BEDTIME STUDIES

Sleep and mental health in child development

Maria Elisabeth Koopman-Verhoeff

Bedtime Studies: Sleep and Mental Health in Child Development
© Maria Elisabeth Koopman-Verhoeff

Acknowledgements
The author thanks all participants and parents, students, practitioners, hospitals, midwives, and pharmacies. The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. The generation and management of the Illumina 450K methylation array data (EWAS data) for the Generation R Study was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, and the Netherlands. The authors thank all colleagues involved in generation and management of methylation data and genotyping.

The general design of the Generation R Study is made possible by financial support from Erasmus MC, Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development and the Ministry of Health, Welfare and Sport. The EWAS data was funded by a grant from the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA; project nr. 050-060-810), by funds from the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, and by a grant from the National Institute of Child and Human Development (R01HD068437).

The work presented in this thesis was conducted at the Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center, Rotterdam the Netherlands. This study received support from the Erasmus Medical Center Efficiency Grant (MRC-2013-169). Financial support for the publication of this thesis was kindly provided by the Generation R study, the Erasmus Medical Center, and the Dutch Society for Sleep-Wake Research (NSWO).

Cover	Sleepy owls, Holden Decor Limited
Layout	Renate Siebes | Proefschrift.nu
Printing	Proefschriftmaken.nl
ISBN	978-94-6380-831-6

Bedtime Studies:
Sleep and Mental Health in Child Development

Studies voor het slapengaan:
Slaap- en gedragsproblemen in de kindertijd

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
dinsdag 15 september 2020 om 15.30 uur

door

Maria Elisabeth Koopman-Verhoeff

geboren te Gouda

Erasmus University Rotterdam

Erasmus

Promotiecommissie

Promotor:	Prof. dr. H. Tiemeier
Overige leden:	Prof. dr. G.T.J. van der Horst Prof. dr. M.A. Carskadon Prof. dr. F.C. Verhulst
Copromotoren:	Dr. C.A.M. Cecil Dr. M.P.C.M. Luijk

Paranimfen:	Anouk S. Schimberg Koen Bolhuis

Manuscripts that form the basis of this thesis

Koopman-Verhoeff, M. E., Serdarevic, F., Kocevska, D., Bodrij, F. F., Mileva-Seitz, V. R., Reiss, I. K., Hillegers, M. H. J., Tiemeier, H., Cecil, C. A. M., Verhulst, F. C., & Luijk, M. P. C. M. (2019). Preschool family irregularity and the development of sleep problems in childhood: a longitudinal study. *Journal of Child Psychology and Psychiatry*, *60*(8), 857–865. (Chapter 2.1)

Koopman-Verhoeff, M.E., Mulder, R. H., Saletin, J. M., Reiss I., van der Horst, G. T. J., Felix J. M., Carskadon, M. A., Tiemeier, H., Cecil, C. A. M. (2020). Associations of epigenome-wide DNA methylation with sleep and mental health in children: A population-based study. *Journal of Child Psychology and Psychiatry*, in press. (Chapter 2.2)

Koopman-Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., Verhulst, F. C., Luijk, M. P. C. M., & Tiemeier, H. (2018). The bi-directional association between sleep problems and autism spectrum disorder: A population-based cohort study. *Molecular Autism*, *9*(8), 1–9. (Chapter 3.1)

Koopman-Verhoeff, M.E., Bolhuis, K., Cecil, C. A. M., Kocevska, D., Hudziak, J. J., Hillegers, M. H. J., Duijts, L., Mileva-Seitz, V. R., Reiss, I. K., Luijk, M. P. C. M., & Tiemeier, H. (2019). During day and night: Childhood psychotic experiences and objective and subjective sleep problems. *Schizophrenia Research*, *206*, 127–134. (Chapter 3.2)

Koopman-Verhoeff, M. E., Van den Dries, M. A., Seters, J. J., Luijk, M. P. C. M., Tiemeier, H., Luik, A. I. (2019) Sleep problems and melatonin use in school-aged children. *JAMA Pediatrics*, *173*(9), 883–885. (Chapter 4.1)

Koopman-Verhoeff, M. E. & Saletin, J. M. (2020). A good night's sleep: necessary for young minds. *Frontiers Young Minds*, in press. (Used in adapted form in Chapter 1&5)

Table of contents

Chapter 1

General introduction

Gustav Klimt – Mother and Child (detail)
(The Three Ages of Woman)

General introduction

Rationale

"Toen ging hij slapen, met zijn hoofd op de woorden waar hij het meest van hield: warm, alles, altijd, ik."

"Then he went to sleep, with his head on the words he loved the most: warm, everything, always, me."

— Toon Tellegen, Het vertrek van de mier

In general, the average human being spends 250,000 hours asleep in their lifetime. As we sleep around one third of our lives, sleep is the single most time-consuming behavior. These facts tell us that sleep must be of vital importance to human life. Sleep is essential for daily functioning, brain development, and mental as well as physical health. Several physiological processes differ between awake and sleep states, for example, our brain wave activity is different, we are less alert and mobile, we have a reduced stimulus response, and a lower body temperature. Human sleep is a fascinating phenomenon, and we know surprisingly little about child and adolescent sleep, making it of paramount importance to study.

Humans prefer to sleep at night – making us "diurnal" creatures. "Nocturnal" animals sleep during the day. This preference is hard-wired. Deep in our brain sits the suprachiasmatic nucleus (SCN). The SCN is our biological clock (Moore, 2007), which tells the time for every part of our body. We call this our circadian rhythm (circadian is Greek for "about a day" because the rhythm of sleep and wake repeats once every 24-hours). Like any clock, the SCN can be reset, based on when we see sunlight. When we travel, our bodies adjust to the new pattern of light (Moore, 2007). This is why people who travel across many time zones can adjust to a new pattern of sleep within a couple of days. Another system in the brain keeps track of how much time we are awake and how much we slept the night before: the sleep homeostat (Borbély & Achermann, 1999). Think about it like a piggy bank – when we sleep, we are putting money in the bank. When we are awake, we withdraw money. Eventually, we run out, and need to sleep to refill the bank. The circadian rhythm and the sleep homeostat ultimately work together, which is why you may feel alert in the middle of the day even if you did not get much sleep the night before, or why you suddenly feel tired at night even if you woke late that day.

Our SCN and our sleep homeostat change as we grow. When reaching puberty our SCN gets later – as if it shifted time-zones (Crowley, Wolfson, Tarokh, & Carskadon, 2018). The body wants to wake up later and go to bed later. Eventually – around age 25 years, it starts reversing again. As for the sleep homeostat, during puberty, this process slows down and your need for sleep builds a bit slower than it did when you were younger. These large changes in sleep patterns make pre-puberty and puberty an interesting time window for sleep research.

Although we do not know the exact functions of sleep, research tells us that sleep plays an important role in restorative processes for body and brain. But there is more, sleep helps every-day functioning, such as attention (e.g. *staying focused during the day*) (Wolfson & Carskadon, 1998), memory (e.g. *taking a test*), and emotion (e.g. *not getting too grumpy if things don't go your way*) (Krause et al., 2017). The prefrontal cortex (PFC), a brain region at the very front of our brain, is critical for paying attention, planning, and switching between tasks. If we sleep poorly or insufficiently the PFC cannot function efficiently the next day (Krause et al., 2017), making it extra hard to concentrate and even do little things without getting distracted. However, even if paying attention during the day is not impaired, bad sleep can make it difficult for the information we learn to be stored in our memory. In the center of our brain is a tiny region called the hippocampus, critical for memory. The hippocampus is an information sponge – soaking up what we learn during the day, but it requires a good night's sleep to integrate this information. Without good sleep, it has more difficulty to learn new information. So, sleep is necessary before a working or school day to pay attention, and we need sleep after a day of work to make memories last (Krause et al., 2017). Many scientific studies demonstrate that sleep helps the hippocampus, with other brain regions, keeps memories in place, so we can remember them days or even years later (Walker & Stickgold, 2005). Sleep helps stitching information together into complex ideas so you can "see the bigger picture".

> *"'Laten we maar gaan slapen,' zei meneer Pen. 'We hebben alles gedaan wat we konden. Morgenvroeg komen we alle drie hier. Op dit plekje. Dan zien we verder.'"*
>
> *"'Let's go to sleep,' said Mr. Pen. 'We did everything we could. We'll all be here tomorrow morning. At this place. Then we see further.'"*
>
> — Annie M.G. Schmidt, Pluk van de Petteflet

From other studies we know that after a night without good sleep we feel crankier and more irritable (Lo, Ong, Leong, Gooley, & Chee, 2016). A good night's sleep refreshes the emotional centers of our brain, both in the PFC as in other regions important for emotions, like the amygdala (Krause et al., 2017). Studies indicate that when children do not sleep, they show more inattentiveness, poorer memory, difficulties with shifting attention (J. Owens et al., 2012). Now we understand a little more about why we sleep and why sleep is important.

However, when sleep does not come naturally to us and problems with sleeping arise it can be a recurring struggle. Sleep problems in children can disrupt family life; making it one of the most heard complaints from (new) parents (Sadeh, Mindell, & Rivera, 2011). Sleep problems in healthy children are common with rates up to 50% (Petit, Touchette, Tremblay, Boivin, & Montplaisir, 2007), although these sleep problems often decline over time when the children grow older.

> *"I'm going to bed now, Lovis! Not to sleep. But to think and to curse, and woe better anyone who disturbs me!"*
>
> — Astrid Lindgren, Ronia, the Robber's Daughter

Importantly, the prevalence of sleep problems is particularly high in children with behavioral problems, such as mental health problems like attention problems, depressed mood, behavioral difficulties, or autism (Gregory & Sadeh, 2016). While in typically developing children sleep problems decline over time sleep problems can increase with age in children with mental health problems (Gregory & Sadeh, 2016). Children and adolescents struggling with mental health problems often experience trouble falling and staying asleep or difficulties waking up (Gregory & Sadeh, 2012). Researchers showed that specific neurodevelopmental behavioural problems, such as attention deficit disorder (ADHD) or autism spectrum disorder might underlie these sleep problems (J. A. Owens, 2005; Richdale & Schreck, 2009). For example, children with ADHD have difficulties settling down at the end of the day and have thoughts racing through their head, making it very difficult to fall asleep (J. A. Owens, 2005). On the other hand, children struggling with depression cannot get out of bed because they have a general feeling of anhedonia (lacking energy) (Gregory & Sadeh, 2016).

"It was one of those moments of perfect tiredness, of having conquered not only the work at hand, but the night who had blocked the way."

— Markus Zusak, The Book Thief

Because of all the ways sleep impacts our brain, sleep problems and mental health issues often go hand in hand. However, we are still coming to understand the connection between sleep and mental health; is it that sleep problems increase the risk of mental health problems, or is it the other way around (Gregory & Sadeh, 2016)? There is evidence that sleep problems increase the risk for mental health problems. Because of the strong links from behavioural problems to sleep, and from sleep to behavioural problems it is very likely that the associations are bidirectional or circular (El-Sheikh & Sadeh, 2015; Gregory & Sadeh, 2016).

Despite of many studies investigating sleep and mental health in children, there are still some key gaps that needed to be addressed. First, in order to properly asses the directionality of associations we need longitudinal studies repeatedly assessing sleep and behavioural problems over time in children to disentangle cause and consequence. Second, studies to date are mainly focusing on either reported sleep data or subjective data, rather than using both complementarily. Third, studies using actigraphy data mainly used small sample sizes often focusing on clinical populations rather than the general paediatric population.

Aims

As part of this thesis, I carried out a large sleep study within the Generation R Study to collect, for the first time, objective measures of sleep in a large sample of children from the general population. This enabled me to examine how both subjectively and actigraphically assessed sleep characteristics such as sleep duration and efficiency relate to mental health problems. The main aim of this thesis is to investigate the associations between sleep and mental health in children, and to provide grounds for new hypotheses in experimental and clinical studies. First, I will discuss research on the determinants of sleep problems. Next, I will turn to two distinct areas of child psychopathology and discuss the mechanisms through which sleep contributes to the development of child mental health difficulties or vice versa. Lastly, I will describe sleep medication use in children from the general population with a special focus on children with behavioral problems such as ADHD and autism.

Setting

To answer these questions, I included data from the Generation R Study, a prospective population-based cohort from fetal life onward in a multi-ethnic urban population. During routine visits obstetricians or midwifes invited pregnant women (expected delivery date April 2002–January 2006) living in Rotterdam, the Netherlands, to participate in the study. In total, 9778 mothers were enrolled in the study, a response rate of 61% (Kooijman et al., 2016). Questionnaire data available for this cohort of children and their parents covers, amongst others, measures of sleep, mental health, and the home environment. We examined both environmental and biological determinants of sleep. We were able to include two different methods to assess sleep, both subjective as well as actigraphically assessed sleep. Subjective data includes sleep problems as reported by the mother or the child itself tapping on experiences of dyssomnia, parasomnia symptoms, and perceived sleep quality. In a subsample of 1486 children and adolescents, we had actigraphic measures of sleep available as estimated by the combination of actigraphy and sleep diaries that the children completed for 9 days in a row in regular school-weeks (including five schooldays and 4 weekend days). Actigraphy taps on more objectively derived estimations of for example sleep duration, fragmentation and waking after sleep onset.

From all participants and their parents, we obtained written informed consent. The Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam approved the study.

References

Borbély, A. A., & Achermann, P. (1999). Sleep Homeostasis and Models of Sleep Regulation. *Journal of Biological Rhythms, 14*(6), 559-570. doi:10.1177/074873099129000894

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the perfect storm model. *Journal of Adolescence, 67*, 55-65. doi:https://doi.org/10.1016/j.adolescence.2018.06.001

El-Sheikh, M., & Sadeh, A. (2015). I. SLEEP AND DEVELOPMENT: INTRODUCTION TO THE MONOGRAPH. *Monographs of the Society for Research in Child Development, 80*(1), 1-14. doi:10.1111/mono.12141

Gregory, A. M., & Sadeh, A. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews, 16*(2), 129-136. doi:https://doi.org/10.1016/j.smrv.2011.03.007

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders – a review of the latest science. *Journal of Child Psychology and Psychiatry, 57*(3), 296-317. doi:10.1111/jcpp.12469

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van Ijzendoorn, M. H., . . . Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology, 31*(12), 1243-1264. doi:10.1007/s10654-016-0224-9

Krause, A. J., Simon, E. B., Mander, B. A., Greer, S. M., Saletin, J. M., Goldstein-Piekarski, A. N., & Walker, M. P. (2017). The sleep-deprived human brain. *Nature Reviews Neuroscience, 18*(7), 404-418. doi:10.1038/nrn.2017.55

Lo, J. C., Ong, J. L., Leong, R. L. F., Gooley, J. J., & Chee, M. W. L. (2016). Cognitive Performance, Sleepiness, and Mood in Partially Sleep Deprived Adolescents: The Need for Sleep Study. *Sleep, 39*(3), 687-698. doi:10.5665/sleep.5552

Moore, R. Y. (2007). Suprachiasmatic nucleus in sleep–wake regulation. *Sleep Medicine, 8*, 27-33. doi:https://doi.org/10.1016/j.sleep.2007.10.003

Owens, J., Gruber, R., Brown, T., Corkum, P., Cortese, S., O'Brien, L., . . . Weiss, M. (2012). Future Research Directions in Sleep and ADHD: Report of a Consensus Working Group. *Journal of Attention Disorders, 17*(7), 550-564. doi:10.1177/1087054712457992

Owens, J. A. (2005). The ADHD and Sleep Conundrum: A Review. *Journal of Developmental & Behavioral Pediatrics, 26*(4).

Petit, D., Touchette, É., Tremblay, R. E., Boivin, M., & Montplaisir, J. (2007). Dyssomnias and Parasomnias in Early Childhood. *Pediatrics, 119*(5), e1016-e1025. doi:10.1542/peds.2006-2132

Richdale, A. L., & Schreck, K. A. (2009). Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Medicine Reviews, 13*(6), 403-411. doi:https://doi.org/10.1016/j.smrv.2009.02.003

Sadeh, A., Mindell, J., & Rivera, L. (2011). "My child has a sleep problem": A cross-cultural comparison of parental definitions. *Sleep Medicine, 12*(5), 478-482. doi:https://doi.org/10.1016/j.sleep.2010.10.008

Walker, M. P., & Stickgold, R. (2005). Sleep, Memory, and Plasticity. *Annual Review of Psychology, 57*(1), 139-166. doi:10.1146/annurev.psych.56.091103.070307

Wolfson, A. R., & Carskadon, M. A. (1998). Sleep Schedules and Daytime Functioning in Adolescents. *Child Development, 69*(4), 875-887. doi:10.1111/j.1467-8624.1998.tb06149.x

Chapter 2

Determinants of child sleep

George Hendrik Breitner –
Meisje in rode kimono (Geesje Kwak)
Kunstmuseum, Den Haag

Chapter 2.1

Preschool family irregularity and the development of sleep problems in childhood: A longitudinal study

M. Elisabeth Koopman-Verhoeff | Fadila Serdarevic | Desana Kocevska | F. Fenne Bodrij | Viara R. Mileva-Seitz | Irwin Reiss | Manon H.J. Hillegers | Henning Tiemeier | Charlotte A.M. Cecil | Frank C. Verhulst | Maartje P.C.M. Luijk

Journal of Child Psychology and Psychiatry (2019), 60(8), 857–865

Abstract

Objective: Previous studies have shown that poor family environments are related to more sleep problems; however, little is known about how family irregularity in early life affects the development of sleep problems over childhood using objective sleep measures. The current study tests the hypothesis that early family irregularity contributes to the development of sleep problems.

Method: This population-based study comprises 5443 children from the Generation R Study. Family irregularity was measured with seven maternal reported questions on family routines when children were 2 and 4 years old. Mothers reported on sleep problems at child age 3, 6, and 10 years, whereas children completed questionnaires on sleep problems at age 10. Additionally, we used tri-axial wrist accelerometers for five nights in 851 children (mean age 11.7 years) to assess sleep objectively.

Results: Family irregularity was associated with more mother- and child-reported sleep problems at ages 3, 6, and 10 years as well as with a shorter sleep duration and later objective sleep onset, but not with sleep efficiency or waking time. The association between family irregularity and multi-informant subjective sleep problems at age 10 years was mediated by mother-reported child psychopathology at age 6 years.

Conclusion: Our findings show a long-term robust association of pre-school family irregularity with more sleep problems during childhood as well as shorter sleep duration and later sleep onset as measured objectively with actigraphy. In part, these sleep problems were associated with family irregularity by way of child psychopathology. These findings suggest that interventions improving pre-school family irregularity, which are targeted to reduce child psychopathology, may also impact the development of sleep problems beneficially.

Introduction

Sleep problems in children, such as difficulties falling asleep, nighttime awakenings, or nightmares (Gregory & Sadeh, 2016), are common complaints of parents and can disturb family life (O'Connor et al., 2007). Sleep problems frequently occur in general pediatric populations with prevalence estimates of up to 50% (Petit, Touchette, Tremblay, Boivin, & Montplaisir, 2007). The prevalence of childhood sleep problems typically declines with age, but in a subset of children sleep problems are persistent and predict poor outcomes later in life (Gregory & O'Connor, 2002). Despite the importance of sleep problems for later health and well-being, the etiology of sleep problems in school age children remains unclear (O'Connor et al., 2007). Previous research points to the importance of the family environment in relation to sleep; stressful family environments, a lack of parental rules, and family conflict have all been associated with sleep problems in children and adolescents (Adam, Snell, & Pendry, 2007; Gregory, Caspi, Moffitt, & Poulton, 2006). These negative family influences all occcur more often in the context of an unpredictable family life (Gregory et al., 2006).

Family irregularity, i.e. the lack of day-to-day family routines, refers to the lack of consistency in household routines, such as meal location and bedtime routines rather than more distal family influences (e.g. marital conflict, socio-economic status) (Ivanova & Israel, 2005). Previous studies point at the importance of bedtime routines, which have been found to associate with longer sleep duration as measured with accelerometer in toddlers (Staples, Bates, & Petersen, 2015). Additionally, a recent review points to the potential of promoting bedtime routines as a feasible intervention for reducing sleep problems, especially in high-risk families (Mindell & Williamson, 2018). However, the pathways linking the family irregularity and sleep problems are unclear. Higher levels of family irregularity hamper the ability of young children to develop a stable sleep onset and good quality sleep during the night (Billows et al., 2009; Buxton et al., 2015; Gregory, Eley, O'Connor, Rijsdijk, & Plomin, 2005; Spilsbury, Patel, Morris, Ehayaei, & Intille, 2017; Staples et al., 2015). But separate studies also find that family irregularity is associated with child psychopathology (Ivanova & Israel, 2006; Rijlaarsdam et al., 2016); and that specific symptoms sets of developmental psychopathology, such as ADHD or autism spectrum disorder, might be underlying sleep problems and not the reverse (Owens, 2005; Richdale & Schreck, 2009; Verhoeff et al., 2018). As such, child psychopathology may act as a mediator in the association between family irregularity and sleep problems, but to date this has not been tested.

Despite previous reports of an association between family irregularity and sleep problems, the literature is characterized by several gaps. First, studies have been primarily cross-sectional, thus it has not yet been possible to examine how family irregularity prospectively associates with the development of sleep problems in childhood. Second, studies to date have measured sleep exclusively using subjective reports; as such, the effects of family irregularity on objective indices of sleep have yet to be characterized. Third, no study to date has investigated whether child psychopathology mediates the association between family irregularity in early life and later sleep problems. Here, we address these gaps by examining whether family irregularity is prospectively associated with sleep problems throughout childhood, using – consistent with previous studies – both parent- and child-rated questionnaires that we complement with objective measures of sleep, using data from a large population-based study. Moreover, we tested whether the association between family irregularity and child sleep problems is mediated by child psychopathology.

Methods

Participants

This study was embedded in Generation R, a prospective population-based cohort from foetal life onward. All pregnant women (expected delivery date April 2002–January 2006) living in Rotterdam, the Netherlands, were invited to participate by their midwife or obstetrician during routine visits. All participants received questionnaires and were invited at the research center for observed behavioural assessment (previously described in detail (Kooijman et al., 2016)). The baseline participation rate was estimated at 61%. We obtained written informed consent from all participants and their parents. The Medical Ethical Committee of the Erasmus Medical Center Rotterdam approved the study.

Data on family irregularity at age 2 or 4 years were available for 5842 children. Children without information on sleep problems on at least one assessment from age 3 years onward were excluded (n = 399), yielding a sample size of 5443 children for the present study (follow-up rate 93.2%). In the analyses, the study population varies slightly due to missing data in different assessments rounds.

A subsample of 1153 children was recruited for an accelerometer sample by mail and phone. Of these, 953 children were willing to participate (response rate of 82%).

Children without data on weekday sleep and those with corrupted measures were excluded. The final sample for the analyses with accelerometer measures consisted of 851 children. Mean age at the time of assessment was 11.7 (SD = 0.20) years (see Figure 2.1.1 for participant overview).

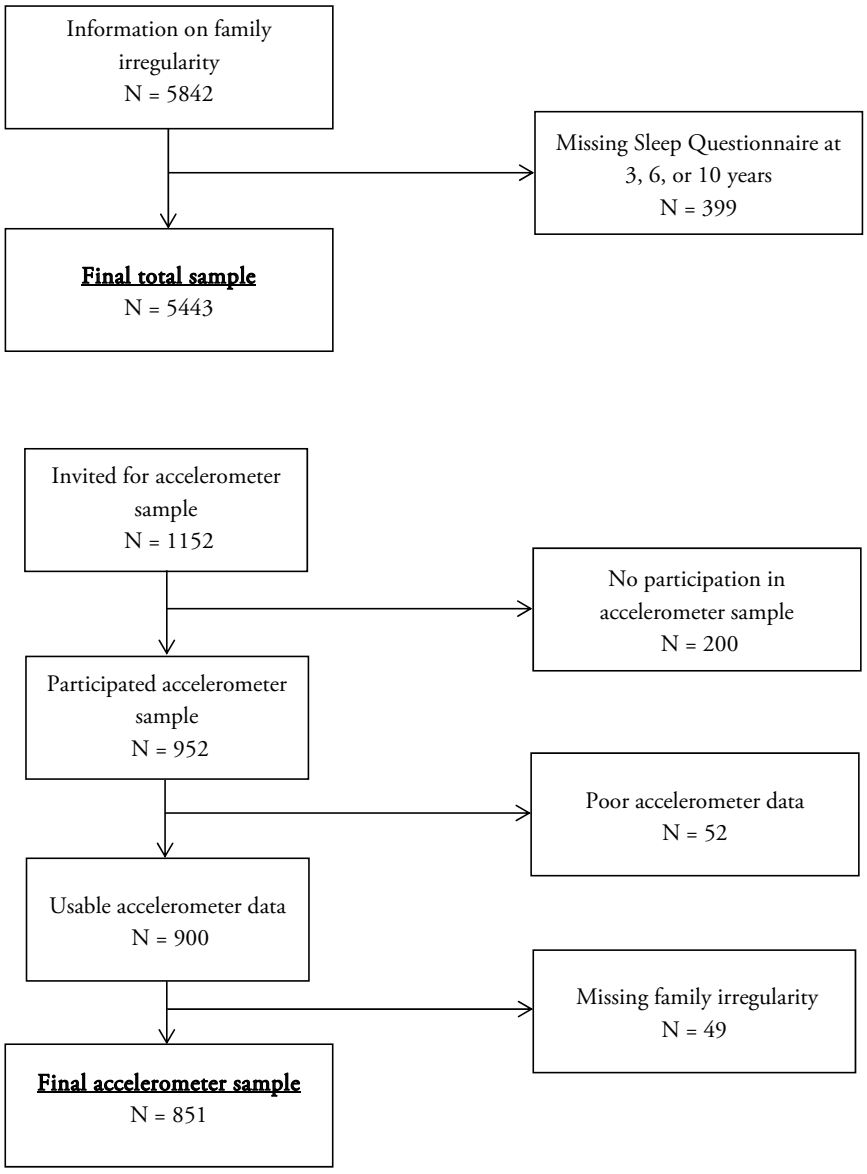

Figure 2.1.1. Flowchart: family irregularity and sleep.

Measures

Family irregularity

Family irregularity was a composite derived from seven questions about multiple domains of family irregularity reported by mothers when children were 2 and 4 years old. This family irregularity scale has previously been used in a reversed format as a measure of family regularity (Rijlaarsdam et al., 2016). The measure included two items on bedtime routines (i.e., "Do you have a set pattern or ritual with your child at bedtime?" and "Has your child gone to bed in the evening at around the same time?") at age 2 years. At age 4 years, two questions on family meal location (i.e., "How often do you have breakfast/evening meal around the table together with your child/children?") and three questions on meal frequency (i.e., "How often does your child eat breakfast/lunch/evening meals?"). Using confirmatory factor analysis (CFA), the seven irregularity items were combined into a single construct to represent family irregularity. CFA in Mplus version 7.11 was employed (Muthén & Muthén, 1998-2012) to test the family irregularity measurement model using the weighted least squares means and variance adjusted (WLSMV) estimator. Model fit was established using the root mean squared error of approximation (RMSEA; acceptable fit ≤ 0.08), the comparative fit index and the Tucker-Lewis index (CFI and TLI; acceptable fit ≥ 0.90).

Child psychopathology

At age 6 years, the primary caregiver, mostly the mother, completed the Child Behavior Checklist for ages 1½-5 (CBCL/1½-5), a valid measure of child psychopathology (Achenbach & Rescorla, 2001). The CBCL/1½-5 is widely used internationally and has been found to be generalizable across 23 societies (Ivanova et al., 2010). Mothers rated various emotional and behavioural problems of the child in the previous six months on a three-point scale (0 = not true, 1 = somewhat true, 2 = very true). All scores, except for five items referring to sleep, were combined into a Total Problems Scale.

Mother-reported child sleep problems

At age 1.5, 3, and 6 years, children's sleep problems were quantified with the Sleep Problems scale, one of the empirically derived scales of the CBCL/1½-5. The Sleep Problems scale comprises seven questions about sleep problems including items on dyssomnia (has trouble falling asleep; sleeps less than most children during the day and/or night; wakes up often during the night) and parasomnia (nightmares; talks

or cries out in sleep). This scale is commonly used as a measure of sleep problems (Gregory & O'Connor, 2002). At age 10 years, we used the CBCL/6-18, which has a slightly different content to fit this older age range. The CBCL/6-18 does not have a specific Sleep Problems scale as the pre-school version of the CBCL has. In order to keep the sleep measure consistent with the other two time points, we selected 5 sleep items from the CBCL/6-18 questionnaire to form a Sleep Problems scale. We used 3 questions representing dyssomnia symptoms: "Trouble with sleeping"; "Sleeps less than most kids"; "Overtired with no good reason", and 2 questions representing parasomnia symptoms: "Nightmares" and "Talks or walks in sleep" (internal consistency of $\alpha = 0.52$), in line with a previous study (Verhoeff et al., 2018).

Child-reported sleep problems

At age 10 years, dyssomnia symptoms were assessed by self-report questionnaire asking six questions about their perceived sleep i.e. "Do you find it difficult to go to bed?"; "Do you find it difficult to fall asleep?"; "Do you think you get enough sleep?"; "If you wake up at night, do you find it difficult to fall asleep again?"; "Do you feel rested when you wake in the morning?"; "When you come out of your bed in the morning, do you feel rested?". These questions were derived from the widely used Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996) and slightly rephrased for our paediatric population. There were three possible responses for each item: "No", "Sometimes" or "Yes", which were scored on a three-point Likert scale. Responses from all six items were summed to calculate a total score with an internal consistency of $\alpha = 0.64$; higher scores indicate more sleep problems.

Objective sleep measures

At age 11 years, sleep was assessed with a tri-axial wrist accelerometer (GENEActiv; Activinsights, UK); the children wore the devices for nine subsequent days on their non-dominant wrist, including five school days and four weekend days. This measure has been validated in children and in adults. In children, thresholds have been calculated to assess sedentary behavior (sitting/lying) with a sensitivity of 97–98% and a specificity of 74–78% (Hildebrand, Hansen, van Hees, & Ekelund, 2017) and the GENEActive has been found to correlate well with both sleep diaries and self-reported sleep duration (Nascimento-Ferreira et al., 2016). In adults, it is shown to be a valid measure of sleep, which provides comparable estimates to other accelerometer brands (Rosenberger, Buman, Haskell, McConnell, & Carstensen, 2016). Additionally,

children filled out a sleep diary each morning answering questions about their sleep during the previous night. The questions "What time did you go to bed?" and "What time did you wake up?" were used as indicators in the actigraphy analysis to guide the accelerometer-based sleep onset and waking detection. The Geneactiv accelerometers record raw accelerometer data, and for the current study they were set a frequency of 50 Hz. The binary files were processed with the R-package GGIR (van Hees et al., 2014). The processing included auto calibration with gravity as reference, detection of atypical values and non-wear, and calculation of the average acceleration. Nights were excluded if the wear time was under 6 hours or if sleep time was calculated as being less than 4 hours. This procedure generated the following variables: sleep duration, sleep efficiency, sleep onset, and waking time (van Hees et al., 2015). Sleep duration is the total time asleep during the night, indicating the time between falling asleep and waking minus the time scored as awake. Sleep efficiency is the total sleeping time divided by bed time and waking time and is presented in percent. Sleep onset is the time a child fell asleep, waking time is the time children woke in the morning. For sake of homogeneity, for the measures of sleep duration, sleep efficiency, sleep onset, and sleep waking time in the current study only school days were included in the analyses, representing the typically pattern of weekday sleep to minimize the influence of atypical weekend events. We did, however, integrate weekend sleep in a sensitivity analysis to test the robustness of associations.

Confounders

Based on the literature (Billows et al., 2009; Gregory et al., 2005), the following variables were considered possible confounders in the association between family irregularity and sleep. Sex of the child was obtained from the medical records completed by community midwives and obstetricians and information on other maternal and child characteristics was obtained by questionnaires. Child ethnicity was based on country of birth of the parents, coded as, Dutch, Other-Western, and non-Western. Additionally, maternal education was defined by the highest attained educational level and classified into three categories (low, middle, and high education). Prenatal maternal psychopathology was assessed using the Brief Symptom Inventory (BSI, (De Beurs, 2004). We considered other potential confounding factors such as siblings, bed-sharing, and asthma but did not add them to our final models. Whilst bed-sharing at age 2 years was found to be positively correlated with sleep duration at age 11 years (indicating a longer sleep duration) and negatively correlated with pre-school family irregularity (indicating less family irregularity), it did not affect

results once included as an additional confounder. The other factors, such as siblings and medical data such as asthma, were not confounders since they were unrelated to the exposure.

Statistical analysis

For ease of comparison over the different instruments and time points, we standardized all independent and dependent variables. For each of the steps described below, we constructed two models. The first model was adjusted for child sex and child age at sleep assessment. In the second model, the following confounders were included: child sex, child age at sleep assessment, gestational age, ethnicity, maternal age at birth, maternal psychopathology, and maternal educational level. Additionally, we controlled for previous sleep problems reported by the mother at age 1.5 years. The analyses were performed in four steps.

First, we examined the longitudinal association between family irregularity and mother-reported sleep problems measured at ages 3, 6, and 10 years. To this end, we used generalized linear mixed models (GLMM) and estimated associations using standardized beta coefficients and 95% confidence intervals (CI). This analysis was conducted exclusively with mother-reported sleep problems given the availability of repeated measures. All models included a subject level random intercept and slope to account for repeated measures of child sleep problems and to model child-specific variable effect. GLMM are robust to loss to follow up under the missing at random assumption.

Second, we used linear regression models to derive individual estimates of the prospective association of pre-school family irregularity with multi-informant sleep problems, including (i) maternal reported (age 3, 6, and 10) and (ii) child-reported (age 10) sleep. Third, we tested associations between family irregularity and objective measures of sleep (age 11), in the subsample with available accelerometer data using linear regression models. Fourth, we tested whether child psychopathology at age 6 years mediated the association between family irregularity and multi-informant sleep problems at age 10 years. We also tested if child psychopathology acted as a mediator between family irregularity and objective measures of sleep. We ran mediation models with 99% bias-corrected bootstrap confidence intervals applying 5000 bootstrap samples using the PROCESS macro in SPSS (Hayes, 2015).

Sensitivity analyses

In addition to the main analyses described above, we ran several sensitivity analyses to test the robustness of our findings. First, to minimize the content overlap between some of the items in the family irregularity and sleep, we reran the CFA analysis to extract a factor of family irregularity without the bed time routine-related items (i.e. including only the five items on mealtime location and mealtime routines). We reran all models using the adapted version of the family irregularity construct. Second, in the accelerometer sample, all models concerning objective sleep measures were rerun using combined weekend and weekday sleep. To reduce bias associated with missing data, we used multiple imputations for missing values of the confounders. Ten imputed datasets were created and analysed separately after which the results were pooled. The statistical analyses were performed using the SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA), MPlus version 7.11 (Muthén & Muthén, Los Angeles, CA, USA) using Monte Carlo integration techniques and maximum likelihood estimation with robust standard errors. Longitudinal analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the children in the total sample and the accelerometer sample are presented in Table 2.1.1. Children in the accelerometer sample had an average sleep duration of 7 hours and 45 minutes (SD = 42 minutes), a mean sleep efficiency of 81% (SD = 5.5%), a mean sleep onset time at 22:04 (SD = 55 minutes), and a mean waking time at 6:46 (SD = 58 minutes). Table S2.1.1 shows the correlations among the sleep variables, showing very modest correlations between the sleep problem scales and accelerometer measures of sleep duration and patterns, f.e. sleep problems reported by the mother at age 6 years is negatively correlated with sleep duration (r = -.117).

