GENERAL DISCUSSION
The aim of this thesis was threefold: (1) to gain more insight into etiological factors associated with adult Attention-Deficit/Hyperactivity Disorder (ADHD); (2) 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; and (3) to gain more insight into consequences of adult ADHD. In the current chapter, we summarize and discuss the main findings of the studies with implications for clinical or research practice, and delineate suggestions for future research. Furthermore, we address methodological considerations.

**Main findings**

In Figure 1, which was introduced in the General introduction, the results of the studies are schematically summarized.

**Figure 1.** Schematic overview of outcomes of the studies in this thesis. The gray part of the arrow indicates the investigated direction of the association in this thesis. Explanation of marks: - , no significant association; +, significant association. ANS: autonomic nervous system; BDNF: brain-derived neurotrophic factor; DIS: difficulties initiating sleep; DMS: difficulties maintaining sleep; EMA: early morning awakening; HPA-axis: hypothalamic-pituitary-adrenal axis; ID: insomnia disorder; OSAS: Obstructive Sleep Apnea Syndrome; PLMD: Periodic Limb Movement Disorder; RLS: Restless legs syndrome.
Etiology of ADHD

The etiology of ADHD is not yet fully understood [275]. The disorder is highly genetic [29], but environmental factors are also implicated [27]. One of these environmental factors is solar intensity [32]. Since the intensity of outdoor daylight varies across seasons, the severity of one’s ADHD symptoms may alter from season to season. In Chapter 3, self-reported seasonal differences in the severity of ADHD symptoms in 5,303 adults from the Dutch general population were examined using data from the NEMESIS-2 study. The main outcome of this study was that in participants who were assessed in spring and summer the severity of ADHD symptoms was higher as compared with participants who were assessed in autumn (Figure 1). Although we do not have a definitive explanation for our finding, it does suggest that researchers should be aware of seasonal variations in ADHD symptom severity in the diagnostic process of ADHD in the adult general population.

So far, it remained unknown whether subclinical ADHD symptoms are associated with the same genetic (e.g., parental psychopathology) and environmental risk factors (e.g., childhood abuse) as full-blown ADHD [139, 276]. Chapter 4 used data from the NEMESIS-2 study in order to investigate whether ADHD is a dimensional trait in the Dutch adult general population (n=5,303) by studying, amongst others, whether an increased number of ADHD symptoms was associated with higher exposure to these risk factors and found that that was indeed the case (Figure 1).

Besides examining genetic biomarkers, research has also focused on other biomarkers related to ADHD in order to better understand the etiology of ADHD [33]. Chapter 5 described whether ADHD symptoms were associated with dysregulation of stress-related biomarkers. We also examined whether ADHD symptoms interact with affective disorders in their association with dysregulated stress-related biomarkers. Data were obtained from 2307 subjects with and without affective disorders participating in the Netherlands Study of Depression and Anxiety (NESDA). Some associations were observed between ADHD symptoms, a hyperactive HPA-axis, and a longer pre-ejection period, but these were mostly driven by depressive and anxiety disorders (Figure 1). In addition, the results showed no evidence that ADHD symptomatology was associated with dysregulations in inflammatory markers and BDNF. It was concluded that ADHD symptoms did not confer an added risk to the disturbances of stress-related biomarkers in an – already at-risk – population with affective disorders.

Comorbidity

A wealth of studies among children and adolescents has been published demonstrating a link between ADHD and sleep problems, such as bedtime resistance and sleep-onset
difficulties [277]. However, little was known about the association of ADHD symptom severity with the current presence and history of sleep problems in adults. In Chapter 2, we studied whether current overall ADHD, inattention, or hyperactivity symptom severities were associated with the current presence and persistent history of sleep problems by using data from 942 adult participants from the Netherlands Sleep Registry (NSR). The most important finding was that ADHD severity, especially the severity of hyperactivity, was associated with the current presence and persistent history of various sleep problems (Figure 1). Clinicians are therefore recommended to evaluate and treat sleep problems in persons with ADHD symptoms, in order to prevent serious health consequences in the long term.

