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Phenotyping sleep disturbances in ADHD and identifying harmonised outcome measures

A personalised precision medicine approach to disruptive behaviours

Osman S. Ipsiroglu[1,2,3] · Gerhard Klösch[3,4] · Mark Stein[5] · Sarah Blunden[6] · Serge Brand[7,8,9,10,11,12] · Stefan Clemens[13] · Samuele Cortese[14,15,16,17,18] · Alexander Dück[19] · Thomas Dye[20] · Paul Gringras[21] · Hans-Jürgen Kühle[22] · Kate Lawrence[23] · Michel Lecendreux[24] · Silvia Miano[25] · Julian Mollin[26] · Lino Nobili[27] · Judy Owens[28] · Parveer Kaur Pandher[1] · Dena Sadeghi-Bahmani[29] · Angelika Anita Schlarb[30] · Barbara Schneider[31] · Rosalia Silvestri[32] · Susan Smith[33] · Karen Spruyt[34] · Margaret Danielle Weiss[35]

Abstract

Attention deficit hyperactivity disorder (ADHD) is a widespread neurodevelopmental disorder. Currently, the diagnosis and treatment of ADHD in children and adolescents is primarily centred on daytime functioning and the associated impairment of academic performance, although disrupted and restless sleep have been frequently reported in individuals with ADHD. Further, it has been recognised that sleep disorders not only intensify existing ADHD symptoms but in some cases can also mimic ADHD symptoms in the paediatric population with primary sleep disorders. Under the title 'The blind spot: sleep as a child's right issue?', professionals from diverse disciplines, including medicine and social sciences as well as individuals with an interest in ADHD and sleep medicine, including laypeople, have initiated a unifying discourse. The objective of this discourse is to improve our understanding of the diagnosis and treatment of ADHD and disruptive behaviours and to develop personalised and precision medicine. Research has shown that the existing, primarily descriptive and categorical diagnostic systems do not capture the heterogeneous nature of youth with attentional and behavioural difficulties and the phenotypic expressions thereof, including nighttime behaviours and sleep. New strategies for clinical phenotyping and the exploration of patient-reported behaviours are necessary to expand our understanding and develop personalised treatment approaches. In this position paper, we outline gaps in the clinical care of ADHD and related sleep disturbances, review strategies for closing these gaps to meet the needs of individuals with ADHD, and suggest a roadmap for escaping the one-size-fits-all approach that has characterised ADHD treatment algorithms to date.

Keywords
Behavioural medicine · Restless legs syndrome · Periodic limb movements in sleep · Vigilance · Sleep disordered breathing

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Introduction

Sleep is a complex neurophysiologic function that involves almost all organ systems and affects both physical and psychological development, including cognition, emotion, behaviour, and social health [31, 60]. The processes of sleep are still not fully understood and are the subject of ongoing research, continually relativising the value of our gold standards with each investigation [7, 17] and highlighting

the value of environmental factors for perceptions and lifestyle situations [8]. Over the past three decades, multiple studies have highlighted the importance of sleep and have improved our understanding of physiological and clinical aspects on an ongoing basis. Additionally, many studies have demonstrated the intrinsic and bidirectional relationship of attention deficit hyperactivity disorder (ADHD) with sleep disturbances [43, 60]. Sleep disorders not only exacerbate existing ADHD symptoms but also mimic ADHD symptoms in children with primary sleep disorders. Implementation of sleep health measures, including a review of physical activity and dietary intake, are the very first steps before sleep disorders are investigated [36]. It is now well established that ADHD and sleep have a complex, close, and intertwined relationship, which impacts functional impairment and reveals ADHD to be a 24-hour disorder, with interventions aimed at children's sleep behaviour improving both sleep and ADHD-related symptoms [15, 58, 64, 71, 72]. Sleep disorders that are associated with ADHD include restless legs syndrome (RLS), restless sleep disorder (RSD), periodic/aperiodic movements of the limbs during sleep (PLMS), insomnia, and circadian sleep–wake rhythm disorders [43]. A strong clinical overlap exists between ADHD and RLS, with both following a circadian profile and presenting lower ferritin levels in affected persons. In line with this, experimental studies have demonstrated the modulating role of inflammation on iron homeostasis and dopamine transmission [59]. Further, recent descriptions of ADHD-related sleep disorders and sleep phenotypes (e.g. narcolepsy, obstructive sleep apnoea, periodic limb movements in sleep, and difficulty falling asleep/insomnia subtypes) prompt a reassessment of the role of sleep disturbances in ADHD [45]. This initiates a discussion on considering individual genetic variability, environmental factors, and lifestyle, i.e., the factors which define the pillars of precision medicine, as precision medicine offers complementary and/or alternative treatment options for affected children, adolescents, and adults. Personalised (older terminology) or precision medicine (newer terminology) is the description of '… a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' [19]. In the present manuscript, we use the term personalised precision medicine (PPM).

ADHD is a widespread disorder with increasing prevalence [1]. Evidence-based therapies include behavioural and pharmacological interventions. Numerous stimulant and nonstimulant medications have been approved, and their use is increasing [65]. However, there are concerns about inappropriate use, diversion, and abuse as well as marked variability in access, acceptability, and availability within regions and across countries. Comparisons between medication prescription recommendations in the United Kingdom (2014) and North America (USA) show that despite many similarities, European (and UK) guidelines are generally more conservative in their medication recommendations [46] but also that clinical practice varies across and within examined states or jurisdictions [57]. The effects of culture or lifestyle need to be acknowledged, not only with regard to the prescription practices of professionals but also considering other factors such as the amount of physical activity of affected individuals. The area of empirical investigation of sleep health procedures has only recently been subject to rigorous randomised clinical trials, showing that low-cost sleep-health-focused interventions delivered at the community level can be very effective for improving sleep disturbances among individuals with ADHD [11, 16, 22, 23, 66]. However, there are marked differences between and within jurisdictions in terms of the approaches to sleep disorders and access to common treatments such as melatonin or sleep hygiene.