Mother-reported sleep problems

The results of the GLMM model indicate a longitudinal association between pre-school family irregularity and mother-rated sleep problems. While this association was found to decline over time, it was still observable at age 10 years (age 3, β = 0.21, 95% CI: 0.17–0.25), age 6, β = 0.16, 95% CI: 0.12–0.20), age 10, β = 0.10, 95% CI: 0.06–0.14)). To illustrate, Table 2.1.2 shows the associations of pre-school family irregularity with sleep problems at ages 3, 6, and 10 years based on the linear regression models, adjusted for

Table 2.1.1. Characteristics of the study population

	N	Total sample N = 5443	N	Accelerometer sample N = 852
Child characteristics				
Sex (% girls)	5443	50.1	852	52.3
Gestational age at birth (weeks)	5418	39.84 (1.80)	852	39.65 (2.24)
Ethnicity				
Dutch %	3518	64.6	715	84.0
Other Western %	509	9.4	49	5.8
Non-Western %	1416	26.0	88	10.3
Sleep duration (hours:minutes)		-	852	7:45 (0:42)
Sleep efficiency (%)		-	852	84 (5.1)
Sleep onset (time to fall asleep)		-	852	22:04 (0:55)
Sleep problem score (maternal report)				
At 3 years	4695	1.91 (2.12)	778	1.68 (1.91)
At 6 years	4805	1.33 (1.81)	808	1.12 (1.62)
At 10 years	3960	0.83 (1.22)	793	0.83 (1.23)
Sleep problem score at 10 years (child-report)	3598	10.88 (2.47)	772	11.00 (2.47)
Family irregularity	5443	1.40 (0.39)	852	1.32 (.34)
Maternal characteristics				
Age at inclusion (years)	5442	31.40 (4.66)	852	32.33 (3.85)
Educational level				
No education/ primary school %	358	6.6	15	1.8
High school / lower vocational training %	2054	37.7	277	32.5
Higher vocational or academic training %	3031	55.7	560	65.7
Psychopathology score	5443	0.24 (0.31)	852	0.19 (0.24)

Data represent means (SDs) unless specified otherwise.

confounders (respectively, $\beta = 0.13$, 95% CI: 0.10–0.16, $p < 0.01$; $\beta = 0.11$, 95% CI: 0.08–0.14, $p < 0.01$; $\beta = 0.06$, 95% CI: 0.02–0.10, $p < 0.01$). Results slightly attenuated after additionally controlling for previous sleep problems at age 1.5 years. In Figure S2.1.1, we show associations between family irregularity and mother-rated sleep problems at all ages (adjusted for confounders and also additionally for previous sleep problems).

Child-reported sleep problems

Pre-school family irregularity was prospectively associated with higher levels of child-reported sleep problems at age 10, over and above adjustment for confounders ($\beta = 0.08$, 95% CI: 0.04–0.13, $p < 0.01$). Results remained similar after additionally controlling for previous sleep problems at age 1.5 years.

Table 2.1.2. The association between pre-school family irregularity and mother- and child-reported sleep problems at ages 3, 6, and 10 years (total sample)

	Maternal reported									Child reported		
	3 year N = 4695			6 year N = 4805			10 year N = 3960			10 year N = 3598		
Family irregularity	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
Model 1	.18	.15–.21	<.01	.17	.14–.20	<.01	.06	.03–.10	<.01	.06	.03–.10	<.01
Model 2	.13	.10–.16	<.01	.11	.08–.14	<.01	.06	.02–.10	<.01	.08	.04–.13	<.01
Model 3	.10	.07–.13	<.01	.08	.05–.11	<.01	.05	.01–.09	<.01	.08	.04–.12	<.01

Model 1 was unadjusted. Model 2 was sex, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Model 3 was adjusted for previous baseline sleep problems at age 1.5 years.

Table 2.1.3. Associations between pre-school family irregularity and objective schooldays sleep at age 11 years (accelerometer sample)

	Sleep duration N = 865			Sleep efficiency N = 865			Sleep onset N = 865			Wake time N = 865		
Family irregularity	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
Model 1	-.10	-.17–-.03	<.01	.01	-.06–.08	.80	.11	.04–.18	<.01	.02	-.05–.09	.55
Model 2	-.09	-.16–-.01	.02	.02	-.05–.10	.56	.10	.03–.17	<.01	.01	-.06–.08	.75
Model 3	-.08	-.16–-.01	.02	.02	-.05–.10	.55	.10	.03–.17	<.01	.01	-.06–.08	.79

Model 1 was unadjusted. Model 2 was adjusted for sex, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Model 3 was adjusted for previous baseline sleep problems at age 1.5 years.

Objective sleep

Family irregularity in the pre-school period was prospectively associated with sleep duration and sleep onset at age 11. Higher levels of family irregularity were associated with a shorter sleep duration (β = -0.09, 95% CI: -0.16–-0.01, p = 0.02) and a later sleep onset (β = 0.10, 95% CI: 0.03–0.17, p < 0.01). Family irregularity was not associated with the other objective sleep parameters (i.e. sleep efficiency and waking time) (Table 2.1.3). Results remained similar after additionally controlling for previous sleep problems at age 1.5 years.

Child psychopathology as a mediator

Child psychopathology was tested as a potential mediator between pre-school family irregularity and sleep problems. With bootstrapped mediation models, we demonstrate an indirect effect of family irregularity on child sleep problems (full-mediation for mother-report and partial mediation for child-report at age 10 years) via child psychopathology at age 6 years (*mother-reported sleep problems:* adjusted β: 0.14; 95% CI: 0.04–0.33 for [Ratio of indirect to direct effect 40%]; *child-reported sleep problems:* adjusted beta: 0.05; 95% CI: 0.00–0.16 [Ratio of indirect to direct effect 13%]). Child psychopathology did not mediate the association between family irregularity and objective sleep indices.

Sensitivity analyses

For the sensitivity analyses, we reran all models using an adapted version of the pre-school family irregularity construct without the items on bedtime routines. Findings were generally robust, except for the association between family irregularity and mother-reported sleep problems at age 10 years, which was attenuated (Table S2.1.2-S2.1.3). Supplementary Table S2.1.4 shows that the findings remained consistent when we reran the models with the objective sleep measures combining weekend plus weekday sleep.

Discussion

This study is unique as it demonstrated a longitudinal association of family irregularity with repeatedly measured, multi-informant sleep problems, as well as objective measures of sleep, even when controlled for previous sleep problems at age 1.5 years. We highlight three key findings here. First, we found that family irregularity

experienced by toddlers is associated with life is associated with long-term mother-reported and child-reported sleep problems and shorter sleep duration and a later sleep onset. These findings are robust across time, raters and methods of assessment (reported and actigraphy), pointing to family irregularity as an early risk marker for later sleep problems. The differential effects for children at various ages and the decline of the effect between family irregularity and sleep problems over time may represent a regression dilution effect. Second, sensitivity analyses indicated that the effect was not purely driven by family regularity items related to bedtime routines. Third, child psychopathology at age 6 mediated the association between family irregularity and reported sleep problems, but did not influence the relation with objective sleep parameters.

By using objective sleep measures, we complement and extend the findings of the only other existing study to examine family irregularity in relation to child sleep, which showed that family irregularity is cross-sectionally related to child-reported shorter sleep duration and delayed sleep onset (Billows et al., 2009). A potential mechanism for this association is that family irregularity interferes with cues that can act as Zeitgebers (Ehlers, Frank, & Kupfer, 1988). Zeitgebers are external signals that help individuals to entrain a day-night rhythm in concordance with the 24-hour light-dark cycle of the earth. In daily life, these cues can help children to get ready to go to bed. Children raised under irregular family circumstances might lack those cues, or might receive irregular cues and struggle to adequately adapt their circadian rhythms. Moreover, adolescents with a delayed sleep onset often have chronic insufficient sleep (Billows et al., 2009; Carskadon, Acebo, & Jenni, 2004; Tarokh, Saletin, & Carskadon, 2016). Importantly, the current findings underscore the potential of family interventions targeted at family irregularity, a documented modifiable risk factor. Indeed, a previous randomized trial targeting household routine aiming to reduce obesity in preschool children effectively increased sleep duration (Haines et al., 2013). In contrast, other family circumstances which influence sleep are harder to address, such as family conflict and maltreatment. Potentially, the intervention targeting family irregularity can be extended to increase sleep duration throughout childhood. As such, it will be important to examine the association between family irregularity and objective sleep in adolescence in future research. We were able to identify a risk factor for child sleep problems that is known to be modifiable.

Psychopathology was investigated as a potential pathway linking family irregularity and sleep problems, given that both have been previously associated with child

psychopathology (Gregory & Sadeh, 2016; Ivanova & Israel, 2006). The association between family irregularity and mother-reported sleep problems at age 10 years was fully mediated by child psychopathology. This mediation may reflect shared-method variance due to the use of maternal reports for the determinant, mediator and outcome; however, partial mediation was observed when using child-rated sleep problems as the outcome. Overall, these findings suggest long-term associations between early family irregularity, child psychopathology and child subjective sleep problems.

The association between family irregularity and psychopathology is well known (Ivanova & Israel, 2006), as is the association between sleep problems and psychopathology (Gregory & Sadeh, 2016). Previous studies have suggested that sleep problems result from psychopathology and not the other way around (Owens, 2005; Richdale & Schreck, 2009; Verhoeff et al., 2018). However, it is also possible that sleep problems lead to psychopathology or that the associations are bidirectional (El-Sheikh & Sadeh, 2015; Gregory & Sadeh, 2016). While our study lends support to the psychopathology as a mediator between early family irregularity and later sleep problems, we are unable to rule out alternative pathways and it is therefore premature to conclude about the direction of the relations between sleep, family circumstances and psychopathology. Future longitudinal studies with repeated measures of these variables are needed to disentangle directionality.

In contrast, child psychopathology did not mediate the association of pre-school family irregularity and objective sleep. These objective and subjective measures reflected not only different assessments but different, albeit related, outcomes. The sleep items in the CBCL tap on experiences of dyssomnia and parasomnia symptoms, whereas accelerometer data indexes parameters such as sleep duration, efficiency, sleep onset time, and waking time. These differences were indeed evidenced by the small correlation between the sleep problem scales and accelerometer measures in our sample, consistent with prior reports (Gregory et al., 2011). As such, our data suggested that child psychopathology may play a stronger role in the development of dyssomnia and parasomnias, as opposed to alterations in accelerometer sleep patterns.

Limitations and strengths

The findings of the current study should be considered in the light of some limitations. First, in the current study we used maternal reports of family irregularity – it would have been optimal to use objective measures of family irregularity. However, objective

measures of family irregularity are often situation and time dependent and not feasible. Second, we did not have repeated measures of family irregularity. This precludes the possibility to examine how changes in family irregularity over time relate to changes in sleep problems. Third, because of the population-based nature of the current study, the generalizability to clinical samples will need to be established in future. This study had, however, also multiple strengths. First, we made use of accelerometer measures of sleep, which is a reliable measure of sleep duration, efficiency, sleep onset time, and waking time. Second, we obtained questionnaire sleep measures across multiple raters and at multiple time points, which enabled us to study the course of sleep problems over time. Third, because of our design and large sample size, we were able to control for multiple confounders.

Conclusion

In summary, this population-based study supports the important role of early family irregularity, over and above the role of bedtime routines, in shaping the development of sleep across childhood. Pre-school family irregularity in toddlers can have lasting consequences on subjectively-assessed sleep problems up to age 10 years, such as dyssomnia and parasomnias, as well as shorter sleep duration and delayed sleep onset, based on accelerometer data. This study also points to child psychopathology as a potential pathway linking family irregularity in early life and later sleep problems. These robust, long-term findings suggest that interventions targeting pre-school family irregularity might be potential avenues for reducing both the development of sleep problems and the risk of child psychopathology.

References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA preschool forms & profiles.* Burlington: University of Vermont, Research Center for Children, Youth and Families.

Adam, E. K., Snell, E. K., & Pendry, P. (2007). Sleep timing and quantity in ecological and family context: a nationally representative time-diary study. *J Fam Psychol, 21*(1), 4-19.

Billows, M., Gradisar, M., Dohnt, H., Johnston, A., McCappin, S., & Hudson, J. (2009). Family disorganization, sleep hygiene, and adolescent sleep disturbance. *J Clin Child Adolesc Psychol, 38*(5), 745-752.

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res, 5*(4), 251-261.

Buxton, O. M., Chang, A. M., Spilsbury, J. C., Bos, T., Emsellem, H., & Knutson, K. L. (2015). Sleep in the modern family: protective family routines for child and adolescent sleep. *Sleep Health, 1*(1), 15-27.

Carskadon, M. A., Acebo, C., & Jenni, O. G. (2004). Regulation of adolescent sleep - Implications for behavior. *Adolescent Brain Development: Vulnerabilities and Opportunities, 1021*, 276-291.

De Beurs, E. (2004). Brief Symptom Inventory, handleiding. Leiden, the Netherlands: Pits Publishers.

Ehlers, C. L., Frank, E., & Kupfer, D. J. (1988). Social Zeitgebers and Biological Rhythms - a Unified Approach to Understanding the Etiology of Depression. *Archives of General Psychiatry, 45*(10), 948-952.

El-Sheikh, M., & Sadeh, A. (2015). I. Sleep and development: introduction to the monograph. *Monogr Soc Res Child Dev, 80*(1), 1-14.

Gregory, A. M., Caspi, A., Moffitt, T. E., & Poulton, R. (2006). Family conflict in childhood: a predictor of later insomnia. *Sleep, 29*(8), 1063-1067.

Gregory, A. M., Cousins, J. C., Forbes, E. E., Trubnick, L., Ryan, N. D., Axelson, D. A., Birmaher, B., … Dahl, R. E. (2011). Sleep Items in the Child Behavior Checklist: A Comparison with Sleep Diaries, Actigraphy, and Polysomnography. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(5), 499-507.

Gregory, A. M., Eley, T. C., O'Connor, T. G., Rijsdijk, F. V., & Plomin, R. (2005). Family influences on the association between sleep problems and anxiety in a large sample of pre-school aged twins. *Personality and Individual Differences, 39*(8), 1337-1348.

Gregory, A. M., & O'Connor, T. G. (2002). Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. *J Am Acad Child Adolesc Psychiatry, 41*(8), 964-971.

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders--a review of the latest science. *J Child Psychol Psychiatry, 57*(3), 296-317.

Haines, J., McDonald, J., O'Brien, A., Sherry, B., Bottino, C. J., Schmidt, M. E., & Taveras, E. M. (2013). Healthy Habits, Happy Homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. *JAMA Pediatr, 167*(11), 1072-1079.

Hayes, A. F. (2015). An Index and Test of Linear Moderated Mediation. *Multivariate Behav Res, 50*(1), 1-22.

Hildebrand, M., Hansen, B. H., van Hees, V. T., & Ekelund, U. (2017). Evaluation of raw acceleration sedentary thresholds in children and adults. *Scand J Med Sci Sports, 27*(12), 1814-1823.

Ivanova, M. Y., Achenbach, T. M., Rescorla, L. A., Harder, V. S., Ang, R. P., Bilenberg, N., … Verhulst, F. C. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry, 49*(12), 1215-1224.

Ivanova, M. Y., & Israel, A. C. (2005). Family stability as a protective factor against the influences of pessimistic attributional style on depression. *Cognitive Therapy and Research, 29*(2), 243-251.

Ivanova, M. Y., & Israel, A. C. (2006). Family stability as a protective factor against psychopathology for urban children receiving psychological services. *J Clin Child Adolesc Psychol, 35*(4), 564-570.

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van IJzendoorn, M. H., … Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology, 31*(12), 1243-1264.

Mindell, J. A., & Williamson, A. A. (2018). Benefits of a bedtime routine in young children: Sleep, development, and beyond. *Sleep Medicine Reviews, 40*, 93-108.

Muthén, L. K., & Muthén, B. O. (1998-2012). *Mplus User's Guide (7th ed.)*. Los Angeles, CA: Muthén & Muthén.

Nascimento-Ferreira, M. V., Collese, T. S., de Moraes, A. C. F., Rendo-Urteaga, T., Moreno, L. A., & Carvalho, H. B. (2016). Validity and reliability of sleep time questionnaires in children and adolescents: A systematic review and meta-analysis. *Sleep Medicine Reviews, 30*, 85-96.

O'Connor, T. G., Caprariello, P., Blackmore, E. R., Gregory, A. M., Glover, V., & Fleming, P. (2007). Prenatal mood disturbance predicts sleep problems in infancy and toddlerhood. *Early Human Development, 83*(7), 451-458.

Owens, J. A. (2005). The ADHD and sleep conundrum: a review. *Journal of Developmental and Behavioral Pediatrics, 26*(4), 312-322.

Petit, D., Touchette, E., Tremblay, R. E., Boivin, M., & Montplaisir, J. (2007). Dyssomnias and parasomnias in early childhood. *Pediatrics, 119*(5), e1016-1025.

Richdale, A. L., & Schreck, K. A. (2009). Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Medicine Reviews, 13*(6), 403-411.

Rijlaarsdam, J., Tiemeier, H., Ringoot, A. P., Ivanova, M. Y., Jaddoe, V. W. V, Verhulst, F. C., & Roza, S. J. (2016). Early family regularity protects against later disruptive behavior. *Eur Child Adolesc Psychiatry, 25*(7), 781-789.

Rosenberger, M. E., Buman, M. P., Haskell, W. L., McConnell, M. V., & Carstensen, L. L. (2016). Twenty-four Hours of Sleep, Sedentary Behavior, and Physical Activity with Nine Wearable Devices. *Med Sci Sports Exerc, 48*(3), 457-465.

Spilsbury, J. C., Patel, S. R., Morris, N., Ehayaei, A., & Intille, S. S. (2017). Household chaos and sleep-disturbing behavior of family members: results of a pilot study of African American early adolescents. *Sleep Health, 3*(2), 84-89.

Staples, A. D., Bates, J. E., & Petersen, I. T. (2015). Bedtime routines in early childhood: prevalence, consistency, and associations with nighttime sleep. *Monogr Soc Res Child Dev, 80*(1), 141-159.

Tarokh, L., Saletin, J. M., & Carskadon, M. A. (2016). Sleep in adolescence: Physiology, cognition and mental health. *Neurosci Biobehav Rev, 70*, 182-188.

van Hees, V. T., Fang, Z., Langford, J., Assah, F., Mohammad, A., da Silva, I. C., … Brage, S. (2014). Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol (1985), 117*(7), 738-744.

van Hees, V. T., Sabia, S., Anderson, K. N., Denton, S. J., Oliver, J., Catt, M., … Singh-Manoux, A. (2015). A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. *Plos One, 10*(11), 1-13.

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., … Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: a population-based cohort study. *Mol Autism, 9*(8), 1-9.

Supplementary material

Table S2.1.1. Correlation between sleep problem scales and accelerometer measures

	1	2	3	4	5	6	7	8	9
1. Sleep duration, accelerometer	1								
2. Sleep efficiency, accelerometer	0.521**	1							
3. Sleep onset, accelerometer	-0.648**	0.060	1						
4. Waking time, accelerometer	-0.062	-0.127**	0.581**	1					
5. Sleep problems 1.5 years, maternal report	-0.086*	-0.053	0.078*	0.053	1				
6. Sleep problems 3 years, maternal report	-0.066	-0.047	0.028	-0.013	0.402**	1			
7. Sleep problems 6 years, maternal report	-0.117**	-0.052	0.069*	-0.019	0.350**	0.439**	1		
8. Sleep problems 10 years, maternal report	-0.040	0.026	0.017	-0.061	0.060	0.179**	0.326**	1	
9. Sleep problems 10 years, child report	-0.049	-0.013	0.058	0.033	-0.016	0.053	0.096**	0.213**	1

Pearson's r coefficients are reported for correlations with the sleep parameters.

* Statistically significant at $p < 0.05$

** Statistically significant at $p < 0.01$

Table S2.1.2. Association between pre-school family irregularity (without bedtime routines) and mother- and child-reported sleep problems at ages 3, 6, and 10 years (total sample)

	Maternal reported								Child reported		
	3 year N = 4695			6 year N = 4805			10 year N = 3960			10 year N = 3598		
Family irregularity	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
Model 1	.14	.11–.17	<.01	.13	.10–.16	<.01	.02	-.01–.06	.24	.05	.01–.09	<.01
Model 2	.09	.05–.12	<.01	.07	.05–.10	<.01	.01	-.02–.05	.51	.06	.02–.10	<.01
Model 3	.06	.03–.09	<.01	.07	.04–.10	<.01	.02	-.02–.06	.56	.06	.02–.10	<.01

Model 1 was unadjusted. Model 2 was sex, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Model 3 was adjusted for previous baseline sleep problems at age 1.5 years.

Table S2.1.3. Associations between pre-school family irregularity (without bedtime routines) at age 4 years and objective sleep at age 11 years (accelerometer sample)

	Sleep duration N = 865			Sleep efficiency N = 865			Sleep onset N = 865			Wake time N = 865		
Family irregularity	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
Model 1	-.12	-.21– -.03	<.01	.02	-.07–.11	.67	.15	.06–.24	<.01	.05	-.04-.13	.30
Model 2	-.10	-.19– -.01	.03	.02	-.07–.12	.59	.13	.04–.21	<.01	.04	-.05–.12	.39
Model 3	-.10	-.19–-.01	.03	.03	-.07–.12	.57	.13	.04–.21	<.01	.04	-.05–.12	.41

Model 1 was unadjusted. Model 2 was sex, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Model 3 was adjusted for previous baseline sleep problems at age 1.5 years.

Table S2.1.4. Associations between pre-school family irregularity at age 2 and 4 years and objective sleep at age 11 years (accelerometer sample) (weekdays and weekend days combined)

	Sleep duration N = 865			Sleep efficiency N = 865			Sleep onset N = 865			Wake time N = 865		
Family irregularity	β	CI	*p*	β	CI	*p*	β	CI	*p*	β	CI	*p*
Model 1	-.08	-.15–-.01	<.05	.04	-.03–.12	.24	.13	.06–.19	<.01	.05	-.01–.11	.44
Model 2	-.06	-.14–.01	.07	.05	-.02–.13	.17	.11	.05–.18	<.01	.04	-.02–.10	.20
Model 3	-.06	-.13–.01	.08	.05	-.02–.13	.16	.11	.04–.17	<.01	.04	-.02–.10	.21

Model 1 was unadjusted. Model 2 was sex, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Model 3 was adjusted for previous baseline sleep problems at age 1.5 years.

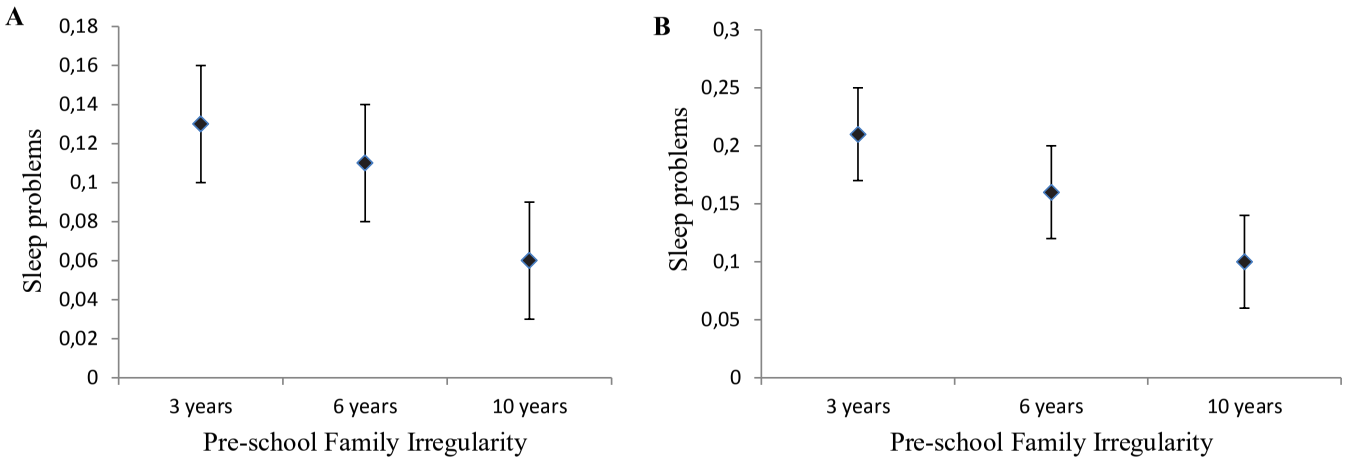

Figure S2.1.1. The longitudinal association of family irregularity and sleep problems.
A. The associations of pre-school family irregularity and sleep problems for each age category were based on linear regression analysis of family irregularity and sleep problems per each age category, adjusted for gender, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Betas are averaged from 10 imputed data sets. **B.** The associations of pre-school family irregularity and sleep problems for each age category were based on generalized linear mixed models of family irregularity and sleep problems per age category. Additionally, they were adjusted for gender, age of the child at sleep assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology. Betas are averaged from 10 imputed data sets.

Chapter 2.2

Genome-wide DNA methylation patterns associated with sleep and mental health in children: A population-based study

M. Elisabeth Koopman-Verhoeff | Rosa H. Mulder | Jared M. Saletin | Irwin Reiss | Gijsbertus T.J. van der Horst | Janine F. Felix | Mary A. Carskadon | Henning Tiemeier | Charlotte A.M. Cecil

Journal of Child Psychology and Psychiatry (2020), in press

Abstract

Objective: DNA methylation (DNAm) has been implicated in the biology of sleep. Yet, how DNAm patterns across the genome relate to different sleep outcomes, and whether these associations overlap with mental health is currently unknown. Here, we investigated associations of DNAm with sleep and mental health in a paediatric population.

Method: This cross-sectional study included 465 10-year-old children (51.3% female) from the *Generation R Study*. Genome-wide DNAm levels were measured using the Illumina450K array (peripheral blood). Sleep problems were assessed from self-report, and mental health outcomes from maternal questionnaires. Wrist actigraphy was used in 188 11-year-old children to calculate sleep duration and midpoint sleep. Weighted gene co-expression network analysis was used to identify highly co-methylated DNAm 'modules', which were tested for associations with sleep and mental health outcomes.

Results: We identified 64 DNAm modules, one of which associated with sleep duration after covariate and multiple-testing adjustment. This module included CpG sites spanning 9 genes on chromosome 17, including *MAPT* – a key regulator of Tau proteins in the brain involved in neuronal function – as well as genes previously implicated in sleep duration. Follow-up analyses suggested that DNAm variation in this region is under considerable genetic control and shows strong blood-brain concordance. DNAm modules associated with sleep did not overlap with those associated with mental health.

Conclusion: We identified one DNAm region associated with sleep duration, including genes previously reported by recent GWAS studies. Further research is warranted to examine the functional role of this region and its longitudinal association with sleep.

Introduction

Sleep is increasingly recognized as an important factor in child mental health. Sleep disturbances, such as short sleep and shifted circadian rhythm, often develop in late childhood and have been implicated in mental health problems (Gregory & Sadeh, 2016; Wolfson & Carskadon, 1998). While poor sleep can exacerbate mental health difficulties (Lovato & Gradisar, 2014; Owens, 2005), mental health problems can also precede and worsen sleep (Verhoeff et al., 2018). Thus, the association between sleep and mental health is complex and likely bidirectional (Gregory & Sadeh, 2016). The mechanisms underlying this association, however, remain unknown.

Complex traits, including sleep, result from the interplay of genetic and environmental influences (Romens, McDonald, Svaren, & Pollak, 2015). How these factors jointly influence normative sleep, or the development of sleep problems, is currently unclear. Epigenetic processes such as DNA methylation (DNAm) have been proposed as a mechanism of interest (Massart et al., 2014; Morales-Lara, De-la-Pena, & Murillo-Rodriguez, 2018). Differential DNAm has been linked to a broad range of developmental outcomes, including sleep, as well as mental and physical health problems (Barker, Walton, & Cecil, 2018; Breton et al., 2017). Most research on this topic emerges from animal models (Gaine, Chatterjee, & Abel, 2018), with only a handful of studies examining DNAm and sleep in humans. These have typically relied on small samples of adults with dysregulated sleep (e.g. shift workers) and utilized a candidate gene approach focusing primarily on 'clock' genes: genes driving circadian rhythms in metabolism, physiology and behaviour (Cedernaes et al., 2015; Gaine et al., 2018; Lahtinen et al., 2019; Wong et al., 2015). In contrast, we are aware of only two epigenetic studies during development, both of which examined adolescence. One reported an association in 18-19 year-olds between sleep duration and DNAm of DOCK1, a gene influenced by circadian rhythmicity (Huang et al., 2017). The second found that higher DNAm in metabolic genes PPARA and HSD11B2 was associated with shorter sleep, specifically in girls (E. C. Jansen et al., 2019).

Despite these promising preliminary findings, existing research has been limited in four key ways, namely (i) the use of small samples of adults or older adolescents; (ii) a focus on a candidate gene approach; (iii) the lack of multi-modal assessments of sleep, making it unclear whether associations between sleep and DNAm differ between self-report and objective measures (e.g., actigraphy); and (iv) despite evidence showing that mental health is related to DNAm alterations (Barker et al., 2018) and sleep (Gregory & Sadeh, 2016), no study has examined these factors jointly.

To address these gaps, we examined the relationship between genome-wide DNAm, sleep and mental health in a general population sample of 10-year old children – an important period for development of sleep and mental health problems alike. The aims of our study were two-fold: first, to characterize cross-sectional associations of DNAm with reported (i.e. dyssomnia symptoms) and actigraphy-assessed (i.e. sleep duration and midpoint) sleep using both a genome-wide approach and an targeted approach focusing on well-characterized clock genes to maximise comparability with existing studies; and second, to investigate whether sleep-associated DNAm patterns are also associated with common mental health problems. Findings were tested for consistency in a small independent sample.

Methods

Participants

This cross-sectional study included 10-year-old children of European ancestry (51.3% female) from the *Generation R Study*, a prospective population-based cohort from foetal life onward. Pregnant women (expected delivery date April 2002–January 2006) living in Rotterdam, the Netherlands, were invited to participate (Kooijman et al., 2016). The current analyses are based on children who had DNAm data and subjectively assessed sleep (n = 410). Of these, 188 also had actigraphy data. Written informed consent was obtained for all participants. The Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam approved the study.

Measures

DNA Methylation

Five-hundred nanograms of DNA were extracted from peripheral blood at age 10 and underwent bisulfite conversion with the EZ-96 DNA Methylation kit (Shallow) (Zymo Research Corporation, Irvine, USA). Samples were plated onto 96-well plates in no specific order. DNAm was analyzed with the Illumina Infinium Human Methylation 450K BeadChip (Illumina Inc., San Diego, USA). Quality control of samples was performed using standardized criteria using the CPACOR workflow (Lehne et al., 2015). Probes with a detection p-value above background ≥ 1E-16 were set to missing per array. Arrays with observed technical problems including failed bisulfite conversion, hybridization or extension, and arrays with a mismatch between child sex and sex determined by the chr X and Y probe intensities were

removed. Nonautosomal probes were excluded. Additionally, only arrays with a call rate > 95% per sample were processed further. Methylation beta values outside a range of the 25th percentile minus 3*interquartile range to the 75th percentile plus 3*interquartile range were set to missing. The final dataset contained 425 samples, analyzing 458,563 CpG sites. For our targeted approach, we examined DNAm levels of CpG sites that were annotated to well-characterized clock-related genes (939 CpG sites across 39 genes (van den Berg et al., 2017, Table S2.2.1). For each CpG site, Beta values represent the ratio of methylated signal relative to the sum of (the methylated and unmethylated signals plus 100).

Child-reported dyssomnia symptoms

At age 10 years, children completed six questions of the Sleep Disturbance Scale for Children (Bruni et al., 1996) about perceived sleep, for example, "Do you find it difficult to fall asleep?"; "If you wake up at night, do you find it difficult to fall asleep again?"; "Do you feel rested when you wake in the morning?" (previously described in Koopman-Verhoeff et al., 2019). The questions were rephrased for our paediatric population. Responses were scored on a three-point Likert scale ("No", "Sometimes" or "Yes"; $\alpha = 0.64$). Items were summed; higher scores indicate greater sleep problems.

Actigraphy-estimated sleep

Sleep patterns were estimated with wrist tri-axial actigraphy (GENEActiv) on the non-dominant wrist for 5 consecutive school nights in 188 children at age 11 (i.e. after DNA sampling) (Koopman-Verhoeff et al., 2018; Koopman-Verhoeff et al., 2019). The Geneactiv accelerometers were set a frequency of 50 Hz. The binary files were processed with the R-package GGIR (van Hees et al., 2014). Accompanying sleep diaries were collected and used to guide actigraphy analyses. Sleep duration was estimated as the total time scored sleep between falling asleep and final waking. Sleep midpoint was estimated as the halfway point between sleep onset and final waking. Sleep duration and midpoint were averaged across the week, excluding weekends to best approximate typical school-day sleep patterns and to minimize the influence of atypical weekend events.

Child psychopathology

The Child Behavior Checklist 6-18 (CBCL/6-18) was assessed using maternal-reports at age 10 to derive broadband Internalizing and Externalizing problem-scales (Achenbach & Rescorla, 2001). The CBCL/6-18 is widely used internationally and

has been found to be generalizable across 23 societies, including the Netherlands (Ivanova et al., 2010). Mothers rated various emotional and behavioural problems of the child in the previous six months on a three-point scale (0 = not true, 1 = somewhat true, 2 = very true).

Covariates

Sex of the child was obtained from medical records and maternal characteristics by questionnaires. Maternal education was defined by the highest attained educational level and classified into two categories (higher vocational education and university: yes or no). Correction for sample plate and cell type proportions was also applied. We used the Houseman method (Houseman et al., 2012) to estimate relative proportions of six white blood cell subtypes (CD4+ T-lymphocytes, CD8+ T-lymphocytes, NK (natural killer) cells, B-lymphocytes, monocytes and granulocytes), based on a standard reference population (Reinius et al., 2012).

Statistical analysis

We had nearly complete cases, with four participants missing data on maternal education (defined as highest educational level). These participants were excluded from the analysis. Statistical analyses were performed in R (R Core Team, 2014), following three steps:

Step 1. Associations between DNA methylation and sleep

We applied weighted gene co-expression network analysis (WGCNA, Langfelder & Horvath, 2008) – a system-level data reduction approach – to reduce the dimensionality of the data and identify clusters (so called 'modules') of highly co-methylated DNAm sites across genome. As such, rather than focusing on individual sites or genes, WGCNA enables utilization of correlation patterns between sites to identify wider DNAm networks, which may also be functionally related (Botía et al., 2017). Block-wise network construction was run using default settings (power threshold of 6; minimal module size of 30 sites; merge cut height of 0.25). Each derived module was coloured by size automatically and summarized by a 'module eigengene' (ME) value, the first principal component of the given module. We numbered the derived modules by significance with outcome for simplicity. CpG sites that do not co-methylate were assigned to an 'unclassified' module. WGCNA analyses were performed twice: first based on the entire genome-wide data (i.e. hypothesis

free; n = 458,563 sites), and second based on the subset of clock genes (i.e., targeted approach, n = 939 CpG sites).

Next, we tested bivariate correlations between the co-methylated modules and the three sleep outcomes (i.e. child-reported dyssomnia symptoms, actigraphy-estimated sleep duration and midpoint sleep). We selected modules that were associated with sleep outcomes after Bonferroni correction for multiple testing (0.05/n modules*3 sleep measures) (Chuang et al., 2017). These modules were further examined using linear regression models controlling for batch, cell-types, child sex and age, and maternal education.

Modules that were significantly associated with sleep were examined further using publicly available resources to characterize (i) their genomic location; (ii) potential genetic influences, by checking whether the CpG sites included in the modules are known to be polymorphic (i.e. overlapping with single nucleotide polymorphisms [SNPs]; Chen et al., 2013), linked to methylation quantitative trait loci (mQTLs; i.e. SNPs that associate with DNAm levels, either in cis or in trans; http://www.mqtldb.org/; GCTA set; Gaunt et al., 2016) or heritable, based on twin data (i.e. explained by additive genetic influences as opposed to shared and non-shared environmental influences; Hannon et al., 2018); and (iii) blood-brain concordance, based on postmortem data from 122 individuals with DNAm from whole blood and four brain regions (the prefrontal cortex, entorhinal cortex, superior temporal gyrus, and cerebellum (https://epigenetics.essex.ac.uk/bloodbrain/; Hannon, Lunnon, Schalkwyk, & Mill, 2015).

Step 2: Testing the overlap of associations with mental health

Bivariate correlations between the co-methylated modules, sleep and mental health measures were examined to establish whether associations of DNAm and sleep are co-localized on the genome with associations of DNAm and internalizing and externalizing problems.

Step 3. Generalizability in independent sample

Associations identified in Steps 1 and 2 were estimated in an independent sample of 63 older adolescents (14.5 ± 0.3 years, 54% girls) of the Generation R Study to judge generalizability of results, with information on DNAm available at 10 years and actigraphy-assessed sleep at 14 years (i.e. prospective association). The children in this sample were recruited for a second actigraphy study at a later age than the first study described above due to logistic reasons (no repeated measurements).

Results

Characteristics of the study sample are presented in Table 2.2.1. For correlations across sleep and mental health variables, see Supplementary Table 2.2.2. The average midpoint sleep was 2:49 (SD = 35 min) and the mean sleep duration was 7:36 (SD = 40 min).

