Improve the night, improve the day

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2020

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Chapter 1

General introduction

The field of pediatric oncology

Currently, there are 3.4 million children living in the Netherlands. Each year, approximately 600 of these children get diagnosed with cancer.[1] There is a large variety in survival between tumor types. Some brain tumors are still incurable, whereas 84% of children with a hematological malignancy survives. Overall, survival rates have improved immensely over the last decades and 5-year survival is now up to 79%.[2] Despite this increased survival rate, cancer remains one of the leading causes of mortality in children and adolescents.[3] Moreover, the higher survival rate is accompanied by an increased risk for adverse effects and a negative impact of cancer on quality of life. Adverse effects and chronic disorders are present in 62-98% of childhood cancer survivors,[4-6] and can impair physical functioning. This impairment includes, but is not limited to, impairment of the orthopedic (e.g. amputation), cardiac (e.g. cardiomyopathy), neurological (e.g. seizures), endocrine (e.g. hormone deficiencies) and reproductive system (e.g. fertility issues).[4-7] Additionally, sleep problems, fatigue and cognitive problems are prevalent in children with cancer, and can all limit the performance of daily activities.[6,8] Finally, though the majority of children proves to be resilient and well adjusted after battling cancer, about one third of children is at risk for psychosocial issues such as anxiety, depression and posttraumatic stress.[7,9]

Normal sleep development in children

As well as a state of rest, sleep is a state in which intense physiological and neurological activity occurs. Sleep is driven by two processes; the circadian process and the homeostatic process. The circadian process is the internal clock and directs the timing and duration of the daily sleep-wake pattern. This internal clock is affected by external cues or ´zeitgebers´ that synchronize the internal circadian rhythm to the environment. The most important zeitgeber is light, which is transmitted to the suprachiasmatic nucleus and regulates the production of melatonin. The circadian rhythm develops around 2-3 months of age, before this the infants' sleep schedule is mostly based on feeding times. The second process - the homeostatic process - drives the body to sleep when sleep debt accumulates and regulates the length and depth of sleep. Thus, where the circadian process provides information about the time of day, the homeostatic process provides information on the length and amount of prior sleep and wake.[10-12]

Normal sleep changes with age. Infants and younger children spend most of their day sleeping, while recommended sleep times decrease from 12-16 h at 4-12 months, to 8-10 h in adolescents.[13] The most drastic changes in sleep architecture occur during infancy, starting with the development of a circadian rhythm and recognizable sleep cycles around the age of 3 months. Sleep cycles are formed by alternating non rapid eye movement sleep, including slow-wave sleep (SWS); and rapid eye movement (REM) sleep, which is assumed to be a time for the brain to recuperate and learn from daytime experiences. As an infant matures, nighttime consolidation of sleep starts to occur and naps decrease. Though napping is also influenced by family routine, culture and school- or daycare schedules; across countries, most children give up a second nap by the age of 8 months. They give up napping in general by the age of 5 years. In the Netherlands school starts at age 4, which means napping occurs less frequently after children reach this age. By age 5, adult-like sleep architecture is developed: The proportion of REM-sleep decreases and sleep cycles gradually extend from 50 minutes in infants to 90 minutes in 5-year olds. During further childhood, nighttime awakening and the amount of SWS and REM latency (i.e. the amount of time between start of sleep and start of the first REM stage) decreases.[10-12]

Adolescence is an important childhood stage when it comes to sleep. During this stage the two processes involved in the regulation of sleep (i.e. the circadian process and the homeostatic process) undergo modifications. The circadian process makes for an increased tendency for later bedtimes, since the secretion of melatonin gets delayed. In the homeostatic process, there seems to be a slower accumulation of sleep debt. Thus both processes push the timing of sleep towards later hours, however, sleep *need* does not decrease. Moreover, social, academic and recreational activities add to a delayed sleep onset by increasing evening stimulation and screen time. With the unchanged wake times in the morning due to the demands of school, this leads to a more irregular sleep pattern where sleep duration on school days often falls short of the recommended time, and catch-up sleep occurs on weekends.[14,15]