Apart from the comorbidity with sleep problems, ADHD is also co-occurring with other Axis I and II disorders [13, 278]. As previously described, Chapter 4 used data from the NEMESIS-2 study in order to investigate whether ADHD is a dimensional trait in the adult general population. To further support this hypothesis, we investigated whether an increased number of ADHD symptoms was associated with higher comorbidity of psychiatric disorders. We observed that respondents with higher ADHD symptom levels were more likely to report Axis I and II disorders, including mood, anxiety, substance use, antisocial personality (ASPD), and/or borderline personality disorder (BPD).

Consequences of ADHD

ADHD is related to disability in different areas of daily functioning [34]. Besides examining the association of the number of ADHD symptoms with comorbidity and exposure to risk factors, Chapter 4 also studied whether an increased number of ADHD symptoms was associated with higher mental and physical disability. We found that respondents with higher ADHD symptom levels were more likely to report increasing mental and physical disability, and that these associations were not driven by sociodemographics or psychiatric comorbidity (Figure 1). In summary, Chapter 4 showed that an increased number of ADHD symptoms was associated with higher comorbidity, exposure to risk factors, and disability. Thus, our study supported the notion that ADHD is a dimensional trait in the adult general population, which was in line with previous studies [16, 137]. The temporal order between these factors has to be established. Nevertheless, if subclinical ADHD symptoms cause burden, treatment and/or indicated prevention targeted at individuals with subclinical symptoms seems relevant in order to decrease the burden and to reduce the risk of progression to full-blown ADHD.

ADHD is also highly comorbid with obesity [39]. In Chapter 6, we were the first to examine whether circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity in participants with obesity (n=114), controls (n=154), and adult ADHD patients (n=202).
Chapter 7

The results confirmed our hypothesis: the relationship between ADHD symptoms and obesity was sequentially mediated through sleep duration and through an unstable eating pattern (both are manifestations of circadian rhythm disruption; Figure 1). The results imply that clinicians should pay attention and treat ADHD symptoms as well as circadian rhythm disruption, in order to prevent additional weight gain or possibly even to facilitate weight loss.

General discussion

Children versus adults with ADHD

In about two-thirds of the childhood cases, ADHD has been shown to persist into adulthood [18]. Despite the awareness of the persistence of the disorder into adulthood, there is much less research about ADHD in adults than in children [2]. A comparison of our results with outcomes of studies conducted in children reveals mostly similarities but also some differences. The first similarity was that parental psychopathology and childhood abuse may be etiological factors associated with adult ADHD (Chapter 4). This is also observed in children with ADHD [138, 139], whereby poor parent-child interactions has been suggested as underlying mechanism [279, 280]. Poor parent-child relationships, whether or not as a result of parental or child psychopathology, may lead to childhood maltreatment in those with ADHD symptoms [281]. Animal studies have shown that stress in early life has a negative impact on the dopamine neurotransmitter system, the main neurotransmitter affected in ADHD, that can continue into adulthood, which may explain why childhood trauma may result in ADHD symptoms in adults [282]. This observation is in line with clinical studies that revealed that parental psychopathology and early psychosocial adversity are risk factors for the persistence of childhood ADHD into adulthood [283, 284]. These findings underline the importance of supporting both the child with ADHD as well as the parents with the intention to lower the persistence rate of the disorder. Second, psychiatric comorbidity is associated with childhood and adulthood ADHD ([21, 285]; Chapter 2-6) and predicts continuation of ADHD symptoms into adulthood [286]. In up to 87% of the children with ADHD, at least one other mental disorder is present, including oppositional defiant disorder in 50–60%, depressive syndromes in 16–26 % and anxiety disorders in about 15% of all children with ADHD [100, 285]. Comorbidity is also substantial in adults with ADHD: three quarter of the cases has at least one other psychiatric disorder [21]. A population-based study among U.S. adults showed that mood disorders occurred in about 40%, anxiety disorders in about 50%, and substance use disorders in about 15% [151]. In Chapter 4, we found that increasing ADHD symptom levels were associated with higher comorbidity, which supported the notion that ADHD is a dimensional trait in the adult general population. This coincides with clinical and community studies in children and adolescents that generally suggest that regarding comorbidities and functioning, those with subthreshold ADHD
have an intermediate position between those with no ADHD symptoms and those with full threshold ADHD (reviewed in [287]). Also, the observed relationship between ADHD symptoms and sleep problems (Chapter 2, 6) concurs with previous studies among children and adolescents [277]. Sleep onset-difficulties are common in children [51] and adults with ADHD (Chapter 2, 6). These sleep onset difficulties may be the result of the delayed evening increase in endogenous melatonin levels, which has been observed in children and adults with ADHD [24, 25]. The third similarity is the disability associated with ADHD. We found that higher ADHD symptom levels were associated with increasing mental and physical disability (Chapter 4). This finding confirms observations from earlier epidemiological and clinical studies showing an association between child ADHD and disability in different areas of daily functioning, including physical, role and social functioning [288, 289]. Finally, both childhood and adulthood ADHD are associated with obesity [41]. A meta-analysis showed that the prevalence of obesity was increased by about 40% in children with ADHD and about 70% in adults with ADHD compared to controls [39]. Longitudinal evidence suggests that ADHD may temporarily precede obesity [219]. Nevertheless, a reverse pattern has also been shown [290], whereby obesity or factors associated with it, such as sleep apnea, cause or mimic ADHD symptoms [41].

