, longer sleep latency, and reduced sleep duration (22–24). In particular, smartphone use close to sleep initiation has been shown to delay circadian rhythm and found associated with total sleep time, where longer usage was associated with poor sleep (25). Furthermore, poor sleep outcomes may mediate the relationships between smartphone addiction and psychopathological symptoms (26). However, despite consistent advice from health bodies concerning the negative impacts of smartphone use on sleep, the majority of adults in the UK use their phones during the night and close to bed time (27).

A recent international systematic review found that the prevalence of smartphone addiction was around 25% in teenagers and young people (4). The weight of this evidence was from South and East Asia, and it has been noted that levels of smartphone addiction are often higher in Asian samples than in Western populations, possibly reflecting cultural practices around internet and smartphone use (28, 29). This study includes the largest UK sample to date to investigate the prevalence of smartphone addiction, and to clarify the association between smartphone addiction and sleep outcomes, in this population.

METHODS

Study Design and Study Population

Participants were recruited opportunistically across multiple campuses at King's College London, England, between January 21st and February 4th, 2019. Participants were approached by researchers to describe the study, and invited to complete a paper-based case report form (CRF) based at four separate locations during the stated data collection period. Additionally, participants were invited to complete an identical online version of the CRF through an internal research recruitment process. Eligibility criteria included students at King's College London aged between 18 and 30 who owned a smartphone. Participants were excluded if they did not adequately complete the Smartphone Addiction Scale – Short version [SAS-SV [3]] or the adapted Pittsburgh Sleep Quality Index [PSQI (30)]. The study was undertaken in accordance with the Declaration of Helsinki. Ethical approval was received from the King's College Research Ethics Office (Study ID: 9138; MRS-18/19-9138) and the full protocol is available on request. All face to face participants provided informed verbal consent prior to involvement and those submitting online gave consent by responding to the questionnaire.

Measures

The case report form (CRF) was co-developed amongst researchers, teenagers and young people with experience of smartphone use (**Supplementary Table 1**). The CRF included demographic information, smartphone use characteristics, a validated scale for smartphone addiction [SAS-SV (3)], an adapted sleep score based on the Pittsburgh Sleep Quality Instrument [PSQI (30)], and a range of reduction strategies. To reduce perception bias, the CRF included neutral non-directive phrasing about smartphone use collecting both positive and negative aspects.

Smartphone Use Characteristics

Participants were asked about the quantity of smartphone use (the average length of daily time) and the timing of use.

Smartphone Addiction Scale – Short Version (SAS-SV)

The SAS-SV is a 10-question validated scale that was developed to assess smartphone addiction in children (mean age of 14.5) (3). Participants are asked to rate statements related to their smartphone use, such as "Using smartphone longer than intended" on a 6-point Likert scale, from "strongly disagree" (1) to "strongly agree" (6). The resulting total score is between 10 and 60, with higher totals indicating higher risk of smartphone addiction. Total scores of 31 and 33 were used as diagnostic thresholds for males and females respectively, in accordance with the original study which found strong internal consistency (Cronbach's alpha = 0.91, AUC = 0.96 for boys, AUC = 0.89 for girls). This scale has been widely used internationally and has been found to have similarly strong internal consistencies using the same thresholds for this study's age group (31, 32).

Sleep

Participants were asked to rate their subjective sleep quality on an average weeknight on a Likert scale of 1–10 and the number of hours they slept on an average weeknight on a Likert scale of <4 to 12, taking into account the expected average number of hours of sleep for adults, in order to assess sleep quality and duration. Participants were additionally asked the number of days a week they felt noticeably tired or fatigued during the day (0–7) and the number of nights a week where they felt it difficult to fall asleep (0–7) to measure daytime tiredness and sleep latency. Based on these responses, scores for each component were calculated, which were then combined to calculate a global sleep score, adapted from the Pittsburgh Sleep Quality Index [PSQI (30)], where a score of ≤5 was considered good sleep (33).

Reduction Strategies

Commonly used strategies to reduce smartphone use included within the CRF were identified from the literature and through consultation with subject matter experts and young people (**Supplementary Table 2**). Participants were asked to rate the effectiveness of any strategies employed from ineffective to very effective.

Sample Size Justification

Estimates of the prevalence of poor sleep prevalence are wide-ranging. At study conception it was estimated that 42% of participants without problematic smartphone usage would exhibit poor sleep (34), and this would increase to 55% in those exhibiting problematic smartphone usage (4). In order to detect this difference using an independent chi-squared test of proportions with 90% power and 5% significance, we would need to include 650 participants. Building on this, to account for 15% missing data, we would need to include at least 780 participants in total.

Outcomes

The primary outcome was the association between sleep quality and smartphone addiction. Secondary outcomes were to determine: the association of smartphone addiction with demographics and usage characteristics; and the impact of reduction strategies on mitigating the effect of smartphone addiction on sleep.

Statistical Analysis

Demographic and smartphone usage characteristics of the sample were summarized, comparing participants with good, and poor sleep. Crude logistic regression models were included, to assess poor sleep and demographic (site, sex, and age) and smartphone usage characteristics. An adjusted multivariable logistic regression was carried out fitting the demographic with important characteristics found from the crude univariable analyses.

Both crude odds ratio[s] (OR) and adjusted OR (aOR) were presented alongside their respective 95% confidence intervals (95%CI), and *P*-values (<0.05 considered statistically significant). SPSS Versions 25 and 26 (IBM Corp., Armonk, N.Y., USA) were used to input and analyse data.

To determine the association between smartphone addiction and the demographic and usage characteristics, a multivariable logistic model adjusting for the same covariates as for the primary outcome was created. Due to multi co-linearity total usage, latest time of use and usage cessation prior to sleep were not fitted within the same analysis models.

Missing Data and Population Under Investigation

Individuals with missing item data of no more than 30% of the SAS-SV, or the adapted sleep score were proportionally mean imputed (35). Due to the completeness of the data collected, a complete case analysis was used.

Role of the Funding Source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Characteristics of the Participants

We received 1,071 completed CRFs, of which 1,043 participants were eligible and included (completion rate 97.8%). The 28 excluded participants were ineligible due to age, or non-completion of the SAS-SV or items from the PSQI score. Of those included, 38 of the SAS-SV score, and 85 of the adapted

TABLE 1 | The included population sociodemographic and phone use characteristics.

Included participant characteristics	Full sample		Good sleep		Poor sleep	
	n	%	*n*	%	*n*	%
	1,043		400	38.4	643	61.6
Age						
≤21	680	65.2	247	36.3	433	63.7
22-25	281	26.9	116	41.3	165	58.7
≥26	82	7.9	37	45.1	45	54.9
Gender						
Male	280	26.8	115	41.1	165	58.9
Female	763	73.2	285	37.4	478	62.6
Ethnicity						
Asian	389	37.3	145	37.3	244	62.7
Black	86	8.2	28	32.6	58	67.4
White	452	43.3	186	41.2	266	58.8
Mixed	55	5.3	16	29.1	39	70.9
Other	16	1.5	6	37.5	10	62.5
Missing	45	4.3	19	42.2	26	57.8
Year of degree						
1st	387	37.1	135	34.9	252	65.1
2nd	169	16.2	65	38.5	104	61.5
3rd	212	20.3	81	38.2	131	61.8
4th	48	4.6	21	43.8	27	56.3
5th	42	4.0	15	35.7	27	64.3
Post-graduate (MSc, PhD, post-graduate certificates)	164	15.7	74	45.1	90	54.9
Missing	21	2.0	9	40.9	13	59.1
Faculty						
Arts and Humanities	67	6.4	24	35.8	43	64.2
Dentistry, oral, and craniofacial sciences	53	5.1	15	28.3	38	71.7
Nursing, midwifery, and palliative care	103	9.9	32	31.1	71	68.9
Business School	12	1.2	2	16.7	10	83.3
Law	61	5.8	22	36.1	39	63.9
Life Sciences and Medicine	383	36.7	149	38.9	234	61.1
Natural and Mathematical Sciences	73	7.0	32	43.8	41	56.2
Psychiatry, psychology, and neuroscience	154	14.8	70	45.5	84	54.5
Social Science and Policy	92	8.8	37	40.2	55	59.8
Missing	45	4.3	17	37.8	28	62.2
Recruitment location ($p = 0.007$)*						
1	334	32.0	129	38.6	205	61.4
2	335	32.1	111	33.1	224	66.9
3	144	13.8	69	47.9	75	52.1
4	155	14.9	68	43.9	87	56.1
5	75	7.2	23	30.7	52	69.3
Smartphone addiction ($p < 0.001$)						
Not addicted	637	61.1	273	42.9	364	57.1
Addicted	406	38.9	127	31.3	279	68.7
Total daily hours ($p = 0.004$)						
≤2 h	207	19.8	103	49.8	104	50.2
3 h	247	23.7	91	36.8	156	63.2
4 h	226	21.7	77	34.1	149	65.9
5 h	162	15.5	65	40.1	97	59.9
>5 h	193	18.5	62	32.1	131	67.9

(Continued)

TABLE 1 | Continued

Included participant characteristics	Full sample		Good sleep		Poor sleep	
	n	%	*n*	%	*n*	%
Missing	8	0.8	2	25.0	6	75.0
Latest time of use ($p < 0.001$)						
Before 11 p.m.	122	11.7	70	57.4	52	42.6
11:00	102	9.8	32	31.4	70	68.6
11:30	134	12.8	72	53.7	62	46.3
12:00	168	16.1	65	38.7	103	61.3
12:30	136	13.0	54	39.7	82	60.3
1 a.m. or later	353	33.8	102	28.9	251	71.1
Missing	28	2.7	5	17.9	23	82.1
Smartphone cessation prior to sleep initiation						
<30 min	778	74.6	300	38.6	478	61.4
30 min–1 h	151	14.5	55	36.4	96	63.6
>1 h	84	8.1	39	46.4	45	53.6
Missing	30	2.9	6	20.0	24	80.0

**Recruitment location.*
1, Life Sciences & Medicine campus.
2, Life Sciences, Nursing & Midwifery, and Social Sciences campus.
3, Psychiatry, psychology, and neuroscience campus.
4, Arts & Humanities, Law, Business, Natural & Mathematical Sciences, and Social Sciences & Public Policy campus.
5, Online.

PSQI had a single item of each domain missing and were (within participant) domain mean-imputed.

The mean age of the included participants was 21.1 (IQR 19–22, range 18–30), where 92.1% ($n = 961$) were aged under 26, and 73.2% ($n = 763$) of the participants were female (**Table 1**). In terms of smartphone usage, 23.7% ($n = 247$) used their phones for 3 h per day, while 18.5% ($n = 193$) used their phones for more than 5 h daily. A large proportion of the young adult population exhibited poor sleep quality (61.6%, $n = 643$). Of those exhibiting smartphone addiction, 68.7% ($n = 279$) had poor sleep quality compared to 57.1% ($n = 364$) of those not exhibiting smartphone addiction. Of those participants that ceased smartphone use with 30 min of initiating sleep, 61.4% ($n = 478$) had poor sleep, compared to 53.6% ($n = 45$) of those who ceased use more than 1 h prior to initiating sleep.

Prevalence of Smartphone Addiction, Sociodemographic Characteristics and Smartphone Usage

The overall prevalence of smartphone addiction was 38.9% (95%CI: 35.9–41.9%; $n = 406/1{,}043$). This includes 35.7% of males who were addicted and 40.1% of females (**Table 3**). For participants aged under 21 years, 42.2% exhibited smartphone addiction, compared to 34.2 and 28.0% of participants aged 22–25 years, and over 26 years, respectively. Of participants who used their smartphone for 2 or less hours per day, 20.3% were addicted, compared to 53.9% of those who used it for more than 5 h. Of those that stopped using their device more than an hour before bedtime, 23.8% exhibited addiction, compared to 42.0% of those stopping <30 min before bedtime (**Table 3**).

Primary Outcome of Poor Sleep Associated With Smartphone Usage

We assessed demographic factors', phone usage characteristics', and reduction strategies' associations with poor sleep. Age, sex or site were not associated with poor sleep (**Table 2**). There was an association between poor sleep and those addicted (compared to not addicted, OR = 1.65, 95%CI:1.27–2.14, $p < 0.001$); and screen time (compared to 3, 2 h OR = 0.59, 95%CI 0.41–0.86, $p = 0.007$).

In the multivariable analysis after adjustment for age, gender, site, screen time, and location of phone at night, those addicted exhibited a 41% increased odds of poor sleep (aOR = 1.41, 95%CI: 1.06–1.87, $p = 0.018$) (**Table 2**). Age, sex or site was not significantly associated with poor sleep. Total daily use of 2 or less hours reduced odds of poor sleep by 38% (aOR = 0.62, 95%CI: 0.42–0.92, $p = 0.018$).

Secondary Outcome of Demographics Associated With Smartphone Addiction

In a crude analysis, age, site and ethnicity were associated with smartphone addiction (**Table 3**). There was a decreased odds of smartphone addiction in older groups, with 22–25 year olds having a 29% decreased odds compared with those 21 and younger (OR = 0.71, 95%CI: 0.53–0.95, $p = 0.015$), and participants 26 or older having a 47% decreased odds (OR = 0.53, 95%CI:0.32–0.89, $p = 0.015$). Those of Asian ethnicity had increased odds of addiction (OR = 1.75, 95%CI: 1.32–2.32, $p < 0.001$) when compared to a White reference population.

The total number of hours spent on smartphones per day was significantly and positively associated with the SAS-SV

TABLE 2 | The association between poor sleep and smartphone addiction, using crude and multivariable logistic regression.

Variable	Total: *n* (%)	Crude OR (95%CI)	*p*-value	Adjusted OR[†] (95% CI) (*n* = 995)[‡]	*p*-value
Age					
≤21	680 (65.2)	1.00	-	1.00	-
22–25	281 (26.9)	0.81 (0.61–1.08)	0.150	0.95 (0.69–1.32)	0.767
≥2	82 (7.9)	0.69 (0.44–1.10)	0.121	0.85 (0.51–1.42)	0.540
Gender					
Male	280 (26.8)	1.00	-	1.00	-
Female	763 (73.2)	1.17 (0.88–1.55)	0.274	1.08 (0.79–1.46)	0.637
Recruitment Site[§]					
1	334 (32.0)	1.00	-	1.00	-
2	336 (32.1)	1.27 (0.93–1.74)	0.139	1.13 (0.80–1.58)	0.498
3	144 (13.8)	0.68 (0.46–1.02)	0.059	0.69 (0.45–1.08)	0.102
4	155 (14.9)	0.81 (0.55–1.19)	0.271	0.83 (0.55–1.25)	0.369
5	75 (7.2)	1.42 (0.83–2.44)	0.199	1.37 (0.77–2.42)	0.283
SAS-SV					
Not addicted	637 (61.1)	1.00	-	1.00	-
Addicted	406 (38.9)	1.65 (1.27–2.14)	<0.001**	1.41 (1.06–1.87)	0.018*
Total daily hours					
≤2	207 (19.8)	0.59 (0.41–0.86)	0.006**	0.62 (0.42–0.92)	0.018*
3	247 (23.7)	1.00	-	1.00	-
4	226 (21.7)	1.13 (0.77–1.65)	0.529	1.01 (0.68–1.49)	0.957
5	162 (15.5)	0.87 (0.58–1.31)	0.504	0.73 (0.47–1.12)	0.152
>5	193 (18.5)	1.23 (0.83–1.83)	0.303	1.10 (0.72–1.69)	0.653
Smartphone at night					
In bedroom	625 (59.9)	1.00	-	1.00	-
In other room	409 (39.2)	0.95 (0.74–1.23)	0.718	1.02 (0.77–1.34)	0.913
Missing	9 (0.9)				

Crude Odds Ratio (OR) and adjusted ORs. OR, odds ratio; CI, confidence interval; SAS-SV, Smartphone Addiction Scale–Short Version.

**p < 0.05; **p < 0.01.*

[†]Adjusted for age, gender, ethnicity, recruitment site, smartphone addiction, total daily hours and smartphone location at night. Model fit with the adjusted Chi-squared = 36.760, p = 0.002.

[‡]52 participants were excluded due to having missing covariate data.

[§]Recruitment location.

1, Life Sciences & Medicine campus.

2, Life Sciences, Nursing & Midwifery, and Social Sciences campus.

3, Psychiatry, psychology, and neuroscience campus.

4, Arts & Humanities, Law, Business, Natural & Mathematical Sciences, and Social Sciences & Public Policy campus.

5, Online.

score. After adjustment, age, ethnicity, site and screen time were associated with addiction.

Secondary Outcome of Smartphone Usage Characteristics and Addiction

Use for 2 h or less per day showed significantly decreased odds of smartphone addiction, compared with a reference of 3 h (OR = 0.55, 95%CI 0.36–0.85, $p = 0.007$, **Table 4**). Use for 5 or more hours per day showed a 2.5 times increase in odds (OR = 2.53, 95%CI: 1.71–3.74, $p < 0.001$). After adjustment for confounding factors, a consistent pattern of association was found between usage characteristics and addiction. There was a 39% reduction in odds of addiction for those using their phones for 2 h or less compared with typical usage of 3 h (aOR = 0.61; 95%CI 0.39–0.96; $p = 0.031$).

Later time of usage was also significantly associated with smartphone addiction in a crude logistic regression analysis (**Table 3**). Use at 1 a.m. or later resulted in a four times increased risk of smartphone addiction, compared to those whose latest time of phone use was before 11 p.m. (OR = 4.06, 95%CI:2.48–6.65, $p < 0.001$). After adjustment, this finding remained consistent (aOR = 3.91, 95%CI:2.32–6.61, $p < 0.001$). Use within 30 min of initiating sleep resulted in a two times increased risk of smartphone addiction, which remained significant and consistent after adjustment (aOR = 2.17, 95%CI:1.27–3.70, $p = 0.004$).

Smartphone Usage Reduction Strategies

92.1% of participants attempted at least one reduction strategy (**Supplementary Tables 2**, **3**). The most popular strategies were putting your phone on "do not disturb" or in "airplane mode"

TABLE 3 | The association between sociodemographic factors and smartphone addiction, using crude and multivariable logistic regression.

Variable	Not Addicted *n* (%)	Smartphone Addicted *n* (%)	Crude OR (95%CI)	*p*-value	Adjusted OR[†] (95%CI)	*p*-value
Age						
≤21	393 (57.8)	287 (42.2)	1.00		1.00	
22-25	185 (65.8)	96 (34.2)	0.71 (0.53–0.95)	0.021	0.77 (0.55–1.08)	0.129
≥26	59 (72.0)	23 (28.0)	0.53 (0.32–0.89)	0.015	0.55 (0.31–0.96)	0.036*
Gender						
Male	180 (64.3)	100 (35.7)	1.00	-	1.00	-
Female	457 (59.9)	306 (40.1)	1.21 (0.91–1.60)	0.198	1.06 (0.78–1.45)	0.711
Ethnicity						
Asian	212 (54.5)	177 (45.5)	1.75 (1.32–2.32)	<0.001	1.49 (1.10–2.01)	0.010*
Black	50 (58.1)	36 (41.9)	1.51 (0.94–2.42)	0.087	1.15 (0.69–1.90)	0.598
White	306 (67.7)	146 (32.3)	Ref.	-	1.00	-
Mixed & other	44 (62.0)	27 (38.0)	1.29 (0.77–2.16)	0.341	1.18 (0.69–2.03)	0.542
Missing						
Recruitment site[‡]						
1	195 (58.4)	139 (41.6)	1.00	-	1.00	-
2	191 (57.0)	144 (43.0)	1.06 (0.78–1.44)	0.720	0.81 (0.58–1.13)	0.218
3	99 (68.8)	45 (31.3)	0.64 (0.42–0.97)	0.033*	0.74 (0.47–1.17)	0.201
4	108 (69.7)	47 (30.3)	0.61 (0.41–0.92)	0.017*	0.61 (0.40–0.95)	0.027*
5	44 (58.7)	31 (41.3)	0.99 (0.60–1.64)	0.964	0.99 (0.57–1.71)	0.966
Daily total hours						
≤2	165 (79.7)	42 (20.3)	0.55 (0.36 - 0.85)	0.007**	0.61 (0.39–0.96)	0.031*
3	169 (68.4)	78 (31.6)	1.00		1.00.	-
4	123 (54.4)	103 (45.6)	1.81 (1.25–2.64)	0.002**	1.75 (1.19–2.57)	0.005**
5	88 (54.3)	74 (45.7)	1.82 (1.21–2.74)	0.004**	1.67 (1.09–2.57)	0.019*
>5	89 (46.1)	104 (53.9)	2.53 (1.71–3.74)	<0.001**	2.45 (1.63–3.69)	<0.001**

Crude Odds Ratio (OR) and adjusted ORs. OR, odds ratio; CI, confidence interval; SAS-SV, Smartphone Addiction Scale–Short Version.
**p < 0.05; **p < 0.01.*
[†]Adjusted for age, gender, ethnicity, recruitment site and hours total. Model fit with the adjusted Chi-squared = 77.801, p < 0.001.
[‡]Recruitment location.
1, Life Sciences & Medicine campus.
2, Life Sciences, Nursing & Midwifery, and Social Sciences campus.
3, Psychiatry, psychology, and neuroscience campus.
4, Arts and Humanities, Law, Business, Natural & Mathematical Sciences, and Social Sciences & Public Policy campus.
5, Online.

at night (67.7%); turning off notifications (68.4%); and putting your phone on silent (85.1%). Those who reported smartphone addiction used more strategies than those who did not (mean difference = 0.28, 95%CI: 0.021–0.54, $p = 0.034$).

DISCUSSION

This study included 1,043 young adults at a UK university and examined the phenomenon of smartphone addiction. The prevalence of smartphone addiction was 38.9%. Smartphone addiction had associations with both ethnicity and age. Smartphone addiction was associated with poorer sleep.

Our estimated prevalence is consistent with other reported studies in young adult populations globally, which are in the range of 30–45%, and with Yang et al. (29) who studied a similar university population in the UK (4, 36–39). Noe et al. (40). estimate a UK prevalence of 19% using the SAS-SV with the same thresholds; however this study included an older population (up to 46 years) with a smaller sample size ($n = 64$). The inverse association between age and smartphone addiction highlighted in our study may explain this variation in prevalence estimates. It is likely that differences in prevalence across the field may be due to the varying criteria of instruments used, or different applications of cut-off scores, and we have previously outlined the differences between the most widely used instruments [Sohn et al. (4)].

Smartphone addiction was more prevalent amongst younger participants. This may reflect increased willingness amongst younger generations to adopt newer uses for smartphones (e.g., gaming, social media), which may confer greater risk of addiction (41). This could also related to younger participants potentially having more time for such endeavors. Participants from Asian ethnic backgrounds were at greater risk for smartphone indication, which may be due to cultural differences, such as social norms and characteristics including individualism (29, 42). There was no association between smartphone addiction

TABLE 4 | The association between smartphone use characteristics and smartphone addiction, using crude and multivariable logistic regression.

Variables	Not addicted *n* (%)	Smartphone addicted *n* (%)	Crude OR (95%CI)	*p*-value	Adjusted OR[†] (95%CI)	*p*-value
Total hours spent on phone per day						
≤2	165 (79.7)	42 (20.3)	0.55 (0.36–0.85)	0.007**	0.61 (0.39–0.96)	0.031*
3	169 (68.4)	78 (31.6)	Ref.	-	Ref.	-
4	123 (54.4)	103 (45.6)	1.81 (1.25–2.64)	0.002**	1.75 (1.19–2.57)	0.005**
5	88 (54.3)	74 (45.7)	1.82 (1.21–2.74)	0.004**	1.67 (1.09–2.57)	0.019*
>5	89 (46.1)	104 (53.9)	2.53 (1.71–3.74)	<0.001**	2.45 (1.63–3.69)	<0.001**
Latest time on phone						
Before 11 p.m.	98 (80.3)	24 (19.7)	Ref.	-	Ref.	-
11:00	78 (76.5)	24 (23.5)	1.26 (0.66–2.38)	0.484	1.14 (0.58–2.24)	0.697
11:30	92 (68.7)	42 (31.3)	1.86 (1.05–3.32)	0.034*	1.82 (1.00–3.32)	0.049*
12:00	99 (58.9)	69 (41.1)	2.85 (1.66–4.89)	<0.001**	2.51 (1.42–4.43)	0.002**
12:30	74 (54.4)	62 (45.6)	3.42 (1.96–5.99)	<0.001**	3.29 (1.83–5.90)	<0.001**
1 a.m. or later	177 (50.1)	176 (49.9)	4.06 (2.48–6.65)	<0.001**	3.91 (2.32–6.61)	<0.001**
Time between latest phone use and bed time						
1 h or more	64 (76.2)	20 (23.8)	Ref.	-	Ref.	-
30 min−1 h	103 (68.2)	48 (31.8)	1.49 (0.81–2.74)	0.198	1.47 (0.78–2.76)	0.230
< 30 min	451 (58.0)	327 (42.0)	2.32 (1.38–3.91)	0.002**	2.17 (1.27–3.70)	0.004**

Crude Odds Ratio (OR) and adjusted ORs. OR, odds ratio; CI, confidence interval; SAS-SV, Smartphone Addiction Scale–Short Version.
*$p < 0.05$; **$p < 0.01$.*
[†]*Adjusted for age, gender, ethnicity, and recruitment site. For total hours per day, model fit with the adjusted Chi-squared = 77.801, p<0.001. For latest time on phone, model fit with the adjusted Chi-squared = 78.502, $p < 0.001$. For time between latest phone use and bed time, model fit with the adjusted Chi-squared, 43.977, $p < 0.001$.*

and gender, at odds with other studies which have found that females are more at risk, but it should be noted that the SAS-SV applied a gender-based standardized threshold to determine addiction (43).

Longer use was significantly associated with smartphone addiction, which is consistent with other studies that have found that increased exposure is linked with increased dependency (44). Furthermore, later time of use was also significantly associated with smartphone addiction, with use after 1 a.m. conferring a 3-fold increased risk. This association may be indicative of impaired control and use despite harm, which are a characteristic of a behavioral addiction. Smartphone ownership has previously been linked with more electronic media use in the night and later bedtimes in a survey of adolescents (45).

Our study provides further support to the growing body evidence that smartphone addiction has a deleterious impact on sleep (16, 20, 23). However, this relationship remained significant after adjusting for daily screen time (which was not seen as predictive after adjustment for smartphone addiction). This finding suggests that although duration of exposure, as with any addiction, is a risk factor for smartphone addiction, it is not the only determining component, reflecting the ICD-11 criteria for gaming and gambling disorders, in which duration of use may be one component of diagnosis but is not the only indicator (6, 14). Furthermore, this result indicates that the relationship between sleep quality and smartphone addiction is not simply due to the duration of exposure, as suggested by other studies (46). It highlights that studies reporting a lack of association between smartphones and clinical outcome when using screen time alone should be interpreted with caution, as they have perhaps overlooked smartphone addiction as the harmful exposure (47).

The results of this study indicate that self-reported smartphone addiction is prevalent amongst young adults attending university and that it is linked with use at later times of the day in addition to total duration of use. Public health bodies should take this evidence into account when developing guidelines around smartphone use and sleep hygiene. Furthermore, clinicians, parents, and educators should be aware of the pervasiveness of smartphone addiction, and be prepared to consider the potential wide-reaching impact of smartphones on sleep. Despite the cross-sectional nature of this study, the findings suggest that the amount of time spent on their phones, and latest time of use can be indicative of those at risk for an addicted pattern of smartphone use. Should smartphone addiction become firmly established as a focus of clinical concern, those using their phones after midnight or using their phones for 4 or more hours per day are likely to be at high risk, and should guide administration of the SAS-SV. However, it should be noted that duration of smartphone use alone does not indicate smartphone addiction; it is merely indicates increased risk for development of this pattern of behavior. Future studies should examine longitudinal associations between smartphone use patterns and smartphone addiction, and between smartphone addiction and health harms, as well as exploring strategies to reduce harms, particularly in relation to sleep. As there is continued debate concerning the possibility that smartphones may be a means to access addictive material, such as social media applications or games, rather than the addiction themselves, future research

should also focus on identifying types of use associated with higher risk of smartphone addiction.

This study collected data from a large sample of 18–30 year olds in the United Kingdom using a validated and widely used scale. There were several limitations to this study. Namely, due to the cross-sectional nature of data collection, no causal relationships can be drawn, and we cannot ignore the possibility of reverse causality. In particular, it is possible that poor sleep may be a result of concurrent mental health disorders that were not assessed for in this study, which may result in or be independently associated with increased smartphone usage and smartphone addiction risk. In addition, the self-reported data collection method we used may introduce common-method and response biases. Caution should be taken over the estimate of prevalence since a convenience sampling method was used. Additionally, caution should be taken in generalizing the results of this study, as the sampled population is not representative of the UK-wide population of young adults. Finally, these data were collected before the global pandemic, which may have led to a shift in smartphone usage patterns.

CONCLUSIONS

Smartphone addiction is prevalent and occurs more frequently amongst younger adults. Proxy measures of screen time were not synonymous with addiction; a validated addiction instrument should be used to capture this phenomenon. Those exhibiting smartphone addiction experienced poorer sleep.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical approval was received from the King's College Research Ethics Office (Study ID: 9138; MRS-18/19-9138). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BC, NK, and SS: conceived the study, were responsible first draft of the manuscript, and approved the final draft of the manuscript. BC, NK, LK, and SS: generated the study material. LK and SS: collected the data. BC and SS: analyzed and interpreted the data. BC, NK, PR, and SS: edited the manuscript. BC was the study Guarantor. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.629407/full#supplementary-material

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Brain Arousal as Measured by EEG-Assessment Differs Between Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD) and Depression

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Objective: Disturbed regulation of vigilance in the wake state seems to play a key role in the development of mental disorders. It is assumed that hyperactivity in adult ADHD is an attempt to increase a general low vigilance level via external stimulation in order to avoid drowsiness. For depression, the avoidance of stimulation is interpreted as a reaction to a tonic increased vigilance state. Although ADHD is assumed to start during childhood, this vigilance model has been barely tested with children diagnosed for ADHD so far.

Methods: Resting-state EEG (8 min) measures from two groups of children diagnosed with either ADHD [$N = 76$ (16 female, 60 male), age: (mean/SD) 118/33 months] or depression [$N = 94$ (73 female, 21 male), age: 184/23 months] were analyzed. Using the VIGALL toolbox, EEG patterns of vigilance level, and regulation were derived and compared between both groups. In correlation analysis, the relations between vigilance measures, attentional test performance (alertness and inhibition), and mental health symptoms were analyzed.

Results: Children with ADHD differed from children with most prominent depressive symptoms in brain arousal regulation and level, but EEG vigilance was not related to behavior problems and not related to the attentional test performance. Brain arousal was dependent on the age of the participant in the whole sample; younger children showed lower vigilance stages than teenagers; this effect was not present when analyzed separately for each diagnostic group. EEG assessment time and received medication had no effect on the EEG vigilance.

Discussion: Although based on a small sample, this explorative research revealed that EEG vigilance level is different between children with ADHD and with depression. Moreover, even the standard procedure of the clinical routine EEG (resting state) can be used to differentiate brain arousal states between participants with ADHD and depression. Because routine EEG is not specialized to vigilance assessment, it may not

be sufficiently sensitive to find vigilance–symptomatology associations. Further research should address developmental changes in EEG measurements in children and use bigger samples of participants within the same age range.

Keywords: EEG, vigilance, brain arousal, ADHD, depression, children, vigall

INTRODUCTION

The arousal regulation model of affective disorders (1) keeps the focus on a dysfunctional brain arousal state in wakefulness regarding its level and maladaptive autoregulation and assumes a causal connection of brain arousal to psychiatric disorders of the affective system like depression and mania. In terms of dysfunctional brain arousal state, the brain can be up- or downregulated. Adult patients with depression often show upregulated brain states, resulting in inner tension and inhibition of drive (2) and prolonged sleep latency (3). The opposite, downregulated brain states with short sleep latency and a high prevalence of excessive daytime sleepiness and sleep and circadian disorders are related to ADHD (4) and mania (1). According to that model, many behavioral patterns have the autoregulatory function to compensate for dysfunctional instability of brain arousal (e.g., stimulus avoidance of individuals with depression in order to lower the inner tension and hyperactivity in individuals with ADHD to avoid drowsiness) and these patterns can result not only in personal traits but also in clinically relevant behavioral syndromes, when vulnerable subjects are affected (1, 5).

Brain arousal regulation is mainly driven by coupled activity of the thalamus and the formatio reticularis (FR) in the brainstem. An activation of the medial part of the FR, described as the ascending reticular activation system (6), leads to an increased vigilance state and a desynchronized EEG. Projections from the activated FR to the thalamus lead to increased brain arousal, partly due to decreased inhibition of thalamic relay cells forwarding specific (e.g., sensoric) projections and partly due to non-specific thalamic projection systems, facilitating cortical activity (7). Other projections modulating brain arousal also exist from hypothalamus, limbic system, and the basal forebrain (8).

Like EEG-based assessment of different vigilance stages during sleep, it is also possible to identify different vigilance levels during wakefulness, from high alertness down to the onset of sleep. This vigilance shift before sleep is related to typical changes of brain potentials: A desynchronized non-alpha EEG without eye movements during high alertness is shifting to dominant alpha activity during relaxed wakefulness; alpha activity is then dissolving again with slow eye movements (SEM) occurring during drowsiness. This stage transits furthermore to dominant theta/delta activity with occurring patterns of transitions to sleep like vertex waves and finally with markers of sleep onset present, like sleep spindles, and K-complexes.

For a classification of these vigilance levels, the software tool VIGALL was developed by the Department of Psychiatry of the University of Leipzig, Germany (http://research.uni-leipzig.de/vigall/). VIGALL was used to validate the arousal regulation model in many studies on adult samples. For participants with diagnosis of depression, a hyperstable vigilance regulation was confirmed: More arousal and later decline were present in depressive patients compared to healthy controls (9). A clustering analysis revealed a more stable vigilance regulation pattern in individuals with diagnosis of depressive compared to controls (10). Higher arousal level and slower decline were related to more severe depressive symptoms (11). Interestingly, vigilance level of responders to antidepressant medications at baseline and also the decline after the therapy were both higher than those of non-responders (12). Similar effects on the vigilance level were shown by the same research group for individuals with depression after sleep deprivation (13).

An unstable arousal regulation may be present not only for affective disorders but also as the basic brain dysfunction for ADHD (14). Confirmed by a study report using VIGALL, individuals with diagnosis of ADHD had lower mean vigilance stages and a faster vigilance decline than healthy controls and furthermore arousal regulation predicted the retrospectively-assessed severity of childhood ADHD symptoms (15).

Because the VIGALL algorithm depends on a stable alpha rhythm in order to work properly, EEG measures from children $<$10 years should be analyzed with special caution. At the age of 7 years, a mean alpha peak frequency (APF) at 9 Hz will be reached and an APF of 10 Hz at the age of 15 years (16). Beside Alpha, Theta, and Delta band EEG activity is also relevant for the vigilance classification by the algorithm and can be different from adult EEG. About 25% of typically developing children and early adolescence show Theta and Delta slowing (17). Single arrhythmic pattern of Delta EEG activity in occipital and posterior–temporal regions are known as the "posterior slow waves of youth" and have its maximum expression between 8 and 14 years (16). Posterior rhythmic activity in the 2.5–4.5 Hz band occur with closed eyes at the age of 5–7 years and disappear up to the age of 15 years (16). Probably because of these well-known age-related EEG patterns, we found only one study report using VIGALL in a sample of children. In a study by Sander et al., resting-state EEG segments with closed eyes of 2 min length of children with diagnosis of ADHD were compared to age-matched healthy controls in the overall age range from 6 to 18 years. The authors confirmed model assumption of hyperstable arousal regulation of ADHD and found that the children with ADHD spend less time in the high aroused state and shift more often between the vigilance states (18). Additionally there seems to be evidence for a higher theta/beta ratio present in ADHD compared to healthy controls. This was confirmed in some studies but also one study revealed no differences between

ADHD and the healthy control group, as described in a review of quantitative EEG as a possible biomarker in child psychiatry (19).

A different study comparing children with ADHD to healthy controls and using resting-state EEG together with behavioral and cognitive characteristics in a latent class analysis revealed a heterogeneity of EEG subgroups over all subjects, suggesting that there is no single resting-state profile dominant for children with or without ADHD (20).

To our knowledge, no study report exists about the evaluation of EEG vigilance using VIGALL in children and adolescents with depression. When looking for study reports using other physiological parameters related to the model of hyperarousal regulation in children with depression, the findings are mixed. The ultradian synchronization of sleep EEG rhythms was lower in children with major depression compared to healthy controls (21).This was associated with dampened amplitude of the circadian rest–activity cycle in that sample (22). Other studies showed mixed findings on objective sleep parameters (23) and there was also no clear direction whether cortisol level differences in children with depression exist compared to healthy controls (24, 25). One study reported changes in cardiac activity associated with depression, resulting in increased heart rate but no differences in heart rate variability (HRV) occurred (26).

Taken together, there are a limited number of studies in the literature about brain arousal regulation in children with psychiatric disorders compared to adults. Furthermore, it is not currently possible to claim that a particular brain arousal regulation type is predominantly associated either with externalizing behavior like ADHD or internalizing symptoms like depression in childhood. The same heterogeneous EEG profile distribution has been found for ADHD children and healthy controls (20). HRV and cortisol levels as markers of self-regulation did not differ in depressive compared to healthy children. Therefore, the present explorative study using vigilance EEG measures had the aim to examine whether the assumption of divergent arousal regulation types between ADHD and depression in adults can also be supported for children.

MATERIALS AND METHODS

Participants

In this study, we examined two groups of children and adolescents aged 6–18 years, one group consisting of participants with a clinical diagnosis of depression or emotional disorders with most prominent depressive symptoms (ICD-10 codes: F32.x, F33.x, F43.2, F93.8), and one group of participants with a clinical diagnosis of ADHD (ICD-10 codes: F90.0; F90.1). The children and adolescents were inpatients and outpatients who were consecutively admitted to the Department of Child and Adolescent Psychiatry, Neurology, Psychosomatics, and Psychotherapy of the University Medicine Rostock in the years between 2015 and 2017. Clinical diagnoses were established by a team of experienced child and adolescent psychiatrists and psychologists according to the ICD-10 criteria. The diagnostic procedure included self- and other-informant psychiatric screening questionnaires [i.e., Child Behavior Check List /6-18R (CBCL), Teacher Report Form (TRF), and Youth Self-Report (YSR)], disorder-specific questionnaires [e.g., Beck Depression Inventory (BDI-II), Hamilton rating scale for depression (HAM-D), and Depression inventory for children and youth (DIKJ) in the depression group; Diagnostic system for psychiatric disorders according to ICD-10 and DSM-5 for childhood and adolescence (DISYPS-III): external rating report for ADHD (FBB-ADHS) in the ADHD group], intelligence quotient (IQ) testing [e.g., Hamburg-Wechsler-Intelligence-test for children (HAWIK-IV), Wechsler adult intelligence scale (WAIS-IV), Kaufman assessment battery for children (K-ABC-II), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and Culture fair intelligence test (CFT 20-R)], behavioral observations, as well as neuropsychological investigation of attentional functions in the ADHD group. The following exclusion criteria were defined: intellectual disabilities (F70-F79), neurological (e.g., seizure history), or severe endocrine (e.g., thyroid dysfunction) disorders known to affect brain function, head injury with loss of consciousness, lifetime schizophrenia spectrum disorder, autism spectrum disorders, a diagnosis of depression in the ADHD group, and vice versa.

The EEG data were originally acquired for clinical routine diagnostic purposes and retrospectively analyzed for this study. First, we identified patients with a diagnosis of depression or with emotional problems with most prominent symptoms of depression and patients with diagnosis of ADHD in the EEG database. From those patients, we excluded all individuals where the EEG validation criteria were not met, resulting in a sample of 76 individuals (16 female, 60 male) with ADHD and 94 individuals (73 female, 21 male) with most prominent depressive symptoms. This was the basis for covariate analysis of age, medication, and assessment time effects. On separate subsamples, we tested vigilance differences between the diagnostic groups and effects of vigilance on children's problematic behavior and on attentional performance. The study design is represented in the flowchart in **Figure 1**. We performed case–control matching with random case selection using the FUZZY plugin v.2.0.1., implemented in in SPSS 27. We allowed 2-month age differences in the matched pairs of individuals resulting in a sample of 19 individuals for analysis of vigilance differences between the diagnostic groups. Gender was not an explicit matching criteria, in order to keep the sample size not too low. Nevertheless, 63% of the individuals in this subsample were also gender matched.

The sample of eligible EEG measurement was used for covariate analysis of medication effects on the EEG vigilance; 68.8% of the patients were drug-naive, while the others were examined on medication: methylphenidate: $n = 23$ (13.5%), antipsychotics: $n = 16$ (9.4%), and antidepressants: $n = 10$ (5.9%). Because the received medication could probably influence brain arousal, we analyzed possible medication effects on brain arousal as described later. Both experimental groups differed from each other with regard to age. As expected, they also differed in their clinical profile, i.e., subjects in the depression group yielded higher depression scores, whereas subjects in the ADHD group yielded higher inattention scores. Clinical characteristics are presented in **Table 2**.

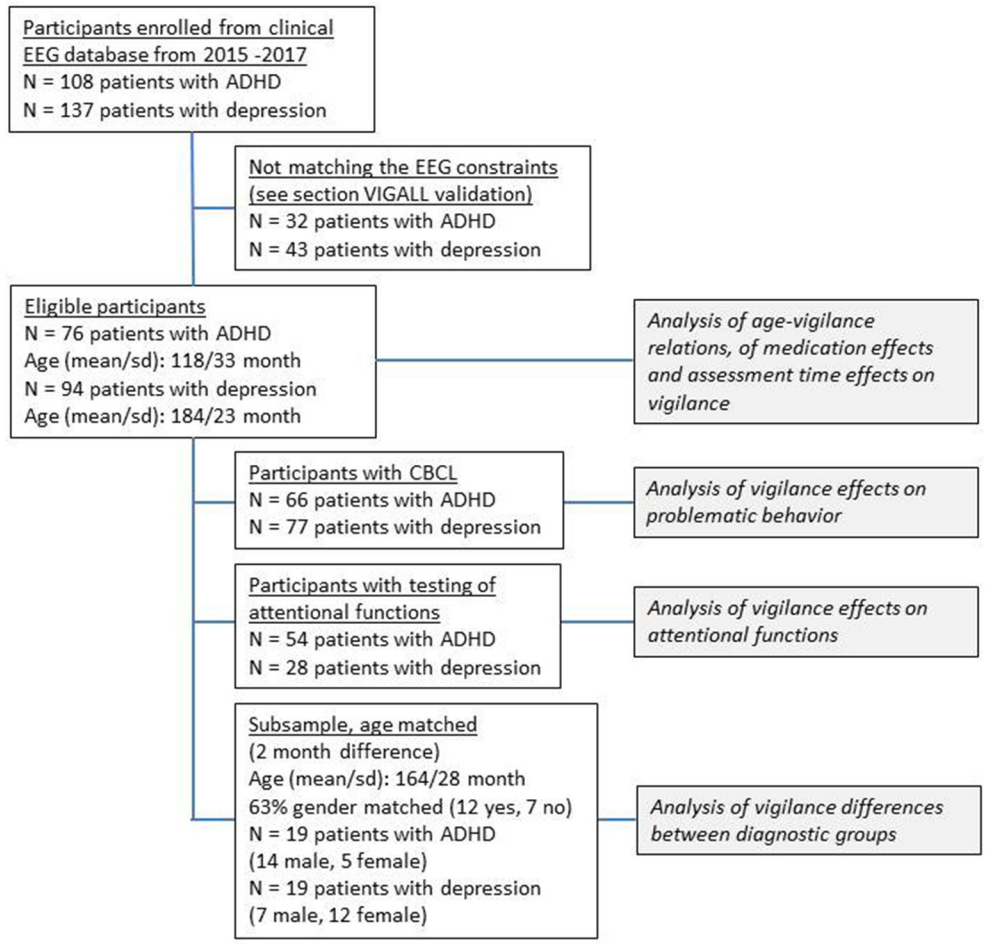

FIGURE 1 | Study design flow chart. This is a sketch of the study design; in order to maximize the number of participants, we analyzed the effect of the covariates age, medication, and time of assessment on the EEG vigilance in the first subsample of all eligible participants.

EEG Acquisition

The EEG acquisition was conducted by a certificated medical technical assistant using the XLTEK EEG system (eeg32u amplifier, Natus Europe GmbH, Planegg, Germany). The EEG acquisition was done as part of routine clinical diagnostics. Continuous EEG was recorded while the participants were seated comfortably with closed eyes on a semi-reclined armchair. Nineteen electrodes were placed according to basic international 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) and were referenced to linked earlobes. Ground electrode was placed between Fz and Cz electrode and one electrode on each wrist to measure the electrocardiogram (ECG). The impedance across all electrodes were quite similar and below 10 kohm. The sampling frequency was 512 Hz. The EEG data were recorded for about 13 min, including 10 min of normal breathing and 3 min of hyperventilation. In order to obtain similar artifact-reduced EEG for all participants, 8 min of the normal breathing part was used for further processing.

EEG Preprocessing Pipeline

Further processing was done with the BrainVision Analyzer (Mesmed GmbH, Gilching Germany). The EEG data were preprocessed according to the manual of the VIGALL toolbox (https://research.uni-leipzig.de/vigall/), including the following steps: Filtering with Butterworth zero phase filter (0.5–70 Hz, notch at 50 Hz), creating 1-s segments, rough artifact screening by visual inspection, execution of independent component analysis (ICA), and exclusion of ICA components reflecting continuous artifacts like blinks, eye movements and cardioballistic artifacts, and marking of remaining artifacts. EEG data were screened for sleep graphoelements (sleep-spindles, K-complexes), but none were identified, which is expectable because the assistant was permanently monitoring the EEG recording during acquisition and prevents the proband from directly falling asleep.

EEG Vigilance Classification

The consecutive segments of 1-s length were classified into six different EEG vigilance stages: 0, A1, A2, A3, B, and B2/3 (C

was not observed) from wakefulness to drowsiness by using the add-on VIGALL 2.1 for the BrainVision Analyzer. VIGALL uses source localization in different frequency bands with LORETA. Further information about VIGALL, which is licensed under GPL3, is available at https://github.com/danielboettger/VIGALL or at https://research.uni-leipzig.de/vigall/.

VIGALL uses continuous electro-occulogram (EOG) data to detect SEM for discrimination B1 stage from stage 0. Because EOG data were not recorded, we were using the particular ICA component reflecting SEM, which can be determined by its typical topography. Furthermore, we omitted the Delta range during classification, because of the absence of sleep pattern and neuronal Delta range activity and in order to suppress probably occurring non-neuronal artifacts in the 2–4 Hz range as described before (11).

In order to keep data comparable to prior reported EEG vigilance research (11), we used similar methods for arousal analysis. We calculated the arousal stability index, based on 1-min intervals (interval 1, segments 1–60; interval 2, segments 2–61; etc.; for scoring criteria, see **Table 1**). Furthermore, we calculated the mean arousal level from the whole EEG acquisition period and the percentage of EEG vigilance stage occurrence (number of segments of one stage * 100/number of all artifact-free segments).

TABLE 1 | Scoring criteria of the arousal stability index.

Scoring criteria	Score
>2/3 of all segments classified as 0 or A1	8
≥2/3 of all segments classified as 0 or A1, A2, A3	7
≥1/3 of last 160 s classified as B1	6
≥1/3 of second 160 s classified as B1	5
≥1/3 of first 160 s classified as B1	4
≥1/3 of last 160 s classified as B2/3	3
≥1/3 of second 160 s classified as B2/3	2
≥1/3 of first 160 s classified as B2/3	1

The arousal stability index quantifies the extent of the arousal regulation. This index was developed by the VIGALL research group (11); lower values mean earlier arousal decline.

VIGALL Validation

The VIGALL toolbox has also some limitations in application, in particular with respect to variant alpha rhythms. Therefore, we included only the data with the following constraints:

1. Alpha frequencies between 8.5 and 12.5 Hz.
2. The amount of artifacts was <15%.
3. A plausible automatic detection of alpha activity: the absolute power of automatic detected alpha activity was more than 25,000 and the alpha activity was detected on early segments.
4. Less than 95% of the segments are classified as 0 or B1, in order to exclude low-voltage EEG.

Statistical Analyses

Statistical analyses were performed with SPSS Statistics 27 (IBM Corp; Armonk, NY, USA). This study has an explorative approach because it was conducted retrospectively on a convenience sample of in- and outpatients stratified for diagnosis, and therefore, the data incorporate some covariates that have to be considered in the analysis strategy. Firstly, we tested the possible effects of the following covariates on the vigilance level and regulation scores: time of EEG acquisition, medication, and age. The diagnostic groups of ADHD and depressive patients were different in age and gender; therefore, we additionally analyzed the relation of age on the EEG vigilance for each diagnostic group separately; 31.2% of the included eligible participants also received psychopharmaceutic medication at the time of EEG measurement, and we addressed possible effects of medication in separate statistical analysis as described further on. Nevertheless, all included participants had symptoms related

TABLE 2 | Behavioral problems.

	ADHD ($N = 66$)		Depression ($N = 77$)		
	Mean	SD	Mean	SD	Z; p; r
Age in months	117.11	29.65	183.65	22.51	**−9.17; <0.001; 0.77**
Internalizing score	59.21	9.93	65.95	7.15	**3.91; <0.0001; 0.33**
Externalizing score	64.44	12.10	56.16	10.64	**4.26; <0.0001; 0.36**
Total score	64.60	9.51	62.84	7.26	1.81; 0.07; 0.15
Withdrawn/Depressed	59.46	9.59	64.41	7.93	**3.69; <0.001; 0.31**
Somatic complaints	58.63	7.59	60.92	8.91	1.63; 0.103;0.14
Anxious/Depressed	58.42	10.58	64.95	7.39	**4.26; <0.0001; 0.36**
Social problems	60.89	10.02	57.24	7.53	**2.30; 0.016; 0.19**
Thought problems	58.74	8.56	61.82	8.82	**1.79; 0.022; 0.15**
Attention problems	65.32	8.09	59.30	7.21	**4.38; <0.0001; 0.37**
Rule-breaking behavior	74.51	84.08	59.75	9.12	2.73; 0.006; 0.23
Aggressive behavior	65.89	11.57	57.07	9.15	**4.66; <0.0001; 0.39**

The Mann–Whitney U-test was used for testing group effects. r, Pearson's correlation index as effect size $r = Z/\sqrt{n}$; n, number of all participants; SD, standard deviation. Shown are mean and SD of standardized T-values. The statistical significant group differences are shown in bold.

to ADHD or depression and met the diagnostic criteria for one of these conditions despite having started psychotherapeutic treatment at the time of the EEG. Therefore, we assumed that the received medication did not compensate effects of ADHD or depression diagnosis on the EEG vigilance In order to examine this assumption, we tested the effects of medication for each diagnosis separately. We tested with the Mann–Whitney *U*-test differences in arousal (stability and mean vigilance) related to medication (yes/no). With the Kruskal–Wallis test, we additionally analyzed the effects of the different medication types in the depressive group (no/antipsychotics/antidepressants) and in the ADHD group (no/antipsychotics/stimulants). Because we did not find any effects of the received medication on the EEG vigilance and because we would not decrease the sample size in this explorative study, we performed the following analysis on the whole sample, regardless of medication.

Secondly, we tested for significant associations between EEG vigilance and diagnostic assessment of problematic behavior and of attentional performance: In a correlation analysis with Spearman's correlation, we tested whether problematic behavior in any of the eight sub scores of the CBCL (27) as well in the total score and the scores of externalizing and internalizing behavior is associated with a particular EEG arousal regulation or arousal level. The association of EEG vigilance with the attentional performance was analyzed with the Spearman's correlation of vigilance stability, mean vigilance, and occurrence with A1 and B2/3 vigilance level with amount of Go errors of the Go/NoGo task (standardized percent range) and with median of reaction times of the alertness task, corrected for age-related variability (tonic alertness). Both attentional performance measures were assessed by the computer-based Test Battery for Attentional Performance (28).

Thirdly, we tested for differences in arousal regulation and arousal level (mean EEG vigilance and amount of segments in A1 and B2/3) between children with ADHD and children with depression with Mann–Whitney *U*-test,

TABLE 3 | Attentional task performance.

	ADHD ($N = 44$)		Depression ($N = 26$)		
	Mean	**SD**	**Mean**	**SD**	***Z*; *p*; *r***
Age in months	121.98	30.81	178.07	29.19	**−5.69; <0.001; 0.68**
Tonical alertness, reaction time (ms)	290.22	53.0	288.22	61.24	−0.86; 0.853; 0.1
Error in go task (percent range)	33.21	11.34	42.27	17.31	−1.99; 0.046; 0.24

The Mann–Whitney U-test was used for testing group effects. r, Pearson's correlation index as effect size $r = Z/\sqrt{n}$; n, number of all participants; SD, standard deviation. The statistical significant group differences are shown in bold.

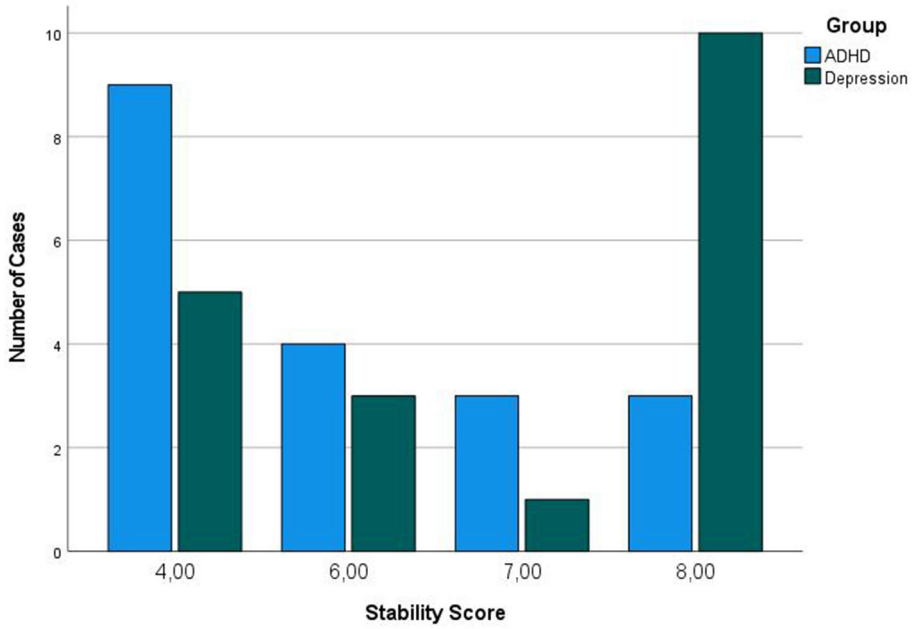

FIGURE 2 | EEG stability distribution between diagnostic groups. Here are shown the vigilance stability index distribution in the age-matched subsample with 19 participants in each diagnostic group. For stability score, see **Table 1**; lower stability value means faster vigilance decline. The stability distribution was different between the groups: Pearson Chi-Quadrat = 10.9, $df = 3$, $p = 0.012$.

TABLE 4 | EEG vigilance measures in all subsamples.

Sample		Group (*N*)	Stability	Mean vigilance	0	A1	A2	A3	B1	B23
All eligible	Mean (SD)	ADHD (76)	5.92 (1.44)	**3.63 (1.08)**	**5.90 (10.46)**	**55.84 (28.79)**	0.89 (2.59)	**1.04 (2.31)**	**5.40 (7.96)**	**30.93 (27.09)**
patients		DEP (94)	6.14 (1.64)	**4.21 (0.81)**	**8.64 (11.48)**	**64.32 (28.71)**	2.65 (7.72)	**1.48 (5.74)**	**9.54 (14.34)**	**13.37 (18.85)**
	Z; *p*; *r*		−0.99; 0.32; 0.08	**−3.77; <0.001; 0.29**	**−3.25; <0.001; 0.25**	**−2.08; 0.04; 0.16**	−1.01; 0.31; 0.08	**−2.01; 0.04; 0.15**	**−2.53; 0.01; 0.19**	**−5.54; <0.001; 0.43**
CBCL	Mean (SD)	ADHD (66)	6.00 (1.45)	**3.64 (1.06)**	**5.11 (9.26)**	57.32 (28.4)	0.87 (2.7)	1.04 (2.31)	**4.92 (7.13)**	**30.74 (26.52)**
		DEP (77)	6.09 (1.62)	**4.18 (0.82)**	**9.06 (11.71)**	62.6 (29.35)	2.93 (8.43)	1.75 (6.31)	**9.57 (13.55)**	**14.08 (19.72)**
	Z; *p*; *r*		−0.44; 0.66; 0.04	**−3.19; <0.001; 0.27**	**−3.56; <0.001; 0.3**	−1.26; 0.21; 0.1	−1.5; 0.13; 0.13	−1.5; 0.13; 0.13	**−2.59; 0.01; 0.22**	**−4.88; <0.001; 0.41**
TAP	Mean (SD)	ADHD (54)	5.81 (1.47)	**3.63 (1.04)**	6.35 (10.15)	**54.89 (28.86)**	1.08 (2.96)	1.36 (2.67)	6.03 (7.89)	**30.29 (26.29)**
		DEP (28)	6.25 (1.76)	**4.41 (0.60)**	7.94 (9.87)	**71.26 (26.60)**	1.62 (3.62)	0.96 (3.02)	9.51 (13.22)	**8.71 (11.76)**
	Z; *p*; *r*		−1.21; 0.23; 0.13	**−3.38; <0.001; 0.37**	−1.38; 0.17; 0.15	**−2.68; 0.01; 0.3**	−0.35; 0.73; 0.04	−1.67; 0.09; 0.18	−1.24; 0.21; 0.14	**−4.38; 0; 0.48**
Age-matched	Mean (SD)	ADHD (19)	5.53 (1.61)	4.17 (0.65)	10.08 (12.78)	62.22 (23.17)	2.27 (4.61)	1.38 (2.23)	7.90 (10.17)	**16.14 (14.23)**
		DEP (19)	6.58 (1.74)	4.31 (0.77)	8.62 (12.16)	67.96 (31.04)	1.04 (2.01)	1.27 (3.65)	10.04 (14.21)	**11.08 (17.13)**
	Z; *p*; *r*		**−1.981; 0.048; 0.32**	−1.299; 0.194; 0.21	−0.044; 0.965; 0.01	−1.445; 0.148; 0.23	−1.13; 0.258; 0.18	−0.79; 0.43; 0.13	−0.438; 0.661; 0.07	**−2.409; 0.016; 0.39**

Mean and standard deviations (in parentheses) of all subsamples are shown. The statistical significant group differences are shown in bold. Less vigilant classification is existent in depressive patients in all subsamples, in particular lower percentage of B23 stage. Because the youngest patients are mainly patients with the diagnosis of ADHD and the eldest mainly are patients with diagnosis of depression, it is not possible to determine to what extent the group differences in the non-age-matched samples is due to age effects or to the diagnosis. Notably, covariate correlation analysis with age revealed differences in mean vigilance and B23 classification only in the whole sample, not for each diagnostic group separately. See Analysis of Covariates section. ***Table 6*** *CBCL, Child Behavior Check List/6-18; TAP, Testing of Attentional Performance; r = Z/sqrt(N), Pearson's correlation coefficient as effect size measure for the Mann–Whitney U-test.*

because of the non-normality of the data. Because of the above-described age effects on the EEG in childhood, we performed all tests for group effects (ADHD vs. depression) on a subsample, parallelized for age and partly for gender.

Because this study has an explorative character, we did not apply a correction for multiple testing, but limited the correlation analysis of single vigilance classification levels only to the vigilance level A1 and B2/3, because about 81% of EEG acquisition time was classified as one of these levels (see **Table 5**).

Effect sizes were reported as Pearson's correlation coefficient r for Mann–Whitney U-test and as η^2 for Kruskal–Wallis test, with $r = Z/\sqrt{n}$ and $\eta^2 = (H - k + 1)/(n - k)$ [n = number of subjects, k = number of groups, test variables Z (Mann–Whitney U-test), and H (Kruskal–Wallis test)].

We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study (29).

RESULTS

Study Sample

Internalizing and externalizing and problematic behavior scores are listed in **Table 2**. As expected, the ADHD group showed more attentional problems as well as more rule breaking and aggressive behavior. This is also reflected by a higher score of externalizing behavior. In contrast, the depressive group showed more withdrawn- and anxious-depressive behavior and a higher internalizing score. **Table 3** shows the median of tonic alertness reaction time from the alertness task and the Go errors from the Go/NoGo task. Patients with diagnosis of ADHD were making more errors in the Go task than, and similar reaction times to, the depressive patients, but both groups revealed task performance in a clinically normal range.

Comparison of Vigilance Measures Between the Diagnostic Groups

We tested diagnostic group effects on the vigilance measures by using an age-adjusted subsample of $N = 19$ in each group in order to control for age effects. The age-matched groups differed statistically significantly in vigilance stability, and higher stability scores occurred in the depressive group, meaning a faster vigilance decline in the ADHD group compared to the depressive children. In the depressive group, we found statistical significant lower percentages of less alerted vigilance stage B23 (see **Figure 2** and **Table 4** for more details).

Analysis of Associations Between Vigilance, Behavioral Problems, and Attentional Performance

The correlation analysis revealed no statistically significant association of any vigilance measure with the behavioral problems, measured by CBCL. Additionally, we did not

find an effect of EEG vigilance measures on the attentional performance, in particular no effects on the response time in the alertness task and no effect on the Go errors in the GFO/NoGo task.

Analysis of Covariates

Time of EEG Acquisition

The acquisition time distribution of all eligible patients is shown in **Figure 3**.

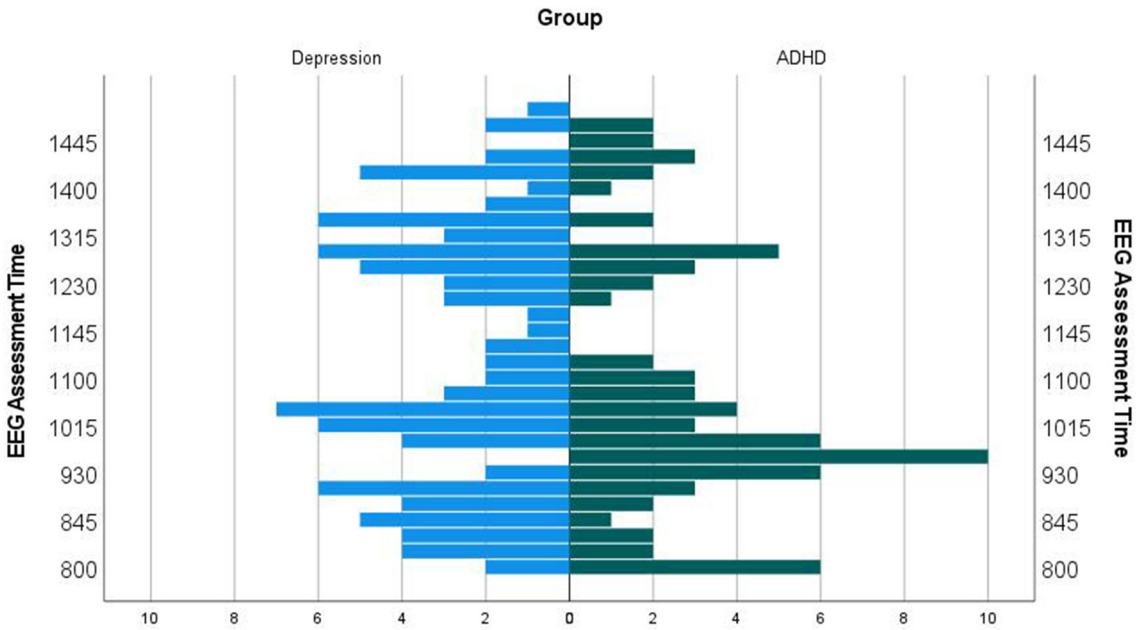

FIGURE 3 | EEG assessment time. The time of the EEG assessment has no effect on the EEG vigilance measures.

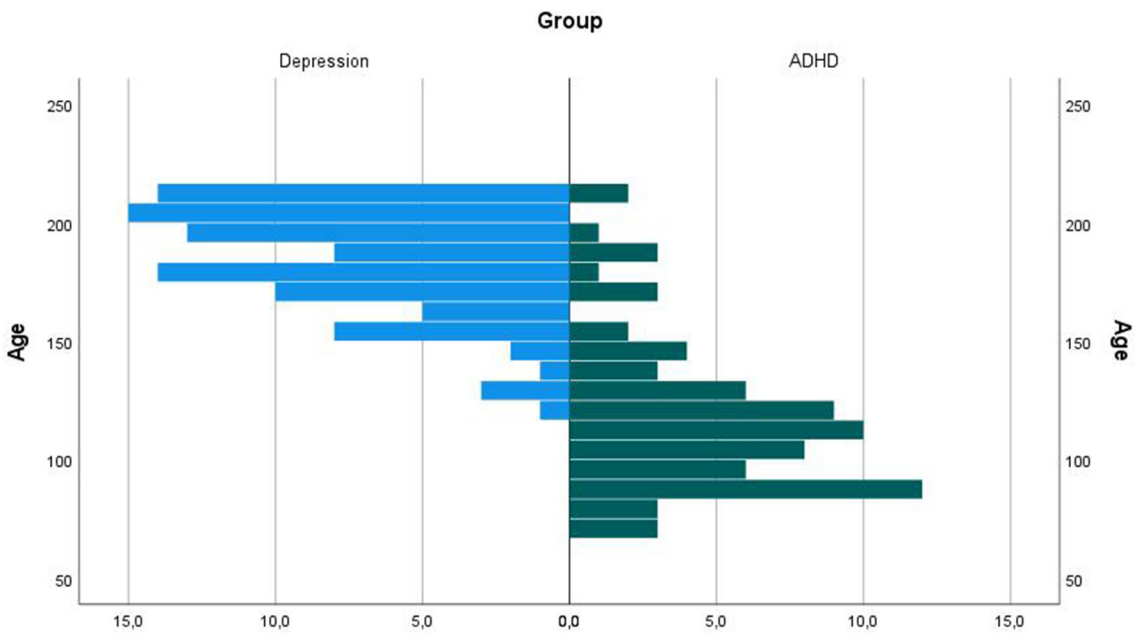

FIGURE 4 | Age of participants. This is the age histogram of the all-eligible participant subsample, $N = 76$ (ADHD), $N = 94$ (Depression). As can be seen, the ages are differently distributed; the oldest participants are in the group of children with diagnosis of depression and the youngest participants are mainly in the group of children with ADHD diagnosis. In order to control for possible age effects on the EEG vigilance, we compared the vigilance measures between the diagnostic groups in an age-matched subsample of 19 participants in each group with a 2-month age difference.

There was no statistically significant correlative association between time of EEG acquisition and EEG vigilance measures (**Table 6**). Additionally, the mean EEG assessment time was not different between the diagnostic groups in the age-matched sample: Mean/SD of assessment time, ADHD: 11:30 a.m./2.3 h, depression: 11:45 a.m./2.2 h, $T_{(36)} = -0.39$, $p = 0.70$, $d = 2.27$.

Age

The diagnostic groups of all eligible patients differed in age with a mean difference of 5.5 years, as can be seen in **Figure 4** and **Table 2**.

The above-described age-dependent changes in EEG activity from childhood to adolescence, e.g., the increase and stabilization of posterior dominant rhythms until the age of 16 (30), also probably influence EEG vigilance measures. Therefore, as expected, we were facing age effects on EEG vigilance measures in this study. Age was negatively associated to vigilance stage; in particular, B23 stage occurrence decreased in children of higher age (**Figure 5**). Nevertheless, these age effects only occurred in the analysis of all participants combined, including the eldest and the youngest children for both diagnostic groups. In correlation analysis of vigilance and age relations for each diagnostic group separately, we did not find a significant correlation between age and vigilance level (see **Table 6**).

Medication

As described before, 30% of the patients received medication at time of EEG (see **Table 7** for more details), and we analyzed any possible effects of this medication on the vigilance regulation and arousal level. We did not find any effects of the received medication on the EEG vigilance: There was no statistically significant difference in vigilance measures comparing medication yes or no with Mann–Whitney test and additionally there was no significant difference when we tested for each kind of received medication separately with Kruskal–Wallis test (see **Table 8**). However, the validity of this result is somehow limited because the obtained power was low. For comparing effects of received vs. no medication, given an alpha error of 0.05 and a power of 80% and the low sample size in our study (ADHD, no: 42/yes: 34; depression, no: 79, yes: 15), we could only detect medium effect sizes of about Cohen's $d = 0.47$ for the group of children with ADHD and $d = 0.57$ for the group of children with depression. In our study, we achieved an effect size d between 0.1 and 0.23. Because of the small sample size and the explorative character of this study, we did not include the medication as a covariate in the analysis.

DISCUSSION

In this study, EEG measures acquired from a convenience sample of in- and outpatients of the childhood psychiatry department diagnosed with ADHD or depression were analyzed for vigilance effects with VIGALL 2.1. As has already been shown for adult patients with ADHD and depression, we found lowered vigilance level and a faster vigilance decline in a sample of children and adolescents with ADHD compared to patients with depressive symptomatology.

This study confirms the several findings of divergent arousal regulation in adult samples of ADHD and depression in a sample

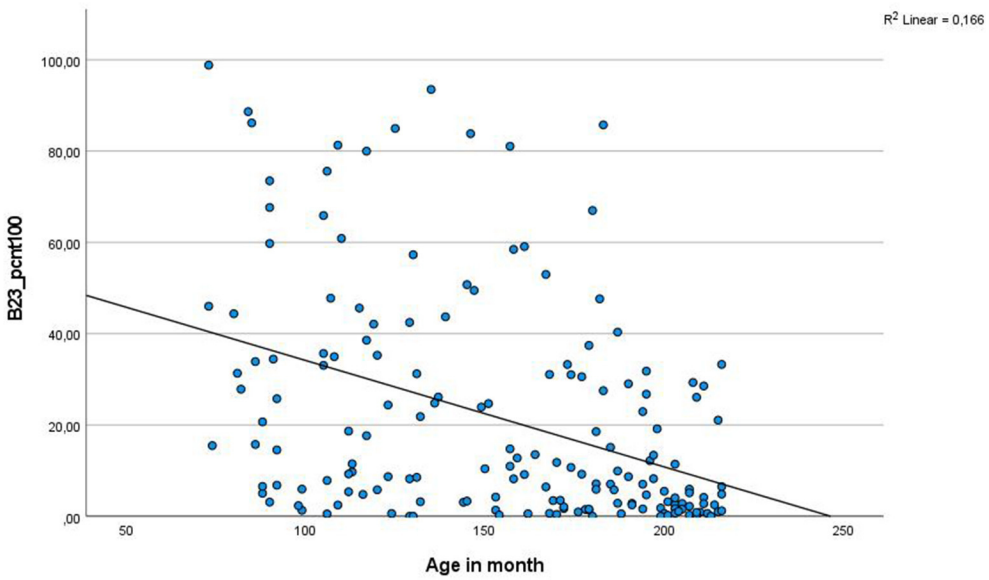

FIGURE 5 | Correlation between age and EEG vigilance stage B2/3. Here, the scatter plot between age and vigilance classification of stage B23 (drowsiness) of all eligible patients can be seen. The age drowsiness association is mainly due to the difference between the youngest and the eldest patients, but who also differed in their diagnosis in our study. Therefore, it is not decidable here whether this effect is caused by the diagnosis, by age, or by a mixture of both. The B23 difference was significant in all tested subsamples (see **Table 4**).

TABLE 5 | Correlation statistics of problematic behavior, attentional performance, and EEG vigilance.

		Vigilance measure			
	Stability	**Mean vigilance**	**A1**	**B23**	
ADHD	**CBCL**				
	Internalizing score	−0.17; 0.18	−0.04; 0.75	−0.06; 0.61	0.03; 0.81
	Externalizing score	−0.2; 0.1	−0.18; 0.15	−0.23; 0.06	0.21; 0.09
	Total score	**−0.289; 0.02**	−0.14; 0.26	−0.2; 0.11	0.15; 0.22
	Withdrawn/Depressed	−0.03; 0.83	0.09; 0.5	0.03; 0.78	−0.09; 0.47
	Somatic complaints	−0.16; 0.21	−0.16; 0.2	−0.12; 0.33	0.17; 0.19
	Anxious/Depressed	−0.11; 0.37	−0.07; 0.6	−0.08; 0.54	0.06; 0.61
	Social problems	**−0.257; 0.04**	−0.06; 0.63	−0.18; 0.14	0.05; 0.72
	Thought problems	**−0.285; 0.02**	−0.15; 0.24	−0.18; 0.16	0.13; 0.3
	Attention problems	−0.22; 0.08	−0.07; 0.59	−0.11; 0.4	0.07; 0.6
	Rule-breaking behavior	−0.18; 0.16	−0.14; 0.28	−0.18; 0.16	0.16; 0.21
	Aggressive behavior	−0.23; 0.06	−0.21; 0.1	−0.24; 0.05	0.24; 0.06
	TAP				
	Go error	0.04; 0.81	−0.02; 0.91	0.03; 0.85	0.03; 0.87
	Tonic alertness rt	−0.15; 0.31	0.07; 0.65	0; 0.98	−0.1; 0.48
DEP	**CBCL**				
	Internalizing score	−0.16; 0.16	0.01; 0.95	−0.04; 0.76	0.07; 0.53
	Externalizing score	0.04; 0.73	0.1; 0.41	0.18; 0.12	0.07; 0.52
	Total score	−0.12; 0.3	−0.02; 0.89	−0.01; 0.91	0.12; 0.31
	Withdrawn/Depressed	−0.09; 0.45	0.01; 0.96	0.03; 0.79	0.06; 0.61
	Somatic complaints	−0.01; 0.91	0.1; 0.38	0.05; 0.67	−0.1; 0.4
	Anxious/Depressed	−0.11; 0.33	0.07; 0.56	0.01; 0.96	0; 0.99
	Social problems	−0.03; 0.81	0.07; 0.54	0.17; 0.14	−0.13; 0.27
	Thought problems	−0.04; 0.73	−0.07; 0.58	0; 0.98	0.08; 0.5
	Attention problems	−0.09; 0.45	−0.01; 0.93	0; 1	0.01; 0.93
	Rule-breaking behavior	−0.07; 0.59	0.05; 0.66	0.06; 0.63	0.07; 0.58
	Aggressive behavior	0.07; 0.53	0.08; 0.47	0.2; 0.09	0.03; 0.8
	TAP				
	Go error	0; 0.99	−0.14; 0.49	−0.03; 0.88	0.09; 0.67
	Tonic alertness rt	0.17; 0.39	0.24; 0.25	0.28; 0.17	−0.3; 0.14

Shown are the Spearman's correlation coefficient rho and the p-value. The statistically significant correlations are shown in bold. CBCL, Child Behavior Check List/6-18; TAP, Testing of Attentional Performance, psytest.de.