This narrative review is the basis of a position paper that aims to develop a consensus approach to ADHD and to how sleep disorders should be investigated before the final diagnosis of ADHD is reached. We analyse the framework in which clinical work and research are conducted, and we explore the extent to which we may be able to overcome the gap between empirical and evidence-based knowledge and bridge the time gap until evidence-based knowledge is implemented in clinical practice.

Methods

'The blind spot: sleep as a child's right issue?' discourse (by OSI, SB, GK and BC) [55, 56] framed the goal of this narrative review to develop a shared understanding for the creation of an ADHD and SLEEP protocol (OI and MS) [26]. To support this goal, we invited a number of experts to develop a course (OSI, TD, GK, KS, RS and SS) and two 90-minute sessions (OSI, MS, AD, SCI, TD, ML, JM, KL, SM and AAS) to be presented at the International Pediatric Sleep Association (IPSA) congress in Glasgow in April 2024. Further, we invited discussants with an arms' length distance to the presentations to give feedback and review the presented concept and suggestions from an ADHD and sleep protocol perspective (SB, SCo, PG, LN, JO, DSB and MDW). This manuscript is based on extensive discussions of all listed coauthors. Due to time restrictions, there were changes in the final course and scientific session schedules and listed presenters. However, in order to achieve our shared goal, the initiated academic discussion continued. Further, at a pre-conference think-tank meeting in April 2024 the implementation of knowledge listed in the environmental scan for a stepped-care model was discussed in more detail, with additional co-authors who contributed conceptually to this paper joining the discussion (PG, HJK and PP).

The final version of the paper was written in Google Docs. The link was shared with all of the authors, thereby enabling them to edit and comment, and all authors engaged in the discussion based on the provided comments and critiques. The motto and aim of this collaborative effort were to develop a mutually shared language and to ultimately reach a consensus on the presented content in the article. This process helped to present the challenges experienced in clinical practice from the perspective of the two different academic communities—the 'pheno-

typers' and the 'interventionists'—using simplified language that is understandable and supportive for decision making by interested third-party persons. All coauthors reviewed the manuscript and signed the conflict of interest form for the publication.

Environmental scan

Positioning paediatric sleep medicine?

In the past, paediatric sleep medicine was long considered sub-specialist knowledge, with methodological dominance stemming from adult sleep medicine topics. Today, paediatric sleep medicine is currently at the interface between preventive medicine (public health), care medicine (in clinical practice), and various paediatric subspecialties such as developmental paediatrics, paediatric neurology, child and adolescent psychiatry, psychology and psychotherapy, health sciences, and organ-related paediatric sleep medicine. In contrast, the importance of sleep for the cognitive, emotional, and social development of the child is still underestimated, both in medical practice and in the minds of parents. Despite the efforts of sleep physicians to counteract such common practices and mindsets through publications, the paediatric sleep medicine community remains small, with the effect of it taking a long time to implement knowledge and establish structures for efficient patient care. The recognition of sleep disturbances in individuals with ADHD serves as an excellent example for this situation. Despite early recognition of the role of sleep disturbances in psychosocial development and despite the fact that some of the ADHD questions in ADHD questionnaires read like a description of RLS or RSD, sleep disorders as an entity were removed from the ADHD diagnostic criteria within the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1987, as evidence was not proven [3, 12]. In the meantime, European and American consensus guidelines recommend excluding sleep disturbances before diagnosing ADHD [2, 4]. However, there is a lack of guidance on how to do this, which has led to an increased reliance on referral medicine. Professionals direct patients to sleep centres, which results in waitlists of up to 1 year or more, depending on the capacity of the centre.

Advances in medicine

The COVID-19 pandemic has exposed multiple gaps in our existing healthcare systems, emphasising the importance of adopting a more holistic approach to the physical and psychological health of children and adolescents [41, 47]. From a behavioural perspective, the pandemic highlighted the need to develop more efficient structures for primary prevention and timely care in order to avoid secondary damage resulting from the 'blind spots' caused by missing knowledge dissemination [41, 51, 52]. Hence, such blind spots of professionals require a review of our knowledge-dissemination concepts. The question of where to place paediatric sleep medicine (e.g. in neurology, respirology or general paediatrics), reflects the confusion experienced by many professionals and health care managers. Sleep is a core physiological function and teaching paediatrics without integrating sleep into the curriculum can be considered as a failure to provide evidence-based treatment pervasive enough to be considered as a violation of the right to best practice health care for children.

Knowledge exchange and the role of professional societies

The rapid exchange of information, which has been accelerated by new digital media in the 21st century, has led to an increase in knowledge amongst all involved parties. However, knowledge alone is not enough: understanding facts and connections has become more important than ever. Therefore, it is imperative to establish connections between information from various disciplines; to engage in critical questioning as clinicians, researchers, affected individuals, and advocates; and to appropriately apply these insights in the best interests of the patients. The role of professional societies in collaboration with affected individuals and their advocacy groups becomes crucial for speeding up the dissemination process and implementing new knowledge to improve the day-to-day management of patients, including the transition processes to adulthood [48].

