The rhythm of adult ADHD

On the relationships between ADHD, sleep and aging

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"**Living with ADHD is like walking up a down escalator**. **You can get there eventually but the journey is exhausting**."

- Kathleen Ely [1]

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"**The domain of rhythm extends from the spiritual to the carnal**." Bruno Walter [1a]

Biological rhythms pervade every aspect of life. In this thesis, we explore a quartet of physiological functions which are believed to show rhythmic patterns. These are firstly, those risk factors associated with developing cardiovascular disease and diabetes, known as Metabolic Syndrome (MetSyn). Secondly, sleep and its disturbances, such as insomnia and circadian rhythm disorders, also show rhythmic fluctuations. A third part of the quartet is Seasonal Affective Disorder (SAD), depression occurring on a yearly basis at the onset of winter. Finally, aging is also an inevitable physiological process which shows an accelerated rhythm in some individuals and a more languid pace in others.

Attention-Deficit/Hyperactivity Disorder (ADHD) is often thought of as a purely psychiatric disorder. In this thesis, we explore how its effects and associations extend to the somatic, or carnal, realm. Specifically, we investigate how ADHD is associated with MetSyn, sleep/circadian rhythm disorders and SAD. The subsequent consequences on health and illness are examined. Sleep disorders are also investigated in relation to aging that occurs on a cellular level.

The quartet includes seemingly disparate physiological processes. How are they linked? In this thesis we propose that a pro-inflammatory state may be a common link in these disturbed rhythms.

1.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) – HISTORY

Many people believe that ADHD is a disorder that emerged in the modern era. But in the late 18th century, Sir Alexander Crichton described children with "mental restlessness", a "disease of attention" and "the fidgets" [2]. Crichton's recognition of this clinical entity and its subsequent effect on schooling was two hundred years ahead of its time. About a century later, the pediatrician Sir George Still, identified children with a "morbid defect of moral control", displaying disinhibition, poor self-regulation and "a quite abnormal incapacity for sustained attention" [3]. Until recently, ADHD was considered a disorder of childhood. Recently, several studies have shown that ADHD persists into adulthood in up to 60% of affected children [4] – and extends into old age in 2.8% [5].

1.2 ADULT ADHD – PREVALENCE, SYMPTOMS AND TREATMENT

"I prefer to distinguish ADD as attention abundance disorder. Everything is just so interesting . . . remarkably at the same time." Frank Coppola [6]

The world cross-national estimated prevalence of adult ADHD is 2.8% [7], with a range of 2.5 - 4.9% [8, 9]. Today, adult ADHD is considered a neurodevelopmental disorder characterized by inattention and/or impulsivity, hyperactivity, mood instability and mind wandering [10 - 12]. In adult ADHD, inattention, disorganization and procrastination predominate [13]. Hyperactivity symptoms are less obvious and are often internalized as inner restlessness [14].

Adult ADHD is a rewarding condition to treat as positive results of pharmacological treatments versus placebo are impressive [15]. Stimulant medications such as amphetamines and methylphenidate are first line agents [16]. Non-stimulants such as atomoxetine are second line, and considered when there are tolerability, response or safety concerns with stimulants. Psychosocial treatments include cognitive behavioral therapy, with emphasis on organization, prioritizing, and time management. Combining pharmacotherapy and psychosocial treatments is considered most effective [17].

1.3 ADULT ADHD – COMORBIDITIES

ADHD in adults is highly comorbid with psychiatric and metabolic disorders, such as sleep, anxiety and mood disorders, Post Traumatic Stress Disorder (PTSD), autism spectrum disorder, personality disorders, obesity, amongst others [18 - 20]. In practice, clinicians frequently treat ADHD in the presence of several comorbidities. Of these, some are disorders of the biological rhythm. We now explore the quartet MetSyn, sleep/circadian rhythm disorders, SAD and aging in more detail.

1.4 BIOLOGICAL RHYTHMS

"We learned we are truly rhythmic organisms, it's hard to find a cell that does not oscillate in response to these clocks." Michael W. Young, joint recipient Nobel Prize in Physiology/Medicine 2017 [21]

Underpinning all life, from the simplest unicellular organisms to the most complex, are the biological rhythms. The study of biological timekeeping, or chronobiology, examines how these cyclical rhythms control vital aspects of our physiology [22]. Of relevance to this thesis are three types of biological rhythms:

Ultradian: occurring many times per day, for example the rhythmic control of digestive processes. Ultradian rhythm disorders may be associated with MetSyn [23].

Circadian: occurring approximately every 24 hours: *circa* (approximately) and *dies* (day). A rhythm disturbance here refers to desynchronization of the sleep-wake cycle.

Circannual: occurring approximately once yearly. A disorder of this rhythm is for example SAD, where major depressive episodes occur yearly during fall and/or winter [10, 24].

The literature also describes infradian (repeating at intervals much longer than 24 hours) and tidal, weekly and circalunar (monthly) rhythms occurring in animals and plants [25].

2. THE RHYTHM OF INSOMNIA

Many sleep disorders have a higher prevalence in the presence of adult ADHD (illustrated in Figure 1). Of importance to this research are insomnia and delayed circadian rhythm.
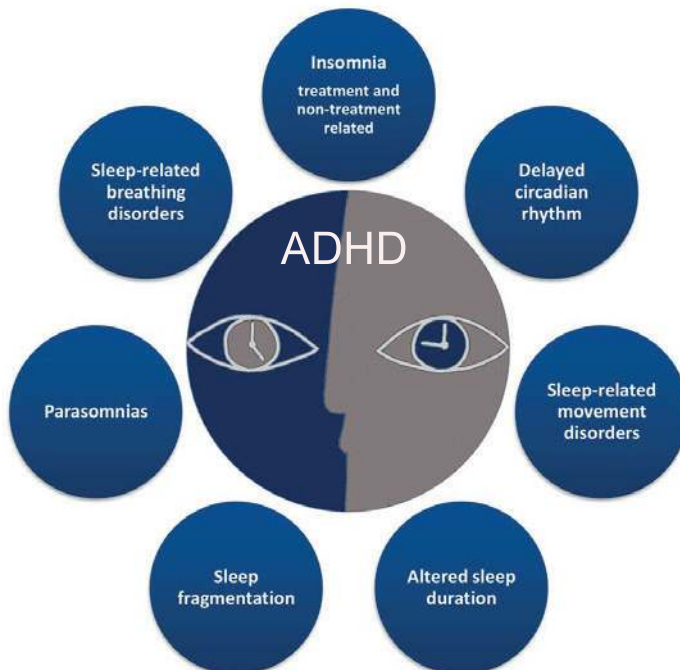
FIGURE 1. Some of the sleep disorders with increased prevalence in adult ADHD

Two examples of delayed circadian rhythm are delayed chronotype and an extreme version of this, the Delayed Sleep Phase Syndrome. Examples of sleep-related movement disorders include periodic limb movements during sleep and restless legs syndrome.

2.1   INSOMNIA – HISTORY

"O sleep, O gentle sleep, Nature's soft nurse, how have I frightened thee? That thou no more will weigh my eyelids down, and steep my senses in forgetfulness?"
William Shakespeare [26]

The understanding of insomnia has changed over recent decades. Today, it is considered normal to go to bed before midnight and to sleep 7-8 uninterrupted hours per night. Yet, anthropological research and historical evidence show that this has not always been the case [27]. For example, before the industrial age there is ample (European) documentation of fragmented sleep occurring normally. A "first sleep" started 4 hours after dinner, followed by 2 hours awake in bed after midnight, where people remained and ate, read, prayed and wrote – and then a "second sleep" of 4 hours commenced [28]. By the late 17th century, references to this interrupted pattern had disappeared and sleep was considered of no academic interest. Interestingly, a study from the early 1990s demonstrated a segmented sleep pattern when volunteers were placed in a dark environment for 14 hours per day [29]. The official birth of modern sleep science was in 1953, when Rapid Eye Movement sleep was first described [30].

2.2   INSOMNIA – PREVALENCE IN ADHD AND SYMPTOMS

Insomnia is an important comorbid condition in adult ADHD, where the cross-sectional prevalence is 43-80% [31-33]. This association is complicated by the finding that pharmacological treatments for ADHD are also reported to cause insomnia. One of the most common sleep disorders, insomnia, is now classified as a sleep-wake disorder in DSM-5 [10]. Sufferers experience problems with the quality and quantity of sleep, and have decreased functioning during the daytime. The timing of sleep is also affected, with difficulty initiating or maintaining sleep; or early-morning awakening over at least 3 months, 3 nights per week [10].

2.3   ADHD AND INSOMNIA – RESEARCH QUESTIONS

The relationship between insomnia and ADHD is discussed in **Chapter 2**, where a literature review provides an update of cross-sectional and longitudinal studies, as well as discussing how insomnia is associated with pharmacological treatments for ADHD. **Chapter 3** tests the relationship between ADHD and insomnia, sleep duration and ADHD in another population study, NEMESIS-2 (Netherlands Mental Health Survey and Incidence Study-2). **Chapter 4** briefly raises the possibility that the relationship between ADHD and insomnia is related to a pro-inflammatory state.

3.   THE RHYTHM OF DELAYED CIRCADIAN TIMING

"The circadian system has its tentacles around everything…It's ticking away in almost every tissue in the human body." Michael Robash, joint recipient Nobel Prize in Physiology/Medicine 2017 [34]

Several other sleep disorders that are studied in this thesis relate to a possible biological rhythm disturbance in ADHD. A delayed circadian rhythm is highly prevalent in ADHD: particularly the late chronotype and an extreme version of this, the Delayed Sleep Phase Syndrome (DSPS).

3.1   THE SLEEP-WAKE CYCLE

As elegantly described by Bourguinon and Storch, many species on earth have evolved a self-sustaining timing system, which facilitates robust 24 hour rhythms in physiology and behavior, despite non-24 hour variations in the environment [35]. Hence organisms function over a 24 hour cycle, even when there are no cues in the form of changes in light and dark [22]. This adaptive, endogenous timing system is also known as the circadian clock. Interdisciplinary research over the past decades is uncovering its cellular and molecular basis. In 2017, the Nobel Prize for Medicine was awarded to Hall, Robash and Young, three scientists investigating the molecular mechanisms of circadian rhythm [34].
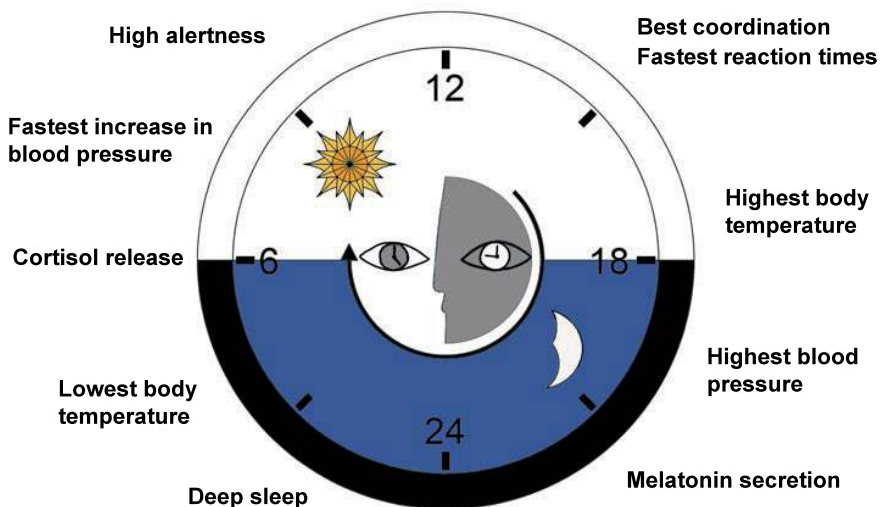
FIGURE 2. The circadian rhythm and physiological processes
Adapted from: The Nobel Assembly at the Karolinska Institutet, Stockholm [36]

While most cells in the human body show circadian activity, the master clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus, anticipating and adapting human physiology to the different phases of the day (Figure 3). Disorders of circadian rhythm have far-reaching consequences.

3.2 DELAYED SLEEP PHASE SYNDROME - HISTORY

Several circadian rhythm sleep disorders are described in DSM-5 and of relevance to this thesis is DSPS [10]. Weitzman and colleagues first described a chronobiological disorder with sleep-onset insomnia in 1981. They named it "delayed sleep phase insomnia" [37]. Today, it is still poorly recognized by clinicians, often dismissed, or misdiagnosed as chronic insomnia due to the presence of sleep initiation problems and some overlap between its diagnostic criteria [38].

3.3 DELAYED SLEEP PHASE SYNDROME – PREVALENCE AND SYMPTOMS

Two types of DSPS are described: a temporary adolescent variety (more common among boys) in 7 - 16% of teenagers [39] and a lifelong variety, beginning in early childhood or puberty, with prevalence range from 0.13 to 10% [38]. In DSPS, there is believed to be a discrepancy between the internal setting of the biological clock and the sleep-wake schedule required by one's occupational, social or educational obligations [10]. Difficulty in falling asleep at socially acceptable hours is thought to occur because sleep is being attempted at a time when the biological clock is strongly promoting wakefulness.

The results are sleep-onset usually after midnight, shorter sleep duration, difficulty awakening and chronic sleep deprivation, resulting in daytime fatigue and impaired functioning. The other essential component of DSPS is the difficulty to shift one's schedule to an earlier time. The circadian phase of sleep in DSPS is stable: individuals will fall asleep and awaken at consistent, albeit *delayed* times when left to their own schedule (e.g., on weekends or holidays). Once sleep is initiated, it is normal.

3.4 CHRONOTYPE

A person's chronotype refers to the behavioral manifestation of underlying circadian rhythms, as evidenced by regular rising and sleep-onset times during 24 hours. Chronotype consists of morning, evening and intermediate types [40]. Timing of sleep and wakefulness may differ during work and free days, as sleep deficit accumulates during working days, but is compensated for on free days, when rising time can be later [41]. Phase and duration of

sleep on *free* days are believed to reflect circadian rhythm most accurately as there are fewer externally enforced schedules [42].

3.5   ADHD AND DELAYED CIRCADIAN RHYTHM – RESEARCH QUESTIONS

In this thesis, we investigate delayed circadian rhythm in two studies. **Chapter 5** examines the well-recognized relationship between ADHD and SAD (discussed in the next paragraph), and particularly whether indicators of disturbed sleep and delayed circadian rhythm mediate this relationship. **Chapter 7** tests the relationship between cellular aging and delayed circadian rhythm.

4.   THE RHYTHM OF SEASONAL AFFECTIVE DISORDER

4.1   SEASONAL AFFECTIVE DISORDER – HISTORY

"Whoever wishes to pursue the science of medicine in a direct manner must first investigate the seasons of the year and what occurs in them." Hippocrates [43]

Observers of depression have long noted synchrony between the seasons and mood (extensively reviewed in [44]). In 1621, Burton[1] remarked that "of all the seasons, the autumn is the most melancholy" [45]. In the 1980s, when psychiatrist Norman Rosenthal moved to the USA from South Africa, he noticed his own loss of productivity and increased depression during the short, dark days of winter. However, his functioning returned to normal as soon as spring arrived. Based on this personal experience, his own research and the collaboration of other experts investigating the neurohormone melatonin and circadian rhythm, the first paper on light therapy for SAD was published. SAD is now a well-documented disorder [24].

4.2   SEASONAL AFFECTIVE DISORDER – PREVALENCE AND SYMPTOMS

Winter depression or SAD has a prevalence of up to 27% in adult ADHD [46 - 48]. In the general population the estimated prevalence is much lower: 3-6% [47, 49]. SAD occurs four times more often in women than in men, and the age-of-onset is between 18 and 30 years [50].

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1   The book is referred to as "The Anatomy of Melancholy", but with a full title: "The Anatomy of Melancholy, What it is: With all the Kinds, Causes, Symptomes, Prognostickes, and Several Cures of it. In Three Maine Partitions with their several Sections, Members, and Subsections. Philosophically, Medicinally, Historically, Opened and Cut Up".

Symptoms of SAD occur during the fall and winter months and include sadness, thoughts of death or suicide attempts, feeling worthless or guilty, difficulty concentrating or making decisions, anhedonia, fatigue, forgetfulness, as well as the so-called atypical depressive symptoms: sleep disturbance (tendency to sleep longer), hyperphagia and weight increase, with carbohydrate cravings [51]. Without treatment, the symptoms of SAD tend to remit in the spring, so that SAD lasts about 40% of the year [52]. Depressive episodes can occur in summer too, but this is far less common.

4.3   ADHD, SEASONAL AFFECTIVE DISORDER, INSOMNIA AND CIRCADIAN RHYTHM – RESEARCH QUESTIONS

By studying the relationship between SAD, insomnia and delayed circadian rhythm, we are conceptualizing ADHD as a disorder of the biological rhythm. This has been suggested by genetic evidence, which shows underlying CLOCK gene (Circadian Locomotor Output Cycles Kaput) polymorphisms in ADHD [53]. In animal models with mutant circadian genes, ADHD-like symptoms and reduced dopamine levels have been observed [54]. Both SAD and DSPS are known disorders of biological rhythm and share genetic factors with ADHD [55]. In terms of treatment, symptoms of ADHD, SAD and DSPS improve when therapy involves 'phase resetting' of the day-night rhythm [56, 57]. In **Chapter 5**, we explore whether the well-recognized association between SAD and ADHD is mediated by markers of circadian rhythm disturbance in a study from the NESDA cohort.

5.   THE RHYTHM OF METABOLIC SYNDROME

Metabolic disorders such as obesity frequently co-exist with ADHD, although this might seem counterintuitive: association of hyperactivity with raised Body Mass Index (BMI) does not appear consistent [18, 19]. However, impulsivity and inattention in ADHD may lead to disturbed eating patterns and weight gain. A recent meta-analysis reported a significant association between ADHD and obesity [58]. ADHD is also associated with sleep disorders, and recently, evidence has been accumulating that sleep disorders may explain part of the relationship between ADHD and obesity [59]. Abnormal metabolic processes are among the risk factors associated with developing cardiovascular disease and type 2 diabetes mellitus. The MetSyn is a cluster of these frequently co-occurring disturbances.

5.1   METABOLIC SYNDROME – HISTORY

"The syndrome of affluence, (Wohlstandssyndrom)" [60]

The interdependence of vascular hypertension and type 2 diabetes was reported independently by European physicians at the beginning of the 20th century, but the term "metabolic syndrome" was only coined in the 1950s [61]. In 1989, the term "deadly quartet" was coined to refer to the most dangerous type of MetSyn, including disorders of glucose intolerance, hypertriglyceridemia, obesity and hypertension [62].

5.2   METABOLIC SYNDROME – PREVALENCE AND DESCRIPTION

World-wide, obesity and type 2 diabetes have increased rapidly reaching epidemic proportions [63]. Excessive food intake and a sedentary lifestyle have been proposed to explain, at least in part, this increase. The prevalence of MetSyn in U.S. adults is over 25%, with higher rates among various race/ethnic minority groups [64].

According to the widely-used adjusted Adult Treatment Panel III (ATP-III) criteria, MetSyn may be diagnosed if three of the following risk factors co-exist:
- Abdominal obesity: waist circumference > 102 cm in men and > 88 cm in women;
- Hypertriglyceridaemia: triglyceride levels ≥ 1.7 mmol/l (150 mg/dl) or use of medication to reduce hypertriglyceridemia;
- Low high-density lipoprotein (HDL) cholesterol: HDL < 1.03 mmol/l (40 mg/dl) in men and < 1.30 mmol/l (50 mg/dl) in women, or use of medication to reduce HDL cholesterol;
- Hypertension: blood pressure ≥ 130/85 mm Hg, or use of antihypertensive medication;
- Fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or use of anti-diabetic medication [63].

5.3   ADHD AND METABOLIC SYNDROME – RESEARCH QUESTIONS

Obesity has an increased prevalence in the presence of ADHD [58] and mood and anxiety disorders [65 - 67]. Anxiety and depressive disorders are highly comorbid with adult ADHD: occurring in 47% and in 38% respectively [68]. We were interested whether those with both ADHD *and* different stages of depressive/anxiety disorders had an increased risk for MetSyn. This study is reported in **Chapter 6**, using data from the NESDA cohort (the Netherlands Study of Depression and Anxiety). Here we ask: what is the association between MetSyn, obesity-related outcomes and adult ADHD?

6. THE RHYTHM OF CELLULAR AGING

"I am incapable of conceiving infinity, and yet I do not accept finiteness. I want this adventure that is the context of my life to go on without end." Simone de Beauvoir [69]

6.1 CELLULAR AGING AND TELOMERES – HISTORY

Aging is inevitable, and marked by a progressive decline in the function of multiple cells and organs, leading to vulnerability and finally death [70]. Apart from the overt signs of aging such as hair greying and altered adiposity, susceptibility to disease increases dramatically with age [71].

The science of aging was advanced by several key findings. Firstly, on a cellular level, the limited lifespan of normal human cells was described by Hayflick et al. in 1965 [71]. In a classic paper, they showed that normal human fibroblasts do not proliferate indefinitely in culture; they reach a limit after 50 to 70 cellular divisions - termed the *Hayflick limit* [72]. Thereafter, normal cells become senescent or die [73]. Secondly, on an intracellular level, telomeres are crucial to understanding normal aging. Telomeres are short DNA repeats found on the end of chromosomes, much like a plastic tip at the end of a shoelace. They were discovered in flies in the late 1930s, before DNA was known to be the genetic material [74]. In 1978, their exact base pair (bp) sequence was described by Elizabeth Blackburn, who later shared the Nobel prize for this work [75]. Over the lifespan, normal aging is accompanied by telomere shortening in human somatic cells.

6.2 TELOMERIC ATTRITION – MECHANISMS

Before cell division, chromosomal DNA unwinds and separates so that replication can occur. The enzyme, DNA polymerase, reads the existing strands to build the new strands, with the help of short pieces of RNA primer. When copied, each matching strand is slightly shorter than the original strand because of the room needed for the primer, the so-called "end replication problem". Hence, with each cell division, 50 to 100 bp are lost from the end of the telomeres [73]. For example, in leukocytes, telomere length ranges from 10,000 bp in newborns, to 3,000 bp in adults, to 1,500 bp in the elderly [73]. To counteract telomere shortening or attrition, the enzyme telomerase adds bases to the ends of telomeres and thus delays their attrition [71]. This is especially important in young and constantly renewing cells such as hemopoetic cells, sperm and egg cells.

Telomeres have several protective functions for chromosomes [71]. As a plastic tip protects a shoelace's end, telomeres prevent the end of chromosomal DNA from being "misrecognized" as a broken end. This halts the chromosome ends from being repaired, which would lead to instability. A specialized nucleoprotein complex known as shelterin makes the damage invisible [76]. Secondly, telomeres prevent DNA from end-joining, which would further corrupt the cell's genetic blueprint.
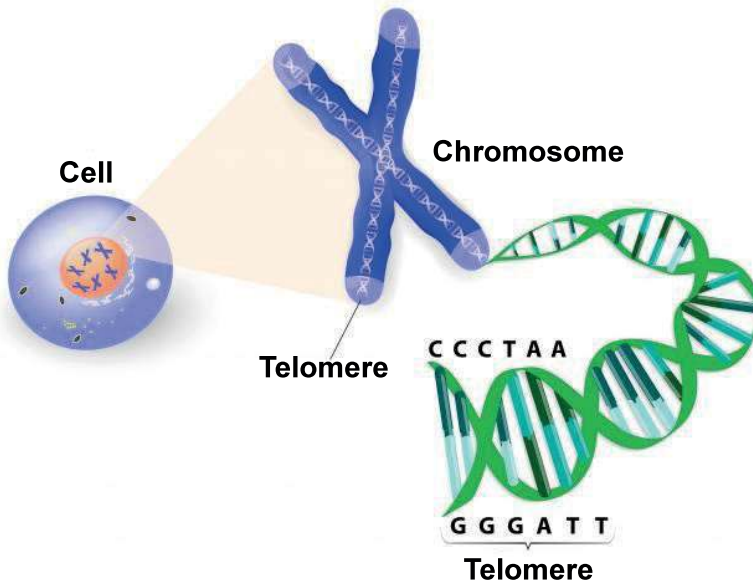
FIGURE 3. The cell, chromosome and telomere

Telomeres are protective caps at the end of linear DNA strands. In humans, telomeres are made of non-coding sequences of the 4 nucleic acid bases: G for guanine, A for adenine, T for thymine and C for cytosine. One telomere strand has repeating sequences of TTAGGG, paired with AATCCC on the other strand. Thus, one section of telomere is a "'repeat" made of six "base pairs" (bp). [77]

6.3 SLEEP AND CELLULAR AGING – RESEARCH QUESTIONS

There is scant research on the biomarker for aging, leukocyte telomere length (LTL), and sleep. When LTL was measured in subjects with insomnia, obstructive sleep apnea, snoring and short and long sleep duration, results were mixed [78 - 85]. The association between circadian dysregulation and LTL has not been studied in humans. In animal models, circadian desynchronization triggers premature cellular aging [86]. In **Chapter 6**, we tested how insomnia, sleep duration and circadian rhythm are related to cellular aging over 6 years, using data from the NESDA study.

7. COHORTS STUDIED IN THIS THESIS

7.1 THE NETHERLANDS STUDY OF DEPRESSION AND ANXIETY (NESDA)

NESDA is an ongoing study aiming to examine the course and consequences of depressive and anxiety disorders. This longitudinal, naturalistic cohort included 2,981 participants aged 18-65 years at baseline assessment, performed between 2004 and 2007 [87]. Participants were recruited from different health care settings (community, primary and specialized mental health care), including a group without psychiatric symptoms ('Controls') and others in different developmental stages of affective disorders. Exclusion criteria included insufficient command of Dutch and a primary clinical diagnosis of bipolar disorder, obsessive-compulsive disorder, PTSD, severe substance use disorder or a psychotic disorder. Initial assessment included a 4-hour clinic visit, followed by face-to-face assessments every two years thereafter. These follow-up assessments had a response rate of 87.1% (N = 2,596) at 2 years, 80.6% (N = 2,402) at 4 years, and 75.7% (N = 2,256) at 6 years. A full description of NESDA has been described in the design paper by Penninx et al. [87].

7.2 THE NETHERLANDS MENTAL HEALTH SURVEY AND INCIDENCE STUDY-2 (NEMESIS-2)

NEMESIS-2 is an epidemiological study examining the prevalence, incidence, course and consequences of psychiatric disorders in the Dutch general population. A full description has been reported elsewhere [88]. In short, NEMESIS-2 was based on a multistage, stratified, random sampling of households, with one respondent randomly selected from each household. Insufficient fluency in Dutch was an exclusion criterion. The first wave included 6,646 subjects aged 18 - 62, with a response rate of 65.1% (November 2007 to July 2009). All baseline respondents were approached for follow-up three years later (November 2010 to June 2012). Here, 5,303 persons were interviewed (response rate 80.4%, excluding those deceased). Three years later, 4,618 persons were interviewed (response rate 87.8%, excluding those deceased, November 2013 to June 2015).

8. AIMS AND OBJECTIVES

The overall objective of this thesis is to explore the associations between MetSyn, sleep disorders and adult ADHD, conceptualizing ADHD as (partly) a disorder of biological rhythm disturbance. In addition, the association between disturbed sleep and cellular aging is tested. The following research areas are explored in the thesis:

1. **The rhythm of insomnia: What is the relationship between adult ADHD and insomnia?**
   The literature review in **Chapter 2** provides an update of cross-sectional and longitudinal studies, as well as insomnia associated with pharmacological treatments for ADHD. **Chapter 3** describes the association between insomnia, sleep duration and ADHD in the NEMESIS cohort. **Chapter 4** briefly raises and discusses the possibility that this relationship is related to a pro-inflammatory state.

2. **The rhythm of SAD: Is the well-recognized association between SAD and ADHD mediated by markers of circadian rhythm disturbance? Chapter 5** explores how ADHD, circadian rhythm and SAD are related in a study from the NESDA cohort.

3. **The rhythm of MetSyn: What is the association between MetSyn, obesity-related outcomes and adult ADHD? Chapter 6** analyses these relationships with data from the NESDA cohort.

4. **The rhythm of aging: How are insomnia, sleep duration and circadian rhythm related to cellular aging?** Telomere length as a biomarker for cellular aging is assessed in those with insomnia, altered sleep duration and circadian rhythm dysregulation in **Chapter 7.**

Finally, **Chapter 8** summarizes the main findings, their implications and possible directions for future research.

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CHAPTER 2

ADULT ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD)AND INSOMNIA: AN UPDATE OF THE LITERATURE

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1.   ABSTRACT

Purpose of review: Insomnia is diagnosed when there is dissatisfaction with sleep quantity or quality. It has a prevalence in the general population ranging from 31 to 56%. Insomnia has previously been associated with adult attention-deficit/hyperactivity disorder (ADHD). In this review, we address three topics: (1) the cross-sectional relationship between ADHD and insomnia in adulthood, (2) the longitudinal relationship between ADHD and insomnia, and (3) insomnia as a side effect of pharmacological treatments for adult ADHD.

Recent findings: Three cross-sectional, clinical and population studies report a prevalence of insomnia in ADHD adults ranging from 43 to 80%. Longitudinal evidence for a link between childhood-onset ADHD and insomnia at later age is mixed, with one study confirming and another study not supporting such a longitudinal association. In randomized, placebo-controlled trials, insomnia is reported significantly more often in the treatment arm than in the placebo arm. In varying percentages of trial participants, insomnia is a treatment-emergent adverse effect in triple-bead mixed amphetamine salts (40 – 45%), dasotraline (35 – 45%), lisdexamfetamine (10 – 19%), and extended-release methylphenidate (11%). Ten to seventeen percent of subjects in placebo-controlled trials of atomoxetine report insomnia, possibly related to poor metabolizer status. The mechanisms explaining the relationship between ADHD and sleep problems are incompletely understood, but both genetic and non shared environmental influences may be involved.

Summary: Adults with ADHD should be assessed for insomnia, which is frequently comorbid, and both conditions should be treated.

Keywords: Adult attention-deficit/hyperactivity disorder, sleep, insomnia, psychostimulants

2. INTRODUCTION

In the general population, the prevalence of insomnia symptoms ranges from 31% in Western Europe to 56% in the USA [1]. It is the most common sleep disorder in the general population, but almost half of people affected receive no treatment for insomnia [1, 2]. Following DSM-5, insomnia is diagnosed when there is dissatisfaction with sleep quantity or quality, difficulty initiating or maintaining sleep, and early morning waking, for at least three nights per week over a period of at least three months [3]. The DSM-5 no longer distinguishes between primary and secondary insomnia [3]. In this broader conception, insomnia is considered a disorder that requires independent clinical study.

Adult attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder marked by inattentiveness, impulsivity, with or without hyperactivity [3, 4]. For 60% of children with ADHD, the disorder persists into adulthood [5], where the cross-national estimated prevalence of ADHD is 2.8% [6]. In 2012, Yoon et al. published a clinical review of sleep disorders in children and adults with ADHD, and stressed that the literature was scant [7·]. No longitudinal studies were included in this review. Seven studies among adults with ADHD, using both self-report and objective methods to assess insomnia symptoms, were discussed. The three studies using self-reports showed an increased prevalence of insomnia in adult ADHD [8–10]; however, one of these was referenced as another study by the same author [11]. Four of the listed studies using objective methods to measure insomnia, showed mixed results. Two actigraphy studies found decreased sleep quality and insomnia symptoms in adults with ADHD [12, 13]. One polysomnographic study showed sleep disturbance [14], but another did not [15]. Yet, both of the polysomnographic studies showed increased nocturnal motor activity in the ADHD patients [14, 15]. These preliminary studies in adult populations suggest that there is an association between adult ADHD and insomnia. While the review acknowledged insomnia in children with ADHD, the authors commented, "It is currently not known whether there are similar sleep problems in adults (with ADHD)" [7·].

Four years later, a systematic literature review by Instanes et al. (2016) on adult ADHD and comorbid somatic disease classified the relationship between adult ADHD and sleep disorders as well-established [16·]. Some new studies showing an increased prevalence of insomnia in clinical and non-clinical samples of adults with ADHD were included [17 – 19]. However, certain fundamental questions about ADHD and insomnia that were raised by Yoon et al., Instanes et al., and Hvolby (2015) cannot be fully answered [7·, 16·, 20·]. For example, what is the role of pharmacological treatments in the relationship between ADHD and insomnia?

This current review summarizes recent findings of cross-sectional and randomized controlled studies exploring the relationship between insomnia and adult ADHD. For the first time, we also review longitudinal studies. We note that other sleep disorders, i.e. circadian rhythm disorders, sleep apnea, hypersomnia, and restless legs, are also associated with adult ADHD [16·] and may result in secondary insomnia. However, we do not review studies of these sleep disorders. We have retrieved key English language papers from Medline, Embase, and Psychnet searches, published since the review by Yoon et al. in 2012. These fall into the following three categories:

1. The cross-sectional relationship between ADHD and insomnia in adults (defined as 18 years or over)
2. The longitudinal relationship between ADHD and insomnia
3. Insomnia associated with pharmacological treatments for ADHD

These subjects together will give more insight into the nature of the relationship between insomnia and ADHD.

3. FINDINGS FROM CROSS-SECTIONAL STUDIES

In a chart review, Fisher et al. (2014) investigated sleep problems in ADHD across the lifespan (N = 1828, of which n = 1163 adults) [21·]. This study distinguished between two ADHD categories: inattentive ADHD and "ADHDplus" (patients with hyperactive/impulsive ADHD symptoms and a documented secondary sleep or affective disorder requiring medication). No patients were assessed while on ADHD medication. Insomnia symptoms were found to be present in ADHD, regardless of sex, age, or ADHD subtype. There was no significant difference in insomnia symptoms between adult ADHD patients with and without other comorbid sleep disorders. In 80% of adults with ADHD, unrefreshing sleep, trouble falling asleep, frequent night-time awakenings, insufficient sleep, excessive sleep, and night-time restlessness were reported. These problems were also significant variables affecting neuropsychological test performance. Sleep complaints were reported significantly more often in adults (80%) than in children or adolescents, where they occurred in 74 and 41%, respectively [21·]. Sleep-onset insomnia (SOI, or difficulty falling asleep at the desired bedtime) and sleep maintenance problems were particularly significant difficulties in the ADHD adults. Several other studies have confirmed an association between SOI and adult ADHD [10, 14, 22].