TABLE 6 | Correlation statistics of age and assessment time and EEG vigilance.

Sample	**Value**	**Vigilance measure**			
		Stability	**Mean vigilance**	**A1**	**B23**
Both groups	Age	0.01; 0.88	**−0.312; <0.001**	0.14; 0.07	**−0.433; <0.001**
ADHD	Age	**−0.249; 0.03**	0.13; 0.25	−0.04; 0.73	−0.19; 0.1
	assessment time	−0.05; 0.65	0.1; 0.4	0.09; 0.46	−0.05; 0.69
DEP	Age	0.07; 0.51	0.18; 0.08	0.12; 0.25	−0.19; 0.06
	assessment time	−0.06; 0.57	0.08; 0.42	0.08; 0.45	0.03; 0.78

Shown are the Spearman's correlation coefficient rho and the p-value: rho; p-value. The statistically significant correlations are shown in bold.

of children and adolescents. To our knowledge, there has been no study measuring EEG vigilance in depressive children and only one study comparing ADHD children with healthy controls (18). Therefore, this study is the first one, investigating the arousal regulation model for ADHD and affective disorders (1) in children directly by comparing children and adolescents with ADHD and depression. Moreover, our data suggest that even the standard procedure of the clinical routine EEG (resting state),

which is not specialized to vigilance assessment, can be used to differentiate brain arousal states between patients with ADHD and depression. Therefore, this study should encourage further EEG research analyzing brain arousal patterns in additional types of mental disorders, using recordings from larger databases and routine, clinical EEGs, including retrospectively.

We analyzed the possible effect of moderator variables such as received medication, time of EEG acquisition, and age of the participants and allowed the relevance of the covariates to determine our further statistical approach. We found no statistically significant difference in the vigilance measures between the categories of received medication. Because the sample size was small, the inference of our covariate analyses is limited. A proposed analysis is equivalence tests, performed on larger samples in future studies, e.g., by comparing the confidence interval of observed effect sizes with the smallest effect size of interest (SESOI) (31). In our study, the SESOI is increased by the effect size we could reliably detect, but because of the exploratory design, we furthermore analyzed only EEG data in accordance to the constraints made by the VIGALL toolbox, regardless of received medication. Nevertheless, because we are aware of no prior report of medication effect sizes in relation to EEG vigilance measures in children, we believe that the covariates analysis will be meaningful for sample size estimation when planning future studies.

This study was conducted on clinical, routine, EEG data acquired on psychiatric patients, and the data were affected by some covariates that possibly have an impact on vigilance measures. Because of this, there are some limitations that need to be kept in mind. Firstly, there are established age-related changes in EEG measures, related to brain development. Age-related EEG changes include a decrease of absolute spectral EEG power at all frequencies at higher ages, possibly as a result of synaptic pruning during maturation (32). Relative spectral EEG power is decreasing with brain development at Delta and Theta, but increasing for higher frequencies (Alpha, Beta, and Gamma). Changes in vigilance, however, are not triggered by changes in topography; the maps oscillating at lower frequencies in lower ages have the same topography but higher frequencies in older groups (33). Another important change during brain development is the individual Alpha peak frequency (iAPF), which has been found to increase to adult values around the age of 11, although further increases may still be present until the age of 15 (30, 34). Recently, in a comprehensive review (35), the developmental change in the resting-state EEG was assigned to different developmental periods, from infancy, over adolescence to adulthood and includes also findings on functional connectivity and networks.

The toolbox VIGALL assumes a stable iAPF in the range from 8.5 Hz up to 12.5 Hz, which was a filter criterion for data inclusion in this study and therefore age-related changes in iAPF should not limit the vigilance classification. In this study, we have seen a significant correlation between age and vigilance level measures, but this correlative effect did not exist in correlation analysis for each diagnostic group separately. Due to the particular characteristics of our samples, it was not possible to separate and explore age and diagnostic group in the correlation analyses. All of the eldest adolescent patients and only a few of the youngest patients had the diagnosis of depression. Therefore, it was not possible to know the extent to which the statistical age effect on EEG vigilance was caused by altered brain arousal associated with the psychiatric diagnosis or caused by normal differences of developmental brain states, e.g., the increased relative spectral power in the Theta frequency in younger brains. The size of our consecutive sample, however, allowed us to draw a sub-sample matched for age in order to compare the groups. The groups differed from each other in vigilance measures and so this study suggests that the different vigilance regulation types that have been found in the adult EEG (1) are probably also existent in children and adolescents.

Nevertheless, beside the group differences of vigilance level and decline, there was no association between the vigilance parameter and the problematic behavior of the children, measured by the parents' rating via the child behavior checklist. In particular, in the present study, there was no association between vigilance measures and attentional problems, withdrawn-depressive, or anxious-depressive behavior.

In contrast, such associations between symptomatology and brain arousal have been found in adult studies. In a first study using EEG vigilance measures in non-medicated depressive patients, results revealed a moderate association between

TABLE 7 | Received medication and related EEG vigilance.

		No medication	Neuroleptics	Stimulants
ADHD	*N*	42	11	23
	Stability	6.07; 1.24	5.82; 1.66	5.7; 1.69
	Mean vigilance	3.59; 1.02	3.42; 1.21	3.8; 1.13
	0	3.69; 5.81	6.99; 13.18	9.4; 14.44
	A1	58.06; 26.93	49.28; 35.83	54.94; 29.3
	A2	0.71; 2.44	0.64; 1.72	1.32; 3.19
	A3	1.02; 2.55	0.39; 0.6	1.39; 2.35
	B1	4.32; 5.71	7.6; 13.1	6.32; 8.47
	B23	32.19; 25.93	35.11; 30.5	26.62; 28.17
		No medication	**Neuroleptics**	**Antidepressants**
Depression	*N*	79	5	10
	Stability	6.19; 1.63	6.4; 1.67	5.6; 1.84
	Mean vigilance	4.19; 0.81	4.21; 1.12	4.38; 0.69
	0	8.78; 11.84	3.77; 4.2	9.97; 11.08
	A1	63.22; 28.3	70.74; 35.09	69.8; 30.98
	A2	3.1; 8.35	0.47; 0.84	0.12; 0.25
	A3	1.74; 6.23	0.17; 0.39	0.12; 0.26
	B1	9.21; 12.91	17.85; 32.34	7.94; 13.16
	B23	13.94; 19.35	6.98; 8.16	12.05; 19.23

Shown are the mean and standard deviations (SD) of the vigilance measures, separated by semicolon: mean; SD. This is the subsample of all eligible patients N = 76 (ADHD), N = 94 (Depression). No antidepressive medication was given to patients with ADHD and no stimulants were given to the patients with depression.

TABLE 8 | No medication effects on vigilance.

		Stability	Mean vigilance	0	A1	A2	A3	B1	B23
General use of medication (yes/no)									
ADHD	*Z*; *p*; *r*	−0.71; 0.477; 0.05	−0.845; 0.398; 0.06	−0.543; 0.587; 0.04	−1.432; 0.152; 0.11	−0.628; 0.53; 0.05	−0.57; 0.568; 0.04	−0.763; 0.446; 0.06	−0.71; 0.477; 0.05
Depression	*Z*; *p*; *r*	−0.4; 0.689; 0.03	−0.918; 0.359; 0.07	−0.353; 0.724; 0.03	−0.735; 0.462; 0.06	−1.076; 0.282; 0.08	−0.871; 0.384; 0.07	−0.155; 0.877; 0.01	−0.4; 0.689; 0.03
Use of specific medication									
ADHD	*H*; *p*; η^2	1.323; 0.516; 0.01	1.428; 0.49; 0.01	0.522; 0.77; 0.02	3.407; 0.182; 0.02	2.251; 0.324; 0	0.331; 0.847; 0.02	1.359; 0.507; 0.01	1.323; 0.516; 0.01
Depression	*H*; *p*; η^2	1.41; 0.5; 0.01	1.64; 0.44; 0	3.88; 0.14; 0.02	3.3; 0.19; 0.01	0.92; 0.63; 0.01	0.81; 0.67; 0.01	1.41; 0.5; 0.01	1.64; 0.44; 0

*Here are shown the statistic results of the analysis of medication effect on vigilance measures. Analysis of general use (yes/no) of medication was performed with Mann–Whitney U-test. The use of specific medication was analyzed with Kruskal–Wallis test. Statistical parameter Z for Mann–Whitney, H for Kruskal–Wallis. Effect size parameter: r, Pearson's regression coefficient = $Z/\sqrt{n}$ and $\eta^2 = (H - k + 1)/(n - k)$; n, number of subjects; k, number of groups (see **Table 7**).*

clinicians' ratings of depression severity (HDRS-17) and vigilance substages A1, B1, and B2/3, but no significant correlation between vigilance measures and self-ratings of depression severity (BDI) (9). Recently, higher arousal level and a slower arousal decline corresponded to higher severity of depressive symptoms measured by BDI in a sample of SSRI-medicated depressive patients (36). In another study by this research group, a sample of adult ADHD patients were divided into a stable and an unstable group, regarding their arousal decline during the EEG measurement. The participants in the slower arousal declining group reported more depressive symptoms than the unstable group, but no association was found to ADHD symptomatology (37). In a study on adult individuals with diagnosis of ADHD, a multiple regression analysis indicated that retrospectively assessed severity of childhood ADHD symptoms was associated to arousal regulation (15). The lack of association between vigilance parameter and symptomatology in the present study could not be fully explained with the present data. Routine EEG procedure may be sensitive to find vigilance differences between clinical groups, but the variance in the vigilance time series of monitored EEG acquisitions could be too low to analyze association with task performance or symptom severity. It is still an open question whether a possible association exists, and if so, possibly it could be revealed using EEG assessments of longer duration without monitoring the alertness of the participants during EEG acquisition and therefore increasing variability in the EEG vigilance measures. Additionally, for a detailed analysis of developmental changes of brain arousal, it would be preferable to include a larger sample, with a smaller age range.

Nevertheless, it should be emphasized that the further topography and frequency-related analysis of clinical routine EEG data with tools like VIGALL for assessment of vigilance regulation could provide an additional diagnostic value. Related to brain arousal, Hegerl and Ulke (38) stated that clinicians have to verify whether patients' motivational problems with fatigue have their cause in hypoarousal with apathy, sleepiness, and lack of drive or in hyperaroused brain states with exhaustion, inhibition of drive, and ambivalence. The evaluation of vigilance regulation profiles from routine EEG could practically support the distinction between these different forms of fatigue with implications for further treatment.

The findings of the different vigilance level and decline between children with diagnosis of ADHD and children with a diagnosis of most prominent depressive symptoms are firstly limited by the small number of only 19 age-matched participants in each group. Secondly, the effects of medication could possibly alter the vigilance regulation, despite the fact that we did not find any medication effects on the EEG arousal. With these limitations, this study has an explorative character and should be repeated on a larger sample, free of any medication. Nevertheless, because we have controlled for all covariates, the findings of this study could be treated as first evidence that similar differences in vigilance regulation processes exist in children with ADHD and depression as has been shown for adult samples.

DATA AVAILABILITY STATEMENT

The data that support the findings presented in the study are available from the corresponding author/s upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Rostock University Medical Center, Rostock, Germany. 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

CB designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content. AD helped in conceptualizing the study. FP acquired the data. KW acquired and interpreted the data, and helped in conceptualizing the study. JB interpreted the data and revised the manuscript for intellectual content. MK revised the manuscript for intellectual content. OR helped in study design and conceptualizing the study, and revised the manuscript for intellectual content. IM helped conceptualizing and analyzing the data, and drafted the diagnostic procedure description for the Methods section. All authors contributed to the article and approved the submitted version.

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Barriers and Facilitators to Seeking Sleep Solutions for Children With Cerebral Palsy: A Qualitative Study

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Background: Published evidence to date suggests that sleep problems are common in children with cerebral palsy (CP). This qualitative study is a follow up to a previously published quantitative phase on the experience and impact of sleep problems in this population.

Aims: The aim of this study was to explore the experience and impact of sleep disturbance and seeking of sleep solutions for parents of school aged children with CP.

Materials and Methods: Semi-structured 19 qualitative interviews were conducted with parents of children with CP aged 6–12 years. Interview data were transcribed verbatim and the thematic analysis techniques by Braun and Clarke was used to identify themes.

Results: Thematic analysis identified 7 themes: (1) *My Child Doesn't Fit into the Box*, (2) *A Mother's Ears are Always On*, (3) *Sleep Disturbance is like Water Torture*, (4) *Sleep is One of Many Spot Fires, I Put it on the Backburner*, (5) *Luck, Money or Jumping Up and Down*, (6) *There is Never One Silver Bullet* and (7) *Help: The Earlier the Better*. The key finding was that parents of children with CP often described their child's needs being distinct from what is provided by systems and services.

Conclusion: Parents face significant challenges sourcing effective sleep solutions for their child with CP. Sleep is often not a priority for either the parent or the clinician as other health problems take precedence. Parents reflected that early sleep intervention for their child was or would have been helpful. The barriers and facilitators to sleep care identified in this study should be used to inform clinical change in care for children with CP. Sleep needs to be prioritized in healthcare for children.

Keywords: sleep, children, cerebral palsy, health services, qualitative study

INTRODUCTION

Cerebral palsy (CP) describes:

"*A group of permanent disorders of the development of movement and posture, causing activity limitations, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, epilepsy, and by secondary musculoskeletal problems*" [(1), p. 9].

Sleep problems are common in school aged children with CP and can have significant impact on the child and their parents. Parents of children with a disability report poor sleep (2–4) and that chronic sleep disturbance results in a negative impact on parent's health and well-being (3–5) including reduced subjective health (4), reduced participation in healthcare activities (4), stress (2, 3), depression (3), anxiety (3) and reduced quality of life (5). Studies (6–13) that have compared the sleep of children with CP to their typically developing peers have found the incidence of sleep problems is significantly higher for children with CP. A Malaysian study (6) showed only 5% of typically developing children had a pathological sleep score, while 30% of their siblings with CP scored within the pathological range on a sleep-screening tool, of particular importance as surveying siblings removed the variance of culture and parenting style. This study was supported by more recent research (14). There are many studies that have explored the frequency and reasons for sleep problems in this cohort (12, 15–25). Positioning, pain, seizures and continence are the most commonly reported care and comfort reasons for sleep disturbance in addition to an association between pathological sleep scores with epilepsy (191, 192), single parent households (24) and poorer psychological health for parents (26). It is important to recognize that studies which limit their data collection to the commonly used validated sleep assessment tools, such as the Children's Sleep Habit Questionnaire (CSHQ) (27) and the Sleep Disturbance Scale for Children (SDSC) (28), will produce results that align with those tools and are broad descriptors of sleep problems. Whilst this broad data is important, it does not consider the complexity of sleep problems or the context of how families seek sleep care for children with neurodisability. There is a paucity of research that explores why sleep issues are so frequent in children with CP or the barriers and facilitators to accessing effective care in this population.

This paper presents the findings of the third of three-phase exploratory sequential mixed methods study. Phase 1 of this study was a scoping phase, via exploratory interviews, with parents of children with CP who had sleep problems; this phase informed the design of a quantitative survey. The second phase of this study was a quantitative survey, including validated sleep screening tools. The first two phases of the study have been described in detail in a previously published paper (25). The aim of this qualitative phase was to explore the experience and impact of sleep disturbance and how parents sought solutions to these problems.

MATERIALS AND METHODS

All participants were parents or primary caregivers of children with CP aged 6–12 years. Participants were purposively sampled from the quantitative Phase 1 of the study (25). Sampling included choosing participants based on their experience of sleep problems: the best and worst sleepers and the severity of their child's CP according to their Gross Motor Function Classification System (GMFCS) level (29). The GMFCS is an internationally recognized method of describing a child's gross motor function using one of five levels. Children classified within GMFCS level I can walk independently with mild gait disturbance, whilst children with CP classified within GMFCS level V experience severe motor impairment, are unable to independently ambulate or have poor head control (30). Participants who met these inclusion criteria and agreed to further contact were invited to interview. The recruitment process was performed in rounds to ensure that there was time to conduct and transcribe each interview before moving on to the next group of participants. This allowed for iterative analysis; data from each round informed subsequent interviews.

Semi structured interviews were conducted face-to-face or over the phone. The interview tool was designed based on the analysis of the previous two phases of the study. In addition to this tool, the information taken from the participant's survey responses was also used as a prompt for questioning.

Interviews were audio recorded and were transcribed verbatim. Participants were not asked to review the interview transcripts, the additional request of time to review their interview may have acted as a deterrent for participation, given the difficulties in recruiting participants and the research fatigue reported by them in previous phases. Inductive thematic analysis, was undertaken (99) following the six phases outlined by Braun and Clarke (31); (1) Familiarizing yourself with your data: (2) Generating initial codes: (3)Searching for themes: (4) Reviewing themes: (5) Defining and naming themes: (6) Producing the report. Authors SP and SL read and re-read the interview transcripts. SP completed the initial coding of the data, SL independently coded the data and both authors convened to decide on final codes to be used. NVivo (32) software was utilized to assist with data management and coding. Steps three through to five of the thematic analysis occurred as an iterative process between authors SP and SL. Step six was performed by author SP and edited by author SL.

Throughout the data collection and analysis phase peer debriefing, and reflexivity was used to minimize bias on behalf of the researchers.

Ethics approval was obtained from The Royal Children's Hospital, Melbourne Human Research and Ethics Committee (HREC #37300).

RESULTS

Recruitment occurred from August 2018 to March 2019. A total of 19 parents were recruited and interviewed. Participant details can be found in **Table 1**. The participants were a diverse group of parents and children, representative of the heterogeneity

TABLE 1 | Participant demographics and interview details.

Pseudonym	Relationship to child	Age of child	GMFCS level	CSHQ score	Family type	Interview format *P* = Phone I = In person	Interview length (minutes)	Type of sleep problems (child)
Vela	Mother	12	IV	44	Partnered, 3 children	P	84	Currently sleeps well. Long history of sleep problem. Sleep latency and frequent wakings
Ursa	Mother	11	V	58	Blended family, 4 children	P	60	Multiple sleep problems related to comorbidities of CP
Halley	Mother	10	II-III	34	Partnered, 4 children	P	30	Good sleep now, did have poor sleep prior to starting school
Juliet	Mother	10	V	36	Partnered, 2 children	P	32	Currently sleeps ok, occasionally wakes. Long history of night-time wakings and screaming at night
Atlas	Father	7	II	38	Partnered, 2 children	P	32	Sleeps well. History of mild sleep latency
Bianca	Mother	7	II	44	Partnered, 3 children	I	56	Sleeps well mostly, always has
Alya	Mother	12	II	36	Partnered, 2 children	P	38	Sleeps well now, some issues with anxiety and sleep latency. Has found strategies that work
Lyra	Mother	12	III	41	Partnered, 3 children	P	33	No sleep problems
Cressida	Mother	12	I	37	Partnered, 3 children	P	42	No sleep problems
Cordelia	Mother	12	I	53	Single, 4 children	P	60	Restless nights and often sleep latency
Orion	Father	13	I	45	Partnered, 2 children	P	22	Good sleeper, no history of sleep problems
Elara	Mother	8	V	48	Partnered, 1 child	P	63	Sleep problems related to comorbidities of severe CP – tone and discomfort
Ariel	Mother	10	II	46	Partnered, 3 children	P	49	Night-time waking and anxiety
Phoebe	Mother	8	III	53	Partnered, 2 children	P	50	Night-time waking and bed time separation anxiety
Ophelia	Mother	11	III-IV	60	Partnered, 3 children	P	70	Co-sleeping. Significant attachment frequent night waking
Pandora	Mother	13	II	46	Partnered, 2 children	P	26	No current sleep problems. History of significant sleep problems as an infant
Portia	Mother	13	V	51	Partnered, 2 children	I	32	Sleeps well, requires repositioning and care overnight
Titania	Mother	10	II	52	Partnered, 2 children	P	40	Long periods awake overnight
Norma and Leo	Mother and Father	7	V	47	Partnered, 3 children	I	27	Light sleeper, but generally sleeps well

that occurs within the CP population. The group consisted of mostly mothers, with three participants being fathers. Notably, of the seven who had a "good" sleep score, five had some experience with poor sleep even if they currently reported no sleep problems. This meant that interviews with those who had no current sleep problems contained rich and informative data

about the experience of sleep problems and what had been done to improve them.

Of the 19 interviews, 12 were parents of children who scored over 41 on the CSHQ (indicating likely poor sleep) and seven scored 41 or less on the CSHQ (indicating no sleep problems); according to the previous phase survey results. Only three parents reported that their child had no current problems and had never had any sleep problems. That is, 16 of the 19 participants had experienced sleep problems in their child. In the instances where parents had no experience with sleep problems, they were asked about their experience of accessing healthcare for other health problems.

The themes identified in this study are represented in the above concept map (**Figure 1**), which uses a series of circles to illustrate the themes with overlapping circles, representing links between the themes. At the center of the concept map is the dark orange circle, which represents the parent and the child with CP and the theme *My Child Doesn't Fit into the Box*. This theme encapsulates data that described how CP or disability makes a child different to the typical child that accesses healthcare and education systems. This difference consequently impacts upon the experience of finding adequate sleep solutions. Furthermore, this difference often created additional challenges due to systems not being designed to serve atypical children. The subsequent orange circles represent the ripple effects of the experience of sleep problems from the parent's perspective, which are linked to this perception of difference. The child's mismatch to the system and care leads to the requirement for parents to always watch out for their child (*A Mother's Ears are Always On*), including the work done overnight to care for their child, or to be awake with their child because of their child's sleep problems (*Sleep Disturbance is like Water Torture*). This then extends to sleep being a health issue that competes with many other, more urgent, health issues (*Sleep is one of Many Spot Fires, I Put it on the Backburner*). The final theme in the map (*Luck, Money or Jumping Up and Down*) illustrates the work that parents do to find sleep and other health-based solutions. That is, the central difference, the context of the sleep problem comorbidities, the inability to find clinicians familiar and skilled in CP care, and the increased care needs of CP, all impacted on sleep and seeking sleep solutions. The blue circles that fall on the opposite side of the map illustrate themes that are linked to effective solutions for sleep, or what the parents think may be effective solutions. These are placed in opposition to the themes that represent the experiences and challenges of systems, care or sleep problems. The individual themes will now be discussed with a focus on the participants' experience of seeking sleep care/sleep solutions with quotations from each theme.

My Child Doesn't Fit Into the Box (My Child Is Atypical)

Overwhelmingly, the majority of parents shared that they thought their child with CP was atypical. This was the first and core theme identified, *My Child Doesn't Fit into the Box*. This theme encapsulates the frequently expressed perception that parents of a child with CP feel as if their child is different to other children. There were many ways in which this difference was described. It may have reflected the parent's own knowledge; not knowing what to expect or what is typical in a child with CP. Several of the parents discussed how their own unfamiliarity with CP and what to expect influenced their experience of their child and their expectations.

I didn't know kids come out that early. Like I had no idea, totally no idea. So, for me, I was like, 'Now what happens?' And because I had nothing to relate it back to, 'Oh so now this happens with him. Oh, ok'. I don't know other kids with CP.

A Mother's Ears Are Always on (Mothers Need to Be Vigilant)

This theme represents the vigilance of parents, usually mothers, in the overnight care of their children. This theme incorporates the data that describe both the overnight work as being the domain of the mother and the impact of that work on the mothers. The name of this theme is taken from a direct quote from Portia. However, it is recognized that it does apply to some fathers. The majority of the participants in this phase were mothers. While three fathers (Atlas, Orion, and Leo) were interviewed, participants Atlas and Orion articulated that their female partners (mothers) were the providers of overnight care, with Leo being the only father undertaking this role. However, his children did not have sleep problems. Of the interviews with mothers, only Pandora, Vela and Phoebe reported that their husbands shared the night-time care equally.

According to the mothers, providing overnight care was a natural expectation and an extension of their caring role. The majority of the mothers did not work, and this was the most common reason why their family accepted that the night-time work would be done by the mother. Many of the mothers described the need for their husbands to sleep so they could fulfill the requirements of paid work.

I don't really sleep very well. It's just a habit now – it's just a routine for me… I'll start at about 11:30 to 12 o'clock, I'll get up the first time, and I'll turn her over, I'll just stretch her legs or she will stretch herself. Sometimes, I just check on her.

Sleep Disturbance Is Like Water Torture (Sleep Disturbance Has a Negative Impact)

The third theme to be identified was *Sleep Disturbance is like Water Torture*, which encapsulates the impact of poor sleep for the parents themselves, their child and their family life. All but three of the study participants discussed this theme. The naming of the theme came from Elara who, when asked about the impact of poor sleep, described disrupted sleep as, *"It's like Chinese torture, water torture."* This theme directly addresses one of the research questions: 'What is the impact of poor sleep on the parents and child?' It covered how the parent described the impact of their child's sleep on themselves and what they perceived to be the impact of poor sleep on their child. Parents gave examples of how poor sleep impacted on their ability to participate in daytime activities with their family. This varied from changes in mood and patience through to opting out of joining in family activities.

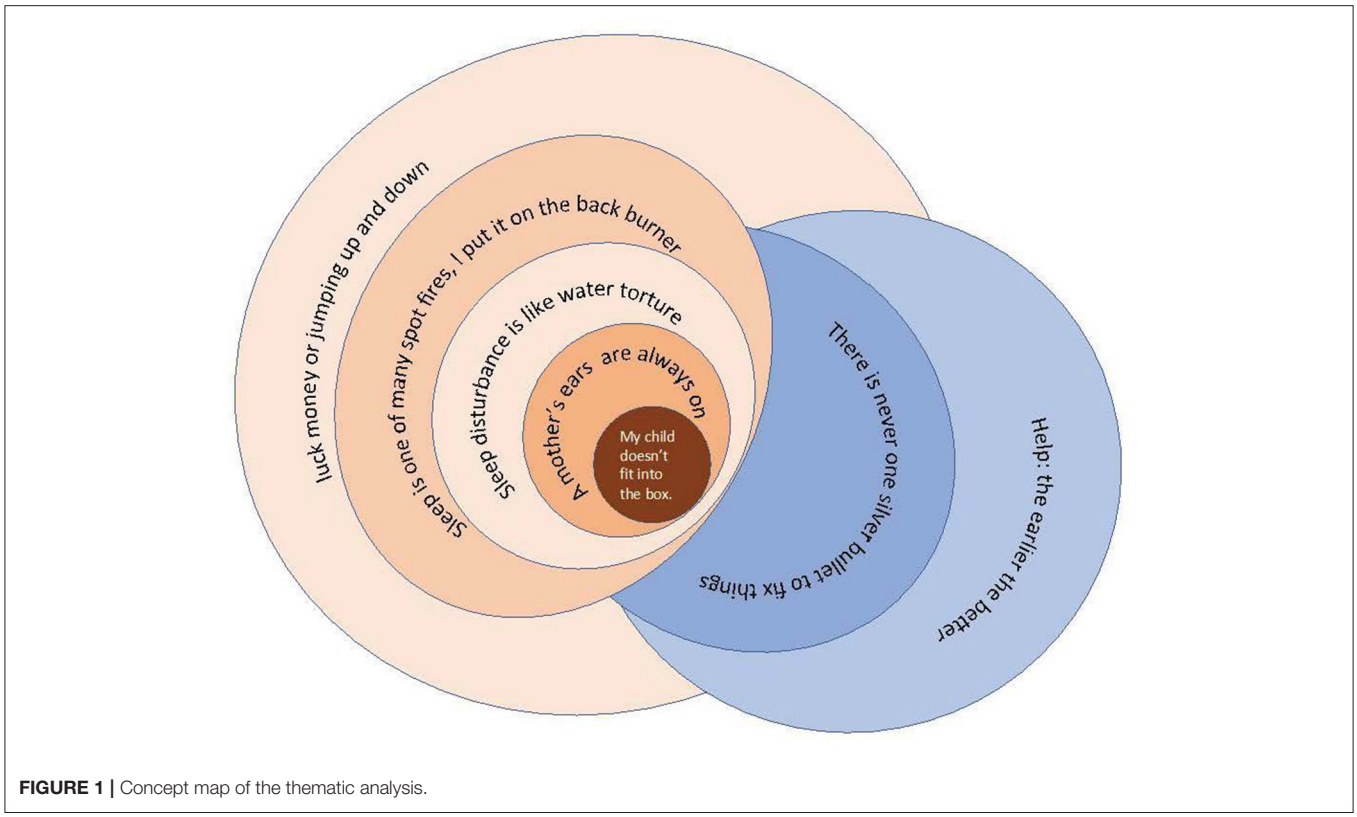

FIGURE 1 | Concept map of the thematic analysis.

I'm just miserable, miserable, lack of energy. He also wakes his sibling up quite a lot, which means that she is feral. Generally, just feeling like crap and then not having that energy that maybe I would have to put the effort into trying… When you're running on empty, you just can't do it.

Sleep Is One of Many Spot Fires, I Put It on the Back Burner (Sleep Is Not a Priority)

Parents frequently talked about their child's sleep problems in the context of a more complex health profile. For all parents interviewed whose child had sleep problems, sleep was not the only health issue experienced by their child. This theme encapsulates data that conveyed where sleep sits as a priority for both parents and for clinicians (as reported by the parents). It was evident that good sleep was valued by the parents but not necessarily prioritized. Within the context of caring for a child with CP and the associated comorbidities and complexities, sleep was one of many problems on a list. It was clear from the interviews that sleep was not a common focus within the clinical setting. When asked, the majority of parents reported that they were rarely asked about their child's sleep in clinic appointments.

*Even though the sleep does go back into [*influencing*] the epilepsy and those sorts of things, I think because it's something that I can lifestyle-manage rather than, 'We'll go in and have an operation and you'll sleep better.' Like yeah. Cool. Look, if we don't sleep for two nights, it's not that big a deal. I'll just won't leave the house for two days and you can sleep during the day. Fine, whatever works… Because it's not a medical something, I feel like it's not as high on the priority list.*

Luck, Money or Jumping Up and Down (Navigating Systems Is Challenging)

This major theme depicts the experience of parents interacting with systems including but not limited, to education systems, to healthcare in general and the NDIS. This theme includes *luck*: parents who described their experience of good care as "lucky"; *money*: parents who described electing to pay for private care (therapy, pediatricians, etc.); and *jumping up and down*: the advocacy and assertiveness required on behalf of the parents in order to navigate the system.

Again, it's a private GP, a private paediatrician, and I think the only way you get these things done fast is if you pay for it, sadly, rather than going through the public system and waiting for your appointments and your referral. And I think that's probably why when we've had stuff and we've needed stuff, it's happened quite quickly. But we've paid for it.

There Is Never a Silver Bullet to Fix Things (There Isn't One Solution for Sleep)

Previously presented themes have highlighted the significant impact of sleep, the difficulty of navigating the system, and the difference created by CP, which is difficult to accommodate in a rigid system. Nine of the 16 parents reported they had obtained sleep solutions for their child. Four parents found pediatricians who helped improve their child's tone and in turn sleep. Five

parents discovered solutions to help with behavioral management of sleep. One parent reported she used mostly homeopathy to treat her child. One mother was advised to prioritize her own sleep over the sleep of her child from early in life and followed this advice consistently. However, of those nine who had reported better sleep, five parents still experienced some sleep problems with their child. That is, better sleep was not always good sleep. What is clear from the data encapsulated in this theme is that the path to improved sleep is not linear. No parent reported a single treatment or intervention that solved their child's sleep problem; there is no 'silver bullet' to fix sleep. Indeed, many parents described trialing many unsuccessful sleep solutions.

*So, we just kept trying and trying and trying ourselves, and I would speak to the GP every now and again when it just got to a crisis level, and we'd just try something else and/or we'd move to a different room or we'd get a new bed, or various things like that [*happened*]… I read up about on the internet that really we just muddled through ourselves obviously.*

Help: The Earlier the Better (Early Intervention Is Important)

A predominant theme that was identified in the interviews was the need for very early intervention in the form of knowledge about sleep. This theme includes what parents reported as being helpful or had helped their child's sleep problem. Overwhelmingly, when parents discussed what was or would have been helpful, the importance of early intervention, from when their child was young and newly diagnosed, was apparent. Many of the parents reported that early intervention had been helpful, or, on reflection, early intervention would have been beneficial. This help may have been specific to sleep or the provision of general information about what to expect in CP or disability.

And then I thought like possibly, the hospital or the paediatrician or someone had said, 'Hey, how's is sleep going?' And I had answered. And then that might've been different, but yeah, I don't know. And I didn't really know who to ask.

DISCUSSION

The findings of this study demonstrate that parents who seek help for sleep problems are often unsuccessful, either not receiving advice or treatment, or receiving advice or treatment that is not effective. This difficulty is punctuated by parents who feel that their child's needs do not match the systemic structures, or conversely, that the system does not match their child.

The parents in this study spoke of sleep not being a priority in the context of other more urgent health problems, and related that they felt clinicians rarely focused on sleep as a health issue. Several parents in this study reported that they had found successful sleep solutions and reported that they were under the care of pediatricians who applied a multi-layered approach to sleep problems in their child. They described a "trial and error" approach to solutions and sleep problems were revisited at subsequent appointments. Interestingly, only one family reported that they attended a sleep specific clinic. Some parents explained that finding sleep solutions was hard, and others just learnt to live with poor sleep. For the majority sleep issues are not a focus of clinical appointments as other, more urgent, health problems take priority.

In contrast to the findings of this study, McHugh (33) found that parents did not ask for sleep help and suggested that the context of the disability may have been a factor for parents not asking for help with sleep. McHugh's qualitative research suggested that the parents were tired, grieving or adjusting to their child's disability diagnosis, and this prevented them from asking for help. A study by Robinson and Richdale (34) reported that up to a third of parents with children with intellectual disability, including children with CP (6.5% of the study group), did not seek help for sleep problems. These two studies contrast with the current findings; in this study parents reported that they frequently asked for help with sleep from their healthcare team.

In the theme *Luck, Money or Jumping Up and Down*, an additional facet of seeking solutions was revealed: the work that parents, usually mothers, were required to do to navigate the system and find effective solutions. Australian studies have presented parents' general experience of navigating the healthcare system. These challenges have been reflected in the work of a Victorian based study by Bourke-Taylor et al. (35). They conducted a qualitative study of four mothers of children with a disability and four clinical professionals who work within the disability sector and Bourke-Taylor et al. (35) found that mothers reported a lack of cohesion between services and spent much time seeking resources, planning, locating and retaining services. This finding is supported by international studies (36). Within Bourke-Taylor's study, both mothers and professionals reported that the mothers were expected to constantly advocate for their children (35).

It is clear that the parents of children with CP are required to be tenacious care managers for their children in order to receive effective care. That is, there are significant gaps within the provision of health and disability care systems that parents are required to fill in order to avoid detrimental outcomes for their children. The theme *Help: The Earlier the Better* reiterates this concept of knowledge equating to empowerment.

There has been significant investigation into the experience of parenting, in particular mothering, children with a disability. A qualitative study from Canada (37) identified that parents of children with complex needs had little time for anything other than caring due to the demands of navigating services for their child. Those findings and other reported studies (36, 38, 39) resonate with the outcomes of the study reported in this paper. The complex context in which sleep problems are situated for these families and expectation of immense workload for parents is global. It might be argued that the volume of work that parents need to do every day to ensure good baseline care for their child is so high that a problem like sleep, for which there is little clinical urgency, could easily be deprioritized. If sleep problems are deprioritized, they likely go untreated, which in turn leads to chronic sleep disturbance and deprivation.

This study has demonstrated that sleep problems are multifactorial and complex and deeply entwined with many other aspects of disability: the parent child relationship, worry for a vulnerable child, the comorbidities of CP, and the non-linear nature of raising a child with a disability. Researchers need to

design research projects that move beyond outcomes that simply count the number of sleep problems in study cohorts. The greater context of sleep problems needs to be considered, and a greater focus on meaningful interventions is required, in order to create clinical change for these families. Indeed, a study by Romeo et al. (40) concluded their paper with the declaration that a structured in-depth interview may have provided more accurate data to make better diagnoses, providing further support for the need for a multi-modal approach to data collection.

The findings of this research confirm that the experience of sleep problems in this cohort is often not linear. The experiences of the parents suggest that the complexity of disability in a child means that children often do not transition through sleep problems in the same way as a typically developing child might. Rather, parents described sleep problems improving and then worsening due to illness, surgical interventions, changes in family routine (for example, school holidays), or due to child or other life stressors and anxieties that impacted on sleep. There is no published literature which describes the experience of sleep problems and their solutions for children with CP over time. However, several studies support the finding that sleep problems are chronic (9, 34). This demonstrates that resolving sleep problems for children with CP may require repeated intervention over time. Any intervention for sleep in this group should incorporate this in its design.

To date, there is no published research regarding what sleep interventions are effective for children with CP, specifically. Clinicians and researchers may argue that diagnostic specific sleep interventions are not necessary, and that the significant overlap between neurodisability diagnoses may mean a transdiagnostic intervention can be used. Indeed, a recent systematic review by Rigney et al. (41). Reviewed the effectiveness of behavioral sleep interventions for children with neurodevelopmental disorders. The majority of the reviewed studies focused on autism spectrum disorder and attention deficit hyperactivity disorder, however, some studies included children with CP within sample groups. Rigney concluded that the current evidence suggests a transdiagnostic behavioral intervention is feasible. The findings of this study suggest that one singular sleep intervention is unlikely to address the needs of children with CP who have complex sleep problems. It is the contention of this paper that the management of sleep problems in children with CP needs to be, at least initially, individualized. As has been described by the parents in this study, an individualized approach to sleep problems allows for the complexity of the problems to be understood, and for treatment of comorbidities of CP that impact sleep to be remedied in the context of sleep problems.

LIMITATIONS

The participants from this study were recruited from a previous quantitative phase. The overall demographics of that phase were parents with a higher than average education and socioeconomic status. It is likely that this research has not captured the experience of parents with less education or who are poorly resourced. The participants on this study were all residents of Victoria, Australia. Australia's health care system is different from state to state and the services and systems used in Victoria may not be generalizable throughout the country or internationally.

CONCLUSION AND RECOMMENDATIONS

This study plainly demonstrated that the experience of sleep in CP is not clear; it is a messy, convoluted and complex experience that is dependent on the resources of families, the individuals navigating the systems and their child's other health needs. The scattered nature of the circles in the concept map illustrates the complexity and the non-linear nature of sleep problems and sleep solution seeking that was demonstrated in this cohort of parents. Sleep and CP cannot be separated, and CP and sleep problems are enmeshed. This enmeshment is at a body systems level and from a healthcare system, family and parenting perspective. This study has captured rich and nuanced data that could not have been captured with quantitative methods. The findings demonstrates the many challenges parents face in sourcing effective sleep solutions for their child and the need for an individualized approach to sleep care. The promotion of sleep as a health priority needs to be elevated and more research is needed in order to determine how to educate both families and clinicians about the importance of sleep health. Consequently, targeted sleep education of clinicians who work with children with CP and their families' needs to be initiated. Allied health and nursing staff could have an important role in promoting and consulting on sleep health and this might be needed to create improvement in sleep for this cohort. This paper presents previously unknown data about the experience of seeking sleep care. This demonstrates the importance of consumer consultation in health services research. Any future research in this area should apply methods that enable consumer engagement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Royal Children's Hospital, Melbourne Human Research and Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SP conducted the research and wrote the paper as a Ph.D. candidate. FN, DR, and AH were Ph.D. supervisors for the project involved in all planning and implementation of the research as well as draft revision. SL also Ph.D. supervisor

as above in addition to being the second researcher for the qualitative data analysis. All authors contributed to the article and approved the submitted version.

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Digital Media Exposure and Predictors for Screen Time in 12-Month-Old Children: A Cross-Sectional Analysis of Data From a German Birth Cohort

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Background: Early exposure to digital media may affect the physical and cognitive development in young children. The *American Academy of Pediatrics* and national guidelines recommend no digital media use at all under the age of 18 months. The aim of our study was to determine the actual exposure to digital media in 12-month-old infants and to reveal potential risk factors for screen time.

Methods: In this prospective cross-sectional survey, data was collected from the KUNO Kids birth cohort study using parent-report questionnaires regarding the media exposure of the study child. We determined age at first contact with different digital media, mean screen time on an average weekday, and the influence of major demographic and socioeconomic factors.

Results: Data for screen time analysis was available for 630 children. In summary, 45% of children had already been exposed to digital media by their first birthday. The most frequent first digital media exposure was the TV (33.0%) followed by smartphones (16.9%), both most commonly exposed to around the age of 8 months. On a regular weekday, 20% of the children spent 0.5–1 h in front of a TV and 9% were exposed to a smartphone for the same time frame, compared to 31% of joint parent-child media use. Predictors for screen time were having one sibling, less living space per person, and excessive TV use in the household, the latter of which doubled the chance of the child being exposed to digital media.

Conclusion: A proportion of 10% of 1-year-old children were already regularly exposed to digital media. The TV remains the most predominant device but new media, particularly smartphones, might be catching up. Our study provides further support that family TV

time is a major predictor of infant screen time. Pediatric recommendations should be re-evaluated in the light of the actual exposure to digital media already in infancy and parents should be proactively counseled regarding possible effects on child development.

Keywords: digital media, screen time, infants, young children, media exposure

INTRODUCTION

Compared to twenty years ago, the digital media environment has flourished (1, 2). Children are growing up with both traditional electronic media (television) and new interactive media, such as entertainment gadgets (game consoles, video/DVD/Blu-ray players, and tablets), work devices (personal computers and laptops), multi-functional devices (smartphones) and not to forget electronic book readers. Infants today may learn to use digital media before they learn to walk.

However, premature contact and overuse of digital media may disturb an infant's development in the first year of life. The *American Academy of Pediatrics* (3) and national guidelines (4) recommend no electronic media use in children under 18 months, other than video-chatting with family members, as children younger than 2 years of age do not benefit from 2D screen media. For children 2–5 years old, a daily amount of less than one hour is advised (3). Yet, in Europe, approximately one third of 2–10-year-old children fail to meet current recommendations (5).

Media exposure can affect child development directly (e.g., consumption of violent media content) or indirectly (e.g., displacement of time) (6). Sleep is paramount for child development (7, 8), and evidence shows that increased daily screen time is associated with shorter sleep per night (9, 10). The displacement of sleeping (9) and physical activity (11), and especially for infants, playing and interacting with their parents or other family members (12) can have multiple negative consequences (11, 13–15).

While parental media use has been proven to be a pivotal predictor for child media use (2, 16), other risk factors must be considered, including child sex, age, hyperactive and sedentary behavior, as well as parental age, BMI, and education. Availability of digital technology in the household, family size and income have also been associated with the amount of electronic media consumption (17).

In the light of this data, it is crucial to collect information on the actual digital media exposure of today's young children. Therefore, analyzing data from a birth cohort, we examined the amount of digital media use in 12-month-old German infants and we determined factors predicting individual screen time.

MATERIALS AND METHODS

General Study Design of KUNO Kids Birth Cohort

The KUNO Kids Health Study aims to evaluate a wide array of factors and determinants of child health and development in a holistic approach (18). All pregnant women presenting for their pre-birth check-up and women post-delivery at the Obstetrics Department of the University Regensburg (Bavaria), Germany, were invited to participate. The actual inclusion into the study took place during the first 48 h after delivery. General exclusion criteria for the birth cohort were inadequate German language skills, outpatient birth and maternal age less than 18 years. In families with twins, only one child per family was included. Participation was voluntary and all participants provided written informed consent. The study was approved by the Ethics Committee of the University Regensburg (file number: 14-101-0347) (18).

Data Collection for Digital Media Exposure Study

Regarding the study question, data was obtained at the child's age of 12 months, in the period of June 2015 to January 2019. For this purpose, the families received questionnaires via mail shortly before the first birthday of the child. Parents completed a questionnaire each, as well as one for the participating child and, if present, for siblings. To reduce recall bias, we excluded 299 questionnaires that were returned later than two months after the child's first birthday.

Outcome Variables

Using five standardized questions with a total of 23 items, parents were asked to estimate the amount of time digital media devices were used by their child on an average weekday. Digital media included TV, Blu-ray/DVD/Video, PC, tablet, smartphone, game console, and, as a reference, books. In addition, parents were asked at what age their child first used various digital media devices, whether their child had a TV in its bedroom, and how long the family TV was running on a typical weekday.

Exposure Variables

Demographic information was gathered from questionnaires directed specifically to the mother or father, sent a few days after delivery, after four weeks and at the child's first birthday. Following risk factors for child media exposure were considered: sex of the child, number of siblings, mother's age at delivery, overweight of one or both parents, single-parent household, high family TV time (delineated as equal or more than 2–3 h per day) and living space per person less than the calculated median (determined by dividing the household size (m^2) by the number of household members). Further sociodemographic factors were assessed, including parents' professional qualification on a four parameter scale ("None": no finished education, not in professional education, "Low": student or still in professional education, "Medium": completed education, under university

level, "High": university education), whether parents had been employed during the first year of the child's life, and parents' nationality (both German nationals, one parent foreign national, both foreign nationals). We assessed the subjective social status (SSS) using the *MacArthur Scale*, which is recommended for use in industrialized countries such as Germany (19).

Statistical Analysis

The reported child's regular daily use of digital media devices was defined as screen time. We then dichotomised the variable *screen time* to group infants with absolutely no screen time compared to those with screen time, as per the AAP guidelines for one-year-old children (3). After excluding questionnaires with a response time lag later than 2 months, a descriptive analysis of *screen time* and sociodemographic data was conducted. Using *screen time* as the dependent variable and the above-mentioned risk factors as independent variables, we ran a univariable binary logistic regression with odds ratio and 95% confidence intervals. To analyse the importance of the predictors relative to each other, we ran a multivariable binary logistic regression, including only those predictors with $p < 0.2$ in the univariable logistic regression. All statistical analyses were performed with IBM SPSS Statistics ® Version 23. Figures were plotted with GraphPad Prism ® 6.07 (La Jolla, USA).

RESULTS

Sample Characteristics

Data from the KUNO Kids questionnaires for screen time analysis was available for 630 children. Sociodemographic information was available for 577 families. The detailed characteristics of the sample population are outlined in **Table 1**. With the birth cohort based in a hospital in South-east Bavaria, most parents were German nationals (86.4%) and had a medium to high professional qualification (98.0% of mothers and 97.7% of fathers). 49.7% of our sample were girls and 60.8% of the children were first-born. Mother's age at delivery was between 22 and 45 years (mean ± SD: 34.7 ± 4.0 years). 38.0% of the mothers were overweight at the time of the survey. The subjective social status on the MacArthur Scale, as noted by both mothers and fathers, was 7 points (mean: 6.9 points and 7.0 points, respectively). Most

TABLE 1 | Characteristics of sample population.

		N	Participants	Percentage
Infants	Sex female	577	287	49.7
	First-born	574	349	60.8
	One sibling	574	183	31.9
	Two or more siblings	574	42	7.3
Mothers	Age at delivery[a] in years (mean) (SD)	571	34.7 (4.0)	
	Overweight[b]	495	188	38.0
	Subjective social status[c] (mean) (SD)	559	7.0 (1.3)	
	Single parent	567	6	1.1
	Professional qualification[d]			
	None	562	4	0.7
	Low	562	7	1.2
	Medium	562	279	49.6
	High	562	272	48.4
	Employed during the child's first year of life	571	156	27.3
Fathers	Overweight[b]	480	326	32.1
	Subjective social status [c] (mean) (SD)	560	6.9 (1.4)	
	Professional qualification[d]			
	None	521	4	0.8
	Low	521	8	1.5
	Medium	521	252	48.4
	High	521	257	49.3
	Employed during the child's first year of life	553	540	97.6
Home environment	One or both parents overweight	558	387	69.4
	One or both parents immigrants/foreign nationals[e]	565	77	13.6
	Household size in m^2 per person (mean) (SD)	562	38.0 (16.6)	
	TV in child's bedroom	598	3	0.5

[a]Excluding mothers under 18 years of age for KUNO Kids birth cohort. [b]Based on BMI ≥ 25 kg/m^2, mothers at one year after delivery, fathers at four weeks after delivery. [c]Based on the MacArthur Scale of Subjective Social Status; numbers range from 1–10. [d]Based on extent of professional qualification ("None": no finished education, not in professional education," Low": student or still in professional education, "Medium": completed education, under university level, "High": university education). [e]Born in a foreign country or with a foreign passport.

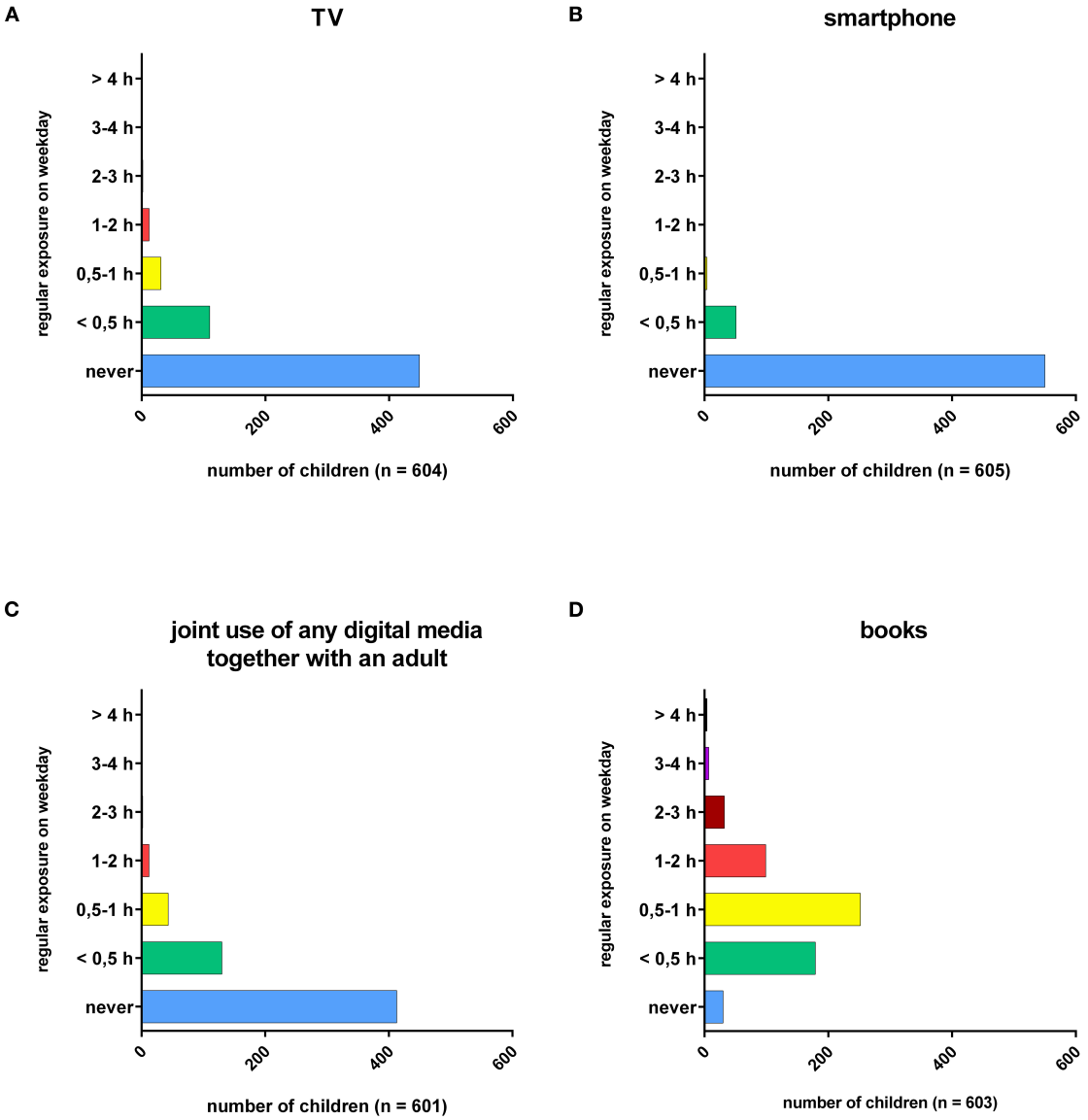

FIGURE 1 | Regular exposure time (in hours) to different types of media on weekdays.

of the fathers had been employed during the first year of their child's life (97.6%).

Pattern and Amount of Exposure to Different Digital Media During First Year of Life

In general, 45% of the 12-month-old children did not meet the AAP guidelines of absolutely no screen time.

On an average weekday, most infants did not watch TV or use smartphones, tablets, Blu-ray/DVD/Video, game consoles or PCs (ranging from 74–99.6%). However, there was a subgroup of children who were regularly exposed to electronic media, most commonly TV **(Figure 1A)** or smartphone (**Figure 1B**), for up to 0.5 hper day (TV: 20 % (110), $n = 604$; smartphone: 9 % (51), $n = 605$). Joint media use was a little higher (**Figure 1C**). 31% of parents reported using digital media together with their child, usually for up to 0.5 h on a typical weekday (130, $n = 601$). Reading books together with children was even more popular **(Figure 1D)**. Most parents and infants read up to 1 h per day together (71.5 %, 431, $n = 603$). Only 5% did not spend any time at all using books.

When examining the particular digital media devices, it became clear that 33.0% of children had been exposed to TV, 16.9% to smartphones, 5.3% to tablets, 4.4% to Blu-ray/DVD/video, 2.2% to PC and 0.2% to game consoles at least once in the first year of life **(Figure 2)**. The age of earliest contact was commonly around 7–9 months (TV,

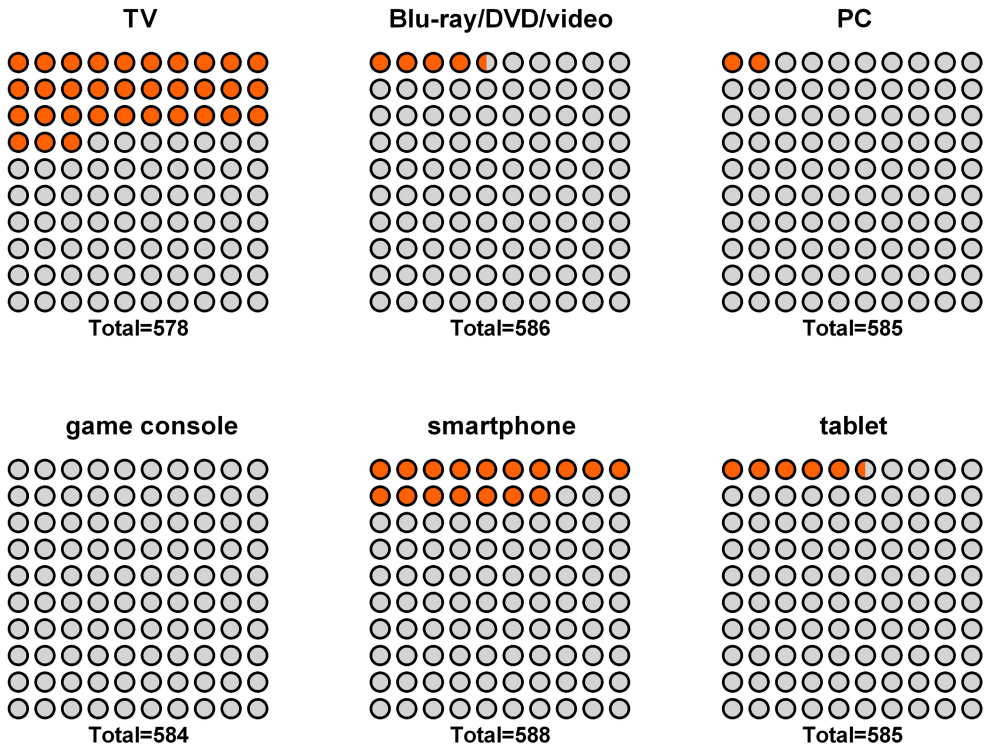

FIGURE 2 | Percentage of infants exposed to different types of media during the first year of life.

smartphone, tablet, Blu-ray/DVD/video, PC) **(Table 2)**. The few children who were exposed to game consoles were about 12 months old.

Family TV Time (Passive Child Media Exposure)

The results of household TV use showed a Gaussian distribution curve, with a peak at 1–2 h of TV screen time on an average weekday (27%, 160, $n = 599$) (**Figure 3**). 21% of parents had a TV running for 2–3 h and 17% between 0.5–1 h. Only 11% stated that they did not watch TV on a regular daily basis.

Factors Associated With Infant's Exposure to Digital Media

In both the univariable **(Table 3)** and multivariable analysis **(Table 4)**, household space per person (multivariable analysis: $p = 0.007$, OR = 0.567, 95% CI = 0.375–0.857) and excessive family TV time (multivariable analysis: $p = 0.027$, OR = 1.631, 95% CI = 1.059–2.512) showed a significant association to the child's media exposure. Family television time of 2–3 h or more per day raised the odds by 63% (multivariable data) of the child having screen time. More living space per person than the median indicated a 43% less chance of child screen time. While the univariable analysis revealed the mother's subjective social status as a predicting factor ($p = 0.001$, OR = 0.795, 95% CI = 0.696–0.909), in the multivariable analysis this association closely missed the level of significance ($p = 0.058$, OR = 0.853, 95% CI = 0.723–1.005) and was no longer independently associated with the infant's screen time. The multivariable analysis uncovered a significant relationship between the presence of a sibling and child screen time ($p = 0.019$, OR = 1.715, 95% CI = 1.093–2.692). Being second-born increased the chance of screen time by 72%.

The other potential risk factors examined did not show statistically significant associations with child screen time. Sensitivity analyses with screen time <0.5 h vs. >0.5 h were conducted for the univariable logistic regression analysis and revealed similar results.

DISCUSSION

The purpose of this study was to report baseline data of young children's digital media use and explore potential risk factors for exposure. Contrary to AAP and national guidelines' recommendations, about half the children have already been exposed to digital media during the first year of their life. While most infants did not have regular screen time, there was a subset of 10% of the study population who had a regular exposure for up to half an h on an average weekday. The usual first contact to digital media occurred at the age of 7–9 months. In addition, the presence of a sibling, less personal living space, and increased

TABLE 2 | Age in months at first exposure to different digital media.

Device	Mean	Median	SD	Min	Max[a]	*n*
TV	8.3	9.0	2.8	1	13	192
Blu-ray/DVD/Video	7.7	8.0	3.0	1	13	27
Tablet	8.3	9.0	3.1	2	12	31
Smartphone	8.6	10.0	2.6	1	13	100
Game console	12.0	12.0	-	12	12	1
PC	8.2	8.0	2.1	6	12	13

[a]*Maximum of 13 months of age is possible as questionnaires were included that were filled out up to 2 months after the child's first birthday.*

family TV time were found to be significant predictors of child screen time.

For the examined age group in our present study, to best of our knowledge, hitherto no data exist. However, previous studies on media consumption in older children reported a higher exposure. For example, the 2017 Common Sense Media survey showed that among American children under 2 years of age, 71% had been exposed at least once to TV, 45% to DVD/video, and 46% to mobile devices (20). In Singapore, 24% of infants up to 6-months-old had TV screen time, rising to 61% of 7–24-month-old infants. When viewing the screen time of TV, computer, and mobile devices together, one third of 6-month-old infants had screen time opposed to two thirds of the older infants (21). Together with our data, this might illustrate a trend of increased child screen time with age, as already corroborated by Duch et al. in their review (22).

Not only are children using digital media devices at an earlier age (22), but they are also exposed to a multitude of new interactive media devices (3). Nearly twenty years ago, Vandewater et al. published results showing 0–3-year-olds having an average screen time of nearly 2 hours per day, including TV, videos/DVDs, computers and video games (23). In 2007, Zimmerman et al. only considered TV and DVD/video viewing time at 2 years of age for American children (24). When looking at the German population, the ULM Spatz birth cohort reported 58% of three-year-old children watching TV/DVDs as well as using smartphones up to 1h/day and 14% for more than 1h (screen time data gathered from 2014–2016) (25). Yet, these studies do not name or differentiate between the different types of electronic media available today.

In turn, the Common Sense Media survey divided digital media use by content. The report stated that 0–2-year-olds spent on average, 40 min of TV/DVD/video time (including videos watched on mobile devices), 21 min reading/being read to and 0 min playing games on mobile devices. Also, although average child digital media time remained about the same between 2011 and 2017, a shift toward new mobile devices became apparent (20). Our data, showing initiation of digital media use primarily with TV and smartphone, could be an indicator of a similar trend beginning among infants in Germany.

Adding to evidence, we show that family TV screen time, living space per person, and being second-born are significant predictors of infant screen time. In 2015, Kabali et al. noted that

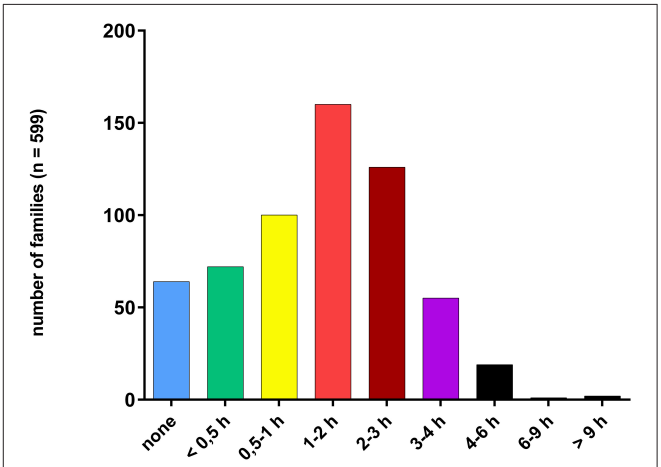

FIGURE 3 | Family TV time (in hours) on average weekday.

97 % of children (0.5–4 years old) from low-income minority families in the US had ever used a mobile device and most watched TV daily regardless of age (1). This is consistent with findings of the Common Sense Media report, showing that children from lower income households had substantially more screen time per day (3:29 h vs. 1:50 h, age group 0–8 years). Lower education and ethnic minority (African American > Hispanic > White) were also associated with significantly more child media time. Similarly, a systematic review by Duch et al. showed positive associations between screen time and child's age, BMI, and family belonging to a minority population in children between 0 and 36 months of age (22). Tandon et al. found that children of families with low socioeconomic status had more electronic media devices in the bedroom and more screen time than families with higher socioeconomic status (26). In our multivariate analysis of influencing factors for mean screen time of the infant, we saw a tendency for the maternal subjective social status (MacArthur Scale) to be a protective factor (OR 0.853, $p = 0.058$). Among other factors with a clear association to socioeconomic status, we found the family's living space to have a strong association with the infant's screen time (OR 0.567, $p = 0.007$).

In our study, a further influencing factor with a significant association to infant's screen time was the family TV time (OR

TABLE 3 | Univariable logistic regression analysis of possible predictors and infant screen time.

		Odds ratio	CI 95%	Significance (*p* value)
Infants	Sex female	0.784	0.560–1.098	0.156
	1 sibling[a]	1.443	0.998–2.085	0.051
	2 or more siblings[a]	1.209	0.621–2.353	0.577
Mothers	Age at delivery (years)	0.968	0.928–1.010	0.138
	Subjective social status	0.795	0.696–0.909	**0.001**
	Single parent	0.307	0.034–2.765	0.292
	Professional qualification low[b]	1.333	0.113–15.704	0.819
	Professional qualification medium[b]	0.243	0.027–2.199	0.208
	Professional qualification high[b]	0.161	0.018–1.464	0.105
	Employed during the child's first year of life	0.969	0.664–1.414	0.871
Fathers	Subjective social status	0.940	0.834–1.058	0.305
	Professional qualification low[c]	0.333	0.023–4.736	0.417
	Professional qualification medium[c]	0.331	0.034–3.223	0.341
	Professional qualification high[c]	0.208	0.021–2.032	0.177
	Employed during the child's first year of life	1.418	0.470–4.278	0.535
Parents	Overweight (one or both)	1.318	0.909–1.911	0.146
	One parent immigrant/foreign national[d]	1.223	0.699–2.140	0.481
	Both parents immigrants/foreign nationals[d]	1.268	0.518–3.105	0.603
Home	Living space[e]	0.610	0.433–0.860	**0.005**
	Excessive family TV time[e]	1.513	1.053–2.173	**0.025**

[a]Reference category: first-born. [b]Reference category: no maternal professional qualification. [c]Reference category: no paternal professional qualification. [d]Reference category: both parents German nationals. [e]As defined in materials and methods. Bold values indicates significant association (p<0.05) in the uni/multivariable analysis.

TABLE 4 | Multivariable logistic regression analysis of possible predictors and infant screen time* ($N = 441$, Nagelkerkes-$R^2 = 0.108$).

		Odds ratio	CI 95%	Significance (*p* value)
Infants	Sex female	0.721	0.485–1.072	0.106
	1 sibling[a]	1.715	1.093–2.692	**0.019**
	2 or more siblings[a]	1.333	0.557–3.193	0.519
Mothers	Age at delivery (years)	0.974	0.920–1.032	0.373
	Subjective social status	0.853	0.723–1.005	0.058
	Professional qualification low[b]	0.151	0.007–3.480	0.238
	Professional qualification medium[b]	0.474	0.045–5.016	0.535
	Professional qualification high[b]	0.387	0.036–4.176	0.434
Fathers	Professional qualification low[c]	0.169	0.010–2.890	0.220
	Professional qualification medium[c]	0.212	0.019–2.406	0.211
	Professional qualification high[c]	0.161	0.014–1.811	0.139
Parents	Overweight (one or both)	1.162	0.753–1.793	0.496
Home	Living space[d]	0.567	0.375–0.857	**0.007**
	Excessive family TV time[d]	1.631	1.059–2.512	**0.027**

**Including the independent variables with $p < 0.2$ in the univariable analysis. [a]Reference category: first-born. [b]Reference category: no maternal professional qualification. [c]Reference category: no paternal professional qualification. [d]As defined in materials and methods. Bold values indicates significant association (p<0.05) in the uni/multivariable analysis.*

1.631, $p = 0.027$). Interestingly, Jago et al. showed that maternal TV viewing was a stronger predictor of child TV viewing than paternal TV viewing for all age (<7 and >7 years) and gender subgroups (16). It should be noted that these associations are made from cross-sectional data, therefore the direction of the relationship between infant and family media ecology as well as sociodemographic characteristics remains to be investigated.

For young infants, the displacement of activities such as sleep and play by screen media may be particularly harmful toward their behavioral, physical, and cognitive development, not to mention their communication abilities (12). A study by Twenge et al. examined screen time and sleep duration in children from 0–17 years. Their findings showed that both portable and non-portable electronic devices influenced sleep duration for children

under age 10 (once over the age of 10, only portable devices had an effect on sleep) (27). This supports the assumption that screen time displaces valuable childhood activities. As numerous studies show, reading or being read to by parents can be supportive in language development (both maternal and foreign language abilities) (28), socio-emotional development (29) and even obesity (30) in young children. Promoting adult-child reading time may be an important protective measure against excessive screen time and stimulate positive child development.

It is important to consider the limitations of our study. First, the study design as a birth cohort with above mentioned exclusion criteria caused a selection bias. Participants are predominantly of German nationality and must be proficient German speakers. In addition, average subjective social status as a proxy for socioeconomic status is relatively high. Second, social desirability bias might play a role when parents state the family's and child's media exposure. Radesky et al. showed that 1/3 of parents underestimated and 1/3 of parents overestimated their child's amount of media use, when comparing online questionnaire to passively measured screen time via an app (31), an observation which indicates that over- and underestimation might be in a balance. Future research will provide more reliable data by directly measuring the time spent with electronic media devices in the homes. Third, in our case of 1-year-old children, child media exposure might simply be passive or background media, if for example infants are with parents while they themselves are using digital media. Still, we did not determine content or motivation of child media use at this young age and can only speculate. Lastly, as a cross-sectional study, the causal direction of the relationship between associated factors and screen time cannot be determined.

In conclusion, our study provides support that excessive family TV time is a major predictor of infant screen time. Moreover, we found smaller living spaces and having one sibling to be significant risk factors. At the age of 12 months, a proportion of 10% of the study population was already regularly exposed to digital media up to half an hour per day. Prospective studies should investigate the effect of passive media exposure, such as background TV. In addition, because child development changes rapidly in the first years, it is crucial to examine younger children and smaller age groups. We suggest that pediatric recommendations should be re-evaluated in the light of the actual exposure to digital media already in infancy and parents should be proactively counseled regarding possible effects on child development.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

KD wrote the manuscript and designed the tables. DW was responsible for the recruitment of study participants, data collection, and validation. SB performed the statistical analyses. BS-G, CA, MM, and MK contributed to the design of the study, the interpretation of the results, and the authoring of the manuscript. SK developed the study question and design, supervised the data analysis, participated in writing the manuscript, and created the figures. All authors contributed to the article and approved the submitted version.

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The Efficacy of Eye Masks and Earplugs Interventions for Sleep Promotion in Critically Ill Patients: A Systematic Review and Meta-Analysis

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Using physical devices such as eye masks and earplugs to improve to the quality of sleep in intensive care units (ICUs) is a very important issue. This study was conducted to assess the efficacy of eye masks and earplugs for sleep promotion in critically ill adult patients in the ICU based on various sleep quality assessment tools. PubMed, Scopus, Web of Science, and ProQuest were systematically retrieved until May 2021. Both randomized and non-randomized experimental and quasi-experimental studies were included if they evaluated the efficacy of eye masks and earplugs interventions on sleep outcomes in critically ill patients. The methodological quality was assessed by the Joanna Briggs Institute (JBI) critical appraisal tool. For the main outcome (sleep quality), a mean difference (MD) and confidence intervals (CIs) of 95% were determined. A total of 2,687 participants from 35 studies met the inclusion criteria. Twenty one studies were included in meta-analysis and 14 studies were included in the qualitative analysis. According to the results based on sleep quality assessment tools; overall scores of Pittsburgh Sleep Quality Index (PSQI) and Richards-Campbell Sleep Questionnaire (RCSQ), eye mask and/or earplug interventions have a positive effect on sleep quality. Based on Verran-Snyder-Halpern Sleep Scale (VSHSS), sleep disturbance was significantly lower in the intervention groups. In terms of polysomnography, the use of eye masks and/or earplugs resulted in a significant increase in total sleep time, sleep efficiency, rapid eye movement (REM) time, significant reduction of awaking, and sleep arousals index. The results of the present study suggest that the use of earplugs or eye masks, separately or combined affects sleep improvement in critically ill patients.

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INTRODUCTION

Sleep in critical care settings was demonstrated to be of a poor quality, which is associated to both environmental-related factors (artificial light, ambient noise, alarms from monitoring devices, patient-care activities monitoring, diagnostic, and therapeutic procedures) and patients-related factors (old age, underlying diseases, pain, stress, psychosis, circadian rhythm disturbances, and organ dysfunction) (1, 2). Evidence suggests that the poor quality sleep in critically ill patients can cause both psychological and physiological consequences and also affect the recovery and treatment (3). Sleep disturbances may reduce immunodeficiency function, inspiratory muscle endurance, alter patients' weaning patterns, cardiorespiratory status, and increased pain scores in critically ill patients (4). In addition, it can leads to negative psychological states such as agitation, confusion and delirium (5, 6).

Sleep promotion interventions include both pharmacological and non-pharmacological treatments. Pharmacological agents that induce sleep provide sedation and analgesia and are commonly used in the ICU setting (7). However, pharmacological interventions can have negative side effects such as impaired cognitive function, the risk of tolerance or dependency, decreased ventilation, and a disruption in normal sleep physiology (8). Additionally, drug-induced sleep is contraindicated in certain patient groups, such as non-ventilated patients with hypercapnic lung disease (9). Therefore, today there is more emphasis and recommendation on non-pharmacological interventions. However, non-pharmacological interventions for improving sleep have been found to be less effective than pharmacological methods while posing no risk of drug-related tolerance or dependency (4, 10). Several non-pharmacological interventions including utilizing physical devices (eye masks and/or earplugs), relaxation techniques (massage and foot baths), music interventions, quiet time, acupuncture, and aromatherapy were attempt to improve to the quality of sleep in ICU (10).

