Improve the night, improve the day

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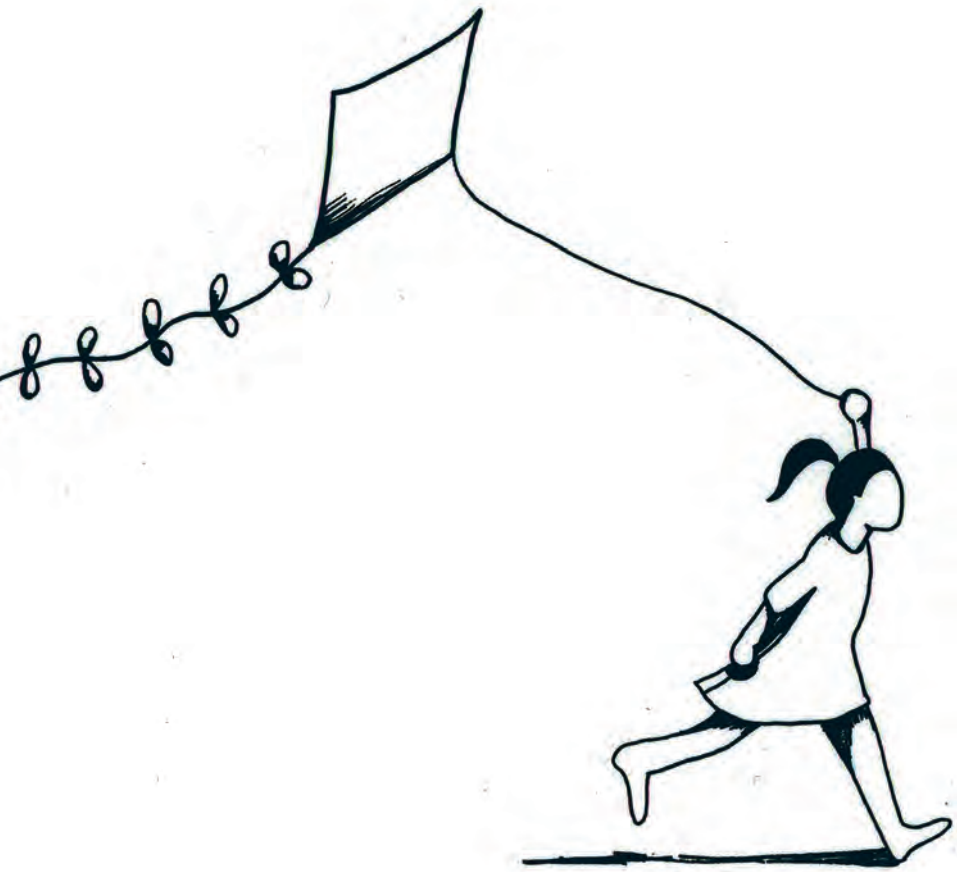
Chapter 9

Summary



The studies described in this thesis are conducted with two main aims. The first aim (part one of this thesis) was to improve the measurement of sleep, especially in adolescents. The second aim (part two) was to gain more insight into sleep in pediatric oncology.

The context of the studies in this thesis is illustrated in **chapter 1** (the introduction). Normal sleep and typical sleep problems change with age. These developmental changes should be taken into account when assessing sleep. Especially In the adolescent phase, sleep can become an issue when bedtimes are pushed towards later hours by biological changes and social/academic demands, and wake up times remain early due to school start times. The negative daytime consequences of sleep problems are extensive and can impact emotional and behavioral regulation, cognitive performance, physical aspects such as pain, and family dynamics. In chapter 1, a conceptual model for the different sleep constructs and methods to measure these is proposed. This thesis contains studies on sleep quantity (e.g. minutes spent asleep and awake), measured with accelerometers - also called actigraphy; sleep quality (e.g. disturbances in falling and staying asleep, and behavioral aspects of sleep), measured with questionnaires; and daytime sleep-related impairment (e.g. consequences of inadequate sleep), also measured with questionnaires. The current measurement instruments are far from perfect and therefore the first aim of this thesis was to improve the measurement of sleep. Specifically, the aim was to validate two sleep item banks in adolescents, since a properly validated questionnaire was not yet available for this age group. Another aim was to obtain reference values for accelerometer outcomes in healthy children, since there is great variation in methodology (e.g. a multitude of accelerometer types and brands is available) and overall reference values had yet to be established.