A recently published, large Norwegian study by Brevik et al. (2017) compared the prevalence of self-reported insomnia symptoms in adult ADHD patients (n = 268) to that in a population-

based control group (n = 202) [23·]. Where information was available, the prevalence of insomnia was compared in two ADHD subtypes (inattentive n = 54 and combined n = 81); for the rest, subtype was not specified. Even though adult ADHD is a highly comorbid condition, no formal exclusion criteria for comorbidities were applied to either group. Insomnia symptoms occurred in 67% of the adult ADHD patients, compared to 29% of controls. They were more common in the combined subtype (80%) compared to the inattentive subtype (56%) [23·].

Investigating women in a nationally representative Canadian population study (aged 20 – 39 years, N = 3,908), Fuller-Thompson et al. (2016) found self-reported ADHD in 2.6% (n = 107) [24·]. Significant insomnia symptoms were present in 43% of those with self-reported ADHD compared to 12.2% in those without ADHD. When the association between ADHD and insomnia was analyzed after correcting for age, race, education, and income, the risk for insomnia was found to be five times greater in women with self-reported ADHD, compared to those without ADHD (OR = 5.08). However, it should be noted that Fuller-Thompson et al. did not report on concurrent or previous (stimulant) medication use, nor correct for affective disorder. Both of these may have accounted for the increased risk of insomnia. Indeed, the women who reported ADHD also had significantly more lifetime affective disorders than those without ADHD [24·]. Similarly, Brevik et al. applied no formal exclusion criteria for comorbid disorders, which may have influenced the associations with insomnia [23·].

Comorbid mental disorders tend to increase the prevalence of insomnia, both in population studies and clinical samples. This was shown in a Dutch general population study, where insomnia was common in those with current and remitted mental disorders [25]. In another study in adult ADHD patients, depressive symptoms increased the risk for insomnia [9]. Other factors associated with adult ADHD, such as substance use [26] or family history of affective disorder, also increase the risk for insomnia [25, 27·]. These cross-sectional findings are summarized in Table 1.

TABLE 1. Recent (2014-2017) cross-sectional and longitudinal studies of the association between insomnia symptoms and ADHD

Study	Classification (sample size)	Age of population in years, range (mean)	Female, %	ADHD medication status	ADHD instrument	Sleep instrument	Major findings	Strengths (S) and/or weaknesses (W)
Cross-sectional studies								
Fisher et al., 2014 [21]	Adults≥18 year (n = 1,163)	9-80		All subjects tested when not on medication	Clinical diagnosis by neuropsychologist: • Personal Problems Checklist for Adults • Personal History Checklist for Adults • Patient Behavior Checklist for ADHD Adults	• Personal History Checklist for Adults[3] • Patient Behavior Checklist for ADHD Adults	Insomnia symptoms in 80% of ADHD adults, regardless of sex, age or ADHD subtype. Insomnia symptoms negatively affected neuropsychological tests of attention	**S:** Large sample size, comprehensive neuropsychological testing, group with comorbid affective disorders identified. **W:** Study sample from a single clinic. No control group. Studied over 20 years when diagnostic criteria may have changed
	ADHDplus[1] (n = 286)	(38)	38					
	ADHD-I[2] (877)	(35)	61					
Fuller-Thompson et al., 2016 [24]	ADHD (n = 107)	20-39	100	No information	Self-report of a previous diagnosis of ADHD	Insomnia measured using a recoded variable to the question: 'How often do you have trouble going to sleep or staying asleep?'	The risk for insomnia in those with self-reported ADHD was 43% compared to 12.2% in those without ADHD	**S:** Nationally representative, comprehensive profile of women. **W:** No information about medication use. Reliance on self-report for ADHD diagnosis. No correction for comorbid affective disorders
	No ADHD (n = 3,801)							
Brevik et al., 2017 [23]	Adult ADHD	18-74		Methylphenidate (n = 69) Amphetamine (n = 12) Atomoxetine (n = 3)[4] Off medication (n = 36)	DSM-IV Adult ADHD Self-Rating Scale	Bergen Insomnia Scale	Insomnia symptoms occurred in 67% of ADHD, compared to 29% of controls. Insomnia symptoms occurred in 66% of patients on current stimulant treatment and in 72% of patients off treatment	**S:** Large, clinically validated sample of adult ADHD patients and representative population controls. **W:** Definition of insomnia may not have differentiated patients with delayed sleep phase disorder. Comorbid disorders may have influenced the risk of insomnia
	Patients (n = 268)	(38)	60					
	Controls (n = 202)	(37)	63					

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TABLE 1. Continued

Study	Classification (sample size)	Age of population in years, range (mean)	Female, %	ADHD medication status	ADHD instrument	Sleep instrument	Major findings	Strengths (S) and/or weaknesses (W)
Longitudinal studies								
Goldman-Mellor et al., 2014 [27·]	No insomnia (n = 761) Insomnia (n = 186)	5-38	53	No information	Childhood hyperactive and inattentive behaviour: Rutter Child Scales Adolescence: DSM-III	DSM-IV	No significant association between childhood hyperactive and inattentive behaviour or ADHD during adolescence and insomnia at age 38	**S:** Longitudinal study, corrected for multiple psychiatric disorders **W:** ADHD at age 38 years not reported
Gregory et al., 2017 [28·]	Childhood ADHD (n = 247) ADHD age 18 (n = 166)	5-18	51	Sensitivity analyses excluding subjects on current ADHD medication did not affect the associations	Childhood ADHD: DSM-IV ADHD age 18: DSM-5	Pittsburgh Sleep Quality Index	Only persistent ADHD (diagnosed in childhood and present at age 18), or late-onset ADHD (diagnosed at 18 years only), were associated with insomnia at age 18	**S:** Longitudinal study, corrected for wide range of possible confounders **W:** No information collected about sleep quality in childhood, possible limitations of twin design

1 ADHD plus: ADHD and a documented secondary disorder (depression or anxiety requiring medication, but not bipolar or major depression, sleep apnea, narcolepsy, circadian rhythm disorders, concerns of mild impact to the brain or behavioural disorder) thought to have affected neuropsychological test performance
2 ADHD-I Inattentive subtype
3 Items from the Personal History Checklist for Adults included problems of unrefreshing sleep, trouble getting to sleep, waking up a lot at night, not getting enough sleep, sleeping too much, and restlessness
4 The 3 patients on ATX were included in the group on current stimulant treatment

4. THE LONGITUDINAL RELATIONSHIP BETWEEN ADHD AND INSOMNIA

A limitation of cross-sectional studies is that they cannot explain causal relationships. Both ADHD and insomnia are heterogeneous disorders, and the relationship between them is complex. Only longitudinal studies can illustrate how childhood events may affect outcomes later in life. While they cannot truly indicate causality, they may give closer insight into possible causality. In addition, longitudinal studies give a better indication on how long-lasting associations truly are, as cross-sectional associations may be more subject to report bias (e.g. ADHD patients reporting more negatively about sleep patterns) and reflecting short-term associations. Two recent studies have investigated how the early trajectory of ADHD and its age-of-onset affect insomnia in adulthood [27·, 28·].

In a large longitudinal twin study (N = 2,232), Gregory et al. (2017) investigated whether children diagnosed with ADHD were likely to have poor sleep quality later in life [28·]. ADHD was determined in childhood (at 5, 7, 10, and 12 years) from mother and teacher reports, using the DSM-IV criteria and Rutter Child Scales. At age 18, an ADHD diagnosis over the past year was made using the DSM-5 criteria in a structured interview. At age 18, sleep disturbance over the past month was ascertained using the Pittsburgh Sleep Quality Index (PSQI), derived as the sum of overall sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. A PSQI global score > 5 is considered to be the cut-off indicating insomnia [29].

A total of 8.1% of the total sample had the ADHD diagnosis at age 18 (n = 166). Of these, 67.5% (n = 112) did not meet criteria for ADHD during childhood and were considered late-onset ADHD. The remaining 21.9% (n = 54) met diagnostic criteria in both in childhood and at age 18 and were therefore classified as having persistent ADHD. The study went on to examine the associations between insomnia at age 18 and childhood-onset ADHD that remitted, childhood-onset ADHD that persisted and late-onset ADHD, respectively. Only persistent ADHD (diagnosed in childhood and present at age 18), or late-onset ADHD (diagnosed at 18 years only), was associated with insomnia at age 18. However, childhood ADHD that had remitted by age 18 showed *no* increased risk for insomnia in early adulthood.

From this study, it appears that longitudinally, the presence of insomnia in early adulthood is associated with the course of ADHD. Only where ADHD symptoms are concurrent, does insomnia appear to occur. These associations remained significant after adjusting for many potential confounders such as maternal insomnia, a diagnosis of depression, generalized

anxiety, alcohol dependence, cannabis dependence or conduct disorder in young adulthood, the presence of young children at home, and taking ADHD medication.

Contrary to the approach of Gregory et al., Goldman-Mellor et al. (2014) examined whether childhood ADHD predicted insomnia in adulthood in a longitudinal study from Dunedin, New Zealand [27·]. They investigated whether a childhood history of mental health problems and family psychiatric history predicted insomnia at age 38 years. At this age, rates of insomnia are high [27·]. A cohort of 1,037 children was followed from birth through to their fourth decade. Subjects were examined and interviewed 12 times prospectively, with a 95% retention rate. During childhood (5 – 11 years), hyperactive and inattentive behavior was determined from parents and teachers using the Rutter Child Scales. During adolescence (11 – 15 years), ADHD was examined using DSM-III criteria. At the 38-year assessment, insomnia (in the last month) and psychiatric diagnoses (affective disorders/alcohol/drug dependence) were diagnosed over the last 12 months according to DSM-IV criteria and the Diagnostic Interview Schedule, respectively.

One fifth of the participants were diagnosed with insomnia at age 38. At this age, insomnia was highly comorbid with psychiatric disorders. Those with family histories of depression or anxiety, and lifelong affective disorders beginning in childhood, were at a uniquely high risk of developing insomnia in adulthood. In contrast, unlike the associations reported by Gregory et al. [28·], no significant association was found between childhood hyperactive and inattentive behavior (5 – 11 years) and insomnia at age 38. Furthermore, neither conduct disorder nor ADHD during adolescence (11 – 15 years) increased the risk for insomnia in adulthood.

However, this study differs from that of Gregory et al. in that neither the presence of ADHD in adulthood nor a possible onset of ADHD after 15 years was reported. Therefore, the question of whether late-onset ADHD or ADHD persisting into adulthood was linked to insomnia at age 38 cannot be answered. An interesting finding from another publication from the Dunedin study could explain the apparent lack of association between ADHD symptoms in childhood and insomnia at 38 years. Moffitt et al. (2015) reported that in the same cohort, the groups with childhood ADHD and adult ADHD were virtually non-overlapping: 90% of adult ADHD cases lacked a history of childhood ADHD [30]. Further analysis of this cohort would determine whether age-of-onset of ADHD was independently associated with insomnia in adulthood, and whether the 10% with persistent ADHD from childhood to adulthood had a greater risk of insomnia at age 38. This analysis however has so far not been reported. The longitudinal studies referred to here are reported in Table 1.

While the mechanisms for the relationship between ADHD and sleep problems are not understood, Hvolby (2015) proposes several possible scenarios that may explain this finding [20·]. Perhaps ADHD and sleep problems are comorbid disorders which interact? Where ADHD is present, insomnia occurs—and vice versa—with reciprocal causation. Poor sleep may worsen ADHD symptoms, as sleep regulates cognitive and emotional brain processes [31, 32]. Symptoms associated with insomnia may also present as ADHD [20·]. Secondly, sleep problems may be intrinsic to ADHD; therefore, insomnia symptoms are part of the ADHD presentation. Symptoms of ADHD such as inattention, difficulty with planning, or nocturnal motricity may lead directly to poor sleep hygiene and insomnia [20·, 33]. Difficulty in organizing tasks and procrastination may delay bedtime. In this scenario, ADHD and insomnia in young adulthood may have a shared neuropathological origin [20·]. In a recent genome-wide association study, strong positive genetic correlations were found between insomnia, anxiety/depressive symptoms, and major depression [34·]. This suggests that insomnia in adult ADHD is often comorbid with depressive symptoms. Interestingly, there was no correlation between the genes found for insomnia and self-reported ADHD symptoms. The top genetic association in this study was found between insomnia and restless legs syndrome (RLS), which is also associated with ADHD [16·]. RLS is a neurological disorder where patients experience an unpleasant sensation in the limbs and feet, combined with an urge to move to relieve the discomfort. It is associated with initial insomnia and poor sleep quality controls [16·]. The population prevalence is wide-ranging, from 3 to 34% [16·]. In small studies, the prevalence of RLS has been shown to be elevated in persons with ADHD compared with controls, and ADHD was more common in patients with RLS compared to controls [16·]. While more research is needed to clarify this association, the relationship between ADHD and insomnia may be mediated through RLS.

Environmental influences on insomnia in ADHD are also relevant, as found by Gregory et al. [28·]. In their twin study, individual differences in ADHD and sleep quality were explained by genetic and non-shared environmental factors, with moderate genetic overlap. In young adulthood, genes explained 55% of the association between ADHD symptoms and sleep quality, and non-shared environmental influences explained 45%. These environmental influences may include (maternal) exposure to neurotoxins, alcohol, drugs, and mobile telephones, which may all impact on sleep and ADHD [28·, 35]. Marital conflict and inconsistent parenting styles are family environmental processes that may play a role in ADHD through the dopamine system, which is believed to be dysregulated in ADHD. A study showed that the tandem repeat insertion allele of the dopamine receptor D_4 gene increased susceptibility to ADHD in the context of marital conflict [36].

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5. INSOMNIA ASSOCIATED WITH PHARMACOLOGICAL TREATMENT FOR ADHD

Another factor complicating the relationship between ADHD and insomnia is that pharmacological treatments of ADHD may cause, worsen [33], or improve insomnia symptoms [10, 13, 14, 37]. However, it is important to acknowledge that even non-medicated adults with ADHD experience insomnia symptoms [9, 10, 13, 14, 17, 18, 21, 22]. In the Norwegian cross-sectional study referred to above, Brevik et al. found that ADHD patients currently using stimulant medication (n = 94) had significantly lower insomnia scores than patients without stimulant treatment (n = 34). Treatment included methylphenidate (n = 69), amphetamines (n = 12), the non-stimulant atomoxetine (ATX, n = 3), or a combination (n = 7). No further information about the dosing or pharmacological agents was given. Insomnia symptoms occurred in 66% of patients currently on stimulants compared to 72% in those off treatment [23·]. These findings could indicate that ADHD medication may be helping patients with managing their insomnia. However, as the authors note, those off medication may also have chosen to stop because of insomnia [23·]. So, interpretation is difficult, and one would require placebo-controlled interventions to evaluate truly whether ADHD medication impacts on insomnia. In this section, we review recent findings concerning the association between insomnia and the stimulants (methylphenidates and amphetamines), non-stimulants (ATX), and an antidepressant, bupropion. The studies reviewed are included in Table 2.

5.1 STIMULANTS

Extended-release formulations of the stimulants were developed to reduce multiple daily dosing and adverse effects [42]. They include compounds under investigation such as the multi-layer, extended-release methylphenidate (PRC-063) and dasotraline, a novel inhibitor of dopamine and norepinephrine reuptake. The triple-bead formulation of mixed amphetamine salts (triple-bead MAS) is awaiting registration in adults. Osmotic controlled-release oral delivery system methylphenidate (OROS-MPH), extended-release mixed amphetamine salts, and lisdexamfetamine dimesylate (LDX) are already licensed and in clinical use in several countries. Possibly because of their neurotransmitter action, stimulants are wake-promoting in most people. Methylphenidate has α_2 and dopamine D_1 receptor actions and increases norepinephrine and dopamine in the prefrontal cortex. Amphetamine is believed to compete with endogenous monoamines for transport into nerve terminals [43·]. Stimulants may be associated with increased difficulty in falling asleep, longer sleep-onset latency, and overall shorter duration of sleep, as extensively reviewed by Stein et al. [44]. While insomnia is a common treatment-emergent adverse event (TEAE), there is inter-individual variability in response to these medications [43·].

TABLE 2. Recent evidence (2014-2017) for a relationship between ADHD treatment and insomnia in cross-sectional, open label trials or randomized double-blind, placebo-controlled ADHD treatment studies

Study	Classification	Duration (weeks)	ADHD medication daily dosage (sample size)	Age of population, years (mean)	Sex (female,%)	Sleep instrument	Insomnia (%)[1]
Brevik et al., 2017 [23·]	Cross-sectional study comparing medicated ADHD vs. non-medicated ADHD	N/A	Stimulants[2] (n = 94) / Off medication (n = 36)	18-74 (34) (37)	66 / 64	Bergen Insomnia Scale	Medicated ADHD: 66.3 / Non-medicated ADHD: 72.2
Frick et al., 2017 [38·]	Randomized double-blind, placebo-controlled, forced-dose trial of triple-bead MAS[3]	6	25mg (n = 104) / 50mg (n = 101) / 75mg (102) / placebo (n = 104)	(38) (37) (38) (36)	50 / 35 / 47 / 46	Pittsburgh Sleep Quality Index	25mg: 40 / 50mg: 40 / 75mg: 45 / placebo: 13
Koblan et al., 2015 [39·]	Randomized, placebo-controlled, fixed-dose trial of dasotraline	4	4mg (n = 114) / 8mg (n = 107) / placebo (n = 110)	34 / 36 / 34	44 / 40 / 40	Insomnia Severity Index	4mg: 35 / 8mg: 45 / placebo: 16
Wigal et al., 2016 [40·]	Randomized, double-blind, placebo-controlled cross-over of extended-release methylphenidate (PRC-063)	7-9	Dose optimization phase 25mg-100mg (n = 59) / Double blind phase cross-over 45-100mg (n = 53) / placebo (n = 53)	32	64	Pittsburgh Sleep Quality Index	Dose optimization phase (PRC-063) 25mg-100mg: 31 / Double blind phase (PRC-063): 11 / Placebo: 4
Fijal et al., 2015 [41·]	Open label comparison of safety and tolerability of atomoxetine among the different CYP2D6[3] metabolizer groups	12	40-100mg Poor metabolizers (n = 117) / Non-poor metabolizers (n = 1,819)	34 / 33	43 / 41	Spontaneously reported treatment-emergent adverse events	Poor metabolizers: 15 / Non-poor metabolizers: 8

[1] Percentage with insomnia in each of the trials
[2] Stimulants: methylphenidate (n = 69), amphetamines (n = 12), non-stimulant ATX (n = 3), or combination (n = 7)
[3] Triple-bead MAS: triple-bead formulation mixed amphetamine salts, CYP2D6: cytochrome P450 2D6

In several recently published, placebo-controlled studies of the extended-release stimulants, the TEAE insomnia occurred significantly more frequently in the treatment arm (11 – 45%) than in the placebo arm (4 – 16%) [38·, 39·, 40·]. Medications and dosages used in these studies were triple-bead MAS (dosage 25, 50, or 75 mg once daily, N = 412) [38·], dasotraline (dosage 4 or 8 mg once daily, N = 341) [39·], and extended-release methylphenidate (PRC-063, dosage 25 – 100 mg, once daily, N = 59) [40·]. Insomnia was listed as the most frequently reported TEAE for triple-bead MAS and dasotraline [38·, 39·]. In the triple-bead MAS study (2017), insomnia occurred in 41% on active treatment, as opposed to 12.5% on placebo. There was no dose-response relationship between active drug and insomnia. This was a forced-dose trial, meaning that the entire randomized group moved through a series of rising doses, allowing for comparisons. This high rate of insomnia might have been lower with a slower upward titration, as is habitual in clinical practice [38·]. In the fixed-dose trial of dasotraline (2015), insomnia occurred in 35% (4 mg/day dose), in 45% (8mg/day dose), and in 15.5% in the placebo group. There was a dose-response relationship between active drug and insomnia in this study. The high percentage with insomnia may have been related to the fixed-dose methodology, where patients were initiated on dasotraline 4 or 8 mg once daily, without titration [39·].

Somewhat lower rates for insomnia were reported in a systematic review of LDX by Coghill et al. (2014). In short-term trials, insomnia occurred in 10 – 19% of those on LDX (dosage 30, 50, or 70 mg) and in 4 – 5% of those on placebo [45·]. Insomnia was reported even less frequently in a (smaller) randomized, double-blind, placebo-controlled, cross-over of trial of extended-release methylphenidate (PRC-063, 2016) [40·]. During the initial open-label, dose optimization phase (n = 59), insomnia occurred in 31% (doses 25-100 mg). During the subsequent 2-week, double-blind phase, insomnia was reported in 11% of the treatment group and in 4% of the placebo group (n = 53, doses 45 – 100 mg). The authors suggest that this lower rate of insomnia in the blinded period was related to a decrease of adverse effects as the trial continued, and as the doses were optimized. Sleep efficiency (the ratio of hours of sleep to hours spent in bed) was poorer on PRC-063 than in the placebo arm. There were no differences observed between extended-release methylphenidate (PRC-063) and placebo for four other items on the PSQI (sleep latency, sleep disturbance, needs medications to sleep, or daytime dysfunction) [40·]. These results are promising, but larger trials are needed to confirm the lower incidence of insomnia. As noted by Childress (2017), extended-release methylphenidate (PRC-063) has efficacy for up to 16 h after dosing, so it will be important to monitor sleep in future research [43·].

When self-reported sleep quality at the start and end of the trial with extended-release methylphenidate (PRC-063) was compared, an interesting finding emerged. Neither the

overall sleep quality nor the PSQI global score showed any significant difference between the treatment and placebo groups [40·]. By the end of the triple-bead MAS trial, sleep quality had improved in the active group by the trial end, based on PSQI score [38·]. Similarly, during the 2-week randomized, blinded phase of the dasotraline trial, there was no significant difference in PSQI score or overall sleep quality between the active and placebo groups [39·]. Findings were similar in the LDX trials reviewed, where available data from all studies indicated no overall worsening of sleep quality in adults, as measured by the PSQI [45·].

The reports of insomnia in both the treatment and placebo arms of all mentioned studies on long-acting stimulants, and an overall sleep quality which improved by trial end in some studies, implies that adult patients with ADHD may begin with poor sleep. These findings were confirmed in a post hoc analysis of two large placebo-controlled trials of amphetamines (triple-bead MAS and LDX). Insomnia was reported in similar proportions in both the active and placebo groups [37]. Some long acting stimulants, such as triple-bead MAS, the extended-release methylphenidate (PRC-063), and LDX, may not worsen overall sleep quality for the duration of the trial [38·, 40·, 45·]. Moreover, a group with ADHD may exist for whom insomnia improves with treatment [37, 38·]. On the other hand, the PSQI which measured insomnia in these trials also measures daily function. One would expect this to improve with treatment for ADHD. Hence, the improvement in overall sleep quality as reflected by the PSQI may reflect daytime improvement rather than a lessening of insomnia. In addition, the onset of insomnia is determined by the drug formulation, the length of the trial, the timing of dosing, and whether maximum doses are fixed, forced, or titrated upwards.

5.2 NON-STIMULANTS

Insomnia has been reported in studies of the non-stimulant, ATX [46], but it is less common compared to studies of the long-acting stimulants [47, 48]. A lower incidence of insomnia may be related to differences in pharmacology, as ATX inhibits the presynaptic norepinephrine transporter and may have less dopaminergic action than the stimulants [43·]. Walker et al. (2015) reviewed studies of ATX published from 1998 to 2014 and concluded that insomnia was mostly non-serious, occurred early and resolved during treatment. Interestingly, insomnia was reported was more frequently with twice daily dosing (17%) than with once daily dosing (10%) [49].

ATX is predominantly metabolized by cytochrome P450 2D6 (CYP2D6), which is encoded by the highly polymorphic CYP2D6 gene [41·]. Genetic polymorphisms are important determinants of CYP2D6 enzymatic activity, which results in variability in the metabolism of ATX. Individuals can be categorized into four metabolizer groups: ultra rapid, extensive, intermediate, and

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poor. The plasma half-life of ATX is approximately four times longer in poor metabolizers, who experience more frequent adverse events than the other groups, significantly more insomnia. A 12-week, open-label study confirmed an increased incidence of insomnia in the poor metabolizer group, compared to the other three groups [41·]. This genetic polymorphism may help explain the heterogeneity in the association between atomoxetine and insomnia, particularly with twice daily dosing and in poor metabolizers.

De Oliveira et al. (2017) conducted a systematic review of the safety profiles of several ADHD treatments [48]. Ten studies were included in a mixed treatment comparison, allowing for the comparison of more than two interventions, even when these were not directly compared in the literature. The findings concerning the ranking of treatments in terms of their probability to provoke insomnia are unclear, as the text of this paper contradicts the results depicted in the figure. According to the figure, when ATX, bupropion, extended-release mixed amphetamine salts, and placebo were compared, extended-release mixed amphetamine salts had the highest probability to provoke insomnia (79% of probability). The safest option (after placebo) was bupropion (29% of probability). Ideally, all available treatments should be compared to give comprehensive results.

6. CONCLUSIONS

Based on cross-sectional studies, in clinical and population samples, insomnia is associated with adult ADHD in 43 – 80% [21·, 23·, 24·], regardless of pharmacological treatment for ADHD [23·]. Longitudinal studies give conflicting results. In one, the persistence of ADHD into early adulthood was strongly associated with insomnia symptoms at age 18 [28·]. In a second, there was no association between childhood or adolescent ADHD and insomnia at age 38 [27·]. Future longitudinal studies are necessary and should consider age-of-onset and the persistence of ADHD symptoms, which appear to be relevant. Certainly, there is a strong association between affective disorders and insomnia in adulthood [25, 27·, 34·]. Therefore, when studying insomnia in adult ADHD, it is important to correct for affective disorders, which also disturb sleep. The strong genetic correlation between insomnia and anxiety/depressive symptoms and major depression was recently shown in a genome-wide association study [34·]. Furthermore, while there was no correlation between the genes found for insomnia and self-reported ADHD symptoms, those for insomnia and RLS were strongly correlated. Therefore, the relationship between ADHD and insomnia may be mediated through RLS. Environmental influences may include (maternal) exposure to neurotoxins, alcohol, drugs, and child self-blame for marital conflict [35, 36]. In the twin study, environmental influences explained 45% of the association between ADHD and sleep quality [28·].

There are some important caveats to consider. Firstly, while an association between adult ADHD and poor sleep quality has been reported in the population-based studies, causality cannot be inferred. The questions remain, how does ADHD in adulthood lead to poor sleep and does poor sleep lead to ADHD symptoms? Furthermore, results from population-based studies may not be applicable in the clinical setting; hence, both settings should be investigated. Secondly, the improvements in sleep quality reported in trials of pharmacological treatments may be related to improvements in daytime functioning. Thirdly, the pharmacological trials had different sizes and designs, which may also have affected the frequency of insomnia. ADHD treatments may also remedy comorbid conditions (such as depression), with the result that sleep improves.

7. TREATMENT RECOMMENDATIONS

Many adults with ADHD have disturbed sleep patterns. For these patients, restoration of healthy sleep may be one of the treatment goals. Sleep quality should be evaluated before and during treatment. Any changes should be carefully tracked. Psychoeducation, sleep hygiene interventions, and cognitive behavioral therapy may minimize the adverse effects of insomnia in adults with ADHD [50]. Extended-release stimulants are frequently associated with insomnia in adult ADHD, but this adverse event should not present a barrier to treatment. There is much individual variation in response to the pharmacological treatments of ADHD. In the trials reviewed, extended-release methylphenidate (PRC-063) showed the least insomnia (11%) [40·]. From the systematic review of LDX, rates of insomnia were higher (10 – 19%) [45·]. Insomnia appeared to be most frequent in triple-bead MAS and dasotraline (40 – 45%) [38·, 39·]. The frequency of insomnia with ATX is relatively low (10 – 17%) [48] and may be related to poor metabolizer status [41·]. For many patients, insomnia exists before any treatment starts. For others, overall sleep quality may improve with extended-release stimulants [37, 38·]. If treatment-emergent insomnia is intolerable with extended-release stimulants, it may be beneficial to switch to another agent. Adjunctive agents such as melatonin and/or light therapy may also be considered to manage insomnia if non-pharmacological methods fail [51]. Clinicians treating ADHD should evaluate sleep quality and insomnia symptoms using standardized instruments, prior to starting treatment.

CONFLICT OF INTEREST

Dr. Wynchank served on the advisory boards of Janssen BV; and until 2014, Novartis and Eli Lilly until 2014. Prof. Penninx has received research grants from Johnson & Johnson, Boehringer Ingelheim, NWO, BBRMI-NL, NIMH, and the EU-FP7 program for research in NESDA. Prof. Beekman has been a speaker for Lundbeck and Eli Lilly and received research grants from Astra Zeneca, Eli Lilly and Shire for other studies. Dr. Kooij was on the speakers' bureau of Janssen, Eli Lilly and Shire until 2012. Dr. Bijlenga declares no conflict of interest.

ETHICAL APPROVAL

This article does not include any studies with human participants or animals performed by any of the authors that would need ethical approval.

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CHAPTER 3

THE ASSOCIATION BETWEEN INSOMNIA AND SLEEP DURATION IN ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM A GENERAL POPULATION STUDY

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1. ABSTRACT

Study Objectives: Insomnia and short or long sleep duration are important comorbid conditions in adults with attention-deficit hyperactivity disorder (ADHD), but reports of the association vary. In a general population study, we evaluated the relationship between ADHD symptom severity, insomnia symptoms, and sleep duration in adults.

Methods: Data were from the third wave of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2; n = 4,618). ADHD symptom severity and symptom dimensions (hyperactivity and inattention) were assessed using the Adult ADHD Self-Report Scale screener. Self-reported insomnia symptoms (Insomnia Rating Scale; IRS) were defined as clinically relevant if IRS ≥ 9. Self-reported short sleep duration was defined as ≤ 6 hours, and long sleep duration as ≥ 10 hours.

Results: Within the group with clinically relevant ADHD symptoms, 43% reported significant insomnia symptoms (odds ratio [OR] = 2.66, 95% confidence interval [CI] 1.74 – 4.07); 41% short sleep duration (relative risk ratio [RRR] = 1.94, 95% CI 1.31 – 2.85) and 6% long sleep (RRR = 5.87, 95% CI 1.97 – 17.45). Increased inattention symptoms were associated with IRS ≥ 9, short and long sleep duration in fully adjusted models (OR = 1.10, 95% CI 1.06 – 1.14; RRR = 1.06, 95% CI 1.02 – 1.09; RRR = 1.16, 95% CI 1.05 – 1.28, respectively). Increased hyperactivity symptoms were associated with IRS ≥ 9 (OR = 1.17, 95% CI 1.11 – 1.23) and short sleep duration (RRR = 1.12, 95% CI 1.05 – 1.19).

Conclusions: Both clinically significant ADHD symptoms and inattention and hyperactivity symptom dimensions were consistently associated with insomnia symptoms and altered sleep duration. These associations confirm that sleep disturbances should be assessed and given appropriate clinical attention in adults with ADHD.

Keywords: ADHD, adults, attention-deficit hyperactivity disorder, general population survey, insomnia, sleep duration

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2.   BRIEF SUMMARY

Current Knowledge/Study Rationale: Insomnia and altered sleep duration are important comorbid conditions in adults with attention-deficit hyperactivity disorder (ADHD). Several cross-sectional clinical and population studies reported a prevalence of insomnia of 43% to 80% in adults with ADHD. One longitudinal study described an association between ADHD and insomnia; another did not. In a general population study, we evaluated the relationship between self-reported ADHD symptom severity, ADHD symptom dimensions, insomnia symptoms, and sleep duration in adults.

Study Impact: Clinically significant ADHD symptoms (four to six symptoms on the Adult ADHD Self-Report Screener) and the inattention and hyperactivity symptom dimensions were consistently associated with insomnia and altered sleep duration. We have confirmed that insomnia and altered sleep duration occur commonly in adults with ADHD; hence, they should be appropriate assessed and treated.

3.   INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that is marked by inattention and impulsivity, with or without hyperactivity [1]. ADHD persists into adulthood in two-thirds of children with ADHD [2], where the cross-national estimated prevalence of ADHD is 2.8% [3]. Some researchers view ADHD as a dimensional disorder, where symptoms are best considered as continuous traits across the general population [4]. At a certain threshold of symptom severity, in combination with significant dysfunction in daily life, a clinical diagnosis of ADHD may be made [1]. Adult ADHD is highly comorbid with other psychiatric disorders: 52% of adults with ADHD have any comorbid psychiatric disorder [3]. The most common comorbidities are anxiety, mood, behavioral, and sleep disorders [3].

There is evidence for an increased prevalence of several sleep disorders in adult ADHD, including insomnia, circadian rhythm disturbances, restless legs syndrome, and obstructive sleep apnea, comprehensively reviewed by Instanes et al. [5]. Several cross-sectional, clinical, and population studies reported a prevalence of insomnia in adults with ADHD ranging from 43% to 80% [6 - 9]. Two longitudinal studies described conflicting findings; in one there was a significant association between persistent childhood ADHD and insomnia at age 18 [10]. The other showed no association between childhood or adolescent ADHD and insomnia diagnosed at age 38 years [11]. ADHD symptom severity correlated with worsening of sleep

quality in a small study among adults [12], but a community study of young adults (aged 18−20 years) did not find this association [13]. Some studies within adult ADHD populations have examined insomnia symptoms, such as subjective sleep quality, which was reported as poorer in adults with ADHD than in controls [reviewed in Instanes et al., 5].