Table 2.2.1. Sample characteristics

Demographics	Reported dyssomnia symptoms (N = 410)	Actigraphic sleep (N = 188)
Sex, female, %	234 (50.3%)	93 (49.5%)
Age (years)	9.8 ± 0.3	11.7 ± 0.1
Maternal education, %		
Low & Intermediate	152 (32.7%)	64 (34.0%)
High	308 (66.2%)	121 (64.4%)
Dyssomnia symptoms, self-reported (score;range)	10.80 (8.00–18.00)	10.86 (6.00–17.00)
Sleep duration, actigraphy (hours:minutes)	-	7:35 ± 0:44
Midpoint sleep, actigraphy, time (hours:minutes)	-	02:48 ± 0:35
Internalizing problems, mother-reported, mean (SD)	4.16 (4.38)	4.03 (4.28)
Externalizing problems, mother-reported, mean (SD)	3.41 (4.25)	3.16 (3.82)

1. Are DNAm patterns associated with sleep outcomes in children?

Genome-wide analyses

We identified 64 co-methylated modules, containing between 30 and 65,804 CpG sites (Table S2.2.3). The majority of sites were unclassified (n = 261,374), suggesting they did not correlate strongly enough to form modules. Two modules correlated with sleep after Bonferroni correction for multiple testing (0.05/64 modules * 3 outcomes = 0.00026042) – both of which associated with sleep duration (module1 r = -0.18, p = 0.00006, module2 r = -0.18, p = 0.0001) (Table 2.2.2), but not with sleep midpoint or dyssomnia symptoms. Only the association between module1 and sleep duration remained significant in a regression model adjusting for covariates (ß = -0.22, 95 CI% -0.37–-0.07, p = 0.004). As a sensitivity analysis we replaced the missing values (n = 4) on maternal highest educational level attained by maternal highest educational level, yielding highly consistent results. Additionally, as time of blood sampling corrected for the time of habitual awakening could be of influence,

Table 2.2.2. Associations between DNAm modules and actigraphy-derived sleep duration in children (N = 188)

	A. Correlations of the WGCNA modules with sleep duration				B. Standardized regression coefficients		
Module	*r*	*p*	N cpgs	N genes	β	CI	*p*
Module1	**-0.18**	**0.00006**	**32**	**9**	**-.22**	**-.37–-.07**	**0.004**
Module2	-0.18	0.0001	5845	3462	-.14	-.54–36	0.07

we re-ran analyses adjusting for these variables, and found that results remained highly consistent (ß = -0.19, 95 CI% -0.34–-0.05, p = 0.008). Lastly, as cell proportions are estimated, rather than derived from actual cell counts, we re-ran analyses without cell type correction to test stability of associations, and found that results were highly consistent (ß = -0.22, 95 CI% -0.36–-0.07, p = 0.004).

Targeted circadian clock CpG site analyses

The targeted WGCNA approach containing exclusively clock-related genes identified 5 modules (ranging from 19–300 CpG sites over 10–39 genes), each including CpG sites spanning multiple genes, as opposed to clustering by gene. The majority of the CpG sites were unclassified (n = 540). No modules were associated with sleep outcomes after multiple testing correction.

Functional characterization of module1 (Table S2.2.4)

Annotation to genes and genomic region. Module1 contained 32 sites spanning 9 genes. The largest number of sites (n = 6) were annotated to the Microtubule-Associated Protein Tau (*MAPT*) gene. The CpCs of module1 were highly correlated with each other (Figure 2.2.1), as well as with sleep duration and were all located in the chromosome 17q21.31 region, chr17:43502999-62843696, with the exception of one CpG site on chromosome 5.

Genetic influences. Six of the CpGs included in module1 were previously identified as polymorphic (three of which in *MAPT*), and twelve (37.5%) were found to be associated to mQTLs on chromosome 17, with a total of 71 associations (between 4 and 10 associations per CpG). The CpG site located on chromosome 5 (cg07870213) associated with both mQTLs on chromosome 5 in cis as well as chromosome 17 in trans, all of which were located in the module1 region (chr17:41993881-44852612).

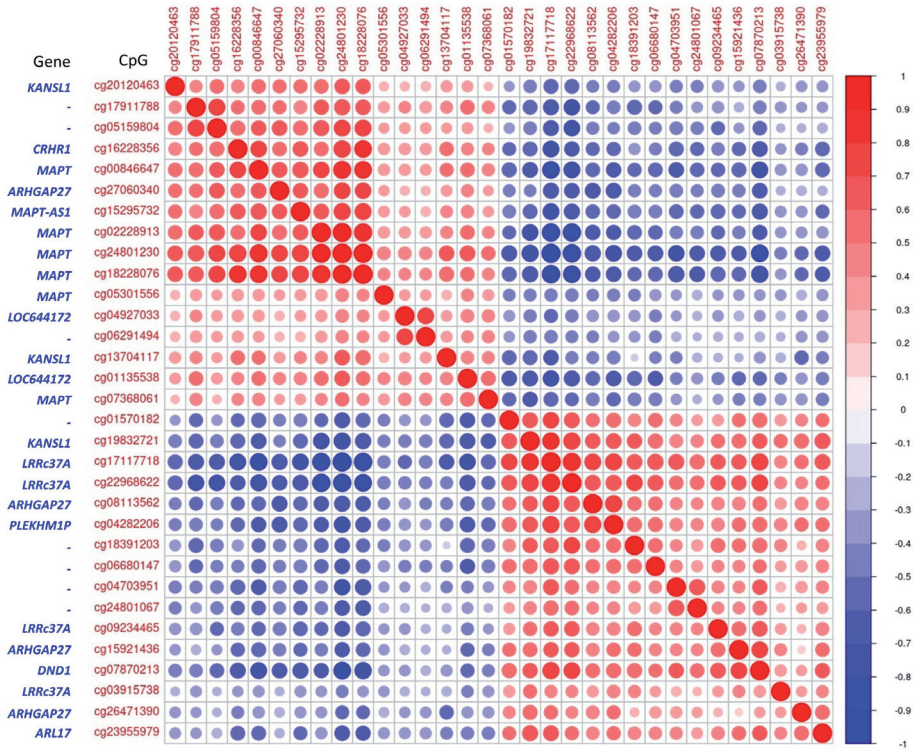

Figure 2.2.1. Intercorrelations between CpG sites in module1.

Finally, 10 of the 32 CpG sites in module1 had twin heritability estimates available, all of which showed moderate to strong genetic influences (r = 0.34–1.00).

Blood-brain concordance. For all but one of the CpG sites in module1, DNAm levels in blood correlated significantly with DNAm levels in at least one brain region. The three MAPT CpG sites that associated most strongly with sleep duration showed high blood-brain correlations (Figure S2.2.1). Of these, cg24801230 (one of the sites found to be polymorphic) showed an almost perfect correlation (r = 0.99) between blood and brain, with DNAm levels across tissues clustering into three alleles (Figure S2.2.1).

2. Are DNAm-sleep associations overlapping with child psychiatric symptoms?
No modules were associated with internalizing and externalizing problems after correction for multiple testing. Generally, we found weak associations between the DNAm modules and internalizing (strongest association: r = 0.15, p = 0.001) and

externalizing problems (strongest association: $r = 0.14$, $p = 0.002$). Associated modules did not overlap with those identified for sleep duration (Figure S2.2.2).

3. Are results consistent in an independent sample?

The association between module1 and sleep duration was tested in an independent sample of older children, in order to test for consistency across developmental stage. Results from a regression analysis, controlling for covariates, yielded a highly comparable effect size (Discovery: ß = -0.22, 95 CI% -0.37–-0.07, $p = 0.004$; Generalization sample: ß = -0.23, 95 CI% -0.50–0.04, $p = 0.09$), although the association was not statistically significant, likely due to the larger confidence intervals resulting from the use of a smaller sample (1/3 of discovery sample).

Discussion

The current study utilized a network-based approach to investigate associations between genome-wide DNA methylation, sleep, and mental health in a pediatric population. We highlight here two key findings. First, we found that DNAm patterns associated with sleep duration, but not with other sleep parameters. Specifically, our hypothesis-free analyses identified one DNAm module associated with actigraphy-assessed sleep duration. This module (i) contained 32 sites annotated to multiple genes previously linked to sleep duration in GWASes, including MAPT; (ii) showed strong evidence of genetic influences based on molecular and twin data; and (iii) showed cross-tissue concordance between blood and brain. In contrast, hypothesis-driven analyses did not reveal associations between DNAm in clock genes and sleep parameters. Second, we found that DNAm patterns were only weakly associated with mental health outcomes. These associations did not overlap with those identified for sleep outcomes, suggesting co-methylation modules associated with sleep and mental health are largely independent.

Self-reported and actigraphic sleep assess distinct sleep domains (Gregory & Sadeh, 2016; Meltzer et al., 2012), as reflected in the weak correlations between these metrics found in the present study. Of note, self-reported measures capture sleep perception and reports may be biased by subject characteristics. Interestingly, we found here that DNAm associated with actigraphic sleep duration but not with self-reported dyssomnia. This could be due to the fact that actigraphic sleep shows greater variability in the general population and has less measurement error (Sadeh,

2011). Furthermore, we did not find associations between DNAm and actigraphic determined midpoint sleep. Nights assessed in our sample have been constrained by school schedules, limiting variability in midpoint. Since circadian preference changes during adolescence (Crowley, Wolfson, Tarokh, & Carskadon, 2018) future research should study the longitudinal association between DNAm, and sleep and circadian rhythm across this age period.

Most epigenetic research on sleep in humans has focused on sleep deprivation (Gaine et al., 2018). In this study, we show that DNAm patterns associate with typical variation in sleep in 10-year old children. Specifically, one DNAm module was found to associate with actigraphic sleep duration. This association was generalizable to a smaller, independent sample of Generation R participants at age 14 years. The lack of significance could be due to low power in this smaller sample. The fact that we found a generally comparable effect size supports the robustness of our findings.

The sleep-associated module contained 32 CpG sites spanning a large region on chromosome 17. Based on accessible databases, we found that several of the sites in the module were located directly on SNPs, and over a third were linked to known mQTLs. Intriguingly, the one CpG site in this module on chromosome 5 was associated with multiple mQTLs located within the chromosome 17 region, supporting a genetically-driven link in DNAm patterns between these two chromosomal regions. Genetic influences were further corroborated by twin data showing moderate-to-high heritability estimates for DNAm sites in this module. Together, these findings suggest that underlying genetic variation might largely account for observed associations between DNAm in this region and sleep duration. This is in line with existing literature indicating that variation in DNAm is best explained by genetic influences and gene-environment interactions, as opposed to environmental main effects (Czamara et al., 2019; Teh et al., 2014). Finally, DNAm variability in the identified module showed high blood-brain concordance, highlighting that the signals currently found in blood might be useful proxies for DNAm status in the brain. Future studies will need to test concordance with other brain areas implicated in sleep duration, e.g. the hypothalamus, and establish whether the degree of correspondence differs across specific cell-types in the brain.

Of the 9 genes annotated to our module, several stood out for their role in brain-related processes and previous links to sleep outcomes based on GWAS data. Specifically, a single-nucleotide polymorphism (SNP) in *MAPT* was recently identified

as a top GWAS hit for self-reported sleep duration (Dashti et al., 2019) and SNPs in *MAPK81P1P2* and *KANSL1-AS1* were identified as top hits in a GWAS on accelerometer-based sleep duration (Doherty et al., 2018). Additionally, a study based on UK Biobank and 23andMe data indicated that variants in *ARHGAP27*, *LRRC37A*, *CRHR1*, *MAPT*, and *KANSL1* associated with various self-reported sleep traits, including sleep duration (P. R. Jansen et al., 2019). These findings further support genetic influences on DNAm and sleep duration in this region.

The most strongly associated probe in module1 was annotated to the *MAPT* antisense RNA 1, a non-protein coding RNA gene identified as epigenetic regulator of *MAPT* expression (Coupland et al., 2016), while six sites where annotated to the *MAPT* gene itself. *MAPT* encodes the Tau protein, which is important for neuronal stabilization. Its aberrant aggregation has been frequently linked to Alzheimer's disease and other neurodegenerative diseases (Wang & Mandelkow, 2015) as well as neurodevelopmental disorders (Rankovic & Zweckstetter, 2019). A recent study suggested the involvement of Tau proteins and sleep in the pathogenesis of neurodegenerative diseases, though this process is not yet fully understood (Cantero et al., 2010; Musiek & Holtzman, 2016). Another gene annotated to module1 was *CRHR1* (corticotropin-releasing hormone receptor 1), a pivotal player in hypothalamic-pituitary-adrenal axis functioning (Wasserman, Wasserman, & Sokolowski, 2010) as well as sleep (Romanowski et al., 2010). Our study adds to this growing body of evidence by showing for the first time that, in childhood, epigenetic variation in *MAPT* and surrounding regions are associated with sleep duration.

The epigenetic patterns associated with sleep in this study did not overlap with those associated with mental health. This may be due to several reasons. First, although the link between sleep and mental health is well-established (Gregory & Sadeh, 2016), it is possible that such associations may not be epigenetically-mediated. Second, associations between sleep and mental health tend to be stronger for self-report than objective measures (Gregory & Sadeh, 2012). As such, there might be different underlying biological correlates driving the associations between mental health and reported sleep and actigraphic derived sleep. For example, cortisol levels, associated with anxiety and depression, have been linked to self-reported sleep quality but not to actigraphy-derived sleep quantity (Bassett, Lupis, Gianferante, Rohleder, & Wolf, 2015). Third, our population-based cohort may have lacked psychiatric severity to detect shared associations. Future studies are needed to clarify the mechanisms underlying associations between sleep and mental health.

Limitations and future directions

This study has several limitations. First, from our cross-sectional data, we are unable to determine the direction of effect for the association between DNAm and sleep regulation, and we cannot exclude that the observed association may result from a common influence (e.g. environmental or genetic modulation). In the future, the use of longitudinal data on DNAm and sleep, the application of advanced causal inference methods (e.g. two-step Mendelian randomization), as well as integration with genetic data will mark important steps for furthering our understanding of DNAm-sleep associations. Second, the sample was based on participants of European ancestry. Studies including other ethnicities are necessary to investigate the generalizability of our findings. Third, our independent sample was smaller, limiting statistical power. Fourth, our measure of midpoint sleep, derived from actigraphy, is constrained by school schedules. Studying free nights may better describe underlying circadian processes. Fifth, while we assume that focusing on modules as opposed to single sites may help us to identify broader, functionally meaningful DNAm networks associated with sleep, (a) this does not preclude that there may be important sleep-associated single CpG sites, which might have been missed by using this approach; and (b) integration with gene expression data will be necessary to establish the extent to which the identified module may play a regulatory role, which we could not do in our study. In addition to the clock genes tested in the current study, it would be interesting to examine associations with CpG sites annotated to genes that have been previously implicated in other sleep parameters, such as sleep duration or chronotype (e.g. by GWAS studies). Sixth, the blood-brain concordance tool we used is based on an elderly population. As such, it is unclear to what extent the identified pattern of concordance extends to the pediatric population, for which there are currently no available tools. Finally, it is unclear whether identified DNAm patterns are functionally relevant. The use of experimental models could inform the biological consequences of these associations. Additionally, it is important to see in future studies whether DNA methylation levels at these sites change across development. If there is no change in DNA methylation levels over time, this could indicate that a regulatory process is acting from birth, whereas an epigenetic mark that changes throughout life might indicate that it may be responsive to environmental stimuli.

Conclusion

In summary, the preliminary results of the current study show promising sleep-associated DNAm patterns in the pediatric population. Specifically, we identified an association between sleep duration and DNAm in the 17q21.31 region, spanning multiple genes previously linked to sleep by GWAS studies, including *MAPT*. These epigenetic patterns did not overlap with those associated with self-reported sleep problems, midpoint sleep or mental health. Future studies are needed to replicate our findings and establish causality. Overall, our findings offer novel insights into epigenetic patterns associated with typical variation in sleep duration in children.

References

Achenbach, T. A., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Barker, E. D., Walton, E., & Cecil, C. A. M. (2018). Annual Research Review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. *J Child Psychol Psychiatry*, *59*(4), 303-322.

Bassett, S. M., Lupis, S. B., Gianferante, D., Rohleder, N., & Wolf, J. M. (2015). Sleep quality but not sleep quantity effects on cortisol responses to acute psychosocial stress. *Stress*, *18*(6), 638-644.

Botía, J. A., Vandrovcova, J., Forabosco, P., Guelfi, S., D'Sa, K., Hardy, J., . . . The United Kingdom Brain Expression, C. (2017). An additional k-means clustering step improves the biological features of WGCNA gene co-expression networks. *BMC Systems Biology*, *11*(1), 47.

Breton, C. V., Marsit, C. J., Faustman, E., Nadeau, K., Goodrich, J. M., Dolinoy, D. C., . . . Murphy, S. K. (2017). Small-Magnitude Effect Sizes in Epigenetic End Points are Important in Children's Environmental Health Studies: The Children's Environmental Health and Disease Prevention Research Center's Epigenetics Working Group. *Environ Health Perspect*, *125*(4), 511-526.

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res*, *5*(4), 251-261.

Cantero, J. L., Hita-Yanez, E., Moreno-Lopez, B., Portillo, F., Rubio, A., & Avila, J. (2010). Tau protein role in sleep-wake cycle. *Journal of Alzheimer's disease : JAD*, *21*(2), 411-421.

Cedernaes, J., Osler, M. E., Voisin, S., Broman, J. E., Vogel, H., Dickson, S. L., . . . Benedict, C. (2015). Acute Sleep Loss Induces Tissue-Specific Epigenetic and Transcriptional Alterations to Circadian Clock Genes in Men. *J Clin Endocrinol Metab*, *100*(9), E1255-1261.

Chen, Y.-a., Lemire, M., Choufani, S., Butcher, D. T., Grafodatskaya, D., Zanke, B. W., . . . Weksberg, R. (2013). Discovery of cross-reactive probes and polymorphic CpGs in the Illumina Infinium HumanMethylation450 microarray. *Epigenetics*, *8*(2), 203-209.

Chuang, Y. H., Paul, K. C., Bronstein, J. M., Bordelon, Y., Horvath, S., & Ritz, B. (2017). Parkinson's disease is associated with DNA methylation levels in human blood and saliva. *Genome Med*, *9*(1), 76-88.

Coupland, K. G., Kim, W. S., Halliday, G. M., Hallupp, M., Dobson-Stone, C., & Kwok, J. B. J. (2016). Role of the Long Non-Coding RNA MAPT-AS1 in Regulation of Microtubule Associated Protein Tau (MAPT) Expression in Parkinson's Disease. *Plos One*, *11*(6), e0157924-e0157924.

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the perfect storm model. *J Adolesc*, *67*, 55-65.

Czamara, D., Eraslan, G., Page, C. M., Lahti, J., Lahti-Pulkkinen, M., Hämäläinen, E., . . . Major Depressive Disorder Working Group of the Psychiatric Genomics, C. (2019). Integrated analysis of environmental and genetic influences on cord blood DNA methylation in new-borns. *Nature Communications*, *10*(1), 2548-2566.

Dashti, H. S., Jones, S. E., Wood, A. R., Lane, J. M., van Hees, V. T., Wang, H., . . . Saxena, R. (2019). Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nature Communications*, *10*(1), 1100-1112.

Doherty, A., Smith-Byrne, K., Ferreira, T., Holmes, M. V., Holmes, C., Pulit, S. L., & Lindgren, C. M. (2018). GWAS identifies 14 loci for device-measured physical activity and sleep duration. *Nature Communications*, *9*(1), 5257-5265.

Gaine, M. E., Chatterjee, S., & Abel, T. (2018). Sleep Deprivation and the Epigenome. *Front Neural Circuits*, *12*, 14-24.

Gaunt, T. R., Shihab, H. A., Hemani, G., Min, J. L., Woodward, G., Lyttleton, O., . . . Relton, C. L. (2016). Systematic identification of genetic influences on methylation across the human life course. *Genome Biology*, *17*(1), 61-75.

Gregory, A. M., & Sadeh, A. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews*, *16*(2), 129-136.

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders--a review of the latest science. *J Child Psychol Psychiatry*, *57*(3), 296-317.

Hannon, E., Knox, O., Sugden, K., Burrage, J., Wong, C. C. Y., Belsky, D. W., . . . Mill, J. (2018). Characterizing genetic and environmental influences on variable DNA methylation using monozygotic and dizygotic twins. *Plos Genetics*, *14*(8), e1007544-e1007571.

Hannon, E., Lunnon, K., Schalkwyk, L., & Mill, J. (2015). Interindividual methylomic variation across blood, cortex, and cerebellum: implications for epigenetic studies of neurological and neuropsychiatric phenotypes. *Epigenetics*, *10*(11), 1024-1032.

Houseman, E. A., Accomando, W. P., Koestler, D. C., Christensen, B. C., Marsit, C. J., Nelson, H. H., . . . Kelsey, K. T. (2012). DNA methylation arrays as surrogate measures of cell mixture distribution. *BMC bioinformatics*, *13*(1), 1-16.

Huang, H., Zhu, Y., Eliot, M. N., Knopik, V. S., McGeary, J. E., Carskadon, M. A., & Hart, A. C. (2017). Combining Human Epigenetics and Sleep Studies in Caenorhabditis elegans: A Cross-Species Approach for Finding Conserved Genes Regulating Sleep. *Sleep*, *40*(6), 1-13.

Ivanova, M. Y., Achenbach, T. M., Rescorla, L. A., Harder, V. S., Ang, R. P., Bilenberg, N., . . . Verhulst, F. C. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry*, *49*(12), 1215-1224.

Jansen, E. C., Dolinoy, D. C., O'Brien, L. M., Peterson, K. E., Chervin, R. D., Banker, M., . . . Goodrich, J. M. (2019). Sleep duration and fragmentation in relation to leukocyte DNA methylation in adolescents. *Sleep*, 1-9.

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., . . . The 23andMe Research, T. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics*, *51*(3), 394-403.

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van, I. M. H., . . . Jaddoe, V. W. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology*, *31*(12), 1243-1264.

Koopman-Verhoeff, M. E., Bolhuis, K., Cecil, C. A. M., Kocevska, D., Hudziak, J. J., Hillegers, M. H. J., . . . Tiemeier, H. (2018). During day and night: Childhood psychotic experiences and objective and subjective sleep problems. *Schizophr Res*, *206*, 127-134.

Koopman-Verhoeff, M. E., Serdarevic, F., Kocevska, D., Bodrij, F. F., Mileva-Seitz, V. R., Reiss, I., . . . Luijk, M. (2019). Preschool family irregularity and the development of sleep problems in childhood: a longitudinal study. *J Child Psychol Psychiatry*, *60*(8),857-865.

Lahtinen, A., Puttonen, S., Vanttola, P., Viitasalo, K., Sulkava, S., Pervjakova, N., . . . Paunio, T. (2019). A distinctive DNA methylation pattern in insufficient sleep. *Scientific Reports*, *9*(1), 1193-1202.

Langfelder, P., & Horvath, S. (2008). WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics*, *9*, 559-572.

Lehne, B., Drong, A. W., Loh, M., Zhang, W., Scott, W. R., Tan, S.-T., . . . Elliott, P. (2015). A coherent approach for analysis of the Illumina HumanMethylation450 BeadChip improves data quality and performance in epigenome-wide association studies. *Genome Biol*, *16*(1), 37-49.

Lovato, N., & Gradisar, M. (2014). A meta-analysis and model of the relationship between sleep and depression in adolescents: recommendations for future research and clinical practice. *Sleep Medicine Reviews*, *18*(6), 521-529.

Massart, R., Freyburger, M., Suderman, M., Paquet, J., El Helou, J., Belanger-Nelson, E., . . . Mongrain, V. (2014). The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes. *Transl Psychiatry*, *4*, e347-e355.

Meltzer, L. J., Biggs, S., Reynolds, A., Avis, K. T., Crabtree, V. M., & Bevans, K. B. (2012). The Children's Report of Sleep Patterns – Sleepiness Scale: A self-report measure for school-aged children. *Sleep Medicine*, *13*(4), 385-389.

Morales-Lara, D., De-la-Pena, C., & Murillo-Rodriguez, E. (2018). Dad's Snoring May Have Left Molecular Scars in Your DNA: the Emerging Role of Epigenetics in Sleep Disorders. *Mol Neurobiol*, *55*(4), 2713-2724.

Musiek, E. S., & Holtzman, D. M. (2016). Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science (New York, N Y)*, *354*(6315), 1004-1008.

Owens, J. A. (2005). The ADHD and sleep conundrum: a review. *Journal of Developmental and Behavioral Pediatrics*, *26*(4), 312-322.

Rankovic, M., & Zweckstetter, M. (2019). Upregulated levels and pathological aggregation of abnormally phosphorylated Tau-protein in children with neurodevelopmental disorders. *Neuroscience & Biobehavioral Reviews*, *98*, 1-9.

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

Reinius, L. E., Acevedo, N., Joerink, M., Pershagen, G., Dahlén, S.-E., Greco, D., . . . Kere, J. (2012). Differential DNA methylation in purified human blood cells: implications for cell lineage and studies on disease susceptibility. *Plos One*, *7*(7), e41361-e41361.

Romanowski, C. P. N., Fenzl, T., Flachskamm, C., Wurst, W., Holsboer, F., Deussing, J. M., & Kimura, M. (2010). Central deficiency of corticotropin-releasing hormone receptor type 1 (CRH-R1) abolishes effects of CRH on NREM but not on REM sleep in mice. *Sleep*, *33*(4), 427-436.

Romens, S. E., McDonald, J., Svaren, J., & Pollak, S. D. (2015). Associations between early life stress and gene methylation in children. *Child Development*, *86*(1), 303-309.

Sadeh, A. (2011). The role and validity of actigraphy in sleep medicine: An update. *Sleep Medicine Reviews*, *15*(4), 259-267.

Teh, A. L., Pan, H., Chen, L., Ong, M.-L., Dogra, S., Wong, J., . . . Holbrook, J. D. (2014). The effect of genotype and in utero environment on interindividual variation in neonate DNA methylomes. *Genome Research*, *24*(7), 1064-1074.

van den Berg, C. B., Chaves, I., Herzog, E. M., Willemsen, S. P., van der Horst, G. T. J., & Steegers-Theunissen, R. P. M. (2017). Early- and late-onset preeclampsia and the DNA methylation of circadian clock and clock-controlled genes in placental and newborn tissues. *Chronobiol Int*, *34*(7), 921-932.

van Hees, V. T., Fang, Z., Langford, J., Assah, F., Mohammad, A., da Silva, I. C., . . . Brage, S. (2014). Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol* (1985), *117*(7), 738-744.

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., . . . Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: a population-based cohort study. *Mol Autism*, *9*(8), 1-9.

Wang, Y., & Mandelkow, E. (2015). Tau in physiology and pathology. *Nature Reviews Neuroscience*, *17*, 5-21.

Wasserman, D., Wasserman, J., & Sokolowski, M. (2010). Genetics of HPA-axis, depression and suicidality. *European Psychiatry*, *25*(5), 278-280.

Wolfson, A. R., & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Dev*, *69*(4), 875-887.

Wong, C. C., Parsons, M. J., Lester, K. J., Burrage, J., Eley, T. C., Mill, J., . . . Gregory, A. M. (2015). Epigenome-Wide DNA Methylation Analysis of Monozygotic Twins Discordant for Diurnal Preference. *Twin Res Hum Genet*, *18*(6), 662-669.

Supplementary material

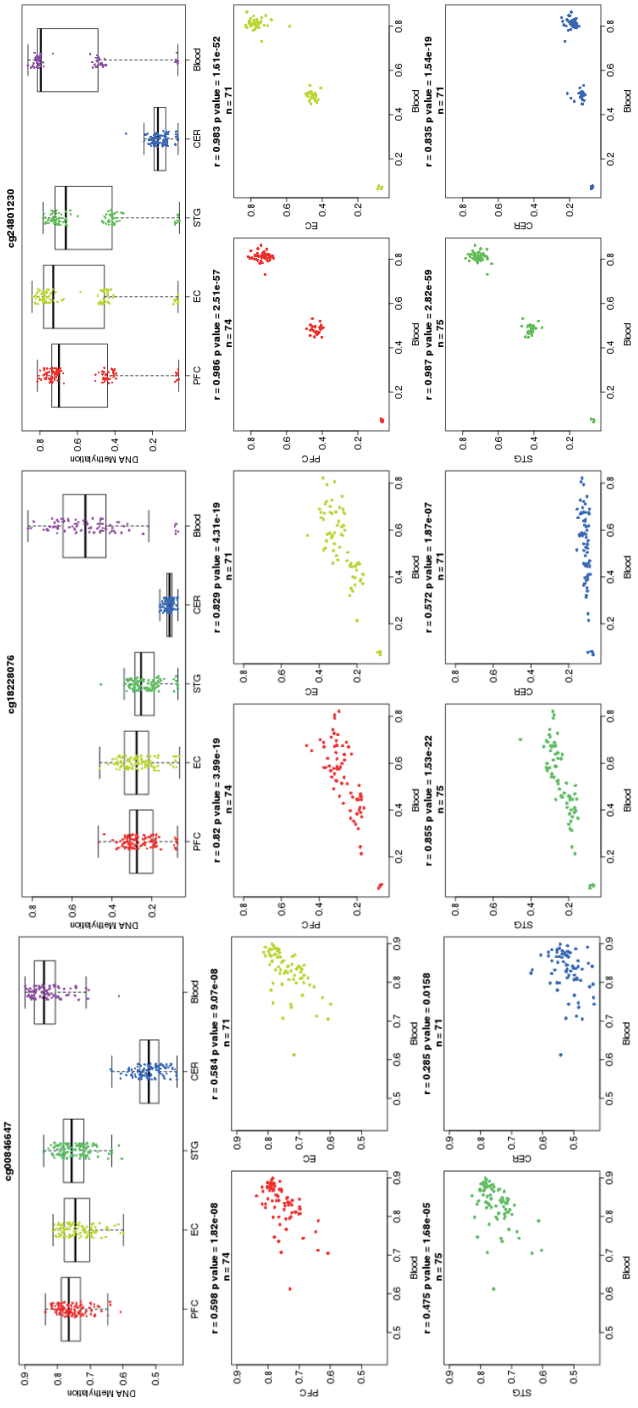

Figure S2.2.1. Blood-brain associations of *MAPT* CpG sites.
Correlation between DNA methylation levels in blood vs brain tissue across three CpG sites in module1 annotated to the *MAPT* gene. PFC: Prefrontal cortex; EC: Entorhinal cortex; STG: Superior temporal gyrus; CER: Cerebellum (https://epigenetics.essex.ac.uk/bloodbrain/; Hannon, Lunnon, Schalkwyk, & Mill, 2015).

Table S2.2.1. Selection of clock and clock-related genes based on van den Berg et al., 2017 (n_{genes} = 39; n_{CpGs} = 939)

Gene	CpG (n)	Gene	CpG (n)	Gene	CpG (n)
AKT1	41	*FOXO3*	44	*PRDX6*	15
ARNTL	23	*GSK3B*	19	*PRKAA1*	9
ARNTL2	13	*MAPK1*	18	*PRKAB1*	11
BHLHE40	19	*NPAS2*	34	*PRKACA*	23
BHLHE41	16	*NR1D1*	24	*PRKCA*	79
CLOCK	14	*NR1D2*	17	*RORA*	106
CRTC1	40	*PER1*	18	*RORB*	11
CRY1	14	*PER2*	24	*RORC*	13
CRY2	24	*PER3*	25	*SIRT1*	17
CSNK1E	24	*PRDX1*	17	*SIRT2*	18
DBP	20	*PRDX2*	12	*STRA13*	22
FGF21	10	*PRDX3*	16	*TIMELESS*	15
FOXO1	33	*PRDX5*	22	*WEE1*	19

Table S2.2.2. WGCNA-derived modules and number of CpG sites

Module	# CpG	Module	# CpG	Module	# CpG	Module	# CpG
Module1	*32*	Module17	*669*	Module33	*963*	Module49	*33*
Module2	*5845*	Module18	*794*	Module34	*132*	Module50	*40*
Module3	*17473*	Module19	*1783*	Module35	*757*	Module51	*42*
Module4	*1952*	Module20	*122*	Module36	*30*	Module52	*65804*
Module5	*31*	Module21	*73*	Module37	*42*	Module53	*68*
Module6	*3845*	Module22	*21133*	Module38	*88*	Module54	*1242*
Module7	*47*	Module23	*33*	Module39	*36*	Module55	*448*
Module8	*33*	Module24	*32*	Module40	*448*	Module56	*191*
Module9	*31*	Module25	*31*	Module41	*786*	Module57	*41*
Module10	*35*	Module26	*2596*	Module42	*50775*	Module58	*33*
Module11	*61*	Module27	*125*	Module43	*35*	Module59	*32*
Module12	*31*	Module28	*5750*	Module44	*267*	Module60	*41*
Module13	*47*	Module29	*788*	Module45	*549*	Module61	*9177*
Module14	*30*	Module30	*86*	Module46	*37*	Module62	*33*
Module15	*218*	Module31	*32*	Module47	*63*	Module63	*41*
Module16	*1040*	Module32	*61*	Module48	*261374*	Module64	*56*

1
0.5
0
Module_1 −0.18 −0.06 0.019 0.065 0.036
Module_2 −0.18 −0.084 0.076 0.1 0.062
Module_3 −0.17 −0.034 0.062 0.063 0.018
Module_4 0.16 0.004 −0.016 −0.0011 0.0018
Module_5 −0.16 −0.02 0.071 0.041 0.059
Module_6 0.15 0.043 −0.094 −0.087 −0.0093
Module_7 0.14 0.066 −0.063 −0.038 −0.045
Module_8 0.14 0.031 −0.087 −0.054 −0.085
Module_9 0.12 0.013 −0.018 −0.087 −0.021
Module_10 −0.11 −0.0014 0.012 −0.062 −0.015
Module_11 0.11 −0.036 −0.036 −0.0013 0.0012
Module_12 −0.1 0.03 0.15 −0.047 0.035
Module_13 −0.097 −0.036 0.1 0.056 −0.014
Module_14 −0.095 −0.054 0.065 −0.033 −0.015
Module_15 −0.094 −0.093 0.05 0.15 0.14
Module_16 −0.085 0.0014 0.064 0.042 −0.0048
Module_17 0.083 0.0094 −0.044 −0.049 −0.034
Module_18 0.081 0.043 −0.046 −0.069 −0.061
Module_19 −0.077 −0.019 0.093 0.078 0.035
Module_20 −0.075 0.033 0.032 −0.0049 0.074
Module_21 0.074 0.007 0.029 −0.0062 −0.008
Module_22 −0.072 0.038 0.045 0.037 −0.013
Module_23 −0.072 −0.046 0.00084 0.019 0.037
Module_24 0.07 −0.068 −0.046 0.1 0.11
Module_25 0.067 0.059 −0.055 0.05 0.036
Module_26 0.066 0.033 −0.032 −0.02 0.03
Module_27 0.062 −0.0073 −0.035 −0.064 −0.06
Module_28 0.058 −0.12 −0.041 −0.0067 0.061
Module_29 0.055 0.0062 0.092 0.019 −0.043
Module_30 −0.054 0.016 0.00015 0.025 0.044
Module_31 −0.052 0.075 0.052 0.016 0.052
Module_32 −0.051 −0.05 0.025 0.043 0.051
Module_33 −0.05 −0.024 0.044 0.046 0.024
Module_34 −0.05 −0.061 0.019 −0.026 0.026
Module_35 −0.049 −0.049 0.022 0.025 0.027

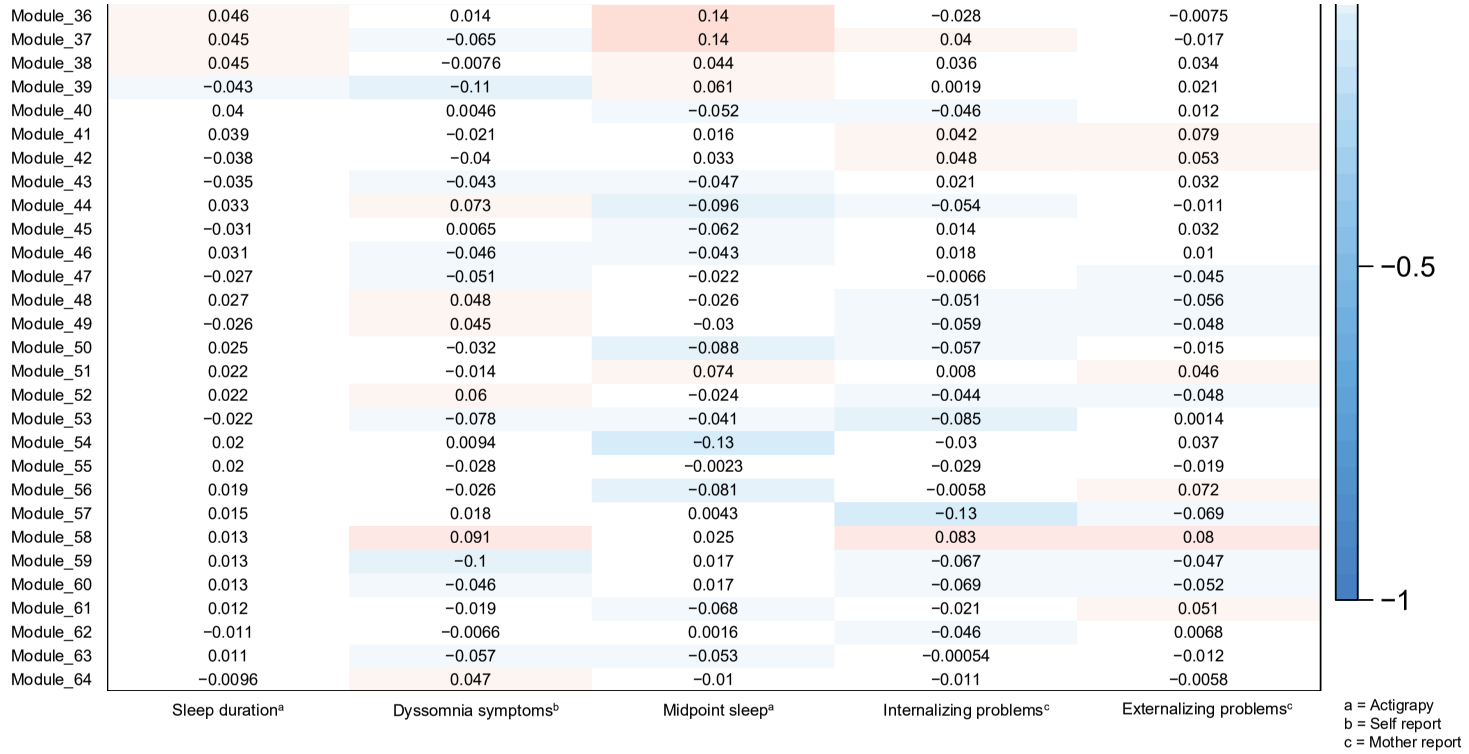

Figure S2.2.2. Correlation matrix of DNAm modules, sleep and mental health.