The consequences

The exclusion of sleep disorders from diagnostic interventions has resulted in the absence of a framework—a binding standard that is evaluated and improved step by step. In consequence, this indeterminate state has resulted in the fact that the methods used in the literature to record sleep disorders in patients with ADHD are variable. Therefore, due to a lack of criteria [43] along with the overlap between ADHD, RLS, RSD, and PLMS and complaints related to insomnia, sleep disturbances or disorders are approached incompletely or unsystematically [60, 70]. An example is that some medication trials involving stimulants do not account for possible underlying sleep disorders [74]. Even in the diagnosis of sleep-disordered breathing, a prevalent public health issue, a significant portion of individuals affected by sleep-disordered breathing remain undiagnosed or are misdiagnosed, despite the rising interest in sleep and awareness of sleep disorders, sleep research, and diagnostic practices [38]. There are many reasons for such blind spots existing in mainstream medicine; however, from a sleep-as-a-child's-right-issue perspective, the interpretation is that experts in professional societies discuss patient-related challenges without direct input or representation of the patients. When explored in an appropriate way, paediatric patients can express, articulate, and/or depict their discomforts and the dimensions of their suffering in an exemplary way through drawings illustrating sensations of restless legs. The lighthouse paper by Picchietti and colleagues [49] highlights this fact with quotations:

A 7-year-old boy: "They (my legs) like feel weird, and they want to kick."
An 8-year-old boy: "It's like my legs are wiggly and like (inaudible)."
A 9-year-old boy: "It's going to be hard to tell that this is like a bruise. I'm trying to stretch my legs out, my thighs out right here, so I'm going

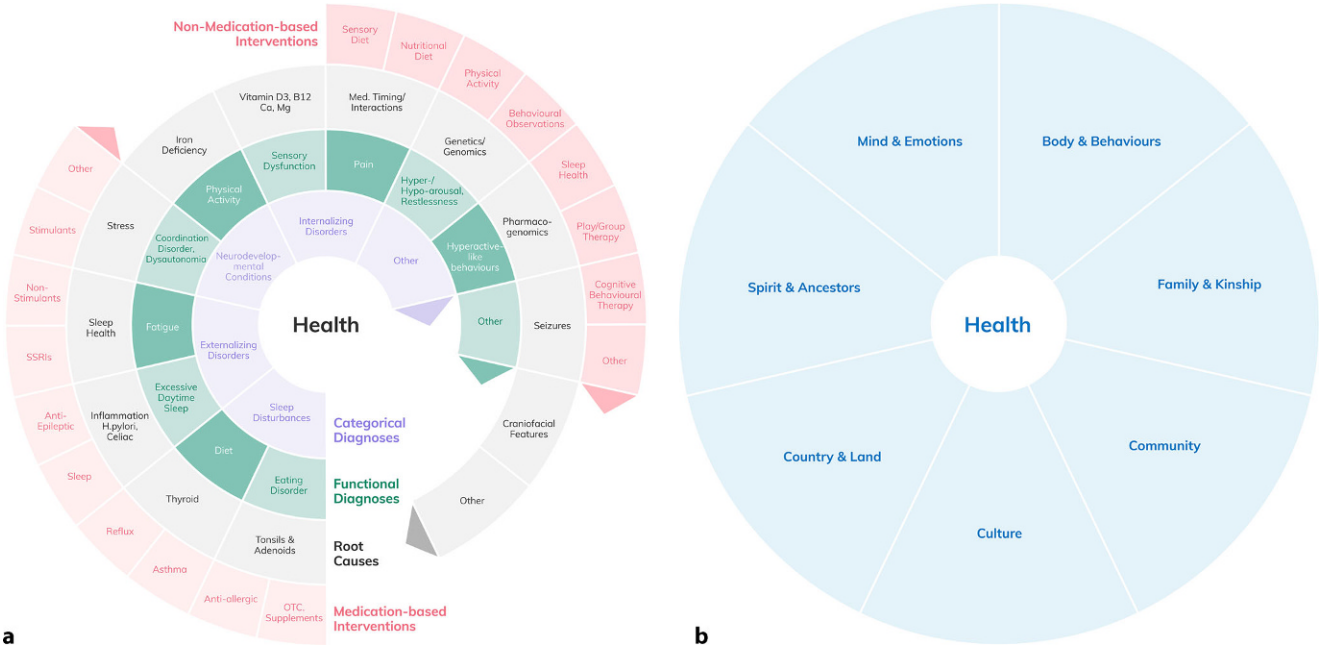

Fig. 1 ▲ Sleep and wake behaviours are influenced by various factors. **a** The causality-focused logic model reviewing the interconnections between sleep and wake behaviours [62] has been adapted in a synthesised wheel model, allowing medical symptoms to be approached from multiple perspectives [8]. The positions of the circles are variable relative to each other. By rotating each circle, segments can show the interactions and therapeutic effects that correspond to the individual case. The first three circles represent categorical diagnoses (first circle; e.g. possible neurodevelopmental, internalising, externalising, and sleep disorders), functional diagnoses (second circle; e.g. special diets or eating behaviour disorders), and root causes (third circle; e.g. iron deficiency) that may aggravate or alleviate clinical symptoms. **b** The social-emotional wellbeing model as applied by Indigenous peoples allows for the screening of predictive and perpetuating factors and predispositions through different cultural perspectives [8]

like this. I'm like trying to stretch my legs out but at the same time it's sort of hurting."…
A 15-year-old female: "My bed, and my pillow, and (inaudible). My head is usually somewhere around here. Sometimes at night I just have to flip my whole body around or else it just bugs me. So then I just sleep at the bottom of the bed for like a week, and then I can go back to sleeping like I'm supposed to. Feeling tired; (inaudible) blue eyes, and they're bloodshot because I didn't get any sleep; (inaudible) all over them. And my legs, they're like tingly, (inaudible) wavy. And my arms kind of do the same thing. So I just have to keep moving them, or else it just bugs me all night long, and then I definitely don't get any sleep."