There are differences in two of the three studied etiological factors; seasonality and dysregulation of the stress-related biomarkers. Our outcome of a greater severity of ADHD symptoms in spring and summer among adults from the general population (Chapter 3), contrasts to the findings of previous studies among children and adolescents that found a higher symptom severity in wintertime as compared to summertime [109, 110]. In addition, while we did not find a relation between ADHD symptoms and dysregulations in the ANS, inflammatory markers, or BDNF (Chapter 5), other studies did find differences in these stress-related biomarkers in children with ADHD [159, 161, 171]. With regard to cortisol awakening and evening levels, there are also discrepancies between studies conducted in children [169] and our results. However, our finding of less cortisol suppression among persons with more hyperactive/impulsive symptoms is in agreement with a study among children with ADHD [176]. As described in the respective chapters, inconsistencies of our results with previous studies may be attributed to differences in confounder adjustment, sample size, design or heterogeneity in the study populations. However, another possibility is that other etiological factors are involved in childhood and adulthood ADHD. In agreement with this, studies in children and adults with ADHD observed that the effects of some genes are linked to age-specific stages (reviewed in [291]). As suggested in this review, additional research and further studies are needed to generate firmer conclusions about age-specific etiological factors that might someday be useful for predicting the remission and persistence of the disorder.
In sum, our results indicate that some etiological factors, mental and physical comorbidity, and consequences are similar in children and adults with ADHD, suggesting that ADHD represents more a vulnerability than a state indicator. Recent studies have shown that ADHD is a lifelong disorder, which is associated with loneliness, physical and mental health problems and poor self-beliefs in older adults [292-294]. Acknowledging and treating ADHD as early in life as possible is therefore important in order to prevent adverse affects in many areas of life.