Evidence shows that light and noise are the main cause of sleep disorders in the ICU (11, 12). Hence, it seems that the use of eye masks and earplugs as a low-cost intervention methods of noise reduction and light control can be superior to other interventions. Several studies found that the use of earplugs and eye masks improved sleep quality (13, 14). In addition, two systematic reviews by Alway et al. (15), and Locihova et al. (16), have highlighted benefits of earplugs and eye masks for improving sleep. But so far no meta-analysis has been done in this field. Therefore, we conducted this study to examine the efficacy of eye masks and earplugs for sleep promotion in critically ill patients based on various sleep quality assessment tools.

METHODS

Search Strategy

This study was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and recommendation by the Cochrane Collaboration for programming and conducting systematic reviews and meta-analyses (17, 18). Ethical approval was obtained from the research ethics committee of Baqiyatallah University of Medical Sciences with the ethics code of IR.BMSU.REC.1398.175. In addition, this systematic review has also been registered in international prospective register of systematic reviews (PROSPERO) with the registry code of CRD42020145830. Extensive electronic search was done in the following databases and search engines: PubMed, Scopus, Web of Science, and ProQuest. Combination of medical subject heading (Mesh terms) or synonyms, "eye masks," "earplugs," and "sleep" were used for carrying out literature search until May 2021 without restrictions in date and countries. Relevant articles in the reference lists of all included published articles were also searched manually. The full search strategy is available in **Supplementary Material 1**.

Eligibility Criteria

Studies were eligible if they met all of the following inclusion criteria: (i) types of studies: randomized controlled trials (RCTs), randomized crossover studies, cluster randomized trials, and randomized or non-randomized quasi experimental (we included all studies, published or unpublished, in English and Persian language); (ii) types of participants: adult patients with stable hemodynamic condition who were admitted to ICUs, critical care units (CCUs), or in a simulated ICU conditions that is completely similar in terms of sound and light with no restrictions on gender or ethnicity; (iii) types of intervention: using eye mask and/or earplugs for improving sleep quality compare to routine standard care; (iv) outcome: the outcome measure sleep quality, which was measured by using standardized instruments including objective and/or subjective tools. Studies were excluded if they (i) enrolling participants who were diagnosed with obstructive sleep apnea or dementia or those who were terminally ill or required palliative care; (ii) conference articles, abstracts and protocols; (iii) examined a combination of other interventions (e.g., massage, foot baths, nursing interventions, valerian acupressure, and aromatherapy).

Study Selection and Data Extraction

Two investigators (S.A, A.V-A) independently screened the full-text of the articles to select the studies satisfying the inclusion criteria. Then, the data and information were extracted according to the following study characteristics required for the current review; (a) general information: first author name, publication year and country; (b) method information: study design, study setting, study participants and sample size; (c) intervention: intervention type and assessment tools for sleep quality; (d) outcome: results of sleep quality. Any disagreements during this selection and extraction process were resolved either through consensus or consultation with third investigator (F.R-B).

Risk of Bias Assessment in Included Studies

The quality assessment was performed by utilizing the Joanna Briggs Institute (JBI) critical appraisal tool (https://jbi.global/critical-appraisal-tools) for quasi-experimental and RCT studies, separately. Two reviewers independently assessed the risk of bias in each study. The RCT and quasi-experimental were evaluated

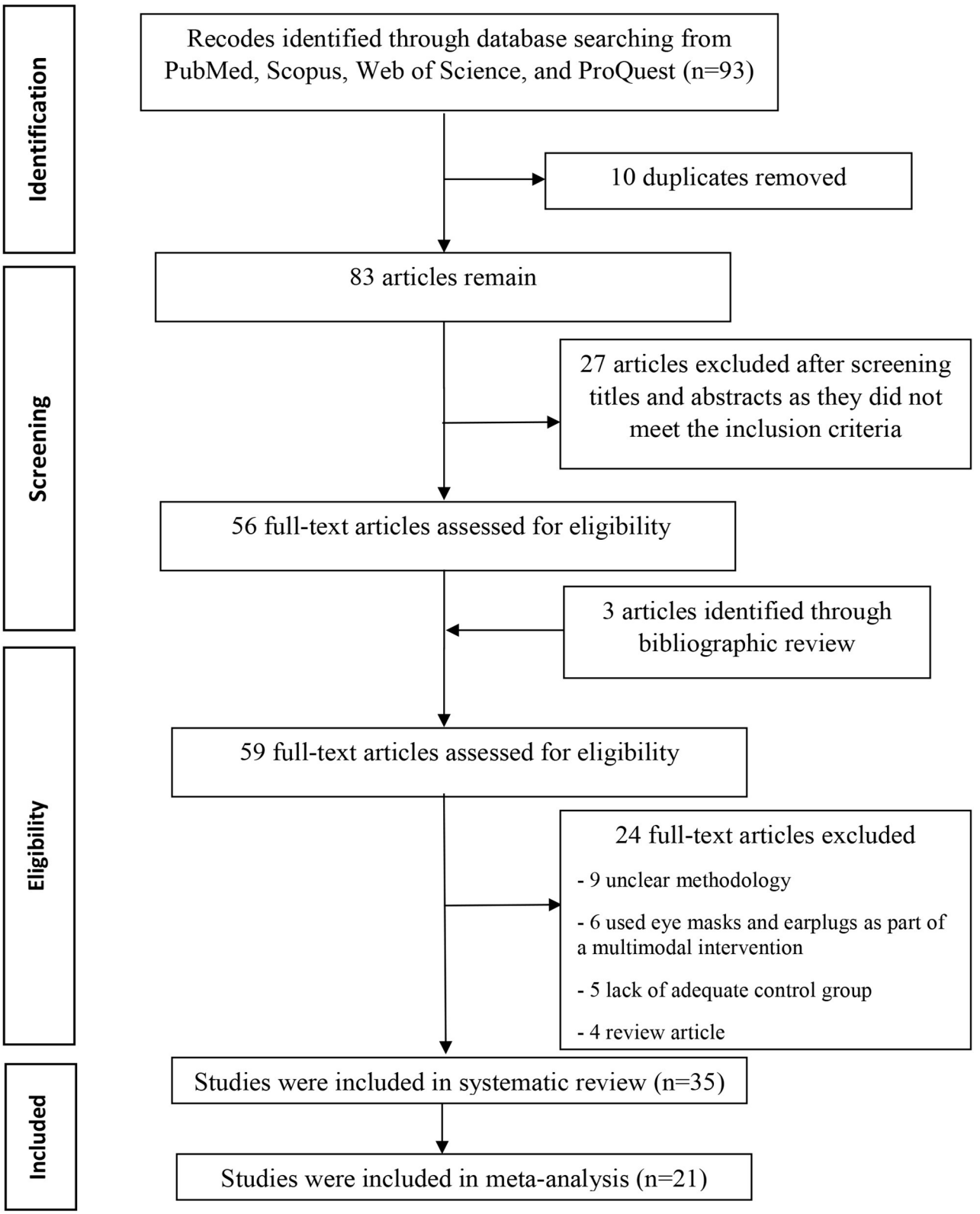


FIGURE 1 | PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart detailing the disposition of screened, included, and excluded records.

based on 13 and nine criteria, respectively. All questions were answered as yes, no, not clear, or not applicable and assessed individually. Eligible studies were rated according to the dictionary and guidelines of the tool. After evaluating all the components of the study, the overall rating was determined using the criteria set out in the tool. Based on the number of "yes" responses, a rating of good = (≥10 yes), medium = (6–9 yes), and poor = (≤5 yes) was assigned to each RCT studies. For quasi-experimental studies, a rating of good = (≥7 yes), medium = (4–6), and poor = (≤3 yes) was assigned for nine questions (**Supplementary Material 1**).

Statistical Analysis

The statistical analyses were conducted by STATA 16.0 (STATA Corp; College Station, Texas, USA) software. Included studies used different scales and instruments to measure sleep quality. Meta-analyses performed if outcomes from two or more studies with similar sleep quality assessment tool were available. To compare the use of earplugs or eye masks or both vs. no use of earplugs or eye masks, we used the mean difference (MD) with a 95% confidence interval (CI) for continuous data. Random effects models were performed to balance the effect quantity of each study. Statistical heterogeneity was assessed by I^2, with $I^2 > 75\%$ regarded as high heterogeneity. $P < 0.05$ was considered statistically significant. Moreover, to assess the publication bias, the Egger's (19) and Begg's (20) tests were conducted.

RESULTS

Study Selection

The literature search results and the screening process are summarized in **Figure 1**. The search strategy yielded 93 records. A total of 37 records were excluded because they did not meet all predefined inclusion criteria or were duplicated. Moreover, we reviewed the bibliographies of the retrieved articles and found three more relevant studies. Fifty-nine full-text articles were evaluated for eligibility. Twenty-four studies were excluded due to unclear methodology, involve the use of eye masks and earplugs as part of a multimodal intervention, and lack of adequate control group. Thus, 35 full-text articles with 2,678 participants were included in the study. Meta-analyses were performed if outcomes from two or more studies with similar scales and sleep quality assessment tool were available. Therefore, 21 studied were included in the meta-analysis and the others (14 studies) were included in the qualitative analysis.

Characteristics of the Studies Included

The characteristics of selected studies are presented in **Table 1**. The studies were conducted in USA (14, 21, 36, 48, 50, 51), UK (13, 22, 43), Belgium (23), China (24, 25, 27, 38), Iran (26, 28–32, 35, 39, 42, 49), France (33, 34), India (37, 41, 46), Australia (40), Jordan (44), Canada (45), Turkey (47), Egypt (52), and Singapore (53). Twenty eligible studies were RCTs (23, 24, 26, 28, 29, 33–35, 37–43, 46, 48, 51–53), six were randomized quasi-experimental (3, 21, 25, 27, 30), four were pre-post studies (5, 22, 31, 47), two were randomized cross-over studies (32, 49), and three were non-randomized quasi-experimental (13, 14, 45). Twenty-four trials were conducted in ICU which including medical ICU (5, 41, 46), cardiac ICU (13), general ICU (22, 33, 37, 44, 53), surgical ICU (32, 40, 48, 51), mixed medical and surgical ICU (23, 43), mixed medical and cardiac ICU (14), mixed medical and general ICU (42, 45, 50), neurology ICU (47), cardiac surgery intensive care unit (CSICU) (24, 52), and post-anesthesia care units (PACUs) (34). Nine trials were conducted in coronary care unit (CCU) (26–31, 35, 39, 49), and three trials were conducted in simulated ICU environment among healthy subjects (21, 25, 38).

Several sleep assessment tools have been used in the reviewed studies. The majority of the publications used subjective tools, while only five of them employed the form of objective evaluation (21, 25, 33, 38, 46). Polysomnography (PSG) was the only form of objective method of assessment that used in these studies. Among the subjective tools for sleep evaluation, the Richards-Campbell Sleep Questionnaire (RCSQ) (5, 24, 44, 46–48, 51–54), and the Verran and Snyder-Halpern Sleep Scale (VSHSS) (14, 27, 31, 32, 37, 42, 45, 49) were the most frequently used in 11 and eight studies, respectively. Five trials used Pittsburgh sleep quality index (PSQI) as sleep assessment tool (26, 28, 29, 35, 39). Five studies (13, 22, 23, 41, 43), used their original sleep questionnaires. In addition, three studies used variable assessment tools such as Medical Outcomes Study Sleep (MOSS) score (34), Insomnia Severity Index (ISI) questionnaire (50), and Leeds Sleep Evaluation Questionnaire (LSEQ) (30).

Sleep Quality Outcomes Based on PSQI

Five studies (26, 28, 29, 35, 39) with 312 participants (156 patients in each control and treatment group), reported data on sleep outcomes using the PSQI scale. A study by Babaii et al. (35), reported the overall scale of PSQI *via* median (IQR), while the others reported by mean (SD). Thus, the meta-analysis was performed in the four studies (26, 28, 29, 39), and the qualitative analysis was conducted in the latter one study because the data of them could not be combined. A total PSQI score ranges from 0 to 21. A higher score suggests worse overall sleep quality, and a total cut-off PSQI score < 5 indicates good sleep (55). The meta-analysis of combined data conducted, showed a positive effect of used eye masks and/ or earplugs interventions on overall sleep quality based on PSQI score (MD= −5.02, 95% CI = −6.16 to −3.89, $P < 0.001$), with substantially heterogeneity among the studies ($I^2 = 59.01\%$, $P = 0.07$) (**Figure 2A**). The result revealed that the average PSQI score of the eye masks and/ or earplugs group was 5.02 points lower than that of the control group and indicating that the interventions might be beneficial to improve overall sleep quality. *P*-values of Egger and Begg tests indicated non-significant coefficient values for publication bias (Egger test: $P = 0.635$ and Begg test: $P = 0.065$) (**Figure 2B**). The PSQI scale consists of seven components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. Three studies (26, 28, 29), provided the data on the PSQI components, thus the meta-analyses were conducted to explore the efficacy of eye masks and/or earplugs interventions on sleep components, as shown in **Table 2**. No significant results were obtained for sleep components based on PSQI score ($P > 0.05$) (**Supplementary Figures 1–3**).

TABLE 1 | Characteristics and outcomes of all studies included.

First author, year, country	Study type	Setting	Sample size	Intervention	Assessment tools for sleep quality	Outcomes measure	Conclusion
Wallace, 1999, US (21)	Quasi-experimental randomized	Healthy persons in simulated ICU environment	Total: 6 I: 3 C: 3	Earplugs	PSG	REM latency (mean): 106.7 (SD:53.0) vs. 147.8 (53.0); $P = 0.02$ REM phase (mean: 19.9 (SD: 4.5) vs. 14.9 (5.4); $P = 0.04$	Positive effect on improved of REM, REM latency and sleep efficiency index
Richardson, 2007, UK (13)	Quasi-experimental Non-randomized	Cardiac ICU	Total: 62 I: 34 C: 28	Eye masks and earplugs	Original questionnaires created by authors	≥4 h sleep in intervention group: 15 (44.1%) ≥4 h sleep in control group: 10 (35.7%)	Improved quantity sleep in intervention group, no improvement in sleep quality
Scotto, 2009, US (14)	Quasi-experimental Non-randomized	Medical and cardiac ICU	Total: 88 I: 49 C: 39	Earplugs	VSHSS	Mean difference of sleep items score between two groups was (−3.253, $P = 0.002$)	Total sleep satisfaction scores were significantly better for the intervention group
Jones, 2008–2009, UK (22)	Pre-post study	General ICU	Total: 100 pre: 50 post: 50	Eye masks and earplugs	original questionnaires created by Richardson et al. (13)	≥4 h sleep in pre-intervention group: 23 (46%) ≥4 h sleep in post-intervention group: 24 (48%)	Patients reported sleeping for longer periods using earplugs and eye masks
Van Rompaey, 2008–2010, Belgium (23)	RCT	Medical and surgical ICU	Total:136 I: 69 C: 67	Earplugs	Original questionnaires created by authors	Sleeping with earplugs showed a significantly better sleep after the first night ($P = 0.042$)	Positive effects on sleep quality
Hu, 2009, China (24)	RCT	Cardiac Surgical ICU (CSICU)	Total: 45 I: 20 C:25	Eye masks and earplugs + relaxing music	RCSQ	Significant improved of subjective sleep quality and components in the intervention group	Positives effects of eye masks and earplugs on sleep quality
Hu, 2010, China (25)	Quasi-experimental randomized	Healthy persons in simulated ICU environment	Total: 14 I: 7 C: 7	Eye masks and earplugs	PSG	Improved REM sleep, shorter REM latency, and fewer arousals, ($P < 0.05$)	Positives effects of eye masks and earplugs on sleep quality
Daneshmandi, 2010, Iran (26)	RCT	Coronary care unit (CCU)	Total: 60 I: 30 C: 30	Eye masks	PSQI	Mean score of overall PSQI after intervention in test and control group was (4.86 ± 1.88 and 8.43 ± 1.97; $P < 0.05$)	Significant improved of subjective sleep quality and components in the intervention group
Ryu, 2010, China (27)	Quasi-experimental randomized	Coronary care unit (CCU)	Total: 58 I: 29 C:29	Eye masks and earplugs with relaxing music	VSHSS	Sleeping quantity: (279.3 ± 43.9 vs. 243.1 ± 42.6, $P = 0.002$ Sleep quality (36.1 ± 5.6 vs. 29.4 ± 3.8, $P < 0.001$) between groups	Sleep-inducing music significantly improved sleep quality in patients
Nieseh, 2010, Iran (28)	RCT	Coronary care unit (CCU)	Total: 60 I: 30 C: 30	Eye masks and earplugs	PSQI	Significant differences in PSQI was observed after intervention between groups (experimental group 6 ± 2.3, control group 8.8 ± 2.4 ($p < 0.05$)	Using the ear and eye protect device significantly improved sleep quality
Neyse, 2011, Iran (29)	RCT	Coronary care unit (CCU)	Total: 60 I: 30 C: 30	Earplugs	PSQI	Significant differences in PSQI was observed after intervention between groups (experimental group 6.3 ± 2.1, control group 8.4 ± 1.9 ($p < 0.05$)	Using earplugs can improve sleep quality in patients

(Continued)

TABLE 1 | Continued

First author, year, country	Study type	Setting	Sample size	Intervention	Assessment tools for sleep quality	Outcomes measure	Conclusion
Baghaei, 2011–2012, Iran (30)	Quasi-experimental randomized	Coronary care unit (CCU)	Total: 40 I: 20 C: 20	Eye masks	Leeds sleep evaluation questionnaire (LSEQ)	After intervention, the average total sleep score in control group was 4.8 ± 0.5, while in the eye mask group it was 6.7 ± 1.1 ($P < 0.001$)	Using of eye mask improves sleep quality in patients hospitalized in intensive cardiac care units
Mashayekhi, 2012, Iran (31)	Pre and post design	Coronary care unit (CCU)	Total: 60 I: 30 C: 30	Eye masks	VSHSS	In sub scale "effectiveness," mean score of sleep quality was 255.33 ± 41.1 before intervention and 291.50 ± 38.9 after intervention	Using eye mask have statistically significant increased the quality of sleep in subscales disturbance and effectiveness
Yazdannik, 2012, Iran (32)	cross-over RCT	Surgery ICU	Total: 50 I: 25 C: 25	Eye masks and earplugs	VSHSS	Significant positive effects on sleep disturbance ($P < 0.001$) sleep supplementation ($P < 0.01$) sleep effectiveness ($P = 0.03$)	Using of eye mask improves sleep quality in patients
Demoule, 2011–2013, France (33)	RCT	General ICU	Total: 51 I: 23 C: 28	Eye masks and earplugs	PSG	- Prolonged awakenings were less frequent in the intervention group (21 vs. 31, $P = 0.02$)	No significant difference was observed between two groups in terms of sleep quality
Guen, 2013, France, (34)	RCT	Post-anesthesia care units (PACUs)	Total: 41 I: 20 C: 21	Eye masks and earplugs	Medical Outcome Study Scale (MOSS) and the Spiegel Scale (SS)	In the intervention group, sleep disruptions evaluated with the MOSS scale were fewer [4 (1–7) vs. 7 (3–10), $p < 0.05$]	Using of eye mask improves sleep quality in patients
Babaii, 2013 Iran (35)	RCT	Coronary care unit (CCU)	Total: 60 I: 30 C: 30	Eye masks	PSQI	Median (IQR) score of overall PSQI after intervention in the experimental group were significantly lower than those in the control group [3 (5–2) vs. 10 (12–7), $P < 0.05$]	Using of eye mask improves sleep quality in patients
Kamdar, 2013, US (36)	Pre-post test study	Medical ICU	Total: 300 I: 110 C: 185	Earplugs	RCSQ	The use of earplugs and eye masks significant improved sleep quality $P = 0.02$	Improvement quality of sleep
Bajwa, 2014, India (37)	RCT	General ICU	Total: 100 I: 50 C: 50	Eye masks and earplugs	VSHSS	sleep fragmentation (14.6 ± 3.44 vs. 4.19 ± 3.58), sleep latency (6.05 ± 1.88 vs. 1.70 ± 1.66), sleep quality (10.5 ± 2.52 vs. 2.14 ± 2.29), sleep length (8.95 ± 2.47 vs. 2.36 ± 2.46), sleep supplementation (11.8 ± 3.26 vs. 4.10 ± 2.33) in intervention and control groups, respectively	Improvement quality of sleep
Huang, 2014, China (38)	RCT	Healthy persons in simulated ICU environment	Total: 40 I: 20 C: 20	Eye masks and earplugs	PSG	Less awakenings and shorter sleep onset latency in the intervention group ($P < 0.05$)	Improvement quality of sleep

(Continued)

TABLE 1 | Continued

First author, year, country	Study type	Setting	Sample size	Intervention	Assessment tools for sleep quality	Outcomes measure	Conclusion
Cheraghi, 2104, Iran (39)	RCT	Coronary care unit (CCU)	Total: 72 I: 36 C: 36	Earplugs	PSQI	The mean ± SD of quality of sleep for the intervention group using earplugs decreased from 8.11 ± 3.00 (before the intervention) to 6.00 ± 2.30 (after the intervention). It increased from 6.33 ± 3.08 to 8.80 ± 2.45 for the control group ($P = 0.001$)	Using of earplugs improves sleep quality in patients hospitalized in intensive cardiac care units
Litton, 2015–2016, Australia (40)	RCT	Surgery ICU	Total: 40 I: 20 C: 20	Earplugs	RCSQ	The median RCSQ sleep summary scores were 43 (IQR, 20–58) and 45 (IQR, 29–64) for the earplugs and no earplugs groups, respectively (median difference, 2; 95% CI,−21 to −25; $P = 0.58$)	No significant difference was observed between two groups in terms of sleep based on RCSQ
Chaudhary, 2016, India (41)	RCT	Medical ICU	Total: 60 I: 30 C: 30	Eye masks and earplugs	Original questionnaires created by authors	The sleep quality score was improved after the administration of earplugs and eye mask among both the groups ($P < 0.001$)	Improvement quality of sleep
Sharafi, 2016, Iran (42)	RCT	General and medical ICU	Total: 73 I: 36 C: 37	Eye masks and earplugs	VSHSS	Sleep quality score in intervention group and control group were 45.41 ± 3.78 and 45.45 ± 5.61, respectively.	No significant difference was observed between the groups
Sweity, 2017, UK (43)	RCT	Medical and surgical wards	Total: 206 I: 109 C: 97	Eye masks and earplugs	Original questionnaires created by authors	Sleep quality was significantly higher in intervention group, (5.09 ± 2.05 vs. 6.33 ± 2.13, mean difference was 1.24, $P < 0.001$)	Improvement quality of sleep
Bani Younis, 2017, Jordan, (44)	Quasi-experimental Randomized	General ICU at 2 Hospital	Total: 103 I: 52 C: 51	Eye masks and earplugs	RCSQ	The mean RCSQ scores were (47.2 ± 16.5 vs. 36.2 ± 15.1, $P < 0.001$) for the intervention and control groups, respectively	Improvement quality of sleep
Dobing, 2017, Canada, (45)	Quasi-experimental Non-randomized	General and medical	Total: 81 I: 40 C: 41	Eye masks and earplugs	VSHSS	Sleep disturbance (median 420 vs. 359, $p = 0.19$), efficacy (median 169 vs. 192, $p = 0.29$), and supplementation (median 97 vs. 100, $p = 0.51$) scales were not significant difference between groups	No significant difference was observed between the groups
Arttawejkul, 2017–2018, India (46)	RCT	Medical ICU	Total: 17 I: 8 C: 9	Eye masks and earplugs	PSG and RCSQ	Polysomnographic parameters including total sleep time, sleep efficiency, wake after sleep onset, sleep latency, % rapid eye movement (REM) sleep, and % N3 sleep were similar between two groups ($P > 0.05$)	Based on PSG sleep quality domains were similar between groups and subjective sleep quality according to RCSQ score did not demonstrate the difference between the groups

(Continued)

TABLE 1 | Continued

First author, year, country	Study type	Setting	Sample size	Intervention	Assessment tools for sleep quality	Outcomes measure	Conclusion
Koçak, 2017–2018, Turkey (47)	Quasi-experimental non-randomized	Neurology ICU	Total: 64 I: 32 C: 32	Eye masks and earplugs	RCSQ	The RCSQ mean (SD) pretest and posttest scores were 50.21 (16.02) and 68.50 (17.57), respectively, for the experimental group and 55.34 (16.62) and 49.03 (15.53), respectively, for the control group	Improvement quality of sleep
Obanor, 2018, US (48)	RCT	Surgical ICU	Total: 23 I: 12 C: 11	Eye mask s and earplugs	RCS)	Postoperative days 1 and 2 respectively, aggregate mean RCSQ scores were (29.42 ± 25 and 38.33 ± 25) in the control group ($n = 9$) vs. (54.77 ± 23) and (65.22 ± 24) in the intervention group ($n = 14$)	Improvement quality of sleep
Baghaie Lakeh, 2018, Iran (49)	Cross-over RCT	Coronary care unit (CCU)	Total: 96 I: 48 C: 48	Earplugs	VSHSS	In the first night; the use of earplugs significantly reduced the quality of sleep disturbance domain in both groups A and B ($P = 0.0001$ and $P = 0.021$, respectively), and the supplementary sleep domain in group A ($P = 0.027$).	No significant difference was observed between the groups
Ho, 2018–2019, US (50)	Non-Randomized Control Trial	General medical	Total: 215 I: 109 C: 106	Eye masks and earplugs	Insomnia severity index (ISI) questionnaire	No significant adjusted OR in terms of insomnia (OR: 0.8, 95% CI: 0.34–1.87, $p = 0.61$) Satisfaction score: (4.22 ± 1.08 vs. 4.36 ± 0.86, $p > 0.05$) duration of stay: (5.14 ± 6.75 vs. 5.47 ± 6.08, $p > 0.05$)	No significant difference was observed between the groups
Obanor, 2018–2019, US (51)	RCT	Surgical ICU	Total: 87 I: 44 C: 43	Eye masks and earplugs	RCSQ	Compared with the control group's average RCSQ total score of 47.3 (95% CI, 40.8–53.8), the intervention group's average RCSQ total score was significantly higher at 64.5 (95% CI, 58.3–70.7; $P = 0.0007$)	Improvement quality of sleep
Mahran, 2107, Eygept (52)	RCT	Cardiac surgery intensive care unit (CSICU)	Total: 66 I: 31 C: 35	Eye masks	RCSQ	A statistically significant difference was found between groups in mean total RCSQ score over the 3-day study period ($P = 0.001$), with the intervention group reporting better sleep quality	Improvement quality of sleep
Leong, 2018–2019, Singapore (53)	RCT	General ICU	Total: 93 I: 48 C: 45	Eye masks and earplugs	RCSQ	Median [IQR (range)] sleep scores were 64 [38–74 (0–100)] and 60 [44–82 (18−100)] for the control and intervention groups, respectively ($P = 0.310$)	No significant difference was observed between the groups

I, Intervention group; C, Control group; PSG, Polysomnography; RCSQ, Richards-Campbell Sleep Questionnaire; VSHSS, Verran-Snyder-Halpern Sleep Scale; PSQI, Petersburg's Sleep Quality Index.

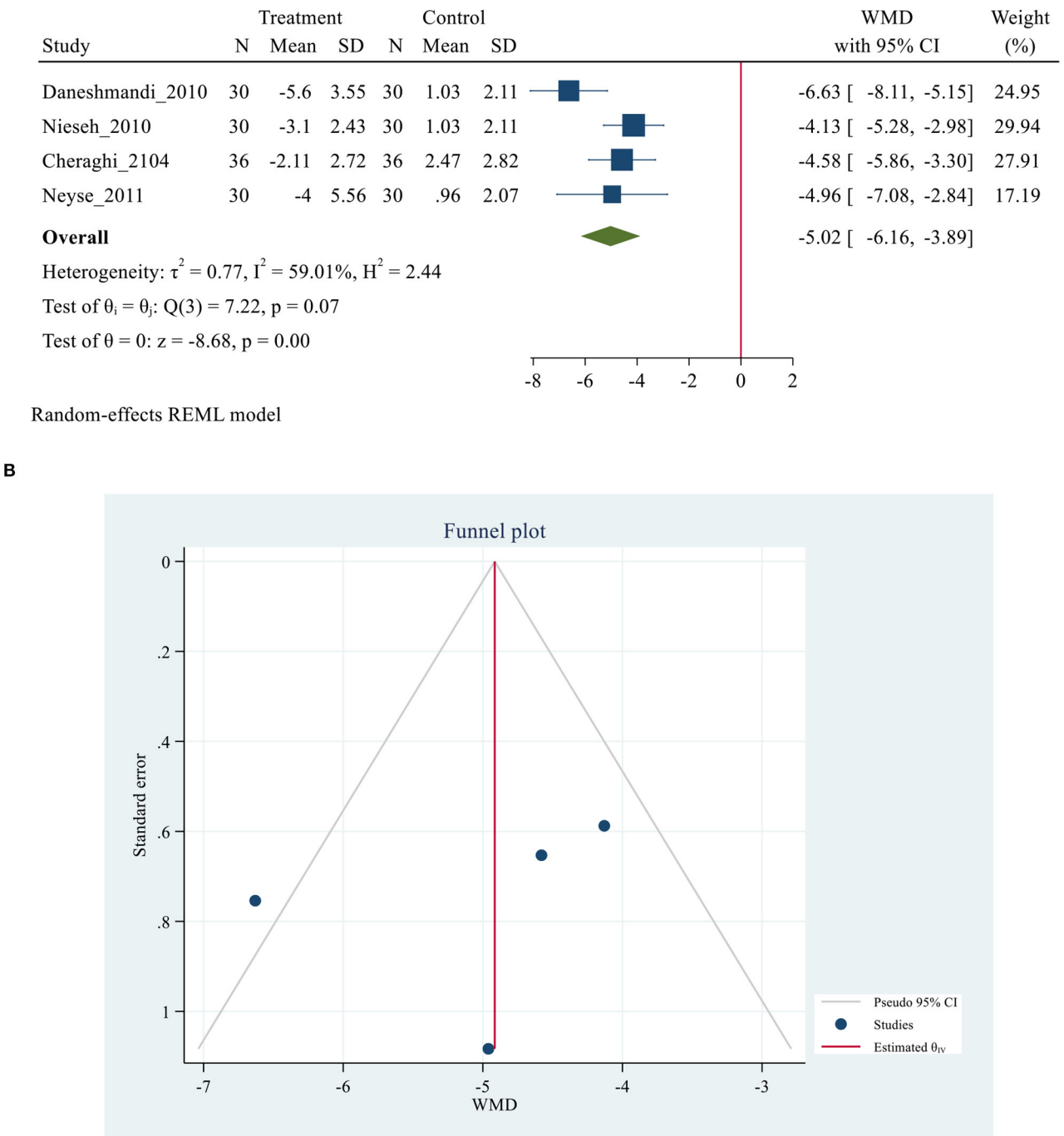


FIGURE 2 | (A) Forest plot of mean difference (MD) for sleep quality based on PSQI between intervention and control groups. **(B)** Funnel plot showing publication bias on PSQI -based sleep quality.

Sleep Quality Outcomes Based on RCSQ

Ten studies (3, 5, 24, 40, 46–48, 51–53), with 1,078 participants (568 and 510 patients in the intervention and control group, respectively), reported data on sleep outcomes using the RCSQ scale. RCSQ responses were graded on a 0–100 mm visual analog scale, with higher scores indicating better sleep. A score of 0–25 indicates poor sleep, while a score of 76–100 indicates good sleep (56). The RCSQ mean score of 11 studies for intervention groups was significantly higher than the mean score of the control groups (55.01 ± 15.43 vs. 40.15 ± 14.71, $P = 0.007$). The

TABLE 2 | Efficacy of eye masks and/or earplugs interventions for sleep components based on PSQI.

Sleep components	Pooled MD (95% CI)	*P*-value	I^2 (%)	Egger *P*-value	Begg *P*-value
Sleep quality	−0.12 (−0.32, 0.09)	0.26	31.3	0.225	0.292
Sleep latency	−0.24 (−0.55, 0.07)	0.13	70.8	0.065	0.055
Sleep duration	−0.12 (−0.35, 0.11)	0.30	60.5	0.377	0.500
Habitual sleep efficiency	−0.11 (−0.38, 0.15)	0.40	59.9	0.067	0.296
Sleep disturbance	−0.34 (−0.81, 0.13)	0.16	90.2	0.060	0.500
Use of sleeping medications	−0.05 (−0.83, 0.73)	0.90	95.5	0.085	0.500
Daytime dysfunction	−0.51 (−1.21, 0.18)	0.15	94.1	0.052	0.296

MD, Mean Difference; CI, Confidence Interval.

meta-analysis demonstrated a positive effect of using eye masks and/or earplugs on overall sleep quality based on RCSQ (MD = 11.46, 95% CI = 7.04–15.88, $P < 0.001$). However, substantial heterogeneity was also observed across the studies ($I^2 = 88.70\%$. $P < 0.001$). The results showing that the average RCSQ score of the treatment group was 11.46 points higher than that of the control group and indicating that the intervention might be beneficial to improve overall sleep quality based on RCSQ score in critically ill patients (**Figure 3A**). *P*-values of Egger and Begg tests indicated non-significant coefficient values for publication bias (Egger test: $P = 0.269$ and Begg test: $P = 0.692$) (**Figure 3B**). The RCSQ is a 5-item questionnaire that is used to assess sleep depth, latency, number of awakenings, efficiency, and sleep quality. Five studies (3, 24, 40, 48, 52), provided the data on the five-subdomain of RCSQ, thus the meta-analyses were conducted to explore the efficacy of eye masks and/or earplugs interventions on sleep subdomains based on RCSQ, as shown in **Table 3**. Significant results were obtained for all subdomains; sleep depth (MD = 9.88, 95% CI = 7.97–11.80, $P < 0.001$), sleep latency (MD = 13.17, 95% CI = 7.45–18.9, $P < 0.001$), number of awakenings (MD = 10.87, 95% CI = 8.90–12.84, $P < 0.001$), sleep efficiency (MD = 15.36, 95% CI = 7.27–23.46, $P < 0.001$), and sleep quality (MD = 12.59, 95% CI = 6.50–18.68, $P < 0.001$) (**Supplementary Figures 4–6**).

Sleep Quality Outcomes Based on VSHSS

Eight studies (14, 27, 31, 32, 37, 42, 45, 49), with 606 participants (307 and 299 patients in the intervention and control group, respectively), reported data on sleep outcomes using the VSHSS scale. Of these 8 studies, only three studies (31, 32, 49), were able to combine their data and implement meta-analysis on them. The VSHSS scale is a visual scale that evaluates the three domains of sleep disturbance (Seven items), effectiveness (Five items) and supplementary sleep (Four items) with separate scoring. Each item is answered by marking the samples on a graded vector with scores varies from 0 to 100 mm (57). Lower scores in sleep disturbance and supplementary sleep and higher scores in the effectiveness of sleep domains indicate a more satisfying sleep quality (57). Three trials reported the sleep disturbance and effectiveness sleep domains (31, 32, 49). However, only two trials reported the supplementary sleep domain *via* VSHSS (31, 49). The meta-analysis demonstrated a positive effect of using eye masks and/or earplugs on domains of sleep disturbance (MD = −19.82, 95% CI= −35.54−4.11, $P < 0.001$). However, substantial heterogeneity was also observed across the studies ($I^2 = 95.67\%$. $P < 0.001$). The result showing that the average of sleep disturbance of the treatment group was 19.82 points lower than that of the control group and indicating that the interventions might be beneficial to improve sleep disturbance in critically ill patients (**Figure 4A**). However, no significant differences were obtained for effectiveness and supplementary sleep domain between treatment and control groups (**Figures 4B,C**). *P*-values of Egger and Begg tests indicated non-significant coefficient values for publication bias for sleep disturbance (Egger test: $P = 0.067$ and Begg test: $P = 0.111$), effectiveness (Egger test: $P = 0.052$ and Begg test: $P = 0.067$), and supplementary sleep (Egger test: $P = 0.063$ and Begg test: $P = 0.296$).

Sleep Quality Outcomes Based on PSG

Five studies (21, 25, 33, 38, 46), with 128 participants (61 and 67 subjects in the intervention and control group, respectively), reported data on sleep outcomes using PSG. Three studies were performed in simulated ICU environment among healthy individuals and reported the outcomes on the mean (SD) scale (21, 25, 38). While two other studies have been done in the ICU and reported the results at different scales (33, 46). Therefore, meta-analysis was performed in three studies that could combine data (21, 25, 38). According to the results of these studies, sleep in simulated ICU environment was shown to be significantly fragmented, with prolonged sleep latencies, frequent arousals, a reduction or absence of rapid eye movement (REM) stage of sleep, an increase in stage 2 of non-REM sleep, and a reduction or absence of deep or slow-wave stage 3 of non-REM sleep. The pooled analyses were conducted to explore the efficacy of eye masks and/or earplugs interventions on sleep quality based on PSG, as shown in **Table 4**. Meta-analysis findings showed that the use of eye masks and/or earplugs resulted in a significant increase in total sleep time (MD = 25.47, 95% CI = 8.05–42.90, $P < 0.001$), sleep efficiency (MD = 0.06, 95% CI = 0.01–0.1, $P = 0.01$), REM (MD = 4.66, 95% CI = 2.7–6.62, $P < 0.001$), and a significant reduction of awaking (MD = −8.40, 95% CI = −10.15−6.64, $P < 0.001$), and sleep arousals index (MD = −5.17, 95% CI = −6.58−3.75, $P < 0.001$) (**Supplementary Figures 7–10**).

A

Study	Treatment N	Mean	SD	Control N	Mean	SD	WMD with 95% CI	Weight (%)
Hu_2009	20	56.9	25.48	25	24.22	19.32	32.68 [19.60, 45.76]	5.02
Kamdar_2013	175	53.2	27.3	110	54.5	27.1	-1.30 [-7.79, 5.19]	7.51
Younis_2017	52	47.2	16.52	51	36.29	15.1	10.91 [4.79, 17.03]	7.65
Arttawejkul2018	8	58.5	5.26	9	56.4	5.17	2.10 [-2.86, 7.06]	8.06
Koçak_ 2018	32	68.5	17.57	32	49.03	15.53	19.47 [11.35, 27.59]	6.88
Mahran_2107_a	31	46.82	8.49	35	36.79	7.31	10.03 [6.22, 13.84]	8.41
Mahran_2107_b	31	60.44	6.87	35	50.23	6.04	10.21 [7.10, 13.32]	8.59
Mahran_2107_c	31	70.12	10.08	35	59.19	7.62	10.93 [6.65, 15.21]	8.27
Obanor_2018_a	12	65.22	24	11	38.33	25	26.89 [6.86, 46.92]	3.15
Obanor_2018_b	12	54.77	23	11	29.42	25	25.35 [5.74, 44.96]	3.24
Obanor_2019	44	64.5	21.1	43	47.3	21.9	17.20 [8.16, 26.24]	6.52
Amirifar_unpublished_a	52	37.44	7.36	48	22.22	9.87	15.22 [11.82, 18.62]	8.52
Amirifar_unpublished_b	52	31.59	7.65	48	18.15	6.36	13.44 [10.67, 16.21]	8.66
Litton_2016	20	43	27.94	20	45	27.94	-2.00 [-19.32, 15.32]	3.77
Leong_2019	48	60	27.94	45	64	26.47	-4.00 [-15.08, 7.08]	5.73
Overall							11.46 [7.04, 15.88]	

Heterogeneity: $\tau^2 = 56.61$, $I^2 = 88.70\%$, $H^2 = 8.85$

Test of $\theta_i = \theta_j$: Q(14) = 65.67, p = 0.00

Test of $\theta = 0$: z = 5.08, p = 0.00

-20 0 20 40

Random-effects REML model

B

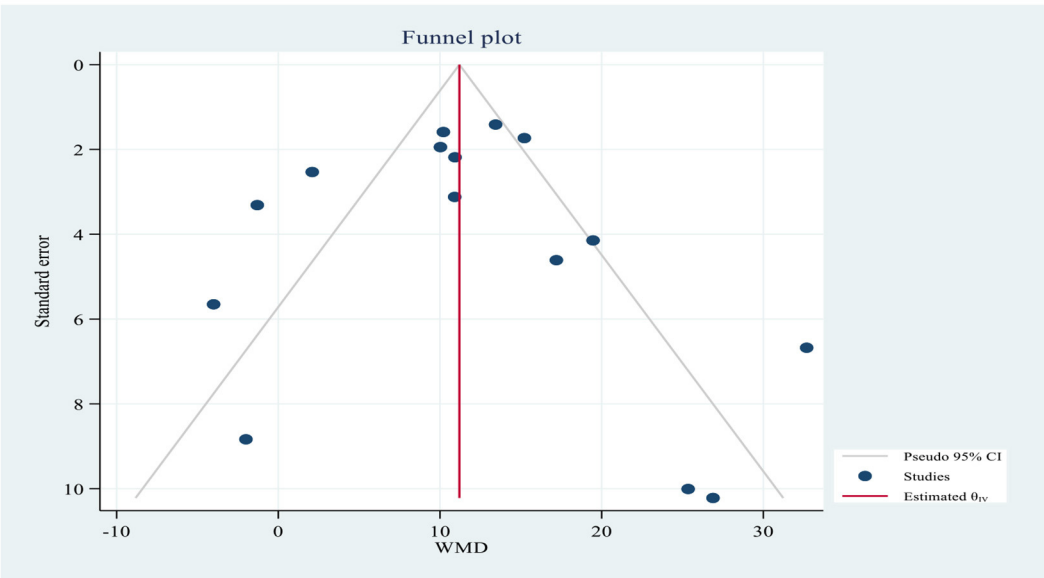


FIGURE 3 | (A) Forest plot of mean difference (MD) for sleep quality based on RCSQ between intervention and control groups. **(B)** Funnel plot showing publication bias on RCSQ -based sleep quality.

TABLE 3 | Efficacy of eye masks and/or earplugs interventions for sleep components based on RCSQ.

Sleep components	Pooled MD (95% CI)	*P*-value	I^2 (%)	Egger *P*-value	Begg *P*-value
Sleep depth	9.88 (7.91, 11.8)	<0.001*	0	0.357	0.368
Sleep latency	13.17 (7.45, 18.9)	<0.001*	82.1	0.060	0.368
Number of awakening	10.87 (8.9, 12.84)	<0.001*	0	0.799	0.368
Sleep efficiency	15.36 (7.27, 23.4)	<0.001*	91.1	0.561	0.368
Sleep quality	12.59 (6.5, 18.68)	<0.001*	82.7	0.386	0.368

*$P < 0.05$ was considered as significant.
MD, Mean Difference; CI, Confidence Interval.

DISCUSSION

In the study, the effect of using eye masks and/or earplugs on quality of sleep was investigated in critical care setting and simulated environment of intensive care. Our study systematically reviewed 36 available studies, and 21 studies were included in the meta-analyses based on various sleep quality assessment tools. The results indicated that eye masks and/or earplugs interventions might have a positive effect on the sleep quality in critically ill patients. According to the overall PSQI sleep quality score, the eye masks and/or earplugs interventions had a positive effect on the sleep quality (26, 28, 29, 39). However, no significant difference was identified for sleep components based on PSQI score (26, 28, 29). Eleven studies reported the efficacy of eye masks and/or earplugs interventions on the overall sleep quality of critically ill patients using the RCSQ, and statistical significance in meta-analyses was observed, especially with respect to sleep depth, sleep latency, number of awakenings, sleep efficiency, and sleep quality (3, 5, 24, 40, 46–48, 51–53). Based on three studies, a positive effect of using eye masks and/or earplugs on domains of sleep disturbance *via* VSHSS was observed (31, 32, 49). Three studies measured sleep variables objectively by using PSG in a simulated critical care environment (21, 25, 38). Because of these similar conditions, we used these three studies. However, the results of these studies are not generalizable and should be interpreted with caution. The pooled results for the intervention groups showed beneficial impact ($P < 0.05$) for increased sleep period, sleep efficiency, REM sleep and decreased awaking and sleep arousals index. But the results should be treated with caution because of the studies were conducted in a simulated ICU environment with healthy adults and small sample sizes.

Eight studies used various instruments to evaluate the effectiveness of eye masks and earplugs on the sleep quality of ICU patients. One author, Le Guen et al. (34), used the Medical Outcome Study Scale (MOSS) and the Spiegel Scale (SS) and confirmed a statistically significant improvement after the intervention ($P = 0.006$). A non-randomized controlled trial study by Ho et al. (50), used the Insomnia Severity Index (ISI) questionnaire and they did not find any statistical significant difference between the intervention and control groups. In an experimental study by Baghaei et al. (30), 40 eligible patients were randomly assigned to control and eye mask groups and the Leeds Sleep Evaluation Questionnaire (LSEQ) was used to assess the effect of eye masks on nighttime sleep in CCU patients. According to the findings of this study, the use of eye masks improves sleep. Other authors; Richardson et al. (13), Jones et al. (22), Van Rompaey et al. (23), Sweity et al. (43), and Chaudhary et al. (41), employed their original questionnaires, which included a varied amount of items with different content focus. Due to the significant variety or lack of further details of questionnaires, these studies were not included in the meta-analysis. However, all of them had consensus on the positive effect of using eye masks and earplugs on the subjective quality of sleep.

In a review of 11 studies by Xie et al. (58), showed that noise was the most important cause of sleep disorders in critical care setting. The most disturbing noise sources were staff conversations and alarms, especially those with high frequencies. In addition to reducing noise by earplugs, this improvement of the sleep pattern *via* using eye masks can be explained by the relation between sleep wakefulness rhythm and the light-dark cycle. In this context, it is known that in the suprachiasmatic nucleus, the connections of the retina orient the nervous system about the existence of the light, which, being absent, stimulates the secretion of melatonin through the pineal gland (59). In a number of studies (13, 22, 25), the convenience of interventions was assessed based on patients' feedback. Many subjects reported that these interventions were comfortable and tolerable, and overall the rankings show that the products were very comfortable, very helpful, and very easy to use. However, it is important to note that earplugs and eye masks are only recommended for patients who are alert enough to cooperate and agree to these measures. Despite the evidence, the use of eye masks and earplugs may be considered invasive, especially if the patient is unable to remove them without assistance.

To our knowledge, this is the first systematic review and meta-analysis to observe the efficacy of eye masks and earplugs interventions on sleep quality in critically ill patients. Consistent with previous review studies (15, 16) on the effects of eye masks and /or earplug interventions on sleep quality in intensive care patients. The difference is that there was no meta-analysis in this area based on sleep quality assessment tools. However, there still exist several limitations in our research. The main limitation of this study was that due to the heterogeneity of studies on participants' demographic and clinical characteristics, methodological limitations, as well as measures and expression of outcomes, many of them did not enter the meta-analysis. In addition, small sample size, short evaluation period, different mental and objective sleep assessment techniques, and other

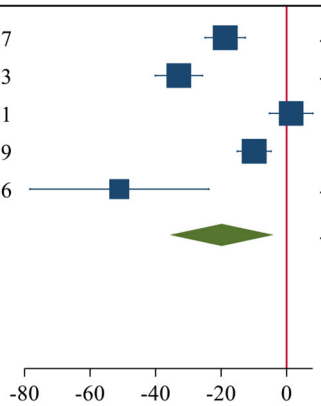
A

Study	Treatment N	Mean	SD	Control N	Mean	SD	WMD with 95% CI	Weight (%)
Yazdannik_2012_a	25	34.48	11.14	25	53.22	10.87	-18.74 [-24.84, -12.64]	21.70
Yazdannik_2012_b	25	17.74	13.57	25	50.64	12.23	-32.90 [-40.06, -25.74]	21.43
Baghaie Lakeh_2018_a	48	67.57	16.77	48	66.19	16.1	1.38 [-5.20, 7.96]	21.58
Baghaie Lakeh_2018_b	48	60.61	13.79	48	70.52	11.9	-9.91 [-15.06, -4.76]	21.90
Mashayekhi_ 2012	30	89.83	52.1	30	140.9	55.66	-51.07 [-78.35, -23.79]	13.38
Overall							-19.82 [-35.54, -4.11]	

Heterogeneity: $\tau^2 = 286.45$, $I^2 = 95.67\%$, $H^2 = 23.09$

Test of $\theta_i = \theta_j$: Q(4) = 59.55, p = 0.00

Test of $\theta = 0$: z = -2.47, p = 0.01



Random-effects REML model

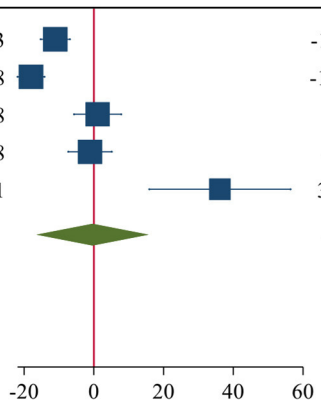
B

Study	Treatment N	Mean	SD	Control N	Mean	SD	WMD with 95% CI	Weight (%)
Yazdannik_2012_a	25	19.12	8.83	25	30.18	6.03	-11.06 [-15.25, -6.87]	21.19
Yazdannik_2012_b	25	13.64	6.21	25	31.66	7.68	-18.02 [-21.89, -14.15]	21.24
Baghaie Lakeh_2018_a	48	55.54	17.6	48	54.45	16.18	1.09 [-5.67, 7.85]	20.71
Baghaie Lakeh_2018_b	48	53.45	16.07	48	54.54	15.08	-1.09 [-7.32, 5.14]	20.83
Mashayekhi_ 2012	30	291.5	38.9	30	255.33	41.1	36.17 [15.92, 56.42]	16.03
Overall							-0.38 [-16.44, 15.68]	

Heterogeneity: $\tau^2 = 312.26$, $I^2 = 97.36\%$, $H^2 = 37.82$

Test of $\theta_i = \theta_j$: Q(4) = 54.87, p = 0.00

Test of $\theta = 0$: z = -0.05, p = 0.96



Random-effects REML model

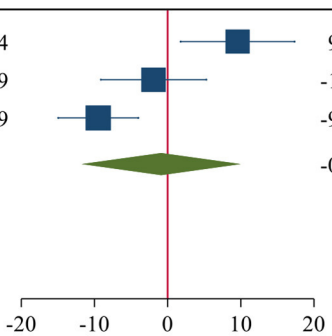
C

Study	Treatment N	Mean	SD	Control N	Mean	SD	WMD with 95% CI	Weight (%)
Baghaie Lakeh_2018_a	48	75.3	18.46	48	65.74	20.4	9.56 [1.78, 17.34]	32.10
Baghaie Lakeh_2018_b	48	68.15	19.65	48	70.07	16.19	-1.92 [-9.12, 5.28]	32.88
Mashayekhi_ 2012	30	12.97	10.7	30	22.45	10.9	-9.48 [-14.95, -4.01]	35.03
Overall							-0.88 [-11.73, 9.97]	

Heterogeneity: $\tau^2 = 79.72$, $I^2 = 87.02\%$, $H^2 = 7.70$

Test of $\theta_i = \theta_j$: Q(2) = 15.48, p = 0.00

Test of $\theta = 0$: z = -0.16, p = 0.87



Random-effects REML model

FIGURE 4 | Forest plot of mean difference (MD) for sleep quality domains based on VSHSS between intervention and control groups, **(A)** disturbance; **(B)** effectiveness and **(C)** supplementary.

TABLE 4 | Efficacy of eye masks and/or earplugs interventions for sleep quality based on polysomnography.

Sleep components	Pooled MD (95% CI)	*P*-value	I^2 (%)	Egger *P*-value	Begg *P*-value
Time in bed (min)	0.28 (−4.32, 4.88)	0.90	0	0.556	0.149
Total sleep time (min)	25.4 (8.05, 42.9)	<0.001*	0	0.310	0.065
Sleep efficiency index	0.06 (0.01, 0.10)	0.01*	0	0.984	0.500
REM (%)	4.66 (2.70, 6.62)	<0.001*	0	0.827	0.149
Stage 1 non-REM (%)	1.65 (−0.26, 3.56)	0.09	0	0.390	0.151
Stage 2 non-REM (%)	−1.85 (−4.43, 0.74)	0.16	0	0.390	0.151
Stage 3 non-REM (%)	−0.35 (−2.10, 1.41)	0.70	0	0.933	0.999
Sleep onset latency (min)	−17.61 (-45.86, 10.63)	0.22	15.9	0.208	0.149
REM latency (min)	−16.93 (−42.48, 8.62)	0.19	16.2	0.201	0.149
No. of awakenings	−8.40 (−10.15, −6.64)	<0.001*	0.63	0.270	0.500
Sleep arousals index	−5.17 (-6.58, −3.75)	<0.001*	0	0.452	0.500

*$P < 0.05$ was considered as significant.
MD, Mean Difference; CI, Confidence Interval; REM, Rapid eye movement.

methodological problems, such as lack of double blindness, and the use of simulation environment were other limitations of this study. Due to these limitations, the results of these studies are not generalizable and should be interpreted with caution. In addition, further high-quality research is needed to strengthen the evidence base.

CONCLUSION

According to the data presented in the study, non-invasive and low-cost sound- and light-masking interventions like as earplugs and eye masks may improve objective sleep characteristics aswell as subjective sleep experiences of patients in critical care settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AV-A, FR-B, and MK-F designed the study. AV-A, SA, and SM contributed to the concept of the review and meta-analysis, acquisition of data, analysis and interpretation of data, and drafting the article. All authors edited and revised manuscript, and approved final version of 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.2021.791342/full#supplementary-material

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Understanding Sleep-Wake Behavior in Late Chronotype Adolescents: The Role of Circadian Phase, Sleep Timing, and Sleep Propensity

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Background: Adolescents with a late chronotype are at greater risk for mood disorders, risk-taking behaviors, school absenteeism, and lower academic achievement. As there are multiple causes for late chronotype, the field lacks studies on the relationship between mood, circadian phase, and phase angle of entrainment in late chronotype adolescents. Three objectives guide this explorative study: (1) to describe sleep, circadian phase, and phase angle of entrainment in late chronotype adolescents, (2) to explore how different levels of lateness are associated with sleep quality, sleep propensity, and mood, and (3) to investigate the influence of circadian phase on bedtime choice and sleep duration.

Methods: Baseline data from 19 male adolescents (M = 16.4 ± 1.0 yrs), who were part of a larger intervention trial, were analyzed. Chronotype was measured with the Munich Chronotype Questionnaire, circadian timing via dim light melatonin onset (DLMO), and sleep habits with a 7-day sleep log. Further questionnaires assessed daytime sleepiness, sleep quality, and mood. Evening sleepiness and sustained attention were used as a proxy for evening sleep propensity.

Results: On school nights, sleep duration averaged 7.78 h (±1.65), and 9.00 h (±1.42) on weekend nights. Mean DLMO was observed at 23.13 h (± 1.65), with a weekend phase angle of entrainment of 2.48 h. Regression fittings revealed a tendency for shorter phase angles with delayed DLMOs. Further analysis with chronotype subgroups revealed that this was only true for light and moderate late types, whereas extreme late types showed wide phase angles. Even though daytime sleepiness and sleep duration did not differ between subgroups, mood and sleep quality declined as lateness increased. Extreme late chronotypes experienced higher evening sleepiness, while slight late chronotypes showed higher evening attention. Chronotype but not DLMO predicted bedtime on school- and particularly weekend-nights.

Conclusions: Our findings suggest that with increasing lateness, the likelihood of experiencing poor sleep quality and mood disorders increases. As DLMO did not predict bedtime, our data indicate that the factors contributing to a late chronotype are versatile and complex, particularly for extreme late types. Further studies involving a larger and gender-balanced sample are needed to confirm findings.

Keywords: delayed sleep-wake phase, mood, dim-light melatonin onset, evening vigilance, depression, sleep deprivation, sedentary, school night

INTRODUCTION

Individual differences in sleep-wake schedules can be classified as early, intermediate and late chronotypes. Early chronotypes ("morning larks") rise early and feel their best in the morning, while late chronotypes ("night owls") stay up late and feel most alert in the evening (1). The latter is well-known to many teenage parents. However, growing evidence supports a link between chronotype and increased risk for affective disorders (2–4). Specifically, a late chronotype has been linked to increased risk for depression, anxiety and substance abuse among adults (3). Few studies have investigated the relationship among adolescents. For example, adolescents with extreme late chronotype (delayed sleep wake phase disorder or DSWPD) show higher caffeine and alcohol consumption, and less sports participation (2). Considering that adolescence is a period of vulnerability for the onset of psychiatric diseases, which may be induced or exacerbated by insufficient and ill-timed sleep, this is of public health concern (5–8). Therefore, the current study aims to close this gap by investigating the specific role of different sleep and circadian related measures in late chronotype adolescents and their impact on mood.

Chronotype is closely related to the circadian rhythm (i.e., body clock), which regulates cyclical changes in cellular, molecular, and biological processes that repeat approximately once every 24 h. Natural daylight is the most potent timekeeper of the human circadian rhythm, hence artificial light exposure in the evening delays circadian timing thus sleep (9). Delayed circadian timing in adolescence is also driven by pubertal and developmental changes including a delay and lengthening of the circadian rhythm (10, 11). For example, the onset of melatonin secretion (a sleep-promoting hormone) and sleep timing becomes later with increasing age and pubertal status (12).

While delayed sleep seems to be a normal part of adolescent development, the misalignment between internal sleep-wake desire and early morning commitments (e.g., school) results in a reduced sleep opportunity. Attempts to initiate sleep at an earlier clock time may result in prolonged sleep onset times (4). The accumulated sleep debt during a school-week is then compensated on non-school days by sleeping in (13). This in turn leads to a reduced exposure to natural daylight in the morning which is necessary to reset and synchronize body clock timing, thus further delaying the circadian rhythm.

Morning bright light therapy with a gradual advanced sleep schedule and supplementation of evening melatonin are the recommended treatments for late chronotype adolescents (14). Although treatment responses are generally positive and remain the gold standard (15), a small but considerable proportion of adolescents show only small or negligible treatment effects on circadian markers, such as the timing of melatonin onset under dim light conditions (DLMO) (16). Moreover, not all observed phase-advances translate to earlier bedtimes, suggesting other factors in the etiology of late chronotypes (15). In fact, several studies have identified further factors that contribute to a late chronotype, such as homeostatic sleep pressure, circadian length, phase angle of entrainment, light exposure, and sensitivity (17–21). Circadian phase angle is the duration between circadian markers (i.e., DLMO) and sleep timing (i.e., onset or wake time) and often used as an indicator for circadian entrainment. Evaluations among adult populations revealed that only a subset of extreme chronotypes have primarily a circadian cause (17, 22–25). For example, in a recent study with patients diagnosed with DSWPD, only half presented with abnormally delayed circadian rhythms, while the other half showed abnormal phase angles between their biological rhythms and behavioral sleep-wake schedule (25). While both types are prone to suffer from negative physical and mental health consequences, the distinction may lead to a more tailored treatment approach. However, the literature lacks a concise definition toward "normal" and "abnormal" phase angles among adolescents. Among young and healthy adult populations, phase angles average 2–2.5 h (24, 26–29). Studies on extreme late chronotypes, including clinical samples with DSWPD, report similar (17, 30) or significantly shorter phase angles of 1.7 h (31). Shorter phase angles have been shown to be associated with a longer circadian rhythm (∼25 h) and higher sleep need (20). However, little is known about these phase relationships in late chronotype adolescents. The phase angle of normal sleeping teens on free days has been reported in a study during summer holidays, with 1.18 h in the 9–12 year old cohort, and 1.65 h in the 13–16 year old cohort (32). For weekdays, a longitudinal study with a cohort of 15–16-year-old teens found phase angles closer to that of adults (2.05–2.17 h) (33). In contrast, only one study was found that reported the phase angle in late chronotype children (mean age 10 years), which averaged 1.22 h (34), and thus is larger than in an age matching cohort of healthy sleepers with 1.07 h (33).

In summary, late chronotype among adolescents has been associated with higher risk for mood disorders, risk taking behaviors, school absenteeism, and lower academic achievement. Current treatment approaches to phase advance circadian and sleep timing are widely accepted and promising, but moderate

to large inter-individual differences highlight that not all adolescents benefit equally. Considering the multiple causes for late chronotype, and that adolescence is a critical developmental period for sleep, the field currently lacks data on the relationship between mood, circadian phase, and phase angle of entrainment among late chronotype school-aged adolescents.

Hence, the aim of this explorative study was three-fold: First, to describe differences in sleep, circadian phase, and phase angles of entrainment in late chronotype adolescents. Second, to explore how chronotype is associated with sleep quality, sleep propensity, and mood (i.e. depression, anxiety, and stress). Findings may highlight the importance of early interventions to improve sleep quantity and quality among this at-risk population. Thus, in order to design tailored interventions that address a delayed sleep period, and therefore sleep quantity and quality, our third aim is to explore the role of circadian phase on bedtime choice and sleep duration. Overall, we expect later bedtimes and thus shorter sleep durations on school nights, later circadian phase and reduced phase angle of entrainment, higher daytime sleepiness, lower evening sleep propensity, and worse mood for the more extreme late chronotypes compared to the intermediate chronotypes (5, 11, 35, 36).

METHODS

Participants

The present explorative study investigated baseline data of participants that were part of a randomized controlled intervention trial, aiming to phase-advance circadian timing in late chronotype adolescents (trial registration DRKS00025322). The trial was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC application number OFR 100.16—HREC/16/SAC/90). Written informed consent was provided by all study participants and their parents or caregivers.

Inclusion criteria: male, aged between 15 and 18 years, sedentary (<60 min physical activity/week) (37), absence of evidence of sleep apnea and other pediatric sleep disorders (Paeditric Sleep Questionnaire; PSQ) (38), as well as psychological disorders, which have been linked to altered circadian rhythms [i.e., bipolar (39); ADHD (40), and Autism Spectrum Disorder (41)]. To meet inclusion criteria for a late chronotype, interested adolescents had to score >4.1 on the Munich Chronotype Questionnaire (MCTQ) (42). Exclusion criteria: travel across time zones in the 2 months prior to the study. Female adolescents were not recruited. The present data were drawn from an intervention trial with melatonin onset as the primary outcome. Due to conflicting evidence whether sex differences exist in circadian rhythms (43–46), we chose to include only male adolescents in the study. Further exclusion criteria involved intake of psycho-pharmaceuticals, as some antidepressants impact the biotransformation of melatonin (47, 48).

Procedures

The study was advertised through social media. Interested participants contacted the first author of the study for an initial telephone screening interview. From the 62 adolescents that made contact, 28 male adolescents met inclusion criteria, and were invited with their primary caretaker to the Flinders University Sleep and Circadian Research Laboratory. Of these, 23 followed the invitation and consented to partaking in the study (Mage = 16.4 yrs, SD = 1.0). One week prior to their overnight stay, adolescents were instructed to complete a daily sleep log, while maintaining their habitual sleep-wake schedule during a regular school-week. Following 1 week of daily sleep log, dim light melatonin onset (DLMO) as a marker of circadian timing, was assessed via salivary sampling at the sleep laboratory. This ensured protocol compliance (e.g., continuous dim light condition, i.e., <10 lux) throughout the assessment, which started 4 h before and ended 2 h after participant's regular bedtime (max. 04:00 h). Study participants arrived at the sleep laboratory at 17:00 h. In the 72 h before and during saliva collection, adolescents were asked to avoid caffeine, nicotine, alcohol, and foods thought to impede habitual melatonin secretion (e.g., chocolate, bananas, tomatoes) (49). Self-reported daytime sleepiness and mood were assessed upon arrival (∼17:30–18:00 h). Evening sleepiness and sustained attention were assessed in the last 3 h before their habitual bedtime. At other times, participants interacted with each other and staff members. Board/card games and a television were provided in the communal lounge room. Mobile phones were disallowed. Free access was provided to water. Meals and snacks were provided at set times consistently for all study participants, with no access to food at other times. Participants were monitored to ensure wakefulness until the completion of their last assessment (2 h after habitual bedtime). Thereafter, participants were allowed to sleep in and leave the laboratory (∼11:00–13:00 h).

Measures

Munich Chronotype Questionnaire (MCTQ)

The Munich Chronotype Questionnaire (MCTQ) was developed by Roenneberg et al. for ages 6 to 65 years (42). The self-rated questionnaire estimates chronotype based on the midpoint between average sleep onset and offset on school-free days (midsleep on free days: MSF), corrected for "oversleep" due to the sleep debt that individuals accumulate over a school week (MSFsc) (50). This proxy for chronotype is based on the assumption that sleep timing on school-free days is highly influenced by an individual's circadian clock. Therefore, chronotype (MSFsc) can only be calculated when participants can sleep in on their school-free days. Specifically, the MCTQ asks about bedtime, time spent in bed awake before deciding to turn off the lights, how long it takes to fall asleep, wake up time, and out of bed time for both school- and free days.

The MCTQ has been validated among various populations in Europe, Asia, North-, and South America and generally shows a high test-retest reliability (31, 51, 52). Validation against the gold standard for assessing circadian phase (DLMO) was high (53–56). Based on previously published population data, an MSFsc score of ≥4.1–5.0 was classified as slight late type, ≥5.1–6.0 as moderate late type, and ≥6.1 as extreme late type.

Dim Light Melatonin Onset (DLMO)

Salivary DLMO samples were taken half-hourly in dim light (<10 lux) using salivettes (Sarstedt, Newton, NC, USA). In line with the sampling protocol for adolescents developed by Crowley et al. (10), the measurements started 4 h before and finished 2 h after the participant's typical bedtime. Participants were seated for at least 5 min before and during each saliva sample, to minimize the masking effects of physical movement on endogenous melatonin production. Food and water consumption were only allowed after saliva collection to reduce contamination or dilution of the sample. Participants were instructed to gently chew on the cotton swab in their mouth and accumulate saliva for 2 min. Immediately after, samples were labeled and stored frozen at −20°C. For analysis, samples were thawed and centrifuged for 10 min at 2,500 rpm, the swabs removed from the casing, and the supernatant retained. A sensitive (4.3 pM) direct radioimmunoassay (RIA) using reagents from Buhlmann Laboratories AG (Allschwil, Switzerland) (57) was used to measure melatonin in the saliva. The intra-assay coefficient of variation (CV) was <10% at all times (mean = 4.5%). The inter-assay CV was 8.8% at 12.9 ppm and 13.1% at 104.5 ppm. The functional least detectable dose of the assay was 1.0 pg/ml. DLMO was calculated by linear interpolation across time-points when melatonin concentration increased to 4.0 pg mL or above (58).

Circadian Phase Angle of Entrainment

To determine circadian entrainment, the phase angle is calculated as the interval between circadian phase (i.e., DLMO) and sleep timing (i.e., onset or wake time). In the present study, phase angle of entrainment was calculated as DLMO-to-bedtime interval ($DLMO_{bedtime}$). School-night bedtimes were calculated by averaging the bedtimes from Sunday to Thursday night. For weekend bedtimes, Friday to Saturday night was averaged.

Mood

Mood was measured with the short version of the Depression, Anxiety, and Stress Scale (DASS-21) (59). Each subscale consists of 7 items. Participants were asked to indicate how much each statement applied to them over the past week, using a 4-point Likert scale, ranging from 0 ("Did not apply to me at all") to 3 ("Applied to me very much, or most of the time") (60). The DASS-21 has been shown to be a valid and reliable measure of depression in adolescents, with adequate internal consistency ($\alpha = 0.76–0.90$) (61), as well as satisfactory discriminant validity and convergent validity when compared to other measures of depression (62). This was confirmed in the present study ($\alpha = 0.76$).

Evening Sleepiness and Sustained Attention as a Proxy of Sleep Propensity

The Karolinska Sleepiness Scale [KSS; (63)] was used to measure subjective sleepiness in the 3 h leading up to their averaged habitual bedtime. The KSS consists of a 9-point Likert-type scale, spanning 9 levels from 1 (extremely alert) to 9 (very sleepy, great effort keeping awake, fighting sleep). Adolescents were asked to circle the number that represents their current perceived level of sleepiness at 3, 2, 1, and 0 h before their averaged habitual bedtime.

Go/No-Go Task. Sustained evening attention was measured immediately after each KSS rating. The computerized Go/NoGo task (E-Prime v1.2, Psychology Software Tools, Inc., Pittsburgh, PA, USA, 2006) measures sustained attention in relation to inhibitory functions and consists of two visual stimuli presented in a random order. Adolescents pressed the space bar within 500 ms if the letter "M" was shown on the screen (Go stimuli). If the letter "W" was shown, they were instructed not to press any buttons (No-Go stimuli). A total of 80% of "M" (∼200) letters were shown, in a quasi-random sequence wn across 8 min. Analyses were performed with commission error (falsely pressing the button in "No-Go" trials), as well as reaction time (RT) of correct Go-trials. The latter outcome has been used as a measure of sustained evening attention in previous research among adolescents and young adults (64, 65).

Daytime Sleepiness

To assess daytime sleepiness, the Pediatric Daytime Sleepiness Scale (PDSS), an 8-item self-report scale (e.g., "How often do you fall asleep or feel drowsy in class?") was administered upon arrival at the laboratory (17:00 h) (66). Daytime sleepiness is a common symptom reported by adolescents with late chronotype (67–70). Responses to each item are measured on a 5-point Likert scale (e.g., 0 = "*Never,*" 4 = "*Always*"). Total scores range from 0 to 32, with higher scores indicating higher sleepiness. A total cut off score of 20 has been recommended for clinical samples (71). Drake et al. (66) reported good internal consistency (Cronbach $\alpha = 0.80$); which was confirmed in the current study (Cronbach $\alpha = 0.80$). The PDSS has been shown to be sensitive to chronobiological treatment and was used to measure changes in daytime functioning (72).

Sleep Diary

To assess subjective habitual sleep patterns, adolescents completed a daily sleep log at home over 7 consecutive nights before they came to the sleep laboratory. In the mornings, they indicated their bed- and rise-time, as well as perceived sleep onset latency (SOL), and number of awakenings during the night (WASO). Additionally, an 8-point Likert-type scale asked about sleep quality (1 = very bad sleep quality; 8 = very good sleep quality) each night. Nights were defined as weeknights if they went to school the next day; weekend nights were Friday and Saturday. To compute data, weekday and weekend sleep parameters were aggregated separately.

Statistical Analysis

One-way ANOVA was used to compare baseline characteristics between groups (slight vs. moderate vs. extreme late chronotype). Repeated measure ANOVAs were conducted to compare the progression of pre-bedtime sleepiness and sustained evening attention (at 3, 2, 1, 0 h before bedtime) as a proxy for sleep propensity between chronotype groups. Test results with an alpha level <0.05 were reported as statistically significant. Due to the small sample size, effect sizes were considered when interpreting results (73). Effect sizes for ANOVAs [partial eta-squared (η^2)]

TABLE 1 | Descriptive statistics for sleep and circadian measures in chronotype subgroups.

Characteristics	All ($N = 18$)			Slight late type ($N = 8$)			Moderate late type ($N = 4$)			Extreme late type ($N = 6$)		
	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max	M ± SD	Min	Max
Age in years	16.44 (1.04)	15	18	16.13 (1.13)	15	18	16.50 (1.29)	15	18	16.83 (0.75)	16	18
BMI	23.5 (5.1)	17.3	33.8	23.30 (4.83)	17.28	31.12	23.12 (6.33)	18.17	32.41	24.01 (5.68)	19.05	33.81
MCQ-score	5.56 (1.24)	4.25	8.27	4.53 (0.27)	4.25	5.00	5.27 (0.29)	5.13	5.70	7.13 (0.60)	6.64	8.27
TST (h)												
School night	7.78 (1.65)	5.28	11.83	7.55 (1.27)	5.67	9.75	7.55 (0.80)	6.40	8.25	8.23 (2.50)	5.28	11.83
Weekend night	9.00 (1.42)	5.70	10.72	9.56 (0.75)	8.50	10.50	8.96 (1.62)	7.00	10.42	8.29 (1.86)	5.70	10.72
Mid-sleep time (h:mm)												
School night (MSW)	3:53 (0:49)	2:38	5:55	3:46 (0:38)	2:50	4:52	3:46 (0:23)	3:12	4:07	4:06 (1:14)	2:38	5:55
Weekend night (MSF)	4:30 (0:42)	2:51	5:21	4:46 (0:22)	4:15	5:15	4:28 (0:55)	3:30	5:12	4:08 (0:55)	2:51	5:21
Bedtime												
School night	0.06 (1.09)	22.50	2.10	23.62 (0.97)	22.50	1.50	0.14 (1.61)	22.50	2.10	0.59 (0.74)	23.95	1.88
Weekend night	1.59 (1.67)	23.00	4.45	0.52 (1.18)	23.00	2.50	0.17 (1.06)	23.91	2.50	3.30 (1.15)	1.28	4.45
SOL (min)												
School night	19.11 (19.38)	1.80	72.00	14.68 (14.55)	1.80	36.25	23.60 (21.15)	5.40	54.00	22.02 (25.58)	5.00	72.00
Weekend night	21.36 (28.48)	4.00	120.00	21.91 (17.95)	6.00	52.00	41.31 (53.75)	4.00	120.00	7.33 (4.32)	4.00	15.00
WASO (min)												
School night	0.95 (2.59)	0	10.60	0.11 (0.18)	0	0.50	0.11 (0.13)	0	0.25	2.63 (4.20)	0	10.60
Weekend night	2.04 (4.36)	0	15.00	0.81 (0.92)	0	2.00	0	0	0	5.04 (6.84)	0	15.00
Wake-Up												
School morning	7.90 (1.59)	6.25	12.00	7.18 (0.87)	6.25	9.00	7.69 (0.94)	6.75	8.50	9.00 (2.15)	7.17	12.00
Weekend morning	10.49 (0.99)	9.50	12.50	9.93 (0.52)	9.50	11.00	10.16 (0.81)	9.50	11.15	11.45 (0.93)	10.25	12.50
Sleep quality												
School morning	5.59 (0.89)	3.40	7.00	5.49 (1.21)	3.40	7.00	6.07 (0.76)	5.20	6.60	5.48 (0.24)	5.20	5.80
Weekend morning	5.94 (1.30)	4.00	8.00	6.50 (1.12)	5.00	8.00	6.79 (0.25)	6.50	7.00	4.70 (1.10)	4.00	6.50
DLMO (h)	23.13 (1.65)	20.51	2.51	22.66 (0.96)	21.42	0.13	23.65 (1.70)	21.69	0.69	23.49 (2.36)	20.51	2.51
$DLMO_{bedtime}$ (h)	2.48 (2.12)	−0.13	7.94	1.69 (1.40)	−0.13	4.08	1.57 (0.08)	0.67	2.22	3.98 (2.69)	0.49	7.94

Data are presented as mean ± SD; MCQ, Munich chronotype questionnaire; TST, total sleep time; SOL, sleep onset latency; DLMO, dim light melatonin onset; WASO, wake after sleep-onset.

were regarded as small [S] if $0.01 > \eta^2 < 0.059$, medium [M] if $0.06 > \eta^2 < 0.139$, and large [L] if $\eta^2 \geq 0.14$ (74, 75). To test whether sleep duration is predicted by bedtime, wake-time, DLMO, or chronotype multiple linear regression models were conducted. Likewise, linear regression models were applied to test whether DLMO and chronotype predict sleep-wake times. All statistical analyses were performed using SPSS 28.0 (IBM Corporation, NY, USA).