Reports of sleep duration in adult ADHD vary, with the literature reporting no change as well as a combination of both short and long sleep duration. A very large population study (N = 30,858; ADHD cases n = 1,122) found that both increased and decreased sleep duration were associated with increasing odds of reporting ADHD symptoms [14]. Two other studies reported a mean total sleep duration less than 6 hours in adults with ADHD [15,16]; however, the latter included a very small ADHD sample (N = 24). In contrast, in three small studies (ADHD samples N = 20 – 40) measuring total sleep duration objectively using actigraphy or polysomnography, no significant difference in sleep duration was found between those with ADHD and healthy controls [17 - 19]. Two large studies using self-reported sleep duration also showed no difference in sleep duration in (young) adults with and without ADHD (N = 64 and N = 175, respectively) [13,20].

The clinical implications of suboptimal sleep include worsening of ADHD symptoms, as sleep regulates learning and consolidation of memory [21]. Sleep loss in the general population is well known to impair performance on attention and executive control tasks [22]. These authors showed that 6 hours of sleep restriction for 14 days produced detrimental effects on sustained attention and working memory that were comparable to the effects of 2 nights of full sleep deprivation. In view of the deleterious effects of sleep loss on cognitive functioning, and the conflicting results in the literature, it is important to clarify the relationship between ADHD and sleep duration in a larger adult sample.

Two main symptom dimensions are present in ADHD: hyperactivity/impulsivity and inattention [1]. Research specifically investigating sleep disorders and these two symptom dimensions is preliminary and has given mixed results in adults, as reported in two reviews [5,23]. The relationship between specific ADHD symptom dimensions and sleep problems is important because patients with these separate clinical profiles may require different treatments.

In this study, we aimed to clarify if the burden of insomnia and disturbed sleep duration increases with higher ADHD symptom severity. We examined ADHD symptom severity, ADHD symptom dimensions, insomnia symptoms, and sleep duration among the Dutch general population, taking a range of sociodemographic and lifestyle factors, comorbid mental disorders, and medical conditions into account.

4. METHODS

4.1 PARTICIPANTS

Subjects (aged 18 – 64 years) participated in the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), an epidemiological study of the prevalence, incidence, course, and consequences of psychiatric disorders in the Dutch general population. A full description of NEMESIS-2 has been reported elsewhere [24]. In short, NEMESIS-2 is based on a multistage, stratified, random sampling of households, with one respondent randomly selected from each household. Insufficient fluency in Dutch was an exclusion criterion [24]. The baseline wave included 6,646 subjects, and was conducted from November 2007 to July 2009. The response rate was 65.1%. The sample was nationally representative, although younger participants were somewhat underrepresented [24]. This study is based on wave 3, where 4,618 persons of the 5,303 who had completed wave 2 were interviewed (from November 2013 to June 2015). The response rate at wave 3 was 87.8%. Attrition at wave 3 was not significantly associated with all individual 12-month mental disorders at baseline after controlling for sociodemographics [25]. The research proposal was approved by a medical ethics committee. At each wave, all participants gave written informed consent at enrollment, after the study procedures had been fully explained.

4.2 MEASURES

4.2.1 ADULT ADHD SYMPTOMS

At wave 3, the Adult ADHD Self-Report Scale (ASRS) Screener version 1.1 [26] was used to assess adult ADHD symptoms. There are six items: four indicating inattention symptoms and two indicating hyperactivity symptoms. Symptom frequency was rated over the past 6 months, on a five-point Likert scale ranging from 0 (never) to 4 (very often). Scores on the six items were converted into binary values according to the official scoring system. The ASRS screener has been shown to have moderate sensitivity (68.7%), excellent specificity (99.5%), and excellent total classification accuracy (97.9%) for ADHD [26]. Internal consistency reliability of the ASRS Screener has been shown to fall in the range 0.63–0.72 [27]. Compared to the 18-item version, the ASRS screener is more sensitive and specific, suggesting better classification accuracy [26, 27]. In this study, severity of ADHD symptoms was determined by the number of scored ADHD symptoms on the ASRS screener, where 0 symptoms was labeled "none," 1 - 3 symptoms as "few," and 4 – 6 as "clinically relevant ADHD symptoms" which is an indication for a diagnosis of ADHD [27, 28]. In addition, we assessed ADHD symptoms continuously, using a sum score of possible ratings on the six questions, (range 0–24). For this sum score, we allowed for a maximum of two missing items on the six questions. Where there were missing

values, we used the mean of the responses of that individual for the other questions. The ADHD symptom dimensions of hyperactivity and inattention were assessed as continuous variables using a sum score, with a range of 0 – 8 for the hyperactivity (no missings imputed) and 0 – 16 for the inattention symptom dimensions (maximally one missing imputed by the mean), respectively.

4.2.2 SLEEP MEASURES

Insomnia symptoms were measured with the Women's Health Initiative Insomnia Rating Scale (IRS) [29], which consists of five questions addressing sleep in the past 4 weeks. These address difficulties initiating and maintaining sleep, early morning awakening (two questions), and overall sleep quality. Answers were on a five-point scale, ranging from 0 "less than once a week" to 4 "five times or more a week" for the first four questions, and the last question on sleep quality ranged from 0 "very sound or restful" to 4 "very restless." For each item, a score of 3 or 4 was considered to suggest pathology. The IRS has good test-retest reliability and has high convergent correlation with objective actigraphy sleep measures [30]. In all analyses, the total summary IRS score (0 – 20) was dichotomized at the cutoff point of 9 or higher, which indicated clinically significant insomnia symptoms [29]. We were interested in the contribution of each of the four domains of insomnia symptoms; hence, we examined these separately in relation to ADHD symptoms.

An additional question investigated total sleep duration. Participants were asked to estimate the average number of hours of sleep per night during the past 4 weeks. Answer options were: "10 or more hours," "9 hours," "8 hours," "7 hours,""6 hours," "5 or less hours." In all analyses, the single variable sleep duration was subcategorized into short (≤ 6 h/night), normal (7 – 9 h/night), and long (≥ 10 h/night), in accordance with the American Academy of Sleep Medicine and the Sleep Research Society's consensus statement on the recommended amount of sleep for healthy adults [31].

4.2.3 COVARIATES

Worse insomnia symptoms have previously been associated with increased age, female sex, partner status, and lower income [32]. Shorter sleep duration has been associated with worse health status, increased cardiovascular risk, presence of depression, and increased body mass index (BMI) [33]. In the NEMESIS cohort, insomnia was found to be prevalent across different categories of mental disorders [34]. Therefore, in this study, we controlled for age, sex, living with a partner (yes/no), having a paid job (yes/no), chronic somatic disease (presence of one or more of 17 chronic physical disorders treated or monitored by a medical doctor in the previous 12 months, as assessed with a standard checklist), BMI, smoking last month (yes/no), exercise (< 1 h/wk versus ≥ 1 h/wk); and the presence of any 12-month period of a mood,

anxiety, or substance use disorder, as determined by the Composite International Diagnostic Interview, version 3.0 — a fully structured, lay-administered diagnostic interview. Very few participants (n = 11, 0.2%) reported ADHD medication use. Therefore, we did not include ADHD medication use as a covariate.

4.3   STATISTICAL ANALYSES

We reported general characteristics of the sample using frequencies and percentages for categorical data, in terms of ADHD symptom severity (none, few, clinically relevant). Multivariate logistic regression analyses were performed to demonstrate how the sum scores of ADHD symptom severity and ADHD symptom subtype dimension (hyperactive or inattentive) were associated with the outcome, insomnia symptoms. Multivariate multinomial regression analyses were performed to demonstrate how these associated with sleep duration. Results were adjusted for sex and age in model 1, and additionally for partner status, job status, any chronic somatic disorder, BMI, smoking last month, exercise last week, any 12-month mood, anxiety or substance use disorder in model 2. Results were expressed as adjusted odds ratios or relative risk ratios. All analyses were performed with STATA version 12.1 (Stata-Corp, College Station, Texas, United States), using weighted data to correct for differences in the response rates in several sociodemographic groups and differences in the probability of selection of respondents within households at baseline, with statistical significance inferred at $\alpha < .05$.

5.   RESULTS

Table 1 describes the sample characteristics of the total sample, across ADHD symptom severity categories (none, few and clinically relevant). No ADHD symptoms were found in 43% of the sample, 51% reported few symptoms, and 6% reported clinically relevant ADHD symptoms. Clinically relevant ADHD symptoms were significantly associated with female gender (p = 0.017), younger age group (p < 0.001), living without a partner (p < 0.001), not having a paid job (p = 0.005), smoking in the last month (p < 0.001), and any 12-month mood/anxiety/ substance use disorder (all p < 0.001).

TABLE 1. Sociodemographic and health characteristics of the total Dutch general population sample (N = 4,618) and across ADHD symptom severity categories (none, few and clinically relevant)

		Total sample	ADHD symptoms			
			None	Few	Clinically relevant	P value
		(N = 4,618)	n=2,104 42.8%	n=2,278 51.2%	n=236 6.0%	
		n (%)*	%	%	%	
Sex	male	2,059 (49.8)	51.9	49.3	39.5	.017
	female	2,559 (50.2)	48.1	50.7	60.5	
Age	23-37 year	767 (26.0)	17.7	31.9	34.5	< .001
	38-47 year	1,079 (22.7)	22.2	22.8	26.6	
	48-57 year	1,178 (24.2)	25.8	22.5	26.8	
	58-70 year	1,594 (27.1)	34.3	22.8	12.1	
Education	primary or lower secondary education	1,379 (29.2)	30.0	28.0	33.4	.085
	higher secondary education	1,479 (41.3)	42.4	39.9	44.8	
	higher professional education, or university	1,760 (29.5)	27.6	32.1	21.8	
Partner	living without partner	1,268 (27.8)	25.6	27.8	43.5	< .001
Job	without paid job	1,471 (28.2)	29.2	26.2	38.9	.005
Any chronic somatic disease	yes	2,016 (40.9)	40.7	40.6	44.5	0.644
BMI	Underweight (BMI<18.5)	55 (1.4)	0.9	1.4	4.1	.082
	Normal (BMI 18.5-24.9)	2,237 (48.1)	46.1	49.6	49.6	
	Overweight (BMI 25-29.9)	1,674 (36.4)	38.2	35.1	34.0	
	Obese (BMI≥30)	645 (14.2)	14.8	13.9	12.3	
Smoking last month	yes	1,076 (25.4)	23.1	25.8	37.9	< .001
Exercise number of hours/week	< 1 hour	1,709 (37.2)	35.5	38.0	42.0	0.241
Any 12-month mood disorder	yes	238 (5.4)	1.5	6.0	29.5	< .001
Any 12-month anxiety disorder	yes	270 (6.8)	3.2	7.9	24.4	< .001
Any 12-month substance use disorder	yes	131 (4.1)	2.4	4.8	10.4	< .001

* in unweighted numbers and weighted percentages. ADHD = attention-deficit hyperactivity disorder.

The prevalence of insomnia symptoms and sleep duration across the three ADHD symptom severity groups is described in Table 2. The group with clinically relevant ADHD symptoms had the highest prevalence of clinically significant insomnia symptoms (IRS ≥ 9): 43% reported significant insomnia symptoms, as opposed to 18% in the group with no ADHD symptoms. Those with clinically relevant ADHD symptoms also had the highest prevalence of the separate symptoms defining insomnia (difficulty initiating and maintaining sleep, early morning awakening, poor sleep quality); all $p < .001$. They also reported longer sleep duration as well as shorter sleep duration more often.

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TABLE 2. Percentages of insomnia symptoms and other sleeping problems across ADHD symptom severity categories (none, few and clinically relevant) in the general Dutch population (N = 4,618)

	n (%)*	Number of ADHD symptoms			P value
		None	Few	Clinically relevant	
		%	%	%	
Insomnia Rating Scale ≥ 9	1,109 (22.9)	17.9	24.7	42.9	< .001
Difficulty initiating sleep	379 (8.3)	5.5	9.0	22.2	< .001
Difficulty maintaining sleep	1,439 (29.7)	26.9	30.3	44.8	< .001
Early morning awakening	1,074 (22.6)	19.1	23.5	40.0	< .001
Poor sleep quality	574 (11.7)	8.2	12.8	28.5	< .001
Total Sleep Duration					
Short (≤ 6h/night)	1,376 (29.7)	27.4	30.3	41.2	< .001
Normal (7-9h/night)	3,170 (68.9)	71.7	68.5	52.8	
Long (≥ 10h/night)	70 (1.4)	0.9	1.3	5.9	

* in unweighted numbers and weighted percentages. ADHD = attention-deficit hyperactivity disorder.

When we tested the associations between the insomnia variables and ADHD symptom severity groups (with no symptoms as the reference) in partially and fully adjusted logistic regression analyses, the groups with few and clinically relevant ADHD symptoms were significantly associated with all outcome variables in both models (Table 3). The p for trend was also significant for each outcome variable, meaning that across the three categories of increasing ADHD symptom severity (none, few, clinically relevant), there was a significant increase in the odds ratios for insomnia symptoms and relative risk ratios of short and long sleep duration. In the fully adjusted models, the group with clinically relevant ADHD symptoms had more than double the risk of insomnia symptoms and almost double the risk of short sleep duration, compared to the group with no ADHD symptoms.

The prevalence of both short (≤ 6 hours) and long (≥ 10 hours) sleep duration was highest in subjects with clinically relevant ADHD symptoms: 6% had long sleep duration, and 41% had short sleep duration (Table 2). An unexpected finding was the significant relationship between clinically relevant ADHD symptoms and *long* sleep duration (≥ 10 h), although the significance level was less strong and the confidence interval quite large (for this specific category p < 0.01). Overall, these findings as well as those in Table 3 suggest that worsening ADHD symptom severity is significantly associated with insomnia symptoms and altered sleep duration, after adjustment for a wide range of possible confounders, indicating a dose-response association.

TABLE 3. Ratios of insomnia symptoms and other sleeping problems across ADHD symptom severity categories (none, few and clinically relevant) in the general Dutch population (N = 4,618), using partly and fully adjusted models

	Number of ADHD symptoms (Ref = None)			Number of ADHD symptoms (Ref = None)		
	Few	Clinically relevant		Few	Clinically relevant	
	Model 1		P for trend	Model 2		P for trend
	OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	
Insomnia Rating Scale ≥ 9	1.69 (1.39-2.05)***	4.01 (2.74-5.87)***	< .001	1.51 (1.24-1.84)***	.66 (1.74-4.07)***	< 0.001
Difficulty initiating sleep	1.81 (1.36-2.39)***	5.14 (3.37-7.84)***	< .001	1.40 (1.06-1.85)**	2.03 (1.09-3.80)**	0.009
Difficulty maintaining sleep	1.41 (1.18-1.69)***	2.87 (1.91-4.32)*	< .001	1.30 (1.08-1.58)*	2.17 (1.35-3.48)*	< .001
Early morning awakening	1.41 (1.15-1.74)*	3.11 (2.23-4.35)***	< .001	1.28 (1.03-1.58)*	2.21 (1.50-3.26)***	< .001
Poor sleep quality	1.74 (1.36-2.22)***	4.70 (3.26-6.79)***	< .001	1.46 (1.14-1.87)*	2.60 (1.65-4.09)***	< .001
Total Sleep Duration	RRR (95% CI)	RRR (95% CI)		RRR (95% CI)	RRR (95% CI)	
Short (≤6h/night)	1.24 (1.06-1.44)*	2.29 (1.56-3.35)***	< .001	1.18 (1.01-1.38)*	1.94 (1.31-2.85)***	.001
Normal 7-9h/night	Ref	Ref	Ref	Ref	Ref	Ref
Long (≥ 10h/night)	1.72 (0.80-3.67)	12.04 (4.83-30.02)***	< .001	1.44 (0.63-3.27)	5.87 (1.97-17.45)**	.015

Asterisks indicate statistical significance: * = p < .05, ** = p < .01; *** = p < .001. Model 1 is adjusted OR/RRR for sex and age. Model 2 is adjusted for the factors in Model 1 and additionally adjusted for partner status, job status, any chronic somatic disorder, body mass index, smoking last month, exercise last week, any 12-month mood, anxiety or substance use disorder. ADHD = attention-deficit hyperactivity disorder, CI = confidence interval, OR = odds ratio, Ref = reference, RRR = relative risk ratio.

Table 4 describes the associations between insomnia symptoms, sleep duration, total ADHD symptom score, and the two symptom dimensions hyperactivity and inattention. Again, the continuous variables for ADHD symptoms, hyperactivity and inattention all show a strongly

significant relationship with clinically significant insomnia symptoms in the fully adjusted models (all p < .001). All the separate symptoms defining insomnia showed a significant relationship with ADHD symptoms, hyperactivity and inattention dimensions, assessed continuously, in both models. The predictor variables for all insomnia and sleep duration outcomes did not change markedly with full correction in model 2, demonstrating that the association between ADHD and sleep disturbance is robust, and not attributable to confounding factors. The hyperactivity dimension was significantly associated with short sleep, but not related to long sleep duration.

TABLE 4. Ratios of insomnia symptoms and other sleeping problems across total ADHD symptoms, hyperactivity and inattention as continuous ADHD dimension variables, in the general Dutch population (N = 4,618), using partly and fully adjusted models

	Total ADHD symptoms		ADHD hyperactivity dimension		ADHD inattention dimension	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Insomnia Rating Scale ≥ 9	1.12 (1.10-1.15)***	1.09 (1.06-1.13)***	1.20 (1.15-1.26)***	1.17 (1.11-1.23)***	1.14 (1.11-1.18)***	1.10 (1.06-1.14)***
Difficulty initiating sleep	1.15 (1.12-1.18)***	1.08 (1.04-1.12)***	1.25 (1.16-1.34)***	1.16 (1.07-1.25)***	1.18 (1.14-1.22)***	1.08 (1.04-1.13)***
Difficulty maintaining sleep	1.07 (1.05-1.10)***	1.06 (1.03-1.08)***	1.16 (1.10-1.21)***	1.14 (1.08-1.19)***	1.08 (1.04-1.11)***	1.05 (1.01-1.09)*
Early morning awakening	1.09 (1.07-1.12)***	1.07 (1.04-1.09)***	1.18 (1.13-1.24)***	1.15 (1.09-1.21)***	1.10 (1.06-1.13)***	1.06 (1.02-1.10)**
Poor sleep quality	1.16 (1.13-1.19)***	1.12 (1.08-1.15)***	1.28 (1.20-1.36)***	1.21 (1.14-1.30)***	1.19 (1.15-1.23)***	1.13 (1.09-1.17)***
Total sleep duration	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Short (≤6h/night)	1.07 (1.04-1.10)***	1.06 (1.03-1.09)***	1.13 (1.07-1.20)***	1.12 (1.05-1.19)***	1.07 (1.04-1.11)***	1.06 (1.02-1.09)**
Normal (7-9h/night)	Ref	Ref	Ref	Ref	Ref	Ref
Long (≥10h/night)	1.17 (1.07-1.28**	1.10 (1.01-1.20)*	1.18 (0.92-1.53)	1.05 (0.84-1.32)	1.25 (1.14-1.37)***	1.16 (1.05-1.28)**

Asterisks indicate statistical significance: * = p < .05, ** = p < .01; *** = p < .001. Model 1 is adjusted OR/RRR for sex and age. Model 2 is adjusted for the factors in Model 1 and additionally adjusted for partner status, job status, any chronic somatic disorder, body mass index, smoking last month, exercise last week, any 12-month mood, anxiety or substance use disorder. ADHD = attention-deficit hyperactivity disorder, CI = confidence interval, OR = odds ratio, Ref = reference, RRR = relative risk ratio.

6.   DISCUSSION

In this study, we evaluated the independent association between adult ADHD symptom severity, ADHD symptom dimensions, insomnia symptoms and sleep duration. Our results showed two main findings. Firstly, clinically significant insomnia symptoms were strongly and consistently associated with increasing severity of ADHD symptoms, and with the symptom dimensions of hyperactivity and inattention. There was a dose-response relationship between insomnia symptoms and ADHD symptom severity and ADHD symptom dimensions. Secondly, while self-reported short sleep duration was significantly associated with both inattentive and hyperactive symptom dimensions, long sleep duration was only associated with inattention and not with hyperactivity. After correcting for comorbid psychiatric disorders in the last year (mood, anxiety and substance use disorders), these associations remained significant. This is noteworthy, as it indicates that even in the general population, these relationships are not attributable to another comorbid disorder.

A dose-response relationship between ADHD symptom severity and insomnia was also found in two large [8, 35] and one smaller clinical studies [12]. Ours and these three studies included adults aged up to 74 years [8, 12, 35]. However, in a community study of *young adults* (18 - 20 years), Gau et al. found no such dose response relationship (N = 2,284) [13]. The study of Gau et al. may indicate that in young adults, there is less difference in insomnia between those with and without ADHD. Our larger age range may account for more variability in self-reported ADHD and insomnia symptoms. It is also recognized that ADHD persisting into adulthood causes more severe impairment [36]. Similarly, insomnia symptoms worsen with increasing age [37] and poorer sleep quality in adult ADHD has been attributed to the presence of depressive symptoms [35]. We therefore also adjusted for mood and anxiety disorders and yet still found a dose-response relationship between increasing ADHD symptom severity and insomnia.

In terms of the ADHD symptom dimensions and insomnia symptoms, we found that clinically significant insomnia symptoms correlated strongly and significantly with both inattention and hyperactivity symptom dimensions. The research on ADHD subtypes and sleep disturbance to date has been mixed. Insomnia symptoms have been associated with: (1) the number of hyperactivity/impulsivity symptoms [12]; (2) the combined ADHD and inattentive subtype [8]; (3) inattentive symptoms only [7, 13, 38, 39]. However, one study reported no association [6]. We found that insomnia correlated strongly with *both* inattentive and hyperactive symptoms, even after adjusting for multiple possible confounders, and despite using a population sample, where symptoms tend to be milder than in clinical studies. The clinical study by Fisher et al. (2014, ADHD adult N = 1,163) also demonstrated a strong association between adult ADHD and insomnia, in both ADHD subtypes [6].

Our second significant finding was that ADHD symptoms were associated with self-reported short and long sleep duration, as opposed to normal sleep. Our finding replicates the large population study of Bogdan et al., although they did not correct for comorbid affective disorder [14]. In other clinical studies, ADHD patients reported shorter sleep duration than controls [40, 41]. When sleep duration was objectively measured, it was found to be normal in three studies [17 - 19]. Normal sleep duration was also found in two studies using self-report measures [13, 20]. It is possible that findings for altered sleep duration are less strong when objective sleep measures are used. Finally, a study of 22 ADHD adults found no correlation between number of ADHD symptoms and sleep duration, a negative finding which may be explained by the small sample size [12].

Short sleep duration has been well described in the ADHD literature. Some authors have related it to increased nocturnal motor activity, as measured objectively by polysomnography [17, 42 - 44], although one study did not confirm this [45]. Our results significantly associated short sleep and ADHD symptoms. This relationship may be also explained by the presence of a comorbid delayed circadian rhythm disorder, such as delayed sleep phase syndrome, DSPS [5]. Generally, DSPS is characterized by a preference for sleep onset after midnight, with consequent difficulty awaking, daytime sleepiness and impaired functioning [1]. Individuals with DSPS have sleep-onset insomnia when trying to fall asleep early [46]. When early rising is necessary, a cumulative sleep debt may arise – meaning that total sleep duration is shorter.

In terms of long sleep in ADHD, we found a strong and significant association with ADHD symptom severity and the inattention symptom dimension, showing a dose-response relationship. Long sleep was far less prevalent than short sleep duration in the ADHD group.

A first possible way to explain long sleep duration associated with ADHD is the presence of an (undiagnosed) comorbid disorder [14]. In general, sleep duration shows a U-shaped association with overall mortality, cardiovascular disease, obesity and diabetes [47]. Hence both short and long sleep duration are detrimental to health. In ADHD, such a comorbid disorder might include hypersomnia, affective disorder, or medical illness. Just as it is important to control for comorbid disorders when investigating insomnia (as mentioned above), this is also true when investigating sleep duration. We did correct for mood, anxiety, substance and somatic disorders in the last year, unlike some other studies [12,14,19,48,49]. Still, we found that ADHD symptoms and long sleep duration were significantly associated. This implies that an (atypical) subgroup of those with ADHD may exist on the continuum of adult ADHD. Hypersomnia, characterized by excessive daytime sleepiness and prolonged night-time sleep, is increased in adult ADHD compared to controls [5]. Hypersomnia may be misdiagnosed as ADHD [5]. Hence, where ADHD patients present with long sleep duration, hypersomnia should

be excluded or treated. In general, the group with ADHD and long sleep may be at increased risk for overall mortality [47].

A second possible explanation for long sleep in ADHD comes from the pediatric literature, where some authors have proposed that instability of the sleep-wake system is a characteristic of children with ADHD [50]. This instability (some with long sleep duration, some with short) may also be present in adult ADHD.

Regarding the two ADHD symptom dimensions and sleep duration in adults, there is a dearth of literature. Concurring with two studies, we found that short sleep duration was significantly associated with hyperactivity symptoms [12, 13]. In a minority of subjects, long sleep duration, was significantly associated with both hyperactive and inattentive symptoms. Regarding insomnia symptoms, significant findings in hyperactivity and inattention dimensions were very similar.

A question we were unable to address in our study is whether the treatment of sleep problems in those with ADHD improves the symptoms of inattention and hyperactivity. The cross-sectional nature of our analysis prevented us analyzing this, however, future studies should examine this important clinical outcome.

Another striking finding was that 60.5% of those with clinically significant ADHD symptoms were women, as opposed to 39.5% men. This result contrasts with findings from the pediatric literature, where male children are more than twice as likely to have ADHD than female children [51]. However, ADHD in adult women has been described as underdiagnosed because the symptoms are less overt [52]. It has also been shown that the higher prevalence of ADHD in males tends to decrease with increasing age [52]. A recent study using the ASRS showed that while more men screened positive for ADHD, the difference between the genders was not statistically significant [52]. Beyond this, we are unable to explain the increased prevalence of clinically relevant ADHD symptoms in females.

Despite the strengths of our study, several limitations should be noted. First, as this study is based on the third wave only and thus uses cross-sectional analyses, a clear causal direction of the relationships found cannot be demonstrated. Second, we relied on retrospective self-reports for ADHD symptoms present over the last 6 months using the Adult ADHD Self-Report Scale screener, which did not include a question about childhood-onset of the symptoms. We used retrospective self-reporting for insomnia symptoms (present over the last 4 weeks). According to the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition diagnostic criteria, insomnia occurs where symptoms occur at least 3 nights per week over a period of three months

[1]. The IRS does not take duration of symptoms into account, hence we probably studied subjects with less severe symptoms, yet still we found significant associations between ADHD and insomnia symptoms. Sleep duration in the past 4 weeks were self-reported measures, where the categories of sleep duration may have limited variability. Yet, previous studies using both self-report measures and polysomnography indicate that long sleepers overestimate and short sleepers underestimate their true sleep duration [47]. Thirdly, we controlled for anxiety, depressive and bipolar disorders but we did not explore the potential overlap between ADHD and bipolar disorders. Bipolar disorder 2 can remain undiagnosed for years and exhibit similar symptoms to ADHD. In NEMESIS-2, the prevalence of all bipolar disorders was 0.8% in the last 12 months [53]. The 12-month prevalence of bipolar 2 disorder was 0.6%. This potential overlap would be interesting to investigate further. Fourthly, as regards concomitant medication use, very few subjects used ADHD medication (0.2%), so we did not correct for them as we felt the results would not be meaningful. Neither did we correct for medications treating insomnia or hypersomnia. It would be interesting to note whether treatment of sleep disturbance in ADHD improves the core symptoms of this disorder. Finally, in terms of the ADHD symptom dimensions, hyperactivity was determined by only two questions and there was no assessment of impulsivity, a component of ADHD, meaning that we are unable to comment on the relationship between impulsivity symptoms and insomnia/sleep duration.

In conclusion, we have confirmed that increasing symptom severity of ADHD is significantly associated with clinically significant insomnia symptoms, long and short sleep duration, after correction for a range of potential confounders. Both long and short sleep duration were also significantly associated with inattentive symptoms, in fully adjusted models, whereas hyperactive symptoms were associated with short sleep duration only. Adult ADHD and sleep disturbance symptoms are therefore linked with consistent and strong associations. This has serious implications for morbidity in ADHD, as insomnia, short and long sleep duration are all associated with significantly worse daily functioning [34] and adverse health outcomes [33, 47]. Where the comorbidities of adult ADHD are unrecognized and untreated, it has been shown that treatment costs increase and patients suffer more adverse long-term outcomes [54]. Sleep deprivation also worsens cognitive function [22]. In adult ADHD, attention and executive control are already compromised, hence insomnia should be recognized and treated. Insomnia can be successfully managed pharmacologically [54] and with cognitive behavioral therapy and light therapy [56, 57]. Such treatments could be used to ameliorate the sleep disturbance we have found to be so prevalent in ADHD. Comorbid insomnia and altered sleep duration should be considered by clinicians treating these complex patients, to reduce suffering and improve functioning.

LIST OF ABBREVIATIONS

ADHD: Attention-Deficit Hyperactivity Disorder
ASRS: Adult ADHD Self-Report Scale Screener, version 1.1
BMI: Body mass index
IRS: Women's Health Initiative Insomnia Rating Scale
NEMESIS-2: Netherlands Mental Health Survey and Incidence Study-2

FINANCIAL SUPPORT

DECLARATIONS OF POTENTIAL CONFLICTS OF INTEREST

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CHAPTER 4

INFLAMMATION, SLEEP AND ADHD

RESPONSE TO ARAZ ALTAY.

SLEEP DISORDERS AND ATTENTION DEFICIT: A CONSEQUENCE OF PRO-INFLAMMATORY STATE?

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We thank Dr Araz Altay for raising the important issue of inflammation, sleep and ADHD [1] and the editors of the *Journal of Clinical Sleep Medicine* for giving us the opportunity to respond.

Our group previously investigated adult ADHD symptoms, Metabolic Syndrome (MetSyn) and obesity-related variables in a large population study with different stages of comorbid affective disorders (Netherlands Study of Depression and Anxiety, NESDA) [2]. Interestingly, we showed few clear associations: ADHD was not associated with MetSyn. It is possible that these associations are difficult to detect and therefore we failed to find them. Also, both the concept and definition of MetSyn have been questioned [3] as it is possible that not *all* MetSyn risk factors contribute significantly to cardiovascular diseases/diabetes in the general population [4].

Concerning *obesity*, a meta-analysis showed that it was significantly associated with ADHD [5]. Both obesity and MetSyn are considered pro-inflammatory conditions [6].

Another possible link includes *sleep disturbance*, which was associated with systemic inflammation markers in the NESDA cohort [7]. ADHD is comorbid with insomnia, RLS and circadian dysregulation [8]. Preliminary evidence links ADHD to inflammatory processes [9]. The circadian system and clock genes control both the sleep-wake cycle and metabolism [10]. Fasting glucose, lipid levels, blood pressure and the sleep-wake cycle are rhythmically coordinated by the biological clock. Disruption of either the circadian or metabolic system can lead to derangement of the other, predisposing to MetSyn, obesity or diabetes [10]. Once again, inflammatory processes may be the link between ADHD, circadian rhythm and metabolic disturbance. We therefore support further investigation of these overlapping processes, as causality is unknown.

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CHAPTER 5

ADHD, CIRCADIAN RHYTHMS AND SEASONALITY

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1. ABSTRACT

Objective: We evaluated whether the association between Adult Attention-Deficit/ Hyperactivity Disorder (ADHD) and Seasonal Affective Disorder (SAD) was mediated by the circadian rhythm.

Method: Data of 2,239 persons from the Netherlands Study of Depression and Anxiety (NESDA) were used. Two groups were compared: with clinically significant ADHD symptoms (N = 175) and with No ADHD symptoms (N = 2,064). Sleep parameters were sleep-onset and offset times, mid sleep and sleep duration from the Munich Chronotype Questionnaire. We identified the prevalence of probable SAD and subsyndromal SAD using the Seasonal Pattern Assessment Questionnaire (SPAQ). Clinically significant ADHD symptoms were identified by using a *T* score > 65 on the Conners Adult ADHD Rating Scale.

Results: The prevalence of probable SAD was estimated at 9.9% in the ADHD group (vs. 3.3% in the No ADHD group) and of probable s-SAD at 12.5% in the ADHD group (vs 4.6% in the No ADHD group). Regression analyses showed consistently significant associations between ADHD symptoms and probable SAD, even after adjustment for current depression and anxiety, age, sex, education, use of antidepressants and benzodiazepines (B = 1.81, p < .001). Late self-reported sleep-onset was an important mediator in the significant relationship between ADHD symptoms and probable SAD, even after correction for confounders (total model effects: B = 0.14, p ≤ .001).

Conclusion: Both seasonal and circadian rhythm disturbances are significantly associated with ADHD symptoms. Delayed sleep-onset time in ADHD may explain the increase in SAD symptoms. Treating patients with SAD for possible ADHD and delayed sleep-onset time may reduce symptom severity in these complex patients.

Keywords: Seasonal affective disorder; attention deficit/hyperactivity disorder; delayed sleep phase; circadian rhythm

2. INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that commences in childhood, and often persists throughout the lifespan [1]. The estimated prevalence of ADHD is 3.4% in adults [2]. The clinical presentation of ADHD in adults is marked by inattentiveness and impulsivity, with fewer hyperactivity symptoms than in childhood. Adult hyperactivity may be internalized as inner restlessness [3]. Adult inattention is characterized by difficulty in planning and organizing tasks, poor listening skills, distraction and procrastination [4]. Impulsivity may result in interrupting others, poor self-control, reckless driving and impatience [4].