Good sleep is always important, but may become additionally challenged when a life-threating illness is diagnosed. Each year, approximately 600 Dutch children are diagnosed with cancer. Almost 80% of them survive the first 5 years, but the majority has to deal with adverse effects and chronic disorders, impairing physical and mental functioning and ultimately, lower quality of life. Among these adverse effects are sleep problems. Due to stress, cancer and treatment effects (e.g. pain, nausea) and damage to the regulating structures of sleep in the brain, patients and parents are at-risk for sleep problems. Moreover, during admission, environmental disturbances disrupt sleep. Based on previous research, infusion pump alarms seem to be most disruptive. Good sleep promotes physical and psychological recovery from illness, whereas the negative consequences of sleep disturbances challenge coping with cancer. The second aim of this thesis was therefore to increase insight into the

prevalence of and associations with sleep problems in pediatric oncology. Within the pediatric oncology population, focus was dual. On the one hand the relation between infusion pump alarms and sleep was studied in children admitted for chemo or immunotherapy, and in their parents. On the other hand the relation between sleep and executive functioning was investigated in survivors of a pediatric brain tumor, since they are at risk for problems in both domains.

Part 1 – Measuring sleep

Chapters 2, 3 and 4 report on the validation of the v1.0 PROMIS Sleep Disturbance and Sleep-Related Impairment item banks for adults, in adolescents. It was chosen to validate the PROMIS sleep item banks, since the PROMIS system is gaining international ground and developed item banks with a high methodological standard, using a modern psychometric method called item response theory (IRT). IRT enables computerized adaptive testing (CAT), which allows patients to respond to only a minimal number of relevant items, while still producing a reliable score.

First, content validity was studied in **chapter 2** by asking a community sample of adolescents (n = 24, 12-18 years), their parents (n = 7), and Dutch sleep experts (n = 6) to comment on the content of the item banks on paper, specifically the relevance and comprehensibility of the items. Two items of the Sleep Disturbance item bank were rephrased to make them more comprehensible for adolescents, but overall the content validity was assessed as sufficient by all three groups. The validation process was continued in **chapter 3** by evaluating structural validity through the performance of factor analyses on the item banks with the rephrased items instead of the original items. Factor analyses were performed on data of 958 high school students (11-19 years) and showed that both adult item banks measured multiple constructs in the adolescent sample, as opposed to the one construct they were intended to measure. The items that did represent a unidimensional construct in adolescents were identified through further analyses. The Sleep Disturbance item bank with 23 out of 27 items had better unidimensionality than the full item bank, but still just below recommended criteria. The Sleep-Related Impairment item bank with 11 out of 16 items did have sufficient unidimensionality. Further psychometric properties were investigated in **chapter 4**. We investigated structural validity by testing IRT assumptions and model fit; measurement invariance by performing differential item functioning analyses; performance as CAT; reliability by marginal reliability estimates and test-retest reliability; and construct validity by hypothesis testing. Data of a small adolescent sleep clinic sample (n = 33, 11-19 years) was added to data of

the high school students (n = 1013, 11-19 years) for this purpose. For the Sleep Disturbance-23, a consequence of the lack of unidimensionality was that further IRT analysis, including the CAT simulation, could not be performed. However, test-retest reliability and construct validity of this item bank were found to be sufficient. The Sleep-Related Impairment-11 did meet the IRT assumptions, and subsequently showed adequate CAT performance in a simulation. Construct validity and test-retest reliability were also found to be sufficient. Based on these results, the use of both adapted item banks in full form, and the use of the Sleep-Related Impairment-11 as CAT can be recommended in Dutch adolescents.

In **chapter 5**, focus shifted to the construct sleep quantity, measured with accelerometers. The aim was to report pediatric reference values and to examine the effect of age, sex, accelerometer placement site (e.g. wrist) and accelerometer type (piezoelectric or micro-electrical mechanical system) on these values. In a systematic review, mean accelerometer outcomes were pooled of 83 studies (n = 9068 participants) that reported wake after sleep onset, sleep efficiency (SE), total sleep time (TST) and/or sleep onset latency (SOL) in healthy children, calculated with the Sadeh-algorithm. This is the most widely used algorithm in children. Though the used methods in these studies were already partly standardized through strict inclusion criteria, methodological heterogeneity between the studies remained high and showed an accordingly high I^2 statistic in meta-analyses results. Meta-regression analyses revealed significant differences in TST and SOL between age groups and in the most reported outcome (SE) between accelerometers of the piezoelectric and micro-electrical mechanical system type. Due to the high heterogeneity and the significant differences between subgroups, the results of this meta-analysis cannot be recommended as default reference values, despite small confidence intervals. These values should only be used in case a study-specific control group is not available.