RESULTS

Participants

Four participants withdrew from the study before their overnight stay at the sleep laboratory (other commitments), while one decided to discontinue during the course of the data assessment (not willing to comply). **Table 1** provides sleep and circadian characteristics for the 18 participants who completed the study (M = 16.44 years, SD = 1.04). Of these, 8 participants classified as slight late chronotype, 4 as moderate, and 6 as extreme late chronotype. The average BMI was 23.7, ranking 79.9 percentile in this age group (BMI percentile ≥5 and <85 = healthy weight). No significant differences between late chronotype subgroups (slight, moderate, extreme) were observed for age, $F_{(1,6)} = 0.78$, $p = 0.476$, $\eta = 0.09$ and BMI, $F_{(1,6)} = 0.42$, $p = 0.959$, $\eta = 0.01$.

Sleep-Wake Timing, Sleep Duration, Sleep Quality, DLMO, and Phase Angle of Entrainment

Table 1 provides the descriptive statistics for sleep and circadian measures. The average sleep duration on school nights was 7.78 h (SD = 1.65), and 9.00 h (SD = 1.42) on weekend nights. Bedtimes on school nights ranged between 22.50–2.10 h and 23.0 h−4.45 on weekend nights. Large interindividual differences were also observed for wake-up times, which ranged between 6.25 and 12.0 h on school mornings, and 9.5–12.5 h on weekends. On average, adolescents had a weekend catch-up sleep of 1.22 h. Mean DLMO was observed at 23.13 h (SD = 1.65), with a weekend phase angle of entrainment for $DLMO_{bedtime}$ of 2.48 h. Yet, the present sample revealed large interindividual differences on school-nights (M = 1.12; SD = 1.92; range = −2.56–5.36 h) and particularly on weekend-nights (M = 2.48; SD = 2.12; range = −0.13–7.94 h).

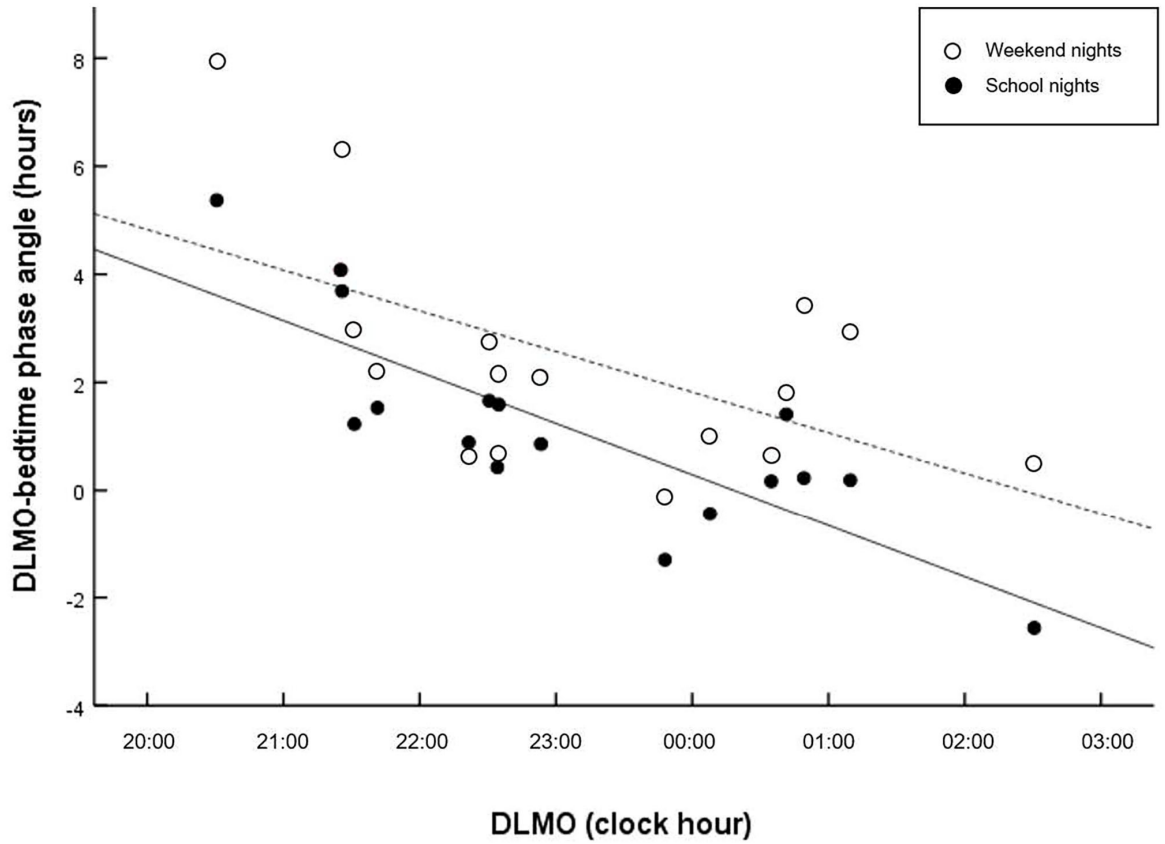

FIGURE 1 | Scatter plots of phase angle relative to DLMO. Regressions are computed separately for school nights (solid line) and weekend nights (dashed lines). Shorter interval (phase angle) between circadian phase and bedtime is related to later circadian phase on school nights ($r = -0.814$, $p < 0.001$), and weekend nights ($r = -0.583$, $p = 0.014$).

Association Between Circadian Phase and Phase Angle of Entrainment

Figure 1 displays the correlations between the circadian phase marker DLMO and the respective phase angle of entrainment ($DLMO_{bedtime}$) for school- and weekend nights. Regression fittings revealed that shorter phase angles were related to later circadian phases (DLMO). However, this relationship was less clear on weekend nights, $r = -0.583$, $p = 0.014$), with larger interindividual variations than on school nights, $r = -0.814$, $p < 0.001$), indicating that a late chronotype may be driven by factors other than circadian phase. In contrast, larger phase angles were related to longer sleep durations on weekend nights, but not on school nights (**Figure 2**).

Differences in Sleep Patterns, Circadian Timing and Phase Angle of Entrainment in Slight, Moderate, and Extreme Late Chronotypes

Table 1 also provides the descriptive statistics for sleep and circadian measures for each chronotype subgroup (slight vs. moderate vs. extreme late chronotype). Inferential statistics for chronotype subgroups are represented in **Table 2**. No significant differences were reported for school nights (all >0.05). Yet, considering effects sizes due to the small sample size, morning wake-time and awakenings after sleep onset (WASO) were considerably later / more frequent among moderate and extreme late chronotypes, compared to their slight late peers. For weekends, significant differences were observed for bed- and morning wake-times, WASO, and perceived sleep quality. However, while large effect sizes for bed- and wake-up times are not of surprise (as chronotype is defined by these measures), sleep quality significantly decreased with increasing lateness in chronotype.

As shown in **Figure 3**, phase angle of entrainment ($DLMO_{bedtime)}$ was reduced among slight and moderate late chronotypes, but wide among extreme late chronotypes. The midpoint of sleep (MSF), defined as the clock time between sleep-onset and waking up, showed no significant differences among chronotype subgroups.

In summary, among this late chronotype sample, further analysis with chronotype subgroups revealed lower sleep quality and more variations in phase entrainment among extreme late types, regardless of MSF. Particularly, chronotype explained the variance in $DLMO_{bedtime}$ on weekend nights (but not on school nights), in that large phase angles are more prevalent in extreme

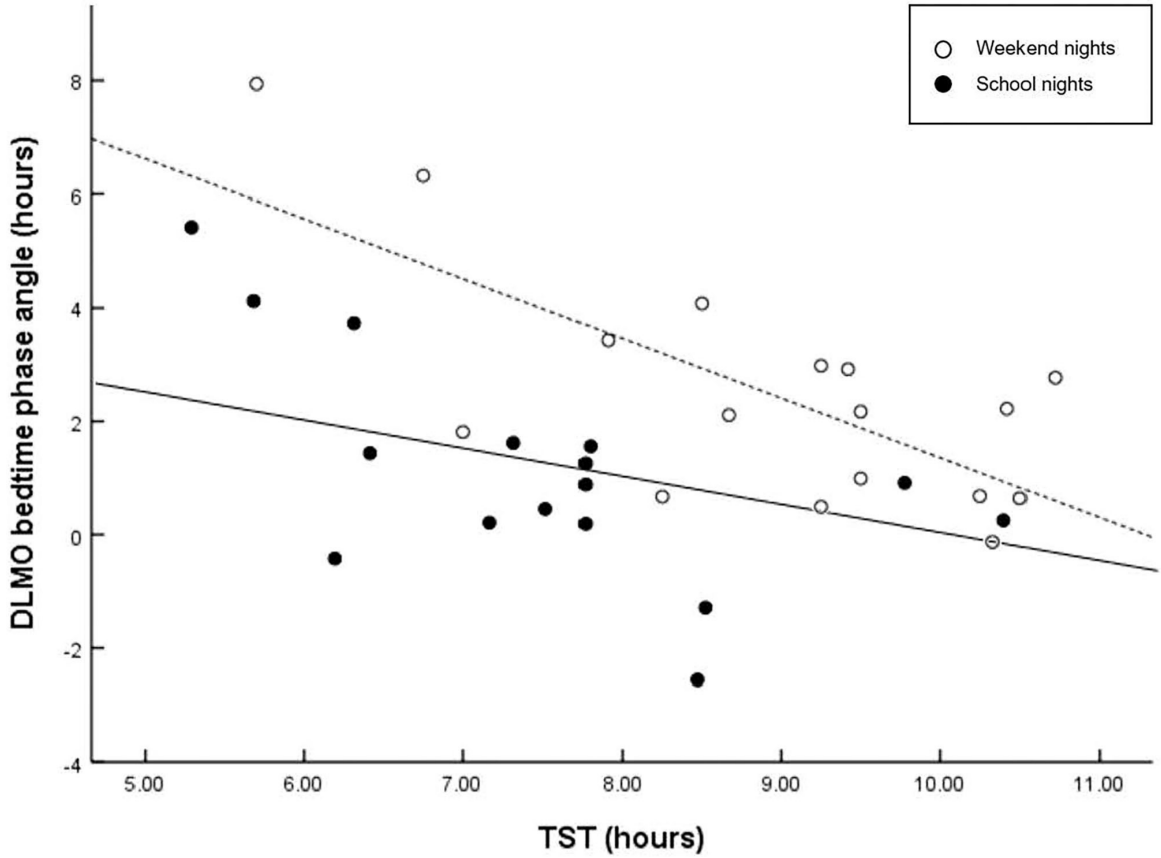

FIGURE 2 | Scatter plots of phase angle relative to TST. Regressions are computed separately for school nights (solid line) and weekend nights (dashed line). Larger interval (phase angle) between circadian phase and bed time is related to longer sleep duration on weekend nights ($r = -0.716$, $p = 0.001$), but not on school nights ($r = -0.436$, $p = 0.080$). A wider phase angle of entrainment between DLMO phase and bedtime has been shown to be associated with a shorter intrinsic circadian period (tau), and reduced sleep need.

TABLE 2 | Overview of inferential statistics for group (slight vs. moderate vs. extreme late type) ($N = 18$).

	School days			Weekend days		
	F	*p*	η^2	*F*	*p*	η^2
Sleep diary						
Bedtime	1.93	0.179	0.205	13.26	0.000	0.639
Wake-Time	2.79	0.093	0.271	7.76	0.005	0.508
SOL	0.36	0.707	0.045	1.89	0.185	0.201
WASO	2.16	0.150	0.223	2.59	0.010	0.256
TST	0.31	0.737	0.040	1.43	0.271	0.160
Sleep quality	0.50	0.618	0.066	6.69	0.013	0.549
Circadian timing and phase angle of entrainment						
DLMO	0.44	0.650	0.060	0.44	0.650	0.060
DLMO-Bedtime	0.11	0.896	0.016	2.87	0.091	0.290
Midsleep-Point	0.31	0.737	0.040	1.43	0.271	0.160

Degrees of freedom: Always = 2, 16.

late chronotypes compared to slight and moderate late types, which tend to have reduced phase angles. Phase angles could not predict TST.

Differences in Daytime Sleepiness and Sleep Propensity in Slight, Moderate, and Extreme Late Chronotypes

Table 3 shows the descriptive and inferential statistics for evening sleepiness and sustained evening, attention separately for chronotype subgroups. The mean daytime sleepiness score was 15.5 (SD = 3.26), and did not differ between chronotype subgroups. As shown in **Figure 4**, evening sleepiness showed a steady increase among all three chronotypes from 3 hours before bedtime (M = 5.11, SD = 1.53) toward bedtime (M = 7.39, SD = 1.24). Yet, adolescents with an extreme late chronotype estimated their evening sleepiness significantly higher at all times, when compared to their moderate and slight late chronotype peers (slight and moderate vs. extreme late chronotype) $F_{(3,17)} = 7.95$, $p = 0.002$, $\eta = 0.63$. With regard to sustained evening attention, significant differences were found for commission errors, $F_{(3,16)} = 4.03$, $p = 0.01$, $\eta = 0.35$, while reaction times remained constant, $F_{(3,16)} = 0.85$, $p = 0.488$, $\eta = 0.10$.

In summary, while the level of daytime sleepiness was equally perceived among all three subgroups, subjective evening sleepiness was significantly higher among extreme late chronotypes, and sustained evening attention was significantly

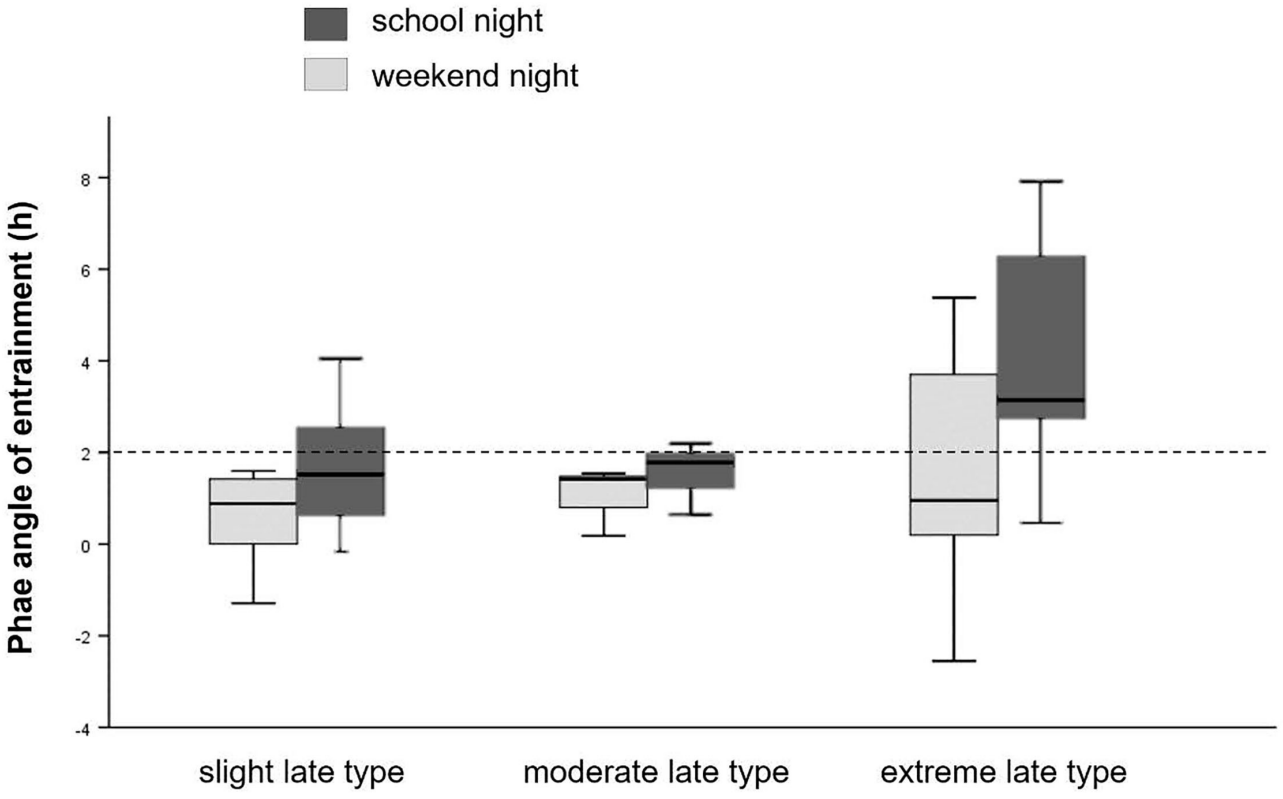

FIGURE 3 | Phase angle of entrainment. Sleep onset timing in relation to DLMO for school- and weekend-nights, separately for chronotype. Dashed line represents the 2 h norm difference between DLMO and sleep onset timing.

higher among slight late chronotypes, with less variance throughout the evening, when compared to their peers with a moderate and extreme level of lateness.

Mood Differences in Slight, Moderate, and Extreme Late Chronotypes

Figure 5 shows the stacked mean of depression, anxiety, and stress scores separately for the three chronotype subgroups. Descriptive and inferential statistics are presented in **Table 3**. Even among this non-clinical late chronotype sample, a greater eveningness was associated with a higher risk tendency for depression $F_{(3,16)} = 2.85$, $p = 0.089$, $\eta = 0.15$, and anxiety $F_{(3,16)} = 3.29$, $p = 0.066$, $\eta = 0.305$, but not stress $F_{(3,16)} = 1.42$, $p = 0.273$, $\eta = 0.159$.

Predictors of Sleep Duration on School- and Weekend Nights

Table 4 shows the results of multiple linear regression models, representing the degree to which bedtime, wake-time, DLMO, and chronotype (MCTQ-score) can predict total sleep time (TST) on a school or weekend night in the present sample. TST on school nights was predicted by morning wake-time, $\beta = 0.79$, $t_{(16)} = 4.69$, $p < 0.001$, and not bedtime, DLMO, and chronotype. In contrast, TST on weekends was predicted by bedtime, $\beta = -0.65$, $t_{(17)} = -4.66$, $p < 0.001$, and chronotype $\beta = -0.54$, $t_{(17)} = -2.11$, $p = 0.051$. Again, DLMO had no predictive power on TST.

Predictive Power of DLMO and Chronotype on Bed- and Wake-Up Times

Table 5 shows the outcomes of several multiple linear regression models, in which the predictive power of DLMO on bed- and wake-up time was weighed against the predictive power of chronotype. Overall, chronotype (MCTQ-score) but not DLMO predicted bedtime on school- and particularly weekend-nights. Similarly, wake-up times for both school- and weekend mornings were not influenced by DLMO, but chronotype.

DISCUSSION

This is the first study to explore the relationship between sleep duration, bedtime and phase angle of entrainment among a non-clinical sample of late chronotype adolescents. In addition, we explored how the level of lateness impacts mood and sleep propensity. The use of subjective and objective measures was a particular strength of the study. This includes the gold standard for determining circadian phase—salivary DLMO in a light and temperature-controlled laboratory environment. A key finding was that even among this late chronotype sample, more extreme

TABLE 3 | Descriptive and inferential statistics for daytime sleepiness, evening sleepiness, and sustained evening attention, as well as mood in chronotype subgroups.

Characteristics	Slight late type ($N = 8$)		Moderate late type ($N = 4$)		Extreme late type ($N = 6$)		Statistics		
	M	SD	M	SD	M	SD	F	*p*	η^2
Daytime sleepiness	15.5	3.46	15.5	2.65	15.5	3.89	0.00	1.000	0.000
Evening sleepiness									
3 h before BT	4.75	1.83	4.75	1.26	5.83	1.17	1.00	0.390	0.118
2 h before BT	5.25	1.58	5.75	0.50	6.83	1.17	2.60	0.107	0.257
1 h before BT	5.50	1.41	6.25	1.50	7.83	0.75	6.00	0.012	0.444
0 h before BT	6.88	1.36	7.50	1.29	8.00	0.89	1.51	0.253	0.168
Evening attention									
RT 3 h before BT	309.63	44.23	319.75	35.82	317.83	26.51	0.13	0.879	0.017
RT 2 h before BT	304.25	47.48	336.25	22.59	323.50	42.13	0.87	0.440	0.104
RT 1 h before BT	310.38	43.13	356.25	43.87	326.00	35.12	1.69	0.219	0.184
RT 0 h before BT	353.75	41.31	353.75	41.31	327.83	44.97	0.731	0.498	0.089
Error % 3 h before BT	2.42	1.45	1.66	0.27	2.19	0.78	0.631	0.546	0.078
Error % 2 h before BT	1.45	0.30	1.94	0.21	1.99	0.50	4.56	0.028	0.378
Error % 1 h before BT	1.87	0.61	4.38	2.60	2.57	0.79	4.88	0.23	0.394
Error % 0 h before BT	1.68	0.63	2.79	0.57	2.17	0.90	3.21	0.069	0.300
Mood									
Depression	7.00	5.24	9.00	3.83	13.67	5.85	2.85	0.089	0.151
Anxiety	5.75	2.71	6.00	6.73	12.00	5.66	3.29	0.066	0.305
Stress	7.00	4.00	8.50	5.26	13.00	9.78	1.42	0.273	0.159

M, mean; SD, standard deviation; BT, bedtime; RT, reaction time Go/NoGo task; error %, commission error percentage of Go/NoGo task; higher sleepiness scores reflect higher sleepiness, sustained evening attention, larger RT and error % reflect lower attention; Mood, higher scores represent higher prevalence of mood disturbances.

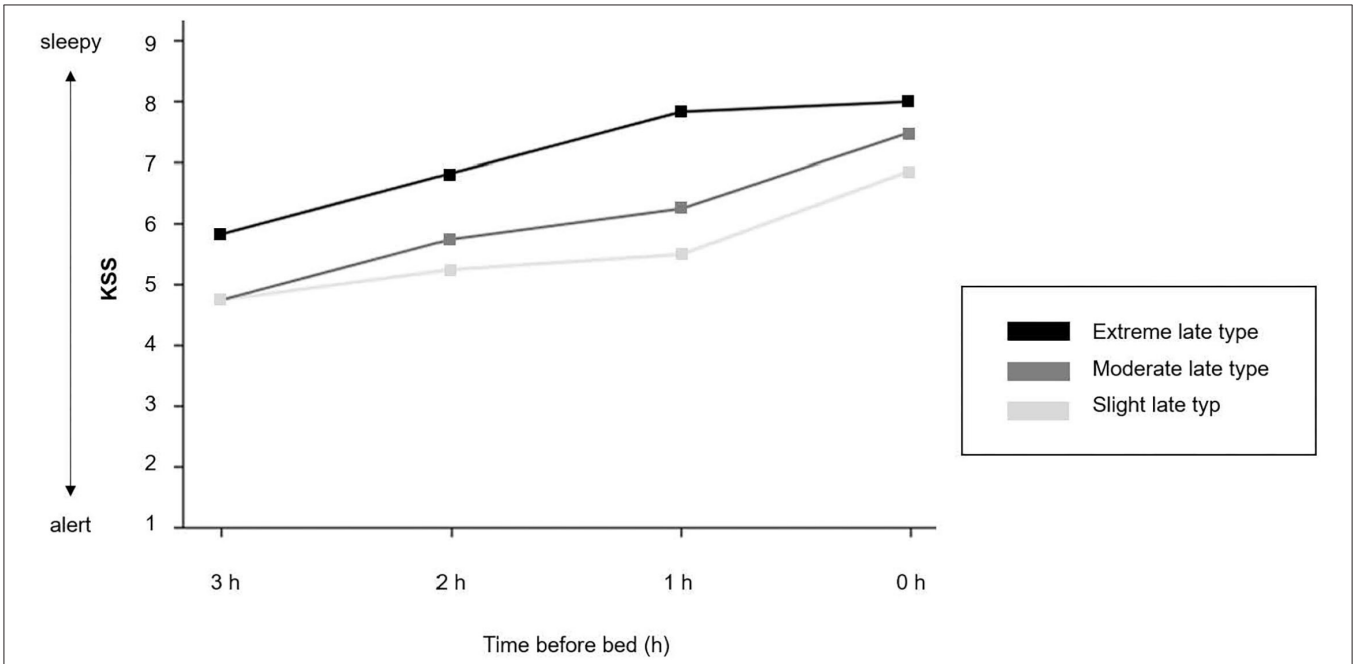

FIGURE 4 | Evening sleepiness. Time course of the Karolinska Sleepiness Scale (KSS) (mean values). 1 = extremely alert; 5 = neither alert nor sleepy; 9 = very sleepy, great effort to keep awake.

lateness was not associated with shorter sleep duration on school nights, but lower sleep quality and worse mood scores. While slight and moderate late types had reduced phase angle of entrainment, the opposite was true for extreme late types. Moreover, bedtime choice among extreme late chronotypes was not driven by circadian phase and sleep propensity, suggesting

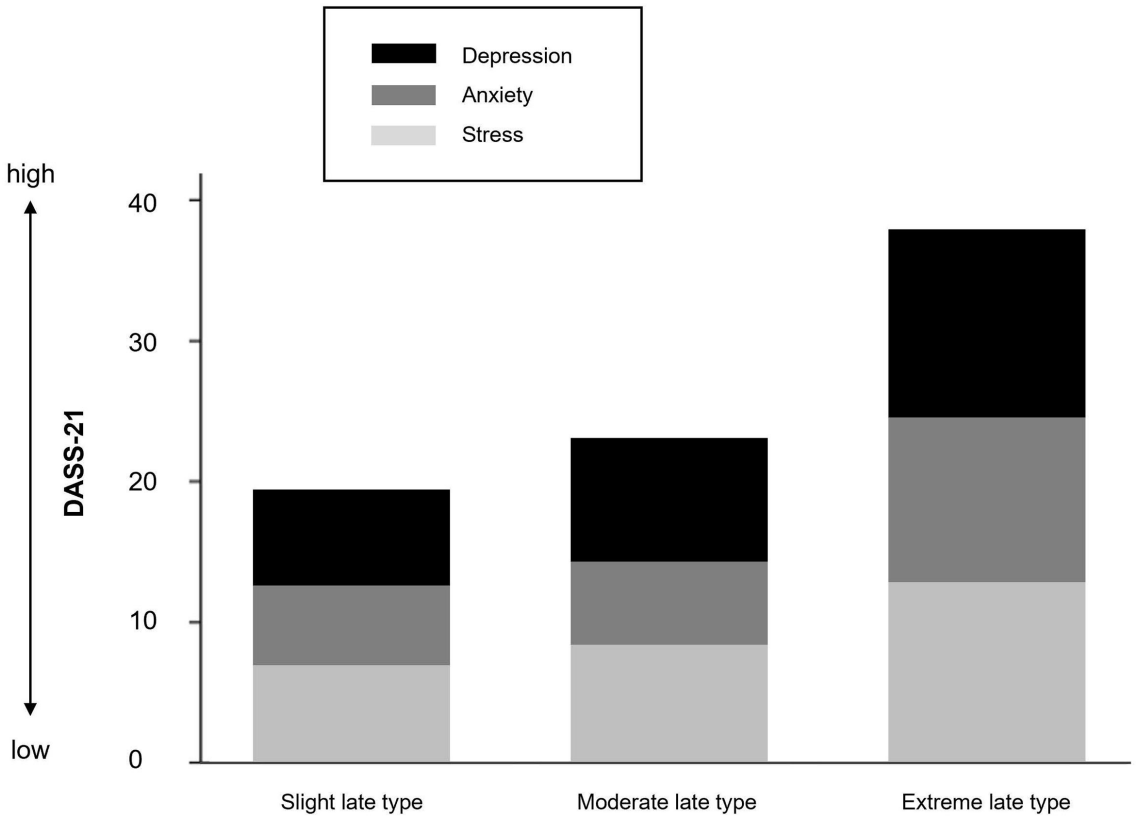

FIGURE 5 | Stacked mean of depression, anxiety, and stress scores separately for chronotype.

that other behavioral factors exert a stronger impact on the observed circadian misalignment.

Three aims were pursued within this explorative study design. First, we wanted to report on sleep, circadian phase, and phase angle of entrainment in late chronotype adolescents, followed by a comparison between three subgroups (slight vs. moderate vs. extreme late). In line with world-wide trends on adolescent sleep duration, the recommended amount of 9–9.25 h for optimal cognitive and emotional functioning among this age group (72, 76, 77) was not achieved during a regular school week with 7.8 h, but reached 9.0 h on weekends. Hence, the findings mirror sleep duration reports from age and region related populations (72). Interestingly, splitting the present sample into slight, moderate, and extreme late chronotypes, results show that weekend catch-up sleep was greatest among the slight late group (2 h), while sleep duration for extreme late chronotypes did not differ between school- and weekend nights. However, the latter group also showed the largest within-group differences in sleep duration, with both shortest and longest sleep periods among the entire sample (5.3–11.8 h on school nights and 5.7–10.7 on weekend nights). This leads to two assumptions: First, long sleep durations on school nights (with wake-up times far beyond school start) may indicate a severely delayed sleep phase and these individuals may have given up trying to adjust to a socially acceptable schedule. Second, some adolescents classifying as extreme late chronotypes are short sleepers. This notion is supported by the observed wide phase angle of entrainment of nearly 4 h, which has been shown to be associated with a shorter intrinsic circadian period (<24 h), and reduced sleep need (20, 78). However, this pattern of results is commonly observed among early chronotypes, and less among late chronotypes, at least when consulting data from adult samples (78). At first, this may seem contrary to our findings, particularly as our overall data show that a wider phase angle is associated with earlier circadian phase. Yet, for an adolescent with an early melatonin onset (∼20:00), going to bed early may reduce the opportunity for social interaction, both digitally and in real life. Irrespectively of the sleep duration, a phase angle of more than 4 h suggests that sleep timing took place very late at an individual's intrinsic biological night. This misalignment between one's optimal sleep window (i.e., biological night) and actual sleep phase is known to impair restorative sleep and induce symptoms of insomnia.

For adolescents with a late chronotype, difficulty waking in the morning for school and daytime sleepiness are often the driving symptoms to seek care in sleep clinics. However, the physiological and psychological consequences are much broader than sleep-wake disturbance, as a growing body of research on circadian misalignment shows e.g., coronary heart disease, diabetes mellitus, mood vulnerability, and depression

TABLE 4 | Predictors of sleep duration on school and weekend nights.

	TST school nights			TST weekend nights		
	β	SE	*t*	*β*	SE	*t*
Bedtime	−0.54	0.35	−1.53	−0.65***	0.14	−4.66
Wake-time	0.79***	0.17	4.69	0.19	0.36	0.52
DLMO	0.26	0.26	1.00	0.11	0.23	0.49
MCQ	0.27	0.33	0.84	−0.54*	0.26	−2.11

*TST, total sleep time; bed- and wake times on school days were used as predictors of TST on school nights; bed- and wake times on weekends were used as predictors of TST on weekends; *p< 0.05, **p< 0.01, ***p< 0.001.*

TABLE 5 | Multiple linear regression models on the predictability of DLMO and chronotype on sleep-wake times, separately for school- and weekend nights.

Dependent variable	Predictor variable	*β*	SE	*t*
School bedtime	DLMO	0.05	0.16	0.31
	Chronotype	0.39+	0.20	1.95
Weekend bedtime	DLMO	0.23	0.26	0.89
	Chronotype	1.08***	0.20	5.34
School wake-up	DLMO	0.28	0.24	1.14
	Chronotype	0.71*	0.27	2.69
Weekend wake-up	DLMO	0.24	0.15	1.66
	Chronotype	0.53**	0.15	3.5

*+p< 0.07 *p< 0.05; **p< 0.01; ***p= 0.001.*

(79). These data highlight that non-circadian delayed sleep patterns are equally important to address than circadian induced late sleep-wake schedules. As for the present sample in general, shorter phase angles were seen in adolescents with later circadian phase, particularly on school nights. This phenomenon has previously been reported among late chronotypes, who aim to entrain to a socially accepted schedule. Despite their late circadian phase, these individuals are still aiming for sufficient sleep during a school week by selecting a bedtime much earlier in their biological night. However, it is not uncommon that this leads to chronic sleep onset problems, and the underlying circadian delay may only become apparent when presenting at a sleep clinic (34, 80). This assumption is supported with our findings, as phase angles were larger on weekends than on school nights. Moreover, the current state of research suggests that during puberty, phase angles increase with maturational stage. For example Lebourgeois et al. (81) showed that the relatively long sleep episodes and early bedtimes in toddlers leads to shorter phase angles (∼0.67 h). Crowley et al. (10) measured phase angles at 1.18 h in a cohort of 9–12 year olds, and 1.65 h among the 13–16-year-old cohort of normal sleeping adolescents during summer holidays. In contrast, adults typically select a bedtime about 2 h after melatonin onset (23, 24, 26–28). In this respect, the phase angles between 1.69 and 1.57 h among our slight and moderate late sample indicates a normal entrainment for 16–18 year olds.

Nevertheless, the average circadian phase among our late chronotype sample was significantly later (23:08 h) than reports from age matching healthy sleeping cohorts on weekdays (∼21 h) (33) and during summer holidays (21:30 h) (32). Interestingly, in a study on adolescents with evening preference by Dolsen and Harvey (82), which assessed affective mood in relation to DLMO, a comparable melatonin onset at 21:19 h was observed. Unfortunately, phase angles of entrainment have not been reported by authors, which would provide insights to what extend the sleep phase delay was induced by a circadian delay. In contrast, a recent study with high school students (14–18 years), who specifically report insufficient sleep on school nights (<7 h) and late bedtimes, DLMO averaged at 23:11 h (15), which is in line with the findings in our present sample. Only among an adolescent subgroup (12–16 years) with clinical diagnosed DSWPD, average DLMO occurred at 01:22 h (31). These heterogeneous findings are not unusual and support the notion of a "circadian" and "non-circadian" etiology of a late chronotype.

In line with this notion, our findings did not fully confirm our initial assumption that later chronotypes would present with a later circadian phase than their less severe peers. Specifically, comparing slight late with moderate late types (22.66 vs. 23.65 h) our assumption was partially confirmed. Yet, extreme late types did not show a more severe delay in circadian phase (23.65 h vs. 23.49 h) compared to moderate types. Thus, for extreme late chronotypes, in addition to the already existing circadian delay, further psychological and behavior-related factors presumably exacerbate the late sleep-wake pattern and observed circadian misalignment.

The second aim of the study was to explore how chronotype influences sleep quality, daytime sleepiness, evening sleep propensity, and mood. Generally, sleep quality decreased with increasing lateness. Yet, considering that a normal entrained circadian phase provides the best opportunity for restorative sleep (that is, an individual's sleep phase is in line with their biological night) our subgroup analyses appear to support that. Irrespectively of the circadian delay, our moderate late chronotypes perceived better and consistent sleep quality for both school- and weekend nights. This is in line with their phase angle, which not only corroborates the phase angles of a normal sleeping teenage cohort (32, 33), but also remains consistent between school- and weekend nights. Slight late types, on the other hand, slept at an earlier time in their biological night on school days, thus, perceived a lower sleep quality on those days. Yet, on weekends, when their phase angles were in line with those of the moderate late types, sleep quality equally improved. With regard to the extreme late chronotypes, which presented with a significantly larger circadian misalignment on weekends by staying up even later into their biological night, sleep quality was significantly worse than on school nights. Therefore, the general assumption that individuals with a delayed sleep-wake phase syndrome sleep just fine when allowed to choose their own bed- and rise time is not as simple. Based on our findings, the best opportunity for a good night's sleep is then achieved, when the bed- and wake time choice is also in line with one's intrinsic biological night. Unfortunately, individuals with extreme late

chronotypes are struggling with just that, particularly those that present with a long circadian rhythm (i.e., 25 h instead of ∼24 h) (21, 25).

Despite the different perceived sleep qualities upon awakening, no differences in daytime sleepiness were detected. However, the present sample compared extreme late types with slight late types, and such differences may only be detectable between early and late chronotypes. With regard to subjective sleepiness over the course of the evening, extreme late types rated their sleepiness significantly higher at all times compared to their earlier peers. Similarly, objectively assessed sustained evening attention was lower among moderate late and extreme late types. Therefore, our findings cannot confirm the hypothesis, that reduced sleepiness scores and higher evening attention in later chronotypes may be driving the delay of their sleep period. Moreover, higher evening attention among slight late types is in agreement with the observed shorter phase angles in this subgroup, implying that these adolescents have chosen a bedtime earlier in their biological night. Overall, while sleep propensity among our study sample might indeed be lower compared to normal sleeping adolescents, our findings highlight that it only explains to some extend the sleep-wake patterns of extreme late chronotypes compared to moderate and slight late types. In other words, genetics and bioregulatory changes of the circadian system during adolescent development play only one part in determining chronotype. The other chronotype-determining factors lay in the psychosocial behavior that inevitably leads to differences in "zeitgeber" signals, such as light exposure, food consumption, and physical activity patterns. A meta-analyses on the effects of electronic device use on adolescent's sleep revealed an increase in inadequate sleep quantity, as well as poor sleep quality, and excessive daytime sleepiness (83). Thus, psychosocial behaviors that strain sleep timing can perpetuate and aggravate a late chronotype.

As indicated in the introduction, late chronotype has repeatedly shown to increase the risk for mood disturbances in children and adolescents, particularly depression (4, 34, 82). Our findings corroborate this concerning fact, as symptoms of depression, anxiety, and stress were perceived considerably worse with increasing lateness. Yet, the strength of this effect between subgroups was somewhat surprising, given that only adolescents without a previous diagnosis of depression and anxiety were included in the study. Thus far, the association between late chronotype and mood disorders among adolescents is generally referred to inadequate sleep duration (84, 85). However, in the present sample, sleep duration did not differ between groups in that a shorter sleep duration would be responsible for the observed negative mood among extreme late types. In line with this, several studies have revealed that independently of sleep duration, later chronotype adolescents show increased symptoms of depression, and less positive mood compared to their early chronotype peers (86–88). Dolsen and Harvey (82) further investigated this assumption among 163 adolescents with an evening circadian preference. Higher negative affect was associated with a later DLMO. Referred to our sample, this would explain lower mood scores among the moderate and extreme late types compared to the slight late types. However, extreme late types did not present with later circadian phase than moderate late types, indicating that the additional circadian misalignment puts these youngsters at an even greater risk. Overall, the mechanism through which chronotype affects mental health is still poorly understood.

Our last aim was to explore the role of circadian timing on bedtime choice and sleep duration. As mentioned earlier, pervious research has shown that not all adolescents benefit equally from the recommended treatment to advance bed- and rise times. Morning bright light and exogenous evening melatonin are applied to phase advance circadian timing, and thus sleep phase (71). But to what extend does DLMO predict bedtimes among late chronotype adolescents? Among the present sample, DLMO did not predict bedtime and overall sleep duration, neither on school- nor on weekend days. This is in contrast to findings from a healthy normally-sleeping cohort of adolescents (32). Yet, our findings indicate that similar to patients with DSWPD (20), late chronotype adolescents show a greater variability in DLMO timing, as observed in the present sample. In contrast, sleep duration on school days was mainly predicted by wake-up time, whereas bedtime was the main predictor for sleep duration on weekends. Indeed, a large body of research supports the major role of early school start times on adolescent's sleep (89). As a result, schools that implement later morning schedules note increased sleep duration, improved class attendance, and reduced depressive symptoms (90).

Taken together, the findings of this explorative study show that as chronotype lateness increases, so does the risk for impaired mood and sleep quality. Moreover, extreme late types stood out not by an even later circadian delay, but by an additional misalignment between their intrinsic sleep timing and actual sleep phase. Considering that there are circadian and non-circadian reasons for a late chronotype, or as in case for the extreme late types a combination of both, studying circadian phase angles of entrainment among extreme chronotypes and psychiatric populations will further help to understand the link between chronotype and affective disorders.

LIMITATIONS AND FUTURE DIRECTIONS

We are aware that our work is not without limitations. First, the present study had a small sample size that limits the generalizability of the findings, particularly when dichotomized to subgroups. To this end, we supplemented inferential statistics with effect sizes that can be interpreted for their meaningfulness. However, it would be beneficial to replicate these explorative findings with a larger sample size. Second, not testing female adolescents could not provide reliable data regarding sex differences in mood and eating disorders in late chronotype adolescents (91). Third, ceiling floor effects among a sample composed only of late chronotypes may have prevented the detection of differences in sleep duration and daytime sleepiness. Future replication studies comparing early, intermediate, and late chronotypes may uncover such differences. In addition, a shorter time interval between the sleepiness ratings (e.g., 15 min instead of 60 min) might have allowed us to detect differences. Fourth,

in our data, phase angle of entrainment was calculated using average bedtimes from a sleep log, which may have contributed to the low correlation between DLMO and bedtime. Fifth, a non-clinical sample was used for the study. In light of recent studies suggesting even higher prevalence rates of circadian rhythm disorders in psychiatric adolescents (92), further investigation of these issues with psychiatric samples may result in more clinically relevant findings. Last, we did not capture daylight exposure, which would shed further light on the etiology of adolescents late chronotype and their risk for lower sleep quality, and mood scores. Indeed, as stated in a recent Nature report, increasing daytime illuminance diminishes the impact of genetic factors that contribute to the interindividual differences in chronotype. In contrast, spending most of the day in relatively dim light conditions not only delays circadian timing, but also amplifies interindividual differences in circadian phase angle and preferred sleep-wake schedules (29). Thus, future studies in which daytime behavior and light exposure are compared between intermediate and late chronotype adolescents could shed further light on influenceable prevention and risk factors in support of a healthy sleep-wake schedule (i.e., active commuting to school, recess, outdoor sports, indoor light illumination).

CONCLUSION

Taken together, our findings highlight that with increasing lateness, the risk to develop mood disorders increases. However, in line with a collective body of research on chronotype, our data indicate that the factors contributing to a late chronotype are versatile and complex. Thus, suggesting that there is no "one-fits all" treatment approach. Therefore, prevention measures early in adolescents' development should be considered. First and foremost, parents, teachers, and pediatricians, as well as adolescents should be educated that late sleep-wake rhythms in adolescence are more than just a normal, temporary condition. Misalignments, such as conflicts between one's internal body clock and outside social world (social jetlag), or between internal biological night and actual sleep phase obtained, lead to several negative physical and psychological health impairments through mechanisms that are yet to be fully understood. In light of this, our work provides insights into the sleep pattern, circadian phase, phase angle of entrainment, and sleep propensity of non-clinical late chronotype adolescents. Based on a recent finding that increasing daytime illuminance diminishes the biological risk factors to develop a late chronotype, we therefore recommend that schools evaluate indoor light conditions and time spent outdoors, so that adolescents are exposed to adequate light conditions during a school day.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC application number OFR 100.16–HREC/16/SAC/90. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CL and MG: conceptualization and methodology. CL and CR: data acquisition. CL: data pre-processing, data analysis, and writing of manuscript. CL, CR, GM, and MG: results interpretation. All authors revised, edited and contributed to the manuscript and approved the submitted version.

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Restless Legs Syndrome Prevalence and Clinical Correlates Among Psychiatric Inpatients: A Multicenter Study

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Background: There are only limited reports on the prevalence of restless legs syndrome (RLS) in patients with psychiatric disorders. The present study aimed to evaluate the prevalence and clinical correlates in psychiatric inpatients in Germany and Switzerland.

Methods: This is a multicenter cross-sectional study of psychiatric inpatients with an age above 18 years that were diagnosed and evaluated face-to-face using the International RLS Study Group criteria (IRLSSG) and the International RLS severity scale (IRLS). In addition to sociodemographic and biometric data, sleep quality and mood were assessed using the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), the Epworth Sleepiness Scale (ESS), and the Patient Health Questionnaire (PHQ-9). In addition to univariate statistics used to describe and statistically analyze differences in variables of interest between patients with and without RLS, a logistic model was employed to identify predictors for the occurrence of RLS.

Results: The prevalence of RLS in a sample of 317 psychiatric inpatients was 16.4%, and 76.9% of these were diagnosed with RLS for the first time. RLS severity was moderate to severe (IRLS ± SD: 20.3 ± 8.4). The prevalences in women ($p = 0.0036$) and in first-degree relatives with RLS ($p = 0.0108$) as well as the body mass index (BMI, $p = 0.0161$) were significantly higher among patients with RLS, while alcohol consumption was significantly lower in the RLS group. With the exception of atypical antipsychotics, treatment with psychotropic drugs was not associated with RLS symptoms. Regarding subjective sleep quality and mood, scores of the PSQI ($p = 0.0007$), ISI ($p = 0.0003$), and ESS ($p = 0.0005$) were higher in patients with RLS, while PHQ-9 scores were not different. A logistic regression analysis identified gender

(OR 2.67; 95% CI [1.25; 5.72]), first-degree relatives with RLS (OR 3.29; 95% CI [1.11; 9.73], ESS score (OR 1.09; 95% CI [1.01; 1.17]), and rare alcohol consumption (OR 0.45; 95% CI [0.22; 0.94] as predictors for RLS.

Conclusions: Clinically significant RLS had a high prevalence in psychiatric patients. RLS was associated with higher BMI, impaired sleep quality, and lower alcohol consumption. A systematic assessment of restless legs symptoms might contribute to improve the treatment of psychiatric patients.

Keywords: restless legs syndrome, RLS, prevalence, psychiatric disorders, sleep quality, multicenter study, psychotropic drugs

INTRODUCTION

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a common neurological sensorimotor disorder often associated with severe sleep disturbances and an impaired quality of life (1). The reported RLS prevalence varies between 3.9 and 14.3% depending on the population studied and the criteria used (2). Some but not all reports suggest marked geographic differences in the prevalence of RLS with a lower prevalence in Asian countries (3–5). If the former four minimal (6) or later revised four essential diagnostic criteria are used (7), RLS is reported in 7.2–10.6% of the Caucasian population (8–14). When so-called RLS mimics are excluded, significantly lower prevalence rates of 0.4–2.4% are seen in different samples (15, 16). The proportion of patients in need of treatment is estimated to vary between 1.5 and 2.7% (15). In two prospective studies with observation periods of 2 and 5.2 years, cumulative incidences of 7.0 and 9.1%, respectively, were reported (17). Women are affected up to twice as often as men presumably due to parity; the risk of developing RLS increases with increasing number of births (3, 9, 18). Risk factors for RLS include genetic predisposition, age, gender, parity, and lifestyle factors (9, 19). Secondary or comorbid RLS may occur as a result of another condition such as iron deficiency, renal disease, or pregnancy (20). In addition, secondary RLS can be induced by psychotropic drugs and other medications (21–23). Current hypotheses on the etiology of RLS favor a heterogeneously genetically determined, complex disorder with involvement of abnormal iron metabolism, multiple neurotransmitters, and the opioid system. As revealed by neuroimaging and neurophysiological studies, a subtle receptor dysfunction of the central dopaminergic system seems to play a critical role in the pathophysiology of RLS (24). Clinically, levodopa and dopamine receptor agonists improve RLS, whereas dopamine antagonists such as antipsychotics may evoke or worsen RLS suggesting a decreased dopaminergic state (25). Furthermore, tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, requires iron as a cofactor; a low brain iron state has been repeatedly demonstrated in RLS (26). However, current evidence points to a pre-synaptic hyperdopaminergic state in RLS as revealed by a decreased dopamine transporter activity and a decreased dopamine reuptake leading to a downregulation of postsynaptic D2 dopamine receptors (27). A circadian regulation of dopaminergic activity, i.e., a nadir at night and a peak in the morning, may explain why dopaminergic drugs are effective in the treatment of restless legs symptoms in the presence of a hyperdopaminergic state (28). However, by further downregulating the dopamine receptors, medication at night might paradoxically worsen restless legs symptoms, a phenomenon known as augmentation which is the most important long-term adverse effect of dopaminergic therapy (29).

Although the underlying mechanisms are not fully understood, epidemiological studies suggest that psychiatric disorders and RLS may frequently co-occur, leading to complex interactions between both conditions (25, 30, 31). A bidirectional cause-and-effect relationship is postulated, however, the available evidence is scarce (25). Particularly, comorbid anxiety and depressive disorders are major factors influencing the course of RLS and quality of life of affected patients (25). Previous studies found that treatment outcomes of RLS with comorbid depression are worse compared to RLS without depressive symptoms (32). Furthermore, longitudinal studies have demonstrated an increased risk of depression in RLS patients and, vice versa, an increased likelihood of the occurrence of RLS in depression, suggesting a bidirectional relationship between both disorders (33). Moreover, patients with mental disorders often require treatment with psychotropic drugs that are associated with an increased risk to induce or exacerbate RLS (21–23). However, an increased risk of depression in patients with RLS may also be independent of psychopharmacological effects (34).

Despite the close relationship between RLS and psychiatric disorders, studies on the prevalence of RLS in psychiatric patients are scarce and refer to limited patient samples in Asia (35–37) or otherwise strongly selected psychiatric samples (38, 39). The aim of the present study was to estimate the prevalence and assess the clinical correlates of RLS in a larger sample of psychiatric inpatients in Germany and Switzerland.

MATERIALS AND METHODS

Study Design and Participants

The multicenter cross-sectional study, which was initiated by sleep medicine experts of the German Association for Psychiatry, Psychotherapy, and Psychosomatics, was conducted at five psychiatric hospitals in Germany and two hospitals in Switzerland. The study protocol was approved by the local ethics committees of each participating site and was conducted in accordance with the ethical guidelines of the current version of

the Declaration of Helsinki. Recruitment of study participants was consecutive in the period from February 2019 to December 2020. Eligible participants were randomly selected and invited to participate in the study. Patients who were approached and expressed willingness to participate were fully informed about the purpose of the study, and written informed consent was obtained from all participants. Participants of any gender and with an age above 18 years with a psychiatric disorder classified in the International Classification of Diseases (ICD-10) were included in the study (40). Exclusion criteria were severe psychotic disorders or significant cognitive impairment preventing the subject to fully understand the nature of the study, acute suicidality, involuntary admission to the hospital, and lack of capacity to understand the purpose of the study. Known or treated RLS was not an exclusion criterion.

Assessments

Sociodemographic and biometric data including gender, age, and education, as well as health information, were obtained at the time of enrollment. Psychiatric and comorbid medical disorders including non-organic and organic sleep disorders according to the criteria of the ICD-10 classification were assessed based on medical history and clinical examination and were documented in the case report form. In addition, the use of the following psychiatric medications was recorded: antidepressants [selective serotonin reuptake inhibitors (SSRI), selective serotonin and noradrenaline reuptake inhibitors (SSNRI), tricyclic antidepressants (TCA), mirtazapine, agomelatine, and others], antipsychotics (atypical and typical), hypnotics (benzodiazepines, non-benzodiazepines), mood stabilizers (lithium, lamotrigine, valproate, carbamazepine), anticonvulsants (pregabalin, gabapentin), opioids, and stimulants.

RLS Diagnosis

Symptoms of RLS were assessed face-to-face by an RLS expert and were based on the five essential diagnostic criteria defined by the International RLS Study Group (IRLSSG) (1): (1) an urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs; (2) the urge to move the legs and any accompanying unpleasant sensations beginning or worsening during periods of rest or inactivity such as lying down or sitting; (3) are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) the urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day; and (5) the presence of the above features cannot solely be accounted for as symptoms primary to another medical or a behavioral condition. According to criterion 5, a diagnosis of RLS is made after careful consideration of differential diagnoses and the exclusion of mimicking conditions such as leg cramps, positional discomfort, anxiety, or drug-induced akathisia.

RLS Severity

In the case of an RLS diagnosis, the intensity, duration, and frequency of RLS symptoms, as well as their impact on sleep, daytime well-being, and mood, were assessed using the International Restless Legs Scale (IRLS), a rating scale developed by the IRLSSG. This scale includes 10 items on a five-point Likert scale. RLS severity is classified as mild with a score of 1–10, moderate with 11–20, severe with 21–30, and very severe with 31–40 (41).

Sleep Quality

Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI) (42). The PSQI is a 19-item questionnaire that assesses subjective sleep quality including sleep latency, duration, disturbances, and daytime dysfunction. PSQI global sleep quality scores are continuous; the total PSQI score ranges from 0 to 21 points, with a score above 5 indicating poor sleep quality.

Insomnia

Insomnia was measured using the Insomnia Severity Index (ISI), a seven-item questionnaire that assesses difficulty falling asleep, nighttime awakenings, early morning awakenings, impairment of daytime functioning, distress and worry about sleep, and current dissatisfaction with sleep (43, 44). Each item is rated on a Likert scale ranging from 0 to 4. The ISI total score ranges from 0 to 28 points and classifies subjects into "no or minimal insomnia," "subthreshold insomnia," "moderate insomnia," and "severe insomnia" groups (45). A score of 7–14 represents subthreshold insomnia; a score above 14 represents manifest insomnia (46).

Daytime Sleepiness

To measure daytime sleepiness, the Epworth Sleepiness Scale (ESS), a self-administered 8-item questionnaire, was used (47). The rating for each item is on an ascending scale from 0 to 3. The ESS asks for the likelihood of dozing off or falling asleep in different everyday situations, in contrast to feeling just tired. A total ESS score greater than 10 (range 0–24) is indicative of increased daytime sleepiness.

Mood

We used the Patient Health Questionnaire (PHQ-9), a 9-question assessment of the occurrence of depressive symptoms that uses a four point Likert scale (0: not at all; 3: nearly every day), to screen for the presence and severity of depression (48–50). Scores from 5 to 9 represent mild depression, 10–14 moderate depression, 15–19 moderately severe depression, and 20 or more severe depression.

Statistical Analysis

The main outcome parameter was the prevalence of an RLS diagnosis. Exploratory analyses were conducted to determine whether there were diagnosis- or treatment-related differences in the frequency of RLS and whether certain aspects of the socio- or biometric data were associated with the occurrence of RLS. Furthermore, differences in daytime sleepiness, insomnia symptoms, and sleep quality between patients with and without RLS were analyzed. For variables assessed at an ordinal or nominal scale, descriptive statistics are provided as frequencies in absolute numbers and percentages. For those variables, Cramer's V is used as an effect size measure,

TABLE 1 | Descriptive statistics for variables measured at with ordinal or nominal scale and results of statistical assessment of differences between patients with and without restless legs syndrome (RLS).

	Total (*n* = 317)		**No RLS (*n* = 265)**		**RLS (*n* = 52)**					
Variables	***n***	**%**	***n***	**%**	***n***	**%**	**p**	**Cramer's V**	**OR**	**95% CI**
Gender										
Female	180	56.8	141	53.2	39	75	**0.0036**	0.1629	**2.64**	**[1.35; 5.15]**
Male	137	43.2	124	46.8	13	25				
BMI (kgm^{-2})										
<18.5	15	4.7	15	5.7	0	0	**0.0161**	0.1928		
18.5 ≤ BMI < 25.0	142	44.8	118	44.5	24	46.2				
25.0 ≤ BMI < 30.0	85	26.81	77	29.1	8	15.4				
30.0 ≤ BMI < 35.0	48	15.1	35	13.2	13	25				
35.0 ≤ BMI < 40.0	19	6	14	5.3	5	9.6				
40.0 ≤ BMI	8	2.5	6	2.3	2	3.9				
Education (years)										
≤10	79	24.9	69	26	10	19.2	0.3811	0.0583	1.47	[0.70; 3.11]
>10	238	75.1	196	74	42	80.8				
Primary psychiatric diagnosis (ICD-10)										
F10-19: Mental and behavioral disorders due to psychoactive substance use	58	18.3	54	20.4	4	7.7	0.2043	0.1387		
F20-29: Schizophrenia, schizotypal and delusional disorders	30	9.5	25	9.4	5	9.6				
F30-39: Mood [affective] disorders	173	54.6	139	52.5	34	65.4				
F40-48: Neurotic, stress-related and somatoform disorders	30	9.5	26	9.8	4	7.7				
F60-69: Disorders of adult personality and behavior	24	7.6	19	7.2	5	9.6				
F90-98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	2	0.6	2	0.8	0	0				
Secondary psychiatric diagnoses										
No	153	48.3	124	46.8	29	55.8	0.2882	0.0665		
Yes	164	51.74	141	53.21	23	44.23				
No. of secondary psychiatric diagnoses										
0	153	48.3	124	46.8	29	55.8	0.4878	0.0876		
1	86	27.1	76	28.7	10	19.2				
2	47	14.8	40	15.1	7	13.5				
≥3	31	9.8	25	9.4	6	11.5				

(Continued)

TABLE 1 | (Continued)

	Total (*n* = 317)		No RLS (*n* = 265)		RLS (*n* = 52)					
Variables	***n***	**%**	***n***	**%**	***n***	**%**	**p**	**Cramer's V**	**OR**	**95% CI**
Somatic diagnoses										
No	151	47.6	127	47.9	24	46.2	0.8798	0.0131	1.07	[0.59; 1.95]
Yes	166	52.4	138	52.1	28	53.9				
Sleep disorders*										
No	231	72.9	193	72.8	38	73.1	1	0.0021	0.99	[0.51; 1.93]
Yes	86	27.1	72	27.2	14	26.9				
RLS in first-degree relatives (n = 313)										
No	292	93.3	249	95	43	84.3	**0.0108**	0.1583	**3.56**	**[1.39; 9.11]**
Yes	21	6.7	13	5	8	15.7				
Psychopharmacological treatment										
No	39	12.3	34	12.8	5	9.6	0.6475	0.0362	1.38	[0.51; 3.72]
Yes	278	87.7	231	87.2	47	90.4				
Tobacco use (n = 316)										
No	137	43.4	115	43.6	22	42.3	1	0.0094	1.05	[0.58; 1.92]
Yes	179	56.7	149	56.4	30	57.7				
Frequency of alcohol consumption (n = 315)										
Never	67	21.7	56	21.3	11	21.2	**0.0016**	0.2356		
1/month	90	28.6	64	24.3	26	50				
2–4/month	60	19.1	52	19.8	8	15.4				
2–3/week	31	9.8	28	10.7	3	5.8				
4–6/week	17	5.4	17	6.5	0	0				
Daily	50	15.9	46	17.5	4	7.8				
No. of alcoholic drinks/day (n = 248)**										
1–2	123	49.6	94	45.2	29	72.5	**0.0081**	0.2356		
3–4	45	18.2	39	18.8	6	15				
5–6	33	13.3	30	14.4	3	7.5				
7–9	10	4	10	4.8	0	0				
≥10	37	14.9	35	6.8	2	5				

(Continued)

TABLE 1 | (Continued)

	Total (*n* = 317)		No RLS (*n* = 265)		RLS (*n* = 52)					
Variables	***n***	**%**	***n***	**%**	***n***	**%**	**p**	**Cramer's V**	**OR**	**95% CI**
ESS (n = 315)										
≤10	227	72.1	199	75.7	28	53.9	**0.0022**	0.1805	2.67	[1.44; 4.94]
>10	88	28	64	24.3	24	46.2				
PSQI (n = 304)										
≤*5*	43	14.1	41	16.1	2	4	**0.0249**	0.1292	4.62	[1.08; 19.76]
>*5*	261	85.1	213	83.9	48	96				
ISI (n = 313)										
≤7	63	20.1	61	23.3	2	3.9	**0.0009**	0.1783	**7.44**	**[1.76; 31.47]**
>7	250	79.9	201	76.7	49	96.1				
≤14	154	49.2	139	53.1	15	29.4	**0.0021**	0.1746	**2.71**	**[1.42; 5.19]**
>14	159	50.8	123	47	36	70.6				
PHQ-9 (n = 315)										
≤4	19	6	15	5.7	4	7.8	0.0951	0.1321		
5 ≤ PHQ-9 ≤ 9	49	15.6	46	17.4	3	5.9				
10 ≤ PHQ-9 ≤ 14	65	20.6	56	21.2	9	17.7				
PHQ-9 ≥ 15	182	57.8	147	55.7	35	68.6				

*Effect size measure, Cramer's V; OR, odds ratio; 95% CI, 95% confidence interval of the odds ratio; BMI, body mass index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire; p, Log-Likelihood χ^2 test p-value or Fisher's exact p, respectively. *Sleep disorders according to ICD-10: F51.0: Non-organic insomnia; F51.1: Non-organic hypersomnia; F51.2: Non-organic disorder of the sleep-wake schedule; F51.3 Sleepwalking (somnambulism); F51.4Sleep terrors (night terrors); F51.5: Nightmares; G25.80: Periodic leg movements in sleep; G47.0: Disorders of initiating and maintaining sleep (insomnias); G47.1: Disorders of excessive somnolence (hypersomnias); G47.2: Disorders of the sleep-wake schedule; G47.3: Sleep apnea; G47.4: Narcolepsy and cataplexy; G47.8: Other sleep disorders; G25.8: RLS was explicitly not taken into account. **A standard drink contains 10–12 g of alcohol (i.e., 0.33l of regular beer, 0.125l of wine or 4cl shot of distilled spirits). Statistically significant results are shown in bold.*

TABLE 2 | Descriptive statistics for variables measured at a continuous scale and results of statistical assessment of differences between patients with and without restless legs syndrome (RLS).

Variables	Total (n = 317)		No RLS (n = 265)		RLS (n = 52)		d	p
	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]		
Age (years)	42.2 ± 15.3	41 [29; 55]	41.6 ± 15.4	40 [29; 53]	45.8 ± 14.4	49 [34; 57]	0.28	0.0512
Age at psychiatric diagnosis (years) (n_T = 312, n_{RLS-} = 260, n_{RLS+} = 52)	33.0 ± 14.4	31 [21; 42]	32.6 ± 14.1	30 [21; 40]	35.0 ± 15.5	33 [22; 46]	0.17	0.3255
Duration of illness (years after diagnosis) (n_T = 312, n_{RLS-} = 260, n_{RLS+} = 52)	9.2 ± 10.2	6 [1; 15]	8.9 ± 9.9	5 [1; 15]	10.7 ± 11.7	7 [2; 17]	0.18	0.2881
PSQI (n_T = 304, n_{RLS-} = 254, n_{RLS+} = 50)	10.6 ± 4.7	10 [7; 15]	10.2 ± 4.7	10 [6; 14]	12.7 ± 4.3	14 [9; 16]	1.29	**0.0007**
ISI (n_T = 313, n_{RLS-} = 262, n_{RLS+} = 51)	14.1 ± 6.9	15 [9; 19]	13.5 ± 7.0	13.5 [8; 19]	17.2 ± 5.3	18 [13; 15]	0.56	**0.0003**
ESS (n_T = 315, n_{RLS-} = 263, n_{RLS+} = 52)	7.7 ± 4.8	7 [4; 11]	7.3 ± 4.8	7 [3; 10]	9.7 ± 4.2	10 [6; 13]	0.51	**0.0005**
PHQ-9 (n_T = 315, n_{RLS-}=264, n_{RLS+} = 51)	15.2 ± 6.6	16 [10; 20]	15.0 ± 6.4	16 [10; 20]	16.4 ± 6.1	17 [13; 20]	0.22	0.1684
No. of cigarettes/day (n_T = 178, n_{RLS-} = 148, n_{RLS+} = 30)	17.3 ± 10.6	15 [10; 15]	17.6 ± 10.7	17.5 [10.0; 20.0]	15.7 ± 10.4	12.5 [10.0; 20.0]	0.18	0.3057
No. of smoker years (n_T = 205, n_{RLS-} 170, n_{RLS+} = 35)	19.7 ± 13.1	30 [18; 40]	19.5 ± 12.0	19 [8; 30]	20.8 ± 14.4	17 [8; 30]	0.10	0.7296

SD, standard deviation; IQR, interquartile range; d, effect size Cohen's d (small effect: d < 0.5; medium effect: 0.5 ≤ d < 0.8; large effect: ≥ 0.8), n_T, number of total; n_{RLS-}, number of RLS negative patients; n_{RLS+}, number of RLS positive patients; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PHQ-9, Patient Health Questionnaire; since all parameters proofed to be not normally distributed by Shapiro–Wilks test, p-value refers to the Wilcoxon-Two-Sample test. Statistically significant results are shown in bold.

where values less than 0.3 indicate a small effect, values from 0.3 to 0.4 a medium effect, and greater than 0.4 a large effect. Differences in the distribution of variables between patients with and without RLS were assessed using a Likelihood-ratio chi-square test if the number of characteristic expressions exceeded two; if the number was equal to two, Fisher's exact test was used. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated to quantify the strengths of associations. For continuously measured variables, the mean and its standard deviation as well as the median and the interquartile range are given as descriptive statistics. Cohen's d was calculated as a measure of effect size, where values less than 0.5 indicate a small effect, values from 0.5 to 0.8 a medium effect, and values greater than 0.8 a large effect. Because all continuously measured variables did not follow a Gaussian distribution as assessed by a Shapiro–Wilk test, differences in distributions between patients with and without RLS were assessed non-parametrically using the Wilcoxon Two-sample test. All tests were performed with a double-sided p (<0.05).

To identify significant risk factors for the occurrence of RLS, all variables that showed significant differences in distribution between patients with and without RLS at the univariate level were considered for inclusion in a logistic regression model. After exclusion of highly correlated variables, logistic regression analysis was performed with age, gender, RLS family history, BMI, ESS, and PSQI scores, frequency of alcohol consumption, use of antidepressants, and use of antipsychotics as independent factors. All statistical analyses were performed using SAS software (version 9.4M3; SAS Institute, Cary, NC, United States).

RESULTS

Overall, 331 patients met the inclusion criteria and were invited to participate in the study. Of these, 14 patients declined the study participation after being fully informed about the purpose of the study. A total of 52 of the 317 patients met the diagnostic criteria of RLS according to the IRLSSG (1), representing a prevalence of 16.4% (95% CI: [12.3; 20.5]). The diagnoses of the patients were classified according to the following ICD-10 codes: F10-19: Mental and behavioral disorders due to psychoactive substance use; F20-29: Schizophrenia, schizotypal, and delusional disorders; F30-39: Mood [affective] disorders; F40-48: Neurotic, stress-related and somatoform disorders; F60-69: Disorders of adult personality and behavior; F90-98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence. Further sample characteristics of patients with and without RLS for ordinally and nominally scaled variables are given in **Table 1**. Among patients with RLS, an RLS diagnosis was previously known in 23.1, and 19.2% were treated with an RLS-specific medication. In 54.8% of all patients with RLS, complaints of symptoms had been present for more than 2 years prior to diagnosis and more than 3 years in 28.6% of patients. In women and in first-degree relatives, RLS prevalence was significantly higher in patients with RLS compared to the

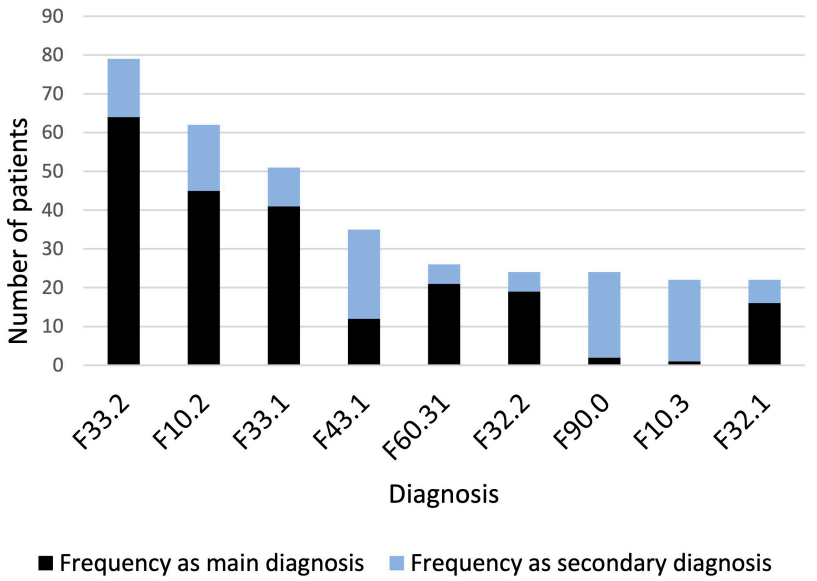

FIGURE 1 | Diagnoses with a cumulative frequency > 20. F33.2: Recurrent depressive disorder, current episode severe without psychotic symptoms; F10.2: Mental and behavioral disorders due to use of alcohol, dependence syndrome; F33.1: Recurrent depressive disorder, current episode moderate without psychotic symptoms; F43.1: Posttraumatic stress disorder; F60.31: Emotionally unstable personality disorder, borderline; F32.2: Severe depressive episode; F90.0: Attention deficit/hyperactivity disorder; F10.3: Mental and behavioral disorders due to use of alcohol, withdrawal state; F32.1: Moderate depressive episode.

non-RLS group. 15.7% of the patients with RLS had a positive family history of RLS. In addition, BMI was significantly higher in patients with RLS, while the frequency of alcohol consumption as well as the number of alcoholic drinks per day was significantly lower. Furthermore, PSQI (sleep quality), ISI (insomnia), and ESS (daytime sleepiness) scores were significantly higher in patients with RLS.

No differences between patients with and without RLS were observed for the distribution of primary and secondary psychiatric diagnoses, somatic and sleep medicine diagnoses, or for current psychopharmacological therapy (except for antipsychotics), smoking, educational status, or PHQ-9-scores (**Table 1**).

Sample characteristics related to the distribution of continuous variables are reported in **Table 2**. Although patients with RLS tended to be slightly older than patients without RLS, this difference was not significant. Statistically significant differences in the prevalence of patients with increased daytime sleepiness, impaired sleep quality, and insomnia symptoms are reflected in significant differences between patients with and without RLS in the overall distribution of these scores. No significant differences were observed in age at psychiatric diagnosis, duration of psychiatric illness, smoking habits, or the distribution of PHQ-9 scores.

Overall, there was a wide diversity of primary and secondary psychiatric diagnoses. To assess the association between specific psychiatric diagnoses and RLS, only diagnoses with a cumulative frequency of more than 20 were considered; this resulted in 9 concomitant diagnoses in the data set. The frequencies of the corresponding diagnoses according to ICD-10 are shown in **Figure 1**.

Treatment with antidepressants, hypnotics, mood stabilizers, or anticonvulsants (when considered at the class level and at the level of specific drugs), as well as with opiates or stimulants were not associated with RLS (**Supplementary Table 2**). A statistically significant association between pharmacotherapy and RLS was observed only for treatment with antipsychotics ($p = 0.0491$). RLS patients received antipsychotics more often than patients without RLS. When atypical and typical antipsychotics were analyzed separately, the effect was restricted to atypical antipsychotics ($p = 0.0317$; **Supplementary Table 2**).

Restless legs syndrome severity according to the IRLS was reported between moderate and severe (mean 20.3; median 22). A comorbidity or secondary RLS was affirmed 21 times, allowing multiple answers. Thyroid disorders were the most frequent comorbidity (15.4%, $n = 8$) followed by drug-induced RLS (13.5%, $n = 7$). In addition, drug-induced worsening of RLS was reported in 17.7% (n = 9) of cases. Further details are reported in **Tables 3**, **4**.

To identify significant predictors for the occurrence of RLS, all variables that showed significant differences in distribution between patients with and without RLS at the univariate level were considered for inclusion in a logistic regression model. After exclusion of highly correlated variables, logistic regression analysis was performed and included age, gender, RLS family history, BMI, ESS, and PSQI scores, frequency of alcohol consumption, use of antidepressants, and use of antipsychotics as independent factors (**Table 5**). Of these, age, gender, positive family history, and ESS score were statistically associated with higher risk of RLS. Psychiatric patients with first-degree relatives who have RLS had the highest RLS risk (OR 3.29, 95% CI [1.1; 9.7]). Women had a 2.7-fold higher

risk (95% CI: [1.25; 5.72]) compared to men. Increased daytime sleepiness was also associated with the occurrence of RLS (OR 1.09, 95% CI: [1.01; 1.17]). On the other hand, a higher frequency of alcohol consumption was associated with a lower risk of RLS (OR 0.45, 95% CI: [0.22; 0.94]). Age, BMI, PSQI score, and the use of antidepressant or antipsychotic medications were not significantly associated with an increased RLS risk (**Figure 2**). A receiver operating characteristic (ROC) curve resulted in an area under the curve of 0.7747, which corresponds to an acceptable discrimination between the RLS yes/no conditions (**Figure 3**).