In addition, adult ADHD is comorbid with mood, anxiety and sleep disorders, amongst others [2, 5, 6]. Seasonal Affective Disorder (SAD) is a type of recurring major depression with a seasonal pattern. It frequently co-occurs with adult ADHD, with a prevalence of up to 27%, as compared to 6% in the general population [7 - 9]. SAD is characterized by major depressive episodes during autumn and/or winter, which remit in spring [10, 11]. Symptoms include difficulty concentrating, anhedonia, fatigue, forgetfulness, as well as the co-called atypical depressive symptoms: sleep disturbance (tendency to sleep longer), hyperphagia and weight increase [10].

ADHD is also associated with circadian sleep problems, as recently reviewed by Coogan [12]. In particular, delayed sleep phase syndrome (DSPS) and late chronotype are frequently comorbid in adults with ADHD [10, 13, 14] and adolescents with ADHD [15]. Individuals with DSPS have sleep-onset insomnia if they try to go to sleep early: sleep-onset is usually after midnight, with consequent difficulty awaking, daytime sleepiness and impaired functioning. The duration of symptoms is at least 6 months [10]. Chronic sleep deprivation and short sleep duration have also been associated with ADHD [16].

A subject's chronotype refers to the behavioral manifestation of underlying circadian rhythms, as evidenced by regular rising and sleep-onset times during 24 hours [17]. Chronotype, regulated by the biological clock in the suprachiasmatic nuclei (SCN), consists of morning, evening and intermediate types [18]. Timing of sleep and wakefulness may differ during work and free days, as sleep deficit accumulates during working days, but is compensated for on free days, when rising time is later [19]. Phase and duration of sleep on *free* days are believed to reflect circadian rhythm most accurately as there are fewer externally enforced schedules [17]. Adults with ADHD are often evening types, up to 78% have initial insomnia if they go to bed early; and initial insomnia in ADHD is associated with a delayed secretion of the sleep hormone, melatonin [20].

SAD and DSPS appear to be overlapping conditions in terms of clinical presentation and comorbidity [21, 22]. Both may result from "phase shifts" in the circadian rhythm. For most SAD patients, it is argued that a phase shift occurs during winter, when the dawn occurs later. Here, the natural daily rhythms of light are out of phase with the patient's sleep/wake cycle, and hence, this cycle is delayed [21]. Therefore, depression occurs in winter when the photoperiods become shorter. Recovery is induced with increasing exposure to sunlight in spring [23]. In DSPS, the late sleep-onset reflects an inability to regulate to the external cue of diminished light, resulting in a phase delay [24].

Several mechanisms for the relationship between disturbed sleep and ADHD have been explored [25]. Sleep disturbance in ADHD may result from nocturnal hyperactivity, where stimulant treatment may ameliorate sleep [25]. Alternatively, sleep problems may precipitate the behavioral and cognitive symptoms of ADHD. This interaction between ADHD and sleep disturbance has been elegantly depicted as a feed-forward loop, where sleep problems cause neurobehavioral morbidity in ADHD, and ADHD results in the sleep problems associated with its comorbid disorders, depression and anxiety [25].

ADHD, DSPS and SAD share features which suggest they are all disorders of the biological rhythm. The mechanism underlying the circadian rhythm disturbance in ADHD is unclear, but a recent animal model showed that disruption of a circadian clock gene elicits an ADHD-like syndrome, with alteration in dopamine levels [26]. Body temperature changes and delayed melatonin secretion are also implicated in ADHD [20, 27]. In winter, SAD and DSPS present with low mood [28] and problems synchronizing to external cues such as daylight, especially when these cues are weak. In terms of treatment, symptoms of ADHD, SAD and DSPS improve when therapy involves 'phase resetting'. Both DSPS and SAD respond to morning bright light therapy and/or evening melatonin administration [21, 29]. In an open study of patients with ADHD and SAD, core ADHD symptoms improved when remediated with light therapy [30]. Finally, the three conditions may have shared genetic factors [31]. ADHD is highly heritable [32] and evidence points to underlying polymorphisms in clock genes in all three disorders [12]. This comorbidity and shared genetic etiology may explain the symptomatic overlap of ADHD, SAD and DSPS.

However, to our knowledge, only one study has investigated all three conditions. Bijlenga and colleagues found an association between ADHD, late sleep and seasonal depressive symptoms [33] and our prior study showed that ADHD symptoms add risk to circadian rhythm sleep problems in depression and anxiety [13]. Our aim in this study was to add new knowledge about the relationships between these disorders. Specifically, we investigated whether indicators of a delayed circadian rhythm (sleep-onset and offset times, mid-sleep) as well as

short sleep duration, mediated in the relationship between ADHD symptoms and seasonal depressive symptoms. If indeed circadian rhythm plays a role in the high prevalence of SAD in ADHD patients, then effective treatments could ameliorate symptoms of both disorders in this group [14]. Improving mood and sleep disorders may well decrease health resource utilization and improve quality of life in ADHD [34].

3.   METHOD

3.1 PARTICIPANTS

Subjects participated in the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal, naturalistic cohort study of 2,981 participants, aged 18 - 65 years. Participants were recruited from different health care settings (community, primary and specialized mental health care) and included a group without psychiatric symptoms ('Controls') and others with current and remitted affective disorders. A full description of NESDA has been reported elsewhere [35]. Ethical Review Boards of all participating centers approved the NESDA study protocol and it was carried out in accordance with the latest Declaration of Helsinki. All participants gave written informed consent at enrolment after the study procedures had been fully explained. All measures in this study were taken from the 2-year follow-up assessment of NESDA, except the assessment of ADHD symptoms, (performed at the 4-year follow-up). Subjects included were those participating in both of these follow-up visits (2,239 respondents, 75.1% of the total sample).

3.2   ADHD SYMPTOMS

To identify clinically significant ADHD symptoms, the Conners Adult ADHD Adult Rating Scale – Self report: Screening Version (CAARS-S:SV) was used at the 4-year follow-up assessment. The CAARS-S:SV is a 30-item questionnaire that assesses ADHD symptoms and behaviors. The 18-item Total symptom scale identifies the presence of DSM-IV criteria for ADHD (range of possible scores 0-54) [10]. The CAARS-S:SV uses a 4-point Likert-scale format in which respondents are asked to rate items pertaining to current behavior and problems. Ratings range from 0 (not at all, never) to 3 (very much, very frequently). The validity and reliability of the CAARS-S:SV have been confirmed [36]. For this study, the raw CAARS-S:SV scores were converted into standardized scores (*T*-scores) using age- and sex-corrected norm values, following the CAARS manual [37]. The ADHD group was defined as those participants obtaining a *T*-score of 65 or above, indicating clinically significant ADHD symptoms; and the No ADHD group obtained a *T*-score < 65 (on either the ADHD Total symptom or Index scales). This instrument

has excellent test-retest reliability, with a median α = 0.89, over the period of approximately one month [38]. We used data from the 4-year follow-up assessment for ADHD, and from the 2-year follow-up for other parameters, because the ADHD assessment took place later than the others. ADHD has a chronic course in the majority of cases, based on follow-up studies [3, 39]. It extends from childhood [40] even into old age [41]. Symptom stability has been shown for adults retrospectively reporting childhood ADHD [42] and the negative impact of ADHD on occupational, social and emotional functioning also persists [43]. Hence we feel that the fact ADHD was measured 2 years after the other parameters would not impact on our results.

3.3 SAD SYMPTOMS

The Seasonal Pattern Assessment Questionnaire (SPAQ), is a self-rating scale assessing seasonal changes in sleep length, social activity, mood, weight, appetite, and energy level in the last year [44]. Likert scales range from (0) 'no change' to (4) 'extreme/marked change' for each item and do not identify time span of symptoms. We used a modified version of the SPAQ that reported symptoms in the last year. The SPAQ is widely used as a screening questionnaire for SAD [45]. It shows a specificity of 94%, but a low sensitivity of 44% [46]. We calculated the Global Seasonality Score (GSS, range 0 - 24) from the SPAQ. The GSS is a composite measure for seasonal change in the six symptoms assessed and has good internal consistency (Cronbach's alpha 0.85), [46].

To identify probable SAD cases, we used the three criteria formulated by Kasper et al. using the SPAQ: 1) GSS score of 11 or more; 2) a 'problem' rating of seasonal mood changes of at least 'moderate' (a score ≥ 2 on a 0 - 5 scale range); 3) a time window of symptoms to diagnose winter SAD, in which subjects feel worst between December and February [45].

Subsyndromal-SAD (s-SAD) is defined as a cluster of milder seasonal complaints less impairing than SAD. We used the following modified Kasper criteria for s-SAD: (1) a GSS score of 11 or more, with a 'problem' rating of 'no' or 'mild' (scores 0 or 1 on a 0-5 scale range); or (2) a GSS score of 9 or 10 and a 'problem' rating of at least 'mild' (≥ 1) [28, 47]. The time window criterion is the same as for SAD cases.

3.4 CHRONOTYPE

Sleep characteristics and chronotype were assessed with the Munich Chronotype Questionnaire (MCTQ) [17]. The MCTQ is a self-report measure with questions on sleep timing on nights before work and free days. Parameters of circadian rhythm used were: sleep-onset and offset times, sleep duration on nights before free days and mid-point of sleep on free days corrected for sleep debt during the work week (MSF_{sc}), [17, 48].

3.5 AFFECTIVE DISORDERS

Depressive (major depressive disorder, dysthymia) and anxiety disorders (panic disorder, social phobia, agoraphobia, generalized anxiety disorder) were assessed using the DSM-IV Composite International Diagnostic Interview (CIDI-2.1) by trained clinical research staff [49]. Test-retest reliability of the CIDI has been described as satisfactorily high [50] and inter-rater kappa values were all 0.94 or higher for depressive and anxiety disorders in the original validation studies [51]. We do not have specific kappa values for the NESDA CIDI interviews but we believe they did not differ from the WHO field trial values, as we used the instrument designed and tested by the WHO in field trials for use in cross-national comparison studies [50]. We assessed affective disorders in three categories: *none; remitted* (present during the lifetime history but not in the last year) and *current* (present in the last year). Affective disorder severity was investigated using the Inventory of Depressive Symptomatology (IDS-SR) and the Beck Anxiety Inventory (BAI) scales, respectively.

3.6 COVARIATES

Sociodemographic variables included age, sex and years of education. Current employment status, presence of a partner, and children in the household were shown to be significant predictors in a NESDA study on chronotype, and hence were included [52]. Potential confounders associated with ADHD, depressive, and anxiety disorders included smoking (non-smoker/current smoker) [53]; alcohol use (number of alcohol consumptions/week: Alcohol Use Disorders Identification Test) [54]; Body Mass Index (BMI) [55]; and the use of psychotropic medications. These included selective serotonin reuptake inhibitors (SSRI; ATC code: N06AB), serotonin-norepinephrine reuptake inhibitors (SNRI; N06AX16, N06AX21), tricyclics (N06AA) and tetracyclics (N06AX03, N06AX05, N06AX11), benzodiazepines (N05BA, N05CF, N05CD, N03AE), and psychostimulants (N06BA). The use of any of these medications was rated positive if used on at least 50% of days during the past month.

3.7 STATISTICAL ANALYSES

We divided the subjects into those with clinically significant ADHD symptoms (ADHD group, N = 175) and those without clinically significant ADHD symptoms (No ADHD group, N = 2,064). Means and standard deviations for continuous data, and frequencies and percentages for categorical data, were reported. We categorized the dates of assessment of the SPAQ into four seasonal categories (spring: March 21–June 20, summer: June 21–September 20, autumn: September 21–December 20, winter: December 21–March 20), to determine if season of assessment varied in the three groups, as this was shown to influence GSS significantly in a previous NESDA study [56]. Between-group comparisons of covariates were made using Chi-

square and ANOVA tests. In the multivariate analysis, we included covariates which were significantly different between the two groups. Lifetime depressive episodes have been shown to be significantly associated with ADHD symptom severity in adults [57] and depressive disorders comorbid with ADHD increased the severity of attention problems in both children [58] and (longitudinally) in adults [59]. Therefore, we did not include affective disorder severity as covariate in multivariate analyses. Linear regression was performed with GSS as the dependent variable, and clinically significant ADHD symptoms (no/yes) as the independent variable, controlling for covariates. In the multinomial logistic regression, s-SAD and SAD were the two levels of the outcome variable of interest. The ADHD predictor variables used in separate analyses were clinically significant ADHD symptoms (yes/no) and continuous CAARS score using the Total symptom scale. All regression models were adjusted for current anxiety and depression (last year), age, sex, education, and medication use (antidepressants SSRI, SNRI, tricyclics, and benzodiazepines). We conducted mediation models following Hayes, with 5000 bootstrapping samples [60]. Here, the effect of ADHD on GSS was entered, with two mediators: sleep-onset time and sleep duration, while controlling for current depressive and anxiety disorders, age, sex, education, and medication use. We excluded 3 outliers from the mediation analysis with a sleep-onset time after 5:00 AM. Data were analyzed using SPSS for Windows (version 23; IBM Company, Chicago, IL, USA). Statistical significance was inferred at $p \leq .05$.

4. RESULTS

General characteristics of the groups are described in Table 1. Participants in the clinically significant ADHD symptoms (ADHD) group were significantly older and had significantly less education than those in the No ADHD group. Ninety eight percent of the ADHD group had a lifetime history of depressive and/or anxiety disorders and it was hence largely a comorbid group. The ADHD group had three times the prevalence of current affective disorders as opposed to remitted affective disorders, whereas in the No ADHD group, remitted affective disorders were more common than current. Scores for measures of severity of both depressive and anxiety disorders were significantly higher in the ADHD group. Apart from SSRI use, few used psychotropic drugs. Significantly more in the ADHD group used antidepressants, benzodiazepines, and psychostimulants.

TABLE 1. General characteristics of the NESDA subgroups: Clinically significant ADHD symptoms (ADHD) and No clinically significant ADHD symptoms (No ADHD) (N = 2,239)

	ADHD n=175	No ADHD n=2064	Comparison Value (df)	P
Sociodemographics				
Age in years at baseline, mean (SD)	46.9 (11.6)	44.0 (13.3)	$F_{(1,2237)}$ =7.78	.005
Females, n (%)	117 (66.9)	1068 (66.1)	$X^2_{(1)}$=0.04	.454
Years of education, mean (SD)	11.6 (3.2)	12.8 (3.3)	$F_{(1,2237)}$ =21.46	<.001
Partner present, n (%)	94 (53.7)	1231 (59.6)	$X^2_{(1)}$=2.35	.126
Presence of children in household, n (%)	59 (33.7)	637 (30.9)	$X^2_{(2)}$=2.37	.306
Life style and Health				
Current smoker, n (%)	59 (33.7)	605 (29.3)	$X^2_{(1)}$=1.50	.221
Number of alcoholic drinks per week, mean (SD)	7.18 (12.0)	6.70 (9.26)	$F_{(1,2191)}$=0.40	.527
BMI, mean (SD)	26.29 (5.70)	25.74 (4.77)	$F_{(1,2165)}$=2.00	.157
Psychopathology, n (%)				
Depressive disorder:			$X^2_{(2)}$=186.81	<.001
- None	5 (2.9)	724 (35.1)		
- Current (last year)	124 (70.9)	498 (24.1)		
- Remitted	46 (26.3)	842 (40.8)		
Anxiety disorder:			$X^2_{(2)}$=145.77	<.001
- None	18 (10.3)	863 (41.8)		
- Current (last year)	118 (67.4)	524 (32.8)		
- Remitted	39 (22.3)	677 (43.0)		
Depressive symptom severity (IDS)[a], mean (SD)	31.3 (13.5)	13.8 (10.8)	$F_{(1,2237)}$=410.31	<.001
Anxiety symptom severity (BAI)[b], mean (SD)	18.5 (10.9)	7.54 (7.7)	$F_{(1,2200)}$=302.75	<.001
Frequent use of psychotropics, n (%)				
Antidepressants				
- no use	117 (66.9)	1695 (82.1)	$X^2_{(3)}$=25.59	<.001
- SSRI	37 (21.1)	250 (12.1)		
- Tricyclic antidepressants	7 (4.0)	48 (2.3)		
- SNRI	14 (8.0)	71 (3.4)		
Benzodiazepines	17 (9.7)	76 (3.7)	$X^2_{(1)}$=14.74	<.001
Psychostimulants	5 (2.9)	8 (0.4)	$X^2_{(1)}$=17.04	.002[c]
Season of assessment: n (%)				
Spring	36 (20.6)	466 (22.6)	$X^2_{(3)}$=1.98	.576
Summer	44 (25.1)	483 (23.4)		
Autumn	46 (26.3)	612 (29.7)		
Winter	49 (28.0)	503 (24.4)		

a. Inventory of Depressive Symptomatology (IDS) scale symptom severity in last week.
b. Beck Anxiety Inventory (BAI) scale symptom severity in last week.
c. With Fisher's exact test.

Table 2 shows that the Global Seasonality Score (GSS) was significantly higher in the ADHD group. Consistently, the ADHD group showed a positive significant association with probable SAD and s-SAD. Food preference across seasons, MSF_{sc}, sleep-onset and offset times on nights before free days were the only variables that were not significantly different in the two groups. There was a trend for shorter sleep duration in the ADHD group compared to the No ADHD group (F = 3.59, p = .058). In a Pearson's product-moment correlation, there was a significant but low correlation between ADHD symptoms and seasonality symptoms (r = 0.30; p < .001; R^2 = 0.09).

Table 3 shows that the presence of ADHD symptoms and current depressive disorder (last year) were positively associated with probable SAD and s-SAD in both a multinomial and binary logistic regression, even after correction for covariates.

TABLE 2. Parameters of biological rhythms: seasonal and circadian rhythm changes in two subgroups: Clinically significant ADHD symptoms (ADHD) and No clinically significant ADHD symptoms (No ADHD) (N = 2,239)

	ADHD n=175	No ADHD n=2,064	Comparisons Value (df)	P
Global Seasonality Score (GSS), mean (SD)	7.01 (4.45)	4.42 (3.82)	F=64.95 (1,2069)	<.001
Seasonal change[a] in: n (%)				
Sleep	38 (21.7)	256 (12.4)	X^2=12.26 (1)	<.001
Social	62 (35.4)	356 (17.2)	X^2=35.12 (1)	<.001
Mood	74 (42.3)	451 (21.9)	X^2=37.53 (1)	<.001
Weight	47 (26.9)	244 (11.8)	X^2=32.25 (1)	<.001
Appetite	37 (21.1)	175 (8.5)	X^2=30.18 (1)	<.001
Energy	72 (41.1)	465 (22.5)	X^2=30.66 (1)	<.001
Food preference	60 (38.7)	704 (36.9)	X^2=0.202 (1)	.653
Caseness of Seasonal Affective Disorder (SAD), n (%)			X^2=36.16 (2)	<.001
No SAD and no subsyndromal SAD	118 (77.6)	1748 (92.1)		
Subsyndromal-SAD	19 (12.5)	87 (4.6)		
Probable SAD	15 (9.9)	63 (3.3)		
Sleep duration free days, mean (SD)	7:41 hr (1:50)	7:57 hr (1:26)	F= 3.59 (1,1754)	.058
Sleep-onset free days, mean (SD)	0:15 hr (2:18)	0:09 hr (1:16)	F= 0.56 (1,1780)	.454
Sleep offset free days, mean (SD)	8:08 hr (1:52)	8:07 hr (1:26)	F= 0.00 (1,1801)	.948
MSFsc free days, mean (SD)	3:41 hr (0:44)	3:48 hr (0:36)	F= 3.20 (1,1754)	.074

a. Indicates that seasonal change score at least moderate on the SPAQ scale

TABLE 3. Multinomial logistic regression for caseness of Seasonal Affective Disorder (SAD) and subsyndromal SAD as the two levels of the dependent variable, and with clinically significant ADHD symptoms as independent variable, controlling for multiple covariates (N = 2,050)

| | Caseness of SAD* | | | |
| | Subsyndromal SAD | | Probable SAD | |
	OR (95% CI)	P	OR (95% CI)	P
Clinically significant ADHD symptoms (no/yes)	2.59 (1.46-4.63)	.001	2.04 (1.07-3.88)	.030
Covariates:				
Current depression (last year)	1.64 (1.03-2.61)	.039	2.81 (1.69-4.70)	.039
Current anxiety (last year)	1.11 (0.70-1.76)	.670	1.46 (0.87-2.46)	.149
Age (continuous)	0.99 (0.97-1.00)	.011	0.99 (0.97-1.01)	.206
Gender (male=ref)	1.69 (1.05-2.70)	.030	1.14 (0.69-1.90)	.608
Education (continuous)	1.01 (0.95-1.07)	.823	1.01 (0.94-1.08)	.839
Use of antidepressants and benzodiazepines	1.46 (0.93-2.29)	.101	1.55 (0.94-2.57)	.088

*Multinomial logistic regression with categorical outcomes s-SAD and SAD. Reference category is no s-SAD and no SAD.

Most importantly, ADHD symptoms and current depression (last year) were significantly positively linearly associated with GSS (see Table 4). The relationship between GSS and ADHD was analyzed in multiple ways, but the linear relationship showed a very similar R squared value to parabolic estimates.

TABLE 4. Linear regressions with continuous Global Seasonality Score (GSS) as dependent variable and clinically significant ADHD symptoms as independent variable, controlling for multiple covariates (N = 2,071)

| | GSS | |
	B (SE)	*P*
Clinically significant ADHD symptoms (no/yes)	1.81 (0.33)	<.001
Covariates:		
Current depression (last year)	1.13 (0.32)	<.001
Current anxiety (last year)	0.49 (0.26)	.058
Age (continuous)	-0.04 (0.01)	<.001
Gender (male=ref)	0.36 (0.18)	.041
Education (continuous)	-0.04 (0.03)	.105
Use of antidepressants and benzodiazepines	0.87 (0.21)	<.001

FIGURE 1 shows the results of mediation models in which the association between ADHD symptoms and GSS was studied, with two mediators: sleep duration and sleep-onset time (nights before free days). One point increase on the CAARS resulted in 0.96 minutes shorter sleep (p = .005; path a), a 0.96 minutes later sleep-onset (p = .004; path a'), and an increase of 0.14 points on the GSS (p ≤ .001; path c). A sleep-onset time that was one hour later resulted in an increase of 0.26 points on the GSS (p ≤ .001; path b'). There was a direct effect of ADHD symptoms on seasonality (c path). The mediated path was positively significant only for sleep-onset time (p ≤ .001; path a'b'), but not for sleep duration (CI = -0.003 – 0.002; path ab), explaining 14% of the relationship between ADHD symptoms and seasonality. Effect sizes of the mediation models were calculated following the methods described by Preacher and Kelly [61]. These were rather small: for sleep-onset time, $P_{m'}$ (the ratio of the indirect effect to the total effect), was 0.30 (CI = 0.010 - 0.063); and $R_{m'}$ (the ratio of the indirect effect to the direct effect), was 0.30 (CI = 0.010 - 0.067).
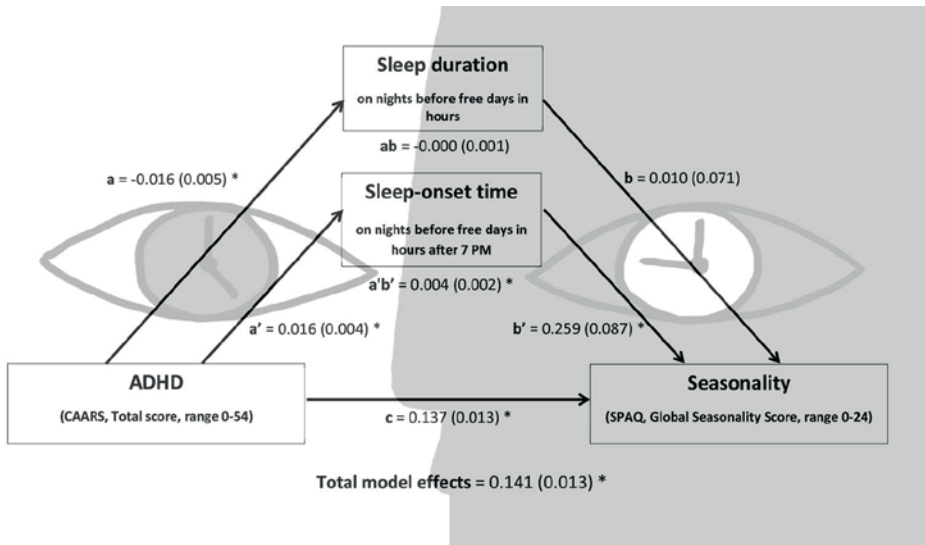
FIGURE 1. Mediation analysis of the effect of ADHD on Global Seasonality Score (GSS), mediated by both sleep-onset time and sleep duration on nights before free days, adjusted for current depression (last year), current anxiety (last year), age, sex, education, use of antidepressants and benzodiazepines (N = 1,738), total effects R^2 = 0.14.

Reported values are betas and standard errors in brackets; a = effect of ADHD on sleep duration; a' = effect of ADHD on sleep-onset time; b = effect of sleep duration on seasonality; b' = effect of sleep-onset time on seasonality; c = direct effect of ADHD on seasonality; ab = indirect effect of ADHD on seasonality through sleep duration; a'b' =indirect effect of ADHD on seasonality through sleep-onset time.

* Significant with p ≤ .001.

5. DISCUSSION

We explored the relationship between clinically significant ADHD symptoms and seasonal depressive symptoms; and the role of circadian sleep disturbances in this association. We found a significant relationship between ADHD symptoms and symptoms of both seasonal depression and circadian sleep disturbance. Furthermore, we found that seasonal depressive symptoms are also significantly increased in those with clinically significant ADHD symptoms, independent of pre-existing depression and/or anxiety. Importantly, we found that the relationship between ADHD symptoms and seasonality symptoms was partly mediated by the best indicator for circadian disturbance, sleep-onset time on nights before free days. These results indicate that chronotype, as demonstrated by sleep-onset time, mediates 14% of the relationship between ADHD symptoms and SAD symptoms. Total sleep duration did not play a significant mediating role. Hence, our study points to possible links between both circadian and seasonal rhythm disturbance in ADHD, and offers a putative explanation for these relationships.

A positive association between adult ADHD and seasonal depressive symptoms has been documented previously [7, 33, 62]. How ADHD and SAD are exactly related remains unclear, but it may be partly because of underlying biological rhythm alterations, common to both conditions. Factors that may explain this include an interplay between circadian clock genes [26], the SCN and individual responses to environmental stressors, where the circadian clock modulates biological responses to environmental factors [63]. Late sleep may be the factor common to ADHD and SAD, partly driving increased winter depression symptoms in these patients. Late sleep is associated with both shorter exposure to sunlight (because of the resulting late rising), and increased exposure to artificial light at night. These may in turn contribute to lowering mood [64]. As for SAD, biological clock disturbance may partially contribute to the development of ADHD, in individuals with heightened sensitivity to changes in light and dark [31]. In ADHD, significant disturbances in circadian clock gene expression have been shown, [31] which may result in abnormalities of endocrine secretion [20]. Indeed, melatonin secretion was delayed in 78% of a consecutive sample of ADHD adults [20, 65].

Late sleep has other far-reaching clinical implications in ADHD. Rhythm delay and chronic sleep deprivation may lead to metabolic and cardiovascular risks [66, 67]. In patients with current depression and a delayed sleep phase, ADHD should therefore be routinely assessed and treated. Furthermore, those presenting with SAD should also be screened for ADHD and circadian rhythm disturbances. Morning bright light therapy and/or evening melatonin administration may advance late sleep-onset and improve seasonal depressive symptoms [21, 29]. A recently published study of children with ADHD and insomnia, showed that both ADHD and insomnia improved following a brief behavioral intervention with benefits sustained six

months post intervention [68]. Such behavioural and psychoeducation techniques merit further exploration in adults.

Our results suggest that a delayed sleep-onset time is only partly responsible for SAD symptoms in ADHD, as the direct relationship between ADHD and seasonality remained significant even after mediation. Other factors mediating seasonality in ADHD are not completely understood. A possible explanation is that mood disorders comorbid with ADHD [69] may increase the vulnerability for seasonal depressive symptoms. Other possible mechanisms include the retinal sensitivity to light in patients with SAD, shown by Roecklein [70] and polymorphisms in genes that are related to both ADHD and SAD, but not to delayed sleep [71]. Women are affected by SAD more frequently than men [11]. Female reproductive hormones may be implicated in the relationship between ADHD and SAD. Although data are limited for ADHD, it has been hypothesized that decreased estradiol levels in the ventromedial hypothalamus are associated with SAD symptoms in women [72].

Some limitations of our study should be mentioned. The cross-sectional study design allowed for limited causal inferences on the relationship between ADHD symptoms and SAD symptoms or probable DSPS. In addition, completing the CAARS-S:SV depends on retrospective self-reporting, as ADHD starts in childhood. This may have introduced recall bias, leading to under or over reporting of ADHD symptoms [73]. Yet, the validity of retrospective ADHD symptom self-reporting has been shown to be reliable [36]. In our study, there was no collateral information provided. ADHD also has some conceptual overlaps in symptom presentation with affective disorders, such as concentration problems and daytime fatigue. However, in a recent large study of adolescents, the association between sleep and ADHD symptoms was still significant even after accounting for depressive symptoms [16]. We measured ADHD symptoms 2 years after the other parameters. Yet by definition, ADHD is a chronic condition that is expected to be relatively stable across development. Symptom stability has been shown for adult ADHD [42] and it is believed to be related to genetic factors [74], structural brain differences [75], neural connectivity [76] and environmental influences [77]. Hence we believed that the fact ADHD was measured 2 years after the other parameters would not impact on our results. We suggest that future research be structured to investigate all symptoms of interest measured at multiple time points, in order to elucidate the exact nature of the relationships between these constructs over time.

Also, although the SPAQ is primarily a screening instrument, in our study it was used as a diagnostic tool [46]. Furthermore, it discriminates poorly between SAD and s-SAD [78] and it does not always agree with longitudinal observations [79, 80]. The circadian hypothesis for SAD states that most patients have a phase-delayed sleep/wake cycle [81]. Our study did not include a biological or objective marker for the circadian rhythm, nor did we perform

parabolic analyses, as in the seminal paper by Lewy et al. [21]. These analyses would be important to elucidate in future studies. Finally, we relied on self-report for chronotype (from the MCTQ) as opposed to objective measurements such as melatonin curves or actigraphy. However, a recent study has suggested that as proxies for determining chronotype, melatonin curves and MCTQ measurements correlate well [82].

In summary, we showed that in a large sample of persons, ADHD symptoms are strongly and significantly associated with SAD symptoms, even after correction for affective disorders. Delayed sleep partly mediates the association between ADHD symptoms and SAD symptoms. It appears to be a disturbed circadian rhythm, as opposed to a short sleep duration, that is one possible pathway linking ADHD to seasonal depression. Our study extends the literature exploring relationships between ADHD and biological rhythm disturbances. There are several clinical implications of these findings. Clinicians treating ADHD should routinely check for late sleep-onset time, DSPS and SAD symptoms; and vice versa. Where these problems co-exist, sleep hygiene, behavioral interventions, pharmacological strategies involving evening melatonin administration, and early morning bright light therapy are recommended. Comprehensive treatment interventions may prevent chronic disability in this complex group of patients.

CONFLICT OF INTEREST

ROLE OF THE FUNDING SOURCE

mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute). These organizations had no further role in study design, collection, analysis and interpretation of data, writing of the report, and in the decision to submit the paper for publication.

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CHAPTER 6

THE ASSOCIATION BETWEEN METABOLIC SYNDROME, OBESITY-RELATED OUTCOMES, AND ADHD IN ADULTS WITH COMORBID AFFECTIVE DISORDERS

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1. ABSTRACT

Objective: ADHD may predispose to obesity, a metabolic syndrome component. Affective disorders are also associated with MetSyn and ADHD. This study examined whether ADHD confers any *added* risk for MetSyn and obesity-related associations in a large sample with varying stages of affective disorders.

Method: Participants included 2,303 adults from the Netherlands Study of Depression and Anxiety. Three groups were compared (controls; those with depressive/anxiety disorders without ADHD; and those with depressive/anxiety disorders and ADHD), for presence of MetSyn risk factors, body mass index and waist-hip ratio). ADHD symptoms were identified by using T-score > 65 (Conners Adult ADHD Rating Scale).

Results: Multivariable analyses were additionally adjusted for sociodemographic, lifestyle, health factors and affective disorders. Analyses showed no significant association between MetSyn, obesity-related variables and comorbid ADHD. High Inattention and Hyperactivity/ Impulsivity symptoms were not associated with MetSyn.

Conclusion: This study did not confirm that MetSyn and obesity-related parameters are increased in comorbid ADHD.

Key words: ADHD, metabolic syndrome, depression, anxiety

2.   INTRODUCTION

ADHD has major public health significance, due to its multinational prevalence of 3.4% to 4.4%, and associated educational, psychological and social impairment [1, 2]. Metabolic syndrome (MetSyn) is a combination of risk factors for cardiovascular disease and diabetes, which include obesity [3]. The criteria are at least three of the following conditions: abdominal obesity, raised levels of triglycerides and fasting glucose, low high-density lipoprotein (HDL) cholesterol and hypertension [3]. The prevalence of MetSyn has been increasing [4], and it presents a significant public health challenge.

While there is theoretical discussion of a possible link between ADHD and MetSyn [5], to our knowledge, the relationship between these two disorders has not been clearly investigated. One study found that adults with ADHD have a higher risk of body mass index (BMI) > 25, high low-density lipoprotein, and diastolic blood pressure > 90 mmHg [6]. We now outline an etiological model where comorbid ADHD is linked to an increased risk for MetSyn because of four groups of associated symptoms: psychiatric and somatic comorbidities, core ADHD symptoms and sleep disturbance.