Part 2 – Sleep in pediatric oncology

The aim of **chapter 6** was to determine sleep quantity (by accelerometer) and sleep satisfaction (by visual analogue scale in a sleep diary), and the influence of infusion pump alarms on these outcomes in pediatric cancer patients and their parents. Parents also rated their sleep quality (PROMIS Sleep Disturbance item bank, Insomnia Severity Index) and daytime impairment (PROMIS Sleep-Related Impairment item bank, PROMIS Fatigue short form). Nineteen children with cancer (2-17 years) were included during admission for chemotherapy (n = 40 nights of data), together with their inrooming parents (n = 30, 46 nights of data, 27-51 years). The results indicate

that alarms sound frequently during the night, median 3 times/6 minutes in parents and 5 times/10 minutes in children. Parents also sleep poorly in the hospital. However, neither in children nor in parents, a direct relation between sleep quantity (sleep efficiency, wake after sleep onset, night awakenings) or sleep satisfaction and the number or duration of nightly alarms was found. This implies that - though clinical experience and previous studies demonstrate a contribution of infusion pumps to poor sleep - there are other environmental or personal influencers of sleep in the hospital that (also) play a role. These should be further identified.

The last study (**chapter 7**) explored whether sleep could be an intervention point to enhance executive functioning in brain tumor survivors. Executive functioning is a subdomain of neurocognitive functioning and encompasses all functions necessary for cognitive control and adaptation of behavior, such as attention, inhibition and working memory. The relation between sleep (Sleep Disturbance Scale for Children) and behavioral executive functioning (Behavior Rating Inventory of Executive Functioning) was investigated. The data of pediatric brain tumor survivors with parent-reported neurocognitive complaints (n = 82, 8-18 years) was baseline data of a randomized controlled trial into an intervention (neurofeedback) to improve these complaints. Our results indicate that these children had significantly more sleep problems compared to their healthy peers: 48% had a clinically relevant sleep problem. Furthermore, emotional problems, hyperactivity and inattention (measured by the Strength and Difficulties Questionnaire) were possible risk factors for these sleep problems. A significant relation between worse sleep and worse executive outcomes was found. This implies that sleep could indeed be a good intervention point to enhance executive functioning.

Finally, **chapter 8** reflects upon the findings above and discusses clinical implications and topics that remain to be investigated in future studies. Since the current PROMIS Sleep Disturbance item bank cannot capture sleep disturbance as one construct in children, the consideration of a modular approach with a set of questions per construct (overall sleep quality, sleep onset, sleep continuity, sleep hygiene and daytime sleep-related impairment) is proposed. Additional age-specific content (items) could be added in the modules where appropriate. When measuring sleep quantity, comparing pediatric accelerometer outcomes to a study-specific control sample - as opposed to general pediatric reference values - is currently the most valid option. Compared to professional devices, currently available commercial accelerometers generate data of lesser quality, and wield less methodological transparency. Caution should therefore be issued when using commercial devices. The importance of using professional, validated devices for assessment of sleep quantity is emphasized.

To improve sleep in pediatric oncology, a multi-system approach to make the hospital environment more suited for sleep is required. Noise, light and nightly interruptions by staff are disruptive factors. These can be reduced by educating staff, implementing non-disturbance periods during the night, and diminishing brightness of light and loudness of sound - technically or with earplugs and eye masks. The second method to improve sleep in pediatric oncology is to systematically monitor sleep quality and daytime sleep-related impairment during treatment and into survivorship. In the Princess Máxima Center this can be realized through the KLIK patient reported outcome measures (PROMs) portal. This portal is already in use to systematically monitor health related quality of life. Since many sleep problems are treatable, a stepped-care approach can be followed in case of sleep problems. Children with mild problems can receive education on sleep hygiene, whereas children with more impairing issues can be referred to a psychologist or sleep clinic. Additionally, when children report neurocognitive complaints, assessing sleep in addition to a neurocognitive test battery can provide more insight and a possible point of intervention. Future research should focus on validating and implementing the modular monitoring of sleep in pediatric cancer patients, and assess the optimal timing for measurement and intervention.

Key messages

- Improve the night, improve the day.
- For each sleep construct measured, whether with questionnaires or with accelerometers, availability of reference values and the choice of a validated measurement instrument are important issues to consider.
- The adapted PROMIS Sleep Disturbance and Sleep-Related Impairment item banks are suited to measure sleep in adolescents. The Sleep-Related Impairment item bank can also be used as CAT.
- A modular approach, with a set of questions per construct including age-specific items (i.e. overall sleep quality, sleep onset, sleep continuity, sleep hygiene and daytime sleep-related impairment) might be best for measuring pediatric sleep quality and daytime sleep-related impairment.
- When measuring sleep quantity, comparison to outcomes of a study-specific control sample, measured using a professional, validated accelerometer is best.
- Sleep in pediatric oncology can be improved by reducing environmental stimuli during hospitalization.
- Sleep in pediatric oncology can also be improved by systematically monitoring sleep during treatment and into survivorship, and following a stepped-care approach in case of sleep problems.

- Future research should focus on validating and implementing the modular monitoring of sleep, and assessing the optimal timing for measurement and intervention.
- When children report neurocognitive complaints, assessing sleep in addition to a neurocognitive test battery can provide more insight and a possible point of intervention.