DISCUSSION

In the present multicenter study, an RLS prevalence of 16.4% was observed in a sample of 317 psychiatric inpatients, which is markedly higher than the RLS frequency in the general population, which is estimated to be 5–10% (2, 12, 51). According to the IRLS, RLS in our patients was moderate to severe. A prior study in a smaller sample of 117 hospitalized psychiatric patients reported an RLS prevalence of 19.7% (39). In contrast to the present study, only patients with comorbid severe sleep disturbances such as insomnia, dyssomnia or daytime sleepiness were included in this retrospective analysis, precluding direct comparison with the present results. In a Spanish cross-sectional study of a sample of 100 non-demented psychogeriatric outpatients (mean age 76.9 ± 6 years), a prevalence of 11.1% was shown for definite RLS with an additional prevalence of 10.1% for possible RLS. Because of the specific age range of the included patients (38), there is no direct comparability with the present study sample (mean age 42.2 ± 15.3), as RLS prevalence is age-dependent (2). Studies in Lebanon revealed RLS prevalence rates of 14.3 (37) and 18.0% (35) in a sample of 203 and 126 hospitalized psychiatric patients, respectively. Both studies used the IRLS not only as a tool to determine the severity of RLS, but also as a diagnostic screening instrument. However, the scale is only validated as an instrument for determining severity and not for diagnosing RLS (41), clearly limiting the results of these studies. A more recent study in Singapore yielded a prevalence of RLS/PLMS (periodic leg movements during sleep) of 14.8% in a sample of 400 psychiatric outpatients with schizophrenia, mood disorders, or anxiety disorders, based on ICD-9 diagnostic criteria (36). In this study, two out of four positive responses on RLS-related questions were considered sufficient for an RLS diagnosis. In addition, the criteria according to the IRLSSG were not applied. Comparability of these results with the present study is highly limited due to methodological differences and limitations. In addition, RLS prevalences have been shown to be much lower in Asia (0.9–7.2%; overview in Ref. (3) than that determined by Hombali et al. (36).

Among the psychiatric inpatients with RLS included the present study, a high proportion (76.9%) were previously undiagnosed, although for 54.8% of the patients, symptoms had been present for more than 2 years. It has been repeatedly demonstrated that RLS is often underdiagnosed and untreated (52, 53) because symptoms are primarily subjective and are based almost exclusively on patient statements. Affected persons may have difficulty adequately describing the unpleasant sensations as well as the urge to move. Often, patients with RLS do not complain of restless legs symptoms, but of insomnia or fatigue, leading the symptoms of RLS to be falsely attributed to a mental condition (54, 55). Specifically in a psychiatric context, the differentiation of RLS complaints and neuroleptic-induced akathisia may be challenging (56).

Patients with a first-degree relative with RLS symptoms were significantly more likely to have RLS themselves. Familial clustering of RLS is a frequent finding (9), which can be interpreted as an expression of increased genetic vulnerability. Currently, 22 gene loci are known to be associated with an increased incidence of RLS (57, 58). In line with previous epidemiological studies in the general population, we found an increased RLS prevalence for women (21.7 vs. 9.5% in men) (9, 18).

Smoking and Alcohol Consumption

Lifestyle factors such as smoking and higher alcohol consumption may be associated with an increased risk for RLS (19, 34, 58, 59). In the present sample, we found no association between smoking and RLS. Nicotine has dopamine-stimulating effects that potentially reduce RLS symptoms (60). However, the association between increased nicotine use and an improvement of RLS has only been published in case reports (61, 62). Another case–control study reported an association between nocturnal smoking and the occurrence of RLS symptoms in 12.0% of patients with RLS and 2.0% in control participants; patients with RLS were more likely to have a comorbid mental disorder. Smoking behavior was also discussed by the authors as an expression of counter regulation with respect to RLS (63). It is well established that psychiatric patients have higher nicotine use compared with the general population (64, 65). In line with these findings, the present sample of patients with RLS reported a higher percentage of smoking (56.5%) compared to the general population (65). Overall, the findings suggest a complex interaction between

TABLE 3 | Restless legs syndrome (RLS) characteristics for variables measured on a continuous scale.

Variables	Mean ± SD	Median [IQR]	95% CI
Duration (months) of symptoms in newly diagnosed RLS (*n* = 29)	70.1 ± 134.8	30 [12;72]	[18.9;121.4]
Duration (months) of symptoms before diagnosis with known RLS (*n* = 12)	62.7 ± 87.2	42 [7;78]	[7.3;118.1]
Number of definable episodes (*n* = 10)	13.1 ± 30.7	3 [2;6]	[-8.8;35.0]
IRLS (*n* = 47)	20.3 ± 8.4	22 [14;26]	[17.8;22.8]

IRLS, International RLS Severity Scale.

TABLE 4 | Restless legs syndrome (RLS) characteristics for variables measured at an ordinal or nominal scale.

Variables	Frequency (%)
RLS diagnosis known before study begin	
No	76.9
Yes	23.1
Duration of RLS (n = 42)	
≤6 months	23.8
6 < duration ≤ 12 months	11.9
12 < duration ≤ 24 months	9.5
24 < duration ≤ 60 months	26.2
>60 months	28.6
Newly diagnosed RLS, duration (n = *30)*	
≤6 months	23.3
6 < duration ≤ 12 months	10.0
12 < duration ≤ 24 months	13.3
24 < duration ≤ 60 months	23.3
>60 months	30.0
Previously diagnosed RLS, duration (n = *12)*	
≤6 months	25.0
6 < duration ≤ 12 months	16.7
12 < duration ≤ 24 months	0.0
24 < duration ≤ 60 months	33.3
>60 months	25.0
Frequency of RLS (n = *52)*	
<1×/month	7.7
1–3×/month	7.7
1–2×/week	25.0
3–6×/week	30.8
Daily	28.9
Iron deficiency	
No	75.0
Yes	5.8
Unknown	19.2
Kidney disease	
No	96.2
Yes	1.9
Unknown	1.9
Polyneuropathy	
No	96.2
Yes	1.9
Unknown	1.9
Thyroid disorder	
No	82.7
Yes	15.4
Unknown	1.9
Pregnancy	
No	89.1
Yes	1.9
Unknown	0.0
Drug-induced RLS	
No	78.9
Yes	13.5
Unknown	7.7
Drug-induced worsening of RLS (N = *51)*	
No	68.6
Yes	17.7
Unknown	13.7
Drug treatment of RLS	
No	80.8
Yes	19.2
Unknown	0.0

RLS, smoking, and psychiatric disorders, which has not been studied systematically.

It has been reported that alcohol consumption may induce or exacerbate RLS symptoms (58, 66, 67), while other studies have not found such an association (68–70) or have found an even lower risk of RLS (71, 72), suggesting a potential protective effect. In the present study, patients with RLS reported moderate alcohol consumption in terms of both frequency and intensity. Interestingly, a polymorphism in the alcohol dehydrogenase 1B (*ADH1B*) gene has been identified, which is associated with an increased risk for RLS and low alcohol consumption (73). The relationship between RLS and alcohol is also complicated by the fact that RLS can be triggered by alcohol withdrawal (74). In the present study sample that includes patients with alcohol dependency (ICD-10 Code F10.2) as well as alcohol withdrawal syndrome (ICD-10 Code F10.3), a trend was found for a lower prevalence of RLS among patients with an alcohol use disorder compared to those with another psychiatric disorder. Due to methodological limitations and the cross-sectional design of the present study, causal conclusions cannot be drawn. However, it is of major clinical and scientific interest to clarify the relationship between alcohol consumption and the manifestation of RLS.

Psychotropic Drugs

Treatment with psychotropic drugs including antidepressants, hypnotics, mood stabilizers and anticonvulsants, opiates, and stimulants was not associated with RLS. No correlation between the number of psychotropic drugs and the occurrence of RLS could be demonstrated. Significant distribution differences were found for the category "antipsychotics" and the subcategory "atypical antipsychotics," which were taken more frequently by patients with RLS than those without. In agreement with the results of the present study, the use of antipsychotics is associated with an increased risk of RLS (23, 75, 76), which may be due to a drug-induced interference with dopamine metabolism. However, the concept of altered dopamine function as the basis of RLS seem to be incomplete (77). In addition to several genetic variants involved with neural development and brain metabolism, there is evidence for a state of spinal and supraspinal hyperexcitability (78), and recent data have demonstrated alterations of glutamatergic and adenosine signaling in the pathophysiology of RLS (27). Therefore, pharmacological effects interfering with a highly complex system should be interpreted cautiously. In our study, the selection

TABLE 5 | Results of logistic regression analysis of 299 patients for occurrence of restless legs syndrome (RLS; 50 patients with and 249 without RLS).

Variable/predictor	β	SE β	Wald's χ^2	df	*p*	OR	OR [95% CI]
Constant	−3.4720	1.1537	9.0571	1	0.0026	NA	
Age (years)	0.0202	0.0116	3.0072	1	0.0829	1.02	[1.00; 1.04]
Gender (default = male, 1 = female)	0.4909	0.1942	6.3867	1	**0.0115**	**2.67**	**[1.25; 5.72]**
RLS in first-degree relatives (default = no; 1 = yes)	0.5952	0.2769	4.6207	1	**0.0316**	**3.29**	**[1.11; 9.73]**
BMI (kgm^{-2})	0.0103	0.0261	0.1563	1	0.6926	1.01	[0.96; 1.06]
ESS	0.0814	0.0372	4.8028	1	**0.0284**	**1.09**	**[1.01; 1.17]**
PSQI	0.0700	0.0393	3.1658	1	0.0752	1.07	[0.99; 1.16]
Frequency of alcohol consumption (2 = ≤ 1/month; 1 = > 1/month)	−0.3981	0.1880	4.4828	1	**0.0342**	**0.45**	**[0.22; 0.94]**
Antidepressants (2 = no; 1 = yes)	−0.4294	0.4423	0.9424	1	0.3317	0.65	[0.27; 1.54]
Antipsychotics (2 = no; 1 = yes)	0.1557	0.1809	0.7410	1	0.3893	1.37	[0.67; 2.78]
Test			χ^2	**df**	***p***		
Overall model evaluation Likelihood ratio test			44.4938	9	<0.0001		
Score test			42.6423	9	<0.0001		
Wald test			33.8414	9	<0.0001		

BMI, body mass index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; β, regression coefficient, SE β, standard error of the regression coefficient; df, degrees of freedom, p, p-value of Wald's χ^2 OR, odds ratio; 95% CI, 95% confidence interval of the odds ratio. Statistically significant results are shown in bold.

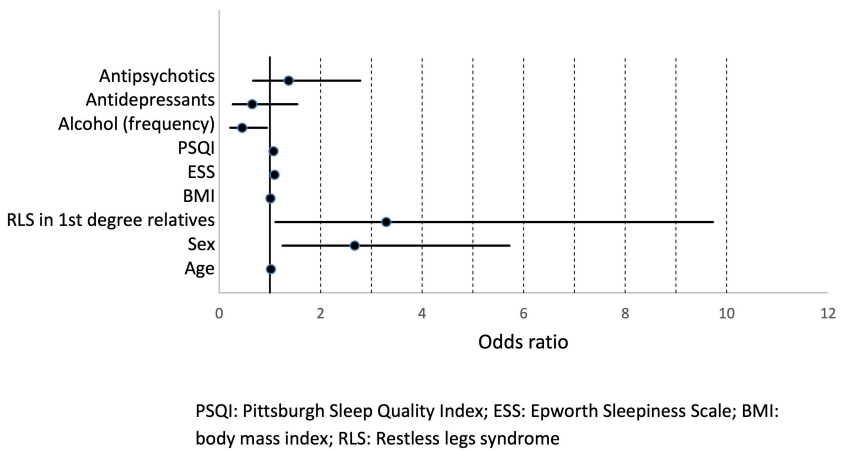

FIGURE 2 | Odds ratios with 95% confidence intervals. PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BMI, body mass index; RLS, restless legs syndrome.

of psychotropic drugs was based on clinical symptoms and not under controlled conditions. An increased awareness at the study sites for the induction of RLS symptoms may also play a role. Dosages of the medications were not assessed, although a dose-dependent effect can often be observed in clinical practice. Randomized controlled trials investigating the association of psycho-pharmacotherapy and RLS are lacking, and most publications are based on single case studies or small case series (22, 23). In a prospective study, RLS occurred or worsened in 9% of patients during treatment with second-generation antidepressants with mirtazapine presenting the highest risk of RLS (28% of cases) (79). Current categorizations of the RLS risk with specific psychotropic drugs are based on expert opinion [overview in Ref. (25)]. A few psychotropic drugs may have a favorable effect on RLS such as aripiprazole (80, 81), bupropion (82), or benzodiazepines (83). However, due to limited evidence, no recommendation can be made for routine clinical use of psychotropic drugs in the treatment of RLS (84).

Non-psychotropic drugs that were not recorded in our study may also induce or exacerbate RLS (85). A drug-independent association of RLS with mental conditions has also been discussed (2, 30, 31). Accordingly, a recent study of Danish blood donors demonstrated that RLS prevalence was increased in people with depression untreated by medication (34).

Psychiatric Diagnosis and RLS

Approximately every second patient (51.7%) had at least one psychiatric diagnosis in addition to the primary diagnosis, and approximately every fourth patient (24.6%) had three or more psychiatric diagnoses. We found no differences between patients with and without RLS regarding the distribution of primary and secondary psychiatric diagnoses. Increased odds ratios were

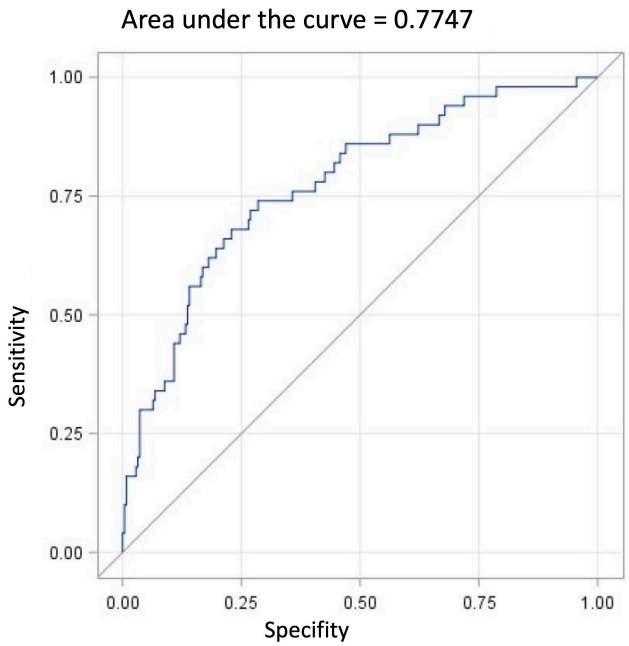

FIGURE 3 | Receiver operating characteristic (ROC) curve of logistic regression model.

observed for the association between RLS and posttraumatic stress disorder (PTSD), but not for other psychiatric disorders such as depression. Accordingly, it is very challenging to map associations of RLS with a specific diagnosis. With regard to somatic or sleep medical diagnoses apart from RLS, no differences were found between patients with and without RLS. However, it must be taken into account that these diagnoses were not systematically explored for the purpose of the present study, and diagnoses were taken from the patients' records.

Sleep Quality and Mood

Subjective sleep quality was markedly impaired in patients with RLS as reflected by a significantly higher mean PSQI score (12.7) compared to the non-RLS group (10.2). Disturbed sleep is a characteristic feature in RLS; however, because no polysomnographic data were available in the present study, it cannot be differentiated whether the sleep problems are due to restless legs symptoms, concomitant periodic leg movements, or possibly due to another comorbid sleep disorder. Insomnia symptoms as measured by the ISI were significantly higher in RLS patients. Approximately 50% of all patients with RLS reported an ISI score above 14, but only about 20% showed an ISI score less than 7, demonstrating that the vast majority of psychiatric patients have complaints of at least mild insomnia. The manifestation of RLS in the form of insomnia symptoms is of great clinical importance, because sleep disturbances are a core symptom of various mental disorders. Therefore, a detailed sleep-related exploration including RLS criteria is essential.

Epworth Sleepiness Scale scores, reflecting daytime sleepiness, were also higher in the RLS patient group; however, this group's mean score of 9.7 is below the pathological cut-off score. According to the IRLSSG, a lack of pronounced daytime sleepiness is regarded as a supportive RLS diagnostic criterion (1). However, 50% of the patients with RLS showed ESS scores above 10, which is indicative of increased daytime sleepiness. It remains unclear whether these patients had an additional specific sleep disorder, such as sleep apnea, so substantial conclusions cannot be drawn. A previous multicenter study on a comparable clinical sample found a high prevalence (21.7%) of previously unknown obstructive sleep apnea syndrome (OSAS) in 298 psychiatric inpatients (86). An increased comorbidity of RLS in patients with OSAS has also been demonstrated, especially in patients with insomnia symptoms (87, 88).

Limitations

The present study has several limitations that should be considered. First, the diagnosis of RLS was based on the five minimal IRLSSG criteria (1); although careful clinical examinations were performed to exclude RLS mimics, no additional technical diagnostic tests were conducted. Therefore, it is possible that the reported prevalence is an overestimation. However, the vast majority of RLS prevalence studies in the general population are based on the former four or five essential RLS criteria without additional diagnostic tests (2, 3). Compared with these prevalence rates, the prevalence of RLS in our sample is most likely slightly inflated. The challenge in correctly diagnosing RLS lies in improving the specificity of the symptoms (55, 89), which is currently viewed as critical (90). Second, sleep quality was not evaluated by objective sleep measurements such as actigraphy or polysomnography, therefore sleep disturbing PLMS associated with RLS or sleep-related breathing disorders could not be detected. Third, somatic and sleep medicine diagnoses

were taken from the patients' records. Fourth, the sample size was probably too small to detect drug-related effects on RLS beyond the association with atypical neuroleptics. However, no consistent classification of drugs in terms of favorable or adverse effects on restless legs symptoms is feasible that would be a prerequisite for definite conclusions in cases of polypharmacy.

CONCLUSION

In this prospective, cross-sectional, multicenter study, RLS was common among psychiatric inpatients. RLS was associated with higher BMI, impaired subjective sleep quality, and lower alcohol consumption. In a logistic regression analysis, after adjusting for confounders, gender, a positive family history of RLS, and increased daytime sleepiness were identified as predictors for the occurrence of RLS, whereas a higher frequency of alcohol consumption was associated with a lower frequency of occurrence. Knowledge of the prevalence of RLS appears important to increase awareness and systematic diagnostic assessment, potentially contributing to improved care for psychiatric patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of the Universities of Regensburg, Berlin, Leipzig, Freiburg, Nuremberg, Heidelberg (Germany), and Bern (Switzerland). The patients provided their written informed consent to participate in this study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FW, HD-H, LF, NM, KR, CS, CN, and TW contributed to conception and design of the study. FW, HD-H, ED-S, LF, AH, NM, CM, DN, KR, CS, MSe, MSp, CN, and TW acquired data, performed investigations, and wrote and reviewed the manuscript. HD-H and FW performed quality control, data entry, and statistical analysis. FW, HD-H, and TW wrote the original manuscript draft. All authors have read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.846165/full#supplementary-material

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A Longitudinal Approach to the Relationships Among Sleep, Behavioral Adjustment, and Maternal Depression in Preschoolers

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This study aimed to investigate the longitudinal associations between children's sleep duration (SD) and problems (SPs), behavioral adjustment [externalizing behaviors (EB) and internalizing behaviors (IB)], and maternal depressive symptoms (MDS) in preschoolers over a period of 3 years (4–6 years of age). For this purpose, latent growth modeling (LGM) was conducted using 2012(W_5) to 2014(W_7) data from the National Panel Study on Korean Children (PSKC), while controlling for family contextual factors (i.e., responsive parenting, developmental stimulations, and marital conflict) and child temperament (children's negative emotionality). First, children who slept longer at four were concurrently associated with lower levels of EB, while more SPs were associated with higher levels of EB and IB, concurrently. Second, greater decreases in SPs were associated with greater decline in EB and IB. Higher levels of MDS at four were associated with higher levels of child EB, IB, and SPs, concurrently. However, no longitudinal associations were found between the rates of change in MDS and children's sleep and adjustment (EB and IB). Finally, the magnitude of the associations among the variables was greater overall in the SPs models than in the SD models. These findings suggest that addressing sleep problems, rather than sleep duration, seem to be more important in predicting and preventing young children's adjustment problems and also that more attention should be paid to MDS during preschool years as much as during the postpartum period for better child adjustment outcomes.

Keywords: sleep duration, sleep problems, child adjustment, maternal depression, trajectory, preschoolers

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INTRODUCTION

Like many other aspects of human development, sleep undergoes dramatic changes during the early years of life, both quantitatively and qualitatively. Compared to adults, young children spend substantially more time sleeping (Thorleifsdottir et al., 2002; Spruyt et al., 2005; Galland et al., 2012). In general, newborns sleep up to 18 h a day, which gradually decreases to approximately 10–12 h (42%–46% decrease) by the time elementary school begins (Thorleifsdottir et al., 2002; Spruyt et al., 2005). During the same period, sleep structure also changes, becoming more similar to that of adults: sleep becomes monophasic with gradual reduction in naptime,

decreases in rapid eye movement (REM) sleep, and increases in non-REM sleep. Sleep maturation is generally achieved during the preschool years (Bathory and Tomopoulos, 2017; Jiang, 2020).

Given the substantial proportion of time spent sleeping during early childhood (Galland et al., 2012), it is crucial to investigate the effects of sleep quantity and quality on young children's behavioral adjustment, such as internalizing and externalizing problems, which have persistent impact on later formal schooling (Bornstein et al., 2010). However, preschool-age children's sleep has received relatively less attention than other age groups'. The majority of prior studies concerning sleep and behavioral adjustment have focused on elementary-level or older students (Becker et al., 2017). Furthermore, there is a dearth of research that examines the impact of maternal depressive symptoms (MDS) on the relationship between children's sleep and behavioral adjustment among preschoolers. Most of the studies examining associations among MDS, children's sleep, and children's adjustment have analyzed cross-sectional data from infants or clinical populations (e.g., Bayer et al., 2007; Armitage et al., 2009; Newland et al., 2016). Therefore, it remains relatively unknown how preschool-age children's sleep patterns, behavioral adjustment, and MDS are interrelated over time in non-clinical samples.

To address these gaps in the literature, the current study aimed to examine individual trajectories of and longitudinal associations among child sleep (duration and problems), behavioral adjustment [externalizing and internalizing behaviors (EB and IB)], and MDS over 2 years with preschoolers from community populations.

Children's Sleep and Behavioral Adjustment

Sleep duration (SD) is one of the most commonly studied sleep-related variables (Galland et al., 2012) along with sleep problems (SPs; e.g., bedtime resistance, delays in falling asleep, night waking, and sleep walking) as a proxy of sleep quantity and quality, respectively (Fisher and McGuire, 1990). SPs are quite prevalent in early childhood and tend to gradually decline from infancy to middle childhood: SP incidence in early childhood ranges from a fourth (e.g., Blader et al., 1997) to a seventh of the samples (e.g., Martin et al., 2007), with lower incidence found among school-aged children (11%–15%, 6–12 years; Owens et al., 2000; Mindell et al., 2009). During early childhood, the types of SPs also change, with night awakening and difficulty falling asleep being more common among 1–5 and 6–11 year olds, respectively (Williamson et al., 2019).

Inadequate quality or quantity of sleep has been reported to exert negative impact on young children's emotional and behavioral development concurrently and longitudinally (Goodnight et al., 2007; Tso et al., 2016; Williams et al., 2016; Cremone et al., 2018; Williamson et al., 2020). Children who had insufficient sleep were found to respond more readily with anger and sadness to social cues compared to those who did not (Leotta et al., 1997; Saghir et al., 2018). Insufficient sleep quantity has been associated with externalizing and internalizing problems (Yokomaku et al., 2008; LeBourgeois et al., 2013; Tso et al., 2016; Bélanger et al., 2018). For example, children with shortened SD tended to display more hyperactive and inattentive responses as well as less prosocial behaviors (Tso et al., 2016; Bélanger et al., 2018). A similar tendency has been observed between nighttime SPs (e.g., night waking and settling problems) and maladaptive behaviors (Gregory and O'Connor, 2002; Williams et al., 2016; Quach et al., 2018; Reynaud et al., 2018; Williamson et al., 2020). Children who had higher than average incidence of SPs during the first 5 years of life tended to be more hyperactive, exhibited more emotional problems, and were less prosocial and self-regulatory at 6–7 years of age (Williams et al., 2016). Furthermore, children who exhibited persistent SPs until lower elementary grades showed higher levels of externalizing and internalizing problems at 10–11 years of age (Williamson et al., 2020).

In this sleep-adjustment association, sleep is assumed to play a leading role by affecting self-regulation, which is involved in daytime social functioning (Dahl, 1996). Sleep reinvigorates the brain by granting it rest, thereby allowing adequate levels of alertness and arousal during the daytime. In addition, sleep re-synchronizes multiple brain regions, facilitating efficient processing of information and communication among them (Dahl, 1996; Fattinger et al., 2017). Sleep deprivation itself is a stress on the body, resulting in increased amygdala activation and secretion of stress hormones, such as epinephrine and cortisol (Hirotsu et al., 2015), which are known to lead to deactivation of the prefrontal cortex involved in the generation and control of emotional responses (Goldstein and Walker, 2014; Bathory and Tomopoulos, 2017). Thus, through these paths, SPs and decreased SD are assumed to negatively affect children's self-regulation, thereby causing problems in behavioral adjustment.

Taken together, SD and SPs seem to be closely linked to children's daytime behavioral adjustment, probably mainly through self-regulation depletion. However, previous research has not investigated how changes in preschool-age children's sleep and adjustment are interrelated. The influence of MDS on the relationship between children's sleep and behavioral adjustment has not been addressed either, despite the fact that child sleep and adjustment problems are susceptible to stress-generating (e.g., maternal depression, marital conflict, and poverty) and compensating factors within a family (e.g., responsive parenting and parental education). Thus, this study focuses on the impact of MDS, considering other domestic factors as covariates in the analysis.

Maternal Depression and Children's Sleep and Behavioral Adjustment

Considering the enormous impact that mothers can have on their children's living and growth during the early years of life, mothers' unstable and negative affect states, especially depressive symptoms, are expected to exert adverse effects on child development, including sleep and behavioral adjustment. However, findings regarding preschool-age children's sleep and

MDS are inconsistent, partly due to a lack of relevant studies. In one study (Schultz et al., 2020), 4–5-year-old children with depressed mothers tended to sleep significantly less. Also, the association between MDS and children's sleep was stronger among mothers with moderate to severe levels of symptoms than among those with minimal to mild symptoms. In contrast, in another study (De Jong et al., 2016), no associations were found between MDS and children's total SD, while higher levels of MDS were related to greater variability in child SD. Regarding SPs, previous research on non-clinical samples mostly focused on elementary school children (e.g., Buckhalt et al., 2009; Kelly and El-Sheikh, 2011; El-Sheikh et al., 2012), overall showing positive associations between MDS and child SPs.

Moreover, cross-sectional research has consistently established the link between MDS and child behavioral adjustment (e.g., Dawson et al., 2003; Gartstein and Fagot, 2003; Koblinsky et al., 2006; Goodman et al., 2011). Only a small number of studies have investigated this relationship longitudinally (Cents et al., 2013; Giallo et al., 2015; Park et al., 2018; Pietikäinen et al., 2020). For instance, Pietikäinen et al. (2020) examined both maternal and paternal depressive symptoms during the first 2 years after childbirth and their relationship with children's internalizing and externalizing problems at 2 and 5 years of age. They found that persistent MDS were related to children's internalizing and externalizing problems at both measurement points, while paternal depressive symptoms did not independently predict child behavioral adjustment. In another study (Cents et al., 2013), similar patterns were observed from mid-pregnancy to 3 years: children with mothers displaying increased depressive symptoms throughout the years exhibited significantly more internalizing and externalizing problems than those whose mothers' showed decreased depressive symptoms.

Biological and environmental factors may explain the paths through which MDS affect children's sleep and behavioral adjustment and vice versa. First, mothers and children shared genes can modulate neurotransmitters involved in sleep and emotional regulation (e.g., norepinephrine and serotonin; Jiang, 2020). Second, irresponsive parenting and insecure attachment resulting from MDS are assumed to contribute to the MDS-child sleep association. MDS are known to be frequently associated with disrupted parenting and fewer attempts of mother–child interactions with overall lower levels of affective, cognitive, and social stimulations (Lovejoy et al., 2000; Teti and Crosby, 2012). These parenting practices are likely to evoke the child's frustration resulting from persistent dissatisfaction of basic needs inducing stress responses (Ulmer-Yaniv et al., 2018). Chronic stress can lead to disorders in emotional regulation (Marusak et al., 2015), the negative effects of which are likely to be more severe, especially during the early period of life because of the higher brain plasticity (Shonkoff and Phillips, 2000). At the same time, considering that children's greater behavioral problems can contribute to mothers' negative mood state eliciting greater levels of caring burden and stress responses (Meltzer and Mindell, 2007; Wagner and Valdez, 2020), MDS and children's behavioral problems [externalizing and internalizing behaviors (EB and IB)] are apt to reinforce each other, creating a vicious cycle (Warren et al., 2006).

The impact of MDS on children's sleep and behavioral adjustment during the preschool period is not likely to be less important than during infancy and other developmental stages. Nevertheless, the vast majority of relevant studies has focused on the impact of postpartum depressive symptoms in the first few months to 3 years after childbirth (e.g., Ystrom et al., 2017; Parade et al., 2019; Cook et al., 2020; Asmussen et al., 2021). Given the importance of early childhood as a transition from infancy to middle childhood in both sleep and behavioral adjustment and the observed developmental changes during this period, understanding how these processes change over time in relation to MDS is crucial. However, few studies have considered the associations among longitudinal trajectories in children's sleep, behavioral adjustment, and MDS, especially focusing on the changes in each variable. Thus, the present study aims to investigate the following research question: *how are the trajectories of these variables and their longitudinal associations*? This study addresses the question with three waves of national-level data using latent growth modeling (LGM). This allows to demonstrate individual trajectories of sleep measures (duration and problems), behavioral adjustment, and MDS as well as longitudinal change dynamics during the preschool period.

MATERIALS AND METHODS

Participants

Data were obtained from the National Panel Study on Korean Children (PSKC). The PSKC has collected annual information from a nationally representative sample of approximately 1,700 children and their families in Korea since 2008. The present study used data from 2012 to 2014 (T_1, T_2, and T_3) that spanned across 3 years of preschool, from ages 4–6. A total of 1,703, 1,662, and 1,620 children and their mothers participated at T_1, T_2, and T_3, respectively. Children's ages were approximately 48–54 months (boys: 51%; girls: 49%), 60–66 months (boys: 51.5%; girls: 48.5%), and 72–79 months (boys: 51.4%; girls: 48.6%) at T_1, T_2, and T_3, respectively. Main caregivers (mostly mothers, T_1: 99.9%, T_2: 99.8%, and T_3: 99.8% of the total respondents) answered on a questionnaire concerning main and confounding variables at the three measurement points, respectively, except negative emotionality (only at T_1) and marital conflict (at T_1 and T_3).

Complete data, with no missing information on main and confounding variables, were available for 1,635 (76%), 1,606 (74.7%), and 1,559 (72.51%) cases at T_1, T_2, and T_3, respectively. Throughout the three time points, the parents [98.6% (T_1), 98% (T_2), and 97.6% (T_3)] remained *married* and less than 1% of the families were from ethnic minority groups. Additionally, approximately 70% of the parents had two or more years of college education and the rest had completed high school.

Measures

Internalizing and Externalizing Behaviors

Information on children's adjustment outcomes was collected using the Child Behavior Checklist for ages 1.5–5 (CBCL/1.5–5), which was validated and standardized in a Korean sample

(Oh and Kim, 2009). The same version was also applied at age 6 (T_3) for continuity of measurement and appropriateness of content, since the sampled children did not enter elementary school until T_4. Mothers rated 100 items related to their child behavior over the past 2 months on a three-point scale ranging from *not true* (0 point) to *very true* or *often true* (2 points). The total score was calculated for the *internalizing domain* [e.g., *emotionally reactive* (nine items), *anxious/depressed* (eight items), *somatic complaints* (11 items), and *withdrawn* (eight items)] and *externalizing domain* [e.g., *attention problems* (five items) and *aggressive behavior* (19 items)]. Cronbach's alphas for the scales at each time point ranged from 0.57 to 0.88, 0.55 to 0.87, and 0.42 to 0.89 at T_1, T_2, and T_3, respectively.

Sleep Problems

Seven items of the CBCL 1.5–5 were used to assess children's sleep functioning on a three-point scale ranging from *not true* (0 point) to *very true* or *often true* (2 points): (1) does not want to sleep alone, (2) has trouble getting to sleep, (3) nightmares, (4) resists going to bed at night, (5) sleeps less than most children during day and/or night, (6) talks or cries out in sleep, and (7) wakes up often at night. The alpha reliabilities across the three time points were 0.71 at T_1, 0.60 at T_2, and 0.84 at T_3.

Sleep Duration

Mothers provided the usual times their children went to sleep and awoke daily through a parental questionnaire (hours and minutes). Since children tend to take naps during the daytime during preschool, SD was calculated as the sum of nocturnal sleep hours (the difference between bedtime and wake-up time) and daytime nap.

Maternal Depression

Maternal depression was assessed using the Kessler Psychological Distress Scale (K6; Kessler et al., 2002), which has been validated in the Korean population (Paik, 2010). The scale consists of six items on one's emotional distress state [e.g., during the past 4 weeks, how much of the time did you feel: (1) so sad that nothing could cheer you up?; (2) nervous?; (3) restless or fidgety?; (4) hopeless?; (5) that everything was an effort?; and (6) worthless?]. Each question was rated on a five-point Likert scale ranging from 1 (*none of the time*) to 5 (*all of the time*). The alpha reliability remained at 0.92 across all measurement time points. A total score was calculated by adding up each item's score, with higher scores indicating higher levels of maternal depression.

Covariates

Negative Emotionality

Five items from the *emotionality* scale of the Korean version of Buss and Plomin's (1984) Emotionality, Activity, and Sociability (EAS)—Temperament Survey for Children-Parental Ratings (Huh et al., 2006) were used to collect information on children's negative emotionality. Mothers rated children's emotionality (e.g., negative mood, irritability, and intensity of negative reactions) on a five-point scale ranging from *not typical of my child* (1 point) to *very typical of my child* (5 points). Information on negative emotionality was collected only at T_1 (alpha = 0.75). Individual item's ratings were added together, with higher scores indicating higher levels of negative emotionality.

Responsive Parenting

Information on responsive parenting behaviors was collected using the *Social Interaction* Scale of the Parental Style Questionnaire (PSQ; Bornstein, 1989). This scale evaluates parental *warmth* and *responsiveness*. The items were rated on a five-point scale ranging from *hardly at all* (1 point) to *all the time* (5 points). Total scores were calculated. Alpha reliability values were 0.86, 0.85, and 0.86 at T_1, T_2, and T_3, respectively.

Home Environment

Children's exposure to developmental stimulations through positive domestic environments was examined using the Early Childhood Home Observation for Measurement of the Environment (EC-HOME; Caldwell and Bradley, 2003), which is validated in a Korean context (Kim and Kwak, 2007). The EC-HOME consists of 55 yes or no questions from eight subscales (i.e., learning materials, language stimulation, physical environment, academic stimulation, modeling, variety, and acceptance). The sum of the eight subscales was used in the analyses.

Marital Conflict

Perceived marital conflict was assessed using the scale used in the Prevention and Relationship Enhancement Program (PREP; Markman et al., 2001), which is validated in a Korean sample (Yu and Kim, 2005). The scale was developed to diagnose the level of couples' distress and predict divorce rates on a five-point scale [*hardly at all* (1 point) to *all the time* (5 points)]. Scores on the eight items were included in the analyses. Since items on marital conflict were measured at T_1 and T_3, but not at T_2, the two available data points were averaged [alpha = 0.92 (T_1) and 0.99 (T_3)]. Higher scores indicate higher levels of marital conflict.

Analysis

Latent growth modeling was conducted to examine the *associations* among the trajectories of children's sleep (SD and SPs), child behavioral adjustment outcomes (internalizing and externalizing problems), and MDS as well as *overall pattern and variability* in developmental trajectory for each variable, while controlling for relevant domestic factors (e.g., responsive parenting, developmental stimulation, and marital conflict) and children's temperament (negative emotionality; Troxel et al., 2013). In the current analyses, only cases with complete data at all three time points were used (n = 1,427). Statistical testing suggested that only minimal bias was introduced by removing cases with missing data. Significant differences were found only sporadically across a few of the

main and confounding variables between the groups of participants included and excluded from the analysis: children's *internalizing problems* at T_3 (higher in the participants included; $t = 1.80$, $p < 0.05$), *responsive parenting* at T_1 and T_2 (higher in the participants excluded; $t = -1.78$, $p < 0.01$; $t = -2.67$, $p < 0.01$), the *home environment* at T_1 and T_2 (higher in the participants included; $t = 4.38$, $p < 0.00$; $t = 2.03$, $p < 0.05$), and *marital conflict* at T_1 and T_3 (higher in the participants excluded; $t = -2.16$, $p < 0.05$; $t = -1.75$, $p < 0.05$).

First, descriptive statistics and zero-order correlations among the variables were examined using Stata 12. To ameliorate the effects of skewed distributions (**Table 1**), SPs and internalizing and externalizing problems were log-transformed. Then, univariate growth models were fitted to examine the overall chronological patterns of changes in MDS, children's sleep, and children's adjustment. Next, to examine the associations among the variables controlling for relevant covariates, multivariate growth models were specified. Separate models for each of the sleep parameters (i.e., SD and SPs) were set up to detect possible differences in longitudinal trajectories of SD and SPs and their association with children's adjustment outcomes and MDS. To reduce problems resulting from multicollinearity between internalizing and externalizing problems (**Table 2**), separate models were fitted for each of them. Thus, in total, four multivariate models were examined as: *Model 1* included SD, externalizing problems, and MDS; *Model 2* included SD, internalizing problems, and MDS; *Model 3* included SPs, externalizing problems, and MDS; and *Model 4* included internalizing problems and MDS. Each model included one growth curve for each construct [SD (SPs), externalizing (internalizing) problems, and MSD] and estimated associations among growth factors (levels and slopes). In all of these models, child negative emotionality (Cremone et al., 2018), responsive parenting (Putnam et al., 2002), home environment, and marital conflict were controlled for as confounding variables. Family socioeconomic status (SES) indicators (i.e., maternal education and family income) and child gender were not controlled in the final models because they had no or very weak correlations with only some of the main variables (**Table 2**) and the model fit indices dropped when they were included in the models. LGM was executed with Mplus 7.4 (Muthén and Muthén, 2012) with equal spacing between measurement occasions (T_1, T_2, and T_3 were coded as 0, 1, and 2, respectively).

RESULTS

Descriptive Statistics and Zero-order Correlations

The means and SDs of the variables used in the analyses are presented in **Table 1**. In average, children's SD and SPs as well as internalizing and externalizing problems tended to decrease gradually over time. SPs and adjustment outcomes (i.e., internalizing and externalizing problems) were significantly positively correlated within and across waves. However, the associations between SD and adjustment outcomes were relatively weak in magnitude and not all significant. Similar patterns were observed between MDS and sleep variables (SD and SPs) and between MDS and children's internalizing and externalizing behaviors.

Univariate Growth Models

The results of the univariate growth model are presented in **Table 3**. Analyses revealed a significant decrease in children's SD over time. Children who slept relatively longer at the

TABLE 1 | Descriptive statistics on children's sleep and adjustment and maternal depression.

	N	M	SD	Min	Max	Skew
Sleep Duration (SD)						
SD at T_1	1703	9.93	0.80	6.01	13.55	0.02
SD at T_2	1,662	9.88	0.74	7.00	13.00	−0.03
SD at T_3	1,620	9.80	0.70	7.00	12.50	−0.18
Sleep Problem (SP)						
SP at T_1	1,694	2.07	1.89	0.00	11.00	1.21
SP at T_2	1,651	1.74	1.69	0.00	12.00	1.36
SP at T_3	1,605	1.63	1.58	0.00	11.00	1.41
Externalizing Behaviors (EB)						
EB at T_1	1,694	7.77	5.83	0.00	32.00	0.76
EB at T_2	1,651	6.33	5.52	0.00	32.00	1.06
EB at T_3	1,605	5.67	5.32	0.00	36.00	1.25
Internalizing Behaviors (IB)						
IB at T_1	1,694	8.42	6.42	0.00	45.00	1.12
IB at T_2	1,651	7.34	6.28	0.00	42.00	1.45
IB at T_3	1,605	6.75	6.03	0.00	37.00	1.37
Maternal Depression (MD)						
MD at T_1	1,672	11.76	4.51	6.00	30.00	0.72
MD at T_2	1,614	11.62	4.43	6.00	30.00	0.79
MD at T_3	1,565	11.74	4.61	6.00	30.00	0.70

T_1 = first measurement wave (2012); T_2 = second measurement wave (2013); T_3 = third measurement wave (2014); and unit of sleep duration = hours.

TABLE 2 | Correlations among the main and socio-demographic variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. SD T_1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
2. SD T_2	0.38*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
3. SD T_3	0.31*	0.54*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
4. SP T_1	−0.09*	−0.05*	−0.06*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
5. SP T_2	−0.05	−0.06*	−0.04	0.50*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
6. SP T_3	−0.03	−0.04	−0.00	0.41*	0.52*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
7. EB T_1	−0.09*	−0.01	−0.03	0.49*	0.28*	0.28*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
8. EB T_2	−0.06*	−0.05*	−0.03	0.29*	0.48*	0.32*	0.59*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
9. EB T_3	−0.08*	−0.02	−0.04	0.27*	0.33*	0.46*	0.55*	0.65*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
10. IB T_1	−0.05	−0.01	−0.01	0.55*	0.36*	0.33*	0.70*	0.43*	0.40*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
11. IB T_2	−0.02	−0.03	−0.02	0.33*	0.56*	0.37*	0.42*	0.72*	0.48*	0.57*	–	–	–	–	–	–	–	–	–	–	–	–	–	
12. IB T_3	−0.02	0.01	0.03	0.30*	0.39*	0.54*	0.41*	0.50*	0.73*	0.54*	0.63*	–	–	–	–	–	–	–	–	–	–	–	–	
13. MD T_1	−0.06*	−0.07*	−0.03	0.19*	0.16*	0.16*	0.27*	0.23*	0.25*	0.27*	0.22*	0.23*	–	–	–	–	–	–	–	–	–	–	–	
14. MD T_2	−0.05*	−0.05	−0.03	0.12*	0.18*	0.21*	0.22*	0.25*	0.23*	0.22*	0.26*	0.24*	0.55*	–	–	–	–	–	–	–	–	–	–	
15. MD T_3	−0.07*	−0.04	−0.04	0.17*	0.21*	−0.10*	0.22*	0.25*	0.27*	0.23*	0.25*	0.29*	0.54*	0.56*	–	–	–	–	–	–	–	–	–	
16. RP T_1	0.04	0.05*	0.03	−0.10*	−0.09*	−0.09*	−0.26*	−0.26*	−0.25*	−0.19*	−0.19*	−0.19*	−0.33*	−0.26*	−0.28*	–	–	–	–	–	–	–	–	
17. RP T_2	0.06*	0.07*	0.03	−0.13*	−0.09*	−0.08*	−0.25*	−0.28*	−0.24*	−0.18*	−0.20*	−0.17*	−0.21*	−0.24*	−0.23*	0.64*	–	–	–	–	–	–	–	
18. RP T_3	0.06*	0.05	−0.02	−0.10*	−0.12*	−0.15*	−0.20*	−0.28*	−0.29*	−0.18*	−0.22*	−0.24*	−0.26*	−0.25*	−0.33*	0.60*	0.59*	–	–	–	–	–	–	
19. ME	0.04	−0.04	−0.02	0.06*	0.05*	0.03	−0.08*	−0.03	−0.09*	−0.01	0.01	−0.02	−0.08*	−0.05*	−0.07*	0.13*	0.16*	0.13*	–	–	–	–	–	
20. FE	−0.05*	−0.06	−0.05	−0.01	−0.01	−0.02	0.01	0.00	−0.05	−0.01	−0.02	−0.05	−0.01	−0.03	0.02	−0.02	0.00	0.01	0.02	–	–	–	–	
21. NE	−0.06*	−0.02*	−0.05	0.24*	0.21*	0.22*	0.44*	0.36*	0.36*	0.43*	0.33*	0.36*	0.30*	0.24*	0.21*	−0.27*	−0.21*	−0.25*	−0.03	0.00	–	–	–	
22. Income T_1	−0.01	0.01	0.03	−0.07*	−0.04	−0.02	−0.06*	−0.02	−0.03	−0.08*	−0.06*	−0.06*	−0.04	−0.04	−07*	0.03	0.08*	0.04	0.16*	−0.00	−0.03	–	–	
23. Income T_2	0.01	−0.07*	−0.06*	−0.06*	−0.04	−0.04	−0.09*	−0.06*	−0.07*	−0.10*	−0.08*	−0.08*	−0.08*	−0.10*	−0.07*	0.07*	0.12*	0.06*	0.30*	−0.00	−0.06*	0.60*	–	
24. Income T_3	−0.02	−0.07*	−0.07*	−0.05*	−0.02	−0.07*	−0.10*	−0.08*	−0.08*	−0.10*	−0.09*	−0.10*	−0.09*	−0.09*	−0.11*	0.10*	0.14*	0.08*	0.31*	0.00	−0.04	0.54*	0.81*	
25. Child sex	0.07*	0.09*	0.08*	0.00	−0.01	−0.00	−0.12***	−0.12***	−0.11***	−0.02	−0.01	0.01	0.02	−0.00	0.00	0.07**	0.05*	0.03	−0.02	−0.00	0.02	0.02	0.02	0.02

*SD, sleep duration; SP, sleep problem; EB, externalizing behaviors; IB, internalizing behaviors; MD, maternal depression; RP, responsive parenting; ME, mother's education; FE, father's education; NE, negative emotionality; and child sex, 1 = boys; 2 = girls. *p < 0.05; **p < 0.01; and ***p < 0.001.*

initial measurement point had a greater decrease in the total amount of daily sleep. The same pattern was found for SPs and adjustment outcomes. Children's SPs significantly declined over the years, more so among children who initially (T_1) exhibited more SPs. Similarly, children's externalizing (internalizing) problems decreased across the 3 years, with greater decreases among those who initially displayed more externalizing (internalizing) problems. MDS did not significantly change over time, and the initial levels of depression were not significantly associated with the degree of change.

Associations of Trajectories of Sleep, Adjustment, and Depression

Tables 4–7 and **Figures 1–4** present the results of the multivariate growth models. Results of Model 1 and 2 (**Tables 4, 5**; **Figures 1, 2**) revealed that initial levels of SD were negatively associated with the initial levels of externalizing behaviors ($\beta = -0.105$, $p < 0.05$), indicating that the longer (vs. shorter) the initial SD, the lower (vs. higher) the initial externalizing behaviors. However, initial SD was not significantly associated with initial internalizing problems. Next, the initial externalizing problems were positively associated with the slope for SD ($\beta = 0.111$, $p < 0.05$), indicating that higher (vs. lower) initial levels of externalizing problems were related to slower decline in SD over time. Links between the initial levels of internalizing problems and the slope for SD were only marginally significant ($\beta = 0.09$, $p < 0.10$). The initial levels of MDS were positively associated with the initial levels of internalizing and externalizing problems ($\beta = 0.156$, $p < 0.01$; $\beta = 0.216$, $p < 0.01$), but not with their slope. Children whose mothers had higher levels of depressive symptoms tended to exhibit higher levels of internalizing and externalizing problems at 4 years of age.

Turning to models of SPs (Models 3 and 4; **Tables 6, 7**; **Figures 3, 4**), some newly significant associations were detected among growth factors. First, the initial SPs were associated with both the initial levels and the slope of externalizing ($\beta = 0.789$, $p < 0.001$; $\beta = -0.663$, $p < 0.001$) and internalizing ($\beta = 0.894$, $p < 0.001$; $\beta = -0.618$, $p < 0.001$) problems. These results indicate that the higher the initial levels of SPs, the higher the initial levels of internalizing and externalizing problems; also, the higher the initial levels of SPs, the steeper the decline in internalizing and externalizing problems. In addition, the initial levels of internalizing and externalizing problems were negatively associated with the rate of change in SPs ($\beta = -0.540$, $p < 0.001$; $\beta = -0.570$, $p < 0.001$), while the respective slopes of internalizing and externalizing problems were positively associated with the slope of SPs ($\beta = 1.654$, $p < 0.001$; $\beta = 1.612$, $p < 0.001$). That is, higher initial levels of internalizing and externalizing problems were associated with greater decreases in SPs, and greater (vs. smaller) decreases in SPs were associated with increased (vs. decreased) decline in internalizing and externalizing problems.

Finally, when mothers' initial levels of depression were high, its over-time decline was greater in all four models; their children initially had higher levels of SPs and internalizing and externalizing problems only in Models 3 and 4 (**Figures 3, 4**).

TABLE 3 | Results of univariate growth curve models.

	Intercept	Slope		Intercept-slope covariance	
	Mean level at T1	Variance	Change per 1-year interval	Variance	
Sleep duration	**9.93(0.02)**	**0.28(0.03)**	**−0.07(0.01)**	**0.09(0.01)**	**−0.06(0.01)**
Sleep problem	**2.01(0.05)**	**1.98(0.15)**	**−0.21(0.02)**	**0.27(0.06)**	**−0.37(0.08)**
Externalizing behaviors	**7.69(0.15)**	**20.90(1.41)**	**−1.05(0.07)**	**1.87(0.59)**	**−1.87(0.69)**
Internalizing behaviors	**8.36(0.16)**	**24.99(1.78)**	**−0.82(0.08)**	**2.32(0.76)**	**−1.84(0.88)**
Maternal depression	**11.78(0.08)**	**10.83(0.91)**	−0.01(0.06)	0.43(0.72)	0.43(0.50)

Values are unstandardized parameter estimates with standard errors in parentheses. Estimates that are significant at $p \leq 0.05$ or $p \leq 0.01$ are denoted in bold font.

Model Fit

Model fit was assessed using the root mean square error of approximation (RMSEA), comparative fit index (CFI), and normal theory weighted least squares chi-square (χ^2). For RMSEA, a value less than 0.05 is considered a good fit, and below 0.08 an adequate fit (Kline, 2004); for SRMR, a value below 0.08 is considered a good fit (Hu and Bentler, 1999). By convention, the CFI should be equal to or greater than 0.90 to accept the model. Chi-square was influenced by sample size and indicated a good fit when $p > 0.05$.

DISCUSSION

This study attempted to examine the developmental trajectories of children's sleep patterns, behavioral adjustment, and MDS during 3 years among preschoolers (4–6 years of age) and the *associations* among these variables' growth factors (initial level and rate of change), while controlling for the effects of confounding variables (i.e., responsive parenting, developmental home stimulation, marital conflict, and children's negative emotionality). The results showed that as children grew, they tended to sleep gradually less and displayed fewer SPs. The over-time reduction in SD and SPs was greater among children who initially, at 4 years old, slept longer and had more SPs. Overall, associations among children's sleep, behavioral adjustment, and MDS were stronger in the SP than in the SD models. Children's longer SD at four was significantly associated with lower levels of concurrent externalizing problems, but not with internalizing problems, when controlling for confounding variables. When the levels of externalizing problems at four were higher, a slower decrease in SD was observed until 6 years. Regarding SPs, children with more SPs at four

TABLE 4 | Coefficients among growth factors in multivariate growth model 1: sleep duration—externalizing behaviors.

	1(i1)	2(s1)	3(i2)	4(s2)	5(i3)
	β	*β*	*β*	*β*	*β*
Sleep duration					
1. Intercept	1				
2. Slope	−0.402***	1			
Externalizing behaviors					
3. Intercept	−0.105*	0.111*	1		
4. Slope	0.017	−0.037	−0.099	1	
Maternal depressive symptoms					
5. Intercept	−0.087	0.063	0.156**	−0.054	1
6. Slope	0.069	−0.016	−0.148	−0.046	−0.312*

*Model fit indices: RMSEA = 0.036; CFI = 0.977; SRMR = 0.025; and Chi-square = 5031.329 (p < 0.00). *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.*

TABLE 5 | Coefficients among growth factors in multivariate growth model 2: sleep duration—internalizing behaviors.

	1(i1)	2(s1)	3(i2)	4(s2)	5(i3)
	β	*β*	*β*	*β*	*β*
Sleep duration					
1. Intercept	1				
2. Slope	−0.398***	1			
Internalizing behaviors					
3. Intercept	−0.063	0.090†	1		
4. Slope	0.074	−0.053	−0.112	1	
Maternal depressive symptoms					
5. Intercept	−0.087	0.064	0.216***	−0.084	1
6. Slope	0.068	−0.017	−0.105	0.244	−0.313*

*Model fit indices: RMSEA = 0.035; CFI = 0.979; SRMR = 0.024; and Chi-square = 4864.974(p < 0.00).†p ≤ 0.1. *p ≤ 0.05; ***p ≤ 0.001.*

TABLE 6 | Standardized coefficients among growth factors in multivariate growth model 3: sleep problem—externalizing behaviors.

	1(i1)	2(s1)	3(i2)	4(s2)	5(i3)
	β	*β*	*β*	*β*	*β*
Sleep problem					
1. Intercept (i1)	1				
2. Slope (s1)	−0.415***	1			
Externalizing behaviors					
3. Intercept (i2)	0.789***	−0.540***	1		
4. Slope (s2)	−0.663***	1.654***	−0.080	1	
Maternal depressive symptoms					
5. Intercept (i3)	0.159**	−0.043	0.156**	−0.056	1
6. Slope (s3)	−0.076	0.230	−0.144	−0.047	−0.323*

*Model fit indices: RMSEA = 0.058; CFI = 0.952; SRMR = 0.028; and Chi-square = 6003.135(p < 0.00). *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.*

TABLE 7 | Coefficients among growth factors in multivariate growth model 4: sleep problem—internalizing behaviors.

	1(i1)	2(s1)	3(i2)	4(s2)	5(i3)
	β	*β*	*β*	*β*	*β*
Sleep problem					
1. Intercept	1				
2. Slope	−0.415***	1			
Internalizing behaviors					
3. Intercept	0.894***	−0.570***	1		
4. Slope	−0.618***	1.612***	−0.082	1	
Maternal depressive symptoms					
5. Intercept	0.159*	−0.042	0.217***	−0.086	1
6. Slope	−0.075	0.230	−0.105	0.251	−0.320*

*Model fit indices: RMSEA = 0.065; CFI = 0.942; SRMR = 0.027; Chi-square = 6068.377 (p < 0.00). *p ≤ 0.05; ***p ≤ 0.001.*

exhibited higher levels of adjustment problems concurrently and a faster decrease in behavioral problems for the next 2 years. The opposite was also the case: when children displayed more adjustment problems at four, the over-time decline in SPs by the age of 6 was faster. In addition, the amount of decrease in SPs was associated with that in children's internalizing and externalizing problems over time: the greater the decrease in SPs, the greater the reduction in children's internalizing and externalizing problems. Finally, when mothers displayed higher levels of depressive symptoms, children exhibited higher levels of SPs and internalizing and externalizing behaviors concurrently at four. However, no significant associations were detected between the rates of change in MDS and those in children's sleep parameters (duration and problems) and internalizing and externalizing problems.

The present study findings on the trajectories of sleep parameters correspond with the prior finding that sleep duration and problems tend to decrease gradually across early childhood, including the preschool period (Petit et al., 2007; Galland et al., 2012; Vriend et al., 2012; Kocevska et al., 2017; Williamson et al., 2019). According to a meta-analysis of sleep research (Galland et al., 2012); daily SD decreases approximately 7.8 min per year between 1 and 4 years of age and 5.9 min per year from 5 to 12 years of age. In the current study, daily SD decreased about 3 min per year between T_1 and T_2 and about 4.8 min per year between T_2 and T_3. These patterns differ from Galland et al. (2012) in that the decrease was smaller initially and greater in the last years, although the general tendency was similar. This discrepancy might be due to the shorter average sleep hours reported among Asian children compared to their Caucasian counterparts (Liu et al., 2005; Mindell et al., 2010) or to the reliance on parental reports regarding children's sleep hours.

The finding that shorter SD and more SPs at four were concurrently related with more behavioral adjustment problems is in line with well-established associations in the extant literature (Yokomaku et al., 2008; LeBourgeois et al., 2013; Tso et al., 2016; Williams et al., 2016; Bélanger et al., 2018). The current study contributes further to the literature by revealing the over-time synchrony in the trajectories of SPs and behavioral adjustment outcomes. The greater the reduction in SPs, the larger the decline in behavioral problems and vice versa. The amount of SPs at four was associated with the amount of decline in behavioral adjustment over the next 2 years and vice versa. In these reciprocally concurrent and prospective associations, the

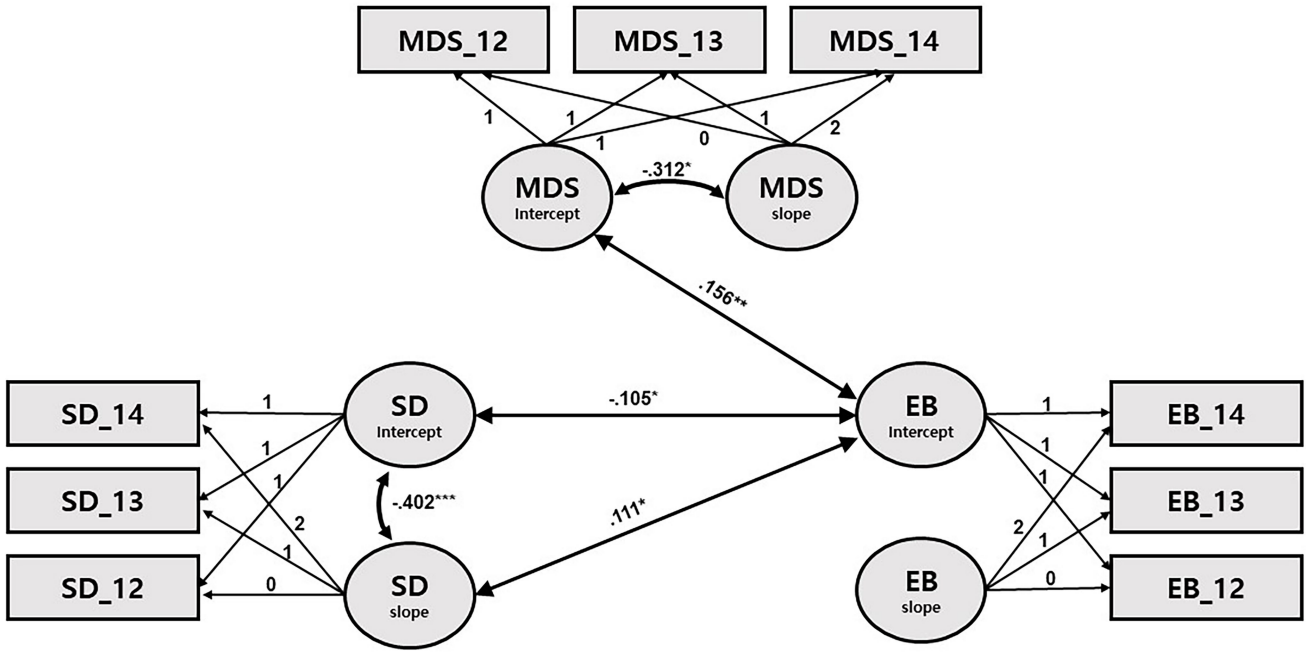

FIGURE 1 | Path diagram for latent growth modeling of sleep duration, externalizing behaviors, and maternal depressive symptoms. SD: sleep duration; EB: externalizing behaviors; and MDS: maternal depressive symptoms. Only significant path coefficients are shown. $^{*}p < 0.05$, $^{**}p < 0.001$, and $^{***}p < 0.001$.

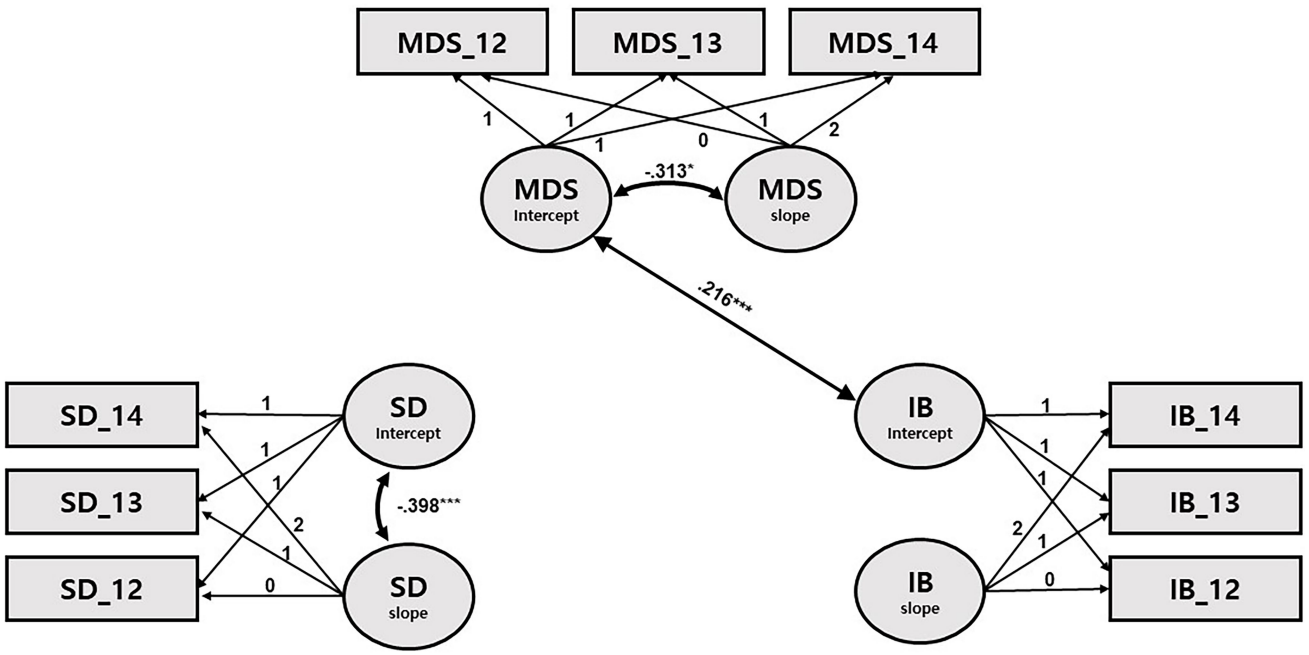

FIGURE 2 | Path diagram for latent growth modeling of sleep duration, internalizing behaviors, and maternal depressive symptoms. SD: sleep duration; IB: internalizing behaviors; and MDS: maternal depressive symptoms. Only significant path coefficients are shown. $^{*}p < 0.05$, $^{**}p < 0.001$, and $^{***}p < 0.001$.

impact of SPs on the change in adjustment behaviors was found to be slightly greater than the impact of adjustment behaviors on SPs, implying that sleep plays a primary role in its relationship with behavioral adjustment, probably through emotional regulation, as reviewed earlier (Dahl, 1996). In another longitudinal study examining SPs and emotional and attentional self-regulation from infancy to 8–9 years of age, the magnitude of the paths from SPs to

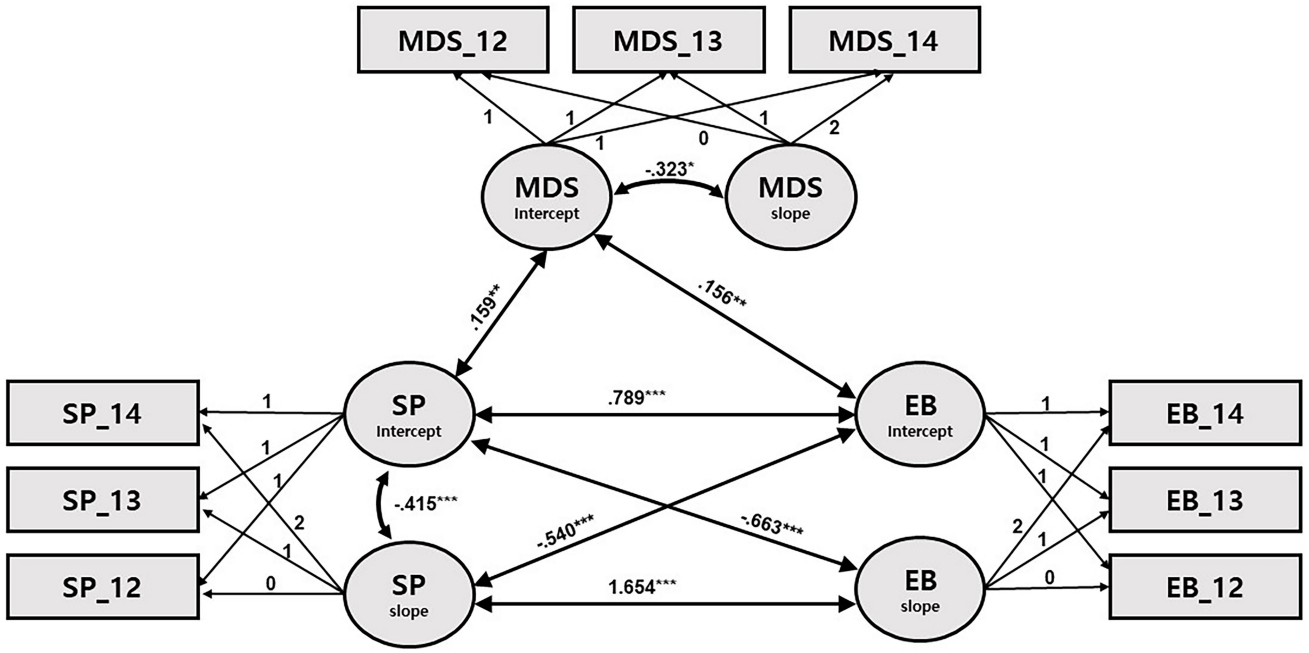

FIGURE 3 | Path diagram for latent growth modeling of sleep problems, externalizing behaviors, and maternal depressive symptoms. SP: sleep problems; EB: externalizing behaviors; and MDS: maternal depressive symptoms. Only significant path coefficients are shown. *$p < 0.05$, **$p < 0.001$, and ***$p < 0.001$.

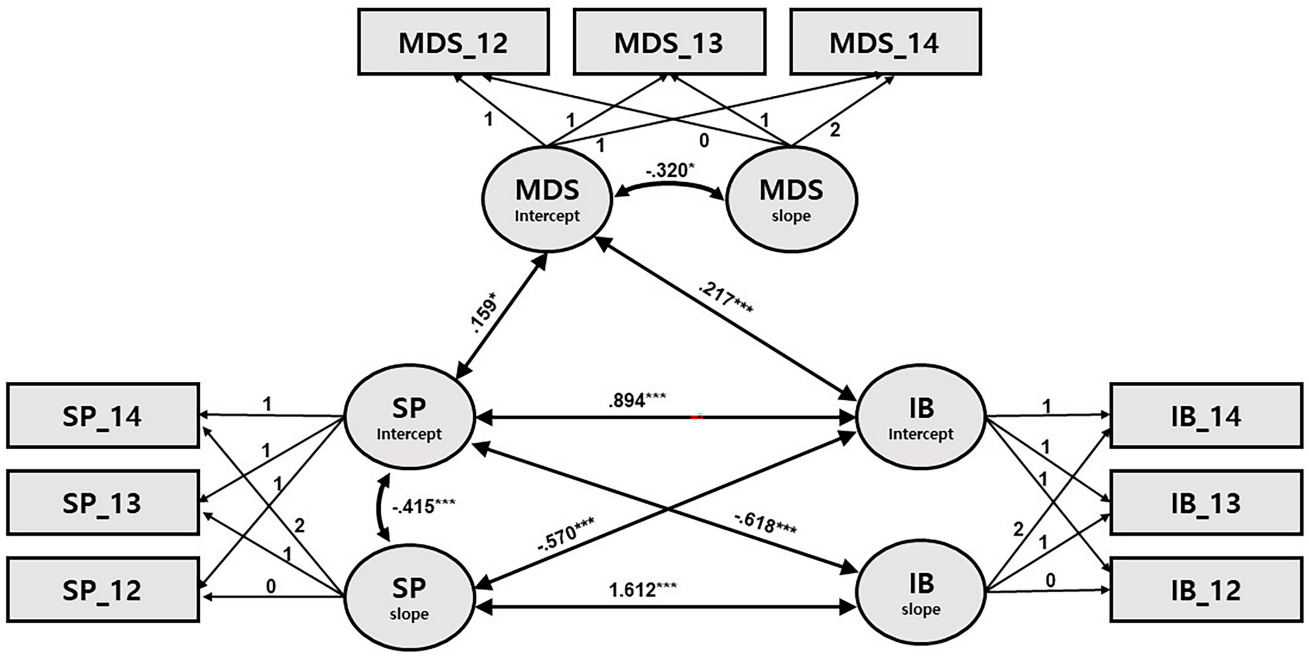

FIGURE 4 | Path diagram for latent growth modeling of sleep problems, internalizing behaviors, and maternal depressive symptoms. SP: sleep problems; IB: internalizing behaviors; and MDS: maternal depressive symptoms. Only significant path coefficients are shown. *$p < 0.05$, **$p < 0.001$, and ***$p < 0.001$.

emotional regulation was stronger than the other way around (Williams et al., 2015).

The observed synchronized change in SPs and internalizing and externalizing behaviors is likely explained by neurobiological mechanisms that generate less efficient functions and/or delayed maturation of the brain regions involved in sleep and emotional regulation (e.g., prefrontal cortex and the limbic system, including the amygdala, hypothalamus, and thalamus; Goldstein and

Walker, 2014; Bathory and Tomopoulos, 2017). Self-regulation, in particular emotional regulation, has been thought of as a potential mediating factor in the sleep-adjustment association (Dahl, 1996) evidenced by links between inadequate sleep and higher negative (lower positive) emotions as well as the common co-occurrence of affective disorders and sleep abnormalities (Goldstein and Walker, 2014; Bathory and Tomopoulos, 2017). Recent neuroimaging studies with adults found that amygdala activation was 60% greater after sleep deprivation (Yoo et al., 2007). In addition, connectivity between the amygdala and prefrontal cortex was found to decrease after sleep deprivation, which implies impaired self-regulation (Yoo et al., 2007). Also, children with SPs seem to experience additional disadvantages in terms of prefrontal cortex maturation, being manifested as thinner cortex in the dorsolateral prefrontal area (Buchmann et al., 2011; Kocevska et al., 2017). More research is needed to identify the neurological mechanisms underlying disorders of sleep and emotional regulation, but interactions between the environment (e.g., parenting) and genes seem to be one of the causes. Previous research (Davis et al., 2017) demonstrated the moderating effects of parenting on the relationship between child sleep outcomes and genes (e.g., 5-HTTLPR and DRD4) pertaining to both sleep quality and emotional regulation (Bouvette-Turcot et al., 2015; Dutta, 2020): children carrying the short allele(s) of the 5-HTTLPR gene displayed significantly fewer sleep problems at low levels of maternal parenting stress while exhibiting more sleep problems at high levels of maternal parenting stress, supporting the differential susceptibility hypothesis (Ellis et al., 2011). It is possible that the observed interconnections between sleep measures and behavioral adjustment outcomes in the current study (e.g., synchronized greater decrease in SPs and externalizing/internalizing behaviors) might have resulted from the workings of these genes and MDS moderation of the sleep-adjustment relations, although this was not examined in this study.

Given that previous studies have reported that shorter SD and more SPs are associated with greater adjustment problems (also found in this study), it was expected that a faster decrease in SD and slower decline in SPs would be related to more behavioral problems. However, the opposite was found in the present study: higher levels of behavioral adjustment problems at four were associated with a slower decrease in SD and faster decline in SPs in the next 2 years. These seemingly puzzling results seem to arise from the fact that *longer* SD and *greater* SPs at four were related to *faster* reduction in each of the variables over the next 2 years. Since there were concurrent *negative* and *positive* associations between behavioral adjustment and SD and SP, respectively, and both SD and SP showed *greater* decline when their initial levels were higher, behavioral adjustment at four was associated with a *slower* decrease in SD and *faster* decline in SP. Thus, future research should investigate how common it is that preschoolers with initially longer SD and more SPs exhibit relatively faster reduction in both SD and SPs. In addition, whether relationships between initial levels and the amount of change in SD and SP differ depending on children's disparate levels of behavioral adjustment problems is worth studying. Unfortunately, to the best of my knowledge, no studies have reported how initial levels of SD and SPs are related to their own decrease rate over time in relation to children's levels of behavioral or emotional regulation. Instead, one study (Williams et al., 2016) examined correlations between SPs at adjacent measurement points throughout the early childhood period and reported a gradual increase in the magnitudes of the correlations over a period of 6–7 years. This differs from the current study's findings; thus, more research is needed.