Symptom dimensions

ADHD is a clinically heterogeneous disorder; adults may present with symptoms of inattention, hyperactivity-impulsivity, or both [5]. Differences between symptom dimensions are present in several areas, including etiology, comorbidity, and consequences [295]. A meta-analysis of twin studies revealed that different mechanisms and combinations of genetic risk factors may give rise to inattention and hyperactivity [296]. With respect to mental comorbidity, meta-analyses of studies of adults indicated that hyperactivity-impulsivity symptoms were more strongly related to symptoms of externalizing disorders, such as antisocial behavior, as compared to inattention symptoms [295]. In contrast, inattention is more strongly associated with internalizing problems of anxiety and depression [295]. Regarding consequences, inattention symptoms were significantly more strongly associated with global impairment and lower life satisfaction in adults than hyperactivity-impulsivity symptoms [295]. The results presented in this thesis also support distinctions between the symptom dimensions. In Chapter 3, we observed that the severity of the inattention symptoms was increased in spring and summer, while the severity of the hyperactivity symptoms was only increased in spring in adults from the general population. Furthermore, we found that inattentive symptoms were particularly related to a higher cortisol awakening curve, and that hyperactive/impulsive symptoms were particularly related to less cortisol suppression after a dexamethasone suppression test (DST) (Chapter 5). In addition, specific associations were observed when studying the association between inattention or hyperactivity symptom severities and the current presence of sleep problems (Chapter 2). The severity of hyperactivity symptoms, but not of inattention, was specifically associated with probable Restless legs syndrome (RLS), Periodic Limb Movement Disorder (PLMD), Insomnia Disorder (ID) with predominant difficulties initiating sleep (DIS) and maintaining sleep (DMS), and short sleep. Inattention symptom severity was only related to the probability of being an extreme evening chronotype. These dissimilarities between symptom profiles suggest that etiological factors and comorbidity may be specific for inattention symptoms and hyperactive/impulsive symptoms. Therefore, prevention and treatment may differ between individuals with inattention symptoms and hyperactive/impulsive symptoms. In line with this, previous researchers suggested to define ADHD as
a single disorder without subtypes, with dimensional modifiers that reflect the number of inattention and hyperactivity-impulsivity symptoms at the time of assessment [297]. Such an approach reflects the consistent finding that most relevant clinical information regarding differences among the three subtypes, i.e., the inattentive, the hyperactive/impulsive, and the combined subtype, is contained in the two symptom dimensions [295]. Nowadays, clinical guidelines provide a general framework for evaluation and management of adult ADHD (e.g., [212, 298]). If, however, future studies provide evidence for better patient outcomes in the case of use of an assessment and treatment approach tailored to the specific symptom dimensions, such an approach should be incorporated in future guidelines.

Physical comorbidity

ADHD in adulthood has been associated with somatic conditions, including asthma, migraine, obesity and sleep disorders [38]. Around 30% of the adults with ADHD are obese (Cortese et al., 2016). Studies have focused on the role of a sedentary lifestyle as possible mechanism underlying the association between ADHD and obesity [41]. Chapter 6 demonstrated that circadian rhythm disruption, manifested by short sleep duration and an unstable eating pattern, is another pathway linking ADHD symptoms to obesity. Sleep restriction has been shown to reduce leptin, an appetite-reducing hormone, and to increase ghrelin, an appetite stimulating hormone [258, 299]. This may lead to chronic high food intake with weight gain and obesity as a consequence [43]. Treatment of obesity has shown to be more complicated in persons with ADHD as compared to persons without ADHD [241], which may be due to a greater tendency to eat in response to negative moods such as sadness and anxiety [300]. Another explanation may be that deficits in executive functioning inherent to ADHD lead to problems with planning meals ahead of time as well as tracking calories [300]. In a longitudinal study, it was observed that treating ADHD with stimulants resulted in weight reduction among adults with refractory obesity [301]. This result was likely because of the positive effects of pharmacotherapy on self-directedness, persistence, and novelty-seeking behaviors [301]. Furthermore, comorbid affective disorders [230] and circadian rhythm disruption should be treated in the management of obesity in patients with ADHD, and vice versa. It is worthwhile to study whether such combined therapies directed at reducing ADHD and comorbid symptoms, and treating circadian rhythm disruption are effective in the prevention and intervention of obesity in patients with obesity and/or ADHD. The treatment of circadian rhythm disruption should combine sleep hygiene advices, bright light therapy in the morning, and/or melatonin in the late afternoon or evening [224].
Apart from the association with circadian-rhythm related sleep disturbances, other sleep problems are also common and persistent in persons with ADHD symptoms (Chapter 2). Longitudinal studies have shown that sleep problems in early childhood are an indicator of subsequent attention problems that may persist into adolescence [302, 303], indicating that sleep problems can lead to ADHD symptoms. Vice versa, ADHD symptoms, such as over-thinking, can result in sleep problems [99]. Thus, the relationship between ADHD symptoms and sleep disturbances seems bidirectional. Our observed association between ADHD symptom severity and the persistent history of sleep problems suggests that people presenting with ADHD symptoms may profit from an evaluation and treatment of sleep problems. Vice versa, persons with sleep problems may benefit from assessment and treatment of ADHD symptoms. Sleep disturbances not only form a risk factor for obesity, as described above, but also for diabetes, cardiovascular disease, and cancer [43, 47, 48]. The link between sleep disturbances and diabetes may be explained directly by a decrease in brain glucose utilization in case of insufficient sleep, which would promote reduced glucose tolerance, and indirectly by obesity as risk factor for diabetes [43]. Disturbed and short sleep is also related to increased sympathetic nervous activity, resulting in an increase in blood pressure, which could predispose persons to the development of cardiovascular disease [43]. There is also evidence for an association between sleep disturbances and cancer [47]. It is suggested that melatonin, the sleep-promoting hormone, inhibits the genesis of tumors by inhibiting cell proliferation and invasiveness [47]. In order to prevent these serious health consequences of sleep problems, assessment and treatment of sleep problems among ADHD patients is necessary. Since ADHD medication may induce sleep problems, it is recommended to screen for sleep problems before starting ADHD medication, to track changes in sleep induced by stimulant treatment [304]. Further prospective longitudinal studies are warranted to examine whether treatment of sleep problems ameliorates the long-term health consequences of chronic sleep problems among ADHD patients.