Table S2.2.3. Functional characterization of module1 (part 1)

	CpG information								
CpG	**Genomic location**	**Proximity to CpG island**	**Position**	**Chromosome**	**Gene**	***Std B***	***p***	**Mean**	**SD**
cg15295732	Body		43942128	17	MAPT-L7:L31AS1	0.3018893	9.9E-05	0.70	0.05
cg00846647	Body	Island	44060252	17	MAPT	0.2465164	0.001391	0.85	0.05
cg18228076	5'UTR		43983362	17	MAPT	0.2514921	0.001591	0.45	0.15
cg23955979			45126661	17	[ARL17]	-0.259001	0.001847	0.57	0.05
cg07870213	Body	Island	140052090	5	DND1	-0.234355	0.002187	0.67	0.05
cg24801067			62843696	17	-	-0.236203	0.003393	0.9	0.03
cg17117718		Island	43663208	17	[LRRc37A]	-0.219581	0.003635	0.13	0.1
cg18391203		N_Shelf	44317291	17	-	-0.211059	0.004529	0.57	0.06
cg24801230	5'UTR	S_Shelf	43978533	17	MAPT	0.2130216	0.005724	0.68	0.23
cg16228356			43848958	17	[CRHR1]	0.1982664	0.012255	0.46	0.06
cg22968622		Island	43663579	17	[LRRc37A]	-0.178802	0.017754	0.22	0.21
cg13704117	Body		44207360	17	KANSL1	0.1851593	0.020294	0.78	0.07
cg19832721	TSS1500		44249866	17	KANSL1	-0.187245	0.02096	0.67	0.1
cg04703951			43578652	17	-	-0.176918	0.022176	0.6	0.06
cg20120463		N_Shore	44301886	17	[KANSL1]	0.1776023	0.025006	0.2	0.03
cg04282206	TSS1500	S_Shore	62833786	17	*PLEKHM1P*	-0.163108	0.029668	0.11	0.03
cg27060340	5'UTR	N_Shelf	43502999	17	*ARHGAP27*	0.1872267	0.032394	0.39	0.09
cg01135538	Body	N_Shore	43678735	17	*LOC644172/MAPK8IP1P2*	0.1659441	0.033713	0.89	0.02

Table S2.2.3. ***Part 1 – Continued***

	CpG information								
CpG	**Genomic location**	**Proximity to CpG island**	**Position**	**Chromosome**	**Gene**	***Std B***	***p***	**Mean**	**SD**
cg03915738			43651976	17	*[LRRc37A]*	-0.166783	0.034135	0.86	0.02
cg01570182		Island	44337453	17	-	-0.151754	0.050768	0.36	0.04
cg15921436		Island	44337874	17	*[ARHGAP27]*	-0.13892	0.064751	0.58	0.04
cg26471390	TSS1500	S_Shore	43511301	17	*ARHGAP27*	-0.156186	0.070719	0.64	0.04
cg17911788		Island	44343683	17	-	0.1410486	0.079972	0.12	0.05
cg05159804		Island	44343776	17	-	0.1404805	0.106976	0.22	0.06
cg02228913	Body	N_Shelf	44058016	17	*MAPT*	0.1238992	0.118991	0.85	0.08
cg06680147		S_Shore	44344931	17	-	-0.104775	0.162643	0.08	0.02
cg09234465		S_Shore	43664173	17	*[LRRc37A]*	-0.091065	0.24945	0.91	0.02
cg08113562	5'UTR	Island	43508428	17	*ARHGAP27*	-0.071283	0.346673	0.09	0.03
cg04927033	Body	Island	43679265	17	*LOC644172/MAPK8IP1P2*	-0.062307	0.439858	0.88	0.02
cg07368061	Body		44090862	17	*MAPT*	0.0542763	0.519156	0.87	0.02
cg06291494		N_Shore	44321403	17	-	0.0399064	0.629656	0.88	0.02
cg05301556	TSS1500	N_Shore	43971177	17	*MAPT/MAPT-AS1*	0.0075591	0.922981	0.85	0.04

CpGs with a dash (-) are not annotated to genes (intergenic).
CpGs with a gene name are actually annotated/located in that gene.
CpGs with a gene in brackets [] are located in proximity to these genes.

Table S2.2.3. Functional characterization of module1 (part 2)

	Blood-CNS concordance 1 (Hannon et al., 2015)							
	PFC		STG		EC		CER	
CpG	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
cg15295732	0.422	1.82E-04	0.535	1.53E-06	0.491	7.87E-06	0.291	1.38E-02
cg00846647	0.598	1.82E-08	0.584	9.07E-08	0.475	1.68E-05	0.285	1.58E-02
cg18228076	0.82	3.99E-19	0.829	4.31E-19	0.855	1.53E-22	0.572	1.87E-07
cg23955979	-0.09	4.17E-01	-0.12	3.18E-01	-0.00282	9.81E-01	0.542	1.02E-06
cg07870213	0.848	1.42E-21	0.753	3.47E-14	0.824	1.06E-19	0.652	7.08E-10
cg24801067	0.682	2.31E-11	0.741	1.45E-13	0.695	4.67E-12	0.707	5.44E-12
cg17117718	0.97	4.87E-46	0.961	4.44E-40	0.973	2.86E-48	0.921	6.23E-30
cg18391203	0.6595	6.45E-12	0.577	1.37E-07	0.684	1.37E-11	0.673	1.31E-10
cg24801230	0.986	2.51E-57	0.983	1.61E-52	0.987	2.82E-59	0.835	1.54E-19
cg16228356	0.243	3.73E-02	0.277	1.91E-02	0.262	2.30E-02	0.073	5.45E-01
cg22968622	0.995	1.03E-72	0.99	5.17E-61	0.996	7.64E-80	0.979	2.36E-49
cg13704117	0.81	2.40E-18	0.839	7.25E-20	0.82	1.89E-19	0.855	2.47E-21
cg19832721	0.08	4.87E-01	0.0396	7.43E-01	0.0387	7.41E-01	0.26	2.85E-02
cg04703951	0.717	6.67E-13	0.841	4.65E-20	0.812	9.15E-19	0.842	3.63E-20
cg20120463	0.358	1.73E-03	0.322	6.16E-03	0.211	6.93E-02	0.232	5.13E-02
cg04282206	*0.10*	0.417	*0.30*	1.10E-02	*0.25*	2.87E-02	*0.12*	3.26E-01
cg27060340	*0.71*	1.3E-07	*0.74*	2.58E-13	*0.73*	1.18E-13	*0.75*	5.79E-14

Table S2.2.3. ***Part 2 – Continued***

	Blood-CNS concordance 1 (Hannon et al., 2015)							
	PFC		STG		EC		CER	
CpG	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
cg01135538	*0.53*	1.54E-06	*0.59*	5.05E-08	*0.52*	2.03E-06	*0.65*	8.70E-10
cg03915738	*-0.08*	0.502	*-0.07*	0.55	*-0.05*	6.72E-01	*0.30*	1.08E-02
cg01570182	*0.77*	1.17E-15	*0.80*	4.08E-17	*0.78*	3.56E-16	*0.62*	7.22E-09
cg15921436	*0.47*	2.83E-05	*0.50*	9.33E-06	*0.67*	4.48E-11	*0.57*	2.61E-07
cg26471390	*-0.23*	0.0229	*-0.41*	0.000352	*-0.52*	1.94E-06	*-0.66*	5.95E-10
cg17911788	*0.51*	3.45E-06	*0.50*	9.72E-06	*0.64*	9.25E-10	*0.17*	1.67E-01
cg05159804	*0.38*	0.00836	*0.22*	7.24E-02	*0.18*	1.21E-01	*-0.35*	3.20E-03
cg02228913	*0.99*	1.32E-61	*0.99*	8.07E-60	*0.99*	1.10E-58	*0.99*	1.27E-54
cg06680147	*0.56*	1.75E-07	*0.46*	6.28E-05	*0.52*	2.28E-06	*0.44*	1.51E-04
cg09234465	*0.41*	0.000242	*0.28*	1.99E-02	*0.44*	7.09E-05	*-0.19*	1.09E-01
cg08113562	*-0.25*	0.0355	*-0.30*	0.0122	*-0.17*	0.155	*-0.19*	0.109
cg04927033	*0.21*	0.0755	*0.22*	6.41E-02	*0.02*	8.44E-01	*0.16*	1.85E-01
cg07368061	*0.12*	0.323	*0.30*	1.09E-02	*0.30*	8.17E-03	*0.16*	1.80E-01
cg06291494	*0.01*	0.89	*0.19*	1.16E-01	*0.00*	9.90E-01	*0.12*	3.26E-01
cg05301556	*0.09*	0.433	*0.21*	7.79E-02	*0.01*	9.46E-01	*0.04*	7.38E-01

Table S2.2.3. Functional characterization of module1 (part 3)

	Twin heritability estimates (Hannon et al., 2018)			Genetic influences	
	Additive genetic (A)	Common environment (C)	Non-shared environment (E)	mQTLs	Polymorphic probes
CpG	Mean	Mean	Mean	(Gaunt et al., 2016)	(Chen et al., 2013)
cg15295732	0.66637303	5E-13	0.33362697		TRUE
cg00846647				TRUE	
cg18228076					TRUE
cg23955979					
cg07870213				TRUE	
cg24801067				TRUE	
cg17117718	0.969856123	5.42E-14	0.030143877	TRUE	
cg18391203					TRUE
cg24801230					TRUE
cg16228356	0.837183536	1.34E-13	0.162816464	TRUE	
cg22968622	0.996728437	5.32E-14	0.003271563	TRUE	
cg13704117					TRUE
cg19832721	0.880572078	2.06E-14	0.119427922		
cg04703951				TRUE	
cg20120463				TRUE	
cg04282206				TRUE	
cg27060340	0.712452588	0.061709448	0.225837964		TRUE

Table S2.2.3. *Part 3 – Continued*

	Twin heritability estimates (Hannon et al., 2018)			Genetic influences	
	Additive genetic (A)	Common environment (C)	Non-shared environment (E)		
CpG	Mean	Mean	Mean	mQTLs (Gaunt et al., 2016)	Polymorphic probes (Chen et al., 2013)
cg01135538					
cg03915738					
cg01570182				TRUE	
cg15921436				TRUE	
cg26471390					
cg17911788				TRUE	
cg05159804	0.787265816	2.07E-13	0.212734184		
cg02228913					TRUE
cg06680147					
cg09234465					
cg08113562	0.712193943	3.45E-12	0.287806057		
cg04927033					
cg07368061	0.344706126	0.068495184	0.58679869		
cg06291494					
cg05301556	0.357656393	0.059606674	0.582736933		

Chapter 3

Sleep and psychopathology

George Hendrik Breitner –
Meisje in witte kimono

Chapter 3.1

The bi-directional association between sleep problems and autism spectrum disorder: A population-based cohort study

M. Elisabeth Koopman-Verhoeff | Laura M.E. Blanken | Desana Kocevska | Viara R. Mileva-Seitz | Vincent W. V. Jaddoe | Tonya White | Frank C. Verhulst | Maartje P.C.M. Luijk | Henning Tiemeier

Molecular Autism (2018), 9(8), 1–9

Abstract

Objective: Sleep difficulties are prevalent in children with Autism Spectrum Disorder (ASD). The temporal nature of the association between sleep problems and ASD is unclear because longitudinal studies are lacking. Our aim is to clarify whether sleep problems precede and worsen autistic traits and ASD or occur as a consequence of the disorder.

Method: Repeated sleep measures were available at 1.5, 3, 6, and 9 years of age in 5151 children participating in the Generation R Study, a large prospective birth cohort in the Netherlands. Autistic traits were determined with the Pervasive Developmental Problems score (PDP) of the Child Behavior Checklist (CBCL) at 1.5, and 3 years and the Social Responsiveness Scale (SRS) at 6 years. This cohort included 81 children diagnosed with ASD.

Results: Sleep problems in early childhood were prospectively associated with a higher SRS score, but not when correcting for baseline PDP score. By contrast, a higher SRS score and an ASD diagnosis were associated with more sleep problems at later ages, even when adjusting for baseline sleep problems. Likewise, a trajectory of increasing sleep problems was associated with ASD.

Conclusion: Sleep problems and ASD are not bidirectionally associated. Sleep problems do not precede and worsen autistic behaviour, but rather co-occur with autistic traits in early childhood. Over time, children with ASD have an increase in sleep problems, whereas typically developing children have a decrease in sleep problems. Our findings suggest that sleep problems are part of the construct ASD.

Introduction

Autism Spectrum Disorder (ASD) affects 0.5 to 1% of children (Baird et al., 2006; Newschaffer et al., 2007; Simonoff et al., 2008) and has an early onset, typically before age 2 (Hutman, 2013; Wolff et al., 2012; Zwaigenbaum et al., 2015). ASD is often characterised by severe deficiencies in social interaction, communication, accompanied by repetive behaviour. Children with ASD frequently suffer from comorbid psychopathologies (Abdallah et al., 2011; Simonoff et al., 2008; Thomas, Lycett, Papadopoulos, Sciberras, & Rinehart, 2015; Wing, 1993). Among those, sleep problems, defined as difficulties falling asleep or nightmares, are common (Patzold, Richdale, & Tonge, 1998) occurring in 40–80% of cases across all ages (Baker, Richdale, Short, & Gradisar, 2013; Cortesi, Giannotti, Ivanenko, & Johnson, 2010; Liu, Hubbard, Fabes, & Adam, 2006; Richdale, 1999; Richdale & Prior, 1995; Richdale & Schreck, 2009; Wiggs, 2001) in comparison to 25–50% in normally developing children (Moturi & Avis, 2010; Petit, Touchette, Tremblay, Boivin, & Montplaisir, 2007; Richdale & Schreck, 2009). The broad range of prevalence estimates is explained by multiple factors, such as different measures for sleep problems, age of the child, IQ of the autistic children studied, and the heterogeneity of ASD. What is more, there is no clear definition of clinically relevant sleep problems in paediatric populations, resulting in various forms of research questions on sleep problems in ASD (for a review on prevalence of sleep problems in ASD see Richdale & Schreck, 2009). As mentioned, the type of sleep problems differs; younger children with ASD exhibit more bedtime resistance, bedtime anxiety, awakenings during the night, and parasomnias (defined as abnormal behaviour during sleep, such as sleep walking, sleep talking, and nightmares), whereas older children mainly exhibit insomnia symptoms (defined as the difficulty falling asleep or staying asleep) (Goldman et al., 2011; Richdale & Schreck, 2009).

The association between sleep problems and ASD can be of two forms. First sleep problems may precede and worsen the behavioural outcome of ASD (Goldman et al., 2011; Goldman, Richdale, Clemons, & Malow, 2012; Richdale & Schreck, 2009; Tudor, Hoffman, & Sweeney, 2012). Second, sleep problems occur as a consequence of the underlying disorder. Sleep problems are common in early childhood with prevalence estimates of up to 50% (Petit et al., 2007); prevalences decline in typically developing children but not in children with ASD (Polimeni, Richdale, & Francis, 2005). Risk factors or correlates of early childhood sleep problems are, for example, maternal psychopathology, parenting practices, child temperament,

difficulties setting bedtime, and feeding patterns (Moturi & Avis, 2010; Touchette et al., 2005; Zuckerman, Stevenson, & Bailey, 1987). The influence of these factors diminishes when the child's sleep patterns becomes more stable (Touchette et al., 2005; Zuckerman et al., 1987). Studies have indicated that children with ASD have more sleep problems than typically developing children (Richdale & Schreck, 2009). A British cohort study showed that children with and without ASD have similar sleep durations in infancy, but from 30 months onwards their sleep is characterized by a shorter duration than typically developing children (Humphreys et al., 2014). Another study showed that children with autistic traits developed more sleep problems in pre-adolescence (Sivertsen, Posserud, Gillberg, Lundervold, & Hysing, 2011). However, most previous studies of sleep problems in children with ASD are cross-sectional and the few longitudinal studies have a lack of baseline measures and diagnosis of ASD (Gail Williams, Sears, & Allard, 2004; Schreck, Mulick, & Smith, 2004; Sivertsen et al., 2011; Tudor et al., 2012). Thus, it is difficult to properly asses the course of sleep problems in children with ASD (Adams, Matson, Cervantes, & Goldin, 2014; Cohen, Conduit, Lockley, Rajaratnam, & Cornish, 2014; Schreck et al., 2004). To unravel the complex temporal nature of the association between sleep problems and ASD, it is essential to have prospective research that measures autistic traits and associated sleep problems repeatedly throughout childhood.

In this study we explored the association between the onset of sleep problems and autistic traits and ASD in the general population. An ASD diagnosis must be confirmed by a licenced clinician, while autistic traits are autistic symptoms that do not meet the diagnostic criteria for ASD assessed by questionnaires. Repeated assessments of autistic traits, and sleep problems were obtained at several developmental stages. It is important to clarify whether sleep problems precede and worsen autistic traits and ASD or occur after (other) symptoms of ASD become manifest. This enables us to gain more insight in the course over time of sleep problems in children with ASD.

First, we expected that the onset of sleep problems precedes and worsens the early manifestations of autistic traits. Second, we hypothesized that sleep problems in children with autistic traits or with ASD emerge early in life and increase over time.

Methods

Design and study population

This study was embedded in Generation R, a prospective population-based cohort from foetal life onward (Kooijman et al., 2016). All pregnant women (expected delivery date April 2002–January 2006) living in Rotterdam, the Netherlands, were invited to participate by their midwife or obstetrician during routine visits. The participation rate was estimated at 61%. We obtained written informed consent from all participants and their parents. The Medical Ethical Committee of the Erasmus Medical Center Rotterdam approved the study.

Data on sleep problems based on at least one assessment from age 1.5 year onward were available for 7464 children. Children without information on autistic traits or a diagnosis of ASD were excluded (n = 2313), yielding a sample size of 5151 children for the present study (follow-up rate 69.0%). In the analyses, the study population varies slightly due to missing data in different assessments rounds (see Figure 3.1.1 for study overview).

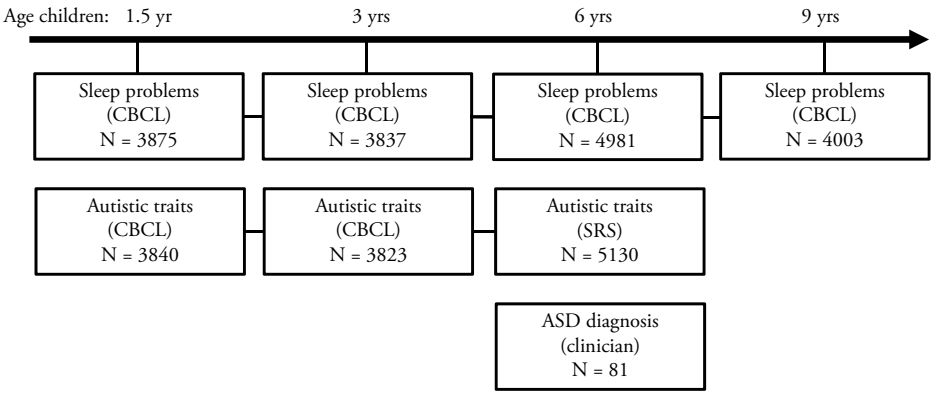

Figure 3.1.1. Population and measurements overview.

Sleep problems

Children's sleep problems were quantified using the Sleep Problem Scale, which is a pre-defined Problem Scale of the Child Behavior Checklist (CBCL), a reliable and valid measure for behavioural problems (Achenbach & Ruffle, 2000; Verhulst & Van der Ende, 2013). The CBCL is widely used internationally and has been found to be generalizable across 23 societies (Ivanova et al., 2010). The CBCL was completed by the primary caregiver, in the majority of cases the mother, who rated various sleep

problems of the child in the previous two months on a three-point Likert scale (0 = not true, 1 = somewhat true, 2 = very true).

The Sleep Problem Scale compromises seven questions about sleep problems including items on dyssomnia and parasomnia. For ages 1.5, 3, and 6, the Sleep Problem Scale was based on CBCL for ages 1.5-5. This scale has previously been used as a measure of sleep problems (Gregory & O'Connor, 2002; Gregory, Van der Ende, Willis, & Verhulst, 2008; Jansen et al., 2011; Kocevska, Rijlaarsdam, et al., 2016). At older ages the CBCL differs slightly to adapt to developmental changes throughout childhood. Because there is not an established subscale for measuring sleep problems at age 9, we a priori selected 5 items from the CBCL 6-18 questionnaire based on the appropriateness to measure sleep problems and ran an exploratory factor analysis in order to construct a scale for sleep problems at 9 years, resulting in a two factor solution dyssomnia and parasomnia with an internal consistency of $\alpha = 0.55$. The low internal consistency is most likely due to the two-factor solution combined in 1 sleep problem scale. As our interest is assessing general sleep problems, we decided to keep a combined scale rather than separate dyssomnia and parasomnia scales. This sleep problem scale has previously been used in the same format as a measure of sleep problems (Thomas, Monahan, Lukowski, & Cauffman, 2015).

Autistic traits

Autistic traits were measured twice with different instruments. First, at ages of 1.5, and 3 years, we used the Pervasive Development Problem (PDP) scale of the CBCL 1.5-5 (see details about CBCL above) to assess autistic like trait/pervasive developmental problems as an indicator of autistic traits. We calculated the sum score of the PDP scale. Second, at the age of 6 years (range: 5–8 years), the Social Responsiveness Scale (SRS) was administered to obtain a measure of autistic traits. The SRS provides a valid quantitative measure of subclinical and clinical autistic traits (Constantino et al., 2003). We utilized the 18-item short-form of the scale, containing three sub-scales: Social Cognition, Social Communication, and Social Mannerism. The subscales show correlations ranging from 0.93 to 0.99 with the full scale in three different large studies. The authors of the scale recommend cut offs for screening in population-based settings (consistent with weighted scores of 1.078 for boys and 1.000 for girls) (Constantino et al., 2003).

ASD diagnosis

All diagnoses in our records were made by a licensed clinical psychologists or psychiatrists, these were only retrieved if diagnoses were formally coded according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV/5 or the International Classification of Primary Care (ICPC). ASD diagnoses were retrieved from general practitioners. In the Dutch health care system, all specialists are obliged to inform the general practitioner as the primary health care provider, who holds the central medical records. The following steps were performed to select children with high sensitivity for potentially retrieving a clinician-made ASD diagnosis. We selected children with one of the three following indicators for a further diagnostic work-up of ASD. First, all children, who scored in the top 15th percentile on the CBCL for ages 1.5-5 total score or those in the top 2nd percentile on the PDP subscale, were screened with the Social Communication Questionnaire (SCQ), a 40-item parent-reported screening instrument for ASD (Berument, Rutter, Lord, Pickles, & Bailey, 1999). We retrieved medical records of all children, who scored positive on the SCQ. Second, we also retrieved medical records of all children, who scored above the cut-off 1.078 for boys and 1.000 for girls on the SRS-short form. Third, we retrieved medical records of all children whose the mother at any moment, in a questionnaire or a research centre interview, up to age 8 years had reported that the child had undergone a diagnostic procedure for possible ASD.

Only children for whom a diagnosis of ASD could be confirmed by specialist medical records before age 9 were classified as ASD in the analyses. The specialist diagnoses of ASD were generally based on clinical consensus by a multidisciplinary team. The standard diagnostic work-up typically involves an extensive developmental case history obtained from parents, as well as school information, and repeated observations of the child. The mean age of diagnosis of ASD in our sample was 6 years, for convenience hereafter referred to as ASD diagnosis at 6 years (range: 2–9 years). See Table S3.1.1 for correlations between all measures of autistic trait and ASD.

Covariates

Based on literature, covariates were included if they were an antecedent of ASD and/or were associated with sleep problems, but not consequences or intermediates such as somatic complains. The following variables were considered possible confounders in the association between sleep problems and autistic traits and ASD (Richdale & Schreck, 2009; E. Touchette et al., 2009; Zuckerman et al., 1987). Sex and gestational

age of the children were obtained from the medical records completed by community midwives and obstetricians. In accordance with Central Bureau for Statistics, child ethnicity was based on country of birth of the parents, which was assessed by questionnaire and coded as, Dutch, Other-Western, non-Western. Information on maternal characteristics was obtained by questionnaire during pregnancy. Maternal education was defined by the highest attained educational level and classified into three categories (low, middle, and high education) in line with the definition of Central Bureau for Statistics (CBS Netherlands, 2006). Finally, maternal psychopathology, such as anxiety, depressive symptoms, hostility, and psychoticism, was assessed prenatally using the Brief Symptom Inventory (BSI) (De Beurs, 2004).

Statistical analysis

First, we tested sleep problems as predictors of continuously measured autistic traits with linear regression and as predictors of the dichotomous ASD diagnosis with logistic regression. Second, we analysed the prospective association of autistic traits and ASD with sleep problems using linear regression.

Subsequently, to compare defined groups of children based on their patterns of sleep disturbances over time, the association of the latent class trajectories with autistic traits and ASD were analysed using linear regression and logistic regression. Trajectories of sleep disturbance up to 6 years of age were defined using Latent Class Trajectory Models (Jung & Wickrama, 2008), as previously applied to this data in Generation R (Kocevska, Muetzel et al., 2016). This is a person-centred modelling approach that estimates growth curves over time across unobserved subpopulations by assigning a most likely latent trajectory class to each individual. The three-class model as previously defined in this cohort fit our sample best (Kocevska, Muetzel et al., 2016). The largest group was the "decreasing to low sleep disturbances" class (n = 2423, 47.0%), which followed a normative developmental decline of sleep problems and was therefore defined as the reference. The "stable at medium sleep disturbances" class comprised 1318 (25.6%) children and the "increasing to high sleep disturbances" class comprised 622 (12.1%) children.

We constructed two models for all analyses. In the first model, the following confounders were included: child sex, gestational age, ethnicity, maternal psychopathology, and maternal educational level. To test the temporal direction of the association between ASD and sleep problems, we additionally adjusted all models for baseline PDP score or baseline Sleep Problem Score. For ease of comparison over

the different instruments and time points, we used z-transformed versions of all independent and dependent variables, except for the ASD diagnosis in all analyses. To reduce bias associated with missing data we used multiple imputations for missing values of the covariates. Ten imputed datasets were created and analysed separately after which the results were pooled (Klebanoff & Cole, 2008). A sensitivity analysis was conducted to test the robustness of our findings. We repeated the analyses excluding children with a diagnosis of ASD, representing the most 'severe' cases of ASD, using only autistic traits as exposure or determinant. The statistical analyses were performed using the SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) and MPlus version 7.11 (Muthén & Muthén, Los Angeles, CA, USA) using Monte Carlo integration techniques and maximum likelihood estimation with robust standard errors.

Results

Characteristics of the children with and without ASD are presented in Table 3.1.1. Children with a diagnosis of ASD (n = 81) were more often boys (86.4%). Their mothers reported more psychopathological symptoms for themselves than mothers of children without ASD. There were no significant differences in the other characteristics, such as maternal age at birth.

We first tested the cross-sectional association between sleep problems and autism. At all ages, they were significantly associated (e.g. sleep problems at age 1.5 years and autistic traits, B = 0.27, 95% CI: 0.23 to 0.31, $p < 0.01$).

The longitudinal association of sleep problems with autistic traits and ASD

Table 3.1.2 shows the longitudinal associations of sleep problems with autistic traits and ASD adjusted for covariates and baseline autistic traits. Children who presented sleep problems at 1.5 and 3 years were more likely to have autistic traits. However, after adjusting for baseline PDP score, no longitudinal association was observed between sleep problems and autistic traits.

The longitudinal association of autistic traits and ASD with sleep problems

Table 3.1.3 shows the longitudinal associations of autistic traits at ages 1.5, 3, and 6 years, and also that of ASD at age 6 years with sleep problems at age 9 years,

Table 3.1.1. Characteristics of the study population

	N	No ASD diagnosis N = 5062	ASD diagnosis N = 81
Child characteristics			
Gender (% girls)	5143	50.1	13.6*
Gestational age at birth (weeks)	5102	39.80 (0.03)	39.36 (0.26)*
Ethnicity (%)			
Dutch	3386	69.7	75.6
Other Western	461	9.5	7.7
Non-Western	1007	20.8	16.7
Sleep problem score			
At 1.5 years	3875	1.51 (0.03)	1.75 (0.26)
At 3 years	3837	1.50 (0.03)	1.77 (0.24)
At 6 years	4981	1.02 (0.02)	1.85 (0.25)*
At 9 years	4003	0.82 (0.02)	1.92 (0.28)*
Trajectories of sleep problems (%)			
Increasing sleep problems	622	15.6	33.8*
Decreasing sleep problems	2432	54.8	43.7*
Stable medium sleep problems	1318	29.6	22.5
Autistic traits			
PDP score – 1.5 years	3840	1.77 (0.03)	2.26 (0.23)*
PDP score – 3 years	3823	2.03 (0.03)	4.81 (0.44)*
SRS score – 6 years	5130	0.22 (0.00)	0.97 (0.08)*
Abdominal pain (%)	5064	7.5	5.7
Functional constipation (%)	4894	3.5	7.5
Maternal characteristics			
Age at inclusion (years)	5143	31.4 (0.1)	31.0 (0.5)
Educational level (%)			
No education/ primary school	275	5.7	2.6
High school / lower vocational training	1885	38.6	51.3*
Higher vocational or academic training	2699	55.7	46.2
Psychopathology score	5295	0.24 (0.00)	0.38 (0.07)*

Abbreviations: PDP: Pervasive Development Problem scale SRS: Social Responsiveness Scale.
* $p < 0.05$.
Data represent means (SDs) unless specified otherwise.

after adjustment for covariates and baseline sleep problems. We found a significant association between autistic traits at age 1.5 and 3 years were related to more sleep problems at 6 years, both unadjusted and adjusted for baseline sleep problems. Furthermore, children with autistic traits and children with ASD at 6 years had more sleep problems at 9 years.

Table 3.1.2. The longitudinal association of sleep problems with autistic traits and Autism Spectrum Disorder

		Autistic traits* at 3 years			Autistic traits** at 6 years			ASD at 6 years		
Sleep problems		**B**	**95% CI**	***p***	**B‡**	**95% CI**	***p***	**OR**	**95% CI**	***p***
1.5 years										
	Model 1	0.12	0.08–0.15	< 0.01	0.08	0.05–0.11	< 0.01	1.11	0. 87–1.42	0.41
	Model 2	0.03	-0.01–0.06	0.13	0.03	-0.02–0.06	0.07	1.05	0. 81–1.35	0.73
3 years										
	Model 1	0.20	0. 17–0.23	< 0.01	0.07	0.04–0.10	< 0.05	1.11	0.86–1.43	0.43
	Model 2	-	-	-	0.01	-0.03–0.04	0.70	0.95	0.72–1.24	0.70

Abbreviations: ASD: Autism Spectrum Disorder, SRS: Social Responsiveness Scale.

‡ Because of the narrow distribution of the SRS, Bs are given in hundredth SRS points.

* Measured with PDP-scale CBCL.

** Measured with SRS score.

Model 1 was adjusted for gender, ethnicity, gestational age, maternal education, and maternal psychopathology. Model 2 was additionally adjusted for prevalent autistic traits.

Table 3.1.3. The longitudinal association of autistic traits and Autism Spectrum Disorder with sleep problems

	Sleep problems at 6 years			Sleep problems at 9 years		
Autism measure	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Autistic traits* 1.5 years						
Model 1	0.13	0.09–0.16	< 0.01	0.10	0.06–0.14	< 0.01
Model 2	0.07	0.03–0.10	< 0.01	0.08	0.03–0.12	< 0.01
Autistic traits* 3 years						
Model 1	0.13	0.10–0.16	< 0.01	0.06	0.04–0.08	< 0.01
Model 2	0.05	0.02–0.08	< 0.01	0.04	0.03–0.06	< 0.01
Autistic traits** 6 years						
Model 1	0.13	0.10–0.16	< 0.01	0.14	0.10–0.18	< 0.01
Model 2	-	-	-	0.11	0.07–0.14	< 0.01
ASD 6 years						
Model 1	0.46	0.24–0.68	< 0.01	0.84	0.58–1.10	< 0.01
Model 2	-	-	-	0.74	0.49–0.99	< 0.01

Abbreviations: ASD: Autism Spectrum Disorder, PDP: Pervasive Development Problem scale SRS: Social Responsiveness Scale.

* Measured with PDP-scale CBCL.

** Measured with SRS score.

Model 1 was adjusted for gender, ethnicity, gestational age, maternal education, and maternal psychopathology. Model 2 was additionally adjusted for prevalent sleep problems.

Sleep problem trajectories

Children with a trajectory of increasing sleep problems and children with stable and moderate sleep problems had higher levels of autistic traits than those with decreasing sleep problems (Table S3.1.2). We found that an increasing course of sleep problems was consistently associated with ASD at age 6 years (Table S3.1.2).

Sensitivity analyses

All analyses were adjusted for gender, ethnicity, gestational age, maternal education, and maternal psychopathology, and, if possible, baseline measures of respectively sleep problems or prevalent autistic traits. There was no significant interaction between gender and sleep problems on the risk of autism or between gender and ASD in the analysis of sleep (data not shown).

Sensitivity analyses indicated our findings were robust. The results of all regression analyses remained unchanged after the children with ASD were excluded (data not shown).

Discussion

In this large population-based cohort, we found that sleep problems in toddlerhood were associated with autistic traits in mid-childhood, but this association disappeared when adjusting for early autistic traits. In contrast, autistic traits and a diagnosis of ASD in childhood were associated with sleep problems at later ages. Consistently, children with increasing sleep problems across development were more likely to have autistic traits and ASD. Our findings suggest that sleep problems are part of the construct of ASD, however do not predict severity of autistic traits over time. We showed that there is no bidirectional relation between sleep problems and ASD.

Our finding that sleep problems are associated with more autistic traits is in line with previous studies (Cohen et al., 2014; Richdale & Schreck, 2009; Schreck et al., 2004; Tudor et al., 2012). However, these previous studies lacked the repeated measurements of sleep problems and autistic traits across ages (Cohen et al., 2014; Richdale & Schreck, 2009; Tudor et al., 2012). When we adjusted for baseline autistic traits in the current study, the association between sleep problems at younger ages and later autistic traits disappeared. We found no evidence for sleep problems preceding autistic traits at baseline. This implies that sleep problems do not predict autistic traits and ASD over and above symptoms such as diminished social and communicative abilities, which are measured by the PDP scale. Moreover, sleep problems do not worsen ASD.

Autistic traits and ASD were associated with more sleep problems in accordance with previous studies (Allik, Larsson, & Smedje, 2006; Mayes & Calhoun, 2009; Schreck et al., 2004). This association remained even after adjusting for baseline sleep problems. Sleep problems in young children are relatively common and can be considered part of normative development in the general population (Gregory & Sadeh, 2016; Humphreys et al., 2014). Yet, as supported by our trajectory analyses, the severity and frequency of sleep problems decreases in typically developing children (Kocevska, Muetzel et al., 2016), whereas sleep problems worsen over time in children with ASD. This strongly suggests that the pathology underlying ASD on the behavioural sequelae, determines the development of sleep problems.