A comparison between the SD and SPs models suggests that what matters in predicting children's behavioral adjustment in relation to MDS is likely *the quality*, rather than *the total amount* of sleep (Bélanger et al., 2018). First, a greater number of associations were detected between SPs than between SD and other variables. While both the initial level (intercept) and the degree of change (slope) were associated with those of behavioral adjustment in the SPs models, only the initial levels of externalizing problems were related to the growth factors of the SD, with no associations found in the internalizing problems model. In addition, the associations between behavioral adjustment (i.e., internalizing and externalizing problems) and SPs were stronger compared to those with SD. These results support the likelihood that sleep quality, rather than quantity propels behavioral adjustment, in accordance with the reviewed literature. Indeed, maladaptive outcomes caused by sleep disruption in adults were found not to be ameliorated by sleep quantity (e.g., Haus and Smolensky, 2006; Genzel et al., 2013).

The associations between MDS, sleep, and behavioral adjustment were not as robust as those between sleep and behavioral adjustment but were more apparent in the SPs models than in SD models. No direct association was found between SD and MDS in this study. Previous research has yielded inconsistent findings, with some showing no associations, as in the current research (e.g., De Jong et al., 2016) and others revealing significant links (e.g., Schultz et al., 2020) between SD and MDS. Concerning SPs, MDS at four were positively associated with the concurrent levels of SPs, in line with the prior findings among elementary school children (e.g., Buckhalt et al., 2009; Kelly and El-Sheikh, 2011; El-Sheikh et al., 2012). Similar to child sleep parameters, MDS was weakly concurrently associated with behavioral adjustment (internalizing and externalizing problems) at four, similar to findings from meta-analytic studies examining the effects of MDS on children's psychosocial functioning, including internalizing and externalizing problems (Connell and Goodman, 2002; Goodman et al., 2011). In these studies, the effect sizes were small in magnitude, comparable to the current study results (internalizing: $r = 0.16–0.23$; externalizing: $r = 0.14–0.21$). In the present study, the associations between MDS and internalizing problems were slightly stronger than those with externalizing problems, which seems sensible given that *internalizing* problems directly concern emotional reactivity, anxiety, depression, social withdrawal, etc. Regarding children's externalizing problems, the observed associations might have arisen from reciprocity in a mother–child relationship (Warren et al., 2006): (1) from a mother to a child through fewer demonstrations of emotionally regulated behaviors, less provision

of instructions and strategies for behavioral and emotional regulation, and fewer expressions of warmth and affection toward a child (Lovejoy et al., 2000; Eisenberg et al., 2003; Coyne and Thompson, 2011; Wagner and Valdez, 2020); (2) from a child to a mother through relatively higher frequencies of problematic and act-out behaviors, which increases a depressed mother's psychological burden and fatigue (Meltzer and Mindell, 2007; Wagner and Valdez, 2020).

However, no significant prospective link was found between the levels of MDS at four and the rate of change in child behavioral problems, which partially contradicts previous studies reporting that MDS profiles predicted later child adjustment outcomes (Cents et al., 2013; Giallo et al., 2015; Park et al., 2018). This absence of predictive interplay might be because a comprehensive set of confounding variables, including responsive parenting and negative emotionality, was controlled for in the analysis. In addition, because the study data were collected from the general population and not a clinical sample, the number of mothers and children in the sample with severe depressive symptoms and behavioral problems is likely small to detect an effect. Although no direct link was found between MDS at four and the rate of change in child behavioral problems, an indirect path can be assumed given MDS's concurrent associations with SPs and behavioral adjustment, each of which significantly predicted the other's degree of over-time change. Thus, the results of the present study suggest that variations in maternal mental health, even within the non-clinical range, are linked to children's SPs and adjustment in both direct and indirect ways, even when the effects of diverse family contextual covariates are controlled for.

Taken together, the current study findings imply that during the preschool years, *SD* has some impact on children's behavioral adjustment, but as children grow, *SPs* seem to be more important in predicting and, thus, probably preventing adjustment problems. While the relationship between SPs and behavioral adjustment seemed to be reciprocal, the magnitude of the path from SPs at four to the rate of change in behavioral adjustment in the next 2 years was somewhat greater than that of the other way around. This finding reinforces the importance of the *quality of sleep* for better socio-emotional developmental outcomes. Therefore, improving sleep quality by addressing any problems in the child's environment as well as practices within the family, especially focusing on the overall parenting quality, may be an effective approach to improve young children's general development and health. MDS were found to have a concurrent impact on children's sleep problems and behavioral adjustment outcomes during the preschool period when children's dependence on mothers declined as compared to infancy. Mothers (or any main caregivers) are, in general, the most influential entity in child development during the first few years. The current study findings, along with previous work showing that high-quality maternal parenting impact some genes' phenotypes intervening in sleep and self-regulation, also tells us that keeping mothers' mental health in check during the immediate postpartum period and throughout the later years, should be the focus of parent support policies and parent education.

LIMITATIONS AND FUTURE RESEARCH

Despite the merits of this study, some limitations should be noted. First, recent studies have shown that the daily amount of media exposure (screen time) relates to sleep quantity and quality (Garrison et al., 2011; Tso et al., 2016; Zhang et al., 2020) and psychosocial and emotional problems among young children (Pagani et al., 2010; Hinkley et al., 2014). However, this study could not control for the effects of media exposure due to a lack of information. Thus, future studies should consider children's daily media consumption. Second, this study relied on parental reports on the main study variables, including sleep quantity and quality, suggesting the possibility of slight over- or under-estimation of the real sleep time and problems, although parental reports have shown generally high agreement with objective measures such as actigraphy (Sadeh, 1994; Tikotzky and Sadeh, 2001; Sekine et al., 2002). The possibility that depressed mothers might have perceived their children's sleep and behavioral problems more severely also necessitates more studies using objective measures concerning preschool period. Next, even though this study tried to comprehensively control for diverse domestic factors, other aspects of family functioning were not represented in this study, in particular, parental practices pertaining to sleep, such as co-sleeping, bedtime routines, sleep hygiene (Arora, 2019), and other related factors like nutrition and daily exercises (Westerlund et al., 2009; Łuszczki et al., 2021). Similarly, the effects of neurobiological factors, such as mother–child shared genetic makeup and mechanisms intervening in sleep and behavioral adjustment independently and jointly, were not considered in the current study. Thus, more research addressing relevant factors at various levels—from biological to environmental (e.g., genes, maturation, relevant brain regions functioning, and daily activities including childcare-related variables)—, would contribute to connecting the dots and completing the whole picture.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study used a national-level open data set. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Revisiting the Concept of Vigilance

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Vigilance deficits can be observed after a period of prolonged, continuous wakefulness. In this context there has been extensive research targeting the impact of sleep deficits on different aspects of vigilance, but the underlying concept of vigilance was hardly ever addressed and discussed. One reason for this shortcoming is the unclear and ambiguous definition of the term vigilance, which is commonly used interchangeably with sustained attention and even wakefulness. This confusion is the result of a wide range of misleading definitions, starting in the 1940s, as psychologists redefined the concept of vigilance suggested by British Neurologist, Henry Head, in 1923. Nevertheless, the concept of vigilance is still useful and innovative, especially in treating sleep problems in children and young adults. This paper reviews the current usage of the term vigilance in sleep-wake-research and describes not only the benefits, but even more clearly, its limitations. By re-focusing on the definitions given by Henry Head, the concept of vigilance is an innovative way to gather new insights into the interplay between sleep– and daytime behaviors. In addition, future research on vigilance should consider three perspectives: 1st vigilance perceived as a process to allocate resources, 2nd vigilance associated with compensatory behaviors and 3rd the role of vigilance in human environmental interactions. This approach, understood as a conceptual framework, provides new perspectives by targeting sleep-wake behaviors as a 'real life' outcome measure, reflecting both physical and cognitive performance as well as sleep quality and quantity.

Keywords: vigilance, sleep-wake behaviors, children sleep disorders, daytime sleepiness, alertness

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THE MANY FACETS OF THE CONSTRUCT VIGILANCE

Hardly any other concept has caused as much confusion with its definition in psychology, physiology, and sleep research than the term vigilance. In everyday language, vigilance (derived from the Latin word, *vigilantia*) is primarily associated with *being highly alert* or having *sustained attention*. In the scientific context, the term *vigilia* has long been used to describe sleeplessness, but in current usage, the psychological definition as a state of *increased and longer-lasting responsiveness* has prevailed. These approaches have little to do with the concept of vigilance, as suggested in 1923 by Henry Head, a British neurologist (1). He referred to vigilance as the organism's ability to reorganize itself and restore damaged functions. After trauma, the first signs of "vigilance" were the reappearance of reflexes, followed by automatic actions and gestures, and finally the regaining of the ability to differentiate between sensory stimuli (readiness to respond). In Head's opinion, the reappearance of sensory processing is purely physiological in nature and independent of higher cognitive functions such as consciousness, motivation or interest. Therefore, vigilance is neither

a cognitive skill nor a matter of consciousness. However, consciousness requires vigilance and adequate processing of sensory inputs or a functioning autonomic nervous system (e.g., to control blood pressure, body temperature, etc.). In this context, vigilance is a universal property of animals and humans in order to react adequately to environmental stimuli and to ensure the survival of the individual.

Head defined three sub-categories as essential for his concept of vigilance: 1st *perception,* to guarantee that a stimulus is registered by the sensory system according to their modality. 2nd *behaviors,* a category which includes all kinds of observable behavior, whereby complex behavior is associated with higher levels of vigilance (and vice versa). And 3rd *reorganization,* referring to the ability of injured organisms to reorganize and restructure their neuronal connections in order to take over or compensate for the function of damaged structures. The goal of reorganization is to ensure the survival of the individual, which is by far the key function of vigilance (1).

Nevertheless, the reorganization aspect of vigilance caused confusion and criticism because it was not entirely clear what it meant. This was partly due to Head's inconsistent use of the term vigilance, which he sometimes referred to as vital energy, in relation to both nervous and mental processes. More than that, it remains unclear whether vigilance is *per se* the reorganizing force or only the result of this process (2).

THE CONCEPT OF VIGILANCE IN EXPERIMENTAL PSYCHOLOGY

In the view of test psychologists, vigilance can be measured by a simple S-R model (stimulus-response). This approach assumes that the presentation of a stimulus leads to similar responses in all individuals or to the same class of responses, observed over a distinct period of time. These time-on-task effects are seen particularly in behavioral automatisms. However, the dynamic aspect of Head's concept of vigilance (as a self-organizing system) is not addressed by conventional S-R models. For this purpose, more sophisticated approaches such as dynamic self-regulation models are necessary. Regardless of these possibilities, in the 1940s, NH. Mackworth developed, on behalf of the British Airforce, vigilance tasks (utilizing the Mackworth clock-test) in order to recruit suitable personnel for radar surveillance activities. Systematic studies with the clock-test (lasting for more than 2 h) demonstrate that even highly motivated individuals found it difficult to maintain their attention at a high level for such a long time without making mistakes. Mackworth (3) defined the ability to be attentive over long time periods as vigilance (or sustained attention) and fluctuations in attention as vigilance decrement, which was by far closer to the everyday understanding of vigilance (in the sense of being highly alert) than to Head's conceptual framework.

As a matter of fact, much of the vigilance research was conducted at the beginning of the Cold War in the 1950s, a time when slogans such as "constant vigilance" were common rhetorical figures in political communication in the Western World and the Soviet Union. Under these circumstances, vigilance research became an important discipline and subject of military defense strategies (4). But the military influence on vigilance research was criticized and not commonly accepted in the research community (5). In addition, the requirements for air traffic controllers had changed radically since the time Mackworth developed his test methods. Instead of reacting to rare events in monotonous situations, the increasing frequency in commercial air traffic generates a continuous stream of information and requires other skills such as a high degree of flexibility and the ability to deal simultaneously with different kinds of stimuli. In comparison, the conditions of the Mackworth clock-test are far less complex. Besides the assumption that vigilance tests should mimic detection performance during prolonged watch-standing conditions, the necessity of additional characteristics to classify a vigilance task was evident. Otherwise, vigilance monitoring would not differ from research on simple reaction time, which is still a common view-point (6). Although this issue was excessively discussed, there is still no agreement on the main characteristics of a vigilance task (e.g., test duration, type of stimulus and their temporal order) and obligatory outcome measurements (performance characteristics, response definitions, etc.). Even Mackworth's assumption that vigilance tests should last sufficiently long (e.g., 2 h and more) has become obsolete since the release of the 10 min version of the PVT (7, 8).

The lack of standardization for measuring vigilant performance and their interpretation led to an extensive and unreflective use of otherwise well-established psychometric test procedures such as simple reaction time tests, forced choice– or go/no-go tasks. This opened the door for an increasing number of alternative explanations and terms such as tonic alertness (9) or vigilant attention (10). Regardless of these developments, the Mackworth clock-test is still in use, even in slightly modified and computerized versions (11, 12). And besides its spongy definition, most studies with sleep deprived subjects refer to the concept of vigilance to describe the significant impairments caused by less or inadequate sleep (10, 13, 14).

Reconsidering Head's concept of vigilance, terms such as sustained or vigilant attention, understood not only as a cognitive skill but also influenced by motivation, experiences and expectations (e.g., assumed rewards), cannot be equated with vigilance *per se*. In the view of test psychologists, vigilance is reflected by behaviors, and adequate reactions are not possible without appropriate stimulus perception. But Head's third aspect, the reorganizing function of vigilance, is not addressed by the usual sustained or vigilant alertness tasks; concepts other than a simple S-R model [e.g., dynamic self-regulation models (15)] may support this aspect but are not commonly in use.

THE NEUROPHYSIOLOGICAL CONCEPT OF VIGILANCE

Findings in neurophysiology in the first half of the twentieth century proved to be largely supporting Head's concept of vigilance. For example, Hess (16) studies on the autonomic nervous system or, most importantly, the investigations of Bremer, Moruzzi and Magoun (17) on the ascending reticular

activation system (ARAS). This pathway turned out to be significantly involved in maintaining wakefulness and alertness, as well as for short-term (phasic) and long-lasting (tonic) activation. Also in sleep, these neurobiological mechanisms are suspected to play a key role in sudden activations (arousals) of the cortex (18, 19). Although arousals show several similarities to Head's concept of vigilance, there are substantial differences. According to Head, vigilance describes a fundamental principle of living organisms rather than the performance of specific anatomical areas such as the ventrolateral preoptic nucleus, which is the case in arousals (20).

Technical innovations were another reason for the increasing interest in the neurophysiology of vigilance. At the end of the 1950s, the recording of brain activity utilizing multi-channel EEG systems was available in many neurobiological research units. Dieter Bente was among the first scientists in Europe creating a classification scheme of wake states, analogous to sleep stages. Attempts at classifying the waking state have existed since the late 1950s by Lindsley (20) and Roth (21). Fluctuations in wakefulness, visualized by flattening and slowing of the EEG-signals, were assigned to corresponding vigilance levels such as relaxed wakefulness (alpha waves; alert, vigilant), tense wakefulness (beta waves; active, overexcited, hypervigilant), or decreased alertness (alpha-theta waves; drowsy, hypo-vigilant) and "sub vigile stages" for the transition to sleep (22). The EEG was considered to be the ideal representative of vigilance because it enables the time-synchronous coupling of neuronal activity with observable behavior (23), which is not the case when solely using psychometric testing. However, there are different opinions on whether sleep stages should be included into the nomenclature of vigilance stages (24). The onset of sleep marks the boundary beyond which wakefulness definitely ends and in this context a semantic ambiguity becomes evident: in many EEG-studies, the term vigilance is synonymously used as wakefulness or even alertness and this vagueness is still evident (25). In addition, also other methodological issues dispatched [e.g., the concept of "local/global" vigilance (26)] and there is an ongoing controversy about the correct definitions of hyper-, hypo-, sub-, super– or supra-vigilance as compared to "normal" vigilance states (see **Figure 1**). Many of these concepts and definitions are deemed to be incompatible with Head's idea of vigilance as an integrative, non-divisible entity (2, 24).

To date, none of the classification schemes for wakefulness have gained acceptance (unlike sleep stages), neither in clinical medicine nor in basic research. As an alternative to define wake stages, a number of EEG-based vigilance indicators (27) such as the alpha slow wave index, the absolute delta power or the 'vigilance index' (28) have been proposed, but still, there is no consensus on which method is most suitable for measuring vigilance. Despite the fact that EEG studies are considered to be the gold standard for identifying fluctuations in vigilance, there are other psychometric methods (6, 29–32) which have proven to be sensitive and even more suitable for long term vigilance monitoring (33).

Head saw an important, if not the most essential function of vigilance in its reorganizing power. But this aspect was also not addressed in the neurophysiological discussion on vigilance. Bente (22) was one of the few who repeatedly pointed out the integrative function of vigilance and was convinced to determine the current level of neuronal organization (understood as an expression of vigilance) by the analysis of spontaneous brain electrical activity. This idea was picked up by Ulrich (2), a student of Bente, who defined vigilance in relation to a closed biological system which is in constant interaction with the environment. In this interplay of disorganization (i.e., partial opening of a closed biological system) and reorganization (i.e., functional development, restoration and system closure), vigilance could be the "force" behind these processes. Reframing the concept of vigilance with cybernetic and system-theoretical models (Norbert Wiener, Ludwig von Bertalanffy) could set new perspectives, especially with regard to the role of sleep as a homeostatic– and restorative process.

VIGILANCE AND THE SLEEP-WAKE CYCLE

Although some scientists consider sleep as a non-vigilant state and hence not a topic of interest, the transition from wake to sleep was intensively discussed in vigilance research. A wide range of hypotheses, classifications and assumptions were suggested to define the line between being awake, conscious, vigilant and asleep (24). In terms of sleep physiology, the process of falling asleep is clearly determined by visual polysomnographic criteria for sleep stages N1 and N2 (34), without further distinctions into sub-stages.

According to current opinion, the transition from wakefulness to sleep is not a succession of stages, but a continuous process, accompanied by highly selective deactivations of different brain areas. This is in line with the presumption that sleep may occur locally and not strictly as a global event (35, 36). In 1988, Koella (37) suggested a theoretical model for sleep/wake regulation, centered on a system which he called the "vigilance controlling apparatus" (VCA). In this model wake and sleep are not fundamentally opposite entities; they differ *phenomenologically* (37) only by their vigilance profiles (e.g., during relaxed wakefulness vigilance is at an intermediate level, whereas in sleep it is relatively low). The variability in these profiles depends on the level of local vigilance [another concept by Koella (26)], which is detectable by behavioral observation (e.g., the intensity, quality, precision and adequacy of behavior). Although Koella's considerations elicit only minor reactions in the sleep community, they are worth being reviewed, not only in the context of the "local/global sleep"-concept, but also in the discussion about default mode-networks (38, 39) and resting state phenomena (40, 41). This reorientation and re-definement of the concept vigilance in the context of sleep is crucial, because the term vigilance/vigilance states is often used interchangeably with sleep stages, sleepiness or wakefulness (25).

In the diagnosis of sleep disorders, vigilance tasks are important to point out the consequences of poor sleep on daytime sleepiness, fatigue or tiredness (42). Besides psychometric tasks such as the PVT or simple reaction time tests also the MSLT, MWT or other psychophysiological

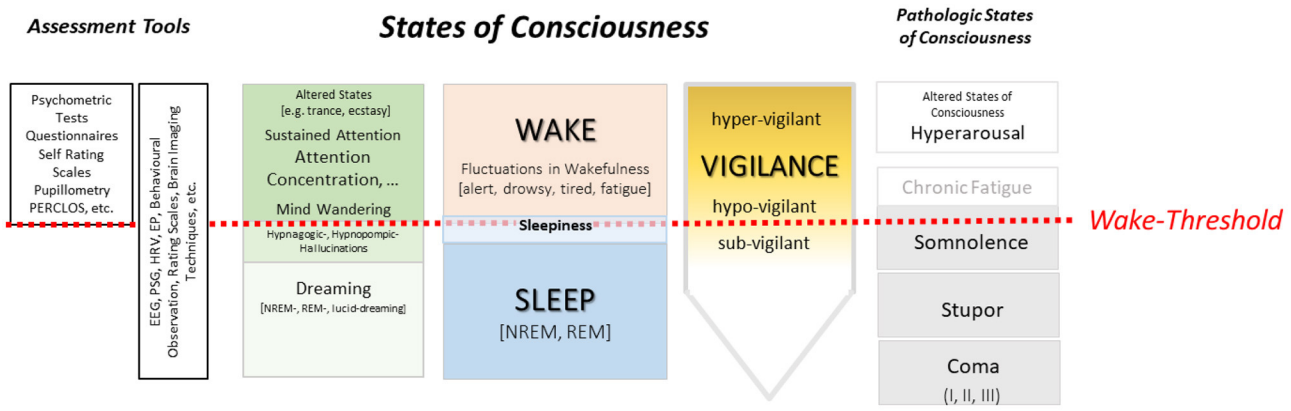

FIGURE 1 | Overview of the different concepts and terminologies related to vigilance and states of consciousness (as well as pathologic states). In the graph also some wiedly used assessment tools are listed. For example, methods such electroencephalography (EEG), polysomnography (PSG), heart rate variability (HRV) or evoked potentials (EP) can be used for sleep and wake, whereas psychometric test or questionnaires are usable only in wake.

measurements (e.g., heart-rate, actigraphy, evoked potential, pupillography) are in use (6) (see **Table 1**). The diagnostic value of such procedures does not always justify the great effort behind some of these tests (57). Moreover, the correlation between the different tasks is rather poor (58), particularly in patients whose subjective ratings of fatigue and tiredness rarely fit with objective measurements (59, 60).

One reason for these shortcomings is the lacking comprehensive concept of vigilance in basic sleep research; an attempt at such a concept by Posner and Rafal (the attention model) has yet to be updated (61). Approaches with attention triggered by cues, inwards (e.g., linked to mind wandering and daydreams) or outwards orientated (directed or selective) or reinforcing behaviors over time (as a sign of vigilance) may foster new insights as well as discussing the role of awareness in the context of vigilance (62). Currently, vigilance testing in sleep medicine is characterized by a cocktail of test methods (6, 30, 42) and confusing definitions taken over from neighboring disciplines, particularly psychology (see **Table 1**). New insights may offer functional magnetic resonance imaging studies with sleep deprived subjects (25, 63, 64).

REVISITING THE CONCEPT OF VIGILANCE

It is certainly not necessary to reinvent the concept of vigilance; A look at the extensive literature on this topic proves that there are already enough concepts and ideas. Looking back and anticipating Head's genuine considerations is enough to gather new ideas and perspectives. As a first step, it is necessary to clearly distinguish vigilance from other concepts such as alertness, attention or arousal (43). By doing this, we suggest a second step to reframe the concept of vigilance as a mindset for collecting data on sleep-wake behaviors (e.g., psychometric testing, sleep studies, behavioral observation, subjective data, etc.) and their interpretation (see **Figure 1**). Research on vigilance should consider three *perspectives*:

Vigilance—Allocation of Resources

From a neurophysiological point of view, tiredness, fatigue, and decrements in attention and concentration are the consequences of neuronal inhibition, habituation or, more generally speaking, the decrease of alertness-promoting compounds (monoamines, acetylcholine). Subsequently, substances inhibiting neuronal signal processing accumulate [e.g., adenosine (65)] and thus produce "sleep pressure". We consider wakefulness and alertness as biological resources which guarantee adequate reactions, ultimately for survival. If these resources tail off, compensatory actions are initiated, which are observable (e.g., behavioral patterns such as stretching, yawning) and measurable. In our opinion, the process of allocating resources is a matter of vigilance.

Vigilance—Compensatory Behaviors

Sleepy subjects try to keep themselves awake through auto-stimulating behavior (yawning, stretching, lolling, singing, whistling) (66, 67). These subsidiary behaviors (68, 69) are an expression of compensatory mechanisms to replace or mitigate diminishing alertness in order to fight against falling asleep. For example, children sometimes show hyperactive behavior at bedtime as a countermeasure for sleepiness. We think that compensatory actions such as subsidiary behaviors are a sign of the vigilant subject and thus relates to Head's 3rd sub-service of vigilance (*reorganization*). Therefore, the identification and documentation of compensatory or subsidiary behaviors should be an essential part of vigilance diagnostics. With the use of video recordings and image processing tools, behavioral observation is feasible without consuming too much time and guarantees objective data analysis (66, 67, 70, 71).

TABLE 1 | Overview of the different definitions of vigilance, attention (vigilant, sustained), alertness, sleepiness, fatigue, tiredness and related tasks paradigms (measurements).

	Definitions	**Measurements** (not a complete overview)
vigilance	- ability to reorganize and restore damaged functions in order to react adequately to environmental stimuli (1) - degree of central nervous activation: • high = hypervigilant (high degree of activartion can lead to a lack of reaction • low = hypovigilant: subject cannot adequately react to external stimuli under monotonous conditions (6) - capability to be aware of potential relevant, unpredictable changes in one's environment, including a quantitative dimension, a sufficient level of alertness, and a temporal dimension (43)	- 'conventional' vigilance tests: monotonuous, long lasting, with infrequently ap-pearing target stimuli [e.g., Mackworth Clock Tests (3)] - alternatively: short tasks, but with more target stimuli (e.g., Psychomotor Vigilance Test (PVT) (8), reaction time tasks (RTT), go/no-go tasks, forced choise tasks (FCT) - electroencephalography (EEG), polysomnography (PSG), evoked potential (EP) - heart rate variability (HRV) - pupillometry - electrodermal activity (EDA) - functional magnetic resonance imaging (fMRI) - videometry
attention	ability to watch, listen to, concentrate, or to focus one's mind on some-thing/someone with interest (requires cognitive control)	- psychometric tests for attention, concentration [e.g., Attention Network Test (44)], go/no-go tasks, FCT - EEG, EP, fMRI
vigilant attention, sustained attention	ability to maintain focused and stable across long time intervals (45); the decline in timely and correct responses is defined as vigilance decrement or time-on-task effects	- Mackworth Clock Test, PVT, RTT, FCT, go/no-go tasks - EEG, PSG, HRV, fMRI
alertness	state of being awake, prepared to act/react; also defined as the result of the interplay between circadian processes, sleep-homeostasis and sleep inertia (46); influenced by time-awake-, time-on-duty or time-on-task	- PVT, RTT, go/no-go tasks, FCT - EEG, PSG, EP, HRV
sleepiness	subjective expression of the individuals need of sleep (feeling of being sleepy); sleepiness characterizes the transition between being alert (awake, fully awake) and falling asleep, accompanied by subjective (cognitive) and objective (physiological, behavioral) changes	subjective (cognitive) measurements: Karolinska Sleepiness Scale (KSS) (47), Stanford Sleepiness Test (SSS) (48), Epworth Sleepiness Scale (ESS) (49) objective (physiological) measurements: Multiple Sleep Latency Test (MSLT) (50), Maintenance of Wakefulness Test (MWT) (51), pupillometry, videometry
fatigue, tiredness	*fatigue* = subjective sense of tiredness; influenced by two biological factors: sleep-homeostasis and circadian processes; depends on the time-awake, time-on-duty or time-on-task; "fatigue" is often interchangeable used with sleepiness or tiredness; therefore it is important to distinguish between mental and physical fatigue (52). *tiredness* = diurnal fluctuations of wakefulness, contrary to sleepiness because (daytime) sleepiness is a sign of non-restorative sleep (53).	subjective (cognitive) measurements: e.g., Fatigue Severity Scale (FSS) (54), Fatigue Assessment Instrument (FAI) (55) objective (physiological) measurements: e.g., PVT, RTT, FCT, go/no-go tasks PERCLOS (56), EEG, PSG, EP, videometry

Vigilance—(Human) Environmental Interactions

Many situations in daily life necessitate increased levels of attention and concentration. Activities like driving on the motorway for several hours at night, paying attention in class, or simply crossing a busy road require a substantial level of attention, not only to the environment, but also to one's 'inner' world (i.e., emotions, motivation). The interplay between self-perception (e.g., 'I'm sleepy because I didn't sleep the night before') and environmental demands (e.g., the consequences of errors) produce tension and activation, which are not considered by conventional vigilance test settings. For example, studies on driver fatigue demonstrate that car driving simulators do not reflect the situations of driving on a road at night. In real life, drivers are less tired and sleepy as compared to experimental settings in a lab (72). Therefore, we suggest including information about the test setting in clinical practice as well as in basic scientific research.

CONCLUSIONS AND FURTHER PERSPECTIVES

Good sleep has numerous effects such as recovery from physical and emotional stress, and being well-rested, alert, concentrated, and productive during wakefulness. Vigilance is essential to guarantees adequate reactions to any kind of stimuli in order to ensure adaptation to changing environmental conditions. Conceived as a theoretical model (or construct), vigilance can be indirectly measured through psychophysiological methods or observed through *visible behavioral cues*, in particular by the degree (e.g., intensity, speed etc.) of ordered reactions including automatic behaviors. In our opinion, behavioral

observation plays a key role in vigilance monitoring. Alertness, awareness or attentiveness are vigilance-associated processes, but not equivalents of vigilance. We suggest three new directions in future research on vigilance: 1st the role of vigilance in allocating resources (as a conceptual and explanatory mindset), 2nd vigilance as a trigger for subsidiary behaviors ("measured" by behavioral observations), and 3rd vigilance embedded in environmental interactions (which consider information about the test setting to be essential for classifying vigilant behaviors). Some of these suggestions have already been implemented with promising results (66, 67, 70, 71, 73).

Vigilance, re-defined as a system of allocation and reorganization of biological resources, provides a better understanding of sleep-wake behaviors and allows for the consequences of non-restorative sleep to be assessed in more detail. This approach may also improve the validity of bio-mathematical models in fatigue risk management to predict fatigue-related decrements in performance (74).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

GK: conceptualization and wirting—draft manuscript. JZ: manuscript editing and review. OI: conceptualization and manuscript editing. All authors contributed to the article and approved the submitted version.

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Disruptive Behaviors and Intellectual Disability: Creating a New Script

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Background: Terms currently used to describe the so-called challenging and disruptive behaviors (CBDs) of children with intellectual disabilities (ID) have different connotations depending on guiding contextual frameworks, such as academic and cultural settings in which they are used. A non-judgmental approach, which does not attempt to establish existing categorical diagnoses, but which describes in a neutral way, is missing in the literature. Therefore, we tried to describe CDBs in youth with ID in an explorative study.

Methods: Interviews with families investigated the CDBs of five youth with Down syndrome. At home, families tracked youth's sleep/wake behaviors and physical activity. Youth were observed in a summer school classroom. The collected information and suggested explanatory models for observed CDBs were reviewed with the families.

Results: We grouped CDBs as *challenging*, if they were considered to be reactive or triggered, or *unspecified*, if no such explanatory model was available. A third category was created for light-hearted CDBs: *goofy*, acknowledging the right to laugh together with peers. We found some relationships between sleep, physical activity, and CDBs and developed an explorative approach, supporting a child-centered perspective on CDBs.

Conclusion: The controversial discussions on terminology and management of CDBs in the literature demonstrate the need for a non-judgmental approach. Such an explorative approach, allowing non-professionals to not label, has been missing. The fact that, up to now, the light-hearted behaviors of an individual with ID have not been integrated in commonly-used behavioral checklists as their natural *right*, proves our concept and indicates that a paradigm change from judgment-based to exploratory-driven approaches is needed.

Keywords: intellectual disability, Down syndrome, disruptive behavior, sleep, physical activity

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INTRODUCTION

Although it is common practice to assess contributing and trigger factors of challenging and/or disruptive behaviors (CDBs) in children with intellectual disability (ID) (1), the terms used to describe these behaviors (2) have different connotations depending on guiding contextual frameworks, such as the academic and cultural settings (3, 4) in which they are used. For example, problem behavior (5, 6) and challenging behavior (4, 7) are used interchangeably and focus on

deviations from conventional social norms and inability to access services. Social, emotional, and behavioral difficulties (8) and disengaged, delinquent, and troubled and troubling behaviors (9) carry different, mainly negative, connotations. Terms for behaviors that may cause concern are shown in **Table 1**. The lack of harmonization may be due to the absence of a shared language among medical and educational professionals, parents who provide lifelong care, as well as individuals with ID themselves (11, 12). In the medical literature (13–15), CDBs is the terminology used. Coming from a clinical background and trying to understand decision-making in a school setting—which is usually influential for parental and clinical decision-making—we use CDBs as it is consistent with the medical and educational systems in our geographical context of British Columbia, Canada. However, which behaviors are connoted as challenging and/or disruptive and who decides that? What are the contributing factors to these CDBs? It is important to be aware of and reflect on these questions because answers result in different models used to manage CDBs (16–20).

Therefore, we investigated the CDBs of youth with ID and explored natures and possible triggers of these behaviors in individuals with Down syndrome. We used a grounded theory methodology, as applied in developmental pediatrics and child psychiatry (21) and tried to review each behavior's meaning from the perspective of the participants using *in dubio pro reo* (in cases of doubt, then for) (22). Down syndrome is a chronic, complex condition with multiple comorbidities (23–25), with ID as a common denominator. Depending on the background of the authors, individuals with Down syndrome are reported to have a range of CDBs (26, 27), but few researchers have investigated their natures and etiologies (26, 28). Mimicking the coining decision-making in the community, we focused on reported and observed CDBs at home (29–31) and at school (32). In addition, we explored lifestyle factors—specifically, physical activity and sleep—and parental perceptions to understand CDBs in everyday lives.

METHODS

We partnered with the Down Syndrome Resource Foundation (DSRF; Burnaby, Canada; www.dsrf.org) for this exploratory study. The DSRF provides resources and services (e.g., library, math instruction, speech-language therapy) "to empower individuals with Down syndrome to reach their full potential" (33). The study took place at the DSRF's summer school program for individuals with Down syndrome aged 10- to 20-years-old in Summer 2016 (http://www.dsrf.org/media/Summer%20School%20FINAL%202016.pdf). Individuals with Down syndrome could attend one or more sessions of the summer school, each lasting two weeks. The daily schedule was: (a) morning reading class (1.5 h), (b) snacktime (15 min), (c) morning math class (1.5 h), (d) lunch (45 min), and (e) afternoon class (2 h)—either art and hip hop dance or Bollywood dance and yoga, depending on session's theme. The study's concept and methodology was developed in consultation with parents and staff at the DSRF and peer-reviewed by parents and professionals not involved in the study. Research ethics approval was obtained from The University of British Columbia (H16-01280).

Participants

Individuals with Down syndrome who were attending the summer school and whose parents/caregivers reported *day- and/or night-time challenging and/or disruptive behaviors* were eligible for participation per an email advertisement. The advertisement did not further specify the terms *challenging and/or disruptive* and we left the interpretation to parents/caregivers. As our intent was observation, no formal medical assessments were done. However, participants' medical backgrounds were discussed during the interviews and summary recommendations were made at the end of the study.

Of the 50 families whose children attended the summer school, five consented to participate. The median age of participants was 13 years ($M = 12.8$, $SD = 0.57$, range = 12–14). Four individuals were male. All individuals had sleep problems and were waiting for a sleep assessment or the next step of sleep medicine-related therapeutic interventions. **Table 2** presents vignettes for all participants. P5 had very severe CDBs (including on the first day of the summer school) and was not permitted to continue attending. He and his family remained enrolled in the study and participated in data collection, except for observations. All other participants attended the summer school and had an assigned educational assistant to support them throughout the program.

Data Collection

Observations

Two research assistants (RAs) independently observed and recorded the CDBs of four participants during the summer school using the partial interval recording method (34). To become familiar with the partial interval recording method, RAs completed two 2-h training sessions with an experienced DSRF staff member. The observers were not explicitly asked to reflect or document the emotions that CDBs generated in themselves, but this was discussed during the team reviews of the descriptions and codes. During the study period, RAs observed each participant for 20 s per min for 20 min at the beginning, middle, and end of each class (total of 180 min of observations over nine periods per day). A brief description accompanied each observed CDB. Participants were not observed for the remaining 40 s of each min. To become familiar with individual behaviors of each participant, the first day of observations was considered a trial and the research team reviewed the observed behaviors and the contexts in which they occurred to develop a shared language and approach for future observations. Participants were observed for four to five days in the classroom, depending on their attendance at the summer school. Inter-observer reliability (Cohen's kappa) across all observations and all participants was 0.945, indicating high agreement on identifying CDBs in the classroom.

Interviews

Individual intake interviews and exit interviews aimed, respectively, to explore individual day- and night-time behaviors

TABLE 1 | Terms for concerning behaviors.

Term	Elaboration	Discipline(s)
Problem behavior	"The problem behavior results in a significant negative impact on the person's quality of life or the quality of life of others. This may be owing to restriction of his or her lifestyle, social opportunities, independence, community integration, service access or choices, or adaptive functioning" OR "The problem behavior presents significant risks to the health and/or safety of the person and/or others." [(10) p84].	Psychology, psychiatry
Challenging behavior	"Culturally abnormal behavior(s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behavior which is likely to seriously limit use of, or result in the person being denied access to, ordinary community facilities" (4 p3).	Psychology, psychiatry, medicine, health
Social, emotional, and behavioral difficulties	"While there is no standard definition of [social, emotional, and behavioral difficulties], the various definitions share commonalities such as the following: behavior that goes to an extreme; behaviors or emotions that are outside societal norms; behaviors or emotions that negatively affect a child's educational functioning" (8 p276).	Psychology, education
Disengaged, delinquent, troubled, and troubling behavior	"Labels such as 'disaffected', 'disengaged', 'disruptive', 'delinquent', 'challenging', 'troubled and troubling' and disorders including ADHD, Oppositional Defiant Disorder and Conduct Disorder, all have a degree of overlap with [social, emotional, and behavioral difficulties] in terms of external behavior" (9 p97).	Psychology, education
Disruptive behavior	"Oppositionality, conduct problems, or aggression" (14 p65).	Medicine, psychology, education

and to summarize and share individual findings and counsel families regarding probable next steps. Core elements of all interviews were explorative semi-structured interviewing for the creation of emplotted narratives utilizing empathy and non-judgmental language to understand familial explanatory models. Explorative semi-structured interviewing employed ethnography with open-ended questions (3, 35) to characterize identified CDBs. Emplotted narratives (36) were created by encouraging parents to describe, in their own words, the sleep/wake-related behaviors of their child in the context of everyday routines and by collaboratively co-constructing the investigated history in a plot-like scenario using visualizing descriptions (21). Empathy involved putting ourselves in the place of another in order to reduce bias (37). In all interviews, special emphasis was given to the exploration of transitioning situations at day-, bed-, and night-times. Video clips of CBDs to provide a deeper understanding of CBDs were described by families verbally, but could not be used in our study due to privacy concerns.

Daily Diary and Log

Over a two-week period, each participant's family completed a daily diary and log that asked about the participant's: (a) amount of physical activity and nighttime sleep received the day/night before; (b) perceived daytime and nighttime challenges the day/night before; and (c) sleep quality (on a 5-point Likert scale), as assessed first thing in the morning based on the participant's mood and how refreshed they presented. The daily diary and log took ∼3–5 min to complete and could be completed on paper forms or via the web [see Heng et al., (38), for information about the web version]. Daily text message reminders were offered to families to complete the diaries and logs; one family requested reminders, which were sent and received during the study period.

Data Analysis

We utilized ethnographic exploration and empathy (3, 21, 37) as the foundational approach to data analysis to understand the triggers of observed CDBs. First, similar descriptions of behaviors were grouped to generate initial codes, and new descriptions were continually tested against the initial codes to revise the coding scheme. Second, we periodically met as a research team to analyze and review the descriptions and codes together. During the review process, the interviews and daily diaries and logs were used to contextualize the descriptions and generated codes. Descriptive statistics were used to explore the effect of sleep and physical activity on CDBs (e.g., determine whether participants had fewer CDBs after a higher quality sleep). Due to the small sample size, inferential statistical analyses were not conducted.

RESULTS

Across all days of observations, each participant was observed to have their own individual pattern of CDBs (**Figures 1–5**). In considering the possible origin of each CDB, three categories emerged (**Table 3**): *challenging*, *unspecified*, and *goofy*. In the following sections, each CDB is listed and explained with descriptions and/or quotations from parents. From the available information about lifestyle factors, we found that physical activity and sleep may have affected the occurrence of CDBs.

Challenging Behaviors

Challenging behaviors responded to triggers. There were four types of *challenging* behaviors: characteristics of temper tantrums, stubbornness, being overly enthusiastic, and being self-conscious. All participants had *characteristics of temper tantrums*, which were often triggered by unpleasant experiences or situations. Examples include:

TABLE 2 | Participant vignettes.

	P1	P2	P3	P4	P5
Demographics	13 years old; male.	13 years old; male.	12.5 years old; female.	13.5 years old; male.	12 years old; male.
Diagnosis	Selective mutism, status post infantile spasms, sensory processing dysfunctions.	Autism spectrum disorder, iron deficiency, tics, status post tonsillectomy/ adenoidectomy, sensory processing dysfunctions.	Status post tonsillectomy/ adenoidectomy, familial restless legs syndrome (RLS), sensory processing dysfunctions.	Status post tonsillectomy/ adenoidectomy, overweight, sensory processing dysfunctions.	Possible ADHD, autism spectrum disorder (under investigation), sensory processing dysfunctions.
CDBs	Sudden withdrawals, anxiety, 'goose-step' marching.	Less focused on academics & favors physical activities, always wants to be in a group, anxiety (sudden withdrawals and shutdowns), fidgety, stubborn, "flips" from activity to activity.	Stubborn, "not look at you and walk away" if she does not want to interact or participate, frequent temper tantrums.	'Class clown' behaviors (described as familial), difficulty regulating emotions, "freaks out" (emotional pain, "collapsing in"), impulse control, defiant, makes "weird" sounds, picks nose.	Fidgety, self-stimulation with paper, copies others, occasionally aggressive, rude and/or disengaged.
Observations	Average inter-observer reliability (Cohen's kappa): 0.927.	Average inter-observer reliability (Cohen's kappa): 0.874.	Average inter-observer reliability (Cohen's kappa): 0.989. Did not have any goofy behaviors in the school setting, which became a concern for us at the end of the observation period because P3's parent reported goofiness at home.	Average inter-observer reliability (Cohen's kappa): 0.997.	Had very difficult behaviors on the first day & was not allowed to attend; general observations about the character and severity of CDBs were recorded by his mother at home.
Physical activities	Special Olympics (bowling), dance, Taekwondo.	Special Olympics, swimming, tennis, walking.	Walking, hiking, "chasing game".	Walking, basketball, swimming.	Walking, running, basketball, swimming, biking.
Sleep problems	Insomnia (nighttime awakenings, early morning awakenings), difficulty breathing, non-restorative sleep (restless sleeper); family history of insomnia (mother & sister).	Insomnia (nighttime awakenings, early morning awakenings), difficulty breathing, non-restorative sleep (restless sleeper); family history of insomnia (mother).	Insomnia (nighttime awakenings, early morning awakenings), non-restorative sleep (restless sleeper); family history of insomnia (mother).	Insomnia (previously; nighttime awakenings, early morning awakenings), nightmares/"horrors", non-restorative sleep (restless sleeper); family history of insomnia (mother).	Insomnia (falling asleep problems, nighttime awakenings), occasional major hyperactivity before bedtime with bedtime resistance, non-restorative sleep (restless sleeper); family history of insomnia (mother & sisters, if no physical activity during daytime).
Physical activity/sleep interactions	More CDBs after a poor quality sleep and fewer CDBs after a good-quality sleep. Physical activity may increase sleep quality, which may reduce CDBs the next day.	May have fewer CDBs after receiving physical activity and a good-quality sleep. Family also sees a difference in behavior after 3–4 days of inconsistent/little sleep.	Physical activity may help her go to bed; however, it is difficult to determine the effect of daily physical activity and sleep quality on CDBs, as she did not receive much daily physical activity (lowest among all participants) and her sleep quality was consistently "poor".	May have more CDBs after shorter sleeps. Physical activity may have a positive effect on his sleep quality. However, it is difficult to determine the effect of daily physical activity and sleep quality on CDBs, as he receives near daily physical activity and his sleep quality was consistently "very good".	Physical activity may have a positive effect on his sleep quality, but did not seem to affect the occurrence of CDBs. However, P5 may have more CDBs following a lower-quality sleep.

Families reported demographic information, diagnoses, challenging and/or disruptive behaviors, physical activities, and sleep problems. Research assistants observed Participants 1–4 during summer school; Participant 5 was observed by his family at home. The interaction between physical activity and sleep was interpreted together by the research team and reported to families. Original quotations from the parents are indicated with quotation marks. CDBs, Challenging and/or disruptive behaviors.

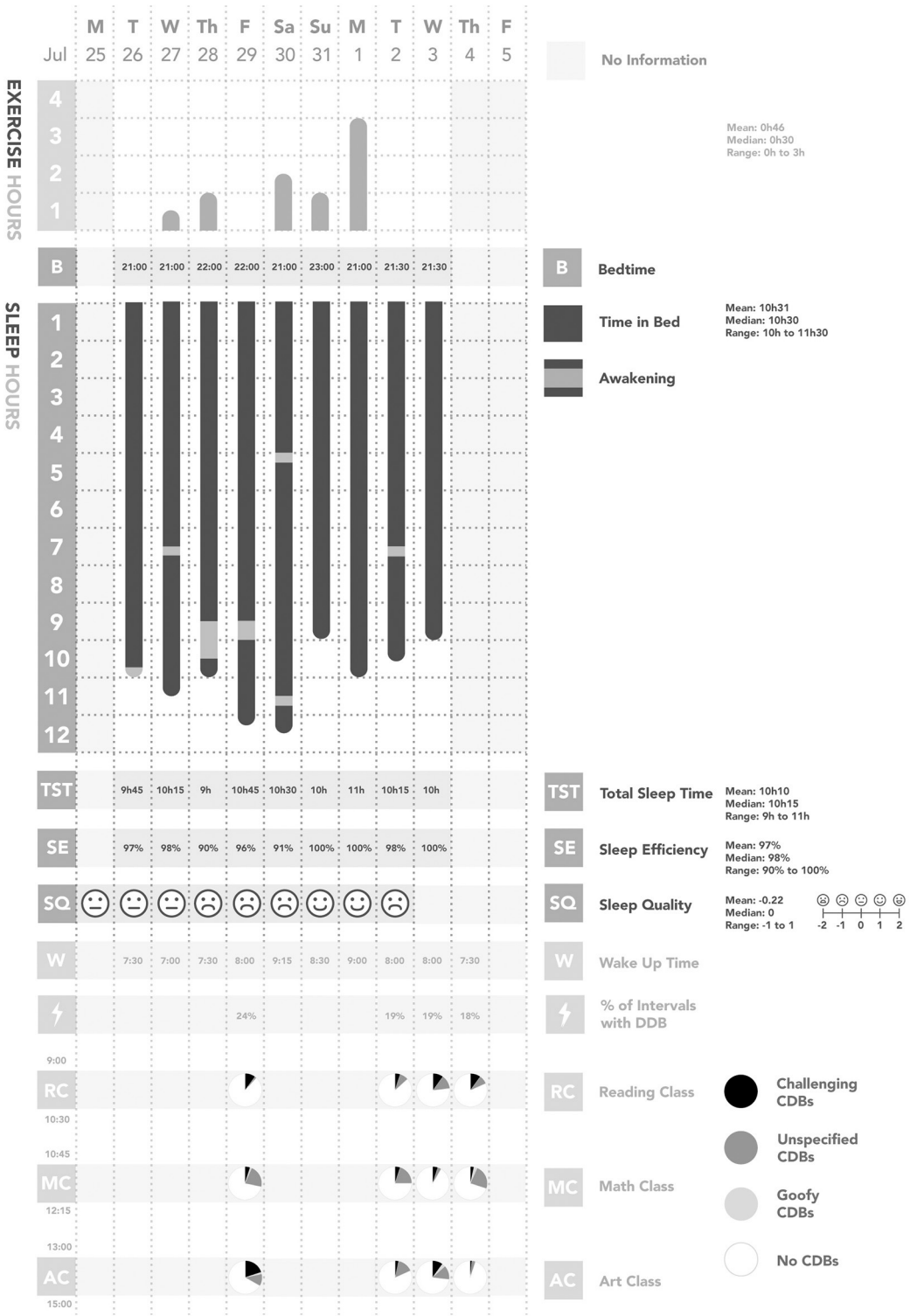

FIGURE 1 | Summary of Participant 1 (P1)'s data. CDBs, Challenging and/or disruptive behaviors.

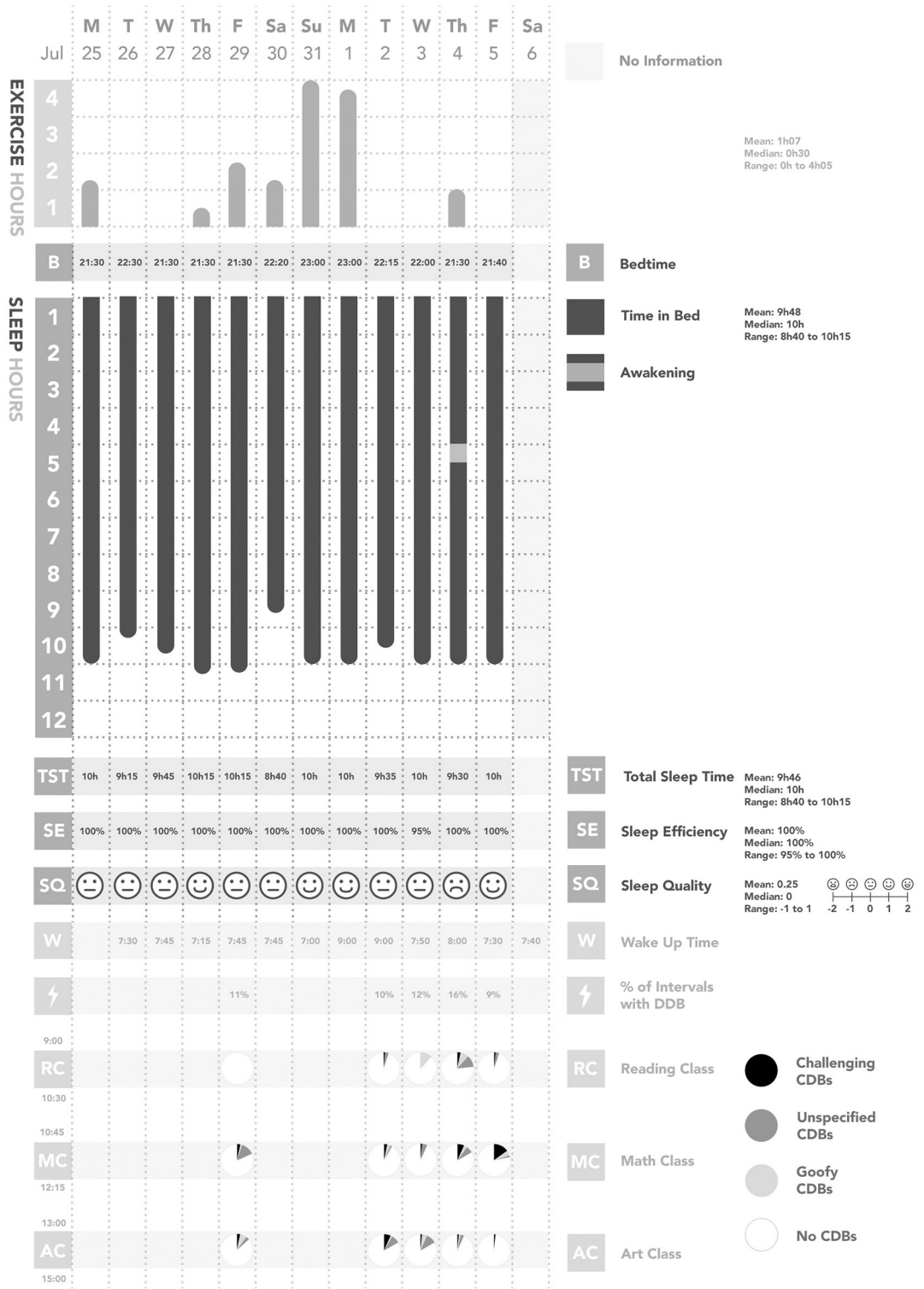

FIGURE 2 | Summary of Participant 2 (P2)'s data. CDBs, Challenging and/or disruptive behaviors.

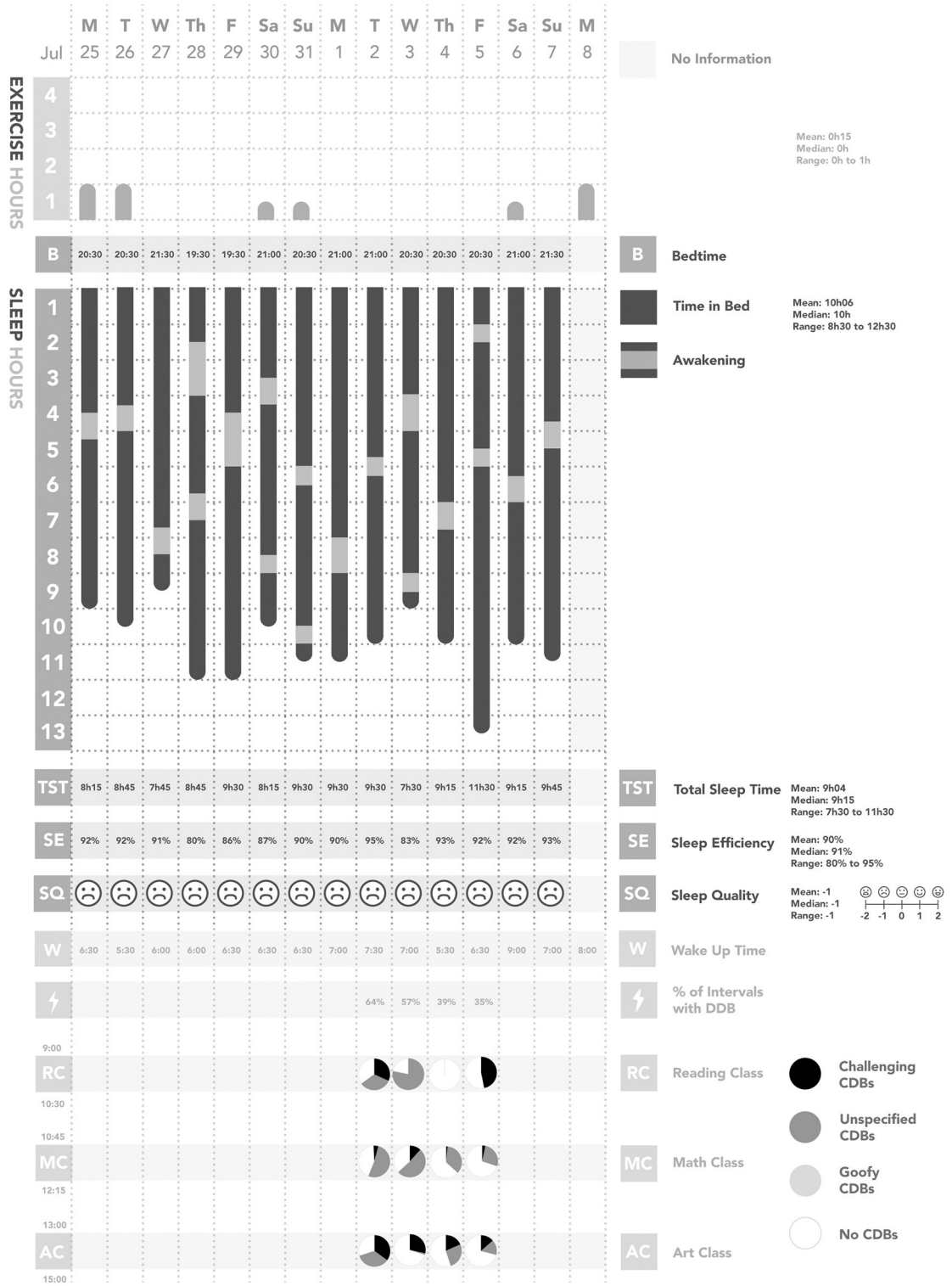

FIGURE 3 | Summary of Participant 3 (P3)'s data. CDBs, Challenging and/or disruptive behaviors.

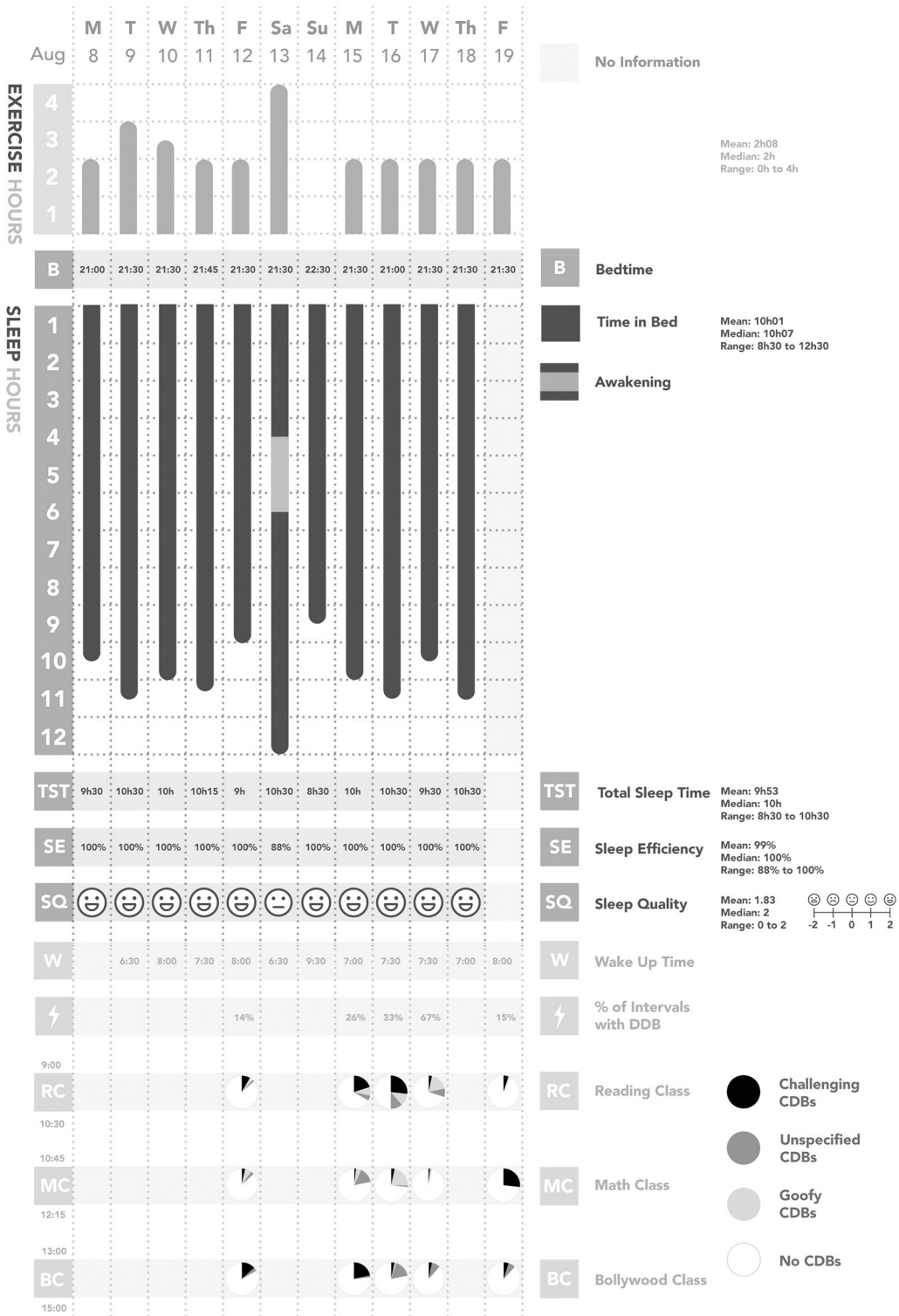

FIGURE 4 | Summary of Participant 4 (P4)'s data. CDBs, Challenging and/or disruptive behaviors.

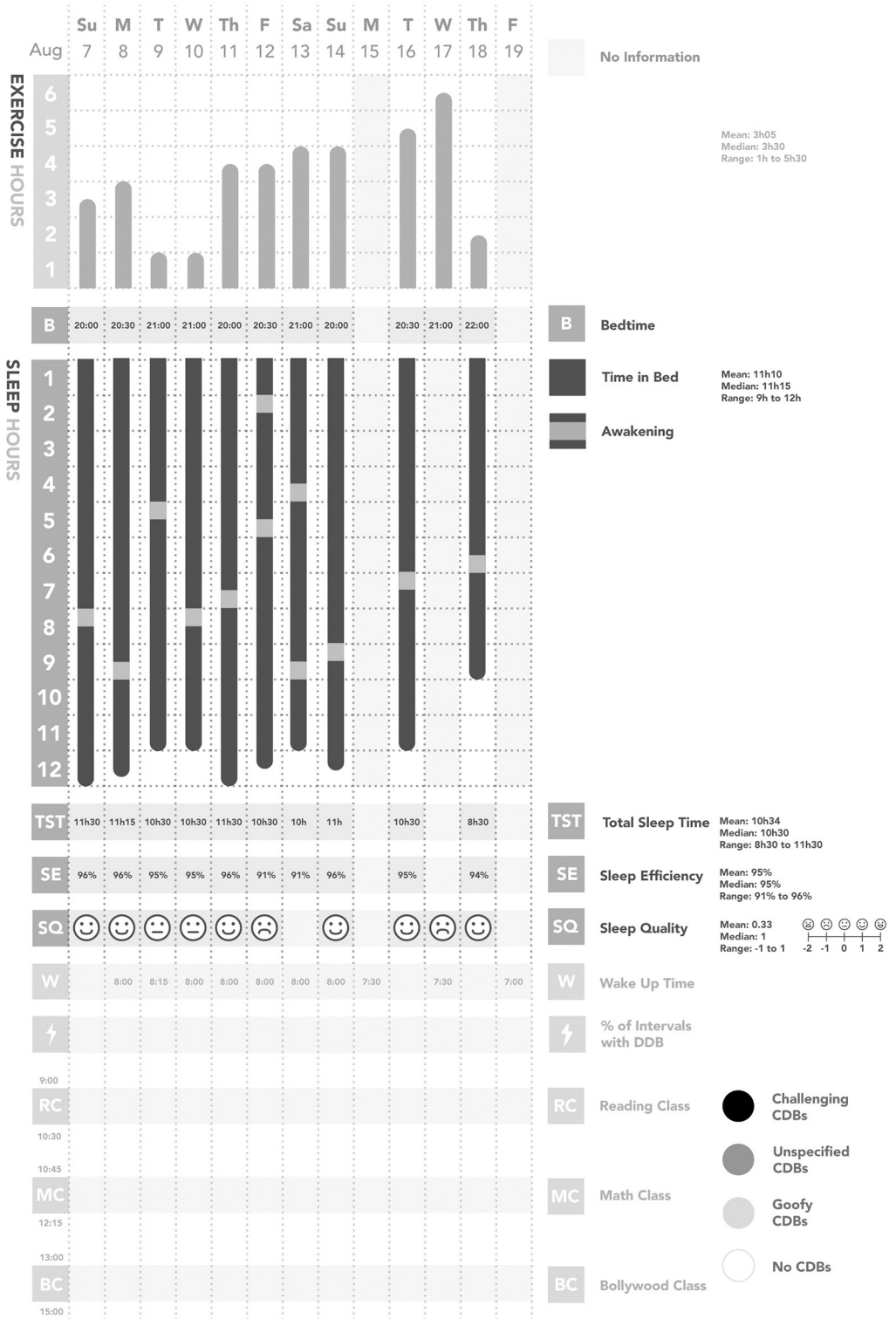

FIGURE 5 | Summary of Participant 5 (P5)'s data. CDBs, Challenging and/or disruptive behaviors.

TABLE 3 | Categories of challenging and/or disruptive behaviors.

Challenging	Unspecified	Goofy
Characteristics of temper tantrums: Outbursts, such as crying, screaming, throwing objects, and pouting	*Disengaging:* Suddenly separating oneself from an activity for no apparent reason; shutting down	*Class clown:* Behaviors were those that were intended to make others laugh
Stubbornness: Unwillingness to move on from the current activity to a new task	*Not doing as told:* Refusing to respond to a request	*Distracted:* Distracting themselves with activities or behaviors that may be more fun or sensory seeking
Being overly enthusiastic: Interjecting when it is not their turn; speaking louder than others to be the central focus	*Intrusive:* Invasion of someone else's personal space	
Being self-conscious: Overly aware of oneself; discomfort in a situation where focus may be directed toward the individual	*Self-stimulation or stimming:* Behaviors that were intended to soothe oneself	

- ***Mild:*** *dismissing an educational assistant during an explanation and saying to an educational assistant, "You're getting nothing! Don't touch it!"*
- ***Moderate****: hitting an educational assistant and kicking a backpack.*
- ***Extreme:*** *cascade — First, P4 ran out of the room and into the stairwell; his educational assistant followed. Then, the educational assistant blocked the participant's path and asked him where he was going. He was breathing deeply and tried to calm himself down. After the educational assistant asked for him to return to class, he kicked the educational assistant in the stomach. He seemed shocked at his kicking behavior. The educational assistant told him firmly that it was not okay to kick and tried to bring them back to the classroom. However, he hid in the washroom. Finally, a teacher and the executive director both had to intervene to return him to the classroom.*

Stubbornness was observed among all participants. Examples include:

- *Refusing to come back to class (after taking a planned/scheduled break) which was characteristic of P3. The trigger may have been her mother's presence in the building; indeed, her mother noted during the intake interview that P3 will "remove herself from the classroom" and run to her when she does not want to participate in the activity.*
- *Turning one's body away to continue using an iPad when asked to put it away, which may have been triggered by a deep engagement with an activity on the iPad.*
- *Not finishing the snack or lunch on time and then refusing to stop eating because the break is over, which may have been triggered by continued hunger.*

Being overly enthusiastic was characteristic of one participant who seemed to be highly interested in most activities during the summer school. The trigger for these behaviors may have been wanting to participate in the activities, but disrupting the teaching flow. Examples include:

- *Interrupting the teacher,*
- *Grabbing a pen from an educational assistant who was explaining the activity, and*
- *Shaking a cue card in someone's face (where the activity involved using the cue card; in this instance, the participant also had a large smile and seemed highly interested in the activity).*

Being self-conscious was observed in only two participants. The trigger for these behaviors may have been difficulties focusing on the task or feeling vulnerable. Examples include:

- *Playing with one's shirt and pants during class,*
- *Wrapping one's arms around oneself, and*
- *Looking around during class.*

Unspecified Behaviors

Unspecified behaviors did not have triggers. There were four types of *unspecified* behaviors: disengaging, not doing as told, intrusive, and self-stimulation or stimming. All participants had *disengaging* and *not doing as told* behaviors, which comprised the majority of *unspecified* behaviors.

- *Examples of "disengaging" are leaving the room suddenly for a break (when the participant was supposed to be in class) and playing with a hat instead of doing work during class.*
- *Examples of "not doing as told" are being uncooperative, not answering a question asked by an educational assistant, refusing to give a book back to an educational assistant by sitting on it, and sitting on the ground instead of participating in the yoga class. One participant also said, "You go, I stay!" to their educational assistant and crossed their arms when asked to stand up and go pretend grocery shopping with the rest of the class.*

All participants also had *intrusive* behaviors, but these occurred infrequently based on classroom and parental observations. Examples include:

- *Pushing an educational assistant's head down toward the table,*
- *Leaning on the teacher instead of working,*
- *Touching or reaching for an educational assistant's face without consent to do so, and*
- *Grabbing items from others.*

Lastly, the only instances of *self-stimulation/stimming* were from P3. P3 often shook her doll toy, sometimes to the point of total distraction.

Goofy Behaviors

Goofy behaviors were developed given our interpretation that participants were having fun and socializing by displaying those behaviors in a protected place among peers, but were also disturbing the flow of the class. These behaviors were categorized as *class clown* or *distracted*.

- *Examples of "class clown" behaviors include pretending to lick an educational assistant, looking at the number line through fingers (like cheating), flicking water onto the table and another student using a paintbrush, and painting on the table instead of the paper.*
- *Examples of "distracted" behaviors are swiveling around in an office chair; hitting a paper worksheet against one's face; and saying "I need your finger please" to a teacher, which was unrelated to the task at hand.*

Although four participants (all boys) had *goofy* behaviors during the summer school, P3 (girl) did not have any.

Contributing Factors

We also found some relationships between physical activity, sleep, and CDBs (**Table 2**; **Figures 1**–**5**). For all participants, physical activity in the daytime seemed to affect sleep quality on the same night. Higher levels of physical activity seemed to increase sleep quality.

- *For P1 and P2, this increased sleep quality may have resulted in fewer CDBs the following day.*
- *For P5, the trend appeared reversed: less physical activity seemed to lower sleep quality, which increased the occurrence of CDBs the next day.*

Families also perceived links between physical activity, sleep, and CDBs. For example:

- *P2's family reported, "When he is sleep deprived, he is not as compliant, more rigid in thinking and more emotional" and "He flips from activity to activity quicker if he hasn't had enough sleep, [which] may be because he knows that he will 'drop' if he stops."*
- *P3's mother reported that "exercise puts her in a state of relaxation and helps her to fall asleep."*
- *P5's family reported that, "He'll be tired when he's done a lot all day" and that he is a "busy kid [who] usually [goes] to bed really well."*

DISCUSSION

Kleinman (35) suggests the utilization of narratives in clinical history-taking to contextualize illness. We adapted this concept for application in the community setting, namely in a summer school setting for individuals with Down syndrome. As a team, we first listened to the parental narratives. Then, we explored and merged our understandings from the narratives with our structured observations. All CDBs were reviewed with visualizing descriptions (like in movie sequences) from the participants' (assumed) perspective using *in dubio pro reo* (in cases of doubt, then for) (22), which in our context meant to not label but describe. We were able to create new narratives as plots or scripts to explain why certain CDBs might have happened, which were shared with the parents and then the summer school team. Mattingly (36) calls the creation of such shared new plots, "therapeutic emplotment" (p811). Our new plots were reviewed and negotiated before presentation among the two independent RAs, with clinicians, and eventually with the parents, and in one case the siblings, of the participants. This exercise resulted in the creation of an explorative approach (**Figure 6**), which can widen our standardized medical and psychological approaches to CDBs. Traditional approaches use Venn diagrams to visually summarize mutually exclusive and co-existing factors, independent of a formal statistical analysis (39). Our understanding is that the perspective of the viewer affects what the viewer can see (3, 21), and the positioning of the spotlight may change the dimension of the shadow and what is visible and not visible. Moreover, depending on the strength of the spotlight (in our context, training-based rigor), a higher or lower visual acuity might be achieved. Thus, our explorative approach allows us to focus on the observed individual and review their behaviors without connoting them as appropriate or inappropriate, despite the fact that the behaviors may be challenging and/or disruptive for parents and teachers alike.

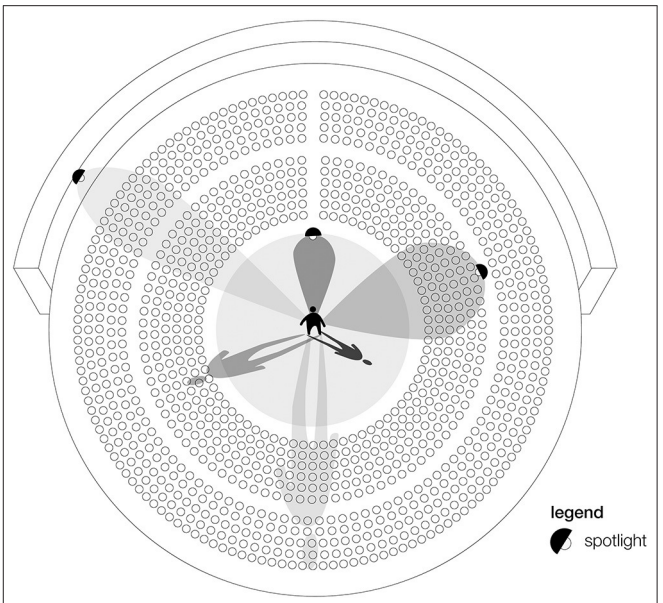

FIGURE 6 | Visualization of our explorative approach. The observed individual is located on the stage and is surrounded by their community (individuals sitting in the theater, including parents, family, healthcare professionals, educators, etc.). Depending on the strength of the spotlight (in our context, training-based rigor), a higher or lower visual acuity might be achieved and depending on the positioning of the spotlights, the dimension of the shadow changes.

Categories of Challenging and/or Disruptive Behaviors

CDBs are constructed (2, 40) and contextual where "the individual shapes his or her environment and in turn is shaped by it" [(41) p228]. In our analysis of observed CDBs, three non-stigmatizing and non-clinical categories emerged to describe the behaviors within the context of a summer school attended by individuals with Down syndrome.