With regard to psychiatric comorbidity, ADHD co-exists with depressive and anxiety disorders in 18% to 23% of cases [2, 7]. The most common comorbid psychiatric disorders in adult ADHD are anxiety (47%), and depressive disorders (38% [2]. In turn, affective disorders have also been associated with ADHD symptoms [8], higher BMI and obesity [9 - 11] and MetSyn [12]. Results are not uniform [13]. In practice, clinicians frequently treat ADHD in the presence of psychiatric comorbidities. The difficulty of studying the relationship between ADHD and MetSyn is that affective disorders may add to the risk of developing MetSyn.

Concerning somatic comorbidities, there are indications that a diagnosis of adult ADHD may increase the likelihood of developing chronic diseases [14, 15]. ADHD has been linked to an increased prevalence of smoking, which may partly account for this increased risk [16]. Despite the paucity of research on MetSyn and ADHD, the relationship between obesity and ADHD has been investigated [17 - 19]. Overall, the risk of obesity in ADHD for children and adults appears to be elevated, according to a recently published meta-analysis, which did control for comorbid affective disorders [20]. In children results vary with age, sex and medication status [21 - 26]. Some studies found increased BMI for ADHD children [21, 23, 24, 26 - 28]. From the literature and as reviewed by Cortese and Vincenzi [29] some studies did not account for comorbidities, lacked an ADHD diagnosis or controls [22, 24, 29 - 31]. Other studies have not found this relationship [29, 32 - 37]. Childhood psychopathology (including ADHD) has been associated with increased adult BMI [17, 38, 39] and obesity [40]. But some studies did not examine affective disorders as possible confounders [29].

In adults, most studies do show a significant relationship between ADHD and obesity [17, 19, 41 - 47], as well as overweight status [15]. Some of these studies controlled for the possible confounder of affective disorders, [17, 19, 42 - 46], but others did not [15, 41]. Adults with extreme obesity and remitted affective disorders, had a higher prevalence of ADHD [41]. ADHD was also more prevalent in obese women [47], and bariatric surgery patients, compared to the general population [42]. Impaired attention in obese participants has recently been linked to low-grade inflammation [48]. In contrast to studies confirming these associations, an epidemiological study by [49] did not show a significant relationship between persistent, lifetime, or remitted ADHD and obesity (N = 34,653) after controlling for affective disorders.

ADHD core symptoms may partly explain the relationship between adult ADHD and obesity, a component of MetSyn. These core symptoms include poor planning, impulsivity and delay aversion, which may influence food choices, resulting in a raised BMI [41, 50]. Unhealthy diet and shorter intervals between meals may be associated with MetSyn [51]. Eating at night has been associated with ADHD [52] and increased BMI [53].

Finally, sleep disturbances may also link ADHD and MetSyn and form part of the etiological model. They include late chronotype, delayed sleep-onset and shorter total sleep duration [54, 55]. Sleep disturbances have been linked to increased BMI with and without ADHD [15, 56].

In short, according to this etiological model, ADHD is associated with a combination of factors, which may all increase the risk for MetSyn. The present study is the first to examine the potential association between MetSyn, obesity-related outcomes and clinical comorbid ADHD symptoms, in a large sample with different stages of affective disorders. Our hypothesis is that according to our etiological model, adult ADHD adds to the risk for MetSyn, beyond the frequently associated affective disorders.

3. METHOD

3.1 PARTICIPANTS

Participants took part in the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal, naturalistic cohort study of 2,981 participants, aged 18 to 65 years [57]. Participants were recruited from different health care settings (community, primary and specialized mental health care) and included a group without psychiatric symptoms ("Controls") and others in different developmental stages of affective disorders. A full description of NESDA has been reported elsewhere [57]. Ethical Review Boards of all participating centers approved

the NESDA study protocol. All participants gave written informed consent at enrollment. Our sample comprised 2,307 respondents, in whom ADHD symptoms were checked at the 4-year follow-up after baseline (77.4% of total sample).

3.2 MATERIALS

3.2.1 CONNORS ADULT ADHD ADULT RATING SCALE (CAARS)

To identify those respondents with clinical ADHD symptoms, the CAARS-Self Report: Screening Version (CAARS-S:SV) was used at the 4-year follow-up assessment of NESDA. As ADHD is a lifelong condition starting in childhood [58], we believed it was acceptable to use data from the 4-year follow-up assessment for ADHD, and baseline data for other parameters. The CAARS-S:SV is a 30-item questionnaire that assesses ADHD symptoms and behaviors. The 18-item Total symptom scale identifies *Diagnostic and Statistical Manual of Mental Disorders* criteria for ADHD (Inattention [IA] and Hyperactivity/Impulsivity symptoms [H/I]; range of possible scores = 0 - 54, [59]). The 12-item ADHD Index scale identifies ADHD behaviors (range of possible scores = 0 - 36). The CAARS-S:SV uses a 4-point Likert-scale rating current behavior and problems. Ratings range from 0 *(not at all, never)* to 3 *(very much, very frequently)*. Several studies have confirmed the validity and reliability of the CAARS-S:SV [60]. For this study, the raw CAARS-S:SV scores were converted into standardized scores (*T*-scores) using age- and sex-corrected norm values [61]. The ADHD group was defined as those participants obtaining a *T*-score value of 65 or above (on either the Total symptom or Index scales), indicating clinically significant ADHD symptoms. For the analysis, we also identified a group of participants with a *T*-score of > 70 (above 98th centile) on these two scales. We calculated the CAARS-S:SV sum score (range = 0 - 90) by combining the Index with the Total score, permitting us to assess ADHD symptoms comprehensively (diagnostic criteria and behaviors). Finally, to determine specific risks of ADHD symptom domains, we analyzed high IA (cutoff *T* > 65; *n* = 165; 7.2%) and high H/I symptoms (cutoff *T* > 65; *n* = 81; 3.5%).

We chose to study only those ADHD subjects with comorbid affective disorders to estimate more accurately any added risk of ADHD for MetSyn. Of the 2,307 persons with CAARS-S:SV data, only four participants (< 1%) had ADHD without comorbid affective disorders, and these were excluded from the analysis as this group was too small to yield meaningful results. The total number used in the analyses was therefore 2,303 (77.3% of baseline sample). Two or fewer items were missing on either the Index or Total score for 108 participants (4.6%). Here, values were imputed using simple imputation.

3.2.2 COMPOSITE INTERNATIONAL DIAGNOSTIC INTERVIEW (CIDI-2.1)

Depressive disorder (major depressive disorder and dysthymia) and anxiety disorders (panic disorder, social phobia, agoraphobia or generalized anxiety disorder) were assessed at the baseline visit using the *DSM-IV* CIDI-2.1 by trained research staff [62]. The reliability and validity of the CIDI are high: Inter-rater agreements for all diagnoses are excellent [63] and test-retest reliability is also satisfactory [63]. We used lifetime diagnoses of affective disorders.

3.2.3 METSYN AND OBESITY-RELATED OUTCOMES

MetSyn was defined at baseline following the widely used adjusted Adult Treatment Panel III criteria [3]. MetSyn was considered present if three or more criteria were met: (a) waist circumference > 102 cm (men); > 88 cm (women); (b) triglycerides ≥ 1.7 mmol/l or use of medication for hypertriglyceridemia; (c) HDL cholesterol < 1.03 mmol/l (men); < 1.30 mmol/l in women, or use of medication for reduced HDL cholesterol; (d) blood pressure ≥ 130/85 mmHg, or use of antihypertensive medication; and (e) fasting plasma glucose ≥ 5.6 mmol/l, or use of anti-diabetic medication. Waist circumference was measured with a tape midway between the lower rib margin and the iliac crest over light clothing. Fasting triglycerides, HDL and glucose levels were determined using standard laboratory method. Blood pressure was defined as the average of two successive Omron monitor readings on the right arm, in a supine position. In addition, we also looked separately at the MetSyn count (number of MetSyn risk factors). BMI and waist-hip ratio (ratio of waist to hip circumferences) were used as measures of obesity-related outcomes.

3.2.4 COVARIABLES

Sociodemographic variables included age, sex and years of education. Potential confounders associated with ADHD, affective disorders, and MetSyn were also included. Lifestyle and health covariables included smoking (nonsmoker/current smoker [16], alcohol use (number of alcohol consumptions/week: Alcohol Use Disorders Identification Test [64], and physical activity, as assessed using the valid and reliable International Physical Activity Questionnaire (IPAQ, [65]). The IPAQ is a 7-item self-reporting questionnaire, which measures time spent on physical activity during the previous week. The overall energy expenditure estimate is expressed in Metabolic Equivalent Total (MET)-minutes per week. We assessed the number of self-reported chronic diseases diagnosed and under treatment, as determined during a 21-item, face-to-face interview.

The use of psychotropic, lipid altering, antihypertensive, or anti-diabetic medications in the previous month, was recorded after drug container inspection and coded according the WHO Anatomical Therapeutic Chemical (ATC) classification [66]. Antidepressants included selective serotonin reuptake inhibitors (SSRI; ATC code: N06AB), serotonin-norepinephrine reuptake

inhibitors (SNRI; N06AX16, N06AX21), tricyclics (N06AA) and tetracyclics (N06AX03, N06AX05, N06AX11). All anxiolytics identified were benzodiazepines (N03AE). Centrally acting psychostimulants (N06BA) were also identified. The use of any of these medications was rated positive if the participant had used it on at least 50% of days during the past month. We defined a variable termed *other psychotropic medications* because of their potential impact on MetSyn. This group included: corticosteroids (H02, R03BA, R03AK, D07), antiepileptics (carboxamide and fatty acid derivates; N03AF, N03AG), anticholinergics (A03AA, A03AB) and antipsychotics (N05A).

3.3   STATISTICAL ANALYSES

Means and standard deviations for continuous data, and frequencies and percentages for categorical data, were reported. Between-group comparisons (controls, depressive and anxiety disorders without ADHD: D/A - ADHD; depressive and anxiety disorders with ADHD: D/A + ADHD) were made using Chi-square and analysis of variance (ANOVA) tests. Linear regressions were performed for all continuous outcome measures, with a log-transformation for triglycerides because of extreme skewness. In the logistic regression, presence of MetSyn was the outcome variable. The ADHD predictor variables used in analyses were ADHD (yes/no), high IA (yes/no), high H/I symptoms (yes/no), and the continuous CAARS-S:SV sum score. All regression models were analyzed in a univariable regression model (Model 1), then adjusted for covariables age, sex and education (Model 2), additionally adjusted for depressive/anxiety disorders (Model 3), and finally adjusted for lifestyle and health covariables (smoking, exercise, number of chronic diseases and use of antidepressants, Model 4). Data were analyzed using SPSS for Windows (version 16; IBM Company, Chicago, Illinois, USA). Statistical significance was inferred at $p \leq .05$.

4. RESULTS

General characteristics of the three groups are described in Table 1. The groups (controls, *n* = 554; D/A - ADHD, *n* = 1,566) differed significantly in their numbers of women. Participants in the D/A + ADHD group (*n* = 183) were both significantly older, and had fewer years of education than in the other two groups. The D/A + ADHD group contained significantly more current smokers than controls. They also exercised significantly less and had three or more self-reported chronic diseases significantly more often than members of the two other groups. Apart from SSRI use, few used psychotropic drugs. While we identified 183 participants with clinical comorbid ADHD symptoms (*T* score > 65 on CAARS-S:SV scale), only three were using stimulant medication.

TABLE 1. General characteristics of the Netherlands Study of Depression and Anxiety subgroups: Controls, Depressive/Anxiety Disorders No ADHD, Depressive/Anxiety Disorders with ADHD, (n = 2,303)

	Controls n=554	D/A - ADHD n=1,566	D/A + ADHD n=183	Group Comparisons	
				Value (df)	P value
Sociodemographics					
Females, n (%)	335 (61)	1,070 (68)	122 (67)	X²(2)=11.32	.003[a]
Age in years at baseline, mean (SD)	41.0 (14.6)	42.3 (12.7)	44.9 (11.6)	F(2,2300)=6.21	.002[b,c]
Years of education, mean (SD)	12.9 (3.2)	12.3 (3.2)	11.4 (3.1)	F(2,2300)= 16.61	<.001[b,c]
Lifestyle and health					
Current smoker, n (%)	146 (26)	594 (38)	68 (37)	X²(2)=24.46	<.001[b]
Number of alcoholic drinks per week, mean (SD)	7.51 (9.41)	6.88 (10.22)	6.80 (9.85)	F(2,2279)=1.02	.362
Physical activity: MET-minutes per week (x1000), median (Inter Quartile Range)	3.08 (3.71)	2.83 (3.73)	2.35 (2.99)	Kruskal-Wallis(2)=9.42	.009[b,c]
Number of self-reported chronic diseases				X²(2)=50.09	<.001[b,c]
- None, n (%)	315 (57)	701 (45)	55 (30)		
- 1 or 2, n (%)	214 (39)	724 (46)	107 (59)		
- 3 or more, n (%)	25 (5)	141 (9)	21 (12)		
Use of psychotropics					
- Tricyclic antidepressants, n (%)	1 (0.2)	47 (3)	6 (3)	X²(2)=14.99	<.001[b]
- SSRI, n (%)	4 (0.7)	320 (21)	48 (27)	X²(2)=133.14	<.001[b]
- SNRI, n (%)	0 (0)	73 (5)	16 (9)	X²(2)=36.67	<.001[b]
- Tetracyclics, n (%)	0 (0)	34 (2)	3 (2)	X²(2)=12.20	.002[b,c]
- Benzodiazepines, n (%)	1 (0)	87 (6)	18 (10)	X²(2)=39.33	<.001[a]
- Psychostimulants, n (%)	0 (0)	3 (0)	5 (3)	X²(2)=33.10	<.001[a]
- Others[d], n (%)	0 (0)	24 (2)	7 (4)	X²(2)=16.44	<.001[a]

Note. MET = Metabolic Equivalent Total
a indicates significant difference between Controls and D/A - ADHD
b indicates significant difference between D/A + ADHD and Controls
c indicates significant difference between D/A + ADHD and D/A – ADHD
d Other psychotropics include: corticosteroids, antiepileptics, anticholinergics and antipsychotics.

Table 2 shows the differences for metabolic parameters between the three subgroups. Triglyceride levels and waist-hip ratios were significantly higher in the D/A + ADHD group compared with the other groups. Participants in the D/A + ADHD group had significantly higher mean BMI compared to controls, although the increase was slight. This finding concurred with expectations from our etiological model. None of the other metabolic parameters showed significant group differences.

Table 3 shows the logistic regression for the association between the dichotomous MetSyn variable and ADHD measures. None of the four regression models showed significant findings: Lifestyle and health factors were therefore not reported in this Table. Neither the presence of clinical ADHD symptoms nor the ADHD symptom domains were associated with an increased risk for MetSyn. This contradicted our etiological model.

Greater waist circumference, triglyceride levels, BMI and waist-hip ratios were significant in the high IA group, with the univariable Model 1 (Table 4). However, these findings disappeared in the multivariable Models 2 and 3, when adjusted for age, sex, education, depressive, and anxiety disorders. Triglyceride levels and waist-hip ratios were also significantly higher in the dichotomous ADHD group, but only with the univariable model.

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TABLE 2. Parameters of MetSyn, BMI, WHR and MetSyn Count in NESDA Subgroups: Controls, Depressive/Anxiety Disorders No ADHD, Depressive/Anxiety Disorders With ADHD, (n = 2,269)

	Controls n = 548	D/A - ADHD n = 1,541	D/A + ADHD n = 180	Group comparisons	
				Value (df)	P value
Metabolic syndrome, n (%)	104 (19)	306 (20)	43 (24)	X²(2)=2.08	.384
Metabolic syndrome components:					
- Waist circumference, mean (SD)	87.98 (13.60)	88.86 (14.18)	90.47 (16.51)	F(2,2300)=2.20	.111
- Triglycerides, mean (SD)[a]	0.03 (0.23)	0.04 (0.22)	0.09 (0.22)	F(2,2258)=4.45	.012[b,c]
- HDL cholesterol, mean (SD)	1.64 (0.43)	1.64 (0.43)	1.65 (0.46)	F(2,2250)= 0.04	.963
- Systolic blood pressure, mean (SD)	136.87(20.96)	135.39 (21.24)	134.47 (25.63)	F(2,2300)= 1.27	.282
- Diastolic blood pressure, mean (SD)	80.57 (11.88)	81.32 (11.83)	81.43 (14.54)	F(2,2300)=0.83	.437
- Fasting plasma glucose, mean (SD)	5.14 (0.87)	5.18 (1,00)	5.20 (0.96)	F(2,2254)=0.53	.587
BMI, mean (SD)	25.05 (4.65)	25.57 (4.99)	26.08 (5.00)	F(2,2300)=4.15	.016[b]
Waist Hip Ratio (WHR), mean (SD)	0.85 (0.08)	0.85 (0.08)	0.87 (0.09)	F(2,2298)=3.26	.039[b,c]
MetSyn count, mean (SD)	1.40 (1.24)	1.42 (1.28)	1.57 (1.34)	F(2,2266)=1.27	.280

Note. NESDA = Netherlands Study of Depression and Anxiety; BMI = body mass index; WHR = waist-hip ratio; HDL = high-density lipoprotein; MetSyn = metabolic syndrome.
a Logarithmically transformed triglyceride level
b. Indicates significant difference between Controls and ADHD + D/A
c Indicates significant difference between ADHD + D/A and D/A

In contrast, triglyceride levels were significantly lower in the high H/I group (multivariable models only). Several definitions of more severe ADHD symptoms were associated with a statistically significantly lower systolic blood pressure (dichotomous ADHD group: Models 2 and 3, ADHD sum score group: all three models). Similarly, lower diastolic blood pressure was significantly associated with high H/I and sum score groups (multivariable Models). There were no other significant relationships observed and hence no increased risk for MetSyn was found in the comorbid ADHD group. Overall, considering the number of associations tested, only a few significant associations emerged, which would not survive multiple testing correction. Adjustment for lifestyle and health factors did not change any of the findings and was therefore not reported.

TABLE 3. Logistic Regression for Presence of MetSyn (adjusted Adult Treatment Panel III Criteria) With Different ADHD Measures (n = 2,303)

	Metabolic Syndrome					
	Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% C.I.)	p value	OR (95% C.I.)	p value	OR (95% C.I.)	p value
ADHD dichotomous	1.32 (0.90-1.92)	.153	1.04 (0.70-1.55)	.836	1.05 (0.70-1.57)	.810
High IA	1.30 (0.85-1.98)	.223	1.08 (0.69-1.69)	.732	1.09 (0.69-1.70)	.721
High H/I	1.03 (0.55-1.91)	.936	0.85 (0.44-1.64)	.633	0.85 (0.44-1.65)	.637
ADHD Sum score	1.00 (0.99-1.01)	.649	1.00 (0.99-1.01)	.686	1.00 (0.99-1.01)	.716

Note. MetSyn = metabolic syndrome; OR = odds ratio; 95% CI = 95% confidence intervals; IA: high Inattention symptoms; H/I: high Hyperactivity/Impulsivity symptoms.
[a] Model 1: unadjusted
[b] Model 2: Model 1 plus adjusted for age, sex, education
[c] Model 3: Model 2 plus adjusted for lifetime Depressive/Anxiety disorder

A previous NESDA article showed that tricyclic antidepressant use increased the odds for MetSyn, independent of depression severity [11]. We therefore added the frequent use of tricyclics as a covariate to all multivariable regressions. However, this did not change the relationships between ADHD and any of the MetSyn parameters. The MetSyn outcome was found to be independent of the lifestyle and health factors included in Model 4. To investigate if the severity of ADHD symptoms was linked to MetSyn, we conducted an analysis using a higher cut-off for CAARS-S:SV *T* score > 70 (> 98th percentile [61]). There were only 41 participants in this group (1.8%), and no significant relationships with MetSyn were found.

TABLE 4. Linear regressions for MetSyn count and obesity-related outcomes with different ADHD measures (N=2303)

		Model 1[a]		Model 2[b]		Model 3[c]	
		β	P	β	P	β	P
MetSyn count	ADHD dichotomous	0.15	.120	-0.02	.834	-0.01	.892
	High IA	0.21	.058	0.04	.670	0.05	.634
	High H/I	-0.09	.544	-0.22	.118	-0.21	.123
	ADHD Sum score	0.00	.764	-0.00	.255	-0.00	.300
Waist circumference	ADHD dichotomous	1.84	.093	0.18	.853	-0.03	.978
	High IA	3.54	.004	1.39	.197	1.21	.265
	High H/I	-0.10	.952	-1.41	.351	-1.49	.326
	ADHD Sum score	0.02	.475	-0.01	.528	-0.03	.238
Triglycerides	ADHD dichotomous	0.05	.005	0.03	.083	0.03	.117
	High IA	0.06	.004	0.03	.078	0.03	.109
	High H/I	-0.04	.167	-0.05	.037	-0.05	.033
	ADHD Sum score	0.00	.186	0.00	.692	-0.00	.991
HDL	ADHD dichotomous	0.01	.783	0.02	.613	0.02	.508
	High IA	-0.05	.187	-0.02	.589	-0.01	.690
	High H/I	0.06	.280	0.09	.077	0.09	.070
	ADHD Sum score	0.00	.859	0.00	.328	0.00	.163
SBP	ADHD dichotomous	-1.31	.432	-3.68	.012	-3.27	.027
	High IA	1.29	.489	-1.75	.286	-1.34	.417
	High H/I	-1.58	.548	-3.02	.190	-2.84	.217
	ADHD Sum score	-0.11	.003	-0.14	.000	-0.13	.000
DBP	ADHD dichotomous	0.31	.742	-0.96	.265	-1.06	.221
	High IA	1.54	.145	0.18	.848	0.09	.930
	High H/I	-2.12	.152	-2.76	.041	-2.80	.038
	ADHD Sum score	-0.03	.121	-0.05	.017	-0.06	.005
Glucose	ADHD dichotomous	0.03	.733	-0.06	.397	-0.07	.341
	High IA	0.08	.313	-0.02	.849	-0.02	.782
	High H/I	-0.00	.983	-0.05	.668	-0.05	.649
	ADHD Sum score	0.00	.925	-0.00	.482	-0.00	.332
BMI	ADHD dichotomous	0.69	.074	0.12	.743	0.04	.915
	High IA	0.93	.031	0.50	.230	0.42	.308
	High H/I	-0.03	.957	-0.48	.411	-0.51	.382
	ADHD Sum score	0.01	.583	-0.01	.456	-0.01	.186
WHR	ADHD dichotomous	0.02	.012	0.01	.170	0.01	.236
	High IA	0.02	.001	0.01	.132	0.01	.174
	High H/I	0.01	.294	0.00	.698	0.00	.730
	ADHD Sum score	0.00	.102	0.00	.616	0.00	.957

[a] Model 1: unadjusted
[b] Model 2: Model 1 plus adjusted for age, sex, education
[c] Model 3: Model 2 plus adjusted for lifetime Depressive/Anxiety disorders

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5. DISCUSSION

We believe this is the first report which analyzes the association between all five MetSyn risk factors and adult ADHD comorbid with affective disorders. In this large-scale study, we investigated the relationship between comorbid ADHD symptoms, MetSyn and obesity-related parameters. According to our etiological model, we expected an increased risk of MetSyn among comorbid ADHD patients, but after adjusting for potential confounders, we did not find this.

We used several different definitions for ADHD. In contrast to previous studies, our wide range of comprehensive analyses and models showed few clear associations between MetSyn, obesity-related outcomes and clinical comorbid ADHD symptoms. We did find some significant, yet unexpected, associations. These were the significant relationships between lower triglyceride levels and hyperactivity symptoms; and lower blood pressure in the comorbid ADHD group, which persisted when we adjusted for sociodemographic factors, affective disorders and health/lifestyle covariables. There were no other significant associations in the adjusted models. Contrary to our expectations, lower triglyceride levels were associated with high H/I symptoms in the multivariable models. This finding contradicts results from three other studies in which raised plasma lipids in adult ADHD patients were found [6, 67, 68]. However, two of these studies were small, with $n = 15$ and $n = 72$, respectively [67, 68]. Ours may well have been a chance finding. Another surprising finding was the negative association between blood pressure and comorbid ADHD. There is little research on associations between blood pressure and ADHD. Available data deal with blood pressure changes in controlled medication studies, which may exclude patients with hypertension risk [69]. Some studies found an association between depression, anxiety and lower blood pressure [70, 71] in participants using antidepressants but without controlling for ADHD [72]. Our finding may indicate the presence of decreased blood pressure in comorbid ADHD, which again contradicts the proposed etiological model linking ADHD to MetSyn.

In terms of the ADHD domains, we found high IA symptoms to be significantly associated with several obesity-related outcomes, (univariable model only). The two large studies which examined obesity and ADHD also distinguished between symptom domains in ADHD, with varying results [46, 49]. In the first, a population-based study ($n = 15,197$), a linear association was found between the number of IA and H/I symptoms and waist circumference, BMI, and blood pressure [46]. However, in the epidemiological study where ADHD symptom domains were analyzed separately, no association was found between the number of Hyperactivity symptoms and obesity, after adjustment [49]. This concurs with our findings.

Possible biological mechanisms associating ADHD and obesity may relate to core ADHD symptoms such as poor planning, influencing diet and resulting in a raised BMI [41, 50]. Other mechanisms deserving further exploration include the intrauterine environment. Low birth weight (LBW) is associated with ADHD [73] and adult obesity [74]. Animal studies propose that LBW offspring are "programmed" to eat more because of reduced hypothalamic satiety pathways [75]. Obesity is considered a low-grade inflammatory disorder [76]. Genome-wide analysis of ADHD implicates genes involved in inflammation, and this may be another mechanism linking the two disorders. In our study, we failed to find obesity in the comorbid ADHD group, even though we analyzed waist circumference, BMI, and high-risk waist-hip ratio separately, using well-validated diagnostic methods. The studies where BMI *is* associated with ADHD may have methodological problems, including the reliance on self-reporting for measurements [19, 45, 49, 53]. In contrast, we measured height, weight and waist circumference objectively in accordance with published guidelines [77]. Raised BMI per se, as opposed to abdominal obesity, may not increase MetSyn risk as BMI cannot distinguish between lean mass and adipose tissue. Waist circumference and waist-hip ratio may give a better indication of visceral fat, the main factor in cardio-metabolic risk [78].

It is possible that associations between the risk factors for MetSyn and comorbid ADHD in adults are very difficult to detect and therefore we failed to find them, despite our large sample. The presence of comorbid affective disorders in the ADHD group may have obscured any increased risk of MetSyn. In addition, the risk of MetSyn increases with age [79]. In the comorbid ADHD group, the average age was 45 years, so it was unexpected that we found no correlation. The negative outcome of this study may also be related to the concept and definition of MetSyn, which have been questioned [80]. While cardiovascular risk factors are prone to cluster, they may not share unifying pathophysiological pathways. It is possible that not all MetSyn risk factors contribute significantly to cardiovascular diseases and diabetes, whether for the general population [81] or those with affective disorders and ADHD. Some researchers have postulated that of the five MetSyn risk factors, abdominal obesity and insulin resistance are major culprits [82]. Previously, an increased prevalence of dyslipidemia and abdominal obesity only was reported in patients with affective disorders [83]. Hence, the relative importance of each of the five MetSyn risk factors is still uncertain. We examined all MetSyn risk factors both separately and together, in order to clarify the relative contribution of each, yet we still failed to find an increased risk for MetSyn in the comorbid ADHD group. Similar to our results, the epidemiological study by Cortese, Faraone et al. (2013) also failed to find a significant association between ADHD and obesity in adults after adjustment for depression and anxiety.

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Our study, in combination with previous work, has several clinical implications. Clinicians frequently encounter ADHD comorbid with affective disorders, so where ADHD is being treated, there should be screening for affective disorders and obesity [84]. Co-existing disorders should be managed in a step-wise fashion. Affective disorders should be treated before ADHD [85]. Patients should be informed of the potential risks of developing obesity and MetSyn. However, these patients may struggle to adhere to preventive measures. Hence, clinicians should structure and target treatment with an emphasis on good sleep hygiene, balanced diet, and exercise.

Our study also has implications for future research. First, it is currently unknown whether treating co-existing affective disorders will lessen the risk for MetSyn in those with adult ADHD; this should be researched. Second, the etiological model associating ADHD with MetSyn may need to be modified. Future studies should investigate whether a "pure" ADHD group increases risk for MetSyn, as comorbid affective disorders may mask the association between ADHD and MetSyn. However, these patients are difficult to find. Ideally, it would be advisable to study MetSyn in a large ADHD cohort, with and without comorbidity. Third, ADHD may increase the risk for obesity, but not for MetSyn as a whole. The concept of MetSyn and its possible association with ADHD needs to be carefully reappraised. MetSyn is a constellation of different risk factors for cardiovascular disease and diabetes. ADHD may have a different impact on each factor and these should be individually studied.

Our study has several limitations. The cross-sectional design did not allow us to make causal inferences on the relationship between ADHD and MetSyn. As we included only those with ADHD and comorbid affective disorders, our results cannot be generalized to all populations. However, clinicians rarely encounter patients with "pure" ADHD, and the inclusion of the comorbid ADHD group could also be seen as a study strength. In addition, completing the CAARS-S:SV depends on retrospective self-reporting, as ADHD starts in childhood. This may have introduced recall bias, leading to under reporting [86]. Yet, the validity of retrospective ADHD symptom self-reporting was shown to be reliable [60]. Finally, while the CAARS-S:SV identified those with clinical symptoms of ADHD, a diagnosis of ADHD had not been made. We were not able to collect collateral information, and only three people were treated with a psychostimulant. Despite these considerations, our study extends the literature exploring relationships between comorbid ADHD and MetSyn.

6. CONCLUSION

ADHD is a complex disorder with frequent psychiatric comorbidity. In our large sample of persons, with and without affective disorders, comorbid adult ADHD did not predispose to MetSyn. ADHD symptoms were examined comprehensively including severity and the domains of IA and H/I. Obesity-related parameters such as raised BMI, high waist-hip ratio and increased Waist Circumference, were also not associated with comorbid ADHD. Hence, those with comorbid ADHD do not appear to have an added risk for MetSyn and its complications, beyond that conferred by affective disorders.

DECLARATION OF CONFLICTING INTERESTS

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CHAPTER 7

LATE SLEEP, EARLY DECLINE: LATE SLEEP IS ASSOCIATED WITH INCREASED CELLULAR AGING

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1. ABSTRACT

Study objectives: We evaluated the relationship between leukocyte telomere length (LTL) and sleep duration, insomnia symptoms, and circadian rhythm, to test whether sleep and chronobiological dysregulations are associated with cellular aging.

Methods: Data from the Netherlands Study of Depression and Anxiety cohort (N = 2,936) were used at two waves six years apart, to measure LTL. Telomeres protect DNA, shorten during the lifespan and are important biomarkers for cellular aging. LTL was assessed by qualitative polymerase chain reaction and converted into number of base pairs. Sleep parameters were sleep duration and insomnia symptoms from the Insomnia Rating Scale. Circadian rhythm variables were: an indication of the Delayed Sleep Phase Syndrome (DSPS), mid-sleep corrected for sleep debt on free days (MSFsc), sleep-onset time, and self-reported chronotype in adulthood and childhood, from the Munich Chronotype Questionnaire. Generalized estimating equation models were used to examine the associations between LTL, sleep and chronobiological factors.

Results: Indicators of delayed circadian rhythm showed a strong and consistent effect on LTL, after adjustment for sociodemographic and health indicators. Late MSFsc (B = -48.5, p =.005), late sleep-onset time (B = -32.0, p =.001), indication of DSPS (B = -71.8, p =.040) and moderately late chronotype in adulthood (B = -72.8, p =.002) were associated with significantly shorter LTL across both waves; whereas sleep duration and insomnia symptoms were not. Extremely early chronotype showed significantly longer mean LTL (B = 157.5, p =.042). No sleep or chronobiological predictors showed accelerated LTL attrition rate over 6 years.⁻

Conclusions: Individuals with indicators of delayed circadian rhythm have significantly shorter LTL, but not faster LTL attrition rates.

Keywords: aging; leukocyte telomere length; delayed sleep phase; circadian rhythms; insomnia

STATEMENT OF SIGNIFICANCE

Late sleep-onset and insomnia symptoms are common. We studied the impact of sleep duration, insomnia symptoms, and circadian rhythm dysregulation on cellular aging by measuring leukocyte telomere length (LTL) in 2,936 adults, twice over 6 years. For the first time, we show an association between delayed circadian rhythm and shorter LTL. Persons with a late self-

reported chronotype and indicators of delayed circadian rhythm had significantly shorter LTL (but not faster LTL attrition), after adjustment for sociodemographic and health indicators. Those with delayed circadian rhythm may thus be at risk for significant morbidity. Insomnia symptoms and sleep duration were not associated with shorter LTL. Extended longitudinal studies should focus on the lifetime risks associated with circadian rhythm disturbance and cellular aging.

