GENERAL INTRODUCTION
Although Attention-Deficit/Hyperactivity Disorder (ADHD) was originally considered a developmental disorder occurring only in childhood, it is now well known that ADHD continues into adolescence, adulthood and even into old age [1]. Despite the recognition of the persistence of the disorder into adulthood, there is much less research about ADHD in adults than in children [2]. However, it is evident that adult ADHD is a prevalent and disabling disorder resulting in enormous societal costs [3, 4]. Taking this into consideration, more insight into the etiology, comorbidity and consequences of ADHD symptoms in adulthood is crucial in order to develop appropriate treatment and preventative strategies.

**Diagnosis**

ADHD is a neuropsychiatric condition defined by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development [5]. According to the Diagnostic and Statistical Manual-5 (DSM-5), ADHD can be categorized into three different presentations: the inattentive (I), the hyperactive/impulsive (HI), and the combined (C) presentation type. This presentation classification is based on the presence of six or more symptoms of hyperactivity-impulsivity (HI) or inattention (I), or both (C) in children. Adults and adolescents (aged 17 years and older) are required to present with a minimum of five (rather than six) symptoms. ADHD has a childhood onset, which means that several symptoms have to be present prior to age 12 years. There must be clear evidence that the symptoms interfere with functioning in two or more settings (such as at home, school or work) [5].

**Prevalence**

Approximately 4 to 12% of children suffer from the condition globally [6, 7]. Adults seem to be affected to a lesser extent; in a cross-national epidemiological study, the estimated prevalence was 2.8% [8]. In the Netherlands, the prevalence rate is estimated to be 2.9% in children [9], and varies between 1 to 5% in adults [8, 10]. There seems to be a preponderance of boys compared to girls in children [11]. However, this may be due to referral bias, since girls more often have the inattentive type with less disruptive behavior and thus lower symptom counts [12]. In adults, results are more conflicting. Some studies have found a male preponderance [13, 14], while others have found no gender difference [15-17]. In about two-thirds of the childhood cases, ADHD has been shown to persist into adulthood [18]. In general, there is an age-dependent decline of hyperactivity/impulsive symptoms, while the inattention symptoms remain stable over time [19].
Chapter 1

Comorbidity
Three quarter of the adults with a diagnosis of ADHD has at least one other mental disorder, such as a mood, anxiety or substance use disorder [20, 21]. Personality disorders and sleep problems, especially Delayed Sleep Phase Syndrome (DSPS), seem also common in adults with ADHD [22, 23]. DSPS is a circadian rhythm sleep disorder characterized by chronic late sleep and late rising, insomnia at night, and significant daytime impairment [5]. Around 73% of children and 78% of adults with ADHD assessed in clinical studies have chronic sleep-onset insomnia [24, 25]. A proportion of these patients fulfill criteria for a diagnosis of DSPS (estimated at 26% in adult ADHD patients; [22]). Little is known about the association of ADHD symptom severity with the history of sleep problems in adults. In Chapter 2, this gap in knowledge was addressed in 942 participants of the Netherlands Sleep Registry (NSR; [26]).

Etiology of ADHD
ADHD is a multi-factorial disorder caused by the interaction of genetic and environmental factors [27]. The risk of ADHD in parents and siblings of children with ADHD is increased two to eight times [28], with heritability estimated at 76% [29]. Various genes have been implied in the etiology of ADHD, each having a small effect. For instance, polymorphisms in the dopamine transporter gene (DAT1, SLC6A3) and the dopamine 4 and 5 (D4, D5) receptor gene (DRD4, DRD5) have been most often related to ADHD [29], and result in impaired dopaminergic neurotransmission, which in turn is associated with the core symptoms of ADHD [30].

Next to these genetic factors, environmental factors that may increase the risk for ADHD are low-social economic status, persistent maltreatment e.g., in foster placement, family dysfunction and pregnancy-related factors, including low birth weight, prematurity, and maternal smoking or alcohol use during pregnancy [27, 31]. Additional factors include global living conditions: a population-based study by Arns et al. showed a lower prevalence of ADHD among children and adults in areas with high solar intensity across U.S. states and also across nine non-U.S. countries [32]. Since the intensity of outdoor daylight fluctuates across seasons, the severity of one’s ADHD symptoms may differ from season to season. We investigated this hypothesis in Chapter 3. Furthermore, we investigated whether an increased number of ADHD symptoms was associated with higher exposure to genetic (i.e., parental psychopathology) and environmental risk factors (i.e., childhood abuse) in order to examine whether ADHD is a dimensional trait in the adult general population (Chapter 4).
In addition to genetic biomarkers, studies have investigated other biomarkers associated with ADHD in order to gain more insight into the etiology of ADHD and eventually for diagnostic purposes. In 2012, a meta-analysis by Scasselati and colleagues revealed lower levels of 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) in urine, monoamine oxidase (MAO) in platelets, zinc in serum, plasma and urine, and cortisol in saliva, and higher urinary levels of norepinephrine (NE) in child ADHD patients as compared with controls. Nevertheless, it remained unclear whether these biomarkers were specific for ADHD. In Chapter 5, we investigated the relationship between adult ADHD symptoms and dysregulation of stress-related biomarkers using a cohort of adults with and without affective disorders. Results of prior studies that examined the association of ADHD with dysregulated stress-related biomarkers had conflicting results and did not adjust for comorbid affective disorders.