First, *challenging* behaviors, such as being slow, inattentive, or moody, may have a variety of triggers. Although individuals with Down syndrome have deficits in processing speed (42), as autonomous individuals, they may have simply wanted more time to finish eating or to engage in a different activity. There may also have been an extrinsic trigger. For example, in P4's temper tantrum cascade described in the previous section, it surfaced that the educational assistant told the participant that he was untrustworthy and he could not go to the washroom by himself, which may have initiated his *challenging* behavior. *Challenging* behaviors may provoke dialogue to understand what happened and to negotiate future activities. However, if individuals are injuring themselves or endangering others, applied behavior analysis (16, 43) or positive behavioral support (44) could be used to extinguish the *challenging* behaviors and/or implement replacement behaviors.

Second, we interpreted behaviors for which we could not identify specific triggers as *unspecified*. These neutral descriptions signal the need for further assessment and exploration to understand the origins of *unspecified* behaviors. *Unspecified* behaviors may not be inherently problematic. Instead, they invite a review of the setting to determine the extent to which it met the needs of the participants. A biomedical explanation could be slower processing speed or sensory processing abnormalities (45, 46), which may limit one's participation in activities and thus cause emotional vulnerability. For example, during the intake interview, one mother told us that her son during a trip would suddenly sit down in the street, become tearful and say, "It's the Down syndrome way." Indeed, all five families reported in the intake interviews that feeling overwhelmed was a trigger for their children's CDBs (for P1, this was described in terms of feeling anxious).

Third, *goofy* behaviors interrupted the teaching flow and were thus considered CDBs. Reviewing the contextual framework, however, we realized that *goofy* behaviors were initiated in a social environment with peers and familiar others. According to our observations, they were not purposefully *challenging* or *disruptive*, but light-hearted. During the review of a previous version of this manuscript, a reviewer challenged our category of *goofy* behaviors by asking, "Goofy behaviors, if disruptive, should still be coded as challenging too? Likely have a root cause of avoidance?" Although teachers or parents may view *goofy* behaviors as avoidance or non-compliance, after reviewing the triggers of *goofy* behaviors in the context of being together with peers in long teaching sessions of 90 min, we interpreted them as stemming from a place of being harmlessly silly. Avoidance was not considered as a possible trigger because the interpretation pathologizes CDBs without considering the context and the variety of factors causing laughter, a basic human emotion that promotes learning and creativity (47). Indeed, *goofy* behaviors may not be issues for individuals with Down syndrome themselves, but actually issues for us (including teachers) who wish to maintain a particular flow to satisfy learning standards. Interestingly, P3 was the only participant who did not have any *goofy* behaviors in the classroom setting, despite her mother's description during the exit interview that her daughter loves to joke around when she is at home. Was P3 possibly constantly stressed or just adherent to the rules of the summer school? Upon further inquiry, P3's mother also mentioned that her daughter has a perfectionistic side, which may have influenced her behavior at summer school, going along with a wealth of *challenging* and *unspecified* CDBs.

Contributing Factors

In addition to the CDB-related considerations, we found some relationships between physical activity, sleep, and CDBs. In one case (P3), physical activity helped the participant to sleep better than usual and be able to fall asleep at the scheduled time. Most participants had higher sleep quality after being physically active during the daytime and, for two participants, this higher sleep quality was associated with fewer CDBs the following day. Further, three families (P2, P4, P5) reported very high levels of daily physical activity. Although a large amount of physical activity could be considered normal, it could also conceal symptoms of medical conditions, such as familial Restless Legs Syndrome (RLS), as is suggested for other patient groups (48, 49). RLS is a sensorimotor neurologic disorder causing sensory seeking behaviors (50). The presence of insomnia and positive family history among participants suggested that these individuals may be on the RLS-spectrum; we assumed that the sensorimotor discomfort was reduced by physical activity. Thus, physical activity may be an important factor to investigate in relation to CDBs.

In addition to RLS, sleep-disordered breathing is highly prevalent in individuals with Down syndrome (51–56). Sleep-disordered breathing can cause non-restorative sleep, which can in turn affect one's executive functioning (57), vigilance and attentiveness (58), and mood (59). This chain of effects compromises one's academic performance and physical and emotional wellbeing and can cause vulnerability, all of which may lead to CDBs. Thus, sleep problems should also be reviewed as potential triggers for CDBs.

Creating a New Script for CDBs: The Value of Narratives and Observations

Although our framework of CDBs was developed using rigorous methods, we acknowledge that whether descriptions such as *stubborn, self-stimulating* or *stimming*, and *intrusive* truly differed in scope and could be labeled as *challenging*, *goofy*, or *unspecified* depended on emotional manifestation (e.g., laughter, violence). Furthermore, the observers' training background and final negotiation or discussion of the context in which behaviors happened will affect labeling. For example, although *being self-conscious* was categorized as a CDB, it may reflect the

vulnerability of the participants. Laughter may interrupt the flow of teaching and may be a CDB for the teacher or parents, but not the RAs and reviewing clinicians, both of whom were at arms-length to the incidents.

Extant diagnostic checklists that capture CDBs [e.g., Behavior Problems Inventory (60); Teacher Report Form (61); Nisonger Child Behavior Rating Form—Teacher Version (62); Vanderbilt ADHD Diagnostic Teacher Rating Scale (63)] include many questions with negative connotations. For example, the first item on the Vanderbilt ADHD Diagnostic Teacher Rating Scale asks if the individual "fails to give attention to details or makes careless mistakes in schoolwork" (63). Are "mistakes" not learning opportunities? Likewise, the first item on the Teacher Report Form asks whether the individual "acts too young for his/her age" (61). To whom is the individual compared when considering if they are "too young"? In contrast to these checklists, interestingly all developed in the context of diagnosing behaviors, we suggest an immediate review of CDBs in the situational context and the exploration of the severity and impression of each CDB without clinical diagnostic labeling. A review of CDBs in a non-judgmental exploratory framework (**Figure 6**) allows one to reflect on the interchangeability of the observers' perceptions and conflicts of interest (e.g., teaching in a quiet environment) and respects the autonomy of the individual subject.

As advocated by Gorman et al. (15), "a primary task for the clinician is to engage the patient and family in a collaborative process to choose among reasonable options, including the option to *forego medication* [emphasis added]" (pp73–74). However, despite the availability of applied behavioral analysis as a non-pharmacological approach to CDBs (16, 64), strategies to manage CDBs rely heavily on stimulant and antipsychotic use, particularly in North American medical practice (65–67). In this context, our explorative approach allows for reflection before medication treatment is considered. The model accommodates the perspectives of the affected individuals and enables a review of the possible explanatory models before any negatively connotated diagnostic labels are made. The recognition of probable familial RLS, which could be partly treated by physical activity, proves that there are many non-pharmacological treatment strategies. This supports a personalized approach to the affected individuals if the root causes of CDBs are recognized. Our grounded, pragmatic approach can be utilized by non-professionals as a beginning step to capture relevant information and to explore CDBs.

Strengths and Limitations

We collected descriptive, non-judgmental information by non-professionals in a first attempt to create an explorative approach for reviewing CDBs. We used interviews and observations and expanded educational and medical perspectives with therapeutic emplotment, a methodology from medical anthropology. This research builds on our previous work integrating narratives in clinical history-taking (68) and structured behavioral observations (21, 50, 69, 70), and on similar studies that have been undertaken in other clinical populations (71–75). Using such a concept (50) was useful for understanding how CDBs may be interpreted and how observable symptoms of physical activity and sleep (e.g., length, disruptions) may affect CDBs.

We focused on five adolescents with Down syndrome as one example of ID, but our concept is applicable to ID in general irrespective of the etiology and categorical diagnoses. However, we had a small sample size and did not investigate unobservable parts of physical activity and sleep, such as affective responses, the significance of restorative sleep, and restlessness. Although participating families appeared to accept our explanations at the exit interview, we did not follow-up with the participants in a medical setting and cannot report to what extent our explanations were used or implemented by the families. Still, our findings were shared with families and professionals at the DSRF, and all (except for a clinician) agreed with our approach and recommendations.

One other limitation is that we were not able to provide detailed medical data and static psychosocial triggers of the subjects enrolled. In future studies aiming to validate our findings in a larger number of subjects, information about concomitant medications, physical comorbidities, the severity of ID, and psychosocial background should be collected. Finally, the category of *unspecified* behaviors needs further exploration. Play therapy (76, 77) may be an appropriate setting for further characterization of this category.

CONCLUSION

In this study, we explored the nature and possible triggers of CDBs of individuals with ID. We focused on five adolescents with Down syndrome, given that they form a cohort with comparable comorbidities. From our interviews and observations, two findings surfaced as significant. The first, and most important, finding was that we should consider our own perceptions and connotations of CDBs in a non-judgmental way, and room for light-hearted behaviors should be created as not all may be truly *challenging* or *disruptive*. The second finding was that physical activity had a visible positive effect on sleep quality and CDBs the following day, suggesting that there may be a biological, in addition to a psychosocial, aspect to CDBs. In summary, this study reminds us that we all need to reflect on our perspectives, to be non-judgmental, and to consider the context in our interpretations. The creation of a new script for CDBs, utilizing *in dubio pro reo*, is a step toward personalized medicine and personal meaningful outcome measures.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of British Columbia Children's and Women's Research Ethics Board. Written informed consent to participate in this study

was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MC-HC, MC, SS, and OI contributed to the conception and design of the study. MC-HC, MC, and OI collected the data. MC-HC, MC, and NB analyzed the data. MC-HC and NB developed the data visualizations. MC-HC and OI wrote the manuscript. All authors contributed to manuscript revision and approved the submitted version.

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Behavioral sleep medicine—The need for harmonization of clinical best practice outcome measures in children and adolescents with intellectual or developmental disabilities and restless sleep

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In behavioral medicine, sleep disorders, insomnia in particular, may be considered comorbidities and precipitating factors to intellectual or developmental disabilities (IDD). Nevertheless, sleep alterations have often been neglected in favor of daytime features and symptoms, albeit simple behavioral nighttime observations may disclose hypermotor features that characterize restless sleep. The root of most hypermotor restlessness is linked to central iron deficiency. The latter is often exacerbated by vitamin D deficiency (VDD), which interferes with both dopaminergic and serotonergic mechanisms. In this way, an imbalance affecting daytime behavior and mood is created. Several sleep-related motor disorders such as bruxism, periodic and aperiodic leg movements, Restless Legs Syndrome (RLS), and Restless Sleep Disorder (RSD) are commonly seen in Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD). However, they are rarely diagnosed and often overlooked in affected children and adolescents. As a result, not only are these disorders not adequately addressed therapeutically, but their symptoms may be worsened by the side-effects of drugs used to contain disruptive daytime behavior, such as antipsychotics and antidepressants. In children with IDDs, obesity, inactivity and metabolic effects of antipsychotics often lead to Sleep Disordered Breathing (SDB), which is currently understood as an inflammatory state leading to "hyperactive" lethargy and further alterations of the hypoxic chain and vitamin D levels. Endorsing simple routine blood tests, including inflammatory markers such as C-reactive protein, ferritin, transferrin, and vitamin D levels, may favorably complement caregiver observations and ambulatory sleep recordings, leading to a sleep disorder diagnosis and consequent therapy. In fact, the treatment of SDB, RLS, and RSD has been copiously demonstrated to favorably impact vigilance, behavior, social competence, and academic skills in healthy and, to a greater extent, in IDD

children. Thus, consulting and deliberating the root causes of functional and categorical diagnoses within a clinical framework may engender a more precise diagnosis and further benefit pediatric daytime and nighttime management of hyperactive behaviors.

KEYWORDS

ASD, ADHD, RLS, iron, vitamin D, restless sleep, intellectual or developmental disabilities

Introduction

This mini review aims to discuss the management of various sleep disorders from a behavioral perspective in the context of "The Mind the Gap Logic Model" for an algorithmic exploration of functional and categorical diagnoses and the impact of root causes on medical and non-medical treatments.

The dimension of the challenge

Up to 80% of pediatric patients with intellectual or developmental disabilities (IDD) may experience sleep disturbances, which aggravate their developmental delays, disruptive behaviors, and mental health problems (1). Some disorders, like sleep disordered breathing (SDB) are audible and visible, and depending on the education level of parents and involved professionals may raise concerns and initiate further investigations. Others are not so clearly apparent, despite having visible characteristic hypermotor-restlessness and hyperarousability in sleep and wake. Among these hidden disorders are Restless Sleep Disorder (RSD) (2) and Restless Legs Syndrome (RLS) (3).

The first description of attention deficit hyperactivity disorder (ADHD) in the Diagnostic and Statistical Manual of Mental Disorders (4) reads like the description of RSD ("moves about excessively during sleep") and RLS ("has difficulty staying seated"). Both of the latter need to be identified and therapeutically addressed to improve daytime behavior.

There is a comprehensive tendency to overmedicate children with disruptive behavior in a desperate attempt to control their symptoms and oblige caregivers who lament feeling powerless. Unfortunately, most of these medications, besides offering a temporary relief, generate long-term, undesired effects on sleep with a longitudinal, enduring impact on daytime symptoms.

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorders; BID, Brain Iron Deficiency; DA, Dopamine; IDD, Intellectual or developmental disabilities; IV, Intravenous; MLT, Melatonin; OSA, Obstructive Sleep Apnea; PLMs, Periodic Limb Movements; PLMD, Periodic Limb Movement Disorder; RLS, Restless Legs Syndrome; RSD, Restless Sleep Disorder; SDB, Sleep Disordered Breathing; VDD, Vitamin D Deficiency.

Sleep, the window to the developing brain

Diverse sleep phenotypic expressions of ADHD have different outcomes and require specific treatments, depending on whether they are associated with features of delayed sleep phase syndrome, hypoarousability with features of narcolepsy, epilepsy, obstructive sleep apnea (OSA), or RLS/periodic limb movements (PLMs) (5).

Similarly, OSA and hypermotor restlessness linked to RLS in children with autism spectrum disorder (ASD) may not be detected through subjective reports, but rather require diagnosis *via* video polysomnogram or actimetric recordings due to nonverbal communication and sensory processing abnormalities in these patients.

Indeed, sleep recordings offer a unique window into the core symptoms, once daytime epigenetic factors, motivation and voluntary control are provisionally disregarded. Under these conditions, genetic aspects and familial predispositions, unconstrained by the daytime factors, could emerge and help elucidate the core intrinsic mechanisms of different neurodevelopmental disorders and support precision medicine.

Therefore, sleep recordings of pediatric patients with disruptive sleep behaviors enable daytime behavioral indexes to be harmonized with structured behavioral observations, nighttime videos and descriptive reports provided by parents/caregivers (6).

Sleep as an outcome measure

Sleep has been seldom considered as an outcome measure to assess the effect of diagnostic and therapeutic interventions in clinical routine protocols for the treatment of neurodevelopmental disorders such as ADHD (7, 8) or ASD. For instance, specific sleep disorders such as RLS convey different risk of comorbidity and may exacerbate final outcome.

In fact, in adults, small and large data suggest that RLS patients, compared with controls, are at higher risk of suffering from anxiety and depressive disorders (9) as well as suicide and self-harm (10). Could the burden of undiagnosed, possibly painful, RLS contribute to these mood alterations also in children and adolescents? While those who can articulate or draw often present devastating descriptions and pictures (11), we do not know the perceptions of those who are not articulate enough to express their painful discomfort or lack a reference point as they experienced RLS from an early age (12). Our own data in two subgroups of IDDs implies frequent use of psychotropic drugs, including neuroleptics and antidepressants, with adverse effects on their underlying sleep (13). Therefore, to capture sleep disturbances, in particular RLS-induced ones, such as sensory dysfunctions which need to be further explored (14), we integrated sleep as an outcome measure for *all* categorical IDD diagnoses as well as for their associated functional diagnoses. This exploratory framework, which we call Mind-the-Gap Logic Model (15) (see Figure 1) grants sleep and IDDs equal central importance while considering their reciprocal effects. Further, this model allows to review frequent or rare "root causes," which may be considered as factors that aggravate sleep as well as waking behaviors. While sleep health measures could be one root cause, they still might be secondary to RLS-induced discomfort or other hypermotor sleep behaviors responsible for restless sleep. Ultimately, this model supports exploration and decision making through the integration of all involved health care professionals. Indeed, it allows members to comprehensively review the interconnections of multiple contributing factors with functional and categorical diagnoses. Most importantly, it grants special attention to root causes such as particular nutrient deficiencies, which all require specific blood tests and laboratory diagnostic screening (e.g., serum iron, ferritin, transferrin, C-reactive protein, parathyroid hormone, and vitamin D3).

Sleep and medication concepts

In particular, it is critical to restrict antidepressant therapy, such as mirtazapine which is known to temporarily aggravate RLS symptoms (16), and selective serotonin reuptake inhibitors, which increase PLMs in adults (17), as well as children (18).

Interestingly, recent data on the effect of antidepressants on sleep in children (19) showed an increase of total and PLMs compared to controls and to drug-naïve RLS children, with features akin to adult RLS, including an inter-movement interval peak between 10 and 60 s, progressively declining throughout the night.

Likewise, neuroleptic drugs, usually an integral part of treatment in children with hyperactive disruptive behavior, negatively impact RLS, especially those with strong antidopaminergic post-synaptic properties such as haloperidol or chlorpromazine, whereas aripiprazole, a relatively recent neuroleptic, is better tolerated (20).

Melatonin (MLT) appears to have a conflicting impact on PLMs *via* its circadian modulation. In fact, according to Kunz and Bes (21), the temporal distribution of PLMs and their coupling with the phase position of the circadian temperature curve would support a chronobiotic effect of exogenous MLT in periodic limb movement disorder (PLMD). By increasing the amplitude/duration of the circadian timing system, MLT would enhance previously disrupted circadian rhythmicity with consequent reduction of sleep motor activity.

Contrary to these preliminary results, Michaud et al. (22) reported, in a small group of patients, that the increase of MLT secretion always precedes sensory-motor symptoms as indirect evidence of an inhibitory effect of MLT on central dopamine secretion.

Subjective vigilance decreases both at night and during the daytime, as proven by the Suggested Immobilization Test; this decline in vigilance strongly correlates with the manifestation and exacerbation of PLMs.

With respect to arousal parasomnias, also common in children with IDDs, tryptophan, as an MLT precursor, reduces awakenings and sleep latency, proving especially helpful in these children through a mean dose of 2,400 mg/day (500–4,500 mg/day) (23).

Non-medical treatment includes physical activity (24), adequate nutritional diet (25), and cognitive behavioral therapy (26, 27). With respect to the former, results depend on exercise routine (acute vs. chronic) and intensity (light vs. vigorous), with acute exercise, at either intensity, having a direct effect on RLS symptoms.

Albeit medical and non-medical treatments are unquestionably important, the root causes of the Logic model (see Figure 1) warrant greater attention to explore the additional benefit of supplementing nutritional deficits in IDD children.

The role of iron

A recent scoping review (28) on iron deficiency and sleep reported iron deficient anemia as one of the dominant global causes of various sleep disorders and conditions, from SDB to, most consistently, RLS and ADHD. Leung et al. also provided compelling evidence of the efficacy of iron supplementation.

Abnormalities in cerebral spinal fluid concentrations of ferritin and transferrin in RLS have been long established (29, 30). Recently, however, children with RSD were found to have even lower ferritin levels than their counterparts with RLS (2).

Children with Tourette syndrome have, by definition, many intruding involuntary disruptions of their daytime activities due to insuppressible tics. Iron supplementation was shown to exert a beneficial effect on tic frequency and severity (31).

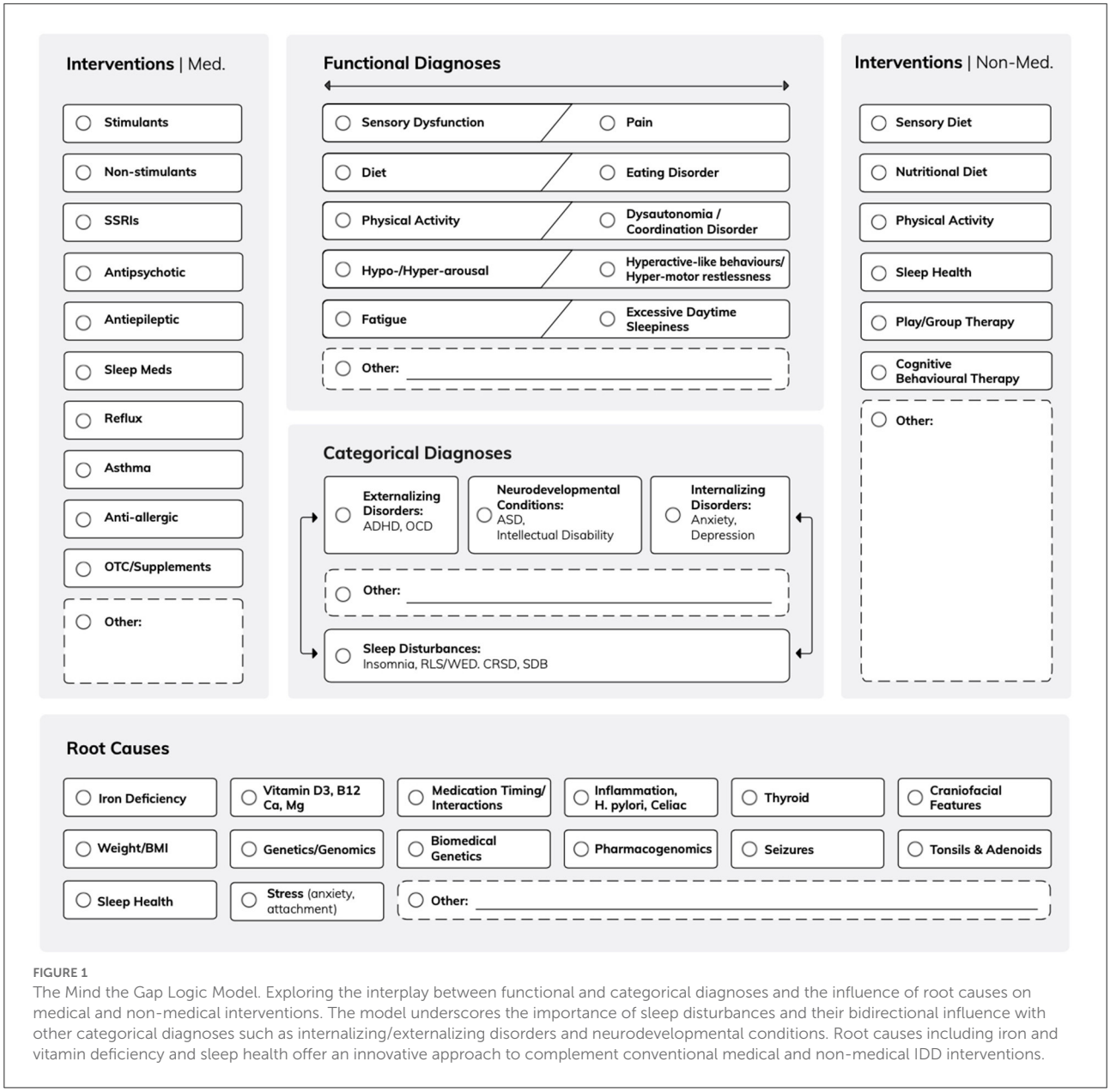

FIGURE 1
The Mind the Gap Logic Model. Exploring the interplay between functional and categorical diagnoses and the influence of root causes on medical and non-medical interventions. The model underscores the importance of sleep disturbances and their bidirectional influence with other categorical diagnoses such as internalizing/externalizing disorders and neurodevelopmental conditions. Root causes including iron and vitamin deficiency and sleep health offer an innovative approach to complement conventional medical and non-medical IDD interventions.

Jiménez-Jiménez et al. (32) note that children with various sleep disorders, including parasomnias and RLS, who are often on antidepressants and/or neuroleptics, present iron deficiency. Furthermore, children with ADHD and RLS have lower ferritin than those affected only by RLS without ADHD (33).

Iron deficiency is the single most common nutritional deficiency in the world and its early manifestation can alter sleep structure (34); these structural abnormalities may persist years after anemia has been cured (35).

Maternal iron status and duration of iron supplementation during pregnancy correlate with life skills and school learning in ADHD children and adolescents (36).

According to the iron deficiency metabolic theory (37), brain iron deficiency (BID) is central to the pathophysiology of RLS and related symptoms. In fact, it is responsible for an increased presynaptic glutamatergic function related to amplified neuropathic pain (and sensory alteration in ASD), a hyperarousal state with insomnia and sleep fragmentation. BID also appears to cause a hypoadenosinergic state with increased A2A receptors and decreased A1 receptors, leading to a reduction in slow wave sleep and slow wave activity (38). Finally, BID is thought to provoke the known increase in presynaptic dopamine (DA) function and DA presynaptic receptors along with decreased postsynaptic D2-D4 receptors,

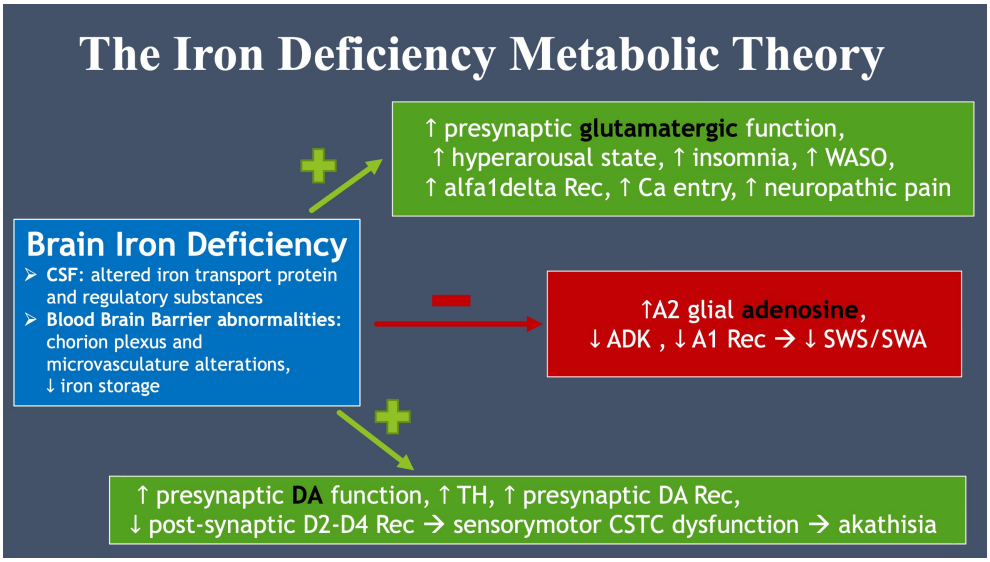

FIGURE 2
The iron deficiency metabolic theory. Brain iron deficiency leads to glutamate, dopamine and adenosine dysfunction, all essential to RLS pathophysiology.

leading to the central sensory motor dysfunction of RLS (see Figure 2).

Therefore, therapy with oral and intravenous (IV) iron in the presence of ferritin values <50 ng/mL have been instrumental for RLS and apt to ameliorate different aspects of sleep and behavior in both RLS and RSD. Oral iron supplementation, 3 mg/kg/day providing transferrin saturation is <45% (39), has been linked to sustained symptomatic improvement after 2 years (40). In light of these encouraging results, it has been suggested that oral iron could be considered a first-line therapy for pediatric RLS and PLMD (41).

As for IV treatment, promising data on iron sucrose are reported by a 2013 study (42) showing a consistent rise in serum ferritin and 65% improvement in sleep. Special indications for IV iron infusion include ferritin <20 ng/mL, especially in children with celiac disease or chronic gastritis on proton-pump inhibitor therapy.

IV ferric carboxymaltose at 15 mg/Kg infusion was reported to improve symptoms and ferritin in children with RLS or PLMD (43), as well as in children with RSD (44). Clinical improvement was assessed 8 weeks post-infusion (Clinical Global Impression rating scales) showing sustained positive effects, with nearly 45% of children going into remission after a single infusion, whereas 30.8% required two infusions. The younger the patients, the higher the probability of needing repeated infusions.

Clinical efficacy of IV ferric carboxymaltose on RLS symptoms and low-serum ferritin has also been recently assessed in children with ASD, documenting a significant clinical improvement in the majority (84.2%) of the cohort *via* the Clinical Global Impression rating scales (45).

The role of vitamin D

Strong evidence links vitamin D depletion (<30 ng/mL) to RLS symptoms and low-quality sleep with increased pain perception and nocturnal restlessness (46). Vitamin D deficiency (VDD) in children has been associated with objectively measured decreased total sleep time and sleep efficiency and with delayed bedtimes (47).

As previously shown for iron, VDD impacts the dopaminergic function by altering DA concentrations in the cortex and exposing DA neurons to neurotoxins (48).

VDD also leads to pain hypersensitivity, crucially important in ASD children, by modulating the opioid signaling system (49). Sleep and sensory alterations are also mediated by a dose-dependent effect on glutamate excitotoxicity (50).

A consistent effect of VDD on sleep and mood also relates to the modification, *via* tryptophan hydroxylase (51), of the serotoninergic system, of which vitamin D modulates synthesis, release, transcription, and function (52, 53). Indeed, vitamin D has been reported to improve both mood and sleep in a healthy population when reaching plasma levels higher (>30 ng/mL) than those conventionally established as sufficient (54).

VDD has been linked to depression and autism (55). Furthermore, vitamin D supplementation (4,000 IU/day) has improved inattention, hyperactivity and impulsivity in ADHD

children and adults (53, 56), possibly by increasing serotonin synthesis *via* tryptophan hydroxylase-2 activation. Serotonin is known to regulate executive functions and sensory gating, in addition to social behavior and impulsivity. Early gestational VDD, a common nutritional flaw of the modern world, is linked to decreased serotonin synthesis especially in genetically predisposed animals. Instead, in humans, early gestational VDD has been associated with the enlargement of lateral ventricles (57), a condition often observed in ASD, ADHD, and schizophrenia (58). These deleterious effects stemming from early VDD are in contrast with more subtle alterations related to VDD later in life (59).

As for adenosine, vitamin D regulates its production and levels, thus playing a role in BID, PLMs, and hyperarousal (32).

Lastly, vitamin D benefits anemia *via* the reduction of pro-inflammatory cytokines and the suppression of hepcidin mRNA transcription (60) in non-anemic iron deficiency linked to inflammation, such as in chronic kidney disease and celiac disease.

Infants diagnosed with iron-deficiency anemia simultaneously present low levels of serum vitamin D (61); hence, addition of vitamin D to their diet may improve blood and tissue iron concentration. Iron deficiency likely induces dopaminergic dysfunction *via* VDD (62).

Approximately 10–15 ng/day of vitamin D should be supplemented in children, with 60–80 ng/mL of D3 providing the most beneficial effects. Instead, in adolescents, supplementation through 25,000 IU/week for 3 months and maintenance with 50,000 IU/month for the following 3 months if vitamin D <10 ng/mL and 50.000–75.000 IU/month for 3 months if values < 20 ng/mL is suggested.

Vitamin D proved beneficial for growing pains as well as RLS in several clinical contexts by reducing RLS severity and sleep disturbance (25, 63, 64).

There is decreased bioavailability of vitamin D in obesity (65) due to adipose tissue sequestration, thus limiting its release into the bloodstream. Vitamin D is also curtailed in children and adolescents with OSA, where it appears to augment excessive daytime sleepiness by increasing inflammatory cytokines (e.g., IL-1, TNF-alpha, and PGD2). The latter, in fact, are central regulators of sleep homeostatic pressure (66). OSA may thus be another comorbidity of children with disruptive behaviors due to primary or secondary iatrogenic weight increase. In these patients, inflammatory cytokines could mediate, *via* hepcidin increase, a reduced iron export to the bloodstream, thereby supporting concomitant iron and vitamin D supplementation in obese patients with anemia of inflammation.

Discussion

Treating insomnia and hypermotor behaviors in ASD/ADHD children may be a challenge due to interference with other drugs and special drug refractoriness or sensitivity often observed in this population. Early employment of drugs impinging on brain chemistry due to receptor immaturity or extreme sensitivity underscores the need of innocuously addressing the child's unmet needs in terms of sleep-wake regulation *via* adequate supplemental therapy.

To date, scanty data have been reported on the benefit of IV iron in ASD children with RLS/RSD. Del Rosso et al. (45) have provided encouraging preliminary results that need to be expanded and further confirmed. The known role of vitamin D in protecting sleep continuity, enhancing daytime vigilance, and, especially, modulating pain perception may be particularly relevant in ASD children known to have abnormal sensory processing (67).

Iron and vitamin D share complementary anti-inflammatory and neurochemical mechanisms to relieve pain and reduce sleep disruption in children that are often overmedicated with questionable, if not dire, results.

Standardized protocols combining iron and vitamin D supplementation have yet to be employed, or even suggested, to our knowledge, as part of the therapeutic management of ASD children. The composite role of these nutritional supplements is often disregarded, albeit animal and clinical preliminary results unconditionally favor their use as first-line treatment.

Rethinking bedtime resistance and exploring a possible diagnosis of RLS in children with autism (68) is only one of the conceivable applications of the Mind the Gap Logic Model. Many more scenarios are viable and would significantly aid disadvantaged IDD children in obtaining better and safer treatments within a 24-h circadian perspective, thus bolstering the recognition of sleep as a crucial and powerful modulator of behavior.

As advocated by the Model, simple measures addressing unmet nutritional needs through the strategic supplementation of iron, vitamins and neuropeptides involved in sleep modulation may represent some of the best yet unexplored therapeutic options for the control of night and daytime behavioral problems of IDD children.

Data availability statement

The data presented in the study are deposited in the National Center for Biotechnology Information Gene Expression Omnibus (NCBI-GEO), accession number GSE205004.

Author contributions

RS: literature review, abstract, introduction, role of iron, role of vitamin D, discussion, and Figure 2. OI: literature review, introduction, Figure 1, editing, and created the logic model. All authors contributed to the article and approved the submitted version.

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.

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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.2022.1003019/full#supplementary-material

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Understanding patient characteristics and medication prescriptions in children with mental health and neurodevelopmental disorders referred to a sleep clinic—A quality improvement/quality assurance analysis

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Introduction: Motivated by challenges faced in outpatient sleep services for mental health and neurodevelopmental disorders (MHNDD) during the COVID-19 clinical shutdown, a pan-Canadian/international working group of clinicians and social scientists developed a concept for capturing challenging sleep and wake behaviours already at the referral stage in the community setting.

Methods: In a quality improvement/quality assurance (QIQA) project, a visual logic model was the framework for identifying the multiple causes and possible interventions for sleep disturbances. Intake forms informed clinicians about situational experiences, goals/concerns, in addition to the questions from the Sleep Disturbances Scale for Children (SDSC), the ADHD Rating Scale-IV and medication history. Descriptive statistics were used to describe the sample.

Results: 66% of the pilot study patients (*n* = 41) scored in the SDSC red domains (highest scoring) with highest sub-scores for insomnia (falling asleep 73%; staying asleep: 51%) and daytime somnolence (27%). A total of 90% of patients were taking at least one medication; 59% sleep initiation/sleep medications, 41% in combination with further non-stimulant medications, 9% with stimulants, 27% with antidepressants and 18% with antipsychotics. Polypharmacy was observed in 62% of all patients and in 73% of the ones medicated for sleep disturbances. Qualitative information supported individualisation of assessments.

Conclusion: Our intake process enabled a comprehensive understanding of patients' sleep and wake profiles prior to assessment, at the referral stage. The high prevalence of insomnia in patients, combined with polypharmacy, requires special attention in the triaging process at the community level.

KEYWORDS

neurodevelopmental disorders (NDDs), polypharmacy, sleep disorders, mental health, medications, pandemic, waitlist, disruptive behaviour

Introduction

Over the last decade, an increasing need for sleep assessments and associated services has revealed existing gaps in service delivery. The COVID-19 pandemic has magnified these shortcomings. Outpatient sleep services for children with mental health and neurodevelopmental disorders (MHNDD) is a crucial healthcare domain that needs to be revisited under the paradigm of public shutdowns and exponentially increasing waitlists (1). Up to 80% of this population experience underlying sleep problems, which often remain undiagnosed and untreated (2). The timely and accurate diagnosis of chronic, often familial, sleep disturbances is further hindered by their early onset and overriding disruptive daytime presentations. Early onset and untreated sleep problems aggravate existing daytime presentations and are rarely considered a primary or priority comorbidity, with the familial dimension often being missed (2).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BEARS, concept or themes; B, for bedtime; E, for excessive daytime sleepiness; A, for awakenings; R, for routines; S, for snoring or sleep disordered breathing; Q, for quality of sleep; NS, not specific to the participant's sleep; CRSD, circadian rhythm sleep disorder; EDS, excessive daytime sleepiness; FASD, foetal alcohol spectrum disorder; MHNDD, mental health and neurodevelopmental disorders; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; OTC drugs, over the counter or non-prescription drugs; QIQA, quality improvement/quality assurance; RLS, restless legs syndrome; SDSC, sleep disturbances scale for children; DIMS, disorders of initiating and maintaining sleep; SDB, sleep disordered breathing; SWTD, sleep wake transition disorders; DA, disorders of arousal (DA); DOES, disorders of excessive somnolence; SHY, sleep hyperhidrosis; SIB, self-injurious behaviours.

During the COVID-19 clinical shutdown, to overcome existing gaps and proactively react to a rapidly growing waitlist, we created a pan-Canadian working group of clinicians and social scientists and reviewed the applicability of the developed concepts with an international group of sleep researchers. Our group reviewed the challenges faced in outpatient paediatric sleep services and agreed on the need for a set of "universal" first line interventions for sleep disturbances that could be utilised in community-based settings. These first line measures were reviewed by international members of the group (3, 4). As causes of sleep disturbances can be diverse and complex, the team first agreed to develop a visual logic model for capturing the possible causes of common paediatric sleep disturbances and mapped these to potential "first-line" intervention options. The quality improvement/quality assurance (QIQA) protocol was developed with the aim of identifying potential risk factors that could be targeted at the referral level in family medicine, paediatrics, and child and adolescent psychiatry. The current version of the QIQA protocol suggests a structured intake process utilising a mixed methods approach using open-ended questions (5), including individual goals (6) and concerns (7) of the patient/family with regards to sleep and daytime functioning, medication information, and validated questionnaires for capturing both sleep and wake behaviours (8, 9). The newly developed intake forms were tested in an ambulatory one-to-one service delivery setting for children and adolescents with MHNDD at an academic sleep programme. The goal of this brief report is to describe the trends of patient characteristics in a pilot cohort at the time of referral to the sleep programme, all assessed using this QIQA protocol.

Methods

Time and location of the quality improvement/quality assurance project

The project started in May 2020 as a pan-Canadian endeavour. Eight scientists (health management/decision support) and five parent advocates joined the pan-Canadian working group consisting of 19 clinicians (7 community-based/12 working in an academic environment). Canadian group members were located in non-hospital and/or research settings in urban (Vancouver, Regina, Winnipeg, Moncton), rural and remote locations (Rexton, Rogersville, Saint-Louis de Kent). International group members, who joined the endeavour over 2020, were located in academic settings in Australia, Austria, Germany, United Kingdom, and Italy. Patient data collection started at the first project site (Vancouver, Canada) in September 2020; the first pilot data were collected at the Interdisciplinary Sleep Clinic of BC Children's Hospital between September-November 2020; the project is currently ongoing and data are collected electronically with REDCap, an electronic data collection tool (10). Under instruction, student research assistants developed the electronic database in REDCap format and performed the analysis; the backend is available for other clinics. International working group members contributed as peer reviewers to this discourse.

Ethics approval

The BC Children's Hospital based QIQA project was registered with the Provincial Health Service Authority, PHSA, British Columbia and electronic data collection approved by the institutional Clinical Research Informatics Committee—a joint committee of PHSA and Research Ethics Board at the University of British Columbia.

The logic model

The logic model is based on the working group discussions about how paediatric sleep disturbances could be assessed and managed in a community setting and supported by developmental paediatrics and mental health clinics. Both of these clinical settings have implemented transdisciplinary and transdiagnostic approaches. The first task for the working group was to use their clinical, social science and parenting expertise to review to what degree sleep is related to functional diagnoses and/or root causes—all factors, which are often not recognised when recommending first-line interventions in the community setting. The model positions sleep in the centre, which encourages the clinical consideration of sleep disturbance as a possible comorbidity, underlying, and/or aggravating factor of any developmental and/or mental health condition. Further, this empirical logic model allows clinical team members not only to review sleep problems within the context of categorical and/or functional diagnoses that drive clinical practice, but also to review the possible interventions and discuss with the patients their priorities (3, 4). The visual representation of the logic model is depicted in **Figure 1**.

Pilot project

This pilot project was performed as part of an ongoing QIQA project with data collected over a period of 3 months, between September-November 2020 at the BCCH Interdisciplinary Sleep Program in Vancouver, BC.

Intake questionnaire

All patients referred for a sleep assessment received an intake questionnaire, which consisted of open-ended questions (5), including individual goals (6) and concerns (7) of the patient/family with regards to sleep and daytime functioning, medication information, and the Sleep Disturbances Scale for Children (SDSC) (8). After the first intake, as attention-deficit hyperactivity disorder (ADHD) was identified as a main diagnosis, we also implemented the (open source) ADHD Rating Scale-IV for capturing the interconnection between sleep and wake behaviours (9).

The questionnaire was applied during the pilot testing period of 3 months in downloadable and/or clickable PDF format sent by email. With an initial phone call, the service booking clerk informed the patients/caregivers about the procedure and those who consented sent back the completed forms.

The SDSC was used for describing the type and severity of sleep problems (8). The SDSC is a 26 question, parent-reported scale that is capable of distinguishing six classes of sleep disturbance: disorders of initiating and maintaining sleep (DIMS), sleep disordered breathing (SDB), sleep wake transition disorders (SWTD), disorders of excessive somnolence (DOES), sleep hyperhidrosis (SHY) and disorders of arousal (DA) (8, 11). Scores were grouped into five different colour groups (dark red, red, amber, yellow, green), with dark red signifying the highest (most severe) score and green signifying the lowest (least severe) score.

Medications were grouped into the following categories: (1) medications for sleep initiation/sleep (i.e., melatonin, zolpidem), (2) benzodiazepines, (3) stimulants, (4) non-stimulants (i.e., clonidine, guanfacine, atomoxetine), (5) antidepressants, (6) antipsychotics, (7) anti-epileptics, and others (e.g., antidiabetic medications, thyroid, and growth

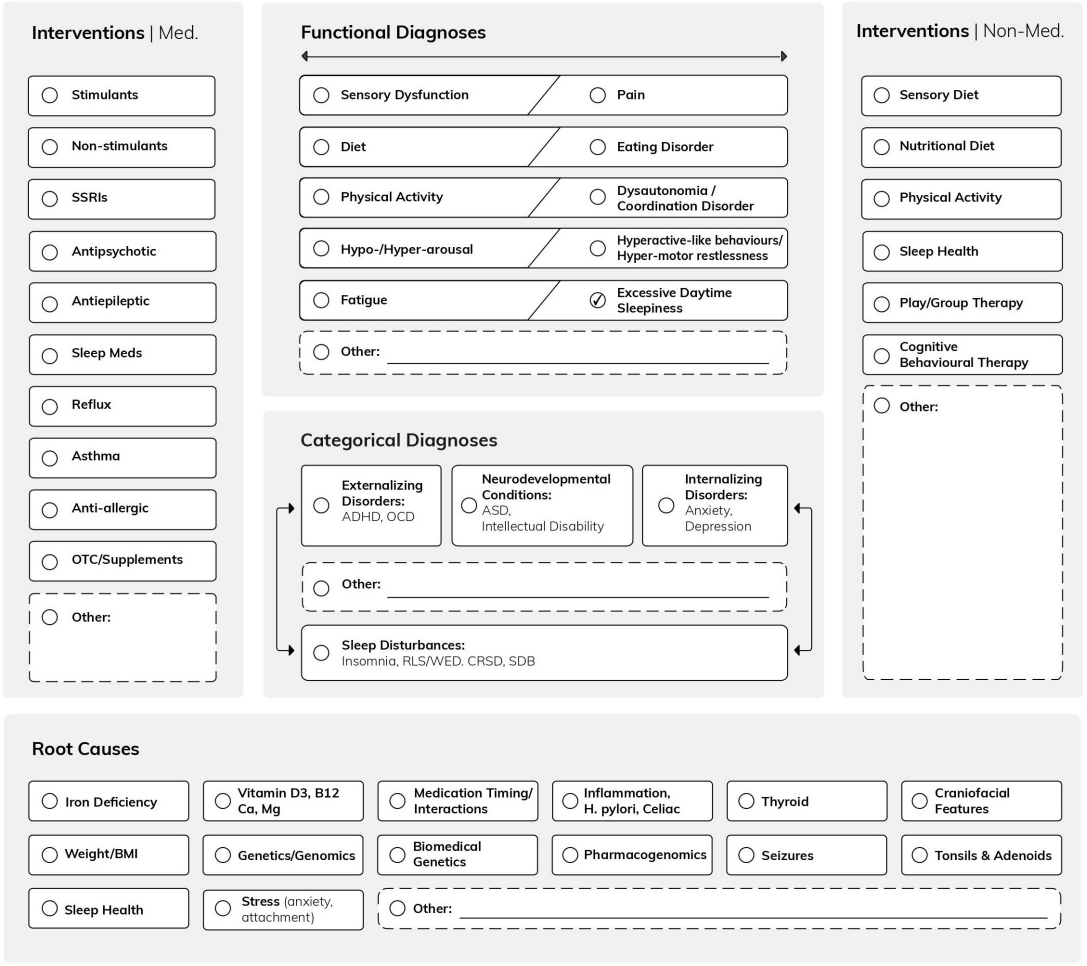

FIGURE 1
The *Mind-the-Gap* logic model shows the interconnections of several contributing factors ("possible root causes") with functional and categorical diagnoses. This conceptual framework allows the addition of further functional diagnoses, possible causes, and interventions, as it is designed as a grid. (Note that the logic model is a conceptual framework and its applicability is tested in clinical practice) (49).

hormones). Paediatric polypharmacy was defined as ≥ 2 concurrent medications for ≥ 1 day (12).

The ADHD Rating Scale-IV is an 18-item easy-to-administer questionnaire for diagnosing ADHD in children and adolescents and following up treatment success similar to the SDSC. We utilised the parent questionnaire pertaining to home behaviours in English (9).

Goals (6) and concerns (7) of the patient/family were categorised using the BEARS concept (5). The BEARS mnemonic (B for bedtime, E for excessive daytime sleepiness, A for awakenings, R for routines, S for snoring or sleep disordered breathing) and two additional categories were added in our analysis to capture the quality of sleep (Q) concerning events such as sleep hyperhidrosis, enuresis, and/or night binge eating; the other being goals or concerns not specific (NS) to the patient's sleep (e.g., less medication, or parents wanting to sleep better themselves).

Results

Pilot project data

During the 3-month pilot period, we received 51 referrals. Fifty-one families were contacted, 41 returned a completed intake form (response rate 80%). Those who did not respond received an invitation to fill out the forms under the guidance of a professional from the clinic. Here, we are presenting the data of these 41 consecutive patients between the ages of 3 and 18, who were seen between September and November 2020, who all were eligible for the sub-specialty sleep/wake-behaviours clinic. Patient characteristics are presented in **Table 1**.

Based on the available information by the referring provider, intake forms and/or available information from existing hospital charts, 8/41 (20%) patients had a dual diagnosis of ADHD and ASD, 15/41 (37%) had ADHD alone and 4/41 (10%)

TABLE 1 Patient characteristics of 41 consecutive patients between the ages of 3 and 18, who were seen between September and November 2020.

Demographics of the patient cohort (*n* = 41, mean 11.3 years, median 11y, min 3y, max 18y)	No. of patients with confirmed diagnosis, n
Neurodevelopmental conditions	
Autism spectrum disorder (ASD)	12
Foetal alcohol spectrum disorder (alcohol related neurodevelopmental disorder; *in utero* exposure)	6 (4; 2)
Global development delay and intellectual disability (mild to severe)	12
Genetic conditions (Down syndrome; Prader-Willi Syndrome; Trisomy 13 Mosaic; Trisomy X; Noonan syndrome)	6 (2; 1; 1; 1; 1)
Neurologic conditions [motor disorders (Cerebral Palsy; Leigh Syndrome); epilepsy, visual impairment; septo-optic dysplasia; mild traumatic brain injury]	10 (1; 1; 2; 2; 1; 3)
Sensory processing dysfunctions	29
Others (tics; hypothyroidism; chronic headaches; Type 1 Diabetes)	6 (1; 3; 1; 1)
Self-injurious behaviours/suicidal ideation	8 (6; 2)
Mental health diagnoses/comorbidities	
Externalising disorders or disorders of disruptive challenging behaviours	
ADHD	23
Oppositional defiant disorder	3
Obsessive compulsive disorder	1
Internalising disorders	
Anxiety disorders	20
Emotional dysregulation (depression; mood disorders, including dysthymia)	11 (8; 3)
Bipolar disorder	1
Sleep disorders (working diagnoses)	
Insomnia	40
Excessive daytime sleepiness	37
Circadian rhythm sleep disorder (CRSD; delayed sleep onset; polyphasic patterns)	32 (31; 1)
Parasomnias	31
Sleep-disordered breathing	22
Probable/possible RLS implicating necessity for structured behavioural observations and blood work investigations (e.g., iron deficiency)	37

Note that multiple conditions may apply for one individual.

had ASD alone. Other diagnoses included anxiety (20/41, 49%), global developmental delay/intellectual disability (12/41; 29%), depression (8/41; 20%); foetal alcohol spectrum disorder (FASD/*in utero* exposure 6/41), and self-injurious behaviours (SIB; 6/41) both 15%.

Two-thirds of the patients 27/41 (66%) scored in the red domain of SDSC (either dark or light red; for the purposes of this descriptive paper, we have collapsed the dark red and red groups together). For the subscale scores, 30/41 (73%) of patients had scores in the red domain for DIMS; 3/41 (7%) for SDB concerns; 10/41 (24%) for DA; 21/41 (51%) for SWTD; 11/41 (27%) for DOES; and 5/41 (12%) for SHY. As the ADHD Rating Scale was added to the intake forms later on, only 13 participants filled it out. 10/13 (77%) scored red overall in their age adjusted percentiles.

37/41 (90%) patients were prescribed at least one medication. As North American regulations differ from European ones, using international terminology, we listed melatonin as a sleep medication and not as an over the counter (OTC) drug. 22/37 (59%) were taking sleep initiation/sleep medications (one patient was taking melatonin and zolpidem); 9/22 (41%) were taking these agents in combination with further non-stimulant medications (i.e., clonidine, guanfacine and atomoxetine), 6/22 (27%) with antidepressants (e.g., fluoxetine, fluvoxamine, trazodone, sertraline, escitalopram), of these six patients, four were also on antipsychotics (e.g., quetiapine, risperidone). In addition, sleep initiation/sleep medications were used in combination with stimulants in 2/22 (9%). Stimulants were prescribed seven times within the entire cohort, four times in combination with non-stimulants, three times with antidepressants and one time with an antipsychotic. Within the group of 22 patients treated for sleep disturbances, polypharmacy was seen in 16/22 (73%) cases, within the group of 37 medicated patients in 23/37 (62%) cases, and within the entire patient cohort in 23/41 cases (56%).

Figure 2 shows the patients (*n* = 41, mean 11.3 years, median 11y, min 3y, max 18y) arranged according to SDSC total scores (highest scores from the left) in the context of prescribed medications and patient/parent goals and concerns. The youngest patient taking melatonin as a sleep medication was 3 years of age; a patient 6 years of age was taking two medications for sleep and/or wake behaviours (clonidine, melatonin); a boy 11 years of age, requiring complex chronic care management, was taking six plus medications for sleep [clonidine, melatonin, zolpidem, gabapentin, quetiapine, trazodone, plus prescribed cannabidiol, and THC (tetrahydrocannabinol)] in addition to synthroid. The youngest patient taking an antidepressant was 10 years of age, whilst the youngest patient taking an antipsychotic was 11 years of age. The patient (6 years of age), who scored dark red/red in the SDSC total score and all subscores was taking a benzodiazepine for epilepsy treatment (clobazam) and non-stimulant (clonidine), both given in the evening for improving sleep.

Goals and concerns were not available for 5 patients; including the two with the highest SDSC scores, two with red scores in the DIMS domain and one with the second lowest scores; in these cases, clinical assessment revealed that non-restorative sleep (sleep quality) was an issue of concern. We grouped family goals and concerns according to the domains in the BEARS themes. Insomnia (B + A: 30/36) was the main concern with 83%. In detail, *B* for: bedtime/falling asleep related comments (24/36; 67%); *E* for excessive daytime sleepiness, also low energy, naps, and trouble waking up in the morning (18/36; 50%); *A* for awakenings and sleep maintenance but also trouble falling back asleep, nightmares, and parasomnia in general (e.g.,

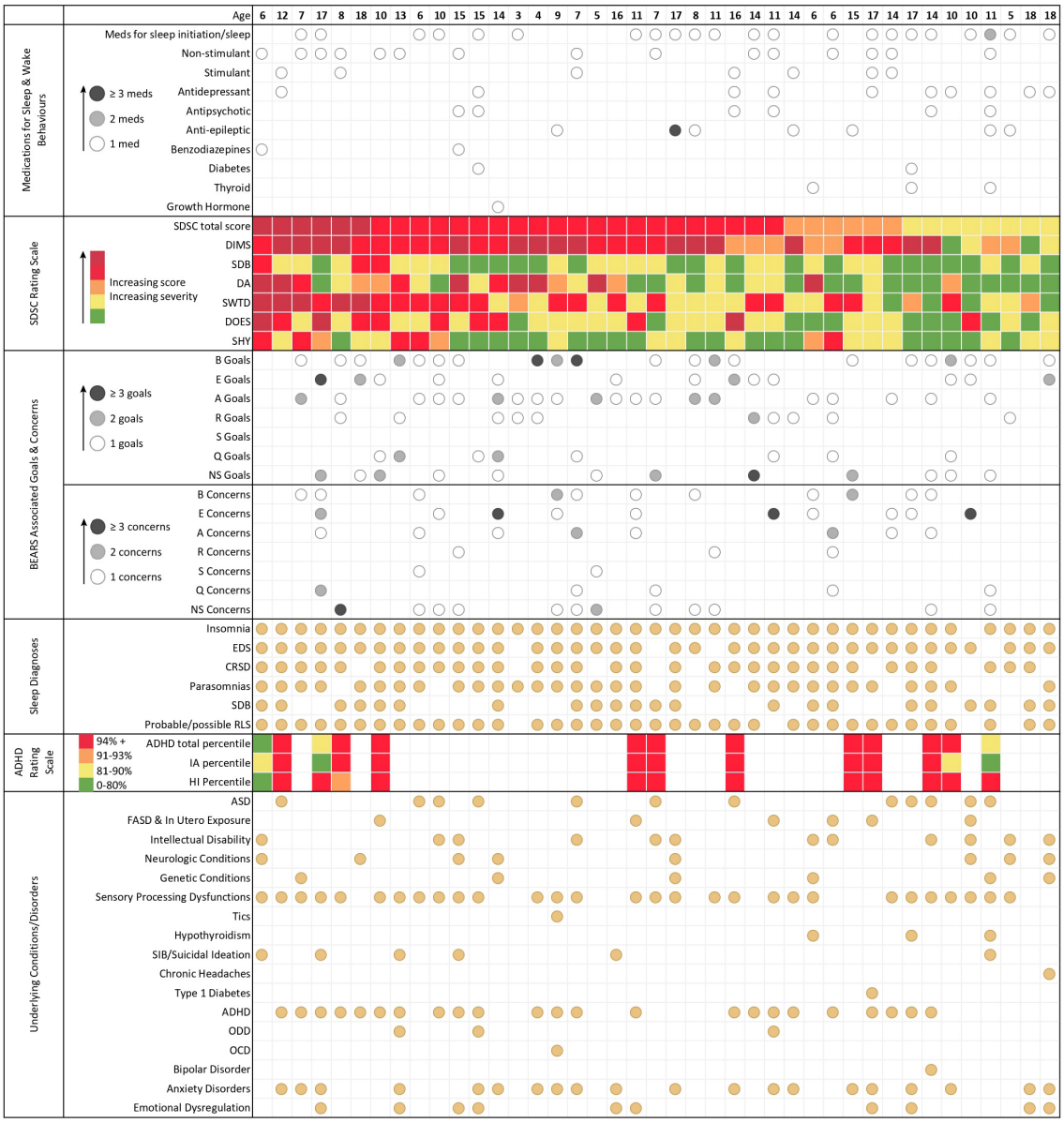

FIGURE 2

An overview of intake data. Each column represents the data for one individual patient. Patients are arranged according to SDSC total score (highest scores from the left. From the top to the bottom: MEDICATION DATA. Medications have been grouped according to categories (e.g., sleep initiation/sleep; non-stimulant, etc.). One medication is marked with a white circle, two medications are marked with a grey circle, and three or more medications are marked with a black circle. Note that melatonin (using international terminology) is listed as a medication and not as an over the counter drug. SDSC TOTAL SCORES AND SUBSCORES. DIMS, disorders of initiating and maintaining sleep; SDB, sleep disordered breathing; DA, disorders of arousal; SWTD, sleep-wake transition disorders; DOES, disorders of excessive somnolence; SHY, sleep hyperhidrosis. Each coloured dot represents a different category of SDSC scoring that increases (and severity of symptoms) from green (lowest score), to yellow, to amber, to red, and finally dark red (highest score). GOALS/CONCERNS. Information on goals and concerns of the patients has been grouped using the BEARS themes. SLEEP DIAGNOSES. The sleep medicine working diagnoses, which were made after the first assessment, are presented in the lowest block. EDS, excessive daytime sleepiness; CRSD, circadian rhythm sleep disorder; SDB, sleep disordered breathing; RLS, restless legs syndrome. ADHD Scores. IA, inattention and HI, hyperactivity-impulsivity sub-scores. Note that ADHD scoring was only available in 13 patients.

sleep walking, talking) (22/36; 61%); *R* for routines, regular duration, regular bed and waketime, and getting enough sleep (12/36; 33%); *S* for snoring and sleep disordered breathing (2/36; 6%). We included all comments on quality of sleep in the *Q* theme, which were otherwise not captured, such as sweating, bed wetting or night binge-eating (11/36; 31%). Finally, *NS* stands for not specific to the participant's sleep (19/36; 53%). Examples of goals that highlight the specific hopes and worries of families

are: *B*, "we would like him to go to bed without anger"; *E*, "Get out of bed without feeling extremely tired independent of sleep amount"; *A*, "To not wake up screaming at night"; *R*, "Sleep the typical number of hours for his age"; *S*, *N/A* in this patient cohort; *Q*, "helping him feel like he has had a restful sleep"; Non-sleep specific goals, "emotional regulation." Exemplar patient (family) reported concerns were: *B*, "He needs to be touching or feeling someone beside him or he will not sleep"; *E*, "Chewing gum and exercise breaks needed to stay awake during classes"; *A*, "Long term effects of sleep interruption"; *R*, "He does not get enough sleep at night time." *S*, "that she has sleep apnea, again." *Q*, "she is not getting a good sleep"; non-sleep specific concerns, "that she will not be developing to her appropriate age."

The initial working diagnoses (after clinical assessment) from a sleep medicine perspective are shown in the second part of **Table 1**. Note that the majority of the patients (40/41; 98%) were suffering from insomnia, fulfilling the criteria for circadian rhythm sleep disorders (CRSD; 32/41; 78%; mainly delayed sleep onset 31/32) and affecting daytime with excessive daytime sleepiness or affected working speed (37/41; 90%). Parasomnias (31/41; 76%) and SDB (22/41; 54%) followed in the ranking. With the high amount of comorbid sensory processing dysfunction (29/41; 71%), probable or possible restless legs syndrome (RLS) requiring structured behavioural observations (13) and haematological and/or functional iron deficiency investigations (37/41; 90%). Probable or possible RLS was considered a main possible organic cause and became a frequent diagnosis.

Discussion

This joint community academia collaboration resulted in *three* major achievements. *First*, the development of a context-framing logic model to capture the multiple causes and intervention options for sleep disturbances; *second*, the development and application of a mixed methods approach for a structured intake process for complex patients with MHNDD; and *third,* a clinical phenotyping of a pilot cohort using this mixed methods approach.

The logic model

Our logic model framed not only the entire QIQA project but also the assessment in each individual case. We called our logic model "Mind-the-Gap" to emphasise its added value in identifying otherwise poorly captured information related to the complexity of sleep disorders in children and adolescents, which, unrecognised, may initiate a cascade of mental health diagnoses (14, 15). An example for a "mind-the-gap" alert are functional diagnoses (e.g., sensory dysfunctions), usually observed by parents/caregivers and/or allied health care professionals, but not necessarily flagged, or identified by physicians in the community (16). As such, the interconnections of sensory dysfunctions with categorical day and nighttime-related diagnoses are not always clear to the providers who make the decisions for further investigations or interventions. Similarly, the interconnections between the wide range of functional diagnoses and potential root causes are often now recognised. Typical examples of root causes of sleep and challenging daytime behaviours are biochemical imbalances, such as iron (17, 18) or vitamin D deficiencies (19, 20).

Clinical phenotyping

Intake information and subsequent clinical assessment resulted in insomnia diagnosis for 98% of all cases. Among the goals and concerns, insomnia (83%) and affected daytime behaviours/DOES/EDS (50%) were explicitly expressed as main concerns. Note that 53% had NS related goals and concerns, revealing that parents connected disturbed sleep with affected daytime behaviours. CRSD-like presentations and parasomnias were diagnosed in 78 and 76% of the cases with insomnia. In 90% of our pilot cohort, probable RLS, requiring further structured behavioural observations (13) and blood work investigations (21), was likely contributing to insomnia and disturbing sleep. The high number of possible RLS diagnoses requiring further investigations may be due to the specific referral pathways qualifying for the specific developmental paediatrics/child and adolescent psychiatry associated *behavioural sleep medicine* and not for respiratory or neurology associated sub-speciality sleep medicine clinics. The rationales for daytime related referral diagnoses were (from a sleep medicine perspective) partly difficult to understand, as it was not obvious who initially had established the diagnosis (e.g., ADHD and/or other mental health diagnoses), under which circumstances the diagnosis was established (e.g., whether sleep problems had been excluded or not) and what measures had been applied to alleviate symptoms (e.g., trials for sleep health recommendations) (22, 23). The low number of patients in this pilot project precludes our ability to assess correlations between sleep disorders, mental health diagnosis and other comorbidities. Continuing to use the logic model to frame clinical presentations will result in larger patient cohorts that will allow us to phenotype patients referred to our clinic with ADHD, MHNDD and sleep disturbances further, as recently suggested (24, 25).

Medication characteristics

Fifty-nine percent of patients were taking medications targeting insomnia (i.e., melatonin and zopiclone), 41% were taking these agents in combination with further non-stimulant

medications (i.e., clonidine, guanfacine, atomoxetine), 9% with stimulants, 27% with antidepressants, and 18% with antipsychotics. While stimulants and non-stimulants can cause insomnia (18, 26), antidepressants and antipsychotics can negatively affect sleep quality and architecture (27, 28). Note that in Canada, most psychiatric medications have a regulatory status of non-approval for treatment of children and adolescents (with the exception of ADHD treatments). Such medication use may still be rational and evidence-based (for example, use of risperidone and aripiprazole for treatment of irritability in autism) (29). However, while polypharmacy may be necessary in a patient with a MHNDD and comorbidities (30), the fact that patients required a referral to sleep medicine despite the medications trials, raises the concern to what degree sleep, as a complex neurophysiologic function, had been integrated in previous assessments and choice of treatment strategies. The youngest patient taking sleep medication (melatonin) was 3 years of age, an age for which the use of behavioural strategies to manage difficulties with sleep initiation and maintenance are highly effective (31). Further, in the 13 referrals where ADHD ratings were assessed, 10/13 patients scored red in the ADHD and in one or more SDSC domains. Overall high percentage of patients scoring red in the DIMS, SWTD and DOES domains of the SDSC and who received clinically affected daytime behaviours or EDS as a working diagnosis supports the notion that sleep was not sufficiently assessed and/or treated. It is possible that the COVID-19 related shutdown in 2020 had an enhancing effect on prescription practices and on the incidence of polypharmacy within this population; however, as we have not analysed any medication data prior to the onset of COVID-19, we can only speculate on this aspect, which is an important limitation of our data.

The role of over the counter drugs

Not only does this QIQA project allow for the ongoing analysis of medication data, it also reveals an eye-opening insight to medication practices and the necessity for medication reconciliation for outpatient clinics on an ongoing basis. Patients' goals and concerns may support this process and allow a more patient-oriented perspective within the framework of the logic model. While PharmaNet, a network linking all pharmacies within the province of British Columbia to a central set of data, captures information from every outpatient prescription dispensed in British Columbia, OTC drugs that may have been used for sleep (e.g., melatonin, antihistamines) are not captured. The main *"sleep medication"* not captured is melatonin, regulated as a prescription drug all over the world, except in North America. Melatonin is an internal cue hormone that synchronises the organism's biological rhythms and indoleamine, adjusting circadian rhythmicity (32). It should be noted that melatonin is *not* a sedative, therefore, should not be used as such (32–34). High dosage applications of melatonin for improving sleep maintenance are obsolete (35) and can pave the way for further medications, as shown in a subgroup of patients with FASD (36). We see it as concerning that the majority of these children received sleep and sedating medication in combination with other prescription drugs, yet the insomnia symptoms continue to be unresolved, likely resulting in the aggravation of behavioural daytime challenges due to non-restorative sleep.

Prescription drugs and first line measures

Among the numerous prescription and non-prescription medications used for sleep, only a few have been investigated in high quality trials, systematic and scoping reviews, and meta-analyses for the paediatric population. Interestingly, most medications used for insomnia, such as clonidine, are used off-label. Clonidine is a non-selective alpha agonist that reduces sympathetic outflow from the central nervous system, causing a decrease in arterial blood pressure and wakefulness (37). Medications such as antidepressants and antipsychotics are commonly employed off-label to treat sleep disturbances, despite limited evidence (38, 39). In contrast, the non-pharmacological intervention of correcting biochemical imbalances, such as iron and vitamin D deficiencies, as an effective management of DIMS and SWTD (e.g., insomnia), has been investigated in multiple trials, systematic and scoping reviews, and meta-analyses (17–20). Similarly, in the domain of SDB, corticosteroid nasal sprays have been implemented as a conservative first line treatment before surgical interventions and/or continuous positive airway pressure (CPAP) are considered (40, 41).

The critical discourse regarding how to use psychotropic medications in children with MHNDDs has been ongoing for several years (42–44). Trends to medicate children seem to be specific to North America. Provincial PharmaNet data has shown that the percentage of children who received psychotropic drugs was two-to-five times higher than rates reported in European countries (45). However, it is worth noting that these rates, although high, are still 30% lower than rates reported in the US (45). Most recently, in the symposium at the Canadian Sleep Society (CSS) 2021 meeting, Bruce Carleton, who had analysed the B.C. PharmaNet data, showed that 35,870/145,170 (24.7%) children under age 5 have been dispensed psychotropic drugs (over the time period 1997–2017; (46). Further, 2,125 children under the age of five had used stimulants; interestingly, only 52.3% (1,112/2,125) of these children had received a diagnosis of ADHD before the prescription was made, implying that the other

47.7% had not yet received a diagnosis of ADHD before commencing stimulants.

Conclusion

The analysis of this pilot project with a limited number of patients reveals insomnia, affected daytime wellbeing/EDS and polypharmacy in the majority of the cases. We know that individuals with MHNDD are at high risk for psychotropic medications (47) and our current understanding is that unrecognised sleep disturbances can often aggravate mental health manifestations and have negative consequences on family dynamics and coping skills (48). In the context of this QIQA project, we have tried to explore pharmacologic interventions in children with MHNDD with qualitative and questionnaire based quantitative data at the entry point to the clinical sleep service. (3, 4). Our findings, despite reporting only a small patient cohort, suggest that chronic insomnia symptoms of patients with MHNDD are not being successfully treated. The electronic forms, which have been developed within this QIQA project, will allow the creation of an electronic registry (10), which may shed light on this challenging and controversially discussed topic with a larger number of patients.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The BC Children's Hospital based QIQA project was registered with the Provincial Health Service Authority, PHSA, British Columbia and electronic data collection approved by the institutional Clinical Research Informatics Committee—a joint committee of PHSA and Research Ethics Board at the University of British Columbia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Members of the international and Canadian working groups

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Author contributions

OI developed the logic model, QIQA project, and wrote the manuscript. RS was involved in the development and international peer review of the logic model. EK and DW helped with implementation of the QIQA project and edited the manuscript. JB and RB developed the electronic intake forms using REDCap and were responsible for backend management of the project. JB, RB, SM, and OH carried out data analysis. SM and OH created all graphics and helped edit the manuscript. DE provided in-depth input regarding pharmacological questions and helped edit the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Functional links between thermoregulation and sleep in children with neurodevelopmental and chronic health conditions

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The bi-directional relationship between sleep and wake is recognized as important for all children. It is particularly consequential for children who have neurodevelopmental disorders (NDDs) or health conditions which challenge their sleep and biological rhythms, and their ability to maintain rhythms of participation in everyday activities. There are many studies which report the diverse reasons for disruption to sleep in these populations. Predominantly, there is focus on respiratory, pharmaceutical, and behavioral approaches to management. There is, however, little exploration and explanation of the important effects of body thermoregulation on children's sleep-wake patterns, and associated behaviors. Circadian patterns of sleep-wake are dependent on patterns of body temperature change, large enough to induce sleep preparedness but remaining within a range to avoid sleep disturbances when active thermoregulatory responses against heat or cold are elicited (to maintain thermoneutrality). Additionally, the subjective notion of thermal comfort (which coincides with the objective concept of thermoneutrality) is of interest as part of general comfort and associated behavioral responses for sleep onset and maintenance. Children's thermoregulation and thermal comfort are affected by diverse biological functions, as well as their participation in everyday activities, within their everyday environments. Hence, the aforementioned populations are additionally vulnerable to disruption of their thermoregulatory system and their capacity for balance of sleep and wakefulness. The purpose of this paper is to present hitherto overlooked information, for consideration by researchers and clinicians toward determining assessment and intervention approaches to support children's thermoregulation functions and promote their subjective thermal comfort, for improved regulation of their sleep and wake functions.

KEYWORDS

thermoregulation, sleep, vigilance, children, disability, chronic health conditions

Introduction

Sleep and thermoregulation are critical biological functions. Through dynamic physiological mechanisms, the functions of both are affected by behavioral, social, and environmental factors, including circadian rhythms of meals, exercise, bathing, indoor and outdoor activity, and associated exposure to ambient temperatures and light (1). They are tightly related, and have direct impacts on each other (2–4). The association between these functions and the impact of biological, behavioral, social and environmental factors is well understood in the general adult population, allowing for strategies to alter thermoregulation and improve sleep onset, maintenance and quality, and to optimize the patterns of sleep, wakefulness and daytime performance (5–8). However, thermoregulation and sleep is less well understood in children, especially those with neurodevelopmental disorders (NDDs) or chronic health conditions (CHCs).

All children need the appropriate quality and duration of sleep, for optimal physical and mental health (9, 10), learning and behavior (11–13), and meaningful participation in their daily lives (14). Sleep is especially important for children with NDDs and CHCs who, along with their caregivers, are vulnerable to additional challenges to their health, participation and wellbeing (15, 16). Indeed, sleep has valuable therapeutic potential for these children (17, 18). Unfortunately, it is common for these children to have difficulties with sleep, and with their patterns of sleep and wake (19–22). Furthermore, they are more susceptible than their peers to thermoregulation difficulties. Thermoregulatory dysfunction is discussed by Svedberg et al. (23) who found a higher incidence of cold extremities in children with severe neurological impairment, compared to their peers, with skin temperatures in the feet significantly lower in the non-ambulant children than those who walked. More specifically, difficulties with thermoregulation during sleep are a concern for these children (24, 25). Indeed, a recent study of 33 children with cerebral palsy (CP), found that 37.5% of children had sleep hyperhydrosis, compared to 4.2% of the control group of typically developing children (26). Similarly, a retrospective study of sleep concerns in 154 children with cerebral palsy, aged 1–18, found that approximately 33% reported temperature and perspiration as major concerns affecting their sleep (27). This was the case across all age groups (aged 1–6, 7–12, 13–18 years). Despite these known difficulties, and the extensive knowledge on the interaction between sleep and thermoregulation, there is no published evidence to guide research and practice for management of sleep and wake in children who have NDDs and CHCs and thermoregulation difficulties.

The dynamic and multi-directional relationships between the biological, behavioral, social, and environmental factors that affect sleep and thermoregulation can be understood when viewed within the framework of the International Classification for Functioning, Disability and Health for Children and Youth [ICF-CY; (28)]. This well-established framework represents the dynamic interaction of biopsychosocial components (body functions and structures, activity and participation, environments and other contextual factors) which influence the determinants of health and wellbeing and the long-term consequences of living with a CHCs or disability. Most importantly, it guides the focus of research and clinical practice toward promoting children's participation (their active engagement in the important and meaningful aspects of their lives) by illustrating the variability of functioning within everyday settings and noting effects of environments and personal factors such as gender, age, ethnicity, social and educational background, behavior patterns, and life events (29).

This paper is aimed at bringing attention to clinicians and researchers who work to support sleep of children with NDDs and CHCs, of the functional relationships between sleep and thermoregulation, and to postulate pathways to optimize this important aspect of participation and quality of life in these children.