2. INTRODUCTION

Telomeres are stretches of DNA, situated at the ends of chromosomes, much like the plastic ends on shoelaces. Telomeres cap and protect chromosomes during successive cellular divisions [1], preventing end-to-end fusion, genomic instability and base pair loss of chromosomal DNA [2]. As humans age, telomeres shorten until they become too short for further cellular division, resulting in cellular senescence [3]. Critically short telomeres may also lead to carcinogenic transformation [4]. Leukocyte telomere length (LTL), expressed as number of base pairs, has been suggested as a potential biomarker for cellular aging [3]. Telomere length and rate of shortening with aging (attrition rate) vary enormously among individuals, and even between chromosomes [5, 6]. Genetic factors contribute to approximately 64 - 70% of the variability in LTL [7] and other factors believed to play a role are lifestyle and illness [3]. Cross-sectional studies have shown that shorter LTL is associated with older chronological age [5, 6, 8], male sex [9], non North European ancestry [10], lifestyle factors such as heavy alcohol use [11], less physical activity [10, 12], psychiatric factors [13] including affective disorders, and somatic illnesses [3, 14, 15]. In terms of the telomere attrition rate, there appears to be a relationship between LTL attrition and chronological age: in the first year of life, telomere loss is very rapid [16]; it stabilizes from childhood to early adulthood; and begins to decrease in older adulthood [5, 8]. Baseline LTL appears to be an important determinant [10], as are male sex [17], greater age [8] and lifestyle factors such as cigarette smoking [12, 17] and less exercise [12]. Other determinants of accelerated LTL attrition include genetic heritability for cellular decline [7] and the presence of childhood trauma [10].

Adequate sleep is an essential requirement for health [18], yet exactly what constitutes adequate sleep duration varies within and between individuals [19]. The National Sleep Foundation, the American Academy of Sleep Medicine and the Sleep Research Society have issued a recommendation of 7 - 9 hours sleep per night for healthy adults aged 18 - 64 years, acknowledging variation in individual need [20], and emphasizing that sleeping less than this is associated with significant morbidity [19]. The research on LTL and sleep factors such as sleep duration, insomnia and obstructive sleep apnea, is scant and results are mixed. Short sleep duration has been associated with shorter LTL in older but not in middle-aged adults [21] or

middle-aged women [22], in women under 50 years [23] and in men [24]. Insomnia has also been associated with shorter LTL in people older than 70 years [25]. But long sleep duration (> 9 hours) has also been associated with shorter LTL [10, 23], hence the association between LTL and sleep duration appears to be non linear, with both shorter and longer sleep duration associated with shorter LTL. Obstructive sleep apnea syndrome and snoring are associated with shorter LTL [26, 27]. However, these sleep factors have not been examined in terms of LTL attrition over time.

Linked to sleep duration are the disorders of the circadian rhythm. The association between circadian dysregulation and LTL has not been studied in humans. In animal models however, circadian desynchronization has already been shown to trigger premature cellular aging [28] and has been suggested as a mechanism underlying telomere activity control, linking the chronobiological systems to the aging process [29]. The circadian rhythm is set by the master biological clock, situated in the suprachiasmatic nuclei in the brain. One's chronotype refers to the behavioral manifestation of underlying circadian rhythms, as evidenced by regular rising and sleep-onset times on free days (i.e. without daytime obligations) [30]. People can have early, intermediate, or late chronotype [31]. People with a late chronotype may have the persistent delayed sleep phase syndrome (DSPS), in which there is a chronic (> 3 months) pattern of delayed sleep-onset, difficulty getting to sleep at a desired earlier time, difficulty awaking in the morning, resulting in daytime sleepiness and impaired social and occupational functioning [32]. Where morning obligations exist, it may also result in chronic short sleep and sleep debt.

Disturbed circadian rhythm may result in sleep and energy metabolism disturbance, cardiovascular disease [33] and increased carcinogenesis [34, 35]. On a cellular level, disturbed circadian rhythm affects the oscillatory behaviour of many blood metabolites, which fluctuate in accordance with the circadian rhythm [36]. We hypothesize that late sleep (indicating disturbed circadian rhythm) will be a significant predictor of both short LTL and accelerated LTL attrition. We investigated whether sleep duration, insomnia and chronobiological variables were related to LTL across two time points over a six-year time period, in a large cohort of adults participating in an epidemiological study on anxiety and depression.

3. METHODS

3.1 PARTICIPANTS

Subjects participated in the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal, naturalistic cohort study of 2,981 participants at wave 1, aged 18 - 65 years. Participants were recruited from different health care settings (community, primary and specialized mental health care) and included a group without lifetime affective disorders ('controls') and others with current and remitted affective disorders. A full description of NESDA has been reported elsewhere [37]. Ethical Review Boards of all participating centers approved the NESDA study protocol and it was carried out in accordance with the latest Declaration of Helsinki. All participants gave written informed consent at enrolment after the study procedures had been fully explained. Measures in this study were taken from the baseline (wave 1), 2-year (wave 3) and 6-year (wave 5) follow-up assessments of NESDA, where the response rates were 87.1% at wave 3 (N = 2,596) and 75.7% (N = 2,256) at the wave 5. Our initial sample was 98.5% (N = 2,936) of the wave 1 group, which included those who had LTL measured and their sleep assessed. At wave 5, 1,883 participants had LTL measured (83.4% of the sample). Those who had LTL measurement at waves 1 and 5 were significantly: older, less likely to be current smokers, had more years of education, less severe anxiety and depression symptoms, shorter baseline LTL, less short and long sleep duration, and fewer insomnia symptoms than those without wave 5 LTL measurement.

3.2 SLEEP MEASURES

Sleep duration was measured at waves 1 and 5 as part of a self-report questionnaire where participants were asked to estimate the average number of hours of sleep during the past 4 weeks. Answer options were: "10 or more hours", "9 h", "8 h", "7 h", "6 h", "5 or less h." In descriptive analyses, the single variable sleep duration was sub-categorized short (≤ 6 h per night), normal (7 - 9 h per night), and long (≥ 10 h per night). This classification was followed in previous NESDA studies [10, 38, 39]. Insomnia symptoms were measured at waves 1 and 5 with the Women's Health Initiative Insomnia Rating Scale (IRS) [40] which consists of five questions addressing sleep in the last 4 weeks (trouble falling asleep, waking up during the night, early morning awakening, difficulty getting back to sleep after waking up, and sleep quality). Answers are on a 4-point scale, with a sum score ranging from 0 to 20. The IRS has good test-retest reliability and has high convergent correlation with objective actigraphy sleep measures [41]. In our sample, the IRS showed good internal validity (Cronbach's α = 0.83). In all analyses, IRS scores were dichotomized at the cut-off point of 9 or higher, which indicates clinically significant insomnia symptoms [40].

3.3 CHRONOTYPE

Chronotype was assessed with the Munich Chronotype Questionnaire (MCTQ) [30] at wave 3, which we deemed acceptable as chronotype is considered to be relatively stable over the lifespan [42]. The MCTQ is a self-report measure with questions on sleep timing on nights before work and free days, both in adulthood and 'as a child'. Subjects rated their chronotype on a 7-point Likert scale ranging from 'extremely early' to 'extremely late'. Parameters of circadian rhythm used were the continuous measures sleep-onset time on nights before free days, and the time of mid-sleep on free days corrected for sleep debt during the work week (MSFsc) [30]. For self-reported chronotype in adulthood, we created a 5-category variable, where slightly early, normal and slightly late were grouped together, forming the middle, intermediate chronotype category. The other categories were extremely early, moderately early, moderately late and extremely late. We defined "indication for DSPS" as the combination of an inability to fall asleep before 12.30 a.m. on work days, and a sleep-onset latency of 30 minutes or more on work days or a self-rating of being an extremely late chronotype in childhood or adulthood, as reported on the MCTQ.

3.4 LEUKOCYTE TELOMERE LENGTH

LTL was measured at waves 1 and 5. An extensive description of LTL assessment in our study has been reported before [43]. In summary, DNA was prepared from fasting blood samples drawn in the morning and stored in a $-20°C$ freezer. Subsequently, quantitative polymerase chain reaction (qPCR) was used to determine baseline and 6-year LT at the laboratories of Telomere Diagnostics (Menlo Park, Calif.) and the University of California, San Francisco, in 2012 and 2014, respectively. The qPCR was adapted from the published original method by Cawthorn [44]. Telomere sequence copy number (T) in each patient's sample was compared to a single-copy gene copy number (S), relative to a reference sample, where the resulting T/S ratio is proportional to mean LTL [45]. As previously described in our study [43], T/S ratios were converted into number of base pairs (bp) with the following formula: $bp = 3274 + 2413 \times ((T/S - 0.0545)/1.16)$. The wave 5 T/S ratios were adjusted relative to the wave 1 samples for systematic differences caused by different reference samples, by rerunning and comparing samples from wave 1 sample plates (N = 226, up to eight samples from each of the wave 1 plates), together with wave 5 samples. On average, the T/S ratios of the wave 5 follow-up runs were at 76% of the T/S ratios of wave 1; consequently, the follow-up T/S ratios were divided by 0.76. DNA samples were de-identified, and the laboratories that performed the assays were blind to all other measurements, and thus samples for case patients and control subjects were randomly distributed over the plates [46]. Of the entire NESDA cohort, 2,936 subjects had LTL measurement at wave 1 and 1,883 at wave 5. Of these, 1,860 had complete LTL data at both time points.

3.5   COVARIATES

Sex, age, years of education and ancestry were determined at the wave 1 interview. Smoking status was categorized as current or not current smoker. Alcohol use was defined as number of alcohol consumptions/week. The majority of published studies have found statistically significant inverse associations between Body Mass Index (BMI) and LTL [47]. Observational and experimental sleep studies have related poor sleep quality and short sleep duration to obesity and shortened LTL [48, 49]. We based our choice of BMI as a proxy for lifestyle following other studies in the NESDA cohort [46, 50]. Measured BMI (calculated by mass divided by height^2) was categorized as underweight (< 18.5), normal (18.5 – 24.9), overweight (25.0 – 30.0), and obese (> 30.0). The number of self-reported chronic diseases diagnosed and under treatment was determined with a 21-item, face-to-face interview. Physical activity was assessed with the International Physical Activity Questionnaire, expressed in Metabolic Equivalent Total (MET)-minutes per week.

We assessed depressive and anxiety disorders using the DSM-IV Composite International Diagnostic Interview (CIDI-2.1), administered by trained clinical research staff [51]. Affective disorders fell into three categories: no lifetime diagnosis; remitted (present during the lifetime history but not in the last year) and current (present in the last 6 months). Depressive and anxiety symptom severity were investigated using the Inventory of Depressive Symptomatology (IDS-SR) [52] and the Beck Anxiety Inventory (BAI) scales, [53] respectively. We excluded the four sleep-related items of the IDS-SR because of overlap with our predictor variables, resulting in a range of 0-72. The Cronbach α for this adjusted scale was 0.83 [54]. Results from this cohort showed that associations were similar for depressive and anxiety symptom severity. Due to multicollinearity we did not additionally correct for anxiety severity. We used the Childhood Trauma Interview (CTI), in which participants were asked whether they were emotionally neglected; psychologically, physically or sexually abused before the age of 16, as previously described [55]. The CTI reports the sum of the categories scored from 0 to 2 (0: never happened; 1: sometimes; 2: happened regularly); resulting in an index score between 0 and 8, which was used as a continuous variable.

3.6   STATISTICAL ANALYSES

We reported general characteristics using means and standard deviations for continuous data, and frequencies and percentages for categorical data. Correlations between predictor variables were tested. The relationship between sociodemographic factors, lifestyle, depression, childhood trauma and LTL was tested using generalized estimating equations (GEE) with LTL as outcome variable. We used unstructured GEE analyses with an exchangeable correlation structure as these take within-person correlations into account when examining multiple observations per

participant [56]. We included all participants who had an LTL and a sleep/chronobiological assessment at least once, because GEE analyses tolerate missing observations. We performed two separate GEE analyses. The first examined the cross-sectional associations between LTL and sleep/chronobiological indicator using both waves of data. Wave was defined as the within subject variable defining the order of measurements, categorized as 1 (wave 1) and 2 (wave 5). The second type of GEE analyses tested whether wave 1 measures of sleep duration and insomnia, as well as chronobiological measurements from wave 3, were associated with LTL change over time using both waves of data. Here, predictor-by-time interaction terms were added to both partially and fully adjusted models. Adding time interactions allowed us to investigate LTL attrition over 6 years. In all GEE analyses, we adjusted for age at baseline, sex and North European ancestry (partially adjusted), and additionally for current smoking, depression severity (both time-dependent) and childhood trauma index (fully adjusted), as these have previously been associated with longitudinal change in LTL in this cohort. To account for multiple testing, in all GEE analyses, the Benjamini-Hochberg false discovery rate was calculated for significant findings [57]. Data were analyzed using SPSS for Windows (version 23.0); IBM Company, Chicago, IL, USA). Statistical significance was inferred at α = .05.

4. RESULTS

4.1 DESCRIPTIVE ANALYSES

Table 1 shows the sample characteristics of the 2,936 subjects who had complete LTL measures at wave 1, those who had LTL measures at wave 5 (N = 1,883) and those who had chronobiological characteristics assessed at wave 3 (N = 2,561). LTL was 5,467 base pairs at wave 1 (SD = 617) and 5,386 base pairs at wave 5 (SD = 433), indicating a mean LTL attrition of 60 base pairs over the 6 years of the study (SD = 573).

Table 2 shows correlations between the different sleep indicators. Late sleep-onset was significantly positively correlated with later MSFsc (r = 0.46; p <.001). Longer sleep duration was significantly and negatively correlated with later sleep-onset time on free days (r = -0.37; p <.001), meaning that longer sleepers tended to fall asleep earlier. Long sleep was also positively correlated with later MSFsc (r = 0.43, p <.001), indicating that midsleep is very much affected by sleep duration. Therefore, sleep-onset time may be a more important indicator of chronotype. There was also a moderate association between self-reported chronotype in adulthood and childhood (not shown, Spearman's correlation coefficient = 0.47, p <.001), which corresponds to the description of chronotype as a lifelong trait [58].

TABLE 1. Sample characteristics at wave 1, wave 3 and wave 5

	wave 1 (N = 2,936)	wave 5 (N = 1,883)	Group comparisons Value (df)	P value
Demographics				
Age, mean (SD)	41.8 (13.1)	48.6 (12.9)	t=17.7 (4817)	<.001
Years of education, mean (SD)	12.2 (3.3)	12.9 (3.3)	7.2 (4817)	<.001
Sex, female % (n)	66.4 (1950)	65.4 (1232)	χ²=0.50(1)	.479
North European ancestry, % (n)	94.8 (2783)	96.0 (1807)	χ²=3.50(1)	.061
Lifestyle and health				
Current smoker, % (n)	38.7 (1136)	28.1 (529)	χ²=57.0(1)	<.001
No. of alcoholic drinks per week, mean (SD)	7.0 (10.0)	6.2 (8.6)	t=2.8 (4817)	.004
Body Mass Index, mean (SD)	25.6 (5.1)	23.5 (9.5)	t=9.95(4817)	<.001
- Underweight, % (n)	64 (2.2)	29 (1.5)		
- Normal, % (n)	1,489 (50.7)	802 (45.1)		
- Overweight, % (n)	889 (30.3)	599 (33.4)		
- Obese, % (n)	492 (16.8)	354 (19.8)		
No. of chronic diseases under treatment, mean (SD)	0.61 (0.88)	0.60 (0.86)	t=0.39(4817)	.678
Physical Activity (in 1000 MET-minutes p/wk), mean (SD)[a]	3.7 (3.1)	4.0 (3.4)	t=3.16(4817)	.001
Psychiatric characteristics				
IDS[b] mean (SD)	17.6 (14.3)	9.9 (17.4)	t=16.7(4817)	<.001
BAI[c] mean (SD)	11.9 (10.6)	7.9(8.7)	t=13.7(4817)	<.001
Depressive or Anxiety disorder, % (n):			χ²=529.4(5)	<.001
- No lifetime diagnosis	21.9 (644)	19.8 (388)		
- Remitted	21.1 (620)	51.4 (967)		
- Current (last 6 months)	56.9 (1672)	28.0 (528)		
Childhood trauma index, mean (SD)	0.87 (1.12)	Not measured		
Leukocyte telomere length (LTL), mean (SD)	5467.8 (617.0)	5386.8 (433.2)	t=4.97(4817)	<.001
Sleep duration[d]			χ²=10.2(5)	.006
- Short sleep duration, % (n)	24.0 (535)	25.0 (452)		
- Normal sleep duration, % (n)	70.1 (1441)	72.4 (1312)		
- Long sleep duration, % (n)	3.5 (79)	2.6 (47)		
Insomnia symptoms, % (n)	44.4 (1128)	38.2 (662)	χ²=5.23(1)	.022
Chronobiological characteristics	**wave 3** (N = 2,561)			
Sleep-onset time, free days, mean (SD)	00:10 a.m. (1h 07 min)			
Midsleep on free days (MSFsc, mean (SD)[e]	03:47 a.m. (37 min)			

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TABLE 1. Continued

	wave 1 (N = 2,936)	wave 5 (N = 1,883)	Group comparisons	
			Value (df)	P value
Indication of Delayed Sleep Phase Syndrome, % (n)	7.9 (147)			
Chronotype adult (self-reported)				
- extremely early, % (n)	2.3 (50)			
- moderately early, % (n)	18.0 (387)			
- intermediate, % (n)	48.6 (1043)			
- moderately late, % (n)	26.2 (562)			
- extremely late, % (n)	4.9 (106)			
Chronotype child (self-reported)				
- extremely early, % (n)	3.5 (74)			
- moderately early, % (n)	22.2 (473)			
- intermediate, % (n)	57.5 (1222)			
- moderately late, % (n)	14.1 (300)			
- extremely late, % (n)	2.7 (57)			

a. Metabolic Equivalent Total minutes (MET-minutes)
b. Inventory of Depressive Symptomatology (IDS)
c. Beck Anxiety Inventory (BAI)
d. Self-rated sleep duration is one variable where duration of short sleep is 6 hours or less, normal sleep is 7-9 hours, long sleep is 10 hours or more on Insomnia Rating Scale
e. MSFsc: Mid sleep on free days corrected for sleep debt on working days

4.2 CROSS-SECTIONAL ASSOCIATIONS WITH LTL

In Table 3, the GEE analyses show that LTL was significantly shorter in those with delayed circadian rhythm, in both the partially and fully adjusted models. Specifically, those with later MSFsc, later sleep-onset time or an indication of DSPS had significantly shorter LTL compared to those without these disturbances in both models (fully adjusted model: MSFsc B = -48.5, p = .005; sleep-onset time B = -32.0, p =.001; indication of DSPS B = -71.7, p =.040). Moderately late self-reported chronotype in adulthood was significantly associated with shorter LTL, compared to the reference of intermediate chronotype (B = -72.7, p =.002). In contrast, self-reported *extremely early chronotype* (in adulthood) was associated with significantly *longer* LTL (fully adjusted model: B = 157.5, p =.042, Table 3). Accounting for multiple testing using the Benjamini-Hochberg false discovery rate did not affect any of the significant findings. In contrast, GEE analyses with sleep duration, insomnia symptoms and self-reported chronotype in childhood did not show a significant relationship with LTL in either model.

TABLE 2. Pearson's intercorrelations between different sleep indicators and chronotype

	Sleep duration (free days)	Insomnia Rating Scale score (wave 1)	Insomnia Rating Scale score (wave 5)	Sleep-onset time (free days)	Midsleep on free days (MSFsc)	Indication of Delayed Sleep Phase syndrome	Chronotype adult (self-reported)
Sleep duration[a]	1						
Insomnia Rating Scale score (wave 1)	-0.25**	1					
Insomnia Rating Scale score (wave 5)	-0.24**	0.60**	1				
Sleep-onset time (free days, hours)	-0.37**	0.03	0.05*	1			
Midsleep on free days (MSFsc)[b]	0.43**	-0.17**	-0.18**	0.46**	1		
Indication of Delayed Sleep Phase Syndrome	-0.18**	0.10**	0.16**	0.37**	0.00	1	
Chronotype adult (self-reported, from early to late)	0.15**	-0.10**	-0.07*	0.46**	0.46**	0.26**	1

$*p < .01$; $**p < .001$

a. Self-rated sleep duration is one variable where duration of short sleep is 6 hours or less, normal sleep is 7-9 hours, long sleep is 10 hours or more on Insomnia Rating Scale, both at wave 1 and wave 5

b. MSFsc: Mid sleep on free days corrected for sleep debt on working days

In terms of the covariates age, sex, North European ancestry (not shown), in all GEE analyses, in both models, older age was consistently significant (p < .001). In all analyses in the fully adjusted model, significance of p < .05 was attained for female sex, except where self-reported chronotype in childhood was the predictor. Similarly, in all analyses, North European ancestry showed significance of p < .05, except where sleep-onset time was the predictor. Current smoking (not shown) attained significance of p < .05 in analyses where sleep duration, insomnia symptoms and DSPS were the predictors. Childhood trauma and depression severity were not significant in any analyses.

4.2 LTL ATTRITION RATE OVER 6 YEARS

Associations between the wave 1 measures of sleep duration and insomnia, as well as chronobiological measurements from wave 3, and repeatedly measured LTL are shown in Table 4, with group-by-time interaction terms. GEE analyses did not show any associations between sleep variables with LTL change over time. While LTL did shorten on average over the 6 years of the study, and time was significant throughout the GEE analyses, no substantial difference in slopes of LTL over time were shown for any predictor, indicated by the non-significant interaction terms. The overall picture emerging from these analyses is that chronobiological dysregulations are consistently associated with shorter LTL throughout the entire follow-up, and this relationship remains consistent over time. Figure 1 illustrates these results in four panels, in fully adjusted models. We plotted the estimated means from the GEE models of LTL at both time points according to different chronobiological predictors. For illustrative purposes, continuous predictors MSFsc and sleep-onset time were categorized into quintiles ranging from early to late. For MSFsc, there were no significant differences for any quintiles compared to the intermediate reference group. However, sleep-onset time in quintiles showed significant differences between the latest 2 quintiles and the intermediate reference quintile. An indication of DSPS at both time points showed significantly shorter mean LTL, in the fully adjusted model. From these results, it appears that the presence of DSPS accelerates cellular aging by 6 years. While moderately late chronotype showed significant significantly *shorter* means for LTL, extremely early chronotype shows significantly *longer* means for LTL (both compared to the intermediate chronotype, in adulthood). In the panel showing significant differences between mean LTL, the slopes are parallel, illustrating the finding that there was no difference in *LTL attrition rate* over time (see Table 4). In other words, wave 1 values of sleep duration and insomnia, and wave 3 measurement of chronobiological variables did not predict accelerated cellular aging.

TABLE 3. Associations across waves 1, 3 and 5 between leukocyte telomere length (LTL) and sleep and chronobiological parameters (N = 2936)*

	Mean LTL, partially adjusted				Mean LTL, fully adjusted			
	B(SE)	P value	F(df)	np²	B(SE)	P value	F(df)	np²
Sleep[a]			0.40(2,3865)	.000			0.26(2,3851)	.000
- Short sleep duration	-7.98(18.95)	.674			2.94(19.45)	.880		
- Normal sleep duration	reference				reference			
- Long sleep duration	25.17(49.05)	.608			43.55(50.38)	.387		
Insomnia symptoms[b]	-3.76(17.10)	.826	0.02(1,3837)	.000	10.29(18.80)	.584	0.55(1,3824)	.000
Chronobiology[c]								
Midsleep on free days (MSFsc, hours)[d]	-48.44(17.18)	.005+	9.24(1,3093)	.003	-48.54(17.29)	.005+	9.05(1,3083)	.003
Sleep-onset time (free days, hours)	-34.93(9.04)	<.001+	17.12(1,3181)	.005	-32.00(9.37)	.001	13.91(1,3171)	.004
Indication of Delayed Sleep Phase Syndrome	-88.77(34.17)	.009+	5.81(1,2996)	.002	-71.76(34.99)	.040+	3.80(1,2986)	.001
Chronotype adult (self-reported)			7.09(4,3441)	.008			6.62(4,3428)	.007
- extremely early	151.05(76.50)	.048+		-	157.54(77.43)	.042+	-	-
- moderately early	26.10(28.92)	.367		-	26.56(28.89)	.358	-	-
- intermediate	reference			-	reference		-	-
- moderately late	-78.83(24.04)	.001+		-	-72.79(24.03)	.002+	-	-
- extremely late	-44.95(44.98)	.318		-	-31.09(45.18)	.491	-	-
Chronotype child (self-reported)			2.03(4,3410)	.002			1.97(4,3398)	.002
- extremely early	57.05(61.80)	.356		-	68.99(62.87)	.272	-	-
- moderately early	16.60(25.51)	.515		-	17.14(25.56)	.503	-	-
- intermediate	reference			-	reference		-	-
- moderately late	-45.59(30.62)	.137		-	-40.42(30.55)	.186	-	-
- extremely late	-80.17(62.81)	.202		-	-74.30(62.60)	.235	-	-

* effect sizes are partial eta squared (np²), N of observations range = 2987 – 3866
partly adjusted: corrected for age at wave 1, female sex, North European ancestry, wave
fully adjusted: additionally corrected for current smoker, depression severity, childhood trauma
a. Self-rated sleep duration is one variable where duration of short sleep is 6 hours or less, normal sleep is 7 -9 hours, long sleep is 10 hours or more on Insomnia Rating Scale, both at wave 1 or wave 5
b. Insomnia Rating Scale score of 9 or more at wave 1 or wave 5
c. All chronobiology parameters assessed at wave 3
d. MSFsc: Mid sleep on free days corrected for sleep debt on working days
+ remained significant when applying the Benjamini-Hochberg false discovery procedure

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TABLE 4. Associations between sleep and chronobiological parameters with leukocyte telomere length (LTL) attrition, (N = 1,863)

	Mean LTL, partially adjusted		Mean LTL, fully adjusted	
	B(SE)	P value	B(SE)	P value
Sleep[a]				
- Short sleep duration	-50.61(28.76)	.078	-39.86(29.15)	.171
- Normal sleep duration	reference		reference	
- Long sleep duration	-8.74(74.33)	.906	2.49(75.53)	.974
Time	-64.25(15.13)	<.001[+]	-70.52(15.38)	<.001[+]
time*short sleep duration	34.45(28.60)	.228	32.53(28.74)	.258
time*normal sleep duration	reference		reference	
time*long sleep duration	-64.00(70.19)	.362	-72.14(72.51)	.320
Insomnia symptoms[b]	-39.30(26.12)	.132	-29.24(27.24)	.283
Time	-72.94(16.39)	<.001[+]	-78.70(16.56)	<.001
time*insomnia	37.28(25.71)	.147	34.93(25.98)	.179
Chronobiology[c]				
Midsleep on free days (MSFsc, hours)[d]	-61.84(23.11)	.007	-61.19(23.24)	.008
Time	-184.74(91.46)	.043	-185.47(92.04)	.044
time*MSFsc	30.47(23.52)	.195	28.66(23.65)	.226
Sleep-onset time (free days, hours)	-44.43(11.84)	<.001[+]	-41.60(12.08)	.001
Time	-580.27(290.44)	.046	-593.14(291.20)	.042
time*sleep-onset time	21.11(11.98)	.078	21.42(12.02)	.075
Indication of Delayed Sleep Phase Syndrome	-124.51(47.19)	.008	-109.28(48.21)	.023
Time	-68.61(15.06)	<.001[+]	-73.22(15.70)	<.001[+]
time*DSPS	77.89(52.91)	.141	81.50(53.37)	.127
Chronotype adult (self-reported)				
- extremely early	205.10(102.52)	.045	213.67(103.94)	.040
- moderately early	59.92(39.40)	.149	57.59(39.40)	.144
- intermediate	reference		reference	
- moderately late	-98.16(31.49)	.002	-89.85(31.53)	.004
- extremely late	-61.79(62.27)	.321	-46.43(62.21)	.455
Time	-60.63(18.62)	.001	-65.56(18.86)	.001
time*extremely early	-123.62(104.22)	.236	-128.93(104.55)	.217
time*moderately early	-68.52(38.97)	.079	-69.10(38.97)	.076
time*intermediate	reference		reference	
time*moderately late	43.48(30.34)	.152	37.91(30.35)	.212
time*extremely late	37.43(65.18)	.566	33.43(65.02)	.607

TABLE 4. Continued

	Mean LTL, partially adjusted		Mean LTL, fully adjusted	
	B(SE)	P value	B(SE)	P value
Chronotype child (self-reported)				
- extremely early	7.79(78.41)	.921	20.40(79.62)	.798
- moderately early	13.29(33.76)	.694	14.64(33.76)	.665
- intermediate	reference		reference	
- moderately late	-57.07(40.55)	.159	-49.53(40.71)	.224
- extremely late	-109.73(83.80)	.190	-103.06(83.04)	.215
Time	-76.59(18.09)	<.001[+]	-76.63(18.07)	<.001[+]
time*extremely early	108.85(75.60)	.357	106.72(75.49)	.157
time*moderately early	7.38(32.55)	.821	5.67(32.52)	.862
time*intermediate	reference		reference	
time*moderately late	25.96(38.61)	.501	20.65(38.94)	.596
time*extremely late	69.83(75.74)	.357	67.92(75.11)	.366

N of observations range = 2987 - 3804

partially adjusted: corrected for age at wave 1, female sex, North European ancestry, wave, group-by-time interaction

fully adjusted: additionally corrected for current smoker, depression severity, childhood trauma

a. Self-rated sleep duration is one variable where duration of short sleep is 6 hours or less, normal sleep is 7-9 hours, long sleep is 10 hours or more on Insomnia Rating Scale, at wave 1

b. Insomnia Rating Scale score of 9 or more at wave 1

c. All chronobiology parameters assessed at wave 3

d. MSFsc: Mid sleep on free days corrected for sleep debt on working days

+ remained significant when applying the Benjamini-Hochberg false discovery procedure
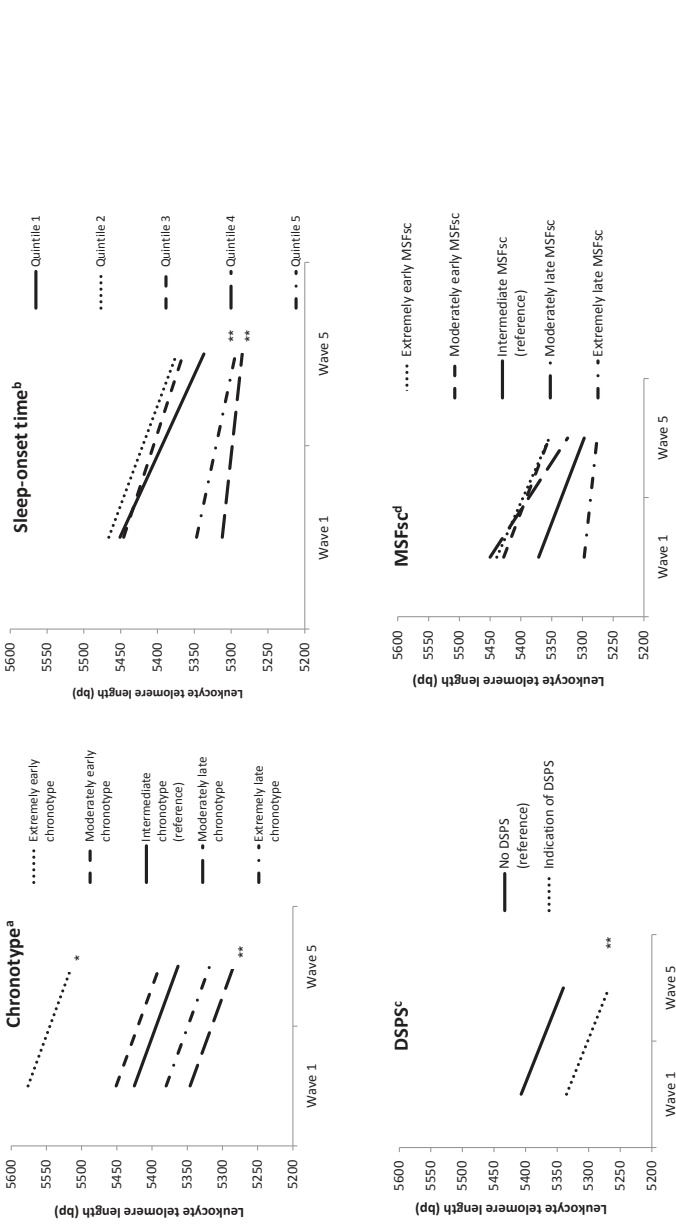
FIGURE 1. Mean leukocyte telomere length (LTL) at wave 1 and wave 5 in different indicators of circadian rhythm in adulthood

** p < .01; * p < .05, in General Estimating Equations models with time interactions (Table 4) including age, female sex, North European ancestry, current smoker, depression severity, childhood trauma, wave

a. 5 different self-reported chronotypes in adulthood where intermediate chronotype is reference

b. Quintiles of sleep-onset time (free days) from early to late: Q1: 7:35 - 11:10 p.m.; Q2: 11:13 - 11:50 p.m.; Q3 (reference): 11:53p.m. - 12:15 a.m.; Q4: 12:18 - 1:04 a.m.; Q5: 1:05 - 4:18 a.m.

c. Subjects with and without (reference) indication of Delayed Sleep Phase Syndrome (DSPS)

d. Quintiles of midsleep on free days (MSFsc) from early to late: Mid sleep on free days corrected for sleep debt on working days: Q1: 1 - 3:20 a.m.; Q2: 3:20 - 3:38 a.m.; Q3 (reference): 3:38 - 3:53 a.m.; Q4: 3:53 - 4:14 a.m.; Q5: 4:14-7:59 a.m.

5. DISCUSSION

While circadian dysregulation has been associated with many deleterious health consequences, to our knowledge there are no published data on circadian desynchronization and cellular aging. In this large-scale study, we explored the relationship between leukocyte telomere length (LTL) and measures of sleep length, insomnia symptoms and markers of circadian dysregulation. We also examined whether these factors were associated with accelerated LTL attrition over 6 years, taking into account baseline LTL [10]. Our results uniformly show that delayed circadian rhythm is associated with shorter LTL, rather than short sleep duration or insomnia. Indicators of delayed circadian rhythm included late MSFsc, later sleep-onset time (on free days), indication of DSPS and moderately late self-reported chronotype in adulthood. Cross-sectionally, these were all significantly associated with shorter LTL across wave 1 and six-year time points, after correction for wide-ranging sociodemographic and lifestyle factors. When we examined LTL attrition rate over time, there was no evidence of accelerated LTL attrition rate for any predictor over 6 years.