Consequences of ADHD

ADHD is related to disability in different areas of daily functioning [34]. Compared to adults without ADHD, adult ADHD patients have higher academic underachievement, higher levels of unemployment, increased risk of workplace injuries, and reduced productivity [35]. Adults with ADHD also show social disability. They more often have friendship problems, unstable relationships, marital problems, and divorces as compared to controls [36, 37]. In Chapter 4, we examined whether an increased number of ADHD symptoms among people from the general population was associated with increasing levels of both mental and physical disability after adjustment for sociodemographic characteristics and psychiatric comorbidity, in order to further examine whether ADHD is a dimensional trait in the adult general population.

Apart from the association with sleep disorders, ADHD in adulthood has been linked to a variety of other somatic conditions, including asthma, migraine, and most frequently to obesity [38]. A meta-analysis found that the prevalence of obesity was 28.2% in adults with ADHD [39]. Because of the associated morbidity and increased risk of mortality associated with obesity [40], it is important to understand possible mechanisms underlying the association between ADHD and obesity. One of the mechanisms that has been suggested is that weight gain in ADHD patients results from decreased physical activity or increased hours watching television [41]. Furthermore, genetic mechanisms may be involved in the association [42]. Moreover, we investigated whether circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity (Chapter 6). As previously mentioned, there is a high prevalence of the circadian rhythm disorder DSPS in ADHD patients [22]. DSPS may lead to obesity in ADHD patients due to chronic sleep debt, which has been associated with weight gain in the long term [43].
Chapter 1

Used studies in this thesis

Netherlands Sleep Registry (NSR)
The study on ADHD symptom severity and sleep disturbances was carried out with data from the Netherlands Sleep Registry (NSR; [26]), an online platform for survey. The NSR aims to research insomnia using multiple surveys in a large cohort compromising the full range from very disturbed to very sound sleepers. The NSR consists of volunteers from the Dutch general population.

Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2)
The study examining seasonal variations in the severity of ADHD symptoms and the study investigating whether ADHD is a dimensional trait in the adult general population were both done with data from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2; [44]). NEMESIS-2 is a longitudinal cohort study on the prevalence, incidence, course, and consequences of psychiatric disorders in the Dutch general population aged 18-64 years at baseline. The study is based on a multistage, stratified, random sampling of households, with one respondent randomly selected from each household. At the baseline assessment in 2007-2009, there were 6364 participants, of which 5303 respondents were reassessed in the second wave (80.4% of the baseline sample).

Netherlands Study on Depression and Anxiety (NESDA)
The study on the association of ADHD symptoms with dysregulation of stress-related biomarkers was executed using data from the Netherlands Study on Depression and Anxiety (NESDA; [45]), a longitudinal cohort study on the predictors, course, and consequences of depressive and anxiety disorders. The NESDA main sample included 2,981 participants aged 18–65 years, and consisted of healthy controls and persons with a remitted or current depressive and/or anxiety disorder. Participants were recruited from community, primary care, and outpatient psychiatric patients.

PsyQ Program Adult ADHD
The study investigating whether circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity was performed using data collected in patients from the PsyQ Program Adult ADHD. Also, an obesity and a control group were recruited from various locations.
General introduction

Aims of this thesis

- To gain more insight into etiological factors associated with adult ADHD.
- To gain more insight into the association of ADHD symptom severity with the history and current presence of sleep problems, and into the association of the number of ADHD symptoms with axis I and II disorders in adults.
- To gain more insight into consequences of adult ADHD.

Outline of this thesis

The studies are summarized in Figure 1.

- Chapter 2 is based on data from the NSR. This chapter studies whether current overall ADHD, inattention, or hyperactivity symptom severities are associated with the history and current presence of sleep problems in adults.
- Chapter 3 investigates self-reported seasonal differences in the severity of ADHD symptoms in adults from the general population using data from the NEMESIS-2 study.
- Chapter 4 uses data from the NEMESIS-2 study in order to investigate whether ADHD is a dimensional trait in the adult general population by studying whether an increased number of ADHD symptoms is associated with higher comorbidity, exposure to risk factors (childhood abuse and parental psychopathology), and mental and physical disability.
- Chapter 5 describes whether (1) ADHD symptoms were associated with dysregulation of stress-related biomarkers, and (2) whether ADHD symptoms interact with affective disorders in their association with dysregulated stress-related biomarkers. Analyses are based on the NESDA baseline and 4-year assessment samples.
- Chapter 6 is based on data from the PsyQ Program Adult ADHD, and examines whether circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity in participants with obesity, controls, and adult ADHD patients.
- Finally, Chapter 7 summarizes and discusses the main findings of the studies included in this thesis.
Figure 1. Schematic overview of studies in this thesis. The gray part of the arrow indicates the investigated direction of the association in this thesis.