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).
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.
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.