Considering that we are discussing discomfort up to a pain-related condition and the impact of insufficient sleep on the cognitive, emotional, behavioural, and social development of an individual, we need to discuss how to target these blind spots and (a) how to explore our patients better for increasing their involvement and (b) how to introduce a transdiagnostic and transdisciplinary screening and diagnostic concept that might solve the currently experienced challenges.

The new perspective

A transdiagnostic and transdisciplinary prevention-focused approach

The traditional approach of referring all patients with ADHD to paediatric sleep medicine for evaluation is not very useful due to the low density of diagnostic sleep medicine centres. An environmental scan conducted among pan-Canadian sleep labs unveiled extended wait times of up to 1 year, even in metropolitan areas [73]. Therefore, as a clinical and research community, aside from enhancing training and promoting sleep medicine, we must agree on a step-by-step screening concept focused on the prevention-based aspect. This basic knowledge needs to be part of the foundational knowledge of all professionals dealing with children, adolescents, and young adults—including medical doctors, psychologists, therapists, social workers, social educators working in the community, and educational staff such as teachers at kindergarten, primary school, middle school, and high school. It should also extend to children and their families. While a critical review of curricula is one step, immediate measures should involve a consensus on human, particularly child-rights-based basics. This involves tailoring medicine to the specific needs of each individual and treating individual people rather than one categorical diagnosis.

Environmental factors or lifestyle

In order to understand the connection between ADHD and the factors that cause or influence ADHD—much like sleep, physical activity, and diet—and to enable a meaningful screening process, we need to review life circumstances. Sleep and wake behaviours are influenced by various factors. ◘ **Figure 1** [8] proposes

Table 1 An example for sleep health recommendations (adapted from Jan et al. [35]) at the community level of the suggested multilevel pyramidal service model. The focus is on promoting healthy living, and the condensed universal knowledge is disseminated in a manner that allows for unselective screening and review of first-line measures without overwhelming the addressee. This is achieved through the three options ("Yes, we already do this!", "Yes, we think this would help!", and "Not right now … This won't work!"), which are disseminated as universal knowledge (e.g. implementation of sleep health measures, review of physical activity). Note, the recommendations were reworked using plain, everyday words and short, simple sentences appropriate for a general public audience at grade six to eight reading level ('plain language')

In the list below, check off which habits you have and which ones you would like to have. In addition, check which habits you consider to be a challenge and therefore do not want to focus on at this time.

Sleep health habits	☺ **Yes, we already do this!**	☺☺ **Yes, we think this would help!**	☹ **Not right now … This won't work!**
Your child is exposed to sunshine (bright light) during the day. Exposing children to sunshine during the day, particularly in the morning, may help them to sleep better at night. Bright light helps the body to produce melatonin (a natural sleep hormone) that promotes better sleep and mood	☐	☐	☐
Your child's day has a balance of activity and rest. The planning of daily activities is important. Children benefit from routine structures and well-balanced patterns of both activity and rest during the day and night. Recognizing the contribution of daytime activities to sleep promotion is important	☐	☐	☐
Your child only takes short naps in the early afternoon. Daytime naps should be geared to the child's age and development. We recommend that a nap should never be taken after 3:00 pm	☐	☐	☐
As a general rule, your child engages is quiet activities only in the last hour prior to going to bed. Calming activities include well-structured routine behaviours such as quiet bath and listening to stories or lullabies. Vigorous activities may stimulate the child. It can take several hours for the child to relax. During a bath prior to bedtime, when the light is too bright, or too many toys are in the water, bathing may become exciting rather than calming. Playing together with siblings may be overly exciting. Story-telling should have a calming influence, but unfamiliar stories or books with the sounds of animals may be stimulating	☐	☐	☐
Your child eats/drinks only light healthy foods/beverages before going to bed. Your child does not eat food during the night. Overeating before bedtime can interfere with your child's sleep. Light healthy snacks such as apples, bananas, cheese or oatmeal are recommended. Avoid food and drinks with caffeine (hot chocolate, chocolate cookies, energy drinks, cola, etc.) 4 to 6 h before falling asleep. Allowing regular night mealtimes quickly teaches the body to wake up during the night because it "needs to be fed". If required, they may drink water	☐	☐	☐
You have a regular bedtime routine with your child including story time (see also social stories). A series of regular activities carried out in the same sequence (e.g. changing into pyjamas, brushing teeth, going to the toilette and turning off the lights) allows the body to prepare for going to sleep. Your bedtime routines should not be longer than 30 min. Encourage your child to complete part of the bedtime routine independently, e.g. let your child turn off the lights. This strengthens their sense of control and independence	☐	☐	☐
Your child's TV, DVD computer game (screen) time is limited. Screen time creates an excess of stimuli and should be avoided at night. However, a favourite and familiar DVD following dinner may be calming for some, but it could also result in overstimulation for others	☐	☐	☐
You recognise your child's cue for tiredness. Once your child becomes tired close to bedtime, they follow their (abbreviated) bedtime routine. Even slightly dozing off in the late afternoon or at nighttime can affect the quality of sleep	☐	☐	☐
You put your child to bed while drowsy but still awake in the same place where they sleep all night. Take your child to bed when they are awake and then leave the room before they fall asleep. Otherwise, your child will constantly associate falling asleep with your presence	☐	☐	☐
Your child is in bed by 7:00/8:00/9:00 pm depending on their age and needs	☐	☐	☐
Your child's bed is ONLY used for sleeping. You NEVER send your child to bed as punishment. This prevents the bed from becoming associated with thoughts and activities (e.g. homework and school) that prevent sleep. This only causes your child to associate the bed and the act of going to bed with punishment	☐	☐	☐
You let your child turn off the lights. Let your child turn off the lights by themselves. This strengthens their sense of control and independence	☐	☐	☐
You do not turn on a bright light if you console your child at night or if your child gets out of bed. A bright light tends to cause your child's body to wake up and influences thier inner clock. Additionally, your child may learn to associate light with comfort and consolation, and darkness with solitude and distress. The bedroom should be totally dark; however, some anxious children with fears of the dark might benefit from a dim night light. Try not to turn on any lights in your child's bedroom at night and try to eliminate all noise sources. *Bright light = time to wake up* *Dark = time to sleep*	☐	☐	☐
Do not smoke in your home because smoking disrupts your child's sleep	☐	☐	☐