Psychiatric comorbidity
In Chapter 4, we observed that respondents with a higher number of ADHD symptoms were significantly more likely to experience comorbid mood, anxiety, substance use, and personality disorders. This observation is in agreement with previous clinical and epidemiological work that showed that adults with ADHD are at increased risk for other axis I and II disorders [4, 13, 278]. Though the exact mechanisms underlying the interplay between ADHD and the other axis I and II disorders are not entirely understood, it is likely that comorbidity results from a combination of genetic and biological risks that interact with environmental factors [305]. Insight into these mechanisms underlying comorbidity is of clinical relevance, since this may help to prevent the development of comorbid disorders in patients with ADHD only. This is of great importance, because the presence of
different psychiatric disorders has a negative effect on the course and severity of disorders, on functioning, and is also related to higher service utilization in general [306]. Moreover, comorbid conditions increased the already elevated mortality rate in patients with ADHD compared with persons without ADHD [307]. This excess mortality in both children and adults with ADHD was mainly driven by deaths from unnatural causes, especially accidents [307].

With respect to a genetic risk for ADHD, we observed that persons with a higher number of ADHD symptoms were more likely to report parental mental health problems (Chapter 4), which may be due to the shared genetic liability for ADHD and the other disorders [280]. Regarding candidate genes, genes of the serotonergic and dopaminergic systems are associated with ADHD, affective disorders [308] and substance use disorders [309]. More recently, polymorphisms in core circadian clock genes have been linked to ADHD, depression, and anxiety, amongst others, which suggest that the circadian system may play a role in the development of a variety of psychiatric disorders [310]. Furthermore, alterations in other genes, such as the SPOCK3 gene, which is involved in development of the neuronal system, have been found in ADHD and personality disorders [311, 312].

An underlying biological mechanism behind the association between ADHD and the co-existing disorders may be a disturbance in the HPA-axis [192, 313, 314]. In Chapter 5, we found a hyperactive HPA-axis in patients with affective disorders and comorbid ADHD symptoms. Short sleep duration may explain this observation, since short sleep duration is not only linked to ADHD comorbid with affective disorders [22], but also to a hyperactive HPA-axis [192]. Therefore, and since disturbances in the HPA-axis have been linked to obesity [167], it is possible that the HPA-axis may play a role in our observed association between ADHD symptoms, short sleep duration, and obesity (Chapter 6). This suggests that the HPA-axis is another target for treatment in ADHD patients in order to prevent obesity, besides the already described combined therapies directed at reducing ADHD and comorbid symptoms, and treating circadian rhythm disruption. Two studies described the positive influence of ADHD medication on HPA-axis functioning in children with ADHD [197, 315]. However, another study did not support such an effect, suggesting that further research is needed.