The course of sleep problems over time in these children poorly understood. Previous studies have been unable to determine the temporal association (Cohen et al., 2014). By using trajectories of sleep problems and relating the trajectories to autistic traits and ASD, we show that sleep problems tend to decrease and disappear

in the general population but increase in children with ASD. These trajectories are a further indication that the longitudinal course of sleep problems is a symptom and consequence of ASD, rather than worsen ASD symptomatology (Wing, 1993). Thus, sleep problems are prevalent in children with ASD and should be considered part of the disorder.

Children with ASD suffer from more sleep problems than children without ASD, but the pathophysiology of sleep problems in children with ASD has not yet been fully understood. Some studies point to underlying deficits in endogenous melatonin secretion (Richdale & Schreck, 2009; Tordjman et al., 2012), others to alterations in hypothalamic-pituitary adrenal-axis function and cortisol secretion (Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006; Tomarken, Han, & Corbett, 2015), alterations in neurodevelopmental pathways (Kohyama, 2016), and some to polygenetic variations in circadian rhythm and clock genes related to ASD pathology (Glickman, 2010; Richdale & Schreck, 2009). As ASD is highly heritable (Colvert et al., 2015; Devlin & Scherer, 2012; Glessner et al., 2009; Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010; Marshall et al., 2008), it would be worthwhile to study whether there are shared underlying genetic factors between sleep problems and autistic traits. Another mechanism could be that social problems associated with ASD may worsen the day-night rhythm in these children (Richdale & Prior, 1995) and play a crucial role in the development of sleep problems. Socialization of day-night rhythm, such as bed time routines, night time rituals, and family regularity (Meltzer & Mindell, 2006; Mindell, Telofski, Wiegand, & Kurtz, 2009; Wittmann, Dinich, Merrow, & Roenneberg, 2006), are important in young children as they can act as social zeitgebers and thereby contribute to the development of a healthy sleep pattern and the prevention of the occurrence of sleep problems (Ehlers, Frank, & Kupfer, 1988; Glickman, 2010; Richdale & Prior, 1995; Richdale & Schreck, 2009). Children with ASD have difficulty to adequately respond to the social zeitgebers and therefore struggle to develop a healthy sleep pattern (Glickman, 2010). More research is needed to unravel the socialization of day-night rhythm in children with ASD and the linkage with the development of sleep problems. Future studies should emphasize bed time routines and family regularity when investigating children with ASD and sleep problems.

Our findings indicate that sleep problems do not contribute to an exacerbation of autistic traits, but rather that sleep problems manifest as part of the broad ASD symptomatology. This is important information for parents who worry sleep problems

may precipitate or perpetuate autistic symptoms. Based on our findings, we underline the importance of addressing sleep problems in children with ASD, possibly in the context of ASD treatments. Whereas sleep problems do not have a direct effect on autistic traits, sleep problems are known to negatively affect daytime functioning, such as attention processes and executive functioning (Durmer & Dinges, 2005; Tarokh, Saletin, & Carskadon, 2016; Turnbull, Reid, & Morton, 2013). Executive dysfunction co-occurs with the core symptoms of ASD (Craig et al., 2016; Hill, 2004; Pennington & Ozonoff, 1996), but the pathways remain unclear. We speculate that sleep problems can contribute to the development of executive dysfunction in children with ASD but this needs further research. Future research should also investigate the effect of treatment of sleep problems and its concurrent effects on neurocognitive outcomes in children with ASD.

Strengths and limitations

The current study has relevant strengths. First, the large sample size and longitudinal design enabled us to study sleep problems and autistic traits at multiple ages across a broad time span and to control for baseline characteristics and confounders. Our longitudinal design also enabled us to account for reverse causality. Second, we were able to complement parent-reported autistic symptoms with a diagnosis of ASD.

The current study, however, also had some limitations. First, we used a mother-reported questionnaire to assess sleep problems. It would have been ideal to use actigraphic or polysomnographic measures for studying sleep problems. However, mothers are known to be reliable reporters of children's sleep at younger ages (Carskadon, 2011). Second, our earliest assessment of autistic traits was performed at 1.5 years. Although measuring autistic traits in the general population in younger children is not very reliable (Bolton, Golding, Emond, & Steer, 2012), mostly retrospective studies documented that many children who develop ASD will have had symptoms prior to age 1.5 years. As such, our earliest measurement may not represent the pathophysiological onset of the disorder. However, our study characterizes the nature of the longitudinal association between sleep and autistic traits in early childhood. Third, children with ASD were slightly more likely to be lost to follow-up than typically developing children. Nevertheless, our sensitivity analyses yielded similar results after excluding all ASD cases and were therefore likely not affected by the lost to follow-up. Fourth, we used different age-appropriate measures of autistic traits that had a low to moderate correlation at different ages. The effect of adjustment for

baseline autistic traits may be influenced by using different measures. Nevertheless, when we adjusted for baseline autistic traits, the association between sleep problems and autistic traits disappeared. If anything, if adjustment with the same measure had been possible, this would have further attenuated any observed association.

Conclusions

To conclude, we showed that sleep problems do not precede and worsen autistic behaviour, but rather co-occur with autistic traits in early childhood. Furthermore, sleep problems increase over time in children with ASD. Although sleep problems in young children are often considered part of normal development, our findings suggest that sleep problems persisting to later ages can be considered as symptoms of ASD.

References

Abdallah, M. W., Greaves-Lord, K., Grove, J., Norgaard-Pedersen, B., Hougaard, D. M., & Mortensen, E. L. (2011). Psychiatric comorbidities in autism spectrum disorders: Findings from a Danish historic birth cohort. *European Child & Adolescent Psychiatry, 20*(11-12), pp. doi:10.1007/s00787-011-0220-2

Achenbach, T. M., & Ruffle, T. M. (2000). The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review, 21*(8), 265-271.

Adams, H. L., Matson, J. L., Cervantes, P. E., & Goldin, R. L. (2014). The relationship between autism symptom severity and sleep problems: Should bidirectionality be considered? *Research in Autism Spectrum Disorders, 8*(3), 193-199. doi:https://doi.org/10.1016/j.rasd.2013.11.008

Allik, H., Larsson, J.-O., & Smedje, H. (2006). Sleep Patterns of School-Age Children with Asperger Syndrome or High-Functioning Autism. *Journal of Autism and Developmental Disorders, 36*(5), 585-595. doi:10.1007/s10803-006-0099-9

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., & Charman, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet, 368*(9531), 210-215. doi:S0140-6736(06)69041-7

Baker, E., Richdale, A., Short, M., & Gradisar, M. (2013). An investigation of sleep patterns in adolescents with high-functioning autism spectrum disorder compared with typically developing adolescents. *Dev Neurorehabil, 16*(3), 155-165. doi:10.3109/17518423.2013.765518

Berument, S. K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: diagnostic validity. *Br J Psychiatry, 175*, 444-451.

Bolton, P. F., Golding, J., Emond, A., & Steer, C. D. (2012). Autism Spectrum Disorder and Autistic Traits in the Avon Longitudinal Study of Parents and Children: Precursors and Early Signs. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(3), 249-260.e225. doi:https://doi.org/10.1016/j.jaac.2011.12.009

Carskadon, M. A. (2011). Chapter 8 - Sleep's effects on cognition and learning in adolescence. In H. P. A. Van Dongen & G. A. Kerkhof (Eds.), *Progress in Brain Research* (Vol. 190, pp. 137-143): Elsevier.

Centraal Bureau voor de Statistiek, Nederland. (2006). Allochtonen in Nederland 2006. Voorburg/Heerlen.

Cohen, S., Conduit, R., Lockley, S. W., Rajaratnam, S. M. W., & Cornish, K. M. (2014). The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *Journal of Neurodevelopmental Disorders, 6*(1), 44. doi:10.1186/1866-1955-6-44

Colvert, E., Tick, B., McEwen, F., Stewart, C., Curran, S. R., Woodhouse, E., . . . Bolton, P. (2015). Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample. *JAMA Psychiatry, 72*(5), 415-423. doi:10.1001/jamapsychiatry.2014.3028

Constantino, J. N., Davis, S. A., Todd, R. D., Schindler, M. K., Gross, M. M., Brophy, S. L., . . . Reich, W. (2003). Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the autism diagnostic interview-revised. *Journal of Autism and Developmental Disorders, 33*(4), 427-433. doi:Doi 10.1023/A:1025014929212

Corbett, B. A., Mendoza, S., Abdullah, M., Wegelin, J. A., & Levine, S. (2006). Cortisol circadian rhythms and response to stress in children with autism. *Psychoneuroendocrinology, 31*(1), 59-68. doi:S0306-4530(05)00127-7 10.1016/j.psyneuen.2005.05.011

Cortesi, F., Giannotti, F., Ivanenko, A., & Johnson, K. (2010). Sleep in children with autistic spectrum disorder. *Sleep Medicine, .11*(7), pp. doi:10.1016/j.sleep.2010.01.010 20605110

Craig, F., Margari, F., Legrottaglie, A. R., Palumbi, R., de Giambattista, C., & Margari, L. (2016). A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *Neuropsychiatric disease and treatment, 12*, 1191-1202. doi:10.2147/ndt.S104620

De Beurs, E. (2004). Brief Symptom Inventory. Leiden, Netherlands; Handleiding.

Devlin, B., & Scherer, S. W. (2012). Genetic architecture in autism spectrum disorder. *Current Opinion in Genetics & Development, 22*(3), 229-237. doi:https://doi.org/10.1016/j.gde.2012.03.002

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive Consequences of Sleep Deprivation. *Semin Neurol, 25*(01), 117-129. doi:10.1055/s-2005-867080

Ehlers, C. L., Frank, E., & Kupfer, D. J. (1988). Social Zeitgebers and Biological Rhythms: A Unified Approach to Understanding the Etiology of Depression. *Archives of General Psychiatry, 45*(10), 948-952. doi:10.1001/archpsyc.1988.01800340076012

Gail Williams, P., Sears, L. L., & Allard, A. (2004). Sleep problems in children with autism. *Journal of Sleep Research, 13*(3), 265-268. doi:10.1111/j.1365-2869.2004.00405.x

Glessner, J. T., Wang, K., Cai, G., Korvatska, O., Kim, C. E., Wood, S., . . . Hakonarson, H. (2009). Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature, 459*(7246), 569-573. doi:10.1038/nature07953

Glickman, G. (2010). Circadian rhythms and sleep in children with autism. *Neuroscience & Biobehavioral Reviews, 34*(5), 755-768. doi:https://doi.org/10.1016/j.neubiorev.2009.11.017

Goldman, S. E., McGrew, S., Johnson, K. P., Richdale, A. L., Clemons, T., & Malow, B. A. (2011). Sleep is associated with problem behaviors in children and adolescents with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders, 5*(3), 1223-1229. doi:https://doi.org/10.1016/j.rasd.2011.01.010

Goldman, S. E., Richdale, A. L., Clemons, T., & Malow, B. A. (2012). Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. *J Autism Dev Disord, 42*(4), 531-538. doi:10.1007/s10803-011-1270-5

Gregory, A. M., & O'Connor, T. G. (2002). Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. J Am Acad Child Adolesc Psychiatry, 41(8), 964-971. doi:S0890-8567(09)61077-7 10.1097/00004583-200208000-00015

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders--a review of the latest science. J Child Psychol Psychiatry, 57(3), 296-317. doi:10.1111/jcpp.12469

Gregory, A. M., Van der Ende, J., Willis, T. A., & Verhulst, F. C. (2008). Parent-reported sleep problems during development and self-reported anxiety/depression, attention problems, and aggressive behavior later in life. Archives of Pediatrics & Adolescent Medicine, 162(4), 330-335. doi:DOI 10.1001/archpedi.162.4.330Hill, E. L. (2004). Executive dysfunction in autism. *Trends in Cognitive Sciences, 8*(1), 26-32. doi:https://doi.org/10.1016/j.tics.2003.11.003

Humphreys, J. S., Gringras, P., Blair, P. S., Scott, N., Henderson, J., Fleming, P. J., & Emond, A. M. (2014). Sleep patterns in children with autistic spectrum disorders: a prospective cohort study. *Archives of Disease in Childhood, 99*(2), 114. doi:10.1136/archdischild-2013-304083

Hutman, T. (2013). From attention to interaction: the emergence of autism during infancy. *Biol Psychiatry, 74*(3), 162-163. doi:S0006-3223(13)00472-1

Ivanova, M. Y., Achenbach, T. M., Rescorla, L. A., Harder, V. S., Ang, R. P., Bilenberg, N., . . . Verhulst, F. C. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *J Am Acad Child Adolesc Psychiatry, 49*(12), 1215-1224. doi:S0890-8567(10)00735-5 10.1016/j.jaac.2010.08.019

Jansen, P. W., Saridjan, N. S., Hofman, A., Jaddoe, V. W., Verhulst, F. C., & Tiemeier, H. (2011). Does disturbed sleeping precede symptoms of anxiety or depression in toddlers? The generation R study. *Psychosomatic Medicine, 73*(3), 242-249. doi:PSY.0b013e31820a4abb

Jung, T., & Wickrama, K. A. S. (2008). An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Social and Personality Psychology Compass, 2*(1), 302-317. doi:10.1111/j.1751-9004.2007.00054.x

Klebanoff, M. A., & Cole, S. R. (2008). Use of Multiple Imputation in the Epidemiologic Literature. *American Journal of Epidemiology, 168*(4), 355-357. doi:10.1093/aje/kwn071

Kocevska, D., Muetzel, R. L., Luik, A. I., Luijk, M. P. C. M., Jaddoe, V. W., Verhulst, F. C., . . . Tiemeier, H. (2016). The Developmental Course of Sleep Disturbances Across Childhood Relates to Brain Morphology at Age 7: The Generation R Study. *Sleep, 40*(zsw022). doi:10.1093/sleep/zsw022

Kocevska, D., Rijlaarsdam, J., Ghassabian, A., Jaddoe, V. W., Franco, O. H., Verhulst, F. C., & Tiemeier, H. (2016). Early Childhood Sleep Patterns and Cognitive Development at Age 6 Years: The Generation R Study. *Journal of Pediatric Psychology*. doi:jsv16810.1093/jpepsy/jsv168

Kohyama, J. (2016). Possible neuronal mechanisms of sleep disturbances in patients with autism spectrum disorders and attention-deficit/hyperactivity disorder. *Medical Hypotheses, 97*, 131-133. doi:https://doi.org/10.1016/j.mehy.2016.11.001

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van Ijzendoorn, M. H., . . . Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology, 31*(12), 1243-1264. doi:10.1007/s10654-016-0224-9

Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., & Anckarsäter, H. (2010). The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. *American Journal of Psychiatry, 167*(11), 1357-1363. doi:10.1176/appi.ajp.2010.10020223

Liu, X., Hubbard, J. A., Fabes, R. A., & Adam, J. B. (2006). Sleep disturbances and correlates of children with autism spectrum disorders. *Child Psychiatry Hum Dev, 37*(2), 179-191. doi:10.1007/s10578-006-0028-3

Marshall, C. R., Noor, A., Vincent, J. B., Lionel, A. C., Feuk, L., Skaug, J., . . . Scherer, S. W. (2008). Structural Variation of Chromosomes in Autism Spectrum Disorder. *The American Journal of Human Genetics, 82*(2), 477-488. doi:https://doi.org/10.1016/j.ajhg.2007.12.009

Mayes, S. D., & Calhoun, S. L. (2009). Variables related to sleep problems in children with autism. *Research in Autism Spectrum Disorders, 3*(4), 931-941. doi:https://doi.org/10.1016/j.rasd.2009.04.002

Meltzer, L. J., & Mindell, J. A. (2006). Sleep and sleep disorders in children and adolescents. *Psychiatr Clin North Am, 29*(4), 1059-1076; abstract x. doi:S0193-953X(06)00075-X [pii] 10.1016/j.psc.2006.08.004

Mindell, J. A., Telofski, L. S., Wiegand, B., & Kurtz, E. S. (2009). A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep, 32*(5), 599-606. doi:10.1093/sleep/32.5.599

Moturi, S., & Avis, K. (2010). Assessment and treatment of common pediatric sleep disorders. *Psychiatry (Edgmont (Pa : Township)), 7*(6), 24-37.

Newschaffer, C. J., Croen, L. A., Daniels, J., Giarelli, E., Grether, J. K., Levy, S. E., . . . Windham, G. C. (2007). The epidemiology of autism spectrum disorders. Annu Rev Public Health, 28, 235-258. doi:10.1146/annurev.publhealth.28.021406.144007

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Child Psychology & Psychiatry & Allied Disciplines, 37*(1), 51-87. doi:10.1111/j.1469-7610.1996.tb01380.x

Patzold, L. M., Richdale, A. L., & Tonge, B. J. (1998). An investigation into sleep characteristics of children with autism and Asperger's Disorder. *Journal of Paediatrics and Child Health, 34*(6), 528-533.

Petit, D., Touchette, É., Tremblay, R. E., Boivin, M., & Montplaisir, J. (2007). Dyssomnias and Parasomnias in Early Childhood. *Pediatrics, 119*(5), e1016-e1025. doi:10.1542/peds.2006-2132

Polimeni, M. A., Richdale, A. L., & Francis, A. J. P. (2005). A survey of sleep problems in autism, Asperger's disorder and typically developing children. *Journal of Intellectual Disability Research, 49*(4), 260-268. doi:10.1111/j.1365-2788.2005.00642.x

Richdale, A. L. (1999). Sleep problems in autism: prevalence, cause, and intervention. *Developmental Medicine and Child Neurology, 41*(1), 60-66. doi:Doi 10.1017/S0012162299000122

Richdale, A. L., & Prior, M. R. (1995). The sleep/wake rhythm in children with autism. *European Child & Adolescent Psychiatry, 4*(3), 175-186. doi:10.1007/bf01980456

Richdale, A. L., & Schreck, K. A. (2009). Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Medicine Reviews, 13*(6), 403-411. doi:https://doi.org/10.1016/j.smrv.2009.02.003

Schreck, K. A., Mulick, J. A., & Smith, A. F. (2004). Sleep problems as possible predictors of intensified symptoms of autism. *Research in Developmental Disabilities, 25*(1), 57-66. doi:https://doi.org/10.1016/j.ridd.2003.04.007

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry, .47*(8), pp. doi:10.1097/CHI.0b013e318179964f

Sivertsen, B., Posserud, M.-B., Gillberg, C., Lundervold, A. J., & Hysing, M. (2011). Sleep problems in children with autism spectrum problems: a longitudinal population-based study. *Autism, 16*(2), 139-150. doi:10.1177/1362361311404255

Tarokh, L., Saletin, J. M., & Carskadon, M. A. (2016). Sleep in adolescence: Physiology, cognition and mental health. *Neuroscience and biobehavioral reviews, 70*, 182-188. doi:10.1016/j.neubiorev.2016.08.008

Thomas, A. G., Monahan, K. C., Lukowski, A. F., & Cauffman, E. (2015). Sleep problems across development: a pathway to adolescent risk taking through working memory. *J Youth Adolesc, 44*(2), 447-464. doi:10.1007/s10964-014-0179-7

Thomas, S., Lycett, K., Papadopoulos, N., Sciberras, E., & Rinehart, N. (2015). Exploring Behavioral Sleep Problems in Children With ADHD and Comorbid Autism Spectrum Disorder. *J Atten Disord*. doi:1087054715613439

Tomarken, A. J., Han, G. T., & Corbett, B. A. (2015). Temporal patterns, heterogeneity, and stability of diurnal cortisol rhythms in children with autism spectrum disorder. *Psychoneuroendocrinology, 62*, 217-226. doi:https://doi.org/10.1016/j.psyneuen.2015.08.016

Tordjman, S., Anderson, G. M., Bellissant, E., Botbol, M., Charbuy, H., Camus, F., . . . Touitou, Y. (2012). Day and nighttime excretion of 6-sulphatoxymelatonin in adolescents and young adults with autistic disorder. *Psychoneuroendocrinology, 37*(12), 1990-1997. doi:https://doi.org/10.1016/j.psyneuen.2012.04.013

Touchette, E., Côté, S. M., Petit, D., Liu, X., Boivin, M., Falissard, B., . . . Montplaisir, J. Y. (2009). Short Nighttime Sleep-Duration and Hyperactivity Trajectories in Early Childhood. *Pediatrics, 124*(5), e985. doi:10.1542/peds.2008-2005

Touchette, É., Petit, D., Paquet, J., Boivin, M., Japel, C., Tremblay, R. E., & Montplaisir, J. Y. (2005). Factors Associated With Fragmented Sleep at Night Across Early Childhood. *Archives of Pediatrics & Adolescent Medicine, 159*(3), 242-249. doi:10.1001/archpedi.159.3.242

Tudor, M. E., Hoffman, C. D., & Sweeney, D. P. (2012). Children With Autism: Sleep Problems and Symptom Severity. *Focus on Autism and Other Developmental Disabilities, 27*(4), 254-262. doi:10.1177/1088357612457989

Turnbull, K., Reid, G. J., & Morton, J. B. (2013). Behavioral Sleep Problems and their Potential Impact on Developing Executive Function in Children. *Sleep, 36*(7), 1077-1084. doi:10.5665/sleep.2814

Verhulst, F. C., Van der Ende, J. (2013). Handleiding ASEBA Vragenlijsten voor leeftijden 6 tot met 18 jaar. Rotterdam: ASEBA Nederland.

Wiggs, L. (2001). Sleep problems in children with developmental disorders. *Journal of the Royal Society of Medicine, 94*(4), 177-179.

Williams, P. G., Sears, L. L., & Allard, A. (2004). Sleep problems in children with autism. *Journal of Sleep Research, 13*(3), 265-268.

Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social Jetlag: Misalignment of Biological and Social Time. *Chronobiology International, 23*(1-2), 497-509. doi:10.1080/07420520500545979

Wing, L. (1993). The definition and prevalence of autism: A review. *Eur Child Adolesc Psychiatry, 2*(1), 61-74. doi:10.1007/BF02098832

Wolff, J. J., Gu, H., Gerig, G., Elison, J. T., Styner, M., Gouttard, S., . . . Network, I. (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry, 169*(6), 589-600. doi:10.1176/appi.ajp.2011.11091447

Zuckerman, B., Stevenson, J., & Bailey, V. (1987). Sleep Problems in Early Childhood: Continuities, Predictive Factors, and Behavioral Correlates. *Pediatrics, 80*(5), 664.

Zwaigenbaum, L., Bauman, M. L., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., . . . Wetherby, A. (2015). Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics, 136 Suppl 1*, S10-40. doi:peds.2014-3667C10.1542/peds.2014-3667C

Supplementary material

S3.1.1. Pearson's correlations among measures of Autistic Traits and ASD diagnosis

Autism measure	Autistic traits* 1.5 years	Autistic traits* 3 years	Autistic traits** 6 years	ASD 6 years
Autistic traits* 1.5 years	1	0.47	0.32	0.05
p		< 0.01	< 0.01	< 0.05
N	5151	5151	5138	5143
Autistic traits* 3 years		1	0.40	0.15
p			< 0.01	< 0.01
N		5151	5138	5143
Autistic traits** 6 years			1	0.34
p				< 0.01
N			5138	5130
ASD 6 years				1
p				
N				5143

Abbreviations: ASD: Autism Spectrum Disorder, PDP: Pervasive Development Problem scale SRS: Social Responsiveness Scale.

* Measured with PDP-scale CBCL.

** Measured with SRS score.

S3.1.2. The longitudinal association of sleep problem trajectories with autistic traits and Autism Spectrum Disorder

	Autistic traits* at 6 years			ASD at 6 years		
Sleep trajectory	**B‡**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Increasing course of sleep problems						
Model 1	0.29	0.20–0.37	< 0.01	2.98	1.63–5.43	< 0.01
Model 2	0.19	0.07–0.20	< 0.01	2.39	1.29–4.43	< 0.01
Stable course of medium sleep problems						
Model 1	0.14	0.10–0.27	< 0.01	0.89	0.47–1.70	0.73
Model 2	0.09	0.03–0.15	< 0.01	0.78	0.40–1.51	0.46
Decreasing course of sleep problems						
Model 1	0	(ref.)		1.0	(ref.)	
Model 2	0	(ref.)		1.0	(ref.)	

Abbreviations: ASD: Autism Spectrum Disorder, SRS: Social Responsiveness Scale.

‡ Because of the narrow distribution of the SRS, Bs are given in hundredth SRS points.

*Autistic traits are measured with the SRS score.

Model 1 was adjusted for gender, ethnicity, gestational age, maternal education, and maternal psychopathology. Model 2 was additionally adjusted for prevalent autistic traits.

Chapter 3.2

During day and night: Childhood psychotic experiences and objective and subjective sleep problems

M. Elisabeth Koopman-Verhoeff | Koen Bolhuis |Charlotte A.M. Cecil | Desana Kocevska | James J. Hudziak | Manon H.J. Hillegers | Viara R. Mileva-Seitz | Irwin K. Reiss | Liesbeth Duijts | Frank C. Verhulst | Maartje P.C.M. Luijk | Henning Tiemeier

Schizophrenia Research (2019), 206, 127–134

Abstract

Objective: Psychotic experiences comprise auditory and visual perceptive phenomena, such as hearing or seeing things that are not there, in the absence of a psychotic disorder. Psychotic experiences commonly occur in the general pediatric population. Although the majority of psychotic experiences are transient, they are predictive of future psychotic and non-psychotic disorders. They have been associated with sleep problems, but studies with objective sleep measures are lacking. This study assessed whether psychotic experiences were associated with actigraphic sleep measures, symptoms of dyssomnia, nightmares, or other parasomnias.

Method: This cross-sectional population-based study comprises 4149 children from the Generation R Study. At age 10 years, psychotic experiences including hallucinatory phenomena were assessed by self-report; dyssomnia and parasomnia symptoms were assessed by mother- and child-report. Additionally, at age 11 years, objective sleep parameters were measured using a tri-axial wrist accelerometer in N = 814 children, who wore the accelerometer for five consecutive school days.

Results: Psychotic experiences were not associated with objective sleep duration, sleep efficiency, arousal, or social jetlag. However, psychotic experiences were associated with self-reported dyssomnia (B = 2.45, 95% CI: 2.13–2.77, $p < 0.001$) and mother-reported parasomnia, specifically nightmares ($OR_{adjusted} = 3.59$, 95% CI 2.66–4.83, $p < 0.001$). Similar results were found when analyses were restricted to hallucinatory phenomena.

Conclusion: Childhood psychotic experiences were not associated with objective sleep measures. In contrast, psychotic experiences were associated with nightmares, which are a known risk indicator of psychopathology in pre-adolescence. More research is needed to shed light on the potential etiologic or diagnostic role of nightmares in the development of psychotic phenomena

Introduction

Psychotic experiences compromise auditory and visual perceptive phenomena, such as hearing or seeing things that are not there, or delusional thoughts, in the absence of a psychotic disorder (Kelleher, Jenner, & Cannon, 2010). With a prevalence around 7%, psychotic experiences are common in the general adult population (Linscott & van Os, 2013). The prevalence is particularly high in children aged 9 to12 years with rates up to 17%, whereas in adolescence the prevalence declines to 7.5% (Kelleher, Connor, et al., 2012; Kelleher, Keeley, et al., 2012). It is important to study childhood psychotic experiences because children, who report such symptoms in late childhood or early adolescence, have a 5 to 16 times higher risk for developing psychotic disorders in adulthood (Kelleher & Cannon, 2011; Poulton et al., 2000; Welham et al., 2009). Indeed, psychotic experiences share a genetic risk with psychotic disorders (Jeppesen, Larsen, et al., 2015; Zavos et al., 2014). Further, children with psychotic experiences are at increased risk for various non-psychotic psychopathologies, such as bipolar disorder, suicidal behavior, anxiety, and depressive disorders (Kelleher, Keeley, et al., 2012; McGrath et al., 2016; Wigman et al., 2011), which highlights the trans-diagnostic characteristics of psychotic experiences and supports the need to have a better understanding of their etiology and development across childhood and adolescence.

Sleep problems, such as insufficient sleep, symptoms of dyssomnia (including insomnia or excessive sleepiness), and symptoms of parasomnia (a comprehensive term for nighttime behaviors including sleep-walking, sleep-talking, and nightmares) (Fleetham & Fleming, 2014; Mason & Pack, 2007), are considered as possible triggers of psychotic experiences across age groups (Lee, Cho, Cho, Jang, & Kim, 2012; Oshima et al., 2010; Reeve, Emsley, Sheaves, & Freeman, 2017; Reeve, Sheaves, & Freeman, 2015; Taylor, Gregory, Freeman, & Ronald, 2015; Thompson et al., 2015). In adults, sleep problems are associated with both severity and number of psychotic experiences (Andorko et al., 2017; Reeve et al., 2015). Similarly, in high-risk adolescent populations shorter sleep duration and parasomnia have been associated with psychoses (Lunsford-Avery, LeBourgeois, Gupta, & Mittal, 2015; Lunsford-Avery & Mittal, 2013; Ruhrmann et al., 2010). A few studies using self- or mother-reported measures of sleep problems have been conducted in pediatric populations (Jeppesen, Clemmensen, et al., 2015; Lee et al., 2012) and found that psychotic experiences co-occur with self-reported sleep problems (Jeppesen, Clemmensen, et al., 2015). Consistent with this, others report that psychotic experiences in adolescence

often are preceded by severe nightmares in childhood (Fisher et al., 2014). While there is a rising interest in the role of sleep problems in the development of psychotic experiences, so far very few clinical studies and no population-based studies used objective measures of sleep to study this association. Addressing this gap can help elucidate the developmental mechanisms behind the association between objectively assessed sleep difficulties and psychotic experiences in childhood. In this study, we investigated in a general pediatric population whether childhood psychotic experiences are associated with actigraphically measured sleep duration, sleep efficiency, and arousal. Additionally, previous literature points at the difference of week and weekend sleep in late childhood and adolescents; teenagers tend to sleep less during schooldays and make up for this during weekend days by rising later and sleeping longer (Carskadon, 2011; Crowley, Wolfson, Tarokh, & Carskadon, 2018). Thus, we calculated the "social jetlag". Social jetlag is the discrepancy in sleep between school days and weekend days (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Third, we investigated whether childhood psychotic experiences are associated with self- or mother-reported sleep problems such as dyssomnia and parasomnia symptoms. We examined the associations between our various sleep measures and hallucinatory phenomena specifically as these have been shown to be most predictive of clinically-confirmed psychotic symptoms (Kelleher, Harley, Murtagh, & Cannon, 2011). Based on previous population-based studies (Fisher et al., 2014; Jeppesen, Clemmensen, et al., 2015; Lunsford-Avery et al., 2015), we expect that psychotic experiences in childhood are associated with objective shorter sleep duration and reported sleep dysfunction, such as symptoms of dyssomnia and parasomnia.

Methods

Design and study population

This cross-sectional study was embedded in Generation R Study, a prospective population-based cohort from foetal life onwards. Women who were pregnant between April 2002 and January 2006 and living in Rotterdam were eligible for participation (61% included). This sample was largely representative of the Rotterdam female population (Jaddoe et al., 2006). The Generation R Study aims to identify genetic and environmental risk factors for the growth and development of mothers and children.

All 7393 participants who consented in the age 10 assessment wave received questionnaires and were invited at the research centre for objective behavioural assessment

(Kooijman et al., 2016). Children without information on psychotic experiences or sleep problems were excluded (n = 3244) yielding a sample size of 4149 children for the present study.

The subsample of 1153 children was selected based on the following criteria: first we selected participants who had participated within the Generation R Focus Study: This includes participants with good follow-up rates (Kooijman et al., 2016). Ethnic minorities were not included in order to address genetic and epigenetic questions. Second, we oversampled children who were born premature in this study to counter the selection effects observed for children born preterm. Indeed, our subsample showed similar rates of premature children to the total cohort. Due to logistic reasons, the accelerometer data collection was conducted nearly one year after the 10 years (questionnaire) assessment. Of the invited children, 953 participants consented to participate (response rate of 82%). Children were excluded from the analyses if data on weekday sleep was not available or when data did not pass standard quality control. Data were excluded if the actigraphy wear time was under 6 hours or if sleep time was under 4 hours. Sleep time under 4 hours was often due to exceptional social activities and field trips in this population and did not reflect typical patterns or insomnia (Acebo et al., 1999; Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). The final sample consisted of 814 children with information on psychotic experiences and good quality actigraphy measures on objective sleep (mean age 11.7 years, SD = 0.20). The children participating in the subsample were more often of Dutch nationality and had mothers with higher educational levels and lower levels of psychopathology (all $p < 0.001$). However, there were no differences between the total sample and the actigraphy sample on mother- and self-reported exposure and outcome variables. The Medical Ethics Committee of the Erasmus Medical Center approved all study procedures, and all parents provided written informed assent.

Measures

Psychotic experiences

Psychotic experiences were assessed by self-report questionnaire using three items derived from the widely used Youth Self-Report (Ivanova et al., 2018): "I hear sounds or voices that according to other people are not there", "I see things that other people think are not there", "I have thoughts that other people would find strange". Responses were scored on a three-point scale, i.e. "Not at all", "A bit" or "Clearly". Responses from all three items were summed to calculate a total score which ranged from 0–6,

with higher scores indicating more psychotic experiences; the correlation between the items was moderate to large (.38–.56). Scores were classified into the following categories: no symptoms (0 points), some symptoms (1–3 points), and several symptoms (4–6 points). To asses hallucinatory phenomena separately, we combined the two hallucinatory phenomena questions to a hallucinatory phenomena score categorized as: no symptoms, some symptoms (1–2 points), and several symptoms (3–4 points). These cut-offs were chosen so that the children in the upper category would have endorsed "clearly" on at least one of the items.

Objective sleep measures

Sleep was assessed using a tri-axial wrist accelerometer (GENEActiv; Activinsights, UK) which children wore for nine subsequent days (five school days and four weekend days) on their non-dominant wrist. The GENEActiv accelerometers record raw accelerometer data; for the current study accelerometers were set at a frequency of 50 Hz, which allowed us to use the accelerometers for 14 subsequent days without recharging and in line with another study (Ronnlund, Elovainio, Virtanen, Matomaki, & Lapinleimu, 2016). The GENEActiv PC software version 2.2 was used to download the raw data as binary files. The binary files were processed using the R-package GGIR (van Hees et al., 2014). The processing included auto calibration with gravity as reference, detection of atypical values and non-wear. The algorithm is using an accelerometer-derived arm angle averaged over 5-second epochs to detect sleep. If there is no arm-movement larger 5° for at least 5 minutes this will be classified as a period of sustained inactivity or sleep. This procedure generated the following sleep measures: sleep duration, sleep efficiency, and sleep arousal (van Hees et al., 2015). Sleep duration is the total time classified as sleep during the night, indicating the time between falling asleep and waking minus the time lying awake. Sleep efficiency is the total sleep duration divided by bed time and waking time. Arousal is the number of sleep periods during the night, the higher the number awakenings, the higher the arousal. We calculated social jetlag by taking the average midpoint sleep during the weekend subtracted by the average midpoint sleep during week (Wittmann et al., 2006). For the measures of sleep duration, sleep efficiency, and sleep arousal only school days were included in the analyses, representing the typically pattern of weekday sleep to minimize the influence of atypical weekend events.

Multi-rated sleep problems

Self-reported dyssomnia

At age 10 years, dyssomnia symptoms were assessed by self-report questionnaire asking six questions about their perceived sleep i.e. "Do you find it difficult to go to bed?"; "Do you find it difficult to fall asleep?"; "Do you think you get enough sleep?"; "If you wake up at night, do you find it difficult to fall asleep again?"; "Do you feel rested when you wake in the morning?"; "When you come out of your bed in the morning, do you feel rested?". These questions were derived from the widely used Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996) and slightly rephrased for our paediatric population. Similar questions can be found in other sleep scales for children such as the Sleep Self Report (Owens, Spirito, McGuinn, & Nobile, 2000), and School Sleep Habits Survey (Wolfson & Carskadon, 1998). There were three possible responses for each item: "No", "Sometimes" or "Yes", which were scored on a Likert scale. Responses from all six items were summed to calculate a total score with an internal consistency of $\alpha = 0.64$, higher scores indicate more dyssomnia problems.

Mother-reported child sleep problems

At age 10 years, children's sleep problems were quantified using the Child Behavior Checklist 6-18 (CBCL), a reliable and valid measure for behavioural problems (T. M. Achenbach & Ruffle, 2000; Verhulst, 2013). The CBCL was completed by the primary caregiver, in the majority of cases the mother, who rated various sleep problems of the child in the previous two months on a three-point Likert scale (0 = not true, 1 = somewhat true, 2 = very true).