a dynamic checklist model for reviewing the complexity of systems before arriving at a diagnosis of challenging or disruptive behaviours, such as ADHD, and starting medication-based therapeutic interventions [8, 31, 62]. The positions of the circles are variable relative to each other. By rotating each one, circle segments can show the interactions and therapeutic effects that correspond to the individual case. In the first circle, categorical diagnoses are listed, i.e. the possible neurodevelopmental, internalising, externalising, and sleep disorders. In the second circle containing functional diagnoses, functional disorders that are common are listed in the foreground (e.g. special diets or eating behaviour disorders). These may be strengthened or stabilised by triggers presented in the third circle, which contains root causes such as iron deficiency. This framework extends beyond the traditional cause–con sequence interconnection of western med icine and allows a more holistic appro-ach akin to the perspectives suggested by I ndigenous communities [8, 14, 33]. The beauty of this model lies in its acknowledgement of the patients' personal per spective and individual explanatory mod els, enabling all professions involved to r eview the patient in a patient-centred man ner from multiple perspectives.

From an individual daytime to a systemic day- and nighttime approach

Sleep health

In order to not miss the opportunity for early-onset interventions, screening for sleep disturbances and potential sleep disorders should ideally be offered at the community level (e.g. in clinical practice). Any child with a sleep disturbance and/or potential sleep disorder who is seen by a healthcare professional has the right to a clinical examination; however, before the examination, basic sleep health recommendations should be reviewed in order to avoid medicalisation of a lifestyle-induced sleep disturbance (see **Table 1**, which shows sleep health recommendations for children with neurodevelopmental disorders [35]). Not only sleep disorders but also poor sleep health—a reduced amount of sleep and/or non-restorative sleep—affects cognitive, emotional, behavioural, and social development, but the interpretation of "poor" depends on the cultural context. For example, is the afternoon nap ("siesta") of a 5 or 6-year-old appropriate or an expression of non-restorative sleep or a reduced amount of sleep? Therefore, the current medicalised approach to sleep health (e.g. afternoon naps are expressions of non-restorative or not enough sleep) needs to be reviewed from a social ecological perspective and cannot be informed by standards from countries which conduct their research in different ecological settings.

Behaviours

The understanding as explained above under 'Sleep health' proposes the integration of poor sleep health into the evaluation of ADHD-associated behaviours. However, what are ADHD-associated behaviours, and what is the relationship between ADHD symptoms and sleep? ADHD is the result of complex neurological, psychiatric, and interactional dysfunctions, and the processes of ADHD are the subject of ongoing research, as they are still not fully understood. Hyperkinesia, hypermotor restlessness, and/or hyper- or hypo-arousability (H-behaviours) can be interpreted as behaviours associated with ADHD or ADHD-like traits [5, 10, 18, 34, 53, 54, 61, 63, 67, 75] or, depending on one's training background, as indicators of irritability [18]. Further, from a sleep medicine perspective, the main differential diagnoses of ADHD are RLS and RSD, all presenting with H-behaviours, which have been associated with iron deficiency in human studies and in imaging and animal studies with central iron deficiency leading to restlessness [13, 42]. Despite this strong evidence of possible shared common biological roots, there is a general paucity of ADHD animal models that incorporate iron deficiency from RLS models [40, 59]. Therefore, we suggest a purely descriptive approach to ADHD-associated daytime behaviours using the concept of vigilance [30, 37] and H-behaviours [29, 32, 42, 60]. Vigilance is the ability of an individual to respond appropriately to environmental stimuli to ensure survival. The groundbreaking use of this concept was introduced by the British neurologist, Henry Head, in 1923 [21]. In the wild and typically for our ancestors, reduced vigilance led to being hunted by a predator, while, on the contrary, shifting attention swiftly from one stimulus to another enhanced the odds of detecting different predators in a timely and life-saving fashion. In humans, reduced vigilance can lead to ADHD-like behaviours, which have been perceived as inappropriate or challenging as they may lead to occupational injuries. In the school setting, both impaired vigilance and inappropriate responses to environmental stimuli (including interactions with teachers or peers) are of concern and are associated with non-anaemic iron deficiency, mainly central iron deficiency, allowing restlessness to be included as a 24/7 core characteristic [59].

Breathing

Sleep apnoea is observed in 1–10% of children with ADHD. Sleep-disordered breathing represents a spectrum that includes snoring, upper airway resistance syndrome, obstructive hypopneas, and obstructive (and central) apnoeas [44]. Epidemiological studies have shown significant differences in the factors of socioeconomic status, weight, and abnormalities in the area of the upper airways (nasal tract and pharynx area); however, sleep medicine studies using polysomnography for snoring or upper airway resistance syndrome provide few significant results for the benefit of the individual [68]. This suggests that either the outcome measures were not individualised and, thus, were too broad, and/or that higher education might result in better prevention and, consequently, in better health. Most importantly, today we know that sleep-related breathing disorders can cause chronic inflammation and lead to organ dysfunction, which significantly impairs the general condition of the affected individual [20, 24].