The experience of adverse life events, such as childhood abuse, may be a possible environmental factor underlying the association between ADHD and the co-existing disorders [139, 316, 317]. In Chapter 4, we found that ADHD symptoms had a positive dose-response relationship with childhood abuse. The relationship between negative life events and psychopathology seems reciprocal. On the one hand, psychiatric symptoms
may elevate the risk of experiencing adversity [318]. The attention and impulse control problems in adults with ADHD increase the risk to experience negative life events, including unemployment, marital problems, and divorces [35]. On the other hand, negative life events have been shown to be related to psychiatric disorders which may be mediated by negative cognitive schema [316]. A model by Safren and colleagues [319] can be used to understand how negative life events may lead to depression and anxiety in adults with ADHD. The accumulation of adversity due to attention and impulse control problems leads to the formation of negative beliefs about the self. Based on these negative beliefs, individuals confronted with difficult situations develop maladaptive coping strategies, for instance avoidance. These coping strategies result in maintenance and reinforcement of maladaptive beliefs, which in turn may lead to depression and anxiety [320].

Based on the fact that comorbidity across psychiatric disorders is not yet fully understood, a network approach to psychopathology has been developed. In this approach, symptoms are not interpreted as a measurement of a latent disorder but as interacting elements of a network. The symptoms are causally connected through biological, psychological and societal mechanisms. Mental disorders arise from direct interactions between symptoms in a network [321]. Furthermore, a network approach could provide more insight into which symptoms account for comorbidity between disorders. If only some, and not all, symptoms of ADHD show connections with some, but not all symptoms of, for example, depression, this suggests that the specific symptom pairs connecting the two diagnoses can explain the comorbidity between ADHD and depression [322]. From a clinical point of view, such a network may have implications for diagnosis and treatment. In the network theory, diagnosis should be understood as a process by which a clinician identifies which symptoms are present and which network interactions sustain them. Although quite comparable to a diagnosis based on the DSM-5, network analysis may provide novel insights into the importance of specific symptoms in maintaining disorders. Treatment is thereby aimed at changing or manipulating the network of symptoms. Further studies must be done before this treatment method can be used in clinical practice [323].

As mentioned above, the existence of comorbidity has major clinical implications [306]. Therefore, the evaluation of co-occurring symptoms and disorders must always be part of the clinical assessment of adult ADHD as stated in the “European consensus statement on diagnosis and treatment of adult ADHD” [212]. Specialized mental health care settings directed at specific patient categories, including patients with ADHD, should assess these comorbid psychiatric disorders, for instance by using a diagnostic interview, like the Mini-International Neuropsychiatric Interview (MINI; [324]). The same holds true for specialized mental health care settings directed at other specific patient categories, such as
General discussion

patients with depression, in which ADHD and other comorbidities should be recognized. The “European consensus statement on diagnosis and treatment of adult ADHD” also provides guidelines for treatment of ADHD comorbid with other psychiatric conditions. A multimodal approach to treatment of adults with ADHD and associated co-morbid disorders should be taken. This multimodal treatment approach includes: psychoeducation on ADHD and co-morbid conditions; coaching; cognitive behavior psychotherapy; family therapy; and pharmacotherapy for ADHD and comorbid conditions, whereby the order of pharmacological treatment depends on the type and severity of comorbidity [212].

Methodological considerations

Throughout the prior chapters, various methodological issues have already been addressed. The most important considerations are (re)considered below.