Pediatric sleep disturbances and the daytime consequences

Sleep problems involve disturbances in quality, timing or amount of achieved sleep, which cause daytime problems. Overall, 25-50% of children experience a sleep problem at some point during their childhood.[11,16] The prevalence and typical nature of these sleep problems varies with the different developmental stages of childhood and can range from short term problems to a primary sleep disorder diagnosis. In younger children, behavioral sleep problems are common; around 30% has a problem with bedtime resistance and frequent nighttime awakenings.[11,16] Children of this age also experience problems with getting back to sleep when aroused at the end of a sleep cycle, when certain conditions are not met (e.g. presence of a parent). This is especially true during the peak of separation anxiety around the age of 18-24 months. With the increase of imagination and fantasy, nighttime fears and nightmares can also become problematic.[11] Adolescents face different challenges, since academic and social demands are in contrast with the normative tendency towards later sleep onset; 19-36% of adolescents gets an insufficient amount of sleep,[17,18] and 20-37% experiences a sleep problem or insomnia symptoms.[18-20] Five to 16% is diagnosed with delayed sleep phase disorder, in which case sleep onset is delayed by two or more hours beyond the socially acceptable bedtime.[16,20]

Sleep problems have many negative daytime consequences. The most recognized ones are daytime sleepiness and fatigue. Another one is worse emotional regulation, which can lead to increased stress, anxiety, irritability, depressive symptoms and even suicidality.[19,21-23] There is also an association with behavioral problems such as hyperactivity, inattention and impulsivity.[16,24] In adolescents, associations were found between sleep problems and risk taking behavior like drowsy driving and substance use.[16,19,20] Emotional- and behavioral problems seem to be both predictors and consequences of inadequate sleep in children.[25,26] Another daytime consequence is diminished cognitive performance, which can result in lower academic performance and learning difficulties.[16,22,27,28] Insufficient quality or quantity of sleep also has a bidirectional relation with physical aspects, such as adiposity,[23,29] and exacerbation of atopic conditions and pain.[18,22,30] Sleep difficulties of a child go beyond the individual and are associated with influences on family dynamics, with more heated arguments, more parental anger with the child or finding the child harder to care for, and worse parental general and emotional health.[22] Importantly, around one third of sleep problems tend to persist throughout later years,[31,32] therefore sleep problems and their consequences should be recognized at an early stage.

Pediatric sleep assessment

Several constructs can be distinguished in pediatric sleep assessment. We visualized the different constructs measured and the measurement methods that can be used (Figure 1); sleep quantity (e.g. minutes asleep and minutes awake during sleep time), sleep quality (e.g. disturbances in falling and staying asleep, behavioral and parenting aspects of sleep) and daytime sleep-related impairment (e.g. consequences