From screening to diagnosis—how to operationalise?

Our suggestion for phenotyping sleep disturbances in ADHD and identifying har-

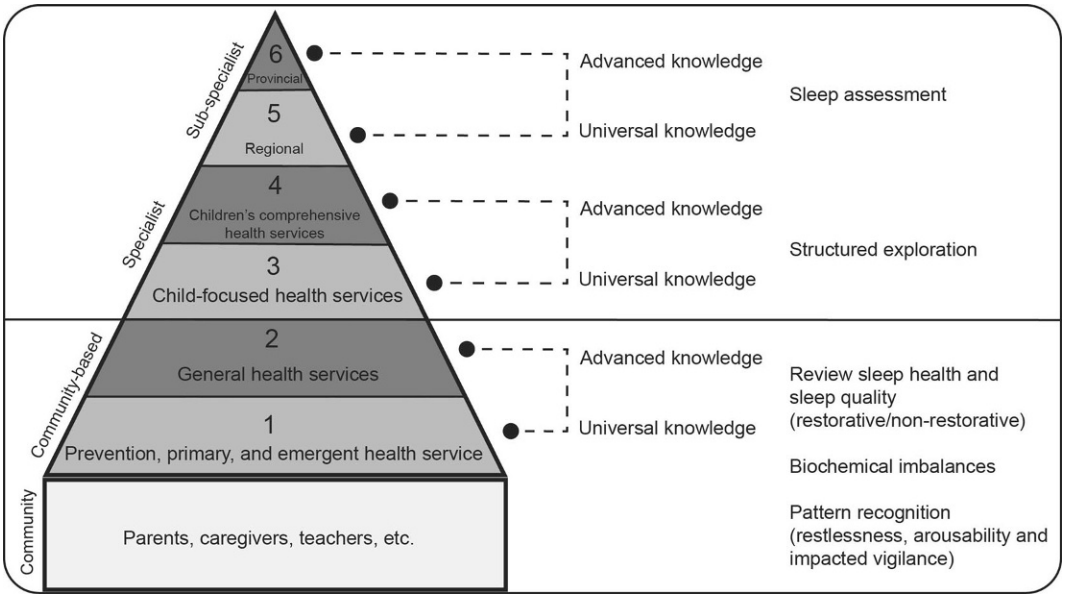

Fig. 2 ▲ Visualisation of the suggested multilevel pyramidal service model. At the community level, the focus is on pattern recognition as an unselective screening concept and review of first-line measures, which are disseminated as universal knowledge (e.g. implementation of sleep health measures and review of physical activity). At the level of community-based services, the focus is on selective screening and on an intervention in the case of a positive screening result (e.g. cognitive behavioural intervention for insomnia or iron supplementation for restlessness). At the specialist level, the focus is on the structured exploration of sleep–wake behaviours and differential diagnostic considerations as well as their potential causes, while at the sub-specialist level of sleep medicine, further investigations are conducted. The implementation of the suggested processes and the differentiation between universal and advanced knowledge will be the subject of the consensus discussions

monised outcome measures starts with general basic knowledge on sleep health and continues with a non-diagnostic description of functioning, restlessness, and breathing. This information prevents a categorical diagnosis of ADHD, before a complete description and review of sleep disorders which may contribute to an ADHD-like presentation and/or mimic ADHD. Alerting keywords in all three domains prompt screening questions and inform about the next steps. While vigilance prompts the question about the amount of sleep and restlessness before falling asleep and/or the question about non-restorative restless sleep, restlessness per se will lead to exploration of physical activity, diet, and investigation of biochemical imbalances (including iron, magnesium, essential fatty acids, and vitamin D status). First, this approach enhances the role of comprehensive bloodwork investigations for excluding RLS or RSD. Second, breathing-related symptoms such as snoring or heavy breathing and associated risk factors, such as allergies, which might affect sleep quality have to be reviewed and excluded before a primary ADHD diagnosis is made (◘ **Fig. 1**). The advantage of this suggestion is the diagnosis of possible causes of ADHD-like behaviours and avoidance of the diagnosis of secondary ADHD due to sleep disorders. The novelty of this suggestion is that the knowledge dissemination to parents and professionals working in the community with children, adolescents and/or young adults with ADHD will be structured by peer-reviewed information about potential causes and/or aggravating factors of ADHD. Such an approach has the potential to move the field away from a trial-and-error approach and towards a PPM approach, while also providing opportunities for prevention and informing treatment algorithms for combining and sequencing interventions throughout the lifespan. As initially stated, such an approach has been suggested by international bodies for some years [2, 4], but due to knowledge gaps and blind spots, a rounded protocol has not yet been worked out.

Discussion

A comprehensive approach to measuring improvement is central for assessing the effective outcome of any therapeutic intervention. Given the paucity of validated assessment tools, this may be a difficult and challenging process [43]. Moreover, ADHD symptoms and sleep-related perceptions are extremely variable in their clinical presentation and also etiologically heterogeneous; therefore, their change over time might be overlooked due to the missing involvement of the affected child or adolescent and/or due to parental fatigue and burn-out [39]. To set the stage for a constructive transdisciplinary and transdiagnostic approach which respects the significant impact of multiple factors, we have recently suggested a logic model [8, 62] and have adapted this logic model for transcultural application in various professional and lay settings (◘ **Fig. 1**). This approach enables participatory research and patient-oriented communication, as it broadens the assessment and allows screening of most common causes and/or aggravating factors, such as poor sleep,

lower physical activity patterns, and poor diet to name but a few, and this approach helps to conduct individualised precision medicine. On the flip side, such a thorough assessment might cause a major financial burden in terms of healthcare costs [6]. Consequently, the question arises of how to operationalise PPM without further limiting access to care or increasing the costs.