In line with a previous study (Verhoeff et al., 2018), we selected 5 items from the CBCL/6-18 questionnaire a priori because there is no established subscale for measuring sleep problems from the CBCL/6-18. We ran a confirmatory factor analysis in order to construct a sleep problems scale at 10 years and to examine which questions loaded together. This resulted in a two-factor solution (combined internal consistency of $\alpha = 0.52$). The first factor compromised 3 questions representing dyssomnia symptoms: "Trouble with sleeping"; "Sleeps less than most kids"; "Overtired with no good reason" (internal consistency of $\alpha = 0.55$), the second factor compromised 2 questions representing parasomnia symptoms: "Nightmares" and "Talks or walks in sleep" (internal consistency of $\alpha = 0.33$).

Mother-reported child emotional and behavioural problems

The CBCL/6-18 was also used to assess child emotional and behavioural problems at age 10 years, (T. A. Achenbach & Rescorla, 2001). The CBCL/6-18 consists of 8 syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour measured on a continuous severity scale. Items were scored by mothers on a three-point scale (0 = not true; 1 = somewhat true; 2 = very true), based on behaviour in the past six months. We computed a total problem scale including all items of the CBCL and excluding the items measuring sleep problems.

Confounders

Based on previous literature we considered the following confounders (Kelleher & Cannon, 2011; Morgan et al., 2009). Sleep problems and psychotic experiences are both associated with age, ethnicity, and sex of the child (Kelleher & Cannon, 2011; Sadeh, Raviv, & Gruber, 2000; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2003). Likewise, both sleep problems and psychotic experiences are related to maternal educational level and psychopathology, such as depressive symptoms (Kelleher & Cannon, 2011; Sadeh et al., 2000). Gestational age was added as a confounder because we specifically added children born prematurely to this study. Sex and age of the children were obtained from the medical records completed by community midwives and obstetricians. Child ethnicity was considered as Dutch when both parents were born in the Netherlands, while children were classified as non-Dutch if at least one of the parents was born outside the Netherlands (further specified as 'Other Western' or 'Other Non-Western'). Information on maternal educational level was obtained by questionnaires during pregnancy. Maternal education was defined by the highest attained educational level and classified into three categories (low, middle, and high education). Finally, maternal depressive symptoms were assessed using the Brief Symptom Inventory (BSI) (De Beurs, 2004) when child was at mean age 10 years.

Statistical analysis

Self-reported dyssomnia was square root transformed in order to approach normality as on inspection of the data self-reported dyssomnia was not normally distributed. Because of the low prevalence of sleep problems, we categorized the scores for mother-reported dyssomnia into two categories, "no or one symptom" and "two or more symptoms" and mother-reported parasomnia into two categories, "no symptoms"

and "one or more symptoms". First, we tested the association of psychotic experiences with objective sleep-duration, sleep efficiency, arousal, and social jetlag in those with accelerometer data using linear regression models. Second, we analysed the association of psychotic experiences with self-reported continuous dyssomnia symptoms using linear regression. Next, to test the association of psychotic experiences with mother-reported symptoms of dyssomnia, parasomnia, and more specifically nightmares, sleep walking and sleep talking, we conducted logistic regression analyses for these binary outcome variables. All analyses were repeated separately for hallucinatory phenomena, considered the most typical positive symptom of the psychosis continuum (Kelleher & Cannon, 2011). Analyses were adjusted for the confounders, described above. To reduce bias due to missingness, missing data on the confounders were ten times imputed. All analyses were conducted in SPSS version 24 (IBM Corporation).

Sensitivity analyses

For sensitivity analysis, models concerning objective sleep measures were rerun using combined weekend plus weekday sleep as it has been suggested that weekend sleep may better represent children's natural sleep (Snell, Adam, & Duncan, 2007). In an additional step we adjusted for concurrent child psychopathology assessed with mother-reported CBCL, in order to derive specific insight into the association between psychotic experiences and sleep problems. Further, in order to obtain the estimates for the sleep duration of all weekday nights and psychotic experiences, sensitivity analyses were conducted including nights with less than 4 hours sleep duration. Finally, post-hoc Bonferroni adjustments were carried out for our 8 hypotheses, yielding more conservative alphas ($\alpha = 0.05/8 = 0.00625$).

Results

Characteristics of the study population are presented in Table 3.2.1. High scores ('several symptoms') of psychotic experiences were reported by 6.0% of the children.

The association of psychotic experiences with objective weekday-sleep

Psychotic experiences were not associated with objective sleep duration (B = -0.04, 95% CI: -0.17–0.09), sleep efficiency (B = 0.33, 95% CI: -0.82–1.48), arousal (B = -0.29, 95% CI: -1.06–0.48), or social jetlag (B = -0.20, 95% CI: -0.52–0.12) (Table 3.2.3). Similarly, hallucinatory phenomena were not associated with sleep duration

(B = 0.07, 95% CI: -0.11–0.26), sleep efficiency (B = 1.11, 95% CI: -0.68–2.90), arousal (B = -0.62, 95% CI: -1.66–0.43), and social jetlag (B = -0.26, 95% CI: -0.71–0.18) (Table 3.2.2).

Table 3.2.1. Characteristics of the study population

Child characteristics	N	Total sample N = 4149	N	Accelerometer sample N = 814
Sex (% girls)	2111	50.9	814	52.6
Ethnicity			814	
Dutch %	2814	67.8	691	84.9
Other Western %	348	8.4	45	5.5
Non-Western %	987	23.8	78	9.6
Psychotic experiences	4149		814	
No symptoms %	2261	54.5	404	49.6
Some symptoms %	1641	39.6	352	43.2
Several symptoms %	247	6.0	58	7.1
Hallucinatory phenomena	4149		810	
No symptoms %	2865	69.1	546	67.1
Some symptoms %	1076	25.9	221	27.3
Several symptoms %	208	5.0	43	5.3
Dyssomnia (child-reported)	4074	10.9 (2.5)	802	11.0 (2.5)
Dyssomnia (mother-reported)	4118		814	
Sometimes %	489	11.8	88	10.8
Not at all %	3629	87.5	694	685.3
Parasomnia	4121		814	
Sometimes %	1141	27.5	216	26.5
No or one symptom%	2980	71.8	566	69.5
Nightmares	4121		814	
Sometimes %	711	17.1	126	14.6
Not at all %	3422	82.5	668	77.2
Sleep (weekday)				
Duration (hours: minutes)	-	-	814	8:00 (0:36)
Efficiency %	-	-	814	82.3 (5.2)
Arousal (number awakenings)	-	-	814	24.3 (3.3)
Social jetlag (hours:minutes)	-	-	813	0:45 (1:01)
Maternal characteristics				
Age at inclusion (years)	4149	31.6 (4.6)	814	32.2 (3.9)
Educational level	4149		814	
No education/ primary school %	200	4.8	14	1.8
High school / lower vocational training %	1605	38.7	254	32.1
Higher vocational or academic training %	2344	56.5	523	66.1
Depressive symptoms	4149	0.2 (0.4)	814	0.2 (0.3)

Data represent means (SDs) unless specified otherwise.

Table 3.2.2. The association of psychotic experiences and hallucinatory phenomena with weekday-sleep in preadolescence

	Sleep duration, hours:minutes N = 814			Sleep efficiency, % N = 814			Arousal, no N = 814			Social jetlag N = 813		
	B	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Psychotic experiences												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	.00	-.08–.10	.960	-.05	-.83–.74	.903	.17	-.33–.67	.511	-.03	-.24–.19	.820
Several symptoms, yes	-.04	-.17–.09	.551	.33	-.82–1.48	.588	-.29	-1.06–.48	.452	-.20	-.52–.12	.240
Hallucinatory phenomena												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	-.03	-.10–.08	.534	.21	-.22–.64	.621	.28	-.24–.81	.293	-.09	-.31–.14	.454
Several symptoms, yes	.07	-.11–.26	.452	1.11	-.68–2.90	.192	-.62	-1.66–.43	.255	-.26	-.71–.18	.261

The associations were adjusted for sex, child's ethnicity, age at sleep assessment, gestational age, maternal education, and maternal psychopathology.

The association of psychotic experiences with sleep problems

Self-reported sleep problems

Psychotic experiences were associated with higher levels of self-reported dyssomnia (B = 2.45, 95% CI: 2.13–2.77). Likewise, when examined separately, hallucinatory phenomena were associated with higher levels of dyssomnia (B = 2.02, 95% CI: 1.69–2.40) (Table 3.2.3).

Mother-reported sleep problems

Psychotic experiences were also associated with mother-reported dyssomnia ($OR_{adjusted}$ = 3.48, 95% CI: 2.48–4.89). Similarly, hallucinatory phenomena by itself were associated with mother-reported and dyssomnia ($OR_{adjusted}$ = 2.31, 95% CI: 1.59–3.35). We observed a dose-response relationship of psychotic experiences with mother-reported dyssomnia and also of hallucinatory phenomena with mother-reported dyssomnia. For parasomnia, results indicated that more psychotic experiences were related to higher levels of mother-reported parasomnia, and specifically, more nightmares. The association between psychotic experiences of the child was not present for sleep walking or sleep talking (data not shown), indicating that the association for parasomnia was driven mainly by nightmares ($OR_{adjusted}$ = 3.59, 95% CI: 2.66–4.83). When analyzing hallucinatory phenomena specifically, the same dose-response relationship was observed; children with hallucinatory phenomena were more likely to have more mother-reported nightmares ($OR_{adjusted}$ = 2.74, 95% CI: 1.99–3.78) (Table 3.2.3).

Sensitivity analyses

The results were essentially unchanged when we analyzed objective sleep measures including weekend sleep (Table S3.2.1). When we additionally adjusted for co-occurring child emotional and behavioural problems the null findings for objective sleep measures remained. The observed association of psychotic experiences and self-reported dyssomnia symptoms also remained but was slightly attenuated (B = 2.16, 95% CI: 1.84–2.48, $p < 0.001$). Likewise, when tested hallucinatory phenomena separately, hallucinatory phenomena were associated with higher levels of dyssomnia (B = 1.75, 95% CI: 1.40–2.10, $p < 0.001$). Also, the association psychotic experiences and mother-reported dyssomnia symptoms remained but was attenuated ($OR_{adjusted}$ = 2.12, 95% CI: 1.47–3.05, $p < 0.001$) if adjusted for child emotional and behavioural problems. Importantly, when analyses were restricted to hallucinatory phenomena

Table 3.2.3. The association of psychotic experiences and hallucinatory phenomena with multi-rated sleep problems at age 10 years in the total sample

	Child-reported			Mother-reported								
	Dyssomnia N = 4074			Dyssomnia N = 4118			Parasomnia N = 4121			Nightmares N = 4121		
	B	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Psychotic experiences												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	1.22	1.06–1.37	< .001	1.93	1.57–2.38	< .001	1.48	1.28–1.71	< .001	1.83	1.54–2.19	< .001
Several symptoms, yes	2.45	2.13–2.77	< .001	3.48	2.48–4.89	< .001	2.56	1.94–3.36	< .001	3.59	2.66–4.83	< .001
p for trend			< .001			< .001			< .001			< .001
Hallucinatory phenomena												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	1.11	.96–1.31	< .001	1.67	1.35–2.06	< .001	1.55	1.33–1.81	< .001	1.93	1.61–2.31	< .001
Several symptoms, yes	2.02	1.69–2.40	< .001	2.31	1.59–3.35	< .001	2.12	1.57–2.84	< .001	2.74	1.99–3.78	< .001
p for trend			< .001			< .001			< .001			< .001

The associations were adjusted for sex, child's ethnicity, age at sleep assessment, gestational age, maternal education, and maternal psychopathology.

the association between psychotic experiences and mother-reported dyssomnia disappeared. The association for psychotic experiences and mother-reported nightmares remained if adjusted for child emotional and behavioural problems, but with a smaller OR, ($OR_{adjusted}$ = 2.50, 95% CI: 1.83–3.43, $p < 0.001$); similarly the association specifically for hallucinatory phenomena with nightmares was attenuated ($OR_{adjusted}$ = 2.00, 95% CI: 1.42–2.81, $p < 0.001$) (Table S3.2.2) by this adjustment. Results did not change when we reran a sensitivity analysis including the nights with a sleep duration shorter than 4 hours (B = -0.04, 95% CI: -0.17–0.10, $p = 0.61$; B = 0.08, 95% CI: -0.11–0.26, $p = 0.41$) for psychotic experiences and hallucinatory phenomena, respectively. All statistically significant results survived the multiple testing corrections.

Discussion

In this population-based study we extended previous findings (Fisher et al., 2014; Jeppesen, Clemmensen, et al., 2015) by examining how psychotic experiences and hallucinatory phenomena were associated with objective measures of sleep duration. To the best of our knowledge, this study is the first to examine the association of objective and subjective sleep parameters with psychotic experiences in youth. We found no association of psychotic experiences or hallucinatory phenomena with objective sleep duration, sleep efficiency, arousal, or social jet lag. We found that psychotic experiences were consistently associated with subjective sleep problems across raters. Consistent with this, we observed a dose-response association, whereby more child-reported psychotic experiences were associated with higher levels of mother-reported dyssomnia and parasomnia. Taken together, our findings suggest that in the general pediatric population psychotic experiences co-occur with multi-rated sleep problems and most strongly with nightmares.

Our finding that psychotic experiences were not associated with observed sleep problems is at odds with prior studies. Previous studies using actigraphic measures of sleep in young people at high risk for psychosis, reported shorter sleep duration, and more fragmented sleep during the prodromal phase prior to the onset of psychosis (Lunsford-Avery et al., 2015; Lunsford-Avery & Mittal, 2013). The literature about circadian rhythm may help to clarify the seemingly conflicting results. Adolescents at high risk for psychosis often display alterations in circadian rhythm, indicating that more desynchronized day-night rhythms might result in recurrence of psychotic

episodes (Lunsford-Avery et al., 2017). Important clues for the construction of the circadian rhythm are Zeitgebers. Zeitgebers are events such as exposure to light, timing of food intake, but also occupational or educational obligations (Golombek & Rosenstein, 2010). Potentially, these Zeitgebers, in particular the fixed school schedule, of the relatively young children in our sample may have been protective against developing desynchronized day-night rhythms, and subsequently prevented sleep problems occurring.

We found that child self-reported psychotic experiences are associated with mother-reported parasomnia symptoms, and especially nightmares. As the phenotypical resemblance between nightmares and psychotic experiences, child self-reported psychotic experiences might be particularly susceptible to information bias and thereby over-reporting by the child (van der Steen et al., 2018). Of note, a previous study demonstrated that screening questions for psychotic experiences in the general pediatric population have a high level of accuracy for psychotic symptoms confirmed by clinical interview (Kelleher et al., 2011). The endorsement of child self-reported psychotic experiences was similar to that observed in previous work using clinical interview assessments (Kelleher, Connor, et al., 2012; Polanczyk et al., 2010). Additionally, our findings cannot be explained by shared method, i.e. reporter, bias because our observations were based on different reporters and instruments. Our finding that psychotic experiences and hallucinatory phenomena are associated with nightmares is in line with previous work (Fisher et al., 2014; Jeppesen, Clemmensen, et al., 2015; Lee et al., 2012; Thompson et al., 2015). Both psychotic experiences during the day and nightmares indicate subjective experiences produced by spontaneous neural activity (Feinberg, 2011). Although, some studies report fluid passages between sleeping and waking state may result in hallucinatory phenomena (Arnulf et al., 2000; Manni & Mazzarello, 2001) suggesting some sort of continuity between nightmares and hallucinatory phenomena, there is no reason to consider them part of the same phenomenon. Several other studies point out that nightmares and hallucinatory symptoms are physiologically different (Rek, Sheaves, & Freeman, 2017; Waters et al., 2016). Nightmares during REM-sleep are characterized by pre-frontal area "closed-loop circuits" (Waters et al., 2016), whereas hallucinatory phenomena are characterized by abnormally modulated connections between anterior frontal areas and posterior sensory regions (Hoffman & Hampson, 2011; Jardri, Pouchet, Pins, & Thomas, 2011). Additionally, nightmares and psychotic experiences are different in terms of parental awareness. Parents are often not aware of psychotic experiences

of their children (Kelleher et al., 2011), but know of their nightmares. Potentially, in combination with other risk indicators (Polanczyk et al., 2010), mother-reported nightmares could be considered a risk indicator for psychotic experiences.

The finding that childhood dyssomnia is associated with psychotic experiences might be the result of concurrent child psychopathology. Indeed, when controlling for concurrent psychopathology, the associations of psychotic experiences with dyssomnia symptoms attenuated, but remained significant. One possibility for the attenuation of the effect is that co-occurring psychopathology may be a common cause underlying the association between psychotic experiences and dyssomnia symptoms. Indeed, from previous studies we know that both childhood dyssomnia and psychotic experiences are known to frequently co-occur with psychopathology (Gregory & Sadeh, 2016; Kelleher, Keeley, et al., 2012; Wigman et al., 2011). This could suggest that the association was partly explained by co-occurring emotional or behavioral problems, further investigation of the direction of this association is needed.

Strengths and limitations

This study has multiple strengths. First, we made use of actigraphical measures of sleep, which is a reliable way to assess of objective sleep duration, efficiency, arousal, and social jet lag. Second, we obtained sleep measures from multiple raters, both mother and child. This enabled us to control for reporter bias and shared method variance bias as different reporters (i.e. both mother and child) and instruments (i.e. different questionnaires) were used for sleep problems. Third, because of large sample size we were able to control for various important sociodemographic confounders and co-occurring child psychopathology.

The current study also had some limitations. First, we used self-report questions to measure psychotic experiences. It would have been optimal to conduct clinical interviews to assess psychotic experiences, because self-report might inflate the prevalence of psychotic experiences (Kelleher, Connor, et al., 2012). However, self-reported psychotic experiences have been shown to be predictive of clinician-confirmed psychotic disorder (Kelleher et al., 2011), and questionnaires have been reported to increase the willingness to disclose sensitive information (Jones, Fernyhough, de-Wit, & Meins, 2008), which is particularly important for pre-adolescent children. Moreover, from previous studies we know that the genetic factors underlying psychotic experiences and clinician-confirmed psychotic disorders overlap (Jeppesen, Larsen, et al., 2015; Zavos et al., 2014). Second, questionnaires on psychotic experiences

were collected at age 10 years, while actigraphical measures of sleep where at age 11 years. The literature suggests that sleep is relatively stable in school-age children (6–12 years) and typically changes with the onset of puberty only (Galland, Taylor, Elder, & Herbison, 2012). Although psychotic experiences in childhood are not very persistent (Bartels-Velthuis, van de Willige, Jenner, van Os, & Wiersma, 2011), this suggests that similar sleep patterns were present when the psychotic symptoms were assessed. However, future studies should employ longitudinal designs to test the extent to which persistence or desistence of psychotic experiences in children is related to sleep difficulties. Third, our measure of nightmares was based on one item, and therefore not very detailed. However, the "nightmares" item of the CBCL is associated with well-validated sleep measures, such as the parasomnia scale and the sleep anxiety scale of the Children's Sleep Habits Questionnaire, and it is associated with parasomnia sleep disorder diagnosis (Becker, Ramsey, & Byars, 2015). In the future, more in-depth information on nightmares should be assessed, including nightmare severity. Polysomnographic measures would be useful in order to map the sleep activity during nightmares. Fourth, this study was cross-sectional, which precludes the possibility of examining the direction of associations and, hence, any inferences on potential causal relations. Fifth, our study did not include a full range of maternal symptoms. However, we were able to use concurrent maternal depressive symptoms as a confounder, one of the leading causes of disability ranked in the global burden of disease scale (Ferrari et al., 2013). In future research, it will be important to apply longitudinal designs as well as a clinical follow-up to trace the associations between psychotic experiences and nightmares over the developmental course, while accounting for the dynamic course of psychotic experiences and sleep.

Conclusion

Our results suggest that psychotic experiences and hallucinatory phenomena are associated with subjective sleep problems, but that the association is specifically strong for nightmares. This finding can contribute to a broader understanding of the relationship between psychotic experiences and sleep. Additionally, it stresses the role of nightmares as a potential risk-indicator of psychopathology.

References

Acebo, C., Sadeh, A., Seifer, R., Tzischinsky, O., Wolfson, A. R., Hafer, A., & Carskadon, M. A. (1999). Estimating sleep patterns with activity monitoring in children and adolescents: how many nights are necessary for reliable measures? *Sleep, 22*(1), 95-103.

Achenbach, T. A., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms & Profiles. *Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.*

Achenbach, T. M., & Ruffle, T. M. (2000). The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review, 21*(8), 265-271.

Andorko, N. D., Mittal, V., Thompson, E., Denenny, D., Epstein, G., Demro, C., . . . Schiffman, J. (2017). The association between sleep dysfunction and psychosis-like experiences among college students. *Psychiatry Research. Vol.248 2017, pp. 6-12. Feb Psychiatry Res*. doi:10.1016/j.psychres.2016.12.009

Arnulf, I., Bonnet, A. M., Damier, P., Bejjani, B. P., Seilhean, D., Derenne, J. P., & Agid, Y. (2000). Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology, 55*(2), 281-288.

Bartels-Velthuis, A. A., van de Willige, G., Jenner, J. A., van Os, J., & Wiersma, D. (2011). Course of auditory vocal hallucinations in childhood: 5-year follow-up study. *Br J Psychiatry, 199*(4), 296-302. doi:10.1192/bjp.bp.110.086918

Becker, S. P., Ramsey, R. R., & Byars, K. C. (2015). Convergent validity of the Child Behavior Checklist sleep items with validated sleep measures and sleep disorder diagnoses in children and adolescents referred to a sleep disorders center. *Sleep Med, 16*(1), 79-86. doi:10.1016/j.sleep.2014.09.008

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res, 5*(4), 251-261.

Carskadon, M. A. (2011). Sleep in adolescents: the perfect storm. *Pediatr Clin North Am, 58*(3), 637-647. doi:S0031-3955(11)00019-8

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the perfect storm model. *J Adolesc, 67*, 55-65. doi:10.1016/j.adolescence.2018.06.001

De Beurs, E. (2004). Brief Symptom Inventory. Leiden, Netherlands; Handleiding.

Feinberg, I. (2011). Corollary discharge, hallucinations, and dreaming. *Schizophr Bull, 37*(1), 1-3. doi:10.1093/schbul/sbq115

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., . . . Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med, 10*(11), e1001547. doi:10.1371/journal.pmed.1001547

Fisher, H. L., Lereya, S. T., Thompson, A., Lewis, G., Zammit, S., & Wolke, D. (2014). Childhood parasomnias and psychotic experiences at age 12 years in a United Kingdom birth cohort. *Sleep, 37*(3), 475-482. doi:10.5665/sleep.3478

Fleetham, J. A., & Fleming, J. A. (2014). Parasomnias. *CMAJ, 186*(8), E273-280. doi:10.1503/cmaj.120808

Galland, B. C., Taylor, B. J., Elder, D. E., & Herbison, P. (2012). Normal sleep patterns in infants and children: a systematic review of observational studies. *Sleep Med Rev, 16*(3), 213-222. doi:10.1016/j.smrv.2011.06.001

Golombek, D. A., & Rosenstein, R. E. (2010). Physiology of circadian entrainment. *Physiol Rev, 90*(3), 1063-1102. doi:10.1152/physrev.00009.2009

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders--a review of the latest science. *J Child Psychol Psychiatry, 57*(3), 296-317. doi:10.1111/jcpp.12469

Hoffman, R. E., & Hampson, M. (2011). Functional connectivity studies of patients with auditory verbal hallucinations. *Front Hum Neurosci, 6*, 6. doi:10.3389/fnhum.2012.00006

Ivanova, M. Y., Achenbach, T. M., Rescorla, L. A., Guo, J., Althoff, R. R., Kan, K. J., . . . Verhulst, F. C. (2018). Testing Syndromes of Psychopathology in Parent and Youth Ratings Across Societies. *J Clin Child Adolesc Psychol*, 1-14. doi:10.1080/15374416.2017.1405352

Jaddoe, V. W., Mackenbach, J. P., Moll, H. A., Steegers, E. A., Tiemeier, H., Verhulst, F. C., . . . Hofman, A. (2006). The Generation R Study: Design and cohort profile. *Eur J Epidemiol, 21*(6), 475-484. doi:10.1007/s10654-006-9022-0

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry, 168*(1), 73-81. doi:10.1176/appi.ajp.2010.09101522

Jeppesen, P., Clemmensen, L., Munkholm, A., Rimvall, M. K., Rask, C. U., Jorgensen, T., . . . Skovgaard, A. M. (2015). Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence. *J Child Psychol Psychiatry, 56*(5), 558-565. doi:10.1111/jcpp.12319

Jeppesen, P., Larsen, J. T., Clemmensen, L., Munkholm, A., Rimvall, M. K., Rask, C. U., . . . Skovgaard, A. M. (2015). The CCC2000 Birth Cohort Study of Register-Based Family History of Mental Disorders and Psychotic Experiences in Offspring. *Schizophr Bull, 41*(5), 1084-1094. doi:10.1093/schbul/sbu167

Jones, S. R., Fernyhough, C., de-Wit, L., & Meins, E. (2008). A message in the medium? Assessing the reliability of psychopathology e-questionnaires. *Personality and Individual Differences, .44*(2), pp. doi:10.1016/j.paid.2007.08.014

Kelleher, I., & Cannon, M. (2011). Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol Med, 41*(1), 1-6. doi:10.1017/S0033291710001005

Kelleher, I., Connor, D., Clarke, M. C., Devlin, N., Harley, M., & Cannon, M. (2012). Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine, 42*(9), 1857-1863. doi:10.1017/S0033291711002960

Kelleher, I., Harley, M., Murtagh, A., & Cannon, M. (2011). Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophr Bull, 37*(2), 362-369. doi:10.1093/schbul/sbp05

Kelleher, I., Jenner, J. A., & Cannon, M. (2010). Psychotic symptoms in the general population - an evolutionary perspective. *British Journal of Psychiatry, 197*(3), 167-169. doi:10.1192/bjp.bp.109.076018

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., . . . Cannon, M. (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *Br J Psychiatry, 201*(1), 26-32. doi:10.1192/bjp.bp.111.101543

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van, I. M. H., . . . Jaddoe, V. W. (2016). The Generation R Study: design and cohort update 2017. *Eur J Epidemiol, 31*(12), 1243-1264. doi:10.1007/s10654-016-0224-9

Lee, Y. J., Cho, S. J., Cho, I. H., Jang, J. H., & Kim, S. J. (2012). The relationship between psychotic-like experiences and sleep disturbances in adolescents. *Sleep Med, 13*(8), 1021-1027. doi:10.1016/j.sleep.2012.06.002

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol Med, 43*(6), 1133-1149. doi:10.1017/S0033291712001626

Lunsford-Avery, J. R., Goncalves, B. D. B., Brietzke, E., Bressan, R. A., Gadelha, A., Auerbach, R. P., & Mittal, V. A. (2017). Adolescents at clinical-high risk for psychosis: Circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. *Schizophrenia Research, 189*, 37-42. doi:10.1016/j.schres.2017.01.051

Lunsford-Avery, J. R., LeBourgeois, M. K., Gupta, T., & Mittal, V. A. (2015). Actigraphic-measured sleep disturbance predicts increased positive symptoms in adolescents at ultra high-risk for psychosis: A longitudinal study. *Schizophrenia Research, 164*(1-3), 15-20. doi:10.1016/j.schres.2015.03.013

Lunsford-Avery, J. R., & Mittal, V. A. (2013). Sleep Dysfunction Prior to the Onset of Schizophrenia: A Review and Neurodevelopmental Diathesis-Stress Conceptualization. *Clinical Psychology-Science and Practice, 20*(3), 291-320. doi:10.1111/cpsp.12041

Manni, R., & Mazzarello, P. (2001). Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology, 57*(7), 1350-1351.

Mason, T. B., 2nd, & Pack, A. I. (2007). Pediatric parasomnias. *Sleep, 30*(2), 141-151.

McGrath, J. J., Saha, S., Al-Hamzawi, A., Andrade, L., Benjet, C., Bromet, E. J., . . . Kessler, R. C. (2016). The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *Am J Psychiatry, 173*(10), 997-1006. doi:10.1176/appi.ajp.2016.15101293

Meltzer, L. J., Montgomery-Downs, H. E., Insana, S. P., & Walsh, C. M. (2012). Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev, 16*(5), 463-475. doi:10.1016/j.smrv.2011.10.002

Morgan, C., Fisher, H., Hutchinson, G., Kirkbride, J., Craig, T. K., Morgan, K., . . . Fearon, P. (2009). Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. *Acta Psychiatr Scand, 119*(3), 226-235. doi:10.1111/j.1600-0447.2008.01301.x

Oshima, N., Nishida, A., Fukushima, M., Shimodera, S., Kasai, K., Okazaki, Y., & Sasaki, T. (2010). Psychotic-like experiences (PLEs) and mental health status in twin and singleton Japanese high school students. *Early Interv Psychiatry, 4*(3), 206-213. doi:10.1111/j.1751-7893.2010.00186.x

Owens, J. A., Spirito, A., McGuinn, M., & Nobile, C. (2000). Sleep habits and sleep disturbance in elementary school-aged children. *J Dev Behav Pediatr, 21*(1), 27-36.

Polanczyk, G., Moffitt, T. E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R. S., . . . Caspi, A. (2010). Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Arch Gen Psychiatry, 67*(4), 328-338. doi:10.1001/archgenpsychiatry.2010.14

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry, 57*(11), 1053-1058. doi:yoa9496 [pii]

Reeve, S., Emsley, R., Sheaves, B., & Freeman, D. (2017). Disrupting Sleep: The Effects of Sleep Loss on Psychotic Experiences Tested in an Experimental Study With Mediation Analysis. *Schizophr Bull*. doi:10.1093/schbul/sbx103

Reeve, S., Sheaves, B., & Freeman, D. (2015). The role of sleep dysfunction in the occurrence of delusions and hallucinations: A systematic review. *Clin Psychol Rev, 42*, 96-115. doi:10.1016/j.cpr.2015.09.001

Rek, S., Sheaves, B., & Freeman, D. (2017). Nightmares in the general population: identifying potential causal factors. *Soc Psychiatry Psychiatr Epidemiol*. doi:10.1007/s00127-017-1408-7

Ronnlund, H., Elovainio, M., Virtanen, I., Matomaki, J., & Lapinleimu, H. (2016). Poor Parental Sleep and the Reported Sleep Quality of Their Children. *Pediatrics, 137*(4). doi:10.1542/peds.2015-3425

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., . . . Klosterkotter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry, 67*(3), 241-251. doi:10.1001/archgenpsychiatry.2009.206

Sadeh, A., Raviv, A., & Gruber, R. (2000). Sleep patterns and sleep disruptions in school-age children. *Dev Psychol, 36*(3), 291-301.

Snell, E. K., Adam, E. K., & Duncan, G. J. (2007). Sleep and the body mass index and overweight status of children and adolescents. *Child Dev, 78*(1), 309-323. doi:10.1111/j.1467-8624.2007.00999.x

Spauwen, J., Krabbendam, L., Lieb, R., Wittchen, H. U., & van Os, J. (2003). Sex differences in psychosis: normal or pathological? *Schizophrenia Research, 62*(1-2), 45-49. doi:10.1016/s0920-9964(03)00063-x

Taylor, M. J., Gregory, A. M., Freeman, D., & Ronald, A. (2015). Do sleep disturbances and psychotic-like experiences in adolescence share genetic and environmental influences? *J Abnorm Psychol, 124*(3), 674-684. doi:10.1037/abn0000057

Thompson, A., Lereya, S. T., Lewis, G., Zammit, S., Fisher, H. L., & Wolke, D. (2015). Childhood sleep disturbance and risk of psychotic experiences at 18: UK birth cohort. *Br J Psychiatry, 207*(1), 23-29. doi:10.1192/bjp.bp.113.144089

van der Steen, Y., Myin-Germeys, I., van Nierop, M., Ten Have, M., de Graaf, R., van Dorsselaer, S., . . . van Winkel, R. (2018). 'False-positive' self-reported psychotic experiences in the general population: an investigation of outcome, predictive factors and clinical relevance. *Epidemiol Psychiatr Sci*, 1-12. doi:10.1017/S2045796018000197

van Hees, V. T., Fang, Z., Langford, J., Assah, F., Mohammad, A., da Silva, I. C., . . . Brage, S. (2014). Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol (1985), 117*(7), 738-744. doi:10.1152/japplphysiol.00421.2014

van Hees, V. T., Sabia, S., Anderson, K. N., Denton, S. J., Oliver, J., Catt, M., . . . Singh-Manoux, A. (2015). A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. *PLoS One, 10*(11), e0142533. doi:10.1371/journal.pone.0142533

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., . . . Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: a population-based cohort study. *Mol Autism, 9*, 8. doi:10.1186/s13229-018-0194-8

Verhulst, F. C., Van der Ende, J. (2013). Handleiding ASEBA Vragenlijsten voor leeftijden 6 tot met 18 jaar. Rotterdam: ASEBA Nederland.

Waters, F., Blom, J. D., Dang-Vu, T. T., Cheyne, A. J., Alderson-Day, B., Woodruff, P., & Collerton, D. (2016). What Is the Link Between Hallucinations, Dreams, and Hypnagogic-Hypnopompic Experiences? *Schizophr Bull, 42*(5), 1098-1109. doi:10.1093/schbul/sbw076

Welham, J., Scott, J., Williams, G., Najman, J., O'Callaghan, M., & McGrath, J. (2009). Growth in young adults who screen positive for non-affective psychosis: birth cohort study. *Aust N Z J Psychiatry, 43*(1), 61-67. doi:10.1080/00048670802534333

Wigman, J. T. W., Vollebergh, W. A. M., Raaijmakers, Q. A. W., Iedema, J., van Dorsselaer, S., Ormel, J., . . . van Os, J. (2011). The Structure of The Extended Psychosis Phenotype in Early Adolescence-A Cross-sample Replication. *Schizophrenia Bulletin, 37*(4), 850-860. doi:10.1093/schbul/sbp154

Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social jetlag: Misalignment of biological and social time. *Chronobiology International, 23*(1-2), 497-509. doi:10.1080/07420520500545979

Wolfson, A. R., & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Dev, 69*(4), 875-887.

Zavos, H. M., Freeman, D., Haworth, C. M., McGuire, P., Plomin, R., Cardno, A. G., & Ronald, A. (2014). Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence. *JAMA Psychiatry, 71*(9), 1049-1057. doi:10.1001/jamapsychiatry.2014.994

Table S3.2.1. The association of psychotic experiences and hallucinatory phenomena with (week and weekend combined) sleep in preadolescence

	Sleep duration, hours:minutes N = 806			Sleep efficiency, % N = 806			Arousal, no N = 806		
	B	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Psychotic experiences									
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	.04	-.03–.14	.412	.03	-.66–.72	.927	.12	-.35–.59	.629
Several symptoms, yes	-.06	-.20–.06	.347	.13	-.94–1.21	.805	-.51	-1.23–.22	.169
Hallucinatory phenomena									
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	-.03	-.12–.06	.471	.10	-.28–.47	.794	.07	-.43–.57	.777
Several symptoms, yes	.07	-.11–.25	.462	.93	-.54–2.40	.220	-.67	-1.68–.35	.197

The associations were adjusted for sex, child's ethnicity, age at sleep assessment, gestational age, maternal education, and maternal psychopathology.

Table S3.2.2. The association of psychotic experiences and hallucinatory phenomena with multi-rated sleep problems at age 10 years in the total sample adjusted for concurrent child psychopathology

	Child-reported			Mother-reported								
	Dyssomnia N = 4074			Dyssomnia N = 4118			Parasomnia N = 4121			Nightmares N = 4121		
	B	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Psychotic experiences												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	1.08	.92–1.23	< .001	1.49	1.20–1.86	< .001	1.22	1.05–1.42	.011	1.51	1.26–1.81	< .001
Several symptoms, yes	2.16	1.84–2.48	< .001	2.12	1.47–3.05	< .001	1.77	1.33–2.37	< .001	2.50	1.83–3.43	< .001
p for trend			< .001			< .001			< .001			< .001
Hallucinatory phenomena												
No symptoms	0	(ref.)		0	(ref.)		0	(ref.)		0	(ref.)	
Some symptom, yes	.96	.79–1.13	< .001	1.28	1.02–1.60	.035	1.29	1.09–1.51	.003	1.60	1.33–1.93	< .001
Several symptoms, yes	1.75	1.40–2.10	< .001	1.44	.96–2.17	.079	1.54	1.13–2.11	.007	2.00	1.42–2.81	< .001
p for trend			< .001			.013			< .001			< .001

The associations were adjusted for sex, child's ethnicity, age at sleep assessment, gestational age, maternal education, and maternal psychopathology. Additionally, all associations were adjusted for concurrent child psychopathology.