Thermoregulation

Children and adults are homeotherms. Through dynamic physiological and behavioral thermoregulation functions they typically maintain a constant resting core body temperature between 36.5°C and 37.5°C despite changes in the surrounding environment. Thermoregulation is a critical biological function, for maintenance of vital physiological conditions for cell function, systems function and life itself (4). When conditions or environments challenge the thermoneutral state, biological, and behavioral responses are elicited, with effects on other homeostatic systems (hormonal, digestive, cardio-vascular, respiratory) and alterations to behavioral states (sleep, appetite, psychological stress, vigilance, performance) and wellbeing (30).

The body system for thermoregulation is described by two compartments: a core (including organs such as the lungs, heart, abdominal organs and brain) and a peripheral "shell," corresponding to skin layers and associated musculo-skeletal, nervous and circulatory systems. The core system has a relatively stable temperature, and is regulated and maintained by a combination of feedforward and feedback mechanisms (4). Feedback responses occur in response to changes in internal temperatures which are detected by thermoreceptors in the core organs, and are triggered when the core temperature deviates from the homeostatic range. The peripheral "shell" is responsible for feedforward mechanisms—pre-emptive responses to anticipated thermal challenges, which are triggered prior to change in core temperatures, primarily through functions of cold and warm thermoreceptors in the skin. These dynamic interactions are heavily controlled by the autonomic nervous system (ANS), with integration mainly

at the suprachiasmatic nuclei (SCN) in the pre-optic area of the anterior hypothalamus [see (31) for analysis of skin temperatures as feedforward or feedback systems].

Further to this, thermoregulatory responses can be described through a model which includes a passive system (represented by heat exchanges between the body and the environment) and an active controlled system of thermosensors, central controller and effector mechanisms for thermogenesis (heat production), sudomotion (activity of sweat glands), behavior (changes in posture and movement, and adjusting the environment, clothing or bedding), and vasomotion (vasodilation and vasoconstriction) (**Figure 1**). In environments with ambient temperature ranges that are "thermoneutral" an almost constant and normal core body temperature is maintained, through autonomic changes in the peripheral skin blood flow (influencing the thickness of the shell compartment), with minimal metabolic heat production. Both core and skin temperatures are controlled *via* these homeostatic responses, with skin temperature involved in the regulating of core temperature (4). Outside the boundaries of the thermoneutral zone, active thermoregulatory responses are required to maintain homeothermia. Thermoregulatory responses to cold environments involve vasoconstriction, shivering and increased body activity, whereas in warm environments vasodilation and sweating occur. When these responses are not sufficient to compensate for the external thermal challenge, core body temperature decreases or increases and homeothermia is lost. Thus, constant core body temperature is a process of homeostasis which results from the body's balance between heat production and heat losses in association with behavioral and environmental factors.

Such is the complexity of thermoregulation, and the dynamic interaction between the body and environments, it can be viewed through specific models of function of the nervous system (4, 32), or through multi-element models as reviewed by Katic et al. (33), who report 22 different thermophysiological models through the years 1970–2016. Additional complexity emerges when we consider the notion of thermal comfort, and the influence of age, and sex.

Thermal comfort is described as the result of combination and adaptation of factors of the body in context with the environment (34) and can be measured through parameters of subjective comfort sensations, as well as measures of skin temperatures and sweat rate as functions of metabolic rate. It can be used to determine optimal (or otherwise) factors for function in occupational and domestic settings, and accounts for effects of ambient temperatures and airflow, and effects of various types of materials used in buildings, bedding and clothing (35). Additional factors are important to thermal comfort, including acclimatization to natural environments, habituation to different climate zones (for example time spent indoors in air-conditioning vs. the dynamic conditions of naturally ventilated environments), seasonal adaptations, diurnal rhythms and, interestingly, the effects of perceived personal control, light intensity, and personality traits (36).

Thermoregulation and thermal comfort vary according to age and gender. The control of environmental temperature is particularly important in children, since their body surface relative to body mass is typically greater than adults. Thin body segments (arms and legs), and lean body shape are subjected to larger and more rapid heat exchanges with the environment than thicker body segments or larger body shape (37). Interestingly, Inoue et al. (38) found that when the air temperature is lower than skin temperature, prepubertal children can thermoregulate as efficiently as young adults, due to their greater surface area-to-mass ratio and relatively greater heat loss from cutaneous vasodilation on the head and trunk. In contrast, in their study comparing thermoregulatory responses of pre-pubertal boys to young men to exposure to linear increases in air temperature, Inoue et al. (39) found that when heat stress was increased the mean body temperature at the onset of sweating was significantly greater in the boys than in the men. They concluded that compared with young men, prepubertal boys manifest greater physiological and perceptual strain under heat stress when air temperature exceeded skin temperature. Reflecting this, in their review of the literature on human thermal comfort in the built environment, Rupp et al. (40) report that young children are shown to have preference for lower temperatures than adults, with apparently greater sensitivity to changes in their metabolism. In the same review, the authors also reported on the gender differences in thermal sensation between school aged girls (more sensitive to low temperatures) and boys (more sensitive to high temperatures).

Thermoregulation and sleep

Patterns of body temperatures and sleep

The fundamental relationship between the circadian patterns of body temperature change and sleep-wake is well known, with clear patterns of change in the sensitivity and functions of the thermoregulatory system across the sleep-wake cycle and across stages of sleep. Sleep propensity is associated with an observed drop in core body temperature (T_{core}). Correspondingly, readiness for wake is accompanied by a rise in T_{core}. Interestingly, this pattern of rise and fall of core body temperature across the 24 h sleep-wake period is the inverse of patterns of change in melatonin (41). The drop in T_{core} that triggers sleep onset is precipitated by rise in distal skin temperatures (T_{distal}), namely at the extremities (hands and feet). This commences approximately 100 min before sleep onset and is known as "vegetative sleep preparedness," first described by Magnussen in 1938 [cited in van den Heuvel et al. (42)] The rise in T_{distal} is caused by peripheral vasodilation, allowing inflow of heated blood from the core to the shell,

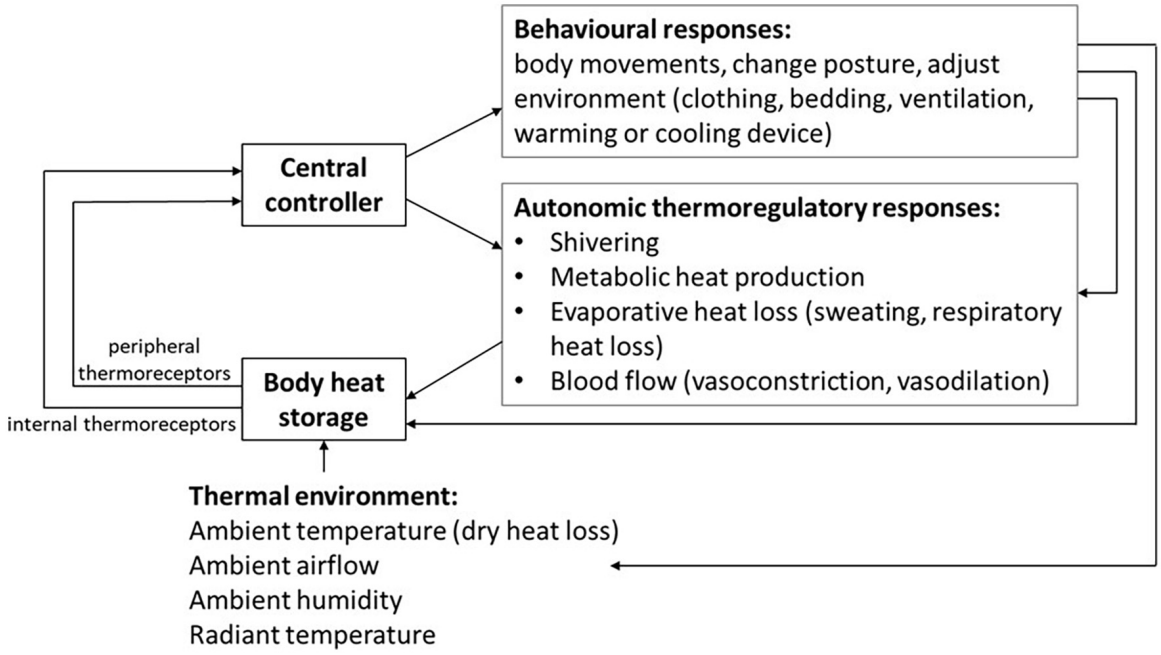

FIGURE 1
Autonomic and behavioral thermoregulatory response systems for homeostasis in varied thermal environments.

and facilitating heat loss to the environment through the small peripheral blood vessels, the arterio-venous anastomoses (AVAs) which are particularly abundant in the glabrous (non-hairy) palms of the hands, soles of the feet, surface of the ears, and certain facial sites (31, 43). The degree of peripheral vasodilation can be estimated by the difference between T_{distal} and proximal skin temperatures ($T_{proximal}$, variously measured at thighs, abdomen, shoulders and back). Importantly, this difference, T_{distal} minus $T_{proximal}$, the distal-proximal gradient (DPG), is regarded as the most significant thermal marker and mechanism of sleep readiness. Indeed, Kräuchi et al. [(44), p.36] wrote that "the degree of dilation of blood vessels in the skin of the hands and feet, which increases heat loss at these extremities, is the best physiological predictor for the rapid onset of sleep."

The relationship between distal skin vasodilation (with rapid rise in T_{distal} and DPG) and sleep onset is understood to be causal, with several studies performed in adults showing that experimentally induced distal vasodilation by subtle skin warming promotes sleep. Accordingly, skin warming for passive body heating (e.g., shower or bath before bedtime) or non-thermal manipulations capable of promoting distal vasodilation (e.g., lights off, lying down, a spicy meal, physical exercise) may increase sleepiness, accelerate the process of falling asleep and improve sleep maintenance in adults (45–48). Interestingly, a recent study of the effects of manipulation of periocular skin temperatures of 19 healthy males showed that a warming eye mask, used prior to sleep, significantly increased the temperatures of hands, feet and the rise of DPG, with significant increase in self-reported sleepiness (49). Most recently, in their randomized controlled study of 11 young healthy males, Haghayegh et al. (50) found that selective thermal stimulation, consisting of a heated pillow that provided mild heating to the cervical spinal skin, in combination with a cool central and warm peripheral temperature-controlled mattress, induced significantly greater distal vasodilation, increased rate of change of DPG, shorter sleep onset latency and significantly better subjective sleep quality in the treatment than the control nights.

Behaviors that lead to pre-sleep relaxation and reduced anxiety when retiring for bed also promote skin vasodilation prior to sleep onset by decreasing sympathetic nervous system activity (51). Additionally, the hypnotic effects of medications such as benzodiazepine and temazepam, and the sleep readiness effect of melatonin is associated with their effects on distal skin vasodilation (52, 53). In contrast, adults with conditions or behaviors which cause attenuated rise in T_{distal} take longer to fall asleep (8, 48). This important relationship between rapid rise in T_{distal} and DPG and sleep onset has also been shown for preterm neonates, infants, and school-aged children (54–56). Logically, the propensity for morning wake correlates with core temperature rise in the morning, as a result of distal skin vasoconstriction which is evident in lowering distal skin temperatures and DPG. Consistent with this, manipulations that induce distal vasoconstriction promote awakening and vigilance in adults (57). Similar studies have not been reported for children.

Consideration of $T_{proximal}$ is also important to understanding sleep, especially in relation to sleep quality and maintenance. This may be especially important for young children. In their study of sleep and skin temperatures of pre-school children and their mothers, Okamoto-Mizuno et al. (58) found that children's proximal temperatures increased more than distal temperatures, and that heat dissipation in this group was dependent more on increase in $T_{proximal}$ than T_{distal}. They noted cardiovascular differences in this younger group, and surmised that $T_{proximal}$ is nearer to the body core and possibly of more benefit for heat loss and decreased cardiovascular strain than the more distal sites. Interestingly, this group of young children were noted to predominantly sleep without bed coverings, and to move about the bed surface during sleep, enabling a greater dry-heat exchange during sleep and indicating a greater dependence on behavioral thermoregulation than for adults. While many studies report $T_{abdomen}$ as a measure of $T_{proximal}$, we have recently demonstrated that T_{back} was a good indicator of $T_{proximal}$ during sleep of school aged children (59). This corresponds with studies of adults, which report that conductive heat loss through the proximal back is critical for slow wave sleep and subjective sleep quality (60, 61). Similarly, Lan et al. (62) found that local cooling of T_{back} was most effective in alleviating thermal stress in a warm environment. Less frequently reported than T_{distal} and $T_{proximal}$, forehead skin temperature ($T_{forehead}$) is also considered to be an important region of thermoregulation (63, 64). It is reported to be affected by the temperature of the underlying brain, and to have a high rate of heat transfer with ambient temperature due to venous as well as arterial systems, making it a unique site of T_{skin} measurement (31). In studies of adults and elderly, $T_{forehead}$ has been shown to be particularly affected by seasonal ambient temperatures (65), and may be an important factor in sleep maintenance within this context.

While there is a wealth of research examining the association between body temperature and sleep in adults, it is not clear if such findings can be directly translatable to children, thus warranting further research in this population.

Thermal comfort and sleep

The notion of thermal comfort is fundamental to understanding the interactions between thermoregulation and sleep. Warm or cool challenges (beyond thermoneutral) before and during sleep affect the timing of sleep onset, the duration of sleep stages and the overall efficiency of sleep (66, 67). They also affect subjective perceptions of "thermal comfort" and elicit associated behavioral thermoregulation strategies such as adjusting bedding and changing body position, affecting sleep depth and propensity to wakefulness (8, 48, 68, 69). While autonomic responses to hot or cold stimuli are reduced during REM compared with NREM sleep, REM sleep is more vulnerable to thermal discomfort than the other sleep stages (70).

Thermal comfort during sleep is underpinned by physiological and behavioral responses to environmental factors: seasonal, household and bedroom temperature and humidity, and, more specifically, the "microclimate" of the bed which is influenced by interactions of bedding and clothing. These factors are affected by building design and the use of heaters, air-conditioners, fans and ventilation (70). In their review of the environmental parameters for optimal sleep, Caddick et al. (71) recommended ambient bedroom temperatures between 17°C and 28°C, depending on effects of bedding and with relative humidity between 40 and 60%. The effects of environmental temperatures have been found to vary across sleep periods. Whilst humid heat is reported to particularly affect slow wave sleep in the earlier phase of sleep period, cold exposure is found to impact on quality of sleep in later segments of sleep (69). Furthermore, in their review study, Lan et al. (62) reported that a cooler sleep environment at the beginning of the sleep period caused delayed sleep onset, while in a warm setting, local cooling to neck and back improved thermal comfort and sleep efficiency during the sleep period. Associated with this, the microclimate of the bed is particularly important for thermoregulation and sleep, for sleep onset and protection of sleep stage structure (70–72). In their review of thermal environment and sleep quality, Lan et al. (70) found that an in-bed microclimate of around 30°C was most consistently associated with thermoneutrality for the sleeping human body, with relatively small variation across seasons and change in ambient temperatures. Various studies in adults have shown that the microclimate can be determined and indeed manipulated by types of mattresses (60, 61, 73–75), bed sheets (76), personal heating or cooling devices such as electric blankets or airflow devices (77–80) and clothing worn during sleep (46, 81). While environment conditions, bedding and the microclimate clearly influence body temperature and perspiration, there is limited research examining the thermal comfort of children within their normal sleeping environments.

Thermoregulation and sleep for children with neurodevelopmental and chronic health conditions

The complex and interactive functions and effects of thermoregulation and sleep are especially important when considered in the contexts of everyday living. This is relevant for people of all ages, in all environments, with varied daily occupations, and with various health and medical conditions. For children with NDDs and CHCs, the dynamic functional relationships between these factors can be best understood when viewed in context of the framework of the ICF-CY. The following sections will discuss the interactions between

thermoregulation and sleep in relation to body structures and functions, activity and participation, environments and personal factors, as illustrated within the adapted model of the framework of the ICF-CY (**Figure 2**).

Children's body structures and functions affect their thermoregulation and sleep

With the understanding that central and peripheral interactions of the ANS involve all body structures and functions, and knowledge of the potent interaction of behavioral and autonomic thermoregulatory responses for thermal homeostasis and for sleep, it is clear that disturbance to structures (anatomy) or the functions (physiology) of body systems can have important implications for thermoregulation and sleep in children with NDDs and CHCs.

For children with NDDs, neurological impairment may occur at cortical and subcortical levels, with direct impact on thermoregulatory and sleep system functions. Children with neuro-motor conditions such as cerebral palsy commonly experience pain, circadian dysregulation and hyper-arousal in association with co-morbid epilepsy, and impairment of their respiratory, cardio-vascular, endocrine, gastro-intestinal, integumentary, musculo-skeletal and sensory functions, with impact on their ANS and associated thermoregulatory and sleep system functions (82, 83). Additionally, vision impairment is also common in this group (84, 85), impacting the SCN pathway of effects of light and dark on circadian functions of thermoregulation, and sleep and arousal. The functional relationships between hormonal, sympathetic and parasympathetic pathways mean that children with developmental conditions such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and fetal alcohol spectrum disorders (FASD) also have ANS dysfunction (86–88). Furthermore, pain and discomfort are common for these children, related to co-morbid anxiety and gastro-intestinal, musculo-skeletal or sensory regulation impairment, compounding disruption to the functional relationship between their thermoregulation and sleep (89).

Sleep disruption is also widely reported in children with CHCs, due to impairment of their body structures and functions, and, associated pain and discomfort, with effects on ANS function and rhythms of thermoregulation, thermal comfort and sleep. Given the importance of skin in thermoregulation, conditions which involve impairment of skin function are of particular interest. Sleep disruptions in children with eczema are commonly reported (90, 91), and the association between skin conditions, thermoregulation and sleep is well described by Gupta and Gupta (92). Sleep disturbance is also commonly reported in people with other conditions which affect skin and peripheral vascular functions, such as burns injury (93, 94), diabetes (95), obesity (96) and connective tissue disorders such as Ehlers Danlos syndrome (97). Individuals with childhood cancer are also reported to experience sleep difficulties (98, 99), with hyperarousal due to pain or anxiety. There is a logical relationship between the effects of these conditions on ANS, thermoregulatory functions and sleep.

There is potential for remediation of sleep and thermoregulation difficulties through intervention at the level of body structures and functions. Children who have NDDs and CHCs and need medications, procedures and hospitalization are likely to experience various levels of pain and anxiety, with effects on ANS and vasomotor functions, and subsequent impact on the patterns of core and peripheral temperature changes that are essential to circadian patterns of sleep and wake. With consideration of the individual responses to interventions, these effects could be mitigated by consideration of the timing and dosage of medications (effects on pain and anxiety; effects on core and proximal temperatures; effects on distal vasodilation) and consideration of timing of medical appointments and procedures. Furthermore, changes in environmental conditions, and types and timing of activities may moderate the physiological functions and responses at the level of the ANS, with impact on thermoregulatory effects on sleep, as discussed below.

Children's activity and participation affect thermoregulation and sleep

The timing and rhythms of activities and behaviors play an important part in circadian biological function, with interactions that affect and are affected by thermoregulation and sleep. van den Heuvel et al. (42) confirmed the importance of regularity in bedtime time and demonstrated that physiological sleep preparedness (i.e., distal vasodilation, with rise in T_{distal}, rise in DPG, drop in T_{core}) was associated with habitual activities for sleep onset. In contrast, when activities associated with sleep onset varied, distal vasodilation was attenuated. Supporting this, Martinez-Nicolas et al. (100) showed that people with the highest contrast between their day and night factors of activity, body position and light exposure had more marked circadian rhythms of T_{distal} and sleep. The authors postulated that intensifying the contrast between day and night lifestyle factors may enhance the rhythm of the circadian system. It is notable that pre-sleep activities (anticipating sleep, assuming supine position, cognitive and physical relaxation, switching off the light) can enhance distal vasodilation and promote sleep onset. It is common for children with NDDs and CHCs to experience disruptions to pre-sleep activities, due to the need for complex personal and medical care prior to sleep, as well as communication, cognitive, sensory or behavioral difficulties which impact their ability to anticipate sleep and

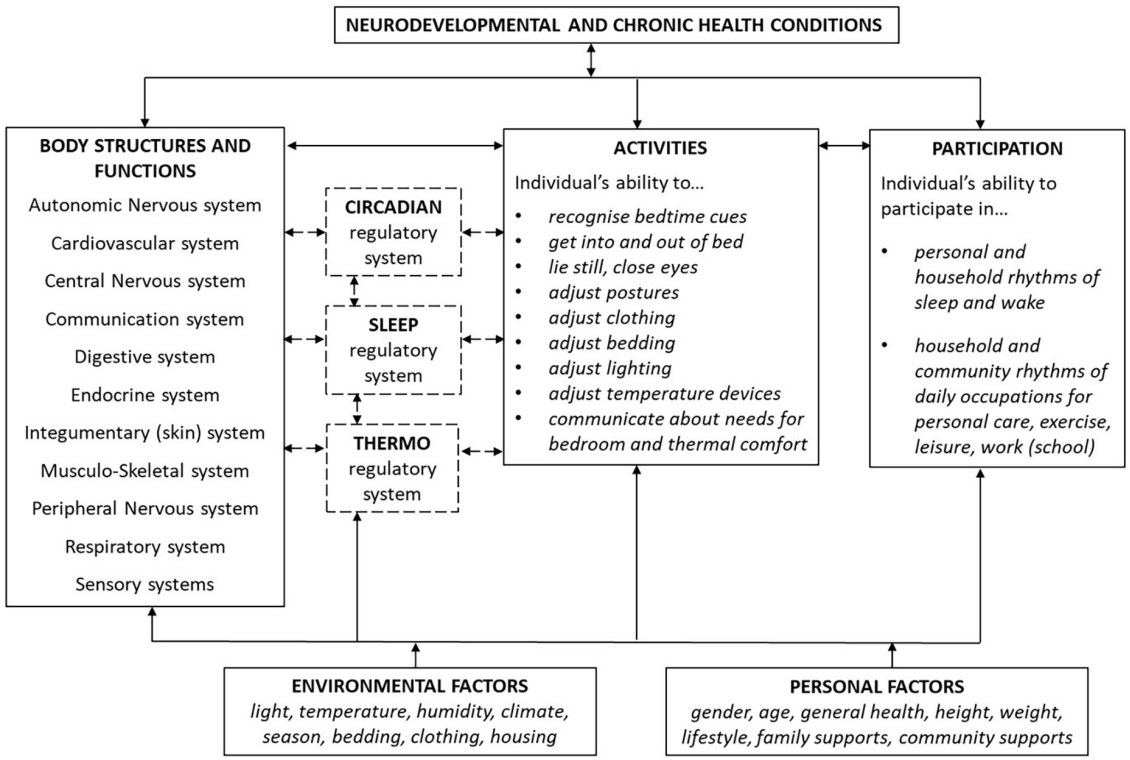

FIGURE 2
Thermoregulation and sleep in context of the ICF.

readily engage in suitable pre-sleep activities (101). There is a likely compounding effect to this, with a bidirectional relationship between parenting stress and inconsistent bedtime routines (102).

More specifically, circadian changes in motor activity promote temperature changes that are associated with patterns of sleep and vigilance (103). This is important when considering the effects of movement impairment on children with neuromotor conditions, who may have consistently limited or disrupted activity level across any 24-h period (104–106), as well as those with developmental conditions and associated dysregulation of their levels of activity and arousal behaviors (107, 108). For sleep onset, there is an additional important effect of postural changes on ANS and thermoregulatory responses when lying down, unloading the cardiovascular system and reducing sympathetic tone (8). Children with neuromotor conditions may need to be supported in an upright position during and following their feeding regime, or to assist with breathing throughout the sleep period (109, 110) creating an additional impediment to the vasomotor process that is essential to sleep onset and maintenance.

The timing and temperature of bathing or showering have been shown to influence the rhythms of thermoregulation and sleep. In particular, studies have shown that warm bath, shower or foot bath in the hour before sleep enhance distal vasodilation, with increased rate of change in DPG and reduced sleep onset latency (45). This is significant for families of children with NDDs and CHCs. Some may need to provide bathing in the mornings, for necessary morning hygiene, or need for a simpler evening routine or because of behavioral or sensory responses which cause them to be increasingly agitated or excited during bath or shower, and thus less able to calm and settled for sleep. Some may simply be unaware of the potentially powerful physiological effects of warm bath or shower before sleep and thus miss the benefits of this routine practice.

The type timing, volume, and stimulant consumption and micronutrient intake food and drink intake is known to directly influence sleep (111). Additionally, diet may also influence sleep though effects on body temperature regulation. Indeed, it is known that various foods have vasomotion effects, such as spicy foods, and those high in nitrates or caffeine (112, 113). Additionally, Fronczek et al. (6) showed that the temperature of food or drink may directly affect thermoregulation and vigilance. Children with NDDs and CHCs may have significant disruption to their intake of food and drink. Those with neuromotor conditions such as cerebral palsy may have disruption to their oral-motor and gastro-intestinal functions, needing modified diets, or overnight tube feeds (oro-gastric, naso-gastric or percutaneous endoscopic gastrostomy), with disturbance to the usual rhythms and timing of oral intake (114). Those

with neurodevelopmental conditions such as autism, ADHD or intellectual disabilities may have sensitivities or aversion to specific food types, being selective about or averse to tastes, textures and temperatures of food and drink (115). The type, amount, temperature and timing of food and drink intake may also be compromised for children with CHCs such as diabetes, and intolerances or allergies (116–118).

Children's environments affect thermoregulation and sleep

The seasonal effects of temperature, humidity and light on sleep onset, maintenance and architecture are widely reported, with variations according to geographical locations, age, occupations, gender, and health conditions. These factors interact with building design and the use of heaters, air-conditioners, fans and ventilation, with varied impact on temperature and humidity of the ambient sleep setting (70). More specifically, the creation of an approximately thermoneutral microclimate of the bed is increasingly recognized as particularly important for thermoregulation and sleep, for sleep onset and protection of sleep stage structure, as described above. With the interactive effect of the ambient room environment, the microclimate of the bed is affected by materials used in the mattress, pillows, bed linen and clothing, and by presence or absence of other bodies (people or pets) in the bed (54, 76, 119, 120). The increasingly diverse and sophisticated range of types and materials used for bedding and clothing, such as blankets or throws with timers and varied heating zones, and the development of "smart" materials such as phase change materials, reflects the prevailing knowledge about the importance of thermal comfort for sleep (121). Clothing insulation is a relevant component of behavioral thermoregulation for management of the sleep microclimate (120, 122). Depending on the season, cultural preferences and age, children may or may not wear clothing (pajamas) in bed. Clothing may be especially effective in reducing heat loss, but when used with bedcovers and in warm settings, can increase the risk of body overheating. The ability to choose and adjust bedding and clothing is an important, dynamic behavioral response toward thermoneutrality and thermal comfort, however, children with impairment of their movement, sensory or cognitive functions may have reduced or no capacity for this.

In addition to the above factors, it is important to consider the impact of timing, type and intensity of ambient light on the rhythms of sleep and thermoregulation. There is synchrony between the strength of circadian rhythmicity and the timing of evening dim light and morning bright light. Evening exposure to bright light will reduce evening sleep propensity, while morning exposure to bright light will increase evening sleep propensity (123), and fragmentation in the rhythms of light and dark exposure is associated with more fragmented sleep (124). Even low light levels during sleep, with eyes closed, can disrupt circadian responses (125). Through interactions at the SCN, light in the evening can reduce melatonin secretion, with associated slowing of rise in T_{distal} and delay in decline in T_{core} (126). In children, the deleterious effects on sleep of portable electronic devices in the bedroom setting are particularly notable (127). The disruptive effects of light on circadian functions of sleep and thermoregulation varies with children's age, as described in the review by Logan and McClung (128), of circadian changes across the lifespan.

The impacts of environmental factors on sleep and thermoregulation in children with NDDs and CHCs is important for many reasons. Children with mobility impairment may be unable to manage their environment (e.g., open or close windows, or adjust their bedding or clothing) as needed. Those with sensory and cognitive impairment may not register the sensation of thermal discomfort, and be unable to make the necessary behavioral adjustments to promote their thermal comfort. Moreover, those with conditions such as autism or ADHD may have sensory preferences which cause them to actively eschew the use of footwear before bedtime, with resulting cold feet and attenuation of the distal vasodilation which is essential to sleep onset. Those with communication impairment may be unable to communicate their comfort needs to their care providers so that the environment is adjusted to best suit them. Additionally, those with communication impairment may rely on electronic devices and use of screens for communication function at bedtime and possibly during occasions of night waking. Furthermore, the child's condition may require instruments or actions which compromise the optimal thermal environment. For some, it is necessary to maintain bedroom lighting, for safe provision of nighttime care and use of technology to support sleep (129). Children with movement or postural impairments require positioning equipment such as padded brackets or customized cushions to support their body shape (130), with the encompassing effect of foam and padding materials likely to cause a warmer microclimate in the bed. Those with incontinence may need moisture proof bedding for hygiene purposes (27), compromising attempts to use thermobalancing bedding and clothing materials for optimal management of the bed microclimate.

Children's personal factors affect thermoregulation and sleep

There are numerous reports of the effects of personal factors on children's sleep. Variously, these factors can be understood to also impact on thermoregulation, although the connection is rarely made clear. In a recent study of the impact of gender differences on the sleep of adolescents (131), it was shown that sleep quality and daytime dysfunction was significantly worse in girls than in boys. For girls, reduced sleep duration was particularly associated with consumption of hot drinks

before bedtime while for boys the key factor was time spent on technology. Body mass index (BMI) is also an important factor, with U-shaped relationships reported between BMI *z*-scores and poor sleep quality. These factors are found to be related to family and household function, with household "chaos" reported to be associated with less physical activity, less sleep and more screen time in households that have elevated stimulation, lack of structure and reduced predictability in activities and routines (132–134).

Children with NDDs and CHCs, and their families, are additionally vulnerable to the effects of personal factors, with impact on related factors which affect their sleep and thermoregulation. A particular concern is the effect of caring for a child with high support needs on caregiver health and wellbeing. Poor child sleep has a strong association with poor parental sleep, with associated impairment in physical and mental health, including an increased risk of cardiovascular and metabolic disease and a weakened immune system (135, 136).

TABLE 1 Case descriptions of children with neuromotor, developmental and chronic health conditions, illustrating the interactions of body structures and function for thermoregulation and sleep, with opportunities for therapeutic modification to activities and environments.

Child 1

***6 yo Sam has cerebral palsy**, with reflux, epilepsy and pain (related to muscle, joint and gastro-intestinal functions). He has severe movement impairment and cannot adjust his position, don/doff clothing or bedding or control his bedroom environment. He has a plastic mattress protector for incontinence. He has cushions in his bed, to support his body in a safe and comfortable position. He is restless and distressed before sleep. He cries out several times each night. His parents report that he is always hot and flushed, even on cold nights, with perspiration on his back and head. They are unsure how to help Sam be comfortable for sleep. They are very tired, and worried about his wellbeing.*

Body functions affected	Activities affected	Opportunities for remediation of T^{o} factors through activities and environments
ANS, CVS, CNS, DS, M-SS, PNS, RS, SS, VS	Get in/out of bed adjust postures adjust clothing adjust bedding adjust lighting adjust T^{o} devices	Activities – warm or tepid shower or bath before bedtime Environments – socks or slippers before bedtime – high heat-capacity mattress or overlay – vapor permeable mattress protector – clothing and bedding made of thermoregulation material – temperature/airflow devices with timer settings – temperature/airflow devices with voice activation

Child 2

***13 yo Hannah has autism**, with gastro-intestinal pain, and anxiety. She has difficulty recognizing body cues of hot and cold, and has an aversion to many textures. She cannot tolerate socks or slippers. She has irregular bedtimes. Once in bed she can take 2–3 h to get to sleep. During this time, she becomes restless and agitated. She uses her iPad for calming/distracting activities. Because of delayed sleep onset she sleeps until late morning and becomes agitated when prompted to get out of bed. She frequently misses school.*

Body functions affected	Activities affected	Opportunities for remediation of T^{o} factors through activities and environments
ANS, CVS, DS, ES, SS, VS	Recognize bedtime cues be calm before bedtime wear socks or slippers lie still, close eyes	Activities – warm or tepid shower or bath in the hour before bedtime – alternative to screens for calming/distraction before sleep Environments – heat pack in foot area of bed at bedtime – high heat capacity mattress or overlay – clothing and bedding made of thermoregulation material – open windows or doors, or cooling fans for airflow

Child 3

***8 yo Eva has eczema**. She frequently has flare-ups, causing her skin to feel hot and itchy. She finds this especially troublesome at night, and she frequently wakes and asks for parent attention. Her parents note that even when she doesn't wake or call out, she appears very restless during sleep. She is often distressed and moody in the mornings, and needs prompts and support to eat her breakfast and get ready in time for school. Her teachers comment that she seems tired and inattentive at school.*

Functions affected	Activities affected	Opportunities for remediation of T^{o} factors through activities and environments
ANS, CVS, IS	be calm before bedtime lie still, close eyes	Activities – tepid shower or bath in the hour before bedtime – relaxation techniques for calming before sleep Environments – socks before bedtime – high heat capacity mattress or overlay – clothing and bedding made of thermoregulation material – open windows or doors, or cooling fans for airflow

ANS, autonomic nervous system; CNS, central nervous system; CS, communication system; CVS, cardiovascular system; DS, digestive system; ES, endocrine system; IS, integumentary system; M-SS, musculo-skeletal system; PNS, peripheral nervous system; PVS, peripheral vascular system; RS, respiratory system; SS, sensory system; VS, vision system.

Discussion

The important interaction between sleep and thermoregulation is well known, as is the fact that children with NDDs and CHCs are more vulnerable than their peers to sleep disturbance and the associated deleterious effects. There is a dearth of studies reporting on thermoregulation and sleep in these groups. It is likely that this is because the questions have not been asked and studies not been done, rather than through absence of an important relationship. Despite the prevailing knowledge about the importance of distal temperatures in relation to sleep onset and maintenance, to our knowledge, there are no standardized or validated pediatric sleep questionnaires which ask about children's temperatures before and during the sleep period. In their recent overview of 70 pediatric sleep tools, Sen and Spruyt (137), describe an extensive range of conditions which are considered, including sleep disordered breathing, morning symptoms, nighttime awakenings, insomnia, excessive daytime sleepiness, daytime behavior, sleep habits and irregular/delayed sleep phase sleep routine, bedtime anxiety, morning tiredness, night arousals, sleep disordered breathing, and restlessness before and during sleep. They note that there is an emerging need for further research into children's sleep, with tools which assess sleep ecology, routines and hygiene, regularity, and treatment. Concerning such research, it is notable that the Children's Sleep Habits Questionnaire [CSHQ; (138)], one of the most widely used questionnaires to assess sleep problems in children, has one question which could pertain to body temperature regulation ("awakens screaming, sweating"), as part of the subscale of parasomnias. It does not include questions about children's observed patterns of body temperature or thermal comfort before and during the sleep period. Similarly, another widely used pediatric sleep questionnaire, the Sleep Disorders Scale for Children [SDSC; (139, 140)] includes 2 questions, specifically about perspiration before sleep and during sleep, to give a score relating to functions of sweating (reported as the domain SHY, sleep hyperhydrosis), with no option to provide information about patterns of skin temperatures or thermal comfort before or during sleep. Further to this, we note, with interest, one recent study (examining sleep hygiene factors in young children with and without ASD) which includes thermal comfort variables. For this study, Richdale and Schreck (141) developed a questionnaire which included a section on Thermal Sleep Environment description, with 16 items which asked about the child's typical bedding, sleep wear and sleep environment. Parents were asked about the use of extra stimuli to keep warm (e.g., hot water bottle, hat, socks), and if the child was too cold or hot at night in relation to warm-hot/cool-cold weather or summer/winter.

Given the clear relationship between sleep and thermoregulation, the vulnerability of children with NDDs and CHCs to difficulties with sleep and thermoregulation, and the known interplay between domains of body structure and function, activities and environments on sleep and thermoregulation, it is clear that there is broad scope for further relevant research, to guide possibly valuable clinical applications (**Table 1**).

Conclusion

The purpose of this translational review is to draw attention to the functional links between sleep and thermoregulation, and to highlight the important implications for the health and wellbeing of children with neurodevelopmental and CHCs. Currently, there are missing links between the knowledge that exists regarding the importance of various aspects of sleep (onset, maintenance, architecture, rhythms, subjective quality, daytime sleepiness) for diverse pediatric populations, and the knowledge that exists regarding thermoregulation and thermal comfort in relation to these same aspects of sleep. When viewed in context of body structures and functions, activities and participation, and environment, there is seemingly boundless scope for targeted research, to promote understanding about practical, ecological assessment of thermoregulatory functions, and related interventions to support good sleep in these vulnerable populations.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

SM and VB conceptualized, drafted, contributed, modeled the manuscript, and developed the models. CA and J-PL contributed to the manuscript. All authors have reviewed and approved the final draft.

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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.

Publisher's note

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Social-ecological considerations informing a universal screening strategy for sleep health in the community

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"Poor sleep health" (PSH), defined as reduced amount of sleep and non-restorative sleep, affects cognitive, social and emotional development. Evidence suggests an association of sleep deprivation and mental health problems; however, there are no universal concepts allowing a first-tier screening of PSH at a community level. The focus of this narrative review is to highlight the cultural context of the current medicalized approach to PSH and to suggest social ecological strategies informing new and holistic community-based screening concepts. We present two conceptual screening frameworks; a "medical" and a merged "social emotional wellbeing framework" and combine them utilizing the concept of "ecologies." The first framework proposes the incorporation of "sleep" in the interpretation of "vigilance" and "inappropriate" labeled behaviors. In the first framework, we provide a logic model for screening the myriad of presentations and possible root causes of sleep disturbances as a tool to assess daytime behaviors in context with PSH. In the second framework, we provide evidence that informs screening for "social emotional wellbeing" in the context of predictive factors, perpetuating factors and predispositions through different cultural perspectives. The distinct goals of both frameworks are to overcome training-biased unidirectional thinking and *a priori* medicalization of challenging, disruptive and/or disobedient behaviors. The latter has been explicitly informed by the critical discourse on colonization and its consequences, spearheaded by First Nations. Our "transcultural, transdisciplinary and transdiagnostic screening framework" may serve as a starting point from which adaptations of medical models could be developed to suit the purposes of holistic screening, diagnosis, and treatment of complex childhood presentations in different cultural contexts.

KEYWORDS

community health, multi-professional team, public health priority, iatrogenic harm, medical anthropology

Sleep health and the need for a community based screening concept

Sleep is essential for one's health and well-being and is at a lifetime maximum during childhood. Conversely, poor sleep health (PSH), defined as a reduced amount of sleep and poor quality of non-restorative sleep, are increasingly common in modern society. Insufficient and/or suboptimal sleep is an emerging public health issue (1). Large epidemiological studies consistently show an association between sleep quality and duration with physiological health outcomes, such as obesity, diabetes, and cardiovascular disease (2) the foundations of which have been recognized in childhood. In the neuropsychological domain, sleep is also essential for academic performance, with meta-analyses confirming the detrimental impact of reduced sleep quality and duration on the ability to learn and subsequently impair academic performance in children and adolescents (3). PSH is a major contributor to reduced attention span (4), as well as slower reaction times, difficulty learning and consolidating memory, reduced capacity to emotionally and physically self-regulate, hyperactivity, risk-taking, and even aggression. It is worth noting that improving sleep health has a positive effect on all of these domains (5–7).

Sleep disturbances and mental health

Furthermore, neurodevelopmental disorders and mental health disorders are associated with a high prevalence of sleep disturbances and disorders. In the past decade, the prevalence for neurodevelopmental and mental health disorders has increased. For example, the most widespread neurodevelopmental disorder is attention deficit hyperactivity disorders (ADHD) which globally affects 7.2% of children and adolescents under the age of 18, and 2.5% of adults (8–10); however, depending on where the study has been conducted, the rates for adults may reach up to 8.1% (11) and 4.4% (12). Similarly, prevalence rates of autism spectrum disorder (ASD) fluctuate between 3.0–11.6% in Europe, and 1.6–18.9% in Asia, respectively, while data from many countries and/or continents, which may not offer nationwide sub-specialized medicine, are missing, e.g., Africa (13, 14).

A transcultural, transdisciplinary, and transdiagnostic approach for a community-based screening concept

Families often conceptualize their child's development, academic difficulties, and poor learning outcomes as medical issues and visit health care professionals for guidance. Thus, poor attention focus and related "*challenging, disruptive and/or disobedient behaviors*" and related concerns are the "medicalized" main complaints (15). However, with the increasing recognition of sleep as the modulating factor of health, there is a need to review sleep related concerns from a community-based and public health perspective. Moreover, publicly-funded pediatric sleep services are still not universally accessible across most high-income countries, such as Australia, Austria, and Canada, and the applicable sleep medicine related information often exceeds available second- or third-tier service-based knowledge (16). These shortcomings have been exacerbated by the COVID-19 pandemic, which led to disruptions in healthcare delivery and worsening mental and sleep health.

Screening for PSH offered at the community level is a strategy to leverage opportunities for early interventions, thus avoiding iatrogenic harm during unduly long wait times. As a first step to revise our current subspecialty-driven sleep medicine practices, we reviewed our traditional modes of service delivery with the goal to introduce a transcultural, transdisciplinary and transdiagnostic approach and to address PSH related concerns in context with basic recognizable patterns of daytime tiredness, affected wellbeing and restlessness at day and night time (16, 17).

In this concept paper, we are justifying the medical and socio-ecological background of this screening concept and review how transcultural, transdisciplinary, and transdiagnostic thinking may support the creation of an individualized, tailored assessment, and intervention framework.

The ecological aspects in sleep health: An overview

The concept of ecology has influenced Western culture for some time. The Oxford Dictionary defines ecology as the branch of biology that deals with the relations of organisms to one another and to their physical surroundings (18). Ecological theories such as Bronfenbrenner's ecological model (19) provide a framework from which observation and exploration can be used to understand the context of an individual's distinct development and interactions at various levels over time. Indeed, when conceptualizing health, based on the contributing factors to the health of the individual, and community, all aspects of social and emotional well-being must be taken into account and exploration of inequities must be considered from a position of *Cultural Humility* with ongoing reflective practices and an awareness of power imbalances (20). In the context of sleep health for children the integration of ecology is an opportunity to close existing gaps in the following aspects:

Child and family centeredness

The core question is how to best assist the needs of families and children with PSH in the community. As an example, in the context of ADHD, inattention, short- or long-term lack of focus and hypermotor-restlessness at day and/or night-time can have many etiologies and parents may describe these symptoms in their children's lives and in *their* terms (21, 22). Exploring daytime behaviors in association with PSH, in collaboration with the affected individual allows for a more *mutually* shared inclusive approach to behavioral sleep- and wake-medicine adding to the clinical gaze. Similar to the work of an athlete with a trainer or coach, understanding the *lived experiences* more in-depth provides insight into the predictive and perpetuating factors that contribute to their predispositions and dispositions (23). Predictive and perpetuating factors include multiple elements that are not restricted to physiological etiologies, but also include psychological, environmental, familial, psychosocial, and potentially genetic or epigenetic factors. Consequently, treatment becomes not only more individualized for these children, but also

more resourceful and efficient, as it considers the crucial areas affecting cognitive and social–emotional development, behavior, and general wellbeing, generally defined as judging life positively (24, 25). The ongoing discussion on how to implement individually meaningful outcome measures in daily practice is the advanced result of this discourse (26).

"Medicalized" vs. "observation-based" semiotics

The term "*attention*" is associated with "*performance against* an *a priori standard*," whereas the term "*vigilance*" (27) allows the notion of self-determined "*sustained attention*" and "*state of concentration on reaching an aim*"—a concept, which is from an ecological perspective more natural or ecologic. The medicalization of the initially observation-based descriptive vigilance concept has resulted in a variety of lab-based tests for its evaluation, such as the Mackworth clock test in 1948 (28–31). However, undertaking such vigilance tests is boring and they do not actively invite participation or attention, particularly not for children and adolescents (32). Therefore motivation, sleepiness, and capacity to attend may be compounding factors on the lab-based assessment of vigilance. Therefore, we suggest revisiting the concept of vigilance and using it in the Head suggested way: "*sustained attention*" and "*state of concentration on reaching an aim*." Similarly, the term "*restlessness*" has been medicalized and is associated by parents and professionals mainly with hypermotor-restlessness at daytime and might be missed as a cause of sleep disturbances if not explicitly explored (33). However, as daytime restlessness often presents jointly with nighttime restlessness and results in PSH, which again perpetuates daytime restlessness and cognitive and behavioral dysfunction (16), the exploration of observation-based nighttime restlessness (e.g., during falling asleep and in sleep) is crucial (16, 17).

Together, the observation-based descriptions of "*vigilance*" and "*hypermotor-restlessness during day and night time*," offer a novel conceptual observation-based exploratory framework to understand "*dysregulation*" or "*challenging, disruptive and/or disobedient*" sleep- and wake-behaviors (16, 32).

Pharmacological vs. collaborative "social ecology-informed" approach. The need for a collaborative approach is readily apparent in the care for children with ADHD

When seeking treatment for their child, parents of children living with ADHD report a positive effect of community-based support (34). Community-based support such as navigation help or coaching, contributes to the resilience of the family and highlights the importance of assistance and collaborative work to implement interventions *with* families rather than *on* families. We can subsume that the individual child's and family's experience must be understood in its community context or social ecology. In behavioral medicine, e.g., for the treatment of ADHD, (cognitive) behavioral therapy has already been developed and evaluated, and is recommended as a first line measure (Subcommittee on Attention-Deficit/Hyperactivity Disorder) (7). However, it is time-consuming and requires involved parties to adopt the understanding of and therefore, lived culture to accept the recommendations (21). The challenge in embarking in this process might explain the upward trend in drug prescriptions, despite the fact that individual physicians are often not convinced of medication effects and/or see medication practices as controversial (21, 35, 36). This trend, without adequate investigation of broader predictive and perpetuating factors, such as family culture and biopsychosocial factors or PSH, reflects an imminent crisis, which builds on solely medication based strategies (35, 37–39). In the context of the COVID-19 pandemic, this trend has already become reality and raises further concerns regarding medication focused interventions (40).

Technology vs. patient as co-participant approach

A major critique in Western medicine and medical training is their narrow focus (41, 42). Historically, the modern, medication-, or technology-centered medicine that we have all grown up with, was built on an in-depth cause-and-effect investigation (single-cause-and-single-effect). Modern medicine, with its foundation in autopsy research approach (i.e., focusing on anatomy and pathology), has been instrumental in creating the contemporary discourse of cause-and-effect-interactions, thus opening the floor for in-depth phenotyping and overcoming the concept of broad hermeneutic interpretations as Foucault describes "*In The Birth of the Clinic: An Archeology of Medical Perception*" (41). Therefore, similar to medications, which we perceive as a "fixing" strategy, data collection that describes symptoms with modern technology, e.g., electrophysiological information has been very much appreciated and thus, has become more prioritized over time. In sleep medicine, this resulted in polysomnography (PSG) focus to the detriment of a deeper discourse about other predisposing and contributing factors.

The modern technology-centered approach enforces the generation of model situations, which are often far from the reality of the lived experiences of individuals or even communities (25). Time and financial constraints in modern day clinical psychiatric practice compound these problems. As clinical scientists dealing with sleep issues, we see every day the restrictions that current clinical sleep health concepts reveal (25, 33, 43, 44). The limited success of sleep health campaigns, e.g., in school settings, might also be explained by their focus on discipline specific professional perspectives and their inability to resonate with lived experiences (43). In consequence, there is a need to transform the patient-as-object in examinations into a co-participant in care through effective co-constructed communication, interaction, and goal setting (25, 45)

Reciprocal communication to overcome boundaries of the norm

There is a need for concepts that support what the individually tailored assessment of what parents/caregivers or professionals in the medical or educational system see and define as the "norm" and/or exceeding the norm and how this informs patient/care provider interaction and goal setting. Whereas the various understandings of

"norms," are based on the very specific, individual background, education, and training culture in other words one's individual culture (23, 46, 47). The medical model is underpinned by a historical power discrepancy between the patient and medical professionals. The resulting power gradient fosters a paternalistic communication in a medico-centric model of care, e.g., the typical Anglo-American communication style, addressing patients with their first names, violating natural boundaries, and affecting goal setting and outcomes. Conversely, a patient-centered communication approach advocates for a reciprocal co-constructed patient-doctor understanding that does not need to fit into the "norm" (48) (pg. 744).

Reciprocal communication is very specific to each situation uniting the dimensions of communication and culture. We live in a symbolic world, shaped by culture. Clifford Geertz (1973, p. 89) (49) understands the concept of culture as symbols, knowledge, and attitudes, and defines culture as "*an historically transmitted pattern of meanings embodied in symbols, a system of inherited conceptions expressed in symbolic forms by means of which men communicate, perpetuate, and develop their knowledge about and attitudes toward life*." Thus, an individual has a personal identity (individuated self) as well as a sociocultural identity which includes ethnic, cultural, religious, spiritual, gender, age, relational, and other role conceptions (50). Recognizing the symbolic world of the other is especially important in mental health services where explorative and person centric interviewing are fundamental in opening new pathways to communication beyond the boundaries of the "norm."

An example of this is neglect of restless legs syndrome in vulnerable children is a modern parable for systemic errors in communication. Restless legs syndrome (RLS), is sensorimotor neurologic disorder causing PSH due to discomfort/pain urging to movements mainly of the legs. RLS is a well-recognized condition in pediatric and adult medicine. However, because the traditional diagnostic criteria are based on patient reported symptoms, RLS has been missed in children with neurodevelopmental conditions or mental health disorders until 2013, when the diagnostic criteria were expanded by descriptions obtained through behavioral observations (51) and reciprocal communication in history taking (25, 52). Another example of missed causes of PSH is the conundrum of restless sleep disorder (RSD), a major complaint of parents, for which we did not have an answer until 2018, when DelRosso and colleagues combined clinical in-depth observations and exploration of individual parental descriptions in junction with technical medicine (53, 54).

Integrating a medical and socio-ecologic framework in sleep assessments for children

The inclusive collaborative approach

In an attempt to overcome the traditional medicalized approach, we, as a large group of clinicians, in dialogue with Indigenous and non-Indigenous community-based partners, reviewed from a broader perspective why sleep health has not been recognized as a public health emergency and what is needed to implement a community based screening for PSH. Because of their wider holistic view of health and historical experiences of suffering and trauma, Canadian and Australian Indigenous models of health perception have informed and framed our clinical understanding. We are presenting first a medical logic model for screening PSH related causes and working out first line measures, and second how this can be implemented in the shared ecology and of experiences and environment, thus not perpetuating e factors within any presenting health problem.

The medical logic model, strengths, and limitations

First, we agreed that a visualized medically informed screening framework was of the utmost importance for making our clinical knowledge transparent and available. This model aims to overcome compartmentalization in the communities as well as in academic settings (16, 55, 56). Given the complexity of individual biopsychosocial circumstances, the first step was the re-set of categorical day and nighttime-related diagnoses (e.g., ADHD and insomnia, respectively) in equal relation. Combining them with functional diagnoses, which are usually observed first by parents/caregivers and allied health care professionals (e.g., vigilance, hyper-motor-restlessness, sensory dysfunctions, pain, and fatigue), and probable predictive factors recognized by the members of multi-professional community or university based teams was the next step. Figure 1A is a visual representation depicting the integration of categorical and functional diagnoses, taking into account etiologies and root causes. Figure 1B visualizes the dynamic interconnections between these areas.

Expanding the medical model by social ecology

To become a learning system, exploration of the culture of the patient/parents/caregivers has been suggested as an integral part of complex assessments as early as in the 1960s (59). In the context of a community-based screening concept for PSH in children, acknowledging the lived experience and ecology of the community is a navigational aid to expand and complement the medical paradigm. Here, the concept of social ecology might be the one offering a pragmatic solution, overcoming cultural barriers and supporting the investigation of root causes with a shared language based on observation and exploration—a form of "*transdisciplinary health*" approach suggested by Assmuth et al. (60). Arguably, in the context of PSH and "*challenging, disruptive, and/or disobedient behaviors*," the medical model could benefit from such an approach, in order to maximize the broader diagnostic perspective and not diagnose the child/adolescent based on a gap-based training culture. See Figures 1A,B below.

Learning from Indigenous people's ecology

As the failure in diagnosing RLS in vulnerable patients and RLS in otherwise not as vulnerable labeled children demonstrates, without considering the entire context and contributing factors, the current subspecialized urban Western diagnostic model may miss important information that can assist with the diagnosis. The failure to understand and implement these disparities is similar in context

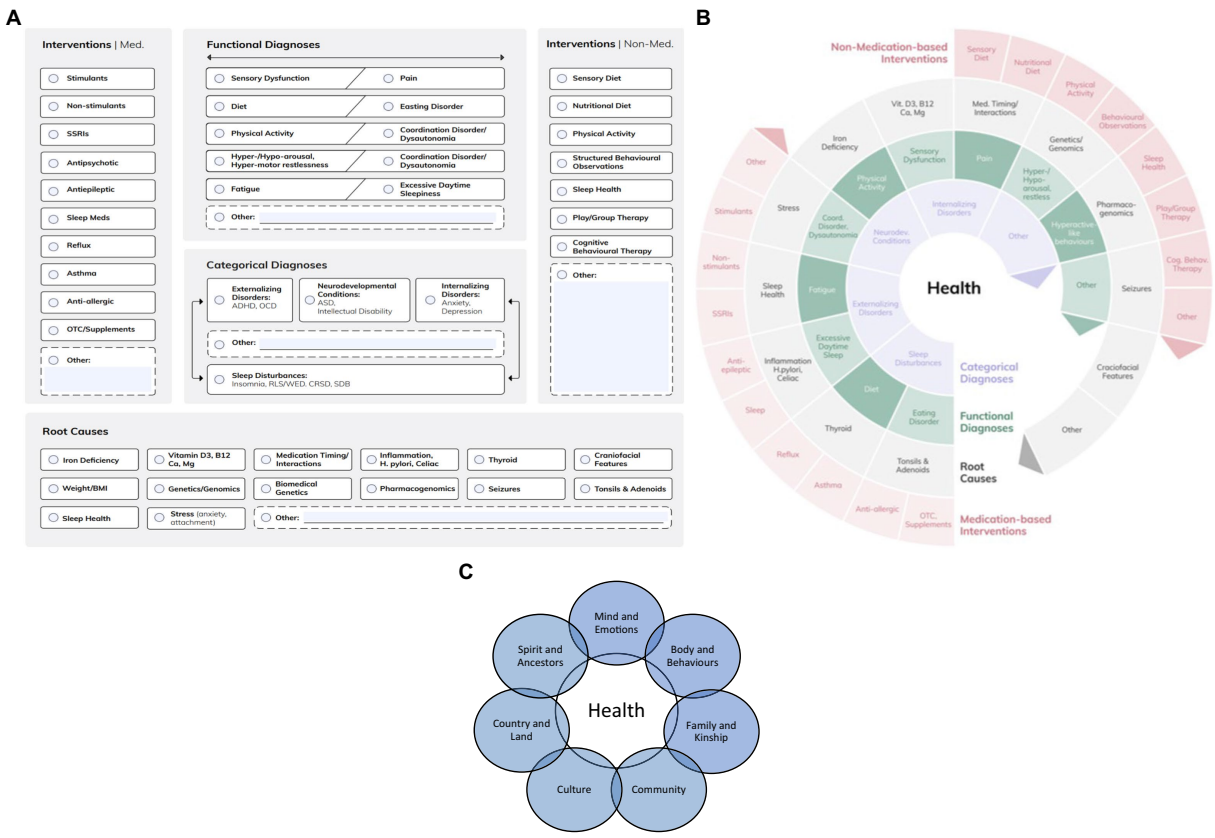

FIGURE 1
(A) The initial Medical Logic Model (16). **(B)** The Medical Logic Model in a wheel format for highlighting the changing and not yet explored interconnections with the permission of Kleanthes Publishers (57). **(C)** SEWB in Indigenous Australians. Adapted from SEWB framework (58).

to that of a vulnerable child with PHS presenting with unexplored, thus not understood behaviors, who based on a gap-based diagnostic model is only treated with medications (17, 25, 44). In developing a shared understanding based on reciprocal communication and acknowledging the ecology of the *lived experience*, there are lessons to be learned from the ongoing discourse with Indigenous peoples (61). The recent discussions surrounding health care and delivery in Indigenous peoples are perhaps driven by different political perspectives, a colonization-induced sense of indebtedness and considerations based on political correctness. However, social ecological concepts and transdisciplinary health do not only support indebtedness and considerations based on political correctness, but also highlights the need for the necessary change and expansion of subspecialized urban Western medical models, as it offers a personalized but neutral and comprehensive discourse on individual goals and outcome measures. For ease of expression, we will refer to Canada's Indigenous peoples (First Nations, Inuit, and Metis) and Australian Aboriginal and Torres Strait Islander populations as "*Indigenous Peoples*." Studies in countries with a shared history of European colonization and disconnection from culture and country, (such as the United States, Canada, Australia, and New Zealand), indicate an increased risk of poor overall health and poor sleep health specifically, for Indigenous peoples compared to their non-Indigenous peers (62). Dispossession from their land, sea, country, historical colonization and interruption of culture, all of which contribute to intergenerational trauma coupled with racism and systemic inequalities have significantly impacted and disrupted Indigenous peoples' capacity to maintain their health (63). Examination of the global literature on Indigenous perceptions of health and wellbeing, shows that concepts of overall well-being differ significantly between Indigenous and non-Indigenous populations (64).

Across Australia for example, Indigenous peoples share important spiritual and cultural beliefs that connect them to land, sea, and country with diverse cultural traditions (65) all of which contribute and are related to their physical and mental health (see Figure 1C below) often referred to as Social Emotional Wellbeing (SEWB) (58). Encompassing aspects of the physiological, psychological, environmental and cultural individual from a truly holistic perspective, is deemed as the *only way* to truly understand a problematic health presentation from an Indigenous' perspective (64, 66). Consequently, differences exist in interactions with the Indigenous view of health versus the Western healthcare system, which are discussed here.

The biopsychosocial and ecological perspective

The concept of acknowledging the lived experience and ecology of the community or family, respectively, as seen from the

Indigenous peoples' and/or Western perspective, is a neutral and advanced way to operationalize the necessary steps and can also support overcoming even prejudice-based perspectives in the medical model (67). If the medical model fails to integrate information from the biopsychosocial and ecological perspective, the mismatch engenders and represents key drivers of health inequity and health care delivery (64).

As behaviors and poor sleep health are interrelated and both are affected by our cultural background, we understand that the way to unravel the complexity of diverse perceptions and understandings in the context of sleep for people with different cultural backgrounds, is by applying the concepts of 'exploration and observation'. Thus, we suggest the biopsychosocial model, applied through the SEWB (58) lens to become an "interface" between Western and non-Western systems or various migrant cultures of knowing. This respectful and authentic incorporation of Indigenous or migrant cultural ways of knowing, could re-inform investigations, diagnoses and interventions and integrate Indigenous epistemologies (68). Australian Indigenous peoples describe this as *"Two ways of knowing,"* while Canadian Indigenous peoples describe this as *"Two eyed seeing"* (66). As such, this model, informed by Indigenous perspectives, may be useful when working with not only Indigenous but also non-Indigenous populations. A merged model, based on an integration of the concepts discussed above is presented in Figure 2.

Sleep health in context of diverse conceptualizations

Examples of lived sleep experiences

Cultural assumptions about sleep form part of the patient's ecology and have strong bidirectional relationships with vigilance and related behaviors. Thus, the awareness about sleep as the first line intervention in behavioral context, is acknowledged by multiple cultures as El Sheikh and co-authors have demonstrated in their impressive work (7, 69).

Sleep stories

Through "sleep stories" sourced directly from a selection of Yolŋu Elders, Arnhem Land Northern Territory, Australia (70), Indigenous communities conveyed that sleep is viewed as important for health and overall well-being, but also spiritually and *via* connection to land and country and kinship (70). Yolŋu Elders recognized that "bad" sleep resulted in "bad" health and wellbeing and impacted all aspects of functioning including behavior. Fatima et al. (71) confirmed that Australian Indigenous communities view sleep and sleep health from a biopsychosocial perspective and thus very differently compared to non-Indigenous culture. Similarly, Mohawk Elders consider changes in sleep practices and sleep health as a significant disruption in children's health and social well-being (72). In conclusion, sleep health cannot be extricated from general health or other elements that contribute to general health. Indeed, sleep disturbances in Indigenous Australian children are associated with obesity (73, 74), poorer academic performance (75), and emotional regulation and behavioral outcomes (76).

Dreams as part of divergent conceptualizations

Dreams, often excluded from medical studies of sleep (with the exception of psychiatry) are another domain which may bring together different perspectives with an explorative approach. Among various North American Indigenous communities, such as the Dene, sleep and dreaming are both valued because they play an important role in cultural epistemology and an individual's access to culturally valued knowledge (77). Reviewing conceptualizations, fascinatingly, Australian Indigenous peoples have also reported very different conceptualization of dreams and its impact on health (70), compared to non-Indigenous Australian families and children. While the meaning and importance of dreams is significant and related, they are different to how sleep health *per se* is seen and understood, subsequently impacting how sleep disturbances are approached in Indigenous children everywhere and have been subject not only for Australian Indigenous communities (70, 78), but universally (79) for thousands of years (7, 80). On the other hand, in Non-Indigenous contemporary psychology and Western theory of mind, dreams are rarely considered due to a range of historic-cultural reasons, such as psychology seeking to align itself with measurable medicalized outcomes and natural sciences identity (81).

Including "lived experiences" in the medical model

Recognizing our own personal and cultural schemas and how they contribute to our individuality, all of which then dictate our perceptions and thus actions, assists in recognizing those of the "other" (82). As explained above, given the social and emotional well-being framework perceived from the Indigenous perspective, treating children from traditional Indigenous or other backgrounds (e.g., refugees) with a purely medical model would not be embracing a mutual and shared language, and neglect to explore a child's broader ecological contributors. Learning from the Indigenous health conceptualization, we acknowledge that all vulnerable populations, such as children from migrant communities, who live or have lived as minorities in different surroundings, e.g., in industrialized countries, as trainees or workers, and similarly all authors of this concept paper, would profit from a merged medical and biopsychosocial, which considers the social ecology of sleep. Our proposed merged SEWB/medical logic models taking into account a holistic and transcultural approach is presented below in Figure 2.

How to operationalize? The 4P factors

The operationalization of the synthesized two models to a transcultural, transdisciplinary and transdiagnostic screening framework can be conducted with four contextual questions:

1/2. *Precipitating and presenting factors* (why did this child/family present NOW to the clinician and what are they presenting with);

3. Predisposing *factors* (what broad spectrum and biopsychosocial cultural factors, including how historical and ongoing health disparities impact and predispose this child to poor sleep health and subsequent daytime dysfunction in the vigilance and behavioral domain); and

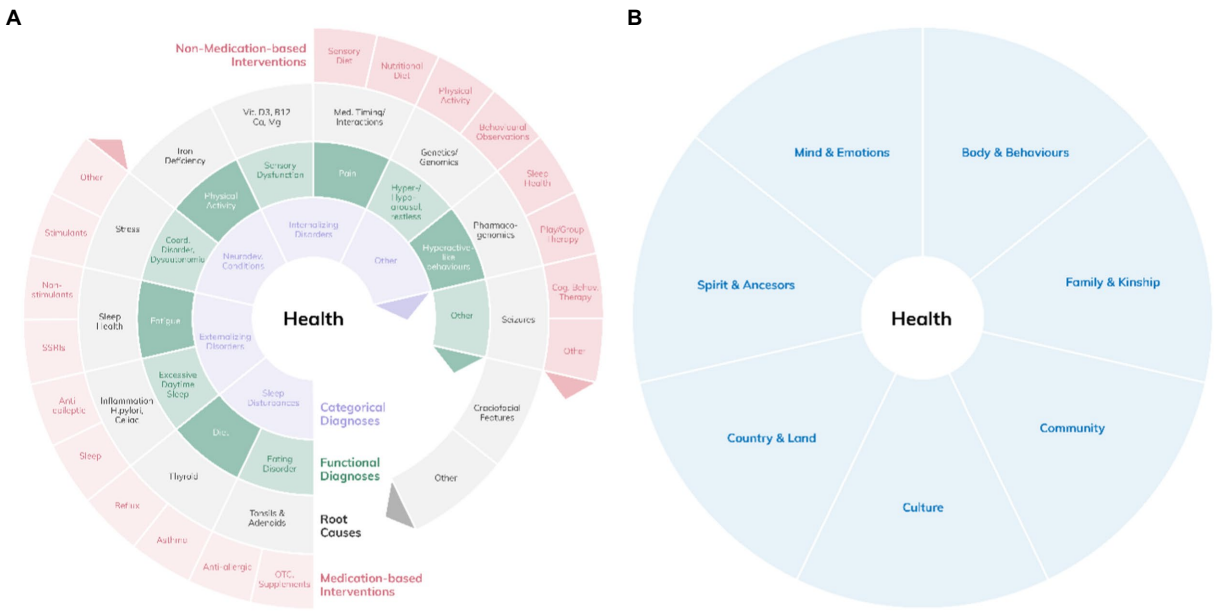

FIGURE 2
The merged Medical Logic **(A)** and SEWB models **(B)** in a transcultural, transdisciplinary and transdiagnostic screening framework. Note that the various domains of functional vs. categorical diagnoses, including sleep and wake behaviors or behavior-related diagnoses, as well as possible root causes and intervention options can be reviewed from multiple SEWB perspectives. Each perspective, e.g., "mind and emotions," "country and land," or "community" may change the way symptoms are perceived.

4. *Perpetuating* (what social ecological and cultural factors and are maintaining this poor sleep health and what epistemology informs this and is the lived experience taken into account; how long has this been going on, how significant is this now).

These four domains, comprehensively explored, offer a first joint transdisciplinary screening based high level understanding and allow a review of the functional or categorical diagnoses from multiple perspectives:

a. The *child's ecology*: at the individual level, physical and mental health contributors, considering the child's temperament, understanding what purpose the behaviors serve for the child and their etiology.
b. The *family unit's ecology:* understanding family dynamics and culture, parenting styles, parent–child interactions, limit sitting capacity in order to understand how much these factors contribute to the presenting behavioral and vigilance symptomology. Factors such as parental and child mental health, disability, socio-economic status, stress levels, social support, and education all interrelate many in a bidirectional manner.
c. The *society and community's ecology:* to which the child belongs-societal expectations and understanding and exploration of childhood behavior in multiple settings, education and school systems. Community attitudes and expectations of treatment for poor vigilance, encompassing current medical model, pharmacological intervention and urgency.

In our opinion, gathering or just being aware of this collateral information ensures considerate and comprehensive exploration and understanding of the etiology of a child's presentation; thus, not to miss systemic gaps with exclusive focus on one medical aspect of the challenge. Furthermore, it ensures diagnoses are not simply viewed through a western centric lens but with the view that the child's behavior maybe be influenced by their specific cultural and societal expectations. For example, inattentive behavior and its relationship with performance maybe be viewed very differently in cultures where the need for performance excellence is heterogeneous. Similarly, restless sleep may not necessarily be viewed as problematic and therefore relevant to a diagnosis for some cultures other than Modern Western Societies. In Figure 2, we propose this a merged, hence holistic model.

Pros and cons of an ecological model in sleep health

Before discussing the pros and cons, but in support of our argument, we should be aware that the definition of health has changed over time. In 1948, the World Health Organization, defined health as "*as a state of complete physical, mental and social well-being*." After a long discourse, in 1984, this definition was changed and included "work actively" for health: *"the extent to which an individual or group is able to realize aspirations and satisfy needs and to change or cope with the environment*." Eventually, the WHO Ottawa Charter (83) states that "*Health is created by caring for oneself and others, by being able to take decisions and have control over one's life circumstances, and by ensuring that the society one lives in creates conditions that allow the attainment of health by all its members*." Therefore, reviewing "*challenging, disruptive or disobedient behaviors*" in context with sleep health and vigilance as outcome measures utilizing the WHO Ottawa Charter, we needed an adaptable concept helping us to operationalize our knowledge within a broader framework. To discover from the patient's perspective how their immediate ecology impinges on their specific health and illness concerns in their individual living setting was the starting point for the merged

medical/SEWB model shown in Figure 2, rather than attempting to develop some general comprehensive competency guidelines.

The Pros

As a response to the listed shortcomings, the merged medical/SEWB model may serve as a clinical framework guide and can be applied with flexibility to cater for diverse populations with equally diverse pools of knowledge (84) in multi-professional teams. The development of such a mutually shared agenda requires for us, health care professionals, subspecialized or without any knowledge in sleep medicine, a logical screening model, to overcome constricted perspectives and disseminate the universal parts of subspecialist knowledge to the community and create a *community health agenda* with a community voice. While it is necessary to appreciate the complex social ecology of patients, it is not necessary, or even possible in a clinical context, to have a comprehensive appreciation of all the factors that affect their health and well-being. Thus, it was important for us to develop a visualized strategy to identify and review what is relevant to the patient. For structuring the approach to the patient, allowing a reflective structure and co-creation of a therapeutic strategy (26, 44, 85), the visualization used a doubled satellite/orbit concept (86). This visualization also reverses any patient profiling, Indigenous or not, based on a presumed set of cultural traits or norms, which actually would reinforce the status quo (87). This concept highlights the interchanging dimension of affecting social emotional wellbeing factors on the medical concepts and allows integrating the patient's perspective insightful in the center.

The Cons

Time allocations restrict medical services and will restrict the application of theoretical concepts in everyday clinical practice. While one is expected and encouraged to consider the *whole patient*, the need for a clinical measurable outcome and immersion in the management of significant illness has reduced the ability of the treating professional to afford the time to consider the whole patient (88). Shah and Mountain suggest the medical model "*is a process whereby, informed by the best available evidence, doctors [health professionals] advise on, coordinate or deliver interventions for health improvement*" (89) (p 119). This necessitates a multidisciplinary and possibly a case management approach. We are aware of these limitations and logistical difficulties with this approach. However, we are also aware that pediatric sleep health services cannot be provided solely by urban sub-specialists and diverse disciplines have to be integrated in, e.g., developmental, mental health, and complex care teams as part of the "health" team. This is particularly the case in community settings based on a concept of tier services and the stepped care model of care (90). The synthesized wheel models (see Figure 2) highlights the necessary fluency in the medical logic model for making it functional and "integratable" into the "health" team; however, makes it difficult to use for operationalization.

Epilogue

In this narrative, we justified why we advocate that the concept of ecology of lived experiences through a bio-psycho-sociocultural perspective should be applied in our clinical sleep medicine practice and why clinicians, who aim to diagnose, should step back and explore or screen possible contributing factors from various perspectives. In sleep medicine, structural limitations cause shortcomings and gaps in our service delivery, limiting access to this highly sub-specialized medical domain. We reviewed the shortcomings and gaps in the domain of sleep health for children and vulnerable populations, and responded to the identified challenges. Utilizing the example of "*challenging, disruptive and/or disobedient*" behaviors, we are suggesting a neutral observation-based explorative screening approach utilizing vigilance, as a reflection of poor sleep health and hyper-motor restless behaviors. The concept of *ecological systems theories* and the Indigenous "*Two ways of knowing*" and "*Two eyed seeing*," allow a neutral framework in which one can approach different understanding and perceptions in a neutral and respectful way within these changing frameworks. This has been overdue in the context of sleep health and sleep medicine as the change in the definition and notion of the term health, as defined by WHO, mirrors the shift in our understanding and perception, opening up the discussion on community and individual cultural background. This model allows the democratization of specialty knowledge while utilizing transdiagnostic methods, as collateral information is necessary, and multiple dimensions must be considered that view child development and mental health and associated poor sleep health from a wider perspective.

Author contributions

SB and OI conceptualized, drafted, contributed, and modeled the manuscript and developed the models. WM and TH contributed to the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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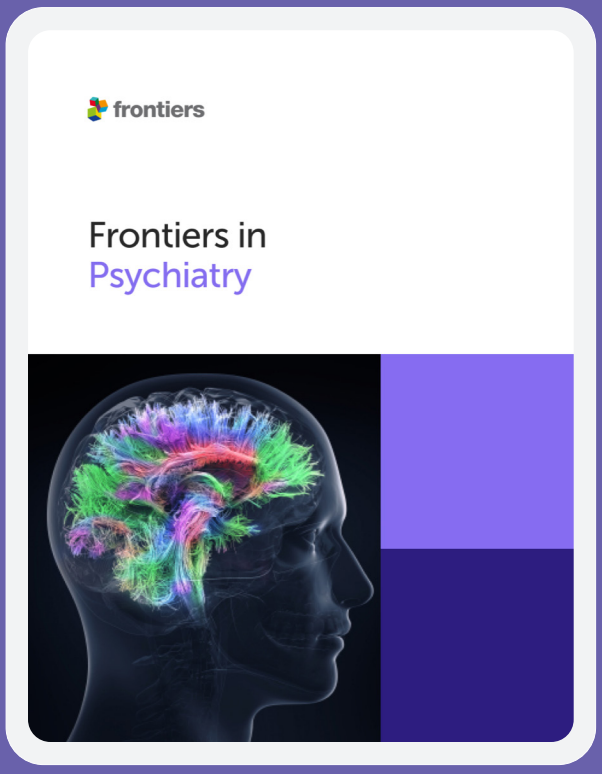

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