Our significant findings of shorter LTL in those with delayed circadian rhythm may have important consequences for health. Circadian desynchrony has been related to several psychiatric disorders (ADHD, bipolar and other mood disorders) [59 - 62]; age [63], environmental actors such as night shift work [64] and metabolic changes (obesity, cardiovascular risk) [18, 33]. Recent research has highlighted that nurses with long periods of consecutive night shifts have telomere shortening associated with an increased breast cancer risk [35]. While it is recognized that the large inter-individual variation in LTL is explained by genetic factors in over two-thirds [6, 7], research has shown that age [8], lifestyle, night shift work [35] and illness also play a role [3]. Our results further show that other possibly modifiable factors, such as delayed sleep-onset time, appear to play a significant role too. Identifying those at high risk for delayed circadian rhythm may be a first step in addressing these deleterious consequences.

The mechanism linking the circadian and metabolic systems is an intriguing area of study, and is only partially understood [reviewed in Ray, 18]. The effects of the circadian rhythm dysregulation on telomeres may relate to oxidative stress. Telomere length is associated with inflammation [65] and possibly shorten as a result of increased oxidative stress [66]. Senescent cells with shortened telomeres also show increased secretion of pro-inflammatory cytokines and extracellular matrix-degrading enzymes [1, 67]. This may drive accelerated disease progression. Hence telomeres may be active and dynamic structures, increasingly considered to be a reflection of a (long-term) state [68]. Dysregulated sleep is also associated with chronic inflammation [69], which can be seen on a cellular level [70, 71]. For example, sleep deprivation in humans adversely affects the oscillatory behavior of many blood metabolites,

which fluctuate in accordance with the circadian rhythm [36]. Healthy humans deprived of sleep show significant elevations in inflammatory activity compared to an undisturbed sleep condition [72, 73], even after one night of sleep deprivation [74]. A cumulative sleep debt frequently ensues from delayed sleep-onset in those with a late chronotype. Mechanisms underlying the shorter LTL seen in delayed circadian rhythm may include increased inflammation and circadian alteration of cellular metabolites, leading to cellular damage and premature cellular aging. Ultimately, this may increase risk for carcinogenic transformation and somatic disease [4]. In contrast, shorter LTL itself may predispose to delayed circadian rhythm: the direction of the relationship is not certain.

We also showed that persons with self-reported, extremely early chronotype in adulthood, had significantly longer LTL than those with intermediate chronotype. While these results are to be interpreted with caution, they may imply a protective role of having an early chronotype. It should be noted that this finding is preliminary. Therefore, we consider our results promising but replication in follow-up studies is required [75, 76].

While we demonstrated an association between indicators of delayed circadian rhythm and shorter LTL, we found no association between LTL, sleep duration and insomnia symptoms. As regards these associations, the literature is scant and study populations are diverse in terms of sex, age, obesity and disease status. Our results concur with the findings of some studies [21, 22, 50, 77] but contradict others [23, 24, 78]. Sleep duration was unrelated to LTL in a sample of healthy women aged between 50 and 65, although sleep *quality* was inversely related to LTL [22]. In another study among healthy women, average sleep duration was not associated with LTL after controlling for BMI, activity, stress, and smoking [77]. Among middle-aged adults, sleep duration was unrelated to LTL, but adequate sleep duration on LTL was beneficial for those 60 years of age or older [21]. Another important study investigated LTL in multiple immune cell subsets in obese adults. Here, it was poorer subjective sleep quality but not sleep duration that was associated with shorter LTL [50]. Unlike our results, short sleep duration *was* associated with shorter LTL in three studies: in women under 50 years (but not in older women) [23], in men sleeping 5 hours or less [24] and in HIV positive adults with sleep duration of at least 7 hours, measured with wrist actigraphy [78]. Although some of these findings suggest a relationship between LTL and sleep duration in the same direction (shorter LTL = shorter sleep duration), such an association might be dependent on age, sex and presence of affective disorder, or may even disappear when a circadian sleep parameter is taken into account. There is less published on insomnia and LTL, barring one negative study in breast cancer survivors with and without insomnia [79]. Another study of older adults found an association between insomnia and LTL in those aged 70 - 88 years, but not in those aged 60 - 69 years [25]. As regards mortality associated with sleep dysregulation, both persistently short (≤ 5 h) and long

sleep (≥ 9 h) were recently associated with an increased risk of all-cause mortality [80]. Night or evening shift work were also associated with increased mortality, compared to day shift [81]. The consequences of delayed sleep and circadian dysregulation of the sleep-wake cycle are severe. Our hypothesis that late sleep (indicating disturbed circadian rhythm) would be a significant predictor of short LTL was shown to be true. However, disturbed circadian rhythm did not predict accelerated LTL attrition over the 6 years of the study.

On average, mean LTL did shorten over the 6 years of the study, but this was not a substantial change, a finding extensively discussed by Révész et al. in a previous longitudinal NESDA study [10]. Our mean telomere attrition rate of 8 bp per year was lower than that described in a systematic review, (32 – 46 bp per year in longitudinal studies, and 20 – 30 bp in the larger cross-sectional studies) [8]. In short, this may be due to our relatively young and healthy study sample compared to the longitudinal studies reviewed where samples were smaller, older and had higher morbidity and mortality rates during follow-up [8]. Our sample also showed a large variation in TL change, with a considerable number of subjects who had stable TL or even lengthened their LTL, similar to those reported in earlier research, as previously outlined by Révész et al. [10].

Some questions remain to be answered concerning LTL *attrition rate* in delayed circadian rhythm. It is possible that we did not find faster LTL attrition because the 6 years of this study were too short a time period to measure any significant difference. Secondly, the timing of LTL attrition may not have been captured in our study. It may have occurred earlier in the lifespan. It is known that in the first year of life, telomere loss is very rapid [16], perhaps more so in those with circadian dysregulation, a lifelong trait [58]. Thirdly, genetic factors are known to determine cellular decline [7] and baseline LTL (which we corrected for) is an important determinant for LTL attrition [10]. Subjects with delayed circadian rhythm may be born with shorter LTL with less subsequent attrition. LTL has been postulated to be determined well before adulthood, and possibly in utero [82].

The large sample size, wide age range, variety of sleep variables and longitudinal design are strengths of this study. However, some limitations should be noted. First, we did not include an objective marker for the circadian rhythm, such as melatonin curves or actigraphy, and relied on self-report for chronotype. However, a recent study has suggested that as proxies for determining chronotype, melatonin curves [83] correlate well with MCTQ measurements. Objectively measured sleep (with polysomnography or actigraphy) is also associated with self-reported sleep duration [84]. Second, we did not measure obstructive sleep apnea, which has been linked to shorter LTL in adults [26, 27]. Third, we measured TL over 6 years, while ideally studies should track telomere length over a lifetime, hence limiting our ability to draw long-

term conclusions. Fourth, TL was measured in in leukocytes as opposed to multiple immune cell subsets. It has been shown in vivo that TL attrition occurs at different rates in different cell types, such as T-cells, B-cells and monocytes, which are also differentially distributed [85]. This may have biased our findings, making it impossible to distinguish what proportion of the lengtheners in NESDA showed actual lengthening and what proportion was a result of differences in cell composition, or alternatively, measurement error [76]. However, it has been shown that TL in leukocytes, muscle, skin and fat tissue display similar rates of age-dependent attrition [86], which suggests that results from LTL studies may be applicable to other cell types. Finally, another limitation is that we did not measure telomerase activity (the enzyme that lengthens LTL), and hence cannot comment on the telomere maintenance system, giving further insight in the dynamics of LTL [87].

In conclusion, delayed circadian rhythm rather than insomnia or altered sleep duration, seems to be deleterious for cellular aging and therefore perhaps for general health and disease status. While a genetically driven late chronotype may not be entirely modifiable, delayed sleep phase advancement can be achieved with sleep hygiene interventions [88]. Other therapies include timed evening melatonin administration, morning bright light therapy, and chronotherapy [89]. An initial open-label report suggests that delayed sleep phase advances with the use of blue light-blocking glasses in the evening [90]. Such interventions may protect against or even reverse accelerated cellular aging and the morbidity with which it is associated. However, the protective effect of such measures on cellular aging should be studied in a large prospective study. Further longitudinal studies of cellular aging in sleep and circadian dysregulation may clarify if the process of telomeric attrition can be slowed or reversed.

LIST OF ABBREVIATIONS

Leukocyte telomere length (LTL)
Netherlands Study of Depression and Anxiety (NESDA)
Women's Health Initiative Insomnia Rating Scale (IRS)
Generalized Estimating Equation (GEE)
Munich Chronotype Questionnaire (MCTQ)
Delayed Sleep Phase Syndrome (DSPS)
Mid-sleep corrected for sleep debt on free days (MSFsc)
Inventory of Depressive Symptomatology (IDS)
Beck Anxiety Inventory (BAI)
Body Mass Index (BMI)
Hour (h)

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C H A P T E R **8**

GENERAL DISCUSSION

DISCUSSION: TABLE OF CONTENTS

8

1. THESIS OUTLINE

"One cannot think well, love well, sleep well, if one has not dined well." Virginia Woolf [1]

The aim of this thesis is to explore the associations between adult Attention-Deficit/Hyperactivity Disorder (ADHD) and certain health risks. It is well known that ADHD is a highly comorbid psychiatric condition. We are interested in comorbid disturbances of biological rhythm, and whether they add any health risk to ADHD. We focus on sleep disturbances (insomnia and circadian rhythm disorders), Seasonal Affective Disorder (SAD) and the disturbed physiology associated with developing cardiovascular disease and diabetes (Metabolic Syndrome, or MetSyn).

Specifically, the research explores relationships in these areas:
1. Adult ADHD and insomnia - analyzed firstly in a literature review of recent cross-sectional and longitudinal studies. Secondly, we test the associations between ADHD, insomnia and sleep duration in a general population sample.
2. Is the well-recognized association between SAD and adult ADHD mediated by markers of circadian rhythm disturbance?
3. The relationship between MetSyn, obesity-related outcomes and adult ADHD.
4. The relationship between cellular aging and insomnia, sleep duration and circadian rhythm disturbance, using the biomarker, leukocyte telomere length (LTL).

We propose that (some of) these health risks may be explained if we view ADHD as a disorder of biological rhythm. This chapter summarizes, discusses and contextualizes the main findings of our research. Methodological considerations are discussed, as well as the potential application of the findings to clinical practice. Ideas for future research are also suggested, and the chapter ends with an overall conclusion.

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2. SUMMARY OF MAIN FINDINGS

"Everybody's individual music has its own rhythm." Yo Yo Ma [2]

Sleep disturbance in the form of insomnia, excessively short or longer sleep duration, or delayed circadian rhythm has serious consequences for health. **Chapter 2** explores the rhythm of the sleep-wake cycle in adult ADHD, focusing on insomnia in particular. We review papers written in English and published between January 2012 and March 2017. Three cross-sectional studies report a prevalence of insomnia in ADHD adults ranging from 43 - 80% (N ranges from 470 - 3,188). The deductions made from the longitudinal studies are not entirely comparable: one large twin study (N = 2,232) confirms that the persistence of ADHD into early adulthood is strongly associated with insomnia symptoms at age 18, while another study shows no association between childhood or adolescent ADHD and insomnia at age 38 (N = 1,037). Only persistent ADHD (diagnosed in childhood and present at age 18), or late-onset ADHD (diagnosed at 18 years only), are associated with insomnia at age 18. However, childhood ADHD that has remitted by age 18 shows *no* increased risk for insomnia in early adulthood. There are significant effects of insomnia as a side-effect of some pharmacological treatments for adult ADHD. Interestingly, animal studies show that chronic use of the stimulant methylphenidate delays the circadian rhythm in diurnal rodents [3 - 6]. Although not a "psychostimulant", daily atomoxetine also exerts similar effects in mice [6].

Continuing with the theme of sleep in ADHD, **Chapter 3** investigates the association between ADHD symptom severity and ADHD symptom dimensions (hyperactivity and inattention), sleep duration and insomnia symptoms. We use data from 4,618 subjects from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) cohort. Our results show two main findings. Firstly, clinically significant insomnia symptoms are strongly and consistently associated with increasing severity of ADHD symptoms, and with both the symptom dimensions of hyperactivity and inattention. Of the group with ADHD symptoms, 43% report significant insomnia symptoms (OR = 2.66, 95% CI = 1.74 - 4.07). There is also a *dose-response relationship* between insomnia symptoms and both ADHD symptom severity and the two ADHD symptom dimensions. Secondly, self-reported short sleep duration (≤ 6 hours) is significantly associated with both inattentive and hyperactive symptom dimensions, while long sleep duration (≥ 10 hours) is only associated with inattention and not with hyperactivity. Insomnia is strongly and consistently associated with adult ADHD.

We present a short letter in **Chapter 4**, which is an invited response to a comment on our ADHD and insomnia study (**Chapter 3**). We agree with the plea to view ADHD and sleep disorders as the consequence of a pro-inflammatory state. Specifically, we mention our own

work investigating the relationship between adult ADHD and MetSyn. Here, we did not find that in ADHD there are increased correlations between MetSyn and obesity-related parameters. However, obesity, which is one of the components of MetSyn, is associated with inflammation, and does have a significant association with ADHD.

The aim of **Chapter 5** is to explore the rhythm of seasonal mood changes in ADHD, and the influence of delayed circadian timing in that relationship. In 2,239 persons from the Netherlands Study of Depression and Anxiety (NESDA) cohort, the prevalence of probable SAD is three times greater in the ADHD group compared to the No ADHD group (9.9% vs. 3.3%). Regression analyses show consistently significant associations between ADHD symptoms and probable SAD, even after full adjustment (B = 1.81, p < .001). An indicator for circadian disturbance, sleep-onset time on nights before free days, is a mediator in the significant relationship between ADHD symptoms and probable SAD. Total sleep duration does not play a significant mediating role. Hence, our study points to possible links between both circadian and seasonal rhythm disturbance in ADHD.

Chapter 6 investigates whether MetSyn shows any particular "rhythm" in ADHD, using data from the NESDA cohort. We expected the prevalence of MetSyn to be increased in ADHD. After studying 2,303 adults with and without ADHD, in varying stages of depressive and anxiety disorders, we were surprised to find no added risk for MetSyn and obesity-related outcomes in adults with ADHD. A meta-analysis published subsequent to our study does show that obesity is related to ADHD in both children and adults [7]. Our analyses reveal no significant cross-sectional associations between ADHD symptoms and MetSyn, Body Mass Index (BMI) and Waist-Hip ratio. Furthermore, we show the symptom domains of high Inattention and Hyperactivity/Impulsivity are also not associated with MetSyn. Hence, this study does not confirm our hypothesis that MetSyn and obesity-related parameters are increased in ADHD.

The final study of this thesis examines the impact of disturbed sleep on the "rhythm of aging". In **Chapter 7,** our study of 2,936 subjects from the NESDA cohort shows that shorter LTL was associated with delayed circadian rhythm, rather than with short sleep duration or insomnia. Late mid-sleep corrected for sleep debt on free days (MSFsc, B = -48.5, p = .005), late sleep-onset time (B = -32.0, p = .001), indication of a Delayed Sleep Phase Syndrome (DSPS, B = -71.8, p = .040) and moderately late chronotype in adulthood (B = -72.8, p = .002) are all associated with significantly shorter LTL, even after correction for sociodemographic and lifestyle factors. However, we find no evidence of accelerated LTL attrition rate associated with any predictor over the six years of the study. Hence, a delayed circadian rhythm appears to be deleterious for cellular aging and therefore perhaps for general health status.

8

3. DISCUSSION OF MAIN FINDINGS

"I am not absentminded. It is the presence of mind that makes me unaware of everything else." G.K Chesterton [8]

3.1 HEALTH RISKS ASSOCIATED WITH ADULT ADHD: INSOMNIA

Sleep disorders are highly comorbid with ADHD and are associated with negative health consequences. Our results focus on insomnia and circadian rhythm disorders in adult ADHD. We confirm this association in our literature review (**Chapter 2**) and from our general population study, using the NEMESIS cohort (**Chapter 3**). In the latter, we show that those with clinically relevant ADHD symptoms have more than double the risk of insomnia symptoms than the group without ADHD symptoms. Clinically significant insomnia symptoms are strongly associated with increasing severity of ADHD symptoms, suggesting a dose-response relationship.

These results are consistent with both earlier studies [9 - 11] and those recently published. In a large study from the Netherlands Sleep Registry study (N = 942), the prevalence rate of insomnia in ADHD was 60.3%. Self-reported ADHD symptom severity and hyperactivity symptoms were associated with a current presence and persistent history of insomnia disorder, amongst other disorders (obstructive sleep apnea, restless legs syndrome and periodic limb movement disorder) [12]. This year, the first meta-analysis on sleep in adults with ADHD also replicated our conclusions [13]. The authors included 13 case-control studies comparing subjective and/or objective sleep parameters in adults, with and without a diagnosis of ADHD. They demonstrated that adults with ADHD had significantly worse sleep outcomes in seven out of nine subjective sleep parameters; and two out of five actigraphic parameters. (Actigraphy involves the patient wearing an 'actiwatch' on the wrist. This will continuously measure limb movement and light intensity, from which a computerized scoring system is used to determine periods of sleep and being awake). However, no significant differences were detected for polysomnographic parameters [13]. Another recent clinical study also confirmed the high prevalence of insomnia in ADHD patients [14]. Interestingly, this study compared three groups: controls, participants with comorbid ADHD + borderline personality disorder (ADHD+BPD) and those with BPD alone. Both patient groups had higher insomnia and lower sleep quality scores than control subjects. For BPD patients, sleep symptoms were mainly explained by depressive symptoms. For ADHD patients, depressive symptomatology explained only some sleep complaints, but sleep efficiency (total sleep time/total time lying ratio) was significantly worse than in ADHD + BPD patients.

CONCLUSION 1

    ADHD SYMPTOMS ARE SIGNIFICANTLY ASSOCIATED WITH INSOMNIA SYMPTOMS IN CROSS-SECTIONAL STUDIES.

3.2 HEALTH RISKS ASSOCIATED WITH ADULT ADHD: ALTERED SLEEP DURATION

In addition to insomnia, the presence of short and to a lesser extent, long sleep duration, are of significance in adults with ADHD. In a large, representative study of the U.S. adult population, the odds of having ADHD were 50% among respondents reporting ≤ 6 hours or ≥ 9 hours sleep duration, as opposed to those reporting 8 hours of sleep. Short sleep in ADHD has been attributed to increased nocturnal motor activity [15 - 18], suggesting that it is a result of ADHD. Alternatively, short sleep duration has been suggested to arise from a comorbid delayed sleep phase syndrome (DSPS) [19]. In our NEMESIS study, we found that self-reported short sleep was significantly associated with both inattentive and hyperactive symptom dimensions. Short sleep carries significant health risks, including chronic cardiovascular disease, stroke, diabetes, obesity, asthma and arthritis [12, 21]. Sleep restriction or loss also impairs performance on attention and executive control tasks [22].

Although less prevalent in our NEMESIS study, long self-reported sleep duration was also significantly associated with ADHD symptoms. We demonstrated a dose-response relationship between long sleep and both ADHD symptom severity and inattention symptoms. This implies that an (atypical) subgroup of those with long sleep may be at increased health risk on the continuum of adult ADHD. It has been shown previously that dim-light melatonin onset (the time in the evening when circulating melatonin levels reach a certain threshold) is delayed in adults who have inattentive symptoms predominantly. These adults also had longer sleep duration than those with the hyperactive/impulsive symptom dimension [23].

Why long sleep in ADHD? Long sleep does initially appear to be difficult to explain in ADHD. It may result from a comorbid disorder such as hypersomnia, affective disorder, or medical illness [19]. Long sleep also predicts all-cause mortality [24] and is associated with an increased risk for atherosclerosis [25]. This implies that an underlying metabolic dysregulation is associated with long sleep and its consequences.

<u>CONCLUSION 2</u>

WHILE SELF-REPORTED SHORT SLEEP DURATION IS SIGNIFICANTLY ASSOCIATED WITH BOTH INATTENTIVE AND HYPERACTIVE SYMPTOM DIMENSIONS, LONG SLEEP DURATION IS ONLY ASSOCIATED WITH INATTENTION AND NOT WITH HYPERACTIVITY.

3.3 SLEEP AND THE ADHD SUBTYPES: INATTENTION AND HYPERACTIVITY SYMPTOMS

To date, correlations described in the literature between sleep disturbance and the ADHD symptom dimensions have been mixed. We show a strong association between clinically significant insomnia symptoms and the symptom dimensions of hyperactivity and inattention. Similar to our results are those of Fisher et al., where insomnia was related to both ADHD subtypes [26]; and those of Yoon et al. [27], where sleep quality was worse in the inattentive subtype than in the combined group (using the Pittsburgh Sleep Quality Index). Interestingly, a recently published paper showed that patients with the inattentive subtype had *better* sleep quality than those with the combined and hyperactive/impulsive subtype ([28], using the Global Sleep Assessment Questionnaire). These different sleep instruments may account for the conflicting results. In addition, it is well recognized that the inattentive subtype is more common in adulthood than the hyperactive/impulsive subtype [29]. Several studies excluded the hyperactive/impulsive subtype from analysis as numbers were too low [9, 12, 28], which may also explain these different findings.

<u>CONCLUSION 3</u>

CLINICALLY SIGNIFICANT INSOMNIA SYMPTOMS ARE ASSOCIATED WITH INCREASING SEVERITY OF ADHD SYMPTOMS, AND WITH BOTH SYMPTOM DIMENSIONS OF HYPERACTIVITY AND INATTENTION.

3.4 HEALTH RISKS ASSOCIATED WITH ADULT ADHD: MOOD DISORDERS

Adults with ADHD have an increased risk for depression and SAD [30, 31]. In our studies, we adjust for mood and anxiety disorders, but this did not affect our findings. We confirm that SAD was three times as prevalent in the ADHD group versus the No ADHD group (**Chapter 5**). We also report significant insomnia symptoms in ADHD, which are not explained by the presence of depressive symptoms.

Comorbid affective disorders and seasonal depression worsen outcome in ADHD. Some preliminary research suggests there is increased metabolic disturbance when seasonality scores are higher. In a large Norwegian study, high self-reported seasonal changes in mood and behavior in men were associated with greater BMI and total cholesterol [32]. Women with higher seasonality scores had greater BMI, exercised less and smoked more. The SAD-ADHD comorbidity adds another layer to the health risk associated with adult ADHD.

CONCLUSION 4

> WE CONFIRM THAT SEASONAL MOOD DISTURBANCES ARE SIGNIFICANTLY ASSOCIATED WITH ADHD SYMPTOMS.

3.5   HEALTH RISKS ASSOCIATED WITH ADULT ADHD: CIRCADIAN RHYTHM DISTURBANCE

"All of western society is a little bit sleep deprived ..., I mean chronically." Michael Robash, joint recipient Nobel Prize in Physiology/Medicine 2017 [33]

8

Night-time lighting is not what it used to be. In modern times, increasing the ambient electric light exposure everywhere has delayed the circadian clock and allowed for work and social activities to occur outside of typical daytime hours, resulting in "social jet lag". Here, sleep debt is likely to occur following different sleep timing on work and free days [34]. Genetic variations in CLOCK genes also contribute to the distribution of late chronotype in the general population [34].

When the sleep-wake rhythm is disturbed, consequences are widespread and dire. Circadian rhythm desynchronization may result in cardiovascular disease [35], metabolic abnormalities, increased carcinogenesis [36] and cognitive dysfunction in adults [37, 38], older adults [39], adolescents [40] and children (reviewed in [41]). People with delayed circadian rhythm more often report poor sleep quality and frequent daytime sleepiness [34]. Students with delayed circadian rhythm achieve less well in school [42].

Circadian rhythm disturbances are highly prevalent in ADHD [43, 44]. Our work explores the associated health risks of late sleep, where SAD and ADHD co-exist (**Chapter 5**), and in terms of cellular aging (**Chapter 7**). We show that sleep-onset time (an indicator of delayed circadian rhythm) is a significant positive mediator in the relationship between ADHD symptoms and seasonality. Fourteen percent of this relationship is explained by sleep-onset time. Underlying biological rhythm alterations may be common to both conditions [45]. Late sleep-onset time in ADHD may drive the increased winter depression symptoms in these patients. On the other

hand, sleep duration is not a significant mediator. One explanation for this finding could be that late sleep-onset time is associated with both shorter exposure to sunlight (because of the resulting late rising after sunrise), and increased exposure to artificial light at night. These have been shown to worsen depressive symptoms [46]. When the days become short and dark in winter, it is believed that the biological clock becomes desynchronized, with longer sleep in SAD [45]. Hence it would be unlikely that shorter sleep duration would mediate in the association between ADHD and SAD.

CONCLUSION 5

CIRCADIAN RHYTHM DISORDERS ARE SIGNIFICANTLY ASSOCIATED WITH ADHD SYMPTOMS. DELAYED SLEEP-ONSET TIME IN ADHD PARTLY EXPLAINS THE INCREASE IN SAD SYMPTOMS IN ADULT ADHD.

3.6   HEALTH RISKS ASSOCIATED WITH ADULT ADHD: OBESITY AND METSYN

ADHD is a lifelong disorder, with associated comorbidity and dysfunction in many life domains [47]. In addition to educational, relationship and employment difficulties, many psychiatric and chronic somatic diseases disorders coexist with ADHD [19, 31]. A systematic review showed consistent associations between ADHD and migraine, asthma, celiac disease and obesity [19].

Obesity makes headlines. Worldwide, the prevalence of obesity has nearly tripled since 1975 – and most of the world's population lives in countries where overweight kills more people than underweight does [48]. Obesity also affects all ethnicities and socioeconomic groups, but to varying degrees. On a positive note, obesity is preventable and to some extent, reversible. In the last decades, obesity has been recognized as a risk factor for cardiovascular disease and diabetes [49]. According to the International Diabetes Federation, central obesity is a prerequisite for MetSyn [50]. Beyond increasing the risk of type 2 diabetes mellitus five fold, and for cardiovascular disease three fold, MetSyn is also associated with several cancers [51]. Hence understanding and preventing MetSyn are of critical public health importance.

Earlier studies from NESDA had shown that depressive disorders are associated with obesity, Waist-Hip ratio and (certain) serum lipid profiles [52]. Anxiety-related somatic arousal is strongly associated with waist circumference, triglyceride levels and blood pressure in NESDA [53]. Some other studies have associated affective disorders with higher BMI and obesity [54 - 57], but not all [58]. As we were interested in investigating risk factors associated with ADHD, and it had been clearly shown that ADHD is comorbid with affective disorders in over a fifth of

cases [31, 59], we were drawn to investigating any added risk for MetSyn in an adult ADHD population with depressive and anxiety disorders.

Underlying our hypothesis that those with adult ADHD might be at increased risk for MetSyn, are several clues from the literature connecting ADHD and obesity, and possibly MetSyn. Firstly, *maternal metabolic status* has been shown to impact on the neurophysiology of the developing child: maternal obesity increases the chance of having a child with ADHD behaviors by up to 2.8 fold [60]. Pre-pregnancy BMI and gestational weight gain are also associated with a 2-fold increased risk of ADHD symptoms in offspring [61]. Secondly, we hypothesize that the *symptoms of ADHD* may predispose to MetSyn in adults. This has been shown by others, where poor planning and impulsivity in ADHD result in poor food choices [62, 63]. Eating at night, skipping meals and sleep disturbances (all associated with ADHD) have also been linked to increased BMI [64, 65]. Neurobiological studies highlight the disturbed *dopaminergic neurotransmission* in ADHD and obesity, where pathways involving reward processing, response inhibition, and emotional regulation are implicated [66]. In animal models, perinatal exposure to maternal obesity and a high fat diet have been demonstrated to alter the dopaminergic systems in offspring [67]. Finally, both ADHD and MetSyn have been linked to alterations in circadian CLOCK genes and environmental factors (MetSyn [68 - 70], ADHD [69 - 71]). Two meta-analyses have been published, with somewhat different outcomes with regards to children [7, 72]. One showed a significant ADHD-obesity association, regardless of a number of confounding factors, including age and gender [7]. The other indicated a non-significant association in children, a possible clinically significant association in girls, and a significant association in adults [72]. For all these reasons we expected a disturbed metabolic rhythm (MetSyn) to be associated with ADHD in adults.

However, our study was negative: there was no significant association between ADHD (defined in several different ways) and MetSyn or obesity-related parameters. Despite the association between adult ADHD and obesity, we found no increased risk for MetSyn. An explanation of this finding is not easy to provide. Firstly, the associations between MetSyn and ADHD may be very difficult to detect and therefore we could not confirm our hypothesis. There may simply be no added risk for developing MetSyn in the presence of affective disorders. In addition, the concept of MetSyn is evolving and there is still discussion in the literature as to its best definition [51]. The pathophysiology underlying MetSyn is also not clear [49] and the list of risk factors may not be complete. For example, a very recent study suggests that increased blood levels of both the amino acid homocysteine and C-reactive protein (indicating systemic chronic inflammation, a pro-inflammatory state) correlate with MetSyn [73]. The authors suggest these are co-founding factors of MetSyn, although they are currently excluded from the definition. In fact, the International Diabetes Federation recommends measurements of a

pro-inflammatory state for the "platinum standard"definition of MetSyn, including C-reactive protein, inflammatory cytokines and adiponectin plasma levels [74]. Finally, MetSyn is not a disorder, but rather the clustering of risk factors which may exert *different* effects. Of the five risk factors associated with MetSyn, some authors consider obesity fundamental as it appears to precede the others [51], and others emphasize insulin resistance [75, 76]. Reaven, who first connected insulin resistance and cardiovascular risk, followed up with a critique of the contemporary criteria for MetSyn, arguing that *any* cardiovascular risk factor present in a patient should be be monitored and treated clinically if necessary [77]. Other relationships between ADHD, MetSyn and obesity-related parameters will perhaps emerge once these definitions and underlying pathophysiology are elucidated.

CONCLUSION 6

> **IN OUR STUDY, ADHD (EVEN WHEN DEFINED SEVERAL WAYS) IS NOT ASSOCIATED WITH METABOLIC SYNDROME. UNLIKE THE RESULTS OF OTHER RESEARCH, OBESITY-RELATED PARAMETERS ARE ALSO NOT SIGNIFICANTLY RELATED TO ADHD, IN A SAMPLE OF PATIENTS WITH DEPRESSION AND ANXIETY.**

3.7 HEALTH RISKS ASSOCIATED WITH LATE SLEEP-ONSET: LEUKOCYTE TELOMERE LENGTH

"Think in the morning. Act in the noon. Eat in the evening. Sleep in the night".
William Blake

Unfortunately, for many people, a stable sleep/wake rhythm is very difficult to achieve. While disturbed sleep has serious implications for somatic health, we question whether it is associated with cellular aging (**Chapter 7**). Genetic factors contribute to most of the variability in LTL (approximately 64 - 70%, [78, 79]). However, some other factors (including lifestyle and illness) may be remediated. In our final study from the NESDA cohort, we show that indicators of delayed circadian rhythm are associated with significantly shorter LTL, whereas sleep duration and insomnia symptoms are not. Further, no sleep or chronobiological predictors showed accelerated LTL attrition rate over 6 years. In other words, late sleep was consistently associated with shorter LTL throughout the entire follow-up, and this relationship remained consistent over time, with no evidence of faster LTL attrition rate. Our results point to an association of delayed circadian rhythm with shorter LTL, which is of extreme concern given the current trend towards late and shorter sleep.

CONCLUSION 7

LATE MSFSC, LATE SLEEP-ONSET TIME, INDICATION OF DSPS AND MODERATELY LATE CHRONOTYPE IN ADULTHOOD ARE ASSOCIATED WITH SIGNIFICANTLY SHORTER LTL. SLEEP DURATION AND INSOMNIA SYMPTOMS ARE NOT ASSOCIATED WITH SHORTER LTL.

CONCLUSION 8

EXTREMELY EARLY CHRONOTYPE SHOWS SIGNIFICANTLY LONGER MEAN LTL.

CONCLUSION 9

NO SLEEP OR CHRONOBIOLOGICAL PREDICTORS SHOW ACCELERATED LTL ATTRITION RATE OVER 6 YEARS.

3.8 IMPLICATIONS OF OUR STUDIES ON HEALTH RISK IN ADHD

8

CLOCK genes and inflammatory processes may be factors linking ADHD and SAD, insomnia, late sleep and shorter LTL. Single-nucleotide polymorphisms of CLOCK genes have been associated with several psychiatric disorders, although the underlying functional mechanisms for these associations remain to be clarified [71]. In ADHD, CLOCK genes are implicated [69, 70, 80 - 82], and single-nucleotide polymorphisms described [69, 70]. ADHD patients also show a flattened rhythmic expression of CLOCK genes, which is significantly correlated with increased nocturnal hyperactive behavior [82]. Conversely, CLOCK gene *disruption* elicits a hyperactive, impulsive and attention deficit-type behaviors in animal models, with a deficit in dopaminergic neurons [83].

CLOCK genes are also implicated in animal models of SAD [80, 84 - 86] and in human susceptibility to SAD ([86, 87], reviewed in [88]). Preliminary experimental research links insomnia to CLOCK gene polymorphism [89]. The role circadian CLOCK genes play in obesity and energy metabolism was recently reviewed [90]. Abnormal expression of CLOCK genes may affect brain maturation and development, sleep, cognition and mood [71].