The in-depth characterisation of ADHD sleep phenotypes [45], the exploration of RLS from a patient perspective [9, 27, 50], and the familial dimension of iron deficiency and RLS-induced insomnia [27, 69] have opened up a new perspective on ADHD-associated challenging and/or disruptive behaviours and a window of opportunity for integrating sleep disorders in a structured manner. Are RLS or RSD comorbidities or, as suggested by Miano and colleagues, are they ADHD phenotypes [45]? Further, is treating a patient with ADHD with medication, without any exploration of triggering factors, appropriate? Can early-onset RLS mimic early-onset ADHD? Considering that the diagnosis of RLS and particularly painful RLS is also a blind spot in paediatric sleep–wake medicine, the treatment of children at the age of 3 or 4 years with stimulants and/or antipsychotics without an in-depth sleep investigation has to be viewed through a critical lens [25, 28].

The ideal global ADHD and sleep protocol consists of standardised and individualised behavioural outcome measures in an $n = 1$ study setting. Standardisation means harmonisation and aims for all ADHD trials to follow a consensus-based standard for making core outcome measures comparable. The main principle of an $n = 1$ approach is a protocol-based observation where the individual of interest is their own control. Single n or $n = 1$ exceeds the classic concept of case report or simple observation before and after the study but rather utilises rigorous clinical trial methodology. As soon as multiple numbers of patients are enrolled in the same n of 1 trial protocol, it may be possible to use meta-analysis to generate group-level estimates of treatment effectiveness, thus opening up a PPM approach to certain ADHD sleep phenotypes. Therefore, $n = 1$ studies can provide robust evidence, e.g. for a new intervention, in a timely fashion to inform care for an individual patient. Further, embedding $n = 1$ trials in patient registries that follow the principles of registry science (e.g. near-complete case coverage and standardised measurement of outcomes) opens up the potential for efficient implementation of high-quality n of 1 trials. The advantages of such n of 1 trials over observational before vs. after designs or case reports include (1) randomisation to multiple rounds of intervention/control conditions in order to monitor for temporal confounding; (2) the ability to launch placebo-controlled or comparative effectiveness trials with blinding of participants and outcome assessors where this is appropriate; and (3) prospective definition of standardised individual outcomes and their measurement, which on the one hand reduces the burden of an RCT and, most importantly, (4) increases the diversity of included cases. The main challenge and focus of our working group consisting of clinicians, scientists and affected laypersons is agreeing on the different information layers. **Figure 2** suggests a structured approach to screening, clinical assessment, and diagnosis as well as to knowledge dissemination. The aim of the pyramidal concept (broad basic information at the bottom and highly sub-specialised knowledge at the top) is to reduce inconsistencies in categorical diagnostic approaches and knowledge dissemination, which informs the public and broader professional opinion.

Conclusion

The suggested framework focuses on the recognition of poor sleep health via vigilance, restlessness at day and nighttime, and difficulty breathing as common symptoms of sleep disorders in individuals with ADHD or ADHD-like presentations. This approach allows us to review variable insufficient or inadequate sleep in an individual at any age, without medicalising sleep per se but also without overseeing sleep disorders. The novelty of the suggested prevention-focused concept lies in reviewing symptoms of concern step by step from a sleep health perspective and proposing a systematic approach to investigating not only sleep disturbances but also sleep disorders. This approach involves breaking down the review process into multiple small, circumscribed steps involving the patient, their parents and caregivers, and the expertise of various professionals. Again, given that sleep is a complex neurophysiological function that involves almost all organ systems, before sleep disorders are investigated, it is crucial to conduct differential diagnostic considerations at multiple levels to ensure that physiological interconnections are not missed. The ChildRight2Sleep context enables us to adapt and apply this transdiagnostic and transdisciplinary needs-oriented concept depending on the local, regional, or national health care framework in a flexible way. It also involves reviewing knowledge dissemination based on the target audience and discerning what is universal and what is advanced knowledge. How we apply this knowledge will be outlined by this working group as the next step.

Corresponding address

Osman S. Ipsiroglu
Interdisciplinary Sleep Program, Sleep/Wake-Behavior Clinic, Departments of Pediatrics & Psychiatry, University of British Columbia
Vancouver, Canada
oipsiroglu@bcchr.ca

Declarations

Conflict of interest. S. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, and from Healthcare Convention for educational activity on ADHD, and has received honoraria from Medice. Samuele Cortese, NIHR Research Professor (NIHR303122) is funded by the NIHR for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH-2022-DISEASE-07-03 from the European Research Executive Agency. O.S. Ipsiroglu, G. Klösch, M. Stein, S. Blunden, S. Brand, S. Clemens, A. Dück, T. Dye, P. Gringras, H.-J. Kühle, K. Lawrence, M. Lecendreux, S. Miano, J. Mollin, L. Nobili, J. Owens, P. Kaur Pandher, D. Sadeghi-Bahmani, A.A. Schlarb, B. Schneider, R. Silvestri, S. Smith, K. Spruyt, and M.D. Weiss declare that they have no competing interests.

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studies mentioned were in accordance with the ethical standards indicated in each case.