Chapter 4

Self-medication of child sleep

George Hendrik Breitner –
Meisje in witte kimono
Rijksmuseum, Amsterdam

Chapter 4.1

Sleep problems and melatonin use in school-aged children

M. Elisabeth Koopman-Verhoeff | Michiel A. van den Dries | Judith J. van Seters | Maartje P.C.M. Luijk | Henning Tiemeier | Annemarie I. Luik

JAMA Pediatrics (2019), 173(9), 883–885

Introduction

Sleep problems are reported in 25% (Janjua & Goldman, 2016) of children and adolescents. Melatonin, in many countries available without prescription, is often considered a pharmacological strategy to treat sleep problems. However, no clinical guidelines are available and effectiveness and long-term effects of melatonin-use in children are largely unknown (Janjua & Goldman, 2016). Melatonin-use has been estimated to be 1% in healthy children. Little is known about the association of objectively measured sleep with melatonin-use in this population. We investigated melatonin-use in school-aged children and its association with subjective sleep and objectively estimated sleep parameters.

Methods

This cross-sectional study included 871 children (mean age 11.7 ± 0.2 years, 52.2% girls, 88.8% western descent, Table 4.1.1) from the Generation R Study, a birth cohort representative of the general population (Kooijman et al., 2016). The Medical Ethics Committee of the Erasmus University Medical Center approved all study procedures and all parents provided written informed consent. At age 11 years, primary caregivers indicated children's use of sleep medication (type and frequency over 6 months). At age 10 years, sleep problems were reported by the primary caregiver using the Child Behavior Checklist 6-18 (CBCL, 5 items) and the child using the Sleep Disturbance Scale for Children (SDSC, 6 items) (Bruni et al., 1996). At age 11, total sleep time (TST), sleep onset latency (SOL), and wake after sleep onset (WASO) were estimated with a sleep diary and tri-axial wrist accelerometer (GENEActiv; Activinsights, UK, R-package GGIR (van Hees et al., 2015), study procedure described previously (Koopman-Verhoeff et al., 2019)). First, the prevalence of caregiver-reported melatonin-use was determined. Second, associations of sleep with melatonin-use were assessed with logistic regression analyses, adjusted for appropriate confounders (See footnote Table 4.1.2). Missing data for confounders were imputed. As melatonin-use has been proposed particularly for children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) we repeated analyses excluding children with these diagnoses. A threshold of $p = 0.005$ was used to correct for multiple testing. Analyses were conducted in SPSS version 24 (IBM Corporation).

Table 4.1.1. Sample characteristics

	Melatonin use (N = 53)	No melatonin use (N = 818)
Demographics	**M ± SD or N (%)**	**M ± SD or N (%)**
Sex, female, %	22 (41.5%)	435 (53.2%)
Age (years)	11.69 ± 0.18	11.67 ± 0.20
Gestational age (weeks)	39.51 ± 2.22	39.55 ± 2.36
Descent, %		
Dutch	46 (86.8%)	677 (82.8%)
Western	1 (1.9%)	50 (6.1%)
Non-Western	6 (11.3%)	90 (11.0%)
ASD, %	5 (9.4%)	4 (0.5%)
ADHD, %	3 (5.7%)	8 (1.0%)
Maternal age (years)	31.80 ± 3.61	32.32 ± 3.83
Maternal education[a], %		
Low	3 (5.7%)	16 (1.7%)
Intermediate	17 (32.1%)	257 (31.4%)
High	32 (60.4%)	519 (63.4%)
Maternal depressive symptoms (score; range)	0.22 (0.00–2.67)	0.17 (0.00–3.50)
Subjectively assessed sleep		
Sleep problems self-reported (score; range)	12.20 (8.00–18.00)	11.00 (6.00–18.00)
Sleep problems mother-reported (score; range)	2.04 (0.00–8.00)	0.83 (0.00–7.00)
TST (hours, sleep diary)	9:18 ± 0:42	9:30 ± 0:51
WASO (times, sleep diary)	0.6 ± 0.5	0.6 ± 0.7
SOL (minutes, sleep diary)	0:31 ± 0:30	0:27 ± 0:21
Objectively assessed sleep		
TST (hours: minutes)	7:30 ± 0:47	7:42 ± 0:42
WASO (hours: minutes)	0:30 ± 0:02	0:32 ± 0:02
SOL (hours: minutes)	1:06 ± 0:52	0:54 ± 0:40
Midpoint Sleep - schooldays, time (hours: minutes)	2:45 ± 0:36	02:40 ± 0:35

[a] For education low = primary school or lower vocational education, intermediate= intermediate vocational education, high = higher vocational education and university.

Results

A total of 53 out of 871 children (6.1%) used melatonin at least once a week in the previous six months. Caregiver- and child-reported sleep problems were associated with more melatonin-use (Table 4.1.2). No other associations were observed after multiple testing correction (p = 0.005, Table 4.1.2). Results did not differ between week and weekend sleep and remained largely unchanged when excluding children with ADHD or ASD (N = 15), except that sleep diary-estimated TST was now associated with melatonin use.

Table 4.1.2. Associations between subjective and objective sleep problems with melatonin use

	Melatonin-use (No/Weekly) with the inclusion of ASD and ADHD cases [a]			Melatonin-use (No/Weekly) with the exclusion of ASD and ADHD cases [b]		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Subjectively assessed sleep [c]						
Sleep problems (Mother-reported)	1.70	1.41–2.05	< .001	1.68	1.38–2.05	< .001
Sleep problems (Self-reported)	1.25	1.10–1.42	< .001	1.25	1.09–1.43	< .001
TST - schooldays (hours, sleep diary)	.63	.42–.93	.020	.55	.37–.81	.005
WASO - schooldays (times, sleep diary)	.94	.61–1.43	.764	.86	.53–1.42	.559
SOL (minutes, sleep diary)	1.01	1.01–1.02	.078	1.01	1.01–1.02	.028
Objectively assessed sleep [c]						
TST (hours)	.65	.44–.98	.038	.63	.42–.96	.033
WASO (minutes)	.98	.87–1.10	.658	.97	.89–1.06	.598
SOL (minutes)	1.62	1.09–2.41	.017	1.68	1.12–2.54	.013
Midpoint sleep (hours)	1.35	.82–2.45	.241	1.53	.90–2.59	.114

[a] N = 824 for self-reported and mother reported sleep problems. N = 871 for Total Sleep Time (Actigraphy), Waking After Sleep Onset (Actigraphy), and Sleep Onset Latency (Actigraphy). [b] N = 811 for self-reported and mother reported sleep problems. N = 856 for Total Sleep Time (Actigraphy), Waking After Sleep Onset (Actigraphy), and Sleep Onset Latency (Actigraphy). [c] Adjusted for gender, age of the child at behavior assessment, child's gestational age, and child's ethnicity, maternal age at birth, maternal education, and maternal psychopathology.

Discussion

This population-based study estimated a prevalence of 6% of melatonin-use in school-aged children, indicating that 1 in 17 children is likely to take melatonin at least once a week. This is despite the unknown effects of the use of melatonin in children (Janjua & Goldman, 2016).

We found that caregiver- and child-reported sleep problems and sleep diary reported shorter TST were associated with melatonin-use. The most likely explanation for our findings is that perceived poor sleep is an indication for melatonin-use. Indeed, a previous study indicates that parents administer "over the counter" melatonin in 12-year-old children to improve sleep problems (Janjua & Goldman, 2016). However, melatonin is often taken without prescription or good advice on dosage and timing

of administration. If melatonin is taken wrongly, for example by administering it shortly before bedtime, it can actually worsen sleep (Bruni et al., 2015). The current study is however cross-sectional, precluding any inference about temporality.

In conclusion, the use of melatonin in school-aged children is common even though potentially harmful effects of melatonin-use in children are unknown. Longitudinal and well-controlled studies are urgently needed to identify the effectiveness and potential negative consequences of melatonin-use in children. This would provide the evidence to formulate clinical guidelines for the indication and dosage of melatonin in children, which is pressing issue as melatonin is currently freely available.

References

Bruni, O., Alonso-Alconada, D., Besag, F., Biran, V., Braam, W., Cortese, S., . . . Curatolo, P. (2015). Current role of melatonin in pediatric neurology: Clinical recommendations. *European Journal of Paediatric Neurology, 19*(2), 122-133. doi:https://doi.org/10.1016/j.ejpn.2014.12.007

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of Sleep Research, 5*(4), 251-261. doi:10.1111/j.1365-2869.1996.00251.x

Janjua, I., & Goldman, R. D. (2016). Sleep-related melatonin use in healthy children. *Canadian Family Physician, 62*(4), 315-316.

Kooijman, M. N., Kruithof, C. J., van Duijn, C. M., Duijts, L., Franco, O. H., van Ijzendoorn, M. H., . . . Jaddoe, V. W. V. (2016). The Generation R Study: design and cohort update 2017. *European Journal of Epidemiology, 31*(12), 1243-1264. doi:10.1007/s10654-016-0224-9

Koopman-Verhoeff, M. E., Bolhuis, K., Cecil, C. A. M., Kocevska, D., Hudziak, J. J., Hillegers, M. H. J., . . . Tiemeier, H. (2019). During day and night: Childhood psychotic experiences and objective and subjective sleep problems. *Schizophrenia Research, 206*, 127-134. doi:https://doi.org/10.1016/j.schres.2018.12.002

van Hees, V. T., Sabia, S., Anderson, K. N., Denton, S. J., Oliver, J., Catt, M., . . . Singh-Manoux, A. (2015). A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. *PLOS ONE, 10*(11), e0142533.

Chapter 5

General discussion

Gustav Klimt –
Mother and Child

General discussion

The main aim of this thesis was to investigate the associations between sleep and mental health by studying (i) the determinants of sleep problems, (ii) the longitudinal associations of sleep and mental health in children, and (iii) the self-medication of sleep problems in healthy children and children with mental health difficulties. To this end, I made use of unique longitudinal data with subjective and actigraphic sleep information as well as child mental health reports obtained from parents and children. By collecting actigraphic sleep measures in a large sample we complemented existing data based on reported sleep characteristics, a novel and challenging undertaking in the pediatric sleep field. Overall, we found that (i) both environmental (family irregularity) and biological factors (epigenetic variation) are associated with sleep in childhood, (ii) we did not find evidence that the relationship between sleep problems and mental health (such measured in autism traits) is bidirectional, rather we found that sleep problems co-occur with autism symptomatology, and (iii) the self-medication of sleep problems is very common in healthy children as well as in children with common neurodevelopmental health difficulties. In this discussion, I first briefly summarize our findings per chapter, before discussing specific findings in the context of current methodological issues. Then, I will continue with the implications of this research for clinicians working with children and adolescents. I will end with proposing future directions for the field and conclude by providing some practical tools to optimize your own sleep.

Main findings

Determinants of child sleep

First, we explored the determinants of child sleep. An important factor for optimal development of a child is the family context, also in relation to healthy sleep patterns. Negative family environments are often characterized by unpredictable family life, and thereby the lack of routines. We identified a robust, long-term association of pre-school family irregularity with children's sleep problems and patterns, over and above the earlier identified influence of bedtime routines on child sleep. This association was in part mediated by child mental health, suggesting that child mental health might be a pathway by which family irregularity influences child sleep problems and patterns.

The second determinant of child sleep we investigated was DNA methylation. Complex behaviors such as sleep patterns result from the interplay of genes and

environment. How these influences together effect childhood sleep problems and patterns however, has been unclear. One of the mechanisms proposed for studying this process is DNA methylation, which regulates gene activity in response to both genetic and environmental factors. We found an association between sleep duration and DNA methylation in a specific region on chromosome 17, including genes previously linked to sleep problems and patterns within GWAS studies, such as the *MAPT* gene (a regulator of Tau proteins and which is biologically involved in neuronal functioning). The epigenetic patterns associated with sleep duration did not associate with common mental health outcomes. Combined, these studies support the literature showing that both environment (Mindell, Telofski, Wiegand, & Kurtz, 2009) and biology (Dashti et al., 2019) are involved in the regulation of sleep. In addition, we identified novel and specific targets for future investigation (i.e. family irregularity and DNA methylation).

Sleep and mental health

In a second step we investigated the association between sleep problems and specific domains of mental health. Sleep problems in children with autism are very common, with a prevalence up to 80% (Carmassi et al., 2019). However, the direction of the association is unknown as most studies are cross-sectional and the previous longitudinal studies lacked a baseline measure of autistic traits. Using a longitudinal design with repeated measures of both sleep problems as well as autistic traits we investigated bidirectional associations between sleep problems and autistic traits. We found no evidence that sleep problems and autism are bidirectionally associated. Sleep problems do not go before and worsen autistic behavior, but seem to co-exist with autistic traits in early childhood. Over time, children with autism have an increase in sleep problems, whereas typically developing children have a decrease in sleep problems. This suggest that reported sleep problems should be considered part of the construct of autism and therefore taken into account by clinicians treating children with autism.

Thereafter we investigated in a cross-sectional study whether reported and actigraphy measures of sleep were associated with childhood psychotic experiences – hearing or seeing things which are not there (Bolhuis et al., 2018). Actigraphic measures of sleep were not associated with childhood psychotic experiences, however, self- and mother-reported sleep problems were associated with psychotic experiences. This was in line with our previous study where we found that mother-reported sleep problems

at age 3 years and age 6 years were associated with childhood psychotic experiences (Bolhuis et al., 2018), suggesting a developmental pattern of shared vulnerabilities.

Taken together, based on this thesis we did not find support for a bidirectional association of sleep and autism in children. Associations between sleep and mental health were only identified for reported sleep and not for actigraphic sleep. Our findings highlight that reported sleep problems should be taken seriously in individuals with mental health problems and that sleep should be more often considered part of the classification.

Self-treatment of child sleep patterns

Lastly, we explored self-treatment of child sleep problems. In the general population we found that the use of melatonin in children was very common, even though possible harmful effects are unknown. More parent- and self-reported sleep problems were associated with melatonin use. Results were similar after excluding children with ADHD and autism, a group for whom melatonin is proposed to treat their co-morbid sleep problems (Bruni et al., 2015; Van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007). These rates point to an urgent need for clinical guidelines for the indication and dosage of melatonin use in children.

Methodological considerations

Actigraphic and reported data – Can we speak of a gold standard?

The findings in the current thesis were different for actigraphic and reported sleep data. While this is in line with previous work, many studies consider measures such as actigraphic sleep and reported sleep as similar (Carmassi et al., 2019; Irwin, Olmstead, & Carroll, 2016; Rossignol & Frye, 2011), even though there are several important differences between actigraphic and reported data. First, actigraphic and reported data tap into different sleep domains, in this thesis this was supported by poor correlations between the two (chapter 2). Actigraphic derived sleep is considered more objective as it is based on activity monitoring (Sadeh & Acebo, 2002; Sadeh, Sharkey, & Carskadon, 1994), rather than reported sleep relying on perceived sleep quality and nightmares (Goelema et al., 2019). From the literature we know that associations between sleep problems and mental health tend to be stronger if sleep is assessed with self-reported sleep problems than with actigraphic measures (Gregory & Sadeh, 2012). Therefore, it is hypothesized that underlying biological processes between mental

health and reported sleep, and mental health and actigraphic sleep may be different. For example, previous studies indicate that cortisol levels, which associate with mental health problems such as anxiety and depression, also associate with reported sleep quality but not with actigraphic sleep duration (Bassett, Lupis, Gianferante, Rohleder, & Wolf, 2015). It could be that actigraphy is a more physiological measure, potentially especially relevant to understand how cardiovascular and genetic factors impact sleep or activity rhythms (Bertisch et al., 2018). Along that line, in the current thesis we found that DNA methylation associated with actigraphic sleep duration, but not with self-reported sleep or mental health (chapter 2).

Second, the time-window covered by reported and actigraphic sleep is different. Often in sleep questionnaires, a child – or their parent – reports on sleep behavior during the past six months, and thus spanning a relatively large time-window compared to actigraphic sleep measures, where the time-window is substantially smaller (Achenbach & Rescorla, 2001; Bruni et al., 1996). The minimum number of nights for actigraphy is five (Acebo et al., 1999), enabling researchers to capture typical variation in sleep. Five nights of sleep might be sufficient when one expects sleep to be a stable phenotype. However, five nights might be too short when studying atypical variation of sleep in pre-adolescent psychiatric populations, where sleep is often disrupted in periods, such as the temporal decreased need for sleep in pediatric bipolar disorder (Hernandez, Marangoni, Grant, Estrada, & Faedda, 2017). Additionally, sleep is influenced by pubertal maturation which can change sleep timing and duration in a time window of 1 to 2 years (Crowley, Wolfson, Tarokh, & Carskadon, 2018; Sadeh, Dahl, Shahar, & Rosenblat-Stein, 2009; Tarokh, Saletin, & Carskadon, 2016). In future studies it is important to have multiple waves of actigraphy combined with measures of pubertal status, as pubertal maturation has the potential to disrupt sleep duration over a short time span (Sadeh et al., 2009).

Based on the issues regarding reported and actigrapic measures, it is questionable which measure of sleep problems or patterns is preferred in mental health research. Typically, polysomnography (PSG) and actigraphy are considered as gold and silver standard, respectively (Sadeh et al., 1994). However, based on previous work (Bassett et al., 2015) and the current thesis (chapter 3), reported sleep problems might be a better indicator of mental health outcomes in children. Although, self- or mother-reported sleep problems are often retrospectively obtained, have a potential perceptual bias, and – in the case of children with psychopathology – often overestimate current sleep problems (McMakin & Alfano, 2015; Reynolds & Alfano, 2016), the retrospect

perception of sleep problems could also be an indicator of mental health. Indeed, this was previously proposed by Gregory and Sadeh (2016), and our findings support this interpretation. This implies that there can be diverse "gold standards" for diverse questions in research and clinical settings. It is therefore important that future studies utilize a multimodal approach using both reported as well as actigraphic measures of sleep and that studies should select the best measure depending on their research question and outcomes examined.

Sleep and mental health – Can we speak of a bidirectional relation?

The association sleep and mental health is well-established (Gregory & Sadeh, 2012, 2016). However, it remains a question what comes first. Previous studies hypothesized that there are bidirectional associations between sleep and mental health, for example sleep and substance use (Colrain, Nicholas, & Baker, 2014), ADHD (Gregory & Sadeh, 2016), psychotic experiences (Waite, Sheaves, Isham, Reeve, & Freeman, 2019), and anxiety and depression (Alvaro, Roberts, & Harris, 2013; Kelly & El-Sheikh, 2014), or that mental health problems are a consequence of sleep problems, for example in the case of insomnia complaints and suicide risk (McCall et al., 2010). Moreover, studies report an improvement of daytime behavior when treating sleep problems in children with anxiety (Alfano, 2018), and that cognitive behavioral treatment targeting insomnia improves depressive complaints and psychotic experiences (Freeman et al., 2017; Manber et al., 2008). In this thesis (chapter 3), we observed a bidirectional association when we did not control for pre-occurring sleep or autism traits, but with control for previous autism traits the bidirectional association disappeared. A first possible explanation could be that bidirectional associations might be only limited to certain mental health traits such as depression (Sivertsen et al., 2012), but not to others such as autism. Second, it could be that the participants in studies such as randomized control trials are designed a fixed similar sleep duration as their typically developing peers (Ringli et al., 2013) but that these children need extra time to restore because of their difficulties during the day. Third, it might be that population-based cohorts and observational cohort studies do not meet levels of clinical severity of mental health problems to detect these associations. Fourth, the pediatric sleep field mimics the adult sleep field, formulating hypotheses based on adult studies (Gregory & Sadeh, 2016). However, there are important developmental differences and processes inherent to sleep problems and patterns between adults and children, e.g. brain maturation and the potential number of life-events experienced (Gregory & Sadeh, 2016). What is more, some adult experimental studies show causal

relations between sleep problems and mental health outcomes (Freeman et al., 2017), but these studies are scarce in the pediatric population. Therefore, future longitudinal studies are needed with more in-depth measures of psychopathology to clarify the mechanisms underlying associations between sleep problems and mental health.

Genetic studies – Are genetics solving our causality issues?

Although the role of genetics and epigenetics is a central topic in the field of sleep and mental health, there are also some considerations regarding these studies. Twin studies demonstrated a substantial heritability of sleep problems in children (Gregory, Rijsdijk, & Eley, 2006). These findings have been used in genome-wide association studies (GWAS), which confirmed that sleep problems, such as insomnia are polygenic traits, i.e. many different genetic factors with individual small effects influence sleep problems and patterns (Dashti et al., 2019; Jansen et al., 2019; Jones et al., 2019). Using genetic information from GWAS studies enables instrumental variable analyses such as Mendelian randomization which can help disentangle cause and effect (Davey Smith & Ebrahim, 2003). Such efforts have demonstrated that sleep disturbances and traits are a cause of increased cardio metabolic risk (Byrne, 2019; Cappuccio & Miller, 2017), breast cancer risk (Richmond et al., 2019), and mental health problems (Freeman et al., 2017). On the other hand, poor sleep is found to be a *consequence* of pain (Finan, Goodin, & Smith, 2013), and bidirectional associations have been observed for insomnia with depression (Sivertsen et al., 2012) and Alzheimer's disease (Ju, Lucey, & Holtzman, 2014). However, several limitations need to be considered. First, because genetic and epigenetic studies have been mainly based on individuals from European descent, it is unclear to what extent findings generalize to other populations and have the potential to lead to even more increased health inequalities in studies and personalized healthcare (Mackenbach, 2005). Second, the biological tissue used to extract epigenetic material is an important factor. Because of cell-type specificity, we do not know to what extent the identified DNA methylation patterns associate with DNA methylation patterns in the brain – the most relevant organ for both sleep patterns and mental health. In this thesis we describe the DNA methylation patterns as extracted from blood and it is not completely clear if it is reflective of the DNA methylation patterns in the brain. It is proposed that DNA methylation patterns derived from saliva is a better estimation of DNA methylation in the brain (Smith et al., 2015). Additionally, blood – the tissue assessed most often for genetic and epigenetic studies – is a tissue which can be difficult to extract in individuals with mental health problems. For example, children with autism are less likely to participate

in studies with blood sampling (Souders, DePaul, Freeman, & Levy, 2002). Fourth, although large sample sizes are needed to have sufficient power for genetic studies, often these studies lack the in-depth phenotyping specificity needed for understanding and accuracy of the associations tested, for example the GWAS on insomnia was based on one question about sleep (Jansen et al., 2019). Even with accurate phenotyping we cannot draw causal conclusions, however, genetically informative designs (twin and molecular epidemiology studies) can help to advance causal inference (e.g. in Mendelian randomization (Davey Smith & Ebrahim, 2003)). Using genetic designs, we are able to identify risk genes for amongst others, bipolar disorder (Dima et al., 2013), autism (Chaste & Leboyer, 2012), and also for sleep (Gregory, Parsons, Barclay, Gehrman, & O'Leary, 2016), which has the potential to identify targets for personalized treatment based on genetic predisposition for sleep problems.

Clinical implications

Studies from this thesis have the potential to serve public health and clinical practice in four key ways. First, we found a robust, long-term association of pre-school family irregularity with sleep problems and sleep patterns. Compared to other risk factors for child sleep problems (e.g. social economic status, parental psychopathology), family irregularity could be relatively easy to intervene on (Haines et al., 2013). Therefore, interventions focusing on family routines are potentially helpful in improving sleep in children.

Second, this thesis highlights the high prevalence of reported sleep problems in children with autism and psychotic experiences. We can conclude that sleep problems are a common problem in children with these types of psychopathology. It is important for clinicians to be alert when patients report sleep problems, as they have the potential to be an indicator of decreased wellbeing. Clinicians should be able to treat sleep problems as they are highly prevalent in children with psychopathology. Third, in this thesis we describe the common use of melatonin in healthy children, while the long-term effects of melatonin use are unknown. Clinicians should be aware of this public health issue and reluctant to prescribe melatonin for children. A therapeutic start with behavioral interventions targeting the sleep problems is preferred (Qaseem et al., 2016). Lastly, parents and children should be educated about the role of sleep problems and patterns in health and mental health and what they themselves can do to optimize their own sleep. Courses, interventions and clinical guidelines are needed

to teach psychologists and psychiatrist to target sleep in children with mental health difficulties, as sleep problems are often part of the problem.

Future directions

Based on this thesis some directions for further research can be formulated. First, it is important to study dreaming and nightmares in children, for example by assessing REM-sleep, the sleep stage where dreaming occurs. From this thesis and previous studies, we know that dreaming and nightmares associate with anxiety, posttraumatic stress disorder and psychotic experiences in children (Reynolds & Alfano, 2016). However, thus far studies have been lacking to study potential associations of dreaming with disorders such as autism.

Second, it is warranted to study interventions aimed at improving parental rules about bedtime and media use and the associations with sleep in adolescence. During adolescence parents become less involved in the daily life of the children, for example letting children decide about bedtime. It is important to study whether adolescents are indeed able to make adequate decisions regarding sleep or whether they need parents to set certain rules.

Lastly, studies investigating sleep and mental health should identify whether different sleep parameters – reported sleep quality, actigraphic sleep quantity, actigraphic sleep timing – differentially associate with various aspects of mental health and distress. Insights from such studies are important to facilitate future treatments. Therefore, we need longer periods of sleep assessment across development using questionnaires, actigraphy and novel measures such as smartphones, to identify certain sleep phenotypes belonging to specific disorders. These assessments will also help capture potential fluctuations in sleep to identify prodromes of transition to more severe clinical states. For example, in ASD, tracking sleep aids in the identification of individuals with more functional impairment and to select individuals for early intervention (Karthikeyan et al., 2020).

Practical implications: What can we do to sleep healthy?

Good sleep health begins with good sleep habits, therefore in this paragraph I provide some tips for anyone with sleep problems. First, go to bed around the same time each

night, to keep the internal clock and the sleep homeostat (the piggy bank) functioning properly (Jan et al., 2008). Second, build a calm bedtime routine to make going to bed easier, like reading a book or dimming the lights (Mindell & Williamson, 2018). Third, limit the amount of digital screen time right before bed (Hale & Guan, 2015). This is for two reasons: (1) the light from our devices might trick our clocks into thinking it's still daytime and (2) the excitement from games, tv-shows, and internet can keep us from settling down for bed. Fourth, keep your bedroom simple, cool, dark, and free of distractions like TV's and devices (try not to take your phone to bed) (Davis, Parker, & Montgomery, 2004). Fifth, when possible, reserve your bed for sleeping and not for other activities such as studying or working (Davis et al., 2004). Finally, limit caffeine (soda, energy drinks, coffee/tea) during the day and avoid these drinks after 4PM. Caffeine essentially fills your piggy bank early, so you can stay up later – which is not helpful when you still have to be on time at your job the next day (Owens, Mindell, & Baylor, 2014).

Conclusion

In summary, we learned from the studies in this thesis that it is important to pay more attention to the role of sleep in child development, especially in children with mental health issues. By identifying multiple determinants, associations and outcomes of sleep this thesis made it clear that as a community we cannot close our eyes to the importance of sleep for healthy development.

References

Acebo, C., Sadeh, A., Seifer, R., Tzischinsky, O., Wolfson, A. R., Hafer, A., & Carskadon, M. A. (1999). Estimating sleep patterns with activity monitoring in children and adolescents: how many nights are necessary for reliable measures? *Sleep, 22*(1), 95-103.

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA preschool forms & profiles.* Burlington: University of Vermont, Research Center for Children, Youth and Families

Alfano, C. A. (2018). (Re)Conceptualizing Sleep Among Children with Anxiety Disorders: Where to Next? *Clinical Child and Family Psychology Review, 21*(4), 482-499. doi:10.1007/s10567-018-0267-4

Alvaro, P. K., Roberts, R. M., & Harris, J. K. (2013). A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep, 36*(7), 1059-1068. doi:10.5665/sleep.2810

Bassett, S. M., Lupis, S. B., Gianferante, D., Rohleder, N., & Wolf, J. M. (2015). Sleep quality but not sleep quantity effects on cortisol responses to acute psychosocial stress. *Stress (Amsterdam, Netherlands), 18*(6), 638-644. doi:10.3109/10253890.2015.1087503

Bertisch, S. M., Pollock, B. D., Mittleman, M. A., Buysse, D. J., Bazzano, L. A., Gottlieb, D. J., & Redline, S. (2018). Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep, 41*(zsy047). doi:10.1093/sleep/zsy047

Bolhuis, K., Koopman-Verhoeff, M. E., Blanken, L. M. E., Cibrev, D., Jaddoe, V. W. V., Verhulst, F. C., . . . Tiemeier, H. (2018). Psychotic-like experiences in pre-adolescence: what precedes the antecedent symptoms of severe mental illness? *Acta Psychiatrica Scandinavica, 138*(1), 15-25. doi:10.1111/acps.12891

Bruni, O., Alonso-Alconada, D., Besag, F., Biran, V., Braam, W., Cortese, S., . . . Curatolo, P. (2015). Current role of melatonin in pediatric neurology: Clinical recommendations. *European Journal of Paediatric Neurology, 19*(2), 122-133. doi:https://doi.org/10.1016/j.ejpn.2014.12.007

Bruni, O., Ottaviano, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC) Construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *Journal of Sleep Research, 5*(4), 251-261. doi:10.1111/j.1365-2869.1996.00251.x

Byrne, E. M. (2019). The relationship between insomnia and complex diseases—insights from genetic data. *Genome Medicine, 11*(1), 57. doi:10.1186/s13073-019-0668-0

Cappuccio, F. P., & Miller, M. A. (2017). Sleep and Cardio-Metabolic Disease. *Current Cardiology Reports, 19*(11), 110. doi:10.1007/s11886-017-0916-0

Carmassi, C., Palagini, L., Caruso, D., Masci, I., Nobili, L., Vita, A., & Dell'Osso, L. (2019). Systematic Review of Sleep Disturbances and Circadian Sleep Desynchronization in Autism Spectrum Disorder: Toward an Integrative Model of a Self-Reinforcing Loop. *Frontiers in Psychiatry, 10*, 366.

Chaste, P., & Leboyer, M. (2012). Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues in clinical neuroscience, 14*(3), 281-292.

Colrain, I. M., Nicholas, C. L., & Baker, F. C. (2014). Alcohol and the sleeping brain. *Handbook of clinical neurology, 125*, 415-431. doi:10.1016/b978-0-444-62619-6.00024-0

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the perfect storm model. *Journal of Adolescence, 67*, 55-65. doi:https://doi.org/10.1016/j.adolescence.2018.06.001

Dashti, H. S., Jones, S. E., Wood, A. R., Lane, J. M., van Hees, V. T., Wang, H., . . . Saxena, R. (2019). Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nature Communications, 10*(1), 1100. doi:10.1038/s41467-019-08917-4

Davey Smith, G., & Ebrahim, S. (2003). 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?*. *International Journal of Epidemiology, 32*(1), 1-22. doi:10.1093/ije/dyg070

Davis, K. F., Parker, K. P., & Montgomery, G. L. (2004). Sleep in infants and young children: Part one: normal sleep. *Journal of Pediatric Health Care, 18*(2), 65-71. doi:https://doi.org/10.1016/S0891-5245(03)00149-4

Dima, D., Jogia, J., Collier, D., Vassos, E., Burdick, K. E., & Frangou, S. (2013). Independent Modulation of Engagement and Connectivity of the Facial Network During Affect Processing by CACNA1C and ANK3 Risk Genes for Bipolar Disorder. *JAMA Psychiatry, 70*(12), 1303-1311. doi:10.1001/jamapsychiatry.2013.2099

Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. *The journal of pain : official journal of the American Pain Society, 14*(12), 1539-1552. doi:10.1016/j.jpain.2013.08.007

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L.-M., Nickless, A., Harrison, P. J., . . . Espie, C. A. (2017). The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *The Lancet Psychiatry, 4*(10), 749-758. doi:https://doi.org/10.1016/S2215-0366(17)30328-0

Goelema, M. S., Regis, M., Haakma, R., van den Heuvel, E. R., Markopoulos, P., & Overeem, S. (2019). Determinants of perceived sleep quality in normal sleepers. *Behavioral Sleep Medicine, 17*(4), 388-397. doi:10.1080/15402002.2017.1376205

Gregory, A. M., Parsons, M. J., Barclay, N. L., Gehrman, P., & O'Leary, R. E. (2016). Genetic Research on Sleep, Sleep Disturbances and Associated Difficulties. In Y. Kovas, S. Malykh, & D. Gaysina (Eds.), *Behavioural Genetics for Education* (pp. 185-204). London: Palgrave Macmillan UK.

Gregory, A. M., Rijsdijk, F. V., & Eley, T. C. (2006). A Twin-Study of Sleep Difficulties in School-Aged Children. *Child Development, 77*(6), 1668-1679. doi:10.1111/j.1467-8624.2006.00966.x

Gregory, A. M., & Sadeh, A. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews, 16*(2), 129-136. doi:https://doi.org/10.1016/j.smrv.2011.03.007

Gregory, A. M., & Sadeh, A. (2016). Annual Research Review: Sleep problems in childhood psychiatric disorders – a review of the latest science. *Journal of Child Psychology and Psychiatry, 57*(3), 296-317. doi:10.1111/jcpp.12469

Haines, J., McDonald, J., O'Brien, A., Sherry, B., Bottino, C. J., Schmidt, M. E., & Taveras, E. M. (2013). Healthy Habits, Happy Homes: Randomized Trial to Improve Household Routines for Obesity Prevention Among Preschool-Aged Children. *JAMA Pediatrics, 167*(11), 1072-1079. doi:10.1001/jamapediatrics.2013.2356

Hale, L., & Guan, S. (2015). Screen time and sleep among school-aged children and adolescents: A systematic literature review. *Sleep Medicine Reviews, 21*, 50-58. doi:https://doi.org/10.1016/j.smrv.2014.07.007

Hernandez, M., Marangoni, C., Grant, M. C., Estrada, J., & Faedda, G. L. (2017). Parental Reports of Prodromal Psychopathology in Pediatric Bipolar Disorder. *Current neuropharmacology, 15*(3), 380-385. doi:10.2174/1570159x14666160801162046

Irwin, M. R., Olmstead, R., & Carroll, J. E. (2016). Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biological Psychiatry, 80*(1), 40-52. doi:https://doi.org/10.1016/j.biopsych.2015.05.014

Jan, J. E., Owens, J. A., Weiss, M. D., Johnson, K. P., Wasdell, M. B., Freeman, R. D., & Ipsiroglu, O. S. (2008). Sleep Hygiene for Children With Neurodevelopmental Disabilities. *Pediatrics, 122*(6), 1343. doi:10.1542/peds.2007-3308

Jansen, P. R., Watanabe, K., Stringer, S., Skene, N., Bryois, J., Hammerschlag, A. R., . . . The 23andMe Research, T. (2019). Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nature Genetics, 51*(3), 394-403. doi:10.1038/s41588-018-0333-3

Jones, S. E., van Hees, V. T., Mazzotti, D. R., Marques-Vidal, P., Sabia, S., van der Spek, A., . . . Wood, A. R. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nature Communications, 10*(1), 1585. doi:10.1038/s41467-019-09576-1

Ju, Y.-E. S., Lucey, B. P., & Holtzman, D. M. (2014). Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nature Reviews Neurology, 10*(2), 115-119. doi:10.1038/nrneurol.2013.269

Karthikeyan, R., Cardinali, D. P., Shakunthala, V., Spence, D. W., Brown, G. M., & Pandi-Perumal, S. R. (2020). Understanding the role of sleep and its disturbances in Autism spectrum disorder. *International Journal of Neuroscience*, 1-14. doi:10.1080/00207454.2019.1711377

Kelly, R. J., & El-Sheikh, M. (2014). Reciprocal relations between children's sleep and their adjustment over time. *Developmental Psychology, 50*(4), 1137-1147. doi:10.1037/a0034501

Mackenbach, J. P. (2005). Genetics and health inequalities: hypotheses and controversies. *Journal of epidemiology and community health, 59*(4), 268-273. doi:10.1136/jech.2004.026807

Manber, R., Edinger, J. D., Gress, J. L., Pedro-Salcedo, M. G. S., Kuo, T. F., & Kalista, T. (2008). Cognitive Behavioral Therapy for Insomnia Enhances Depression Outcome in Patients with Comorbid Major Depressive Disorder and Insomnia. *Sleep, 31*(4), 489-495. doi:10.1093/sleep/31.4.489

McCall, W. V., Blocker, J. N., D'Agostino, R., Kimball, J., Boggs, N., Lasater, B., & Rosenquist, P. B. (2010). Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. *Sleep Medicine, 11*(9), 822-827. doi:https://doi.org/10.1016/j.sleep.2010.04.004

McMakin, D. L., & Alfano, C. A. (2015). Sleep and anxiety in late childhood and early adolescence. *Current opinion in psychiatry, 28*(6), 483-489. doi:10.1097/yco.0000000000000204

Mindell, J. A., Telofski, L. S., Wiegand, B., & Kurtz, E. S. (2009). A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep, 32*(5), 599-606. doi:10.1093/sleep/32.5.599

Mindell, J. A., & Williamson, A. A. (2018). Benefits of a bedtime routine in young children: Sleep, development, and beyond. *Sleep Medicine Reviews, 40*, 93-108. doi:https://doi.org/10.1016/j.smrv.2017.10.007

Owens, J. A., Mindell, J., & Baylor, A. (2014). Effect of energy drink and caffeinated beverage consumption on sleep, mood, and performance in children and adolescents. *Nutrition Reviews, 72*(suppl_1), 65-71. doi:10.1111/nure.12150

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., Denberg, T. D., & for the Clinical Guidelines Committee of the American College of, P. (2016). Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Annals of Internal Medicine, 165*(2), 125-133. doi:10.7326/m15-2175

Reynolds, K. C., & Alfano, C. A. (2016). Things that Go Bump in the Night: Frequency and Predictors of Nightmares in Anxious and Nonanxious Children. *Behavioral Sleep Medicine, 14*(4), 442-456. doi:10.1080/15402002.2015.1017099

Richmond, R. C., Anderson, E. L., Dashti, H. S., Jones, S. E., Lane, J. M., Strand, L. B., . . . Smith, G. D. (2019). Investigating causal relations between sleep traits and risk of breast cancer in women: mendelian randomisation study. *BMJ, 365*, l2327. doi:10.1136/bmj.l2327

Ringli, M., Souissi, S., Kurth, S., Brandeis, D., Jenni, O. G., & Huber, R. (2013). Topography of sleep slow wave activity in children with attention-deficit/hyperactivity disorder. *Cortex, 49*(1), 340-347. doi:https://doi.org/10.1016/j.cortex.2012.07.007

Rossignol, D. A., & Frye, R. E. (2011). Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology, 53*(9), 783-792. doi:10.1111/j.1469-8749.2011.03980.x

Sadeh, A., & Acebo, C. (2002). The role of actigraphy in sleep medicine. *Sleep Medicine Reviews, 6*(2), 113-124. doi:https://doi.org/10.1053/smrv.2001.0182

Sadeh, A., Dahl, R. E., Shahar, G., & Rosenblat-Stein, S. (2009). Sleep and the Transition to Adolescence: A Longitudinal Study. *Sleep, 32*(12), 1602-1609. doi:10.1093/sleep/32.12.1602

Sadeh, A., Sharkey, M., & Carskadon, M. A. (1994). Activity-Based Sleep-Wake Identification: An Empirical Test of Methodological Issues. *Sleep, 17*(3), 201-207. doi:10.1093/sleep/17.3.201

Sivertsen, B., Salo, P., Mykletun, A., Hysing, M., Pallesen, S., Krokstad, S., . . . Øverland, S. (2012). The Bidirectional Association Between Depression and Insomnia: The HUNT Study. *Psychosomatic Medicine, 74*(7), 758-765. doi:10.1097/PSY.0b013e3182648619

Smith, A. K., Kilaru, V., Klengel, T., Mercer, K. B., Bradley, B., Conneely, K. N., . . . Binder, E. B. (2015). DNA extracted from saliva for methylation studies of psychiatric traits: Evidence tissue specificity and relatedness to brain. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 168(1), 36-44. doi:10.1002/ajmg.b.32278

Souders, M. C., DePaul, D., Freeman, K. G., & Levy, S. E. (2002). Caring for children and adolescents with autism who require challenging procedures. *Pediatric Nursing, 28*(6), 555.