While CLOCK genes have been implicated in the disorders we studied, a pro-inflammatory state may also play a role. Furthermore, control of the inflammatory response is also under circadian control. Chronic inflammation is a maladaptive response to tissue damage involving tissue destruction, where cytokines are released [91]. The pro-inflammatory state, or systemic low-grade inflammation, is typically defined by a two- to threefold increase in plasma concentrations of interleukin (IL)-1, tumor necrosis factor-α (TNF-α), and IL-6 [92, 93].

When levels of inflammation markers are raised, this leads to peroxidation of plasma and mitochondrial membranes, resulting in cell death by apoptosis or necrosis [94]. The master clock, located in the suprachiasmatic nucleus (SCN), controls the immune system in a rhythmic manner. Circulating immune cells and cytokines show circadian rhythmicity [95].

Recently, several studies have found evidence of a pro-inflammatory state in SAD [96, 97]. Initial research suggests that sleep dysregulation affects two systems: the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis [98]. Together, these shift basal gene expression, promoting inflammation [98]. In more detail, the SNS involvement is through enhanced β-adrenergic signaling, which in turn induces production of pro-inflammatory cytokines. As regards the HPA axis, sleep disturbance may increase release of cortisol, type 1 cytokines, and possibly inflammatory cytokines [99].

Sleep deprivation may result in obesity [100] and the increased production of pro-inflammatory cytokines ([98, 101], reviewed in [102]). Sleep duration is also implicated. Short (< 6 hours) and long (> 9 hours) nightly sleep durations have been associated with higher levels of inflammation than normal sleep (7 - 8 hours) in large epidemiological studies [103 - 105]. Both long and short sleep are considered pro-inflammatory states [104]. Conversely, inflammation can produce sleep disturbance [106].

Melatonin secretion from the pineal gland is potentially a bridge between the circadian sleep-wake rhythm and a pro-inflammatory state. The pineal gland (mainly) synthesizes melatonin, and melatonin secretion is under control by the SCN, the master biological clock. Melatonin regulates the sleep/wake cycle but also the temporal organization of immunity [107]. Melatonin is considered to be an active anti-inflammatory molecule due to its inhibition of TNF-α production [108] and its downregulation of cortisol secretion [107]. Following surgical excision of the pineal gland (pinealectomy), there is extensive immunosuppression [109]. We show that a delayed circadian rhythm is associated with shorter LTL. Senescent cells with shortened telomeres show increased secretion of pro-inflammatory cytokines [110, 111]. Shortened telomeres have also been associated with a dysregulated stress system [112] and increased oxidative stress [113]. The mechanisms underlying the shorter LTL seen in late sleep may include circadian alteration of cellular metabolites, leading to cellular damage, a pro-inflammatory state and premature cellular aging. Ultimately, this may increase risk for carcinogenic transformation and somatic disease [114]. In contrast, shorter LTL itself may predispose to delayed circadian rhythm: the direction of the relationship is not certain.

It is enticing to speculate that a pro-inflammatory state may be another pathway linking disorders of attention, seasonal depression and delayed circadian rhythm. The comorbid nature

of ADHD may increase vulnerability to inflammation and possibly, advanced cellular aging. However, this interpretation should be made with caution until confirmed by further research.

4.   METHODOLOGICAL CONSIDERATIONS

4.1   STUDY DESIGN

Of the studies we conduct, three use epidemiological data from the Netherlands Study of Depression and Anxiety (NESDA) and one from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). Three studies have a cross-sectional design, which limits the ability to make causal inferences on the relationships found. So these studies may predominantly reflect short-term associations and be more subject to reporting bias. From an epidemiological point of view, results from cross-sectional surveys are best suited to generate hypotheses. Longitudinal studies on the other hand, are more suitable to test such hypotheses. Longitudinal data may have given better insight into the relationship between ADHD and MetSyn. We use six year, longitudinal data in the LTL study, but inevitably we encountered attrition of the number of participating subjects, a built-in disadvantage of this design. Ideally, LTL studies should track telomere length over a lifetime, because of the changes in attrition rate at different ages [115].

As regards our review of insomnia in adult ADHD, the results of population-based studies may not be applicable in the clinical setting – hence both settings should ideally be investigated. In terms of the pharmacological studies reviewed, the varying designs of the trials may have affected the frequency of insomnia. Furthermore, where improvement in sleep quality was reported in these trials, it may be because medications improve daytime functioning, resulting in better sleep. Medications may have no direct (ameliorating) effect on sleep at all.

4.2   MEASUREMENT TOOLS

We use two different instruments to identify ADHD in our studies, each of which is associated with specific limitations. In the NESDA studies, the Connors Adult ADHD Adult Rating Scale – Self report: Screening Version is used, which relies on retrospective self-reporting, as ADHD starts in childhood (**Chapters 5, 6**). This may have introduced recall bias, leading to under reporting [116]. Yet studies of the concordance between childhood symptoms reported by study subjects versus informants have shown mixed results. Four studies showed that adults underestimate their childhood symptoms [117 - 120], but one study demonstrated an overestimation [121]. The NEMESIS study uses the Adult ADHD Self-Report Scale screener (ASRS, **Chapter 3**). This instrument determined hyperactivity by only two questions and there

was no assessment of impulsivity, a component of ADHD. This means that we are unable to comment on the relationship between impulsivity symptoms and insomnia/sleep duration. The ASRS does not include a question about childhood-onset of the symptoms, which is necessary for the diagnosis of ADHD [122]. A clinical diagnosis of ADHD was not made in any of our studies, nor could we collect collateral information on the diagnosis. However, in terms of the validity of self-reported symptoms, two studies revealed equally reliable reporting of attention symptoms between subjects and informants [123, 124]. Very few people in our studies (n = 3, NESDA; n = 11, NEMESIS) were treated with a psychostimulant, so we did not correct for this medication use, as we felt the results would not be meaningful. In contrast, most patients in clinical practice receive pharmacotherapy for ADHD.

We also used retrospective self-reporting to measure sleep and chronobiological variables, which introduced the same limitations.

4.3   STUDY SAMPLES

Our research used data from two large epidemiological cohorts. While this approach has enormous advantages in terms of statistical power, the samples were not specifically collected to analyze the health risks associated with ADHD, which is another limitation.

5.   POTENTIAL APPLICATION OF FINDINGS TO CLINICAL PRACTICE

ADHD is a challenging condition to treat. Its social stigma remains high and it is not considered a "real disorder" by many clinicians. It is highly comorbid with disorders of biological rhythm, which may increase morbidity.

As we show in our review of insomnia and ADHD, the pharmacological agents so frequently used in the treatment of ADHD may worsen [126] or improve insomnia symptoms [127 - 130]. Long-acting stimulant medications shorten sleep duration and delay sleep-onset, which negatively affects executive function and attention [131, 132]. Recently, two placebo-controlled studies of triple-bead Mixed Amphetamine Salts confirmed that insomnia was a frequently reported treatment-emergent adverse event [133]. When stimulant medication is administered in the late afternoon or evening (which is often necessary: ADHD is a 24 hour condition), insomnia may be exacerbated [134]. However, in clinical practice, many patients report that they can fall asleep more easily with short-acting methylphenidate taken before bedtime. This appears to relieve the rebound ADHD symptoms that occur when the medication wears off.

Stimulant treatment during the day has been shown (in an open label study) to reduce motor restlessness during sleep, and improve sleep quality [17]. Hence, before selecting treatment for an ADHD patient, clinicians should appraise comorbid sleep-related disorders using standardized instruments. Any changes in sleep patterns should be carefully monitored during therapy. Any advice for the patient should be tailored to that individual. Finally, in assessing sleep, treating physicians should note that subjective perception of sleep is not necessarily consistent with EEG indications. This mismatch is referred to as "sleep state misperception" [135] and occurs in those with primary or psychophysiological insomnia [13].

Our results suggest that those treating this complex condition should also screen for comorbid circadian rhythm sleep disorder and SAD. Insomnia should be treated with psychoeducation, sleep hygiene interventions and cognitive behavioral therapy (CBT) [136]. Adjunctive agents such as melatonin and/or light therapy may treat insomnia based on a circadian disturbance [137]. Digital health interventions (such as portable phone applications) may help adults with ADHD to monitor and adjust their sleeping patterns [138].

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Delayed circadian rhythm may have significant effects on health. While a genetically-driven late chronotype may not be entirely modifiable, delayed sleep phase advancement can be achieved with sleep hygiene interventions [139], timed evening melatonin administration and morning bright light therapy [140]. The treatment of choice in SAD is morning light therapy, first described over thirty years ago [141]. Serotonergic antidepressants such as the Selective Serotonin Reuptake Inhibitors are the main pharmacological agents used, although there is also evidence for the efficacy of the dopaminergic agent, buproprion [142]. Cognitive behavioral and other therapies and exercise have shown benefit [143].

Where mood and anxiety disorders co-exist with ADHD, MetSyn and obesity should be excluded, and all comorbidities treated. ADHD patients with comorbid disorders may struggle to adhere to good sleep hygiene, balanced diet, and exercise. They should receive therapeutic scaffolding in the form of coaching or CBT interventions, in a structured treatment program.

6.   FUTURE RESEARCH

The 20th century saw the introduction of electric lights, forever changing the spectrum, intensity and timing of ambient light exposure. The effect of light pollution on sleep quality and sleep duration is of great interest, particularly in ADHD, where there is already a vulnerability to circadian rhythm disturbance. Future research should explore the impact of artificial light

and blue-enriched, emitting light emitting diodes on ADHD symptom severity, sleep quality, metabolic parameters and cellular aging.

The role of inflammation in the biological rhythm disorders is intriguing for many reasons. Circadian rhythm has been shown to affect immune responsiveness [96]. Dim-light melatonin onset is delayed in ADHD [23, 144]. However, to our knowledge, the relationship between melatonin secretion, circadian rhythm and immune responsiveness in ADHD has not been studied. This is an area meriting further attention, for it is possible it may greatly increase understanding of auto-immune malfunction.

The importance of inflammation extends beyond the circadian rhythm. Initial research has revealed a pro-inflammatory state in SAD [95], with normalization after light therapy [96]. These findings would be interesting to confirm with further investigation. Inflammatory processes may also be a factor linking cellular aging with delayed circadian rhythm. A pro-inflammatory state appears to be common to ADHD [143, 144], SAD (summarized in [96]), metabolic [73] and sleep disorders [99, 101, 105, 106, 147] and circadian rhythm disturbance [148]. Further studies will reveal the importance of these associations and may reveal further relationships. For example, a recent study has linked a pro-inflammatory state to poor attention, MetSyn and depression [146].

ADHD is a highly comorbid condition and the presence of co-existing psychiatric disorders may confound future studies. Hence, the presence of (seasonal) affective disorders and sleep disorders should be included when studying ADHD and MetSyn. Other factors contributing to the increased vulnerability to biological rhythm disorders in ADHD deserve further clarification. Ideally, studies should be specifically designed to research the health risks associated with ADHD.

Some fascinating and recent findings stress the importance of longitudinal studies in studying ADHD and LTL, as both appear to be determined in part before birth. Older paternal age appears to predict longer telomere length in children [149]. Maternal obesity [150], depression and sleep disorders during pregnancy have been associated with an increased risk of ADHD in offspring [151]. Furthermore, both ADHD and one's chronotype can extend from childhood into old age [152, 153]. Ideally, longitudinal studies with multiple assessments over time would illuminate the course of these conditions and their associations. Similarly, the examination of other possible influences during pregnancy may increase overall understanding of the topics considered in this thesis. The following questions could possibly then be answered: what is the nature of the associations between ADHD and insomnia, SAD and delayed circadian rhythm, and are they consistent over the lifespan? Is delayed circadian rhythm consistently associated

with shortened LTL, and can this telomeric attrition be slowed or reversed? Longitudinal studies of ADHD and insomnia should consider the age-of-onset of ADHD and the persistence of ADHD symptoms, which appear to be relevant where insomnia is comorbid in early adulthood (**Chapter 2**).

We would be interested to confirm whether early chronotype truly has a protective role on cellular aging, as suggested by our findings (**Chapter 7**). Ideally in future studies, delayed circadian rhythm should also be measured with objective measures (actigraphy and polysomnography, and dim-light melatonin onset) to confirm the results obtained with self-reporting. Evidence-based management strategies may protect against or even reverse accelerated cellular aging and the morbidity with which it is associated, but these need to be studied in much more detail.

Concerning sleep problems in ADHD, several interesting questions remain unanswered by the research to date: why are ADHD and sleep disorders so frequently associated? What is the direction of causality in this relationship? The subtype dimensions of ADHD also deserve more study, in order to assist with tailored treatments where one or other predominates.

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In addition, it would be of great interest to study the rhythm of people with ADHD who do not develop sleep and seasonal affective disorders. This may shed light on protective factors and influence new treatments.

Undertaking this research on MetSyn and ADHD made us aware of the debate in the literature around the list of risk factors for MetSyn (**Chapter 6**). While MetSyn is a very useful concept, current understanding of the risk factors may not be complete [49]. Future research into MetSyn and inflammation will clarify whether inflammatory factors need to be included as risk factors [73].

Finally, we feel that future intervention studies would be of great interest. For example, our group is currently exploring the clinical benefits of improving a delayed sleep phase in adult ADHD with melatonin and/or light therapy. The outcomes measured include ADHD severity, sleep parameters, mood, appetite and indicators of metabolic disorders. Such an approach will hopefully provide preliminary guidelines for new treatments, helping future generations of patients.

7. CONCLUSION: THE RHYTHM OF ADHD

This thesis considered ADHD broadly as a disorder of circadian rhythm disturbance. Our results show that there is a close relationship between ADHD symptoms and insomnia symptoms, as well as self-reported altered sleep duration. The more severe the ADHD symptoms, the worse the insomnia symptoms. Those with adult ADHD have increased risk for one of both short and long sleep duration. Insomnia is sometimes related to ADHD treatment: different pharmacological agents used in ADHD management show varying rates of insomnia in clinical trials. We found a connection between the sleep-wake rhythm (delayed sleep-onset time) and seasonal mood changes (SAD) in adult ADHD. While adult ADHD is a highly comorbid diagnosis, ADHD symptoms were not found to be significantly related to Metabolic Syndrome. On a cellular level, we showed that indicators of delayed circadian rhythm were associated with significantly shorter Leukocyte Telomere Length. The presence of DSPS symptoms accelerated cellular aging during the 6 years over which it was observed, whereas altered sleep duration and insomnia symptoms showed no significant effect on LTL. We are on the cusp of an exciting time in biological rhythm research: in the future, these associations will surely be further studied so that more finely tailored treatment strategies can be achieved. The ADHD symptom dimensions may guide specific interventions, and could alert clinicians to recognize and treat comorbidities. With a refined understanding of the underlying pathophysiology, future ADHD patients may benefit from early recognition, deceleration of the usual advancement in these conditions and perhaps even prevention of health risks. We hope that science will strive to make this a clinical reality.

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8

CHAPTER 9

SUMMARY

SAMENVATTING

THESIS SUMMARY

Attention-Deficit /Hyperactivity Disorder (ADHD) is a neuropsychiatric developmental disorder, characterized by a lifelong pattern of inattention, impulsivity and hyperactivity. Adults with ADHD often suffer from comorbid psychiatric and somatic conditions. These may lead to a poorer quality of life, high costs for society and the need for lifelong treatment. ADHD and several of its comorbidities are associated with disturbances in biological rhythm. The circadian (24 hour) rhythm synchronizes certain behaviors, metabolic processes and physiological functions (such as heart rate and blood pressure) with particular times of the day. Most cells have an inbuilt circadian "clock", which is controlled by the master clock in the brain. The circadian clock follows the day and night rhythm, according to cycles of light and dark. This is possible through the action of CLOCK genes, which are able to turn on and off, or "express," in rhythmic patterns throughout the body, regulating physiological conditions and behavior during a 24-hour cycle.

The aim of this thesis is to explore the associations between adult Attention-Deficit/Hyperactivity Disorder (ADHD) and certain health risks. We focus on sleep disturbances (insomnia and circadian rhythm disorders), Seasonal Affective Disorder (SAD) and the disturbed physiology associated with developing cardiovascular disease and diabetes (Metabolic Syndrome, or MetSyn). Specifically, the research explores relationships in the following areas:

1. Adult ADHD and insomnia - analyzed firstly in a literature review of recent cross-sectional and longitudinal studies. Secondly, we tested the associations between ADHD, insomnia and sleep duration in a general Dutch population sample.
2. Whether the well-recognized association between winter depression (SAD) and adult ADHD is mediated by markers of circadian rhythm disturbance.
3. The relationship between MetSyn, obesity-related outcomes and adult ADHD.

We propose that some of these health risks may be explained if we view ADHD as a disorder of biological rhythm.

We also examined the relationship between cellular aging and insomnia, sleep duration and circadian rhythm disturbance, using the biomarker, leukocyte telomere length (LTL). Telomeres are short pieces of DNA found on the end of chromosomes, which shorten with aging.

To pursue these research topics, we used two Dutch population studies: the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2).

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ADHD AND INSOMNIA

Sleep disturbance in the form of insomnia, excessively short or long sleep duration, or delayed circadian rhythm has serious consequences for health. **Chapter 2** explores insomnia in adult ADHD. We review papers written in English and published between January 2012 and March 2017. Three cross-sectional studies report a prevalence of insomnia in ADHD adults ranging from 43 - 80%, independent of psychopharmacological treatment of ADHD.

The deductions made from the longitudinal studies were not entirely comparable: one large twin study confirms that the persistence of ADHD into early adulthood is strongly associated with insomnia symptoms at age 18, while another study shows no association between childhood or adolescent ADHD and insomnia at age 38.

There are significant effects of insomnia as a side-effect of some pharmacological treatments for adult ADHD.

Continuing with the theme of sleep in ADHD, **Chapter 3** uses the NEMESIS-2 data (N = 4,618) to investigate the association between self-reported insomnia symptoms and the following: ADHD symptom severity, ADHD symptom dimensions (hyperactivity and inattention), and self-reported sleep duration. Self-reported short sleep duration was defined as ≤ 6 hours and self-reported long sleep duration was defined as ≥ 10 hours. Our results indicate that more severe ADHD symptoms are significantly associated with more severe insomnia symptoms. Those with ADHD also have an increased risk for short and long sleep duration. Insomnia symptoms are also clearly and consistently associated with both inattentive and hyperactive symptom dimensions. Of the group with clinically significant ADHD symptoms, 43% report serious insomnia symptoms. There is also a *dose-response relationship* between the number of insomnia symptoms, the severity of ADHD and its two symptom dimensions. Short self-reported sleep duration is significantly associated with both inattentive and hyperactive symptom dimensions, while long sleep duration is only associated with inattention and not with hyperactivity.

We present a short letter in **Chapter 4**, which was an invited response to a comment on our ADHD and insomnia study (**Chapter 3**). We agree with the plea to view ADHD and sleep disorders as the consequence of a pro-inflammatory state.

ADHD AND SEASONAL AFFECTIVE DISORDER

The aim of **Chapter 5** was to explore the influence of delayed circadian rhythm in the relationship between ADHD and SAD. In 2,239 persons from the NESDA cohort, the prevalence of probable SAD was three times greater in the ADHD group compared to the No ADHD group. There were consistently significant associations between ADHD symptoms and probable SAD. An indicator for circadian disturbance, sleep-onset time on nights before free days, was a mediator in the significant relationship between ADHD symptoms and probable SAD. Total sleep duration did not play a significant mediating role. Our results point to a link between circadian and seasonal disorders in adult with ADHD.

ADHD AND METSYN

Chapter 6 investigated the relationship between ADHD and MetSyn, in a group of 2,303 adults from the NESDA study, with and without ADHD, in varying stages of depressive and anxiety disorders. We were surprised to find no added risk for MetSyn and obesity-related outcomes in adults with ADHD. A meta-analysis published subsequent to our study did show that obesity is related to ADHD in both children and adults. Furthermore, we showed the symptom domains of high Inattention and Hyperactivity/Impulsivity were not associated with MetSyn. Hence, this study did not confirm our hypothesis that MetSyn and obesity-related parameters are increased in ADHD.

SLEEP DISORDERS AND CELLULAR AGING

In **Chapter 7**, we investigated the influence of circadian rhythm disturbance on cellular aging, in a group of 2,936 subjects from the NESDA cohort. We showed that significantly shorter LTL was associated with several indicators of a delayed circadian rhythm, including an indication for the Delayed Sleep Phase Syndrome, even after correction for sociodemographic and lifestyle factors. However, short sleep duration and insomnia were not associated with shorter LTL. We also found no evidence of accelerated LTL attrition rate associated with any predictor, over the six years of the study.

Symptoms of a delayed sleep phase disorder were associated with an accelerated cellular aging of 6 years. Altered sleep duration and insomnia symptoms over the 6 years did not appear to affect the rate of cellular aging.

The outcome of this research implies that a delayed circadian rhythm appears to be deleterious for cellular aging and therefore perhaps for general health status.

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DISCUSSION

CLOCK genes and inflammatory processes may be factors linking ADHD and SAD, insomnia, late sleep and shorter LTL. Tissue damage can result in chronic inflammation, where cytokines are released. The central biological clock partly controls the immune response. Recently, several studies have found evidence of a pro-inflammatory state in SAD, obesity and long and short sleep duration. Melatonin secretion is potentially a bridge between the circadian sleep-wake rhythm and a pro-inflammatory state. Melatonin regulates the sleep/wake cycle and is considered to be an active anti-inflammatory molecule.

Our results suggest that those treating this complex condition should also screen for comorbid circadian rhythm sleep disorder and SAD. Insomnia should be treated with psychoeducation, sleep hygiene interventions and cognitive behavioral therapy (CBT). Adjunctive agents such as melatonin in the late afternoon or early evening, and/or light therapy may be effective in treating delayed sleep phase and SAD.

SAMENVATTING

Aandachtstekortstoornis met hyperactiviteit (Attention-Deficit/Hyperactivity Disorder, ADHD) is een neuropsychiatrische ontwikkelingsstoornis. ADHD wordt gekenmerkt door een levenslang patroon van o.a. onoplettendheid, impulsiviteit en hyperactiviteit. Volwassenen met ADHD hebben vaak comorbide psychiatrische en medische aandoeningen. Deze leiden tot een slechtere kwaliteit van leven, hoge maatschappelijke kosten en levenslange behandeling. ADHD en een aantal comorbide aandoeningen hangen samen met problemen in het biologische ritme. Ons circadiane (24-uurs) ritme zorgt ervoor dat ons gedrag, de fysiologie van bijvoorbeeld hartslag en bloeddruk, en de stofwisseling optimaal zijn afgestemd op het moment van de dag. De lichaamscellen hebben elk een circadiane klok, die worden aangestuurd door de centrale biologische klok in de hersenen. De circadiane klok volgt het ritme van dag en nacht onder invloed van de licht en donkercyclus, maar wordt ook bepaald wordt door een set van klokgenen die elkaar ritmisch aan- en uitschakelen, met een doorlooptijd van ongeveer 24 uur.

Het doel van dit proefschrift is meer inzicht te krijgen in de associaties tussen ADHD en het circadiane ritme, en of deze samenhangen met bepaalde gezondheidsrisico's. De focus ligt op slaapstoornissen, zoals insomnia of slapeloosheid, en circadiane ritmestoornissen, de seizoensgebonden stemmingsstoornis ('winterdepressie'), en verstoorde fysiologische processen die risicofactoren vormen voor hart- en vaatziekten, diabetes en het metabool syndroom. Wij onderzochten de samenhang tussen ADHD bij volwassenen en verschillende gezondheidsrisico's op de volgende gebieden:

1. ADHD en slapeloosheid: deze associatie werd eerst geanalyseerd door middel van een review van recente cross-sectionele en longitudinale studies. Daarnaast hebben we de associaties tussen ADHD, slapeloosheid en slaapduur onderzocht in de Nederlandse algemene bevolking.
2. ADHD en de seizoensgebonden stemmingsstoornis: we onderzochten of circadiane ritmestoornissen een mediërende rol spelen in de welbekende relatie tussen ADHD en de seizoensgebonden stemmingsstoornis.
3. De relatie tussen ADHD, maten voor overgewicht en obesitas, en metabool syndroom.

We veronderstellen dat sommige van deze gezondheidsrisico's verklaard zouden kunnen worden door ADHD te beschouwen als een stoornis van het biologische ritme.

We onderzochten ook de samenhang tussen cellulaire veroudering, insomnia, slaapduur en de circadiane ritmestoornis, met behulp van de biomarker Leukocyt Telomeer Lengte (LTL). Telomeren zijn de uiteinden van de chromosomen, die inkorten naarmate we ouder worden.

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Om deze vraagstellingen te onderzoeken, is er gebruikt gemaakt van gegevens van twee verschillende Nederlandse bevolkingsstudies: de Netherlands Study of Depression and Anxiety (NESDA) en de Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2).

ADHD EN SLAPELOOSHEID

Slaapstoornissen zoals slapeloosheid, een te korte of te lange slaapduur en een verstoord circadiaan ritme kunnen ernstige gevolgen hebben voor de gezondheid. **Hoofdstuk 2** gaat over slapeloosheid bij volwassenen met ADHD. We beoordeelden de Engelstalige literatuur gepubliceerd tussen januari 2012 en maart 2017. Drie cross-sectionele studies rapporteerden een prevalentie van slapeloosheid bij ADHD volwassenen, variërend van 43% tot 80%, onafhankelijk van de farmacologische behandeling van de ADHD.

De uitkomsten van de longitudinale onderzoeken waren gemengd: een grote tweelingstudie bevestigde dat het voortduren van ADHD tot op 18-jarige leeftijd sterk was geassocieerd met symptomen van slapeloosheid. Een andere studie vond geen verband tussen ADHD bij kinderen of adolescenten, en slapeloosheid op de leeftijd van 38 jaar.

Slapeloosheid is ook duidelijk geassocieerd met de behandeling van ADHD: verschillende farmacologische middelen hebben slapeloosheid als bijwerking.

Voortbouwend op het thema slaap bij ADHD, onderzochten we in **Hoofdstuk 3** binnen het NEMESIS-2 cohort (N = 4,618), de relaties tussen de ernst van de ADHD symptomen, de twee ADHD symptoom dimensies (hyperactiviteit en onoplettendheid), de zelf-gerapporteerde slaapduur en symptomen van slapeloosheid. Een korte slaapduur was gedefinieerd als ≤ 6 uur en een lange slaapduur als ≥ 10 uur.

Uit de resultaten blijkt dat hoe meer ADHD-symptomen, hoe ernstiger de symptomen van slapeloosheid zijn. Degenen met ADHD hebben een verhoogd risico op zowel een korte als een lange slaapduur. Symptomen van slapeloosheid waren ook duidelijk en consistent geassocieerd met de symptoom dimensies van zowel hyperactiviteit als onoplettendheid. Van de groep met ADHD-symptomen rapporteerde 43% een ernstige mate van slapeloosheid. Er was ook een dosis-responsrelatie tussen het aantal symptomen van slapeloosheid, de ernst van de ADHD en de ernst van de twee ADHD-symptoom dimensies. Een korte slaapduur was geassocieerd met zowel onoplettendheid als hyperactiviteit. Een lange slaapduur was alleen geassocieerd met onoplettendheid, maar niet met hyperactiviteit.

Hoofdstuk 4 is een ingezonden brief als reactie op een commentaar op onze studie over ADHD en slapeloosheid (**Hoofdstuk 3**). We zijn het met de commentatoren eens dat zowel ADHD als slaapstoornissen als de gevolgen van een pro-inflammatoire toestand beschouwd kunnen worden.

ADHD EN DE SEIZOENSGEBONDEN STEMMINGSSTOORNIS

In **Hoofdstuk 5** werd de mediërende rol van een verlaat circadiaan ritme tussen de seizoensgebonden stemmingsstoornis en ADHD bestudeerd. In de groep van 2,239 personen uit het NESDA-cohort was de prevalentie van de seizoensgebonden stemmingsstoornis driemaal verhoogd in de ADHD-groep vergeleken met de groep zonder ADHD. Er was een consistente associatie tussen ADHD-symptomen en indicatoren voor de seizoensgebonden stemmingsstoornis. De inslaapduur op nachten vóór vrije dagen, een indicator voor een verlate slaapfase, was een mediator in de relatie tussen ADHD-symptomen en de seizoensgebonden stemmingsstoornis. De totale slaapduur had geen mediërende rol. Vandaar dat onze studie wijst op een verband tussen circadiane en seizoensgebonden stoornissen bij volwassenen met ADHD.

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ADHD EN HET METABOOL SYNDROOM

Hoofdstuk 6 onderzocht de relatie tussen ADHD en het metabool syndroom in een groep van 2,303 volwassenen in de NESDA studie met en zonder ADHD, met verschillende stadia van depressie en angststoornissen. In tegenstelling tot onze verwachting was er geen verhoogd risico voor het metabool syndroom noch voor aan obesitas gerelateerde parameters bij volwassenen met ADHD. Een meta-analyse kort na ons onderzoek gepubliceerd, had juist aangetoond dat obesitas geassocieerd is met ADHD bij zowel kinderen als volwassenen. Ook waren de symptoom dimensies van onoplettendheid en hyperactiviteit/impulsiviteit niet geassocieerd met het metabool syndroom. Dit onderzoek kon dus onze hypothese dat metabool syndroom en obesitas gerelateerde parameters vaker voorkomen bij ADHD, niet bevestigen.

SLAAPSTOORNISSEN EN CELLULAIRE VEROUDERING

Hoofdstuk 7 laat de invloed zien van circadiane ritmestoornissen op cellulaire veroudering binnen een groep van 2,936 personen uit het NESDA-cohort. Een significant kortere LTL hing samen met diverse indicatoren voor een verlaat circadiaan ritme, waaronder een verlate slaapfase, ook na correctie voor sociodemografische en leefstijlfactoren. Een korte slaapduur of slapeloosheid hadden geen invloed op de LTL. Er waren echter geen aanwijzingen voor een versnelde LTL verkorting onder invloed van enige predictor gedurende de 6 jaar van de studie.

Symptomen van een verlate slaapfase waren geassocieerd met het equivalent van een versnelde cellulaire veroudering van 6 jaar. Veranderde slaapduur over een duur van 6 jaar en symptomen van slapeloosheid hadden geen significant effect op kortere LTL.

Dit onderzoek impliceert dat een verlate slaapfase schadelijke effecten kan hebben op cellulaire veroudering, en mogelijk op de gezondheid in het algemeen.

DISCUSSIE

Klokgenen en inflammatie kunnen de verbinding vormen tussen ADHD, de seizoensgebonden stemmingsstoornis, slapeloosheid, de verlate slaapfase, en kortere LTL. Weefselbeschadiging kan leiden tot chronische ontsteking, waarbij cytokines worden afgescheiden. De centrale biologische klok in de hersenen bestuurt gedeeltelijk ook de immuunrespons. Onlangs hebben verschillende onderzoeken aangetoond dat een pro-inflammatoire toestand een rol speelt bij de seizoensgebonden depressie, obesitas, en bij een zowel lange als korte slaapduur. De melatoninesecretie vormt een mogelijke verbinding tussen de verlate slaapfase en een pro-inflammatoire toestand. Melatonine is een biomarker voor de slaap/waak cyclus, en speelt een belangrijke rol in het immuunsysteem als ontstekingsremmer.

Clinici die ADHD behandelen zouden ook moeten screenen op comorbide slaapstoornissen, een verlaat circadiaan ritme en seizoensgebonden depressie. Slapeloosheid kan worden behandeld met psychoeducatie, slaaphygiëne-interventies en cognitieve gedragstherapie. Melatonine in de late middag of vroege avond en/of lichttherapie in de ochtend kunnen effectief zijn voor de verlate slaapfase en de seizoensgebonden depressie.

CHAPTER 10

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DANKWOORD / ACKNOWLEGEMENTS

I remember a beautiful, sunny weekend in the Franschhoek valley in November 2012, near Cape Town, where I first met Sandra Kooij. During that congress, between whale watching and discussing the emotional impact of ADHD, our friendship and colloboration began. San, from the outset, your warmth, wisdom and expertise were magnetic. Two years later, I had moved with my family to the Netherlands to embark on this project. Throughout the last three and a half years of working with you here, I have gained enormously. Veel dank dat je vertrouwen in mij hebt gehad, voor je ondersteuning en voor alles dat je me geleerd hebt. Onze band reikt veel verder dan je internationale status in de psychiatrie. Ik koester je vrijgevigheid, je passie, je humor, je kunst en je joie de vivre.

This thesis combines a quartet of topics, and weaves them together into one whole. Similarly, I have encompassed four areas in my thanks. I appreciate the support I have received while doing the PhD, I thank those who tolerated our leaving South Africa to embark on this adventure and the welcome from so many people in the Netherlands. Finally, I have deep gratitude for the medical care I received during the course of the project.

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ABOUT THE AUTHOR

Dora Wynchank was born on April 3, 1968, in New York, USA. As a young child, she immigrated with her family to South Africa where she attended school in Cape Town. She also lived for two years as a teenager in Bordeaux, France. After returning to South Africa, she studied medicine at the University of Cape Town (before the age of cell phones). She was active in student politics and was student president of SHAWCO, the UCT Students' Health and Welfare Centers' Organization. It was at the University of the Witwatersrand in Johannesburg, South Africa that she specialized in Psychiatry. From 2000 to 2014, she worked as a consultant psychiatrist in state hospitals and private practice. During this time, she conducted a study on an animal model of Obsessive-Compulsive Disorder and undertook some pharmacological research. She served on the Executive Committee of the Society of Psychiatrists of South Africa and as a Director of the patient lobby group, SADAG (South African Depression and Anxiety Support Group). In August 2014, she moved with her family to The Netherlands to begin her PhD at the Vrije Universiteit, Amsterdam. She was based at the Expertise Center Adult ADHD, The Hague. During the last 4 years, she has presented work during symposia and poster sessions at several national and international congresses.

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2018

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