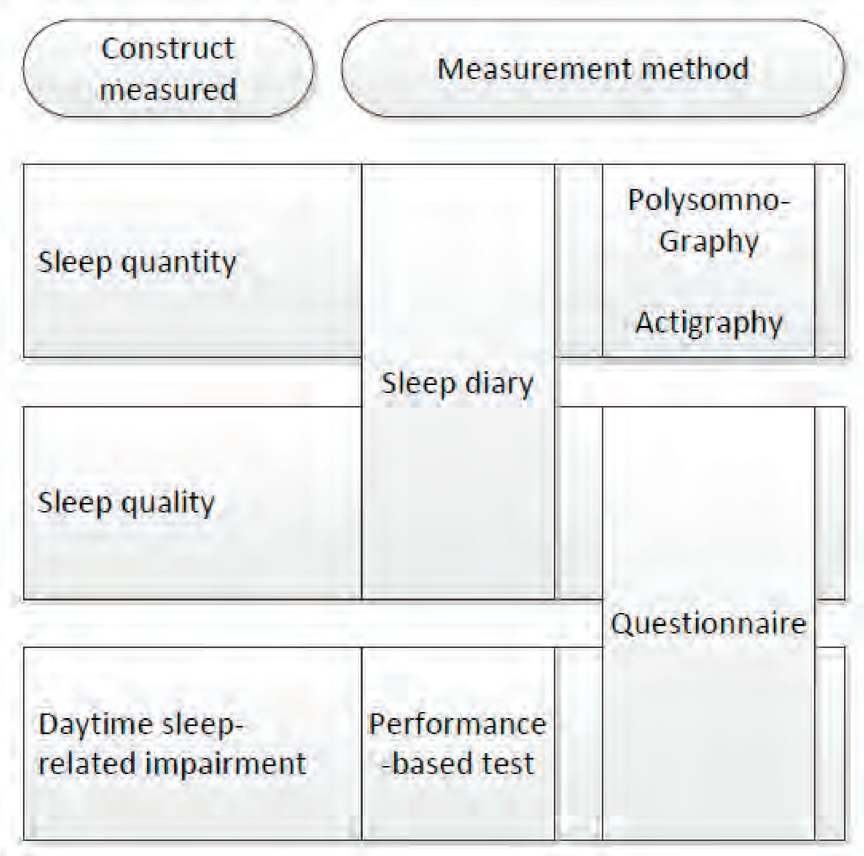

Figure 1 Constructs in sleep measurement

of inadequate sleep such as fatigue, emotional symptoms, behavioral problems and cognitive underperformance).[33] There is a limited correlation between self-reported sleep quality and quantity and objectively measured sleep quantity. These different measurement methods tend to complement each other.[34-36] Measurement methods can be generic, measuring sleep problems in general, or disease-specific, measuring sleep problems due to a specific sleep disorder.

The gold standard in sleep quantity assessment is polysomnography (PSG). It concurrently and continuously measures heart rate, respiratory movements, airflow, oxygen saturation and limb movements, through an electro-encephalogram, electro-oculogram and electro-myogram. PSG can differentiate sleep stages (sleep architecture), measures sleep quantity and provides the most detailed information for some clinical diagnoses. Children suspected of obstructive or central sleep apnea, nighttime seizures or narcolepsy are all indicated to undergo PSG.[37] One of the disadvantages is the need for assessment in a sleep laboratory, thus disrupting the natural sleep environment and schedule. Moreover, PSG is expensive, only suited for a limited timeframe of one to three nights, and burdensome for (young) children.[12,38] A good alternative to measure sleep quantity is actigraphy, where an accelerometer registers movement counts that are concurrently transformed to sleep and wake minutes through an algorithm.[39,40] Bed and wake times reported in sleep diaries are typically used to enhance validity of such an algorithm.[12] Actigraphy has good sleep-wake classification agreement compared to PSG (84% - 96%), and high sensitivity to identify PSG-based sleep minutes as sleep (88% - 97%).[41-44] Advantages are that measurement can take place at home, that it poses less burden on (young) children, is less costly and data collection is possible for long periods of time.[12,38] Although a lot of research using accelerometer-based sleep measurement is currently being performed, there is great variation in methodology and reference values in healthy children have yet to be established.

Sleep quality and daytime sleep-related impairment can both best be measured with questionnaires. Questionnaires can measure a wide range of self or parent-perceived aspects of sleep that cannot be captured by other measurement instruments. These aspects entail behavioral (e.g. bedtime resistance) and parenting (e.g. rules around bedtime) aspects of sleep quality, but also the burden on daytime functioning one experiences due to sleep problems, which is often leading in seeking help and treatment. Questionnaires exist in self-report and proxy-report versions. Proxy-reports are typically used for younger children below the age of 8 years, but are also important for sick children who cannot fill out the questions themselves. Parents (proxy-reports) and children (self-reports) do not always agree. Healthy children often sleep in a separate room from their parents and parents thus might not be aware of sleep problems.[45] Overall, they report less problems than their child does.[17,46] In contrast, parents with sleep problems of their own, sometimes also report worse sleep quality in their child.[47] When children sleep closer by or in their parents bed, like ill children often do, parents are more aware and tend to report more sleep problems.[45] Depending on the goal, a sleep diary can also be used to assess sleep quality. In contrast to a sleep questionnaire, which has a recall period of one to several weeks, a sleep diary measures sleep quality with a single question per night.[48]

A multitude of both generic and disease-specific sleep questionnaires is available, focusing on different aspects of sleep quality and daytime sleep-related impairment. Importantly, there is a lack of standardization, thus scores are often not comparable between questionnaires. This would be preferable, both to pool research results and for the use in clinical settings. Scores are also difficult to compare between populations, since normscores are often lacking.[12,38] Additionally, most currently available questionnaires either do not meet the psychometric requirements, or research into whether or not they meet the requirements is lacking.[49,50]