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Zusammenfassung

Phänotypisierung von Schlafstörungen bei ADHS und Identifizierung harmonisierter Behandlungsziele. Verhaltensstörungen und Präzisionsmedizin

Die Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHS) ist eine weit verbreitete Entwicklungsstörung. Ihre Diagnose und Behandlung konzentrierte sich bisher weitgehend auf die Tagessymptomatik. Das Schlafverhalten blieb dabei weitgehend unberücksichtigt, obwohl Betroffene immer wieder über Unruhe und nicht erholsamen Schlaf klagten. Allerdings wurde in Studien nachgewiesen, dass Schlafstörungen, in Verbindung mit einem bestimmten Lebensstil, bestehende ADHS-Symptome nicht nur intensivieren, sondern auch bei Kindern mit primären Schlafstörungen sogar ADHS-Symptome imitieren können. Unter dem Titel „Der blinde Fleck: Schlaf als Kinderrecht?" haben Fachleute aus unterschiedlichen Disziplinen von der Humanmedizin bis hin zu den Sozialwissenschaften sowie Personen mit Interesse an ADHS eine Diskussion initiiert, um die Lücken in unserem Verständnis von ADHS und deren Behandlung aufzuzeigen und im Sinne einer personalisierten Medizin zu schließen. Es wurde gezeigt, dass die aktuellen kategorialen Diagnosen von Verhaltensstörungen die enorme Fülle phänotypischer Ausprägungen nicht berücksichtigen, wodurch eine Beurteilung der diagnostischen Genauigkeit und die Wirksamkeit therapeutischer Ansätze erschwert werden. Um eine personalisierte Medizin bei der Diagnose und Therapie des ADHS zu gewährleisten, sind neue Ansätze im Rahmen der klinischen Phänotypisierung und bei der Beurteilung des Patientenverhaltens dringend notwendig. In diesem Positionspapier werden die Lücken in der klinischen Versorgung von ADHS-Patienten dargestellt und auf die Notwendigkeit der Berücksichtigung von Schlafstörungen hingewiesen, um in weiterer Folge Strategien zur Schließung der Lücken zwischen den Bedürfnissen von Personen mit ADHS und den aktuellen Behandlungsansätzen aufzuzeigen.

Schlüsselwörter
Verhaltensmedizin · Syndrom der unruhigen Beine · Periodische Bewegungen der Gliedmaßen im Schlaf und Wachzustand · Vigilanz · Schlafbezogene Atmungsstörungen

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Affiliations

[1] Interdisciplinary Sleep Program, Sleep/Wake-Behavior Clinic, Departments of Pediatrics & Psychiatry, University of British Columbia, Vancouver, Canada

[2] Department of Pediatrics, Medical University of Vienna, Vienna, Austria

[3] Institute for Sleep and Wake Research, Vienna, Austria

[4] Department of Neurology, Medical University of Vienna, Vienna, Austria

[5] ADHD and Related Disorders Program, Seattle Children's Hospital, University of Washington, Seattle, USA

[6] Appleton Institute of Behavioural Science, CQUniversity Australia, Adelaide Campus, Monash University, Melbourne, Australia

[7] Center of Affective, Stress and Sleep Disorders (ZASS), Psychiatric Clinics of the University of Basel, University of Basel, Basel, Switzerland

[8] Division of Sport Science and Psychosocial Health, Department of Sport, Exercise, and Health, Department of Medicine, University of Basel, Basel, Switzerland

[9] Substance Abuse Prevention Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

[10] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

[11] Center for Disaster Psychiatry and Disaster Psychology, Centre of Competence for Military and Disaster Medicine, Swiss Armed Forces, Basel, Switzerland

[12] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[13] Department of Physiology, East Carolina University, Greenville, USA

[14] Centre for Innovation in Mental Health, School of Psychology, Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

[15] Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

[16] Solent NHS Trust, Southampton, UK

[17] Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York City, USA

[18] DiMePRe-J-Department of Precision and Rigenerative Medicine-Jonic Area, University of Bari "Aldo Moro", Bari, Italy

[19] Senior Physician, Department of Child & Adolescent Psychiatry and Neurology, University Medical Center, Rostock, Germany

[20] Division of Neurology, Department of Pediatrics, University of Cincinnati, Cincinnati, USA

[21] King's College London and Evelina Children's Hospital, St Thomas' Hospital, London, UK

[22] Giessen, Germany

[23] Psychology, School of Allied Health & Life Sciences, St Mary's University, Twickenham, London, UK

[24] University Hospital, Robert-Debré, Paris, France

[25] Neurocenter of Southern Switzerland, Faculty of Biomedical Sciences, Università della Svizzera Italiana | Sleep Medicine Unit, Ospedale Civico, Lugano, Switzerland

[26] Klinikum Westbrandenburg, Potsdam, Germany

[27] Child Neuropsychiatry UNit, Istituto Giannina Gaslini, Genova, Italy

[28] Sleep Medicine, Center for Pediatric Sleep Disorders, Department of Neurology, Children's Hospital Boston, Boston, USA

[29] Department of Psychology and Department of Epidemiology & Population Health, School of Medicine, Stanford University, Stanford, USA

[30] Department of Psychology, Bielefeld University, Bielefeld, Germany

[31] Sozialpädiatrisches Zentrum Landshut, Kinderkrankenhaus St. Marien gGmbH, Landshut, Germany

[32] Sleep Medicine Center, Neurophysiopathology and Movement Disorders Unit, Department of Clinical and Experimental Medicine, Messina University, Messina, Italy

[33] UNC Nutrition Research Institute, University of North Carolina at Chapel Hill, Chapel Hill, USA

[34] NeuroDiderot, Université Paris Cité, Paris, France

[35] Department of Child Psychiatry, Harvard University, Cambridge, USA