Tarokh, L., Saletin, J. M., & Carskadon, M. A. (2016). Sleep in adolescence: Physiology, cognition and mental health. *Neuroscience and biobehavioral reviews, 70*, 182-188. doi:10.1016/j.neubiorev.2016.08.008

Van der Heijden, K. B., Smits, M. G., Van Someren, E. J. W., Ridderinkhof, K. R., & Gunning, W. B. (2007). Effect of Melatonin on Sleep, Behavior, and Cognition in ADHD and Chronic Sleep-Onset Insomnia. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(2), 233-241. doi:https://doi.org/10.1097/01.chi.0000246055.76167.0d

Waite, F., Sheaves, B., Isham, L., Reeve, S., & Freeman, D. (2019). Sleep and schizophrenia: From epiphenomenon to treatable causal target. *Schizophrenia Research*. doi:https://doi.org/10.1016/j.schres.2019.11.014


GUSTAV KLIMT

Appendices

Gustav Klimt –
The Family

Summary

We all sleep a third of our lives, added up to 250,000 hours, a sign that sleep must be important. Sleep problems with young children are fairly common, especially with children with behavioral problems. The aim of the research described in this thesis is to investigate how sleep and behavioral problems in children are related. To assess this, we formulated three sub-goals:

(1) to study the predictors of childhood sleep problems;
(2) to study bidirectionality in the association between sleep problems and behavioral problems;
(3) to study the role of self-medication in sleep problems.

For these questions we used the Generation R cohort from Rotterdam, the Netherlands, a study that follows almost 10,000 growing children to young adulthood. All of these children and their parents reported on sleep problems and behavioral problems through questionnaires. In addition, we have conducted home visits to 1500 children to map the sleep for 9 subsequent days in great detail with special movement watches, these actigraphy watches measure movement that we have used to estimate the sleep of the participants. The results of this thesis are summarized below.

Predictors of child sleep

In chapter 2 we studied the predictors of sleep problems in childhood. First, we focused at a predictor in the child's environment, unstructured family circumstances. Negative family circumstances are often characterized by a lack of structure within the family. We have shown that family irregularity in early childhood is associated with sleep problems and sleep patterns during childhood. This was in addition to previous studies who reported association with fixed routines for bedtime. Interventions to reduce family irregularity have the potential to improve sleep problems and patterns.

The second predictor we investigated was DNA methylation. Complex behavior such as sleep problems and sleep patterns result from the interaction of genes with the environment. One of the models to investigate this is DNA methylation, DNA methylation regulates gene activity in response to genetic and environmental factors – DNA methylation does this by regulating the degree of 'accessibility' of the gene, if the gene is unreachable, is no transcription possible and the gene is 'off' –. We found an association between actigraphic sleep duration measured and DNA methylation on chromosome 17, including genes previously associated with sleep problems through

GWAS studies. For example, the *MAPT* gene, a gene that regulates Tau proteins and is involved in the functioning of the brain. We found no associations of DNA methylation with behavioral problems or reported sleep problems.

Sleep and behavioral problems

In chapter 3 we looked at how sleep problems are related to specific behavioral problems such as autism and psychotic experiences. First, we assessed whether there is a bidirectional association between sleep problems and autism. Sleep problems are common in children with autism, but many of the studies have measured sleep and autism at the same time, and it is therefore unclear whether sleep problems or autism developed first. In our research we measured sleep problems and autism several times enabling us to identify a potential bi-directional association. We found, however, that sleep problems do not precede autism, but rather that they occur together. We also saw that over time, sleep problems decrease in healthy (typically developing) children and increase in children with autism. Our findings suggest that sleep problems should be seen as part of the autism classification.

Second, we have investigated whether psychotic experiences and reported sleep problems and actigraphic measured sleep duration are associated. Psychotic experiences are hearing or seeing things that are not there. We found that psychotic experiences are not associated with sleep duration, but that psychotic experiences were associated with self and mother-reported sleep problems. These findings help to better understanding the association between psychotic experiences and sleep.

Self-medication of sleep problems

In chapter 4 we investigated the use of medication as sleep aid in children. We found that the use of melatonin in healthy children is common, while we know nothing of possible negative consequences. The use of melatonin was associated with reported sleep problems, however not with actigraphic derived sleep duration. We found the same results when we repeated the analyzes without the children with ADHD and autism, for these children it is known that melatonin can help them falling asleep. These findings indicate that research is urgently needed into the long-term effects of melatonin use and that clinical guidelines must be drawn for the use of melatonin.

Finally, in chapter 5 we discussed the individual chapters. We discussed three methodological considerations, first, the differences between actigraphy and reported sleep

problems and that both make a unique contribution to research and clinical practice. Secondly, the complex bidirectional association between sleep and behavioral problems in children and that it may only be a bi-directional association with certain disorders, such as depression, but not with other disorders such as autism. Lastly, we described the importance of genetic studies, but also mentioned the difficulties associated with these studies. We then discussed recommendations for clinical practice and future research. We closed this chapter with practical tips for all readers to improve sleep problems and patterns at home.

Nederlandse samenvatting

Wij allen slapen een derde van ons leven. Dat is opgeteld zo'n 250.000 uur. Een teken dat slaap wel belangrijk moet zijn. Slaapproblemen bij jonge kinderen komen redelijk vaak voor, met name bij kinderen met gedragsproblemen. Het doel van het onderzoek beschreven in dit proefschrift is het onderzoeken hoe slaap- en gedragsproblemen bij kinderen samenhangen. Dit hebben we gedaan aan de hand van drie subdoelen:

(1) we hebben gekeken naar de voorspellers van slaapproblemen in de kinderleeftijd;
(2) we hebben gekeken of de associatie tussen slaapproblemen en gedragsproblemen bidirectioneel is;
(3) we hebben de rol van zelfmedicatie bij slaapproblemen bestudeerd.

Voor deze vragen hebben we gebruik gemaakt van het Generation R cohort uit Rotterdam, een studie die bijna 10.000 opgroeiende kinderen volgt tot de jongvolwassenheid. Al deze kinderen en hun ouders hebben via vragenlijsten gerapporteerd over slaapproblemen en gedragsproblemen. Bovendien hebben we bij 1500 kinderen huisbezoeken gedaan om heel gedetailleerd hun slaapgedrag van 9 dagen in kaart te brengen met speciale bewegingshorloges. Deze horloges meten beweging. De uitkomsten hiervan hebben wij gebruikt om de slaap van de deelnemers in te schatten. Hieronder staat de samenvatting van de resultaten van dit proefschrift.

Voorspellers van kinderslaap

In hoofdstuk 2 bestudeerden we de voorspellers van slaapproblemen in de kindertijd. We hebben hierbij eerst gekeken naar een voorspeller in de omgeving van het kind, zoals bijvoorbeeld ongestructureerde gezinsomstandigheden. Negatieve gezinsomstandigheden worden vaak gekenmerkt door het gebrek aan structuur binnen het gezin. Wij hebben laten zien dat ongestructureerde gezinsomstandigheden op peuterleeftijd geassocieerd zijn met slaapproblemen en slaappatronen gedurende de kinderleeftijd. Dit was bovenop de al eerder gevonden associatie met vaste routines voor het slapengaan.

De tweede voorspeller die we onderzochten was DNA methylatie. Het samenspel van genen met de omgeving resulteert in complex gedrag, zoals slaapproblemen en slaappatronen. Eén van de modellen om dit te onderzoeken is DNA methylatie. DNA methylatie reguleert de genactiviteit in reactie op genetische en omgevingsfactoren – DNA methylatie doet dit door de mate van 'bereikbaarheid' van het gen te reguleren, als het gen niet bereikbaar is, is er geen transcriptie mogelijk en staat het gen als

het ware 'uit'–. Wij vonden een associatie tussen slaapduur gemeten met actigrafie en DNA methylatie op chromosoom 17, onder andere met genen die eerder door GWAS-studies geassocieerd waren met slaapproblemen. Bijvoorbeeld het *MAPT* gen, een gen dat Tau proteïnen reguleert en betrokken is bij het functioneren van de hersenen. We vonden geen associaties van DNA methylatie met gedragsproblemen of gerapporteerde slaapproblemen.

Slaap- en gedragsproblemen

In hoofdstuk 3 keken we naar hoe slaapproblemen samenhangen met specifieke gedragsproblemen zoals autisme en psychotische ervaringen. Eerst keken we of er een bidirectionele associatie bestaat tussen slaapproblemen en autisme. Slaapproblemen komen veel voor bij kinderen met autisme, maar veel van de studies hebben op hetzelfde moment slaap en autistische symptomen gemeten en daardoor is het onduidelijk wat er eerst was, de slaapproblemen of het autisme. In ons onderzoek hebben we meerdere keren slaapproblemen en autisme gemeten en konden we kijken of er een bidirectionele associatie was. We vonden echter dat slaapproblemen niet voorafgaan aan het moment dat autisme wordt vastgesteld, maar dat ze eerder samen voorkomen. Zo zagen we ook dat na verloop van tijd slaapproblemen afnemen bij gezonde (zich normaal ontwikkelende) kinderen en toenemen bij kinderen met autisme. Onze bevindingen suggereren dat slaapproblemen gezien moeten worden als onderdeel van de autismeclassificatie.

Wij hebben onderzocht of psychotische ervaringen (het horen of zien van dingen die er niet zijn) en gerapporteerde slaapproblemen en actigrafisch gemeten slaapduur zijn geassocieerd. We vonden dat psychotische ervaringen niet geassocieerd zijn met slaapduur, maar dat psychotische ervaringen wel waren geassocieerd met zelf- en moeder-gerapporteerde slaapproblemen.

Zelfmedicatie van slaapproblemen

In hoofdstuk 4 onderzochten we het gemakkelijke gebruik van medicatie als hulp bij het slapen. We vonden dat het gebruik van melatonine bij gezonde kinderen vaak voorkomt, terwijl er niets bekend is over de mogelijke negatieve gevolgen. We vonden dezelfde resultaten toen we de analyses herhaalden met uitsluiting van de kinderen met ADHD en autisme, voor deze kinderen is bekend dat melatonine kan helpen bij het inslapen. Deze bevindingen wijzen erop dat er dringend onderzoek gedaan moet worden naar de langetermijneffecten van melatoninegebruik en dat er

richtlijnen moeten worden opgesteld voor het gebruik van melatonine.

Ten slotte hebben we in hoofdstuk 5 de individuele hoofdstukken bediscussieerd. We bespraken drie methodologische overwegingen. Ten eerste de verschillen tussen actigrafie en gerapporteerde slaapproblemen en dat beiden een unieke bijdrage leveren aan onderzoek en klinische praktijk. Ten tweede de complexe bidirectionele associatie tussen slaap- en gedragsproblemen bij kinderen. Dat er mogelijk alleen bij bepaalde stoornissen, zoals depressie, een bidirectionele associatie is, maar niet bij andere stoornissen zoals bij bijvoorbeeld autisme. Als laatste beschreven we het belang van genetische studies, hierbij benoemden we ook de moeilijkheden die gepaard gaan met deze studies. Vervolgens bespraken we aanbevelingen voor de klinische praktijk en toekomstig onderzoek. We sloten dit hoofdstuk af met praktische tips voor iedereen om eventuele slaapproblemen thuis te verbeteren.

Authors and affiliations

Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam, the Netherlands
Koen Bolhuis, Charlotte A.M. Cecil, Manon H.J. Hillegers, Desana Kocevska, M. Elisabeth Koopman-Verhoeff, Annemarie Luik, Maartje C.P.M. Luijk, Viara M. Mileva-Seitz, Henning Tiemeier, Frank C. Verhulst

The Generation R Study Group, Erasmus Medical Centre, Rotterdam, the Netherlands
Koen Bolhuis, Charlotte Cecil, Janine Felix, Vincent W.V. Jaddoe, Desana Kocevska, M. Elisabeth Koopman-Verhoeff, Rosa Mulder, Irwin Reiss

EP Bradley Hospital Sleep Laboratory, Alpert Medical School of Brown University, Providence, RI, United States of America
Mary A. Carskadon, M. Elisabeth Koopman-Verhoeff, Jared M. Saletin

Alpert Medical School of Brown University, Department of Psychiatry and Human Behavior, Providence, RI
Mary A. Carskadon, M. Elisabeth Koopman-Verhoeff, Jared M. Saletin

Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands
Liesbeth Duijts, Vincent W.V. Jaddoe, Desana Kocevska

Department of Molecular Genetics, Erasmus University Medical Center, Rotterdam, the Netherlands
Gijsbertus T.J. van der Horst

Department of Pediatrics, Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam, the Netherlands
Liesbeth Duijts, Vincent W.V. Jaddoe, Irwin Reiss

Department of Psychology, Education and Child Studies, Erasmus University Rotterdam, The Netherlands
Maartje C.P.M. Luijk

Department of Psychiatry, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands
Manon H.J. Hillegers

Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King´s College London, London, United Kingdom
Charlotte A.M. Cecil

Child and Adolescent Mental Health Centre, Mental Health Services Capital Region, Research Unit, Copenhagen University Hospital, Copenhagen, Denmark
Frank C. Verhulst

Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America
Henning Tiemeier

Department of Psychiatry, Vermont Center for Children, Youth and Families, University of Vermont, Burlington, Vermont, United States of America
James J. Hudziak

List of publications and manuscripts not part of this thesis

Kocevska, D., **Koopman-Verhoeff, M. E.**, Meinderts, S., Jaddoe, V. W. V., Hillegers, M. H. J., Verhulst, F. C., Roza, S., Luijk, M. P. C. M., & Tiemeier, H. (2018). Prenatal and early infant brain development and childhood sleep patterns. The Generation R Study. *Pediatric Research*, *83*(4), 760–6.

Bolhuis, K., **Koopman-Verhoeff, M. E.**, Blanken, L. M., Cibrev, D., Jaddoe, V. W. V., Verhulst, F. C., Hillegers, M. H. J., Kushner, S. A., & Tiemeier, H. (2018). Psychotic-like experiences in pre-adolescence: what precedes the precursory symptoms of severe mental illness? *Acta Psychiatrica Scandinavica*, *138*(1), 15–25.

Mulder, T, Kocevska, D, Muetzel, R.L., **Koopman-Verhoeff, M. E.**, Hillegers, M., White, T., Tiemeier, H. (2019). Childhood Sleep Disturbances and White Matter Microstructure in preadolescence. *Journal of Child Psychology and Psychiatry*, *60*(11), 1242–50.

Otterman, D. L., **Koopman-Verhoeff, M. E.**, White, T. J., Tiemeier, H., Bolhuis, K., Jansen, P. W. (2019). Executive Functioning and Neurodevelopmental Disorders in Early Childhood: A Prospective Population-Based Study. *Child and Adolescent Psychiatry and Mental Health*, *13*, 38.

Koopman-Verhoeff, M. E., Gredvig-Ardito, C., Barker, D. H., Saletin, J. M., Carskadon, M. A. (2020). Methods for assessing pubertal development for sleep studies. *Journal of Adolescent Health*, in press.

PhD portfolio

Name PhD student:	Maria Elisabeth Koopman-Verhoeff
Erasmus MC Department:	Child & Adolescent Psychiatry/Psychology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	Dec 2014 – Dec 2018
Promotor:	Prof. dr. Henning Tiemeier
Copromotors:	Dr. Charlotte Cecil
	Dr. Maartje Luijk

1. PhD training	Year	ECTS
MSc degree Health Sciences, specialization Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University Rotterdam, the Netherlands		
Study design	2015	4.3
Clinical epidemiology	2016	7.5
Biostatistical methods 1	*Ext.*	*5.7*
Biostatistical methods 2	2015	4.3
Methodological topics in Epidemiologic Research	2016	1.4
Principles of research in medicine and epidemiology	2015	0.7
Methods of public health research	2015	0.7
Clinical trials	2016	0.7
Health economics	2016	0.7
The practice of Epidemiological Analysis	2015	0.7
Fundamentals of Medical Decision Making	2015	0.7
Elective courses		
Repeated measurements in Clinical Studies	2017	1.4
Psychiatric Epidemiology	2015	1.1
Missing values in Clinical research	2017	0.7
Causal Inference	2016	0.7
Causal mediation analysis	2016	0.7
Principles of Genetic Epidemiology	2015	0.7
Social Epidemiology	2015	0.7
Psychopharmacology	2015	1.1
Topics in Meta-analysis	2016	0.7
Skills courses		
Basic course on R, Erasmus MC	2016	1.0
Research Integrity, Erasmus MC	2017	0.3
Biomedical English Writing and Communication	2018	2.0
Other courses		
Epigenetic Bootcamp, Columbia University, New York, NY, USA	2017	2.0
Sleep Research Society Leadership Workshop, San Antonio, TX, USA *(award)*	2019	0.5

	Year	ECTS
(Inter)national conferences		
24th congress of ESRS, Basel, Switzerland *(oral & poster presentation)*	2018	1.4
Mind and Brain Research day of Brown University, Providence, USA (*poster presentation*)	2019	0.5
EEARN meeting, Rotterdam (*poster presentation*)	2018	0.5
Epilepsy, Sleep and Neurocognition Symposium, Heeze	2017	0.2
SLAAP, Ermelo (*poster presentation*)	2016	1.0
SLAAP, Ermelo (*poster presentation*)	2017	1.0
SLEEP, San Antonio, TX, USA	2019	0.5
SRCD biannual meeting, Baltimore, MD, USA *(oral & poster presentation)*	2019	1.4
Symposia, meetings & workshops		
Feyenoord Football club, Rotterdam/Portugal *(oral presentation)*	2016	1.0
GenerationR Research Meetings, Rotterdam *(oral presentation)*	2016, 2018	1.0
Sleeping Safe and Sound Symposium, Nijmegen *(oral presentation)*	2017	1.0
Psychiatry Research Meetings, Rotterdam *(oral presentation)*	2018	1.0
Kind en Slaap expert meeting (in Dutch), Zeist *(oral presentation)*	2018	1.0
The Providence Sleep Research Interest Group, Providence, USA *(oral presentation)*	2019	1.0
Sleep Medicine Epidemiology, Brigham and Women Hospital, Boston, USA *(oral presentation)*	2019	1.0
Sleep Research Society Trainee Symposia, San Antonio, TX, USA	2019	1.0
Sleep for Science Retreat Colloquium, Providence, RI, USA	2019	1.0
2. Teaching activities		
Supervising Master's or Bachelor theses		
Debby Verhagen (Child and Family studies, Erasmus University Rotterdam) Longitudinal associations between maternal sensitivity and children's sleep problems	2015-2016	1.0
Eveline de Groot (Child and Family studies, Erasmus University Rotterdam) Executive functioning and sleep	2015-2016	0.5
Marieke van Harten (Child and Family studies, Erasmus University Rotterdam) Externalizing behavioral problems and sleep	2015-2016	0.5
Momoko Rijneveld (Clinical Psychology, Erasmus University Rotterdam) The influence of attachment style on the sleep duration and development of sleep problems of toddlers: The Generation R study	2015-2016	1.0
Sandra van der Sluis (Child and Family studies, Erasmus University Rotterdam) Divorce and family conflict: Predictors for children's sleep problems?	2015-2016	1.0
Selma Meinderts (Clinical Psychology, Erasmus University Rotterdam) Prenatal brain development and sleep	2015-2016	1.0
Cyriella Hermann (Child and Family studies, Erasmus University Rotterdam) Sleep and executive functioning	2016-2017	0.5

	Year	ECTS
Josette Voeten (Child and Family studies, Erasmus University Rotterdam) Sleep and harsh parenting	2016-2017	0.5
Josse Wetzer (Clinical Psychology, Erasmus University Rotterdam) Ghosts in the nursery: Prenatal parental psychopathology and longitudinal sleep problems in early childhood.	2016-2017	1.0
Roos van den Elshout (Child and Family studies, Erasmus University Rotterdam) Sleep and ADHD	2016-2017	0.5
Tim Vulkers (Clinical Psychology, Leiden University) Sleep, White Matter, and ADHD Symptoms: The Generation R Study	2016-2017	1.0
Vera Over de Vest (Child and Family studies, Erasmus University Rotterdam) Sleep and attachment	2016-2017	0.5
Anouk Brunink (Child and Family studies, Erasmus University Rotterdam) De relatie tussen gezinsfunctioneren en slaap van kinderen van elf jaar	2017-2018	0.5
Caroline van Hassel (Child and Family studies, Erasmus University Rotterdam) Are children with autism worse sleepers than children who don't have autism?	2017-2018	0.5
Judith van Seters (Medical Sciences, Erasmus Medical Center) Association of sleep problems and melatonin use in school-aged children.	2017-2018	1.0
Lina Al-Hassany (Medical Sciences, Erasmus Medical Center) Internalizing problems and sleep.	2017-2018	1.0
Lisa Hermans (Child and Family studies, Erasmus University Rotterdam) De invloed van gender, etniciteit en SES op de kwantiteit van slaap bij elfjarige kinderen.	2017-2018	0.5
Louise Otterman (Clinical Psychology, Erasmus University Rotterdam) The prospective association between executive functioning and traits of neurodevelopmental disorders in early childhood.	2017-2018	1.0
Other teaching activities		
Lectures for 3rd year medical students, Erasmus MC, Rotterdam, the Netherlands	2016-2017	1.0
Lectures for master students, Erasmus University, Rotterdam, the Netherlands	2015	0.5
3. Other activities		
Generation R general tasks	2014-2018	
Supervision and training of the Focus @13 scoring and assessment	2015-2018	6.0
Study manager sleep study	2015-2018	90.0
Peer review (e.g. Sleep, Human Brain Mapping, Research in Developmental Disabilities, European Journal of Epidemiology)	2015-present	3.0
Research Fellowship at the Bradley Sleep Lab, Brown University, Providence, RI, USA	2019	

	Year	ECTS
4. Grants and prices		
Fulbright Visiting Scholar Award	2018	
KNAW Ter Meulen Grant	2018	
Jo Kolk Grant	2018	
SRCD Graduate Student Travel Award	2019	
Sleep Research Society Leadership Workshop Award	2019	

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours

Dankwoord

Allereerst wil ik graag de deelnemers van het Generation R onderzoek bedanken. Zonder jullie hulp en trouwe deelname zou dit boekje nooit tot stand zijn gekomen. In het bijzonder de deelnemers van het slaaponderzoek bedankt, het is werkelijk hartverwarmend en bijzonder leerzaam hoe jullie afgelopen jaren op vrijdagavond jullie huizen en tijd voor ons beschikbaar stelden. Bedankt voor alle koffie, thee, warme maaltijden, kaartjes, telefoontjes, baklava, taart en liften terug naar het Erasmus MC als het te koud en te regenachtig was om terug te fietsen. Het was iedere keer een feest om bij jullie allemaal op bezoek te mogen komen! Oneindig veel dank ook aan het team van studenten dat heeft geholpen met de 1500 bezoeken: Lina, Veerle, Selma, Momoko, Bibi, Sandra, Debby, Marieke, Eveline, Berivan, Josse, Cyrriella, Josette, Roos, Tim, Annemiek, Lisa, Anouk, Emma, Judith, Caroline, Duifje, Johanneke, Louise, Tessa en Amber, BEDANKT. Ik weet niet wat ik zonder jullie had gemoeten.

Ten tweede, veel dank aan de dames van het focuscentrum, in het bijzonder Anneke. Dank ook aan Claudia, Marjolein, Patricia, Roos, Sunayna en alle anderen. Fijn dat jullie altijd tijd hadden voor een gezellig praatje en de rust wisten te bewaren als ik dacht dat er een kleine ramp gaande was.

Henning, ontzettend bedankt voor je begeleiding de afgelopen jaren. Je eerlijke en directe stijl van begeleiding vond ik – bijna – altijd erg prettig. Je passie en intelligentie is al vaak bezongen en daar ben ik het natuurlijk ook mee eens. Maar voor mij misschien nog wel belangrijker, op persoonlijk vlak heb ik veel van je geleerd. Jij bent een bijzondere begeleider om de manier hoe je omziet naar al je studenten in je team en ons echt helpt – op wetenschappelijk vlak of op andere vlakken. Ik ben dankbaar voor al jouw zorgzame adviezen (over werk of privé) die je mij in de loop van de jaren hebt gegeven. Bedankt ook voor de vriendschap die we konden opbouwen in Boston, die is ons erg dierbaar!

Maartje, wat fijn om zo'n enthousiaste copromotor te hebben als jou, jij denkt in mogelijkheden in plaats van onmogelijkheden en mijn zelfvertrouwen kreeg altijd een boost door jouw oneindige positieve feedback. Bedankt voor de vrijheid die je mij hebt geboden gedurende mijn project zodat ik echt mijn eigen dataverzameling binnen Generation R op kon zetten. Charlotte, Cha, I am eternally grateful to you for officially joining my team of supervisors. It is incredible how talented you are and I have learned – and learn – so much from you! Thank you for being such a good friend to us together with Nico. Dear Frank and Viara, my un-official PhD-

team; Frank, bedankt dat je in het midden van mijn PhD in bent gesprongen en de taak van interim-promotor op je hebt opgenomen. Van jouw lessen over hoe een klinisch relevant en begrijpelijk paper te schrijven zal ik altijd mijn voordeel mee blijven doen. Dank dat je in mijn leescommissie hebt plaatsgenomen. Viara, how I enjoyed our frequent skypes in the beginning of my PhD and our later meetings in person in Kingston, Rotterdam, and The Hague. Thanks for our discussions about the importance of science, art, family photography, and hagelslag. You are such an inspirational human being and I love how you followed your dreams – and showed all of us how extremely talented you are in science and arts!

Dearest Mary, thank you for being part of my small committee. You are such an incredible inspiration and it was an honor to be part of your lab last year. I miss your beautiful cottage in Providence and you as a fantastic teacher so much. I hope I can come back soon. I look forward to our future collaborations.

Beste Prof. dr. Bert van der Horst, bedankt dat je de secretaris van mijn kleine commissie wilt zijn, een hele eer! Prof. dr. Marike Lancel, Prof. dr. Irwin Reiss en Dr. Kristiaan van der Heijden, dank dat jullie in mijn oppositiecommissie willen deelnemen.

Rosa Mulder, jouw lessen epigenetica (en de tientallen herhalingen daarvan), sleepovers en kletspraatjes heb ik enorm gewaardeerd. Ik ben blij dat je bent aangestoken met het slaap-virus. Desana Kocevska, jij bent de Beyonce of sleep, als jij er niet was geweest had ik nog steeds het verschil niet geweten tussen een parasomnie en een insomnie. Jij maakt het slaaponderzoek zo veel leuker, blijf precies zoals je bent. Dear (international) colleagues (the pediatric sleep superstars): Annemarie Luik, Mary Carskadon, Jared Saletin, Danielle Hendriks, Tom Anders, Dan Dickstein, and Alice Gregory, thank you for your inspirational research and our collaborations. It is so exiting to collaborate and thank you very much for all your wise lessons and supervision. Lieve collega's, de superpowervrouwen van het Erasmus MC, Nina, Sara, Holly, Ivonne, Clair, bedankt voor alle gezellige uren en alle (ongevraagde) wederzijdse adviezen. Dear colleagues of the behavioral group, I feel incredibly lucky to be part of such an amazing team: Pauline, Manon, Alex, Andrea, Annemarie, Cees, Elisabet, Fadila, Hanan, Jolien, Irene, Laura, Lisa, Lisanne, Mannan, Michiel, Monica, Nathalie, Philip, Runyu, Ryan, Tessa, Tonya, Yllza, Yuna, Louk, Nienke, Bing, Fer, Lorenza, Patricia, Sander, en supersterren van de KJPP: Estrea and Evelien. Lieve slaap-vrienden van de JWC – jullie maken samenwerken en conferenties een feest. Lieve Nerdies, jullie zijn het begin van mijn wetenschappelijke carrière, zonder jullie hulp en humor had ik alleen de master al nooit volgehouden!

Dear 'new' US friends, 'congratulations' for making us your new 'European' friends. Dear Tom, Svea and George, Morgan and Emily, Jared and Chloe, we enjoyed our time with you in New England incredibly. Thank you for teaching us the real American life, including visits to cute RI villages such as Little Compton, the Cape-Cod beach house, funfetti cake, and pizza – Jared, seriously, I often dream about your pizzas. Thank you for bearing with us in dealing with our strange sense of humor and odd habits. Also, a big shout out to our friends from Central Church, especially the Altos, thank you for being such a support for us in the States and beyond. We miss you very much.

Lieve meisjes van de steeg, de lessen van de BA zijn te veel om te beschrijven. Lieve vrienden uit Gouda, Leiden en Den Haag, Noor, *nep-zus I*, Chris, Rens, *nep-zus II*, Merry, Margriet, Jeroen, Diet, Jurgen, Peet, Dani, Pieterjan, Elise, de Coronafamilie, wat fijn om jullie als vast en trouw netwerk al zo veel jaren te kennen. Ik weet dat ik bof met de beste vrienden – ook die ik de laatste jaren via Bart heb leren kennen, de drie J's en Des Gueux met aanhang.

Lieve Koen, als 'oud getrouwd stel' vanaf onze eerste werkdag in Rotterdam onafscheidelijk, samen lachen, werken, onderzoeksprojecten verzinnen en kibbelen is ons ding. Jouw intelligentie en oplettend oog ontgaat niets. Het gemak waarmee jij een artikel schrijft is ongeëvenaard, je bent een inspirerend docent en begeleider van vele studenten inclusief ondergetekende. Ik ben zo trots dat jij vandaag naast mij wil staan als paranimf. Lieve Anouk, jij bent mijn thuis-genoot nummertje één. Van samen op de zolder van de steeg, naar de Oude Singel, naar Den Haag. Bankhangen, steden trippen, tandartsbezoekjes, koken, zonder kaart of woordenboek door Zuid-Italië reizen of in een danskelder in Spanje belanden… Jij bent voor mij een inspiratie, met je rustige, zelfverzekerde, optimistische en pragmatische levenshouding en je ontzettende rake opmerkingen met de juiste timing. Loco Peetie, bedankt dat jij mij rugdekking geeft. Lieve Renske, jij bent mijn oudste vriendin en nep-zus. Door als baby's in de box te liggen ontwikkel je vast en zeker een hechte familieband. Wij delen het beste gevoel voor humor, een uitmuntende smaak, een feilloos beoordelingsvermogen en inmiddels 32 jaar aan herinneringen en trouwe vriendschap. Frannie, bedankt dat je vandaag weer net zo dichtbij aanwezig bent als in de afgelopen 32 jaar.

Caroline, thank you for being our family away from home when we were in Providence. We feel so lucky to have you in our lives. Lieve tantes en ooms bedankt voor jullie interesse en aanmoedigingen. Lieve schoon-familie, wat fijn dat het bij jullie altijd

zo'n warm bad is. Liefste broertjes en zusjes, Kees, Madeleine, Sam en Do, Willem, bedankt voor jullie echte wijze lessen. Zonder jullie zou ik waarschijnlijk niets van het echte leven begrepen hebben, nooit een normale rugzak gekocht hebben, nooit een café van binnen hebben gezien, nooit een normaal gesprek hebben gevoerd en zeker nooit met mijn beide benen op de grond zijn blijven staan. Lieve papa en mama, een onverwoestbaar vertrouwen en geloof hebben jullie altijd in ons gehad. Bedankt dat wat ik ook doe, jullie altijd trots zijn. In Gouda is altijd rust en een luisterend oor, hoeveel ik overal ook leer, het kan nooit op tegen wat jullie mij hebben bijgebracht – geloof, hoop en oneindig veel liefde.

Bart, jij die het misschien wel echt altijd beter weet. Jij hebt mijn leven teruggegeven, bij jou ben ik thuis waar we ook zijn. Waar jouw woorden spaarzaam zijn en – bijna – altijd raak, zijn die van mij regelmatig te veel. Bart, als ik jouw waarheid ben, ben jij mijn leven. Ik houd van je!

Wir danken dir, Gott, wir danken dir und verkündigen deine Wunder.
(Psalm 75:1)
J.S. Bach BWV 29 - "Wir danken dir, Gott, wir danken dir"

About the author

Elize Koopman-Verhoeff was born in Gouda, The Netherlands. Elize studied Clinical Child and Education studies and started in 2011 with the two-year research master Developmental Psychopathology in Child and Education Studies at Leiden University, The Netherlands. After her graduation Elize worked as a school psychologist at a basis profession school in Rotterdam and as a teacher at the Erasmus University Rotterdam. In 2014 Elize started her PhD program – the work described in this thesis – at the Department of Child and Adolescent Psychiatry/Psychology and the Generation R Study Group at the Erasmus Medical Centre-Sophia Children's Hospital in Rotterdam. In 2015 Elize started as the study manager of a largescale actigraphic sleep data collection within the Generation R Study – one of the largest objective pediatric sleep samples word wide –. She coordinated the logistics of 1500 home visits in Rotterdam and was responsible for design, support, data management and training and supervision of over 25 students. Additionally, in 2016 Elize conducted a pilot study researching sleep in elite athletes as an invited researcher at the Feyenoord Football Club in Rotterdam. Elize obtained a Master of Science degree in Clinical Epidemiology from the Netherlands Institute for Health Sciences in 2017. From December 2018 to September 2019, Elize was granted a Ter Meulen fellowship from the Royal Netherlands Academy of Arts and Sciences, a Jo Kolk grant, and a Fulbright fellowship to give her the opportunity to work with Prof. dr. Mary Carskadon and Dr. Jared Saletin in the Bradley Sleep Lab of Brown University in Providence (Rhode Island, USA). In Providence Elize received additional (clinical) training of Prof. dr. Dan Dickstein in scoring of the K-SADS interview. Elize will continue her research into factors influencing mental health in children – including sleep – as a postdoctoral fellow at the Erasmus medical center. She aims to ultimately combine research and clinical work as a clinical child psychologist.