In 2004 the Patient-Reported Outcomes Measurement Information System (PROMIS®) initiative was started to standardize questionnaires measuring self-reported generic health outcomes. Two item banks including items on sleep quality - the Sleep Disturbance item bank - and daytime sleep-related impairment - the Sleep-Related Impairment item bank - were created. An item bank is a collection of items (questions) that all measure the same construct, in this case sleep disturbance and sleep-related impairment, respectively. The sleep item banks were developed using a modern psychometric method, called Item Response Theory (IRT). With IRT, every item is assessed for the level of 'difficulty' and gets placed on a metric ranging from low levels of the construct (e.g. no sleep disturbance), to a higher level of the construct (e.g. severe sleep disturbance). Because this linear metric is formed by the questions, IRT enables the use of subsets of items as fixed-length short forms or Computerized Adaptive Testing (CAT). With CAT, participants get an individualized set of the questions. After the first item, subsequent items are selected from the item bank tailored to the (sleep disturbance or sleep-related impairment) level of the individual. This precise and efficient measurement allows patients to respond to only a minimal number of relevant items, while still producing a reliable score.[33,51] Though the PROMIS initiative is off to a promising start, its validation and use has yet to be broadened to Dutch sleep item banks for children.

In addition to questionnaires, daytime sleep-related impairment can also be measured by performance-based tests.[27] In contrast to questionnaires, performance-based measures focus on only one aspect per test and are performed in a laboratory setting. The most widely known tests are incorporated in neurocognitive test batteries which include tests for attention, reaction time, verbal function, motor skills, memory and information processing.[52-54]

Sleep problems in pediatric oncology

Families dealing with cancer experience high levels of stress.[55-58] While stress peaks at the early stages of diagnosis and treatment, and decreases over time in part of the families, it does not normalize for a large proportion of children and parents.[57,59,60] Around 40% of parents and 18% of children still experiences clinical distress after completing cancer treatment.[55,60] Stress leads to both cognitive hyperarousal (e.g. overthinking) and hyperarousal of the central nervous system, and this can cause disturbed sleep.[61,62] In addition, there are multiple other reasons for children with cancer, as well as their parents, to be more at risk for sleep problems than their healthy peers.[8,55] Nighttime cancer and treatment effects such as pain and nausea can interrupt sleep, both for the children that experience the symptoms, and for the parents that have care demands.[63,64] Parent practices around sleep also tend to become more lenient during treatment.[65] In children, one of the key regulating structures of sleep can be damaged by a brain tumor or metastasis, or by cranial treatment: The arousal mechanism of the homeostatic process can be affected by damage to the hypothalamus, and the circadian process can be affected when cells in the suprachiasmatic nucleus are destroyed.[66] Since children with brain tumors are also prone to neurocognitive deficits and studies in other populations found sleep and cognitive functioning to be related,[27,67,68] studying this relation in children with a brain tumor could provide an intervention point to benefit neurocognitive functioning through sleep. Another important factor when it comes to sleep problems is the frequent hospitalization. The hospital environment is not suited for good sleep, disrupting sleep during admission more than at home. Families experience more frequent night awakenings, decreased sleep time and lower sleep quality,[69-71] due to the unfamiliar surroundings, loss of routine, bright light and generally high noise levels.[63,69,71] The adaptation of certain aspects of these surroundings, such as the high noise level, could possibly improve sleep and daytime functioning.

Stress, exhaustion due to poor sleep and the before mentioned negative emotional, behavioral, and cognitive daytime consequences, make coping with cancer and treatment (side) effects even more of a challenge. In addition, parents who sleep poorly feel more forgetful and less equipped to make proper medical decisions for their child.[64,72] Importantly, immune function also has a circadian rhythm. Since sleep deprivation is associated with higher inflammatory markers and worse antibody response to pathogens, adequate sleep promotes physical and psychological recovery from pain, injury and illness not only through better coping, but also through better immune function.[73,74]

Aims and outline of this thesis

The general aim of this thesis is to improve the measurement of sleep and the comparability of sleep outcomes, and identify risk factors for sleep problems in the field of pediatric oncology. This thesis therefore consists of two parts. **Part 1** is devoted to the improvement of pediatric sleep measurement. **Chapter 2, 3 and 4** report on the validation of the PROMIS sleep item banks in adolescents in order to obtain a psychometrically sound questionnaire for this age group. **Chapter 5** discusses the establishment of mean values for accelerometer outcomes in healthy children, through a meta-analysis. **Part 2** consists of research into the prevalence of and associations with sleep problems in two different pediatric oncology populations. **Chapter 6** reports on the relation of infusion pump alarms with sleep quality and quantity in children admitted for chemo or immunotherapy, and in their parents. **Chapter 7** discusses the relation between sleep problems and executive functioning in survivors of a pediatric brain tumor.

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