Self-report

Although validated instruments were used to assess ADHD symptoms, the measurement was based on self-reported data, which may result in an underestimation or overestimation of symptoms. In general, adult ADHD patients underreport their symptoms [10], which may produce overestimated associations. Therefore, it is advised that collateral information from parents or other significant others is also taken into account in further research. Furthermore, the time of onset and ADHD symptoms in childhood were not assessed. Despite the fact that the DSM-5 defines ADHD as a childhood onset disorder [5], i.e., several symptoms have to be present prior to age 12 years, recent longitudinal studies [153, 154] have provided evidence for a ‘late-onset’ ADHD in adults. Since childhood symptoms were not evaluated, it is unclear if results apply to early- and/or late-onset ADHD, although, as previously described, a comparison of our results with outcomes of studies conducted in children reveals mostly similarities. For clarification of this issue, future studies should use a diagnostic interview for ADHD in adults, such as the semi-structured Diagnostic Interview for ADHD in adults (DIVA 2.0) [325], that measures ADHD according to DSM-IV-TR criteria, and therefore measures both symptoms in childhood and adulthood. This interview will be adjusted according to the DSM-5 criteria into ‘DIVA-5’.

Self-report was also used to measure sleep problems (Chapter 2, 6), comorbid psychiatric symptoms (Chapter 2, 4, 6), and other covariates (e.g., height and weight (Chapter 2, 6)), which may result in misclassification of these factors. For example, underweight people tend to overreport their weight, while obese people tend to underreport their weight [326]. Misclassification may lead to under- or overestimated associations between investigated factors, suggesting that the outcomes should be interpreted with some caution.
Another problem with self-report of comorbid psychiatric symptoms is the overlap of symptoms of ADHD and other psychiatric disorders. ADHD symptoms may mimic symptoms of depression and anxiety, such as restlessness and concentration problems, making it hard to distinguish disorders from each other [327]. This may result in higher prevalence rates of ADHD and the other psychiatric disorders than actually exist, suggesting that conclusions on comorbidity needs to be taken with care. Nevertheless, a study by Milberger et al. [128] showed that ADHD is not an artifact of symptoms shared with major depression, and that major depression itself is not an artifact of overlapping ADHD symptoms.

**Cross-sectional studies**

All performed analyses were cross-sectional, which makes it difficult to ascertain the direction of the observed associations. Therefore, it remains unclear whether ADHD symptoms result in parental psychopathology, comorbid psychiatric and sleep disorders, obesity and disability, or that these relationships are in the opposite direction. Longitudinal studies using regular follow-up intervals in children with and without ADHD may reveal whether these factors are co-occurring, causing, or the result of ADHD symptoms and may, therefore, give directions for prevention and treatment strategies.

Regarding the stress-related biomarkers, childhood abuse and their relationship with ADHD symptoms, longitudinal studies may be more difficult. Most stress-related biomarkers, except for BDNF, display day-to-day variations [328]. Further longitudinal research that assesses the biomarkers over several days is therefore needed. Also, childhood abuse is difficult to study because victims may often wait years before reporting the abuse [329].

Furthermore, we performed mediation analyses with cross-sectional data in order to determine if circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity. It would be more ideal to use longitudinal data in mediation analysis in order to draw definitive conclusions on causal inferences.

**Conclusions**

This thesis shows that seasonality, childhood abuse, parental psychopathology, and dysregulations in the HPA-axis may be etiological factors associated with adult ADHD. Furthermore, the severity of adult ADHD symptoms, especially the severity of hyperactivity symptoms, was associated with both the current presence and persistent history of sleep problems, and an increased number of adult ADHD symptoms was associated with higher comorbidity of axis I and II disorders. Moreover, mental and physical disability and obesity may be consequences of adult ADHD. Awareness of etiological factors relevant
for the development of adult ADHD and comorbid psychiatric symptoms and attention to comorbid psychiatric and somatic disorders seems of great importance in persons with ADHD symptoms, in order to prevent or alleviate the mental and physical burden.
References


General discussion


Chapter 7


Chapter 7


Chapter 7


