Sleep Problems in Children with Anxiety and Attention Deficit Hyperactivity Disorders

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“How,” asked the men, “can we forget strife, misery and danger?”

“Sleep,” answered the women.

From “The Answer”, Edward Agate (rewriting from Victor Hugo’s “Autre Guitare”)

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ABSTRACT

Objective: The aim of this thesis is to examine sleep problems in a clinical sample of children with anxiety and attention deficit/hyperactivity disorder (ADHD). The more specific aims are to investigate the frequency, the associations with behavioral and attentional functioning, and the persistence of sleep problems (both overall sleep problems and types of sleep problems). The sleep problems of children in the clinical sample are compared to those of a group of nonreferred children. The thesis also examines the influence of comorbidity on the frequency of sleep problems and explores possible predictors of persistence of sleep problems in the group of referred children.

Methods: The total sample consisted of 141 children aged 7–13 years, 51 girls and 90 boys, comprising 105 children referred to two child and adolescent outpatient clinics and 36 nonreferred children recruited as controls. The clinical sample was recruited from 421 consecutive referrals to the clinics, and the children were eligible for inclusion if they met diagnostic criteria for an anxiety disorder and/or ADHD after diagnostic interview with the parents, given no exclusion criteria applied. The clinical sample was grouped as follows: anxiety disorders without comorbid ADHD (ANX, n = 41), ADHD and no comorbid anxiety disorder (n = 39), anxiety disorders and ADHD (ANX+ADHD, n = 25). Of the 141 children participating at the initial assessment (T1), 76 referred and 31 nonreferred children were retained at the follow-up assessment after about 18 months (T2), giving an overall attrition rate of 24.1%. Diagnoses were assessed at T1 with parental interviews using the Kaufman Schedule for Affective Disorders and Schizophrenia present and lifetime version (Kiddie-SADS-PL). Sleep problems were assessed with mother reports on the Children's Sleep Habit Questionnaire (CSHQ) at both T1 and T2. Attention was assessed at T1 by the Attention Network Test for children (ANT). Emotional and behavioral problems were assessed at T1 by teacher reports on the Achenbach System of Empirically Based Assessment, Teacher Report Form (ASEBA TRF).

Results: Referred children were reported to have more total sleep problems compared to nonreferred controls, and children in the ANX and ANX+ADHD groups more than children in the ADHD group. As to types of sleep problems, children in the ANX and ANX+ADHD groups had more bedtime

resistance, sleep duration problems, sleep anxiety, parasomnias, and more daytime sleepiness compared to controls. Children in the ADHD group had more sleep disordered breathing problems and more daytime sleepiness compared to the controls. Children in the ANX group had more bedtime resistance problems than children in the ADHD group, and children in the ANX+ADHD group more night waking than the other groups of children. Comorbidity with other axis I disorders did not influence the frequency of total sleep problems among the referred children.

A higher reported frequency of overall sleep problems was associated with reduced efficiency of attentional functioning for both referred and nonreferred children, and daytime sleepiness predicted internalizing problems as rated by the teacher in children in the ANX group. No association was found between the sleep problems and teacher ratings of internalizing or externalizing problems in children in the ADHD or the ANX+ADHD groups, or between the sleep problems and teacher ratings of externalizing problems for any group of children.

The persistence rate from T1 to T2 of having sleep problems in a clinical range (total CSHQ score above 41) was 72.4% in the group of referred children. The persistence rates of having a total sleep problem in a clinical range did not differ significantly between children in the ANX group (76.0%), the ADHD group (70.6%), or in the ANX+ADHD group (68.8%). Persistence rates for types of sleep problems varied from 56.3% (bedtime resistance problems) to 86.0% (parasomnias) in the group of referred children. The total CSHQ score at T1 significantly predicted the CSHQ score at T2 in the group of referred children.

Conclusion: The results demonstrate a high frequency of sleep problems as reported by the mother in a clinical sample children with anxiety disorders and/or ADHD. Children with anxiety disorders have more sleep problems than children with ADHD. The sleep problems are associated with impairments in attentional function for both referred and nonreferred children, and with more internalizing problems reported by the teacher in the subgroup of children with anxiety disorders and no comorbid ADHD. The sleep problems are persistent in the majority of children in the clinical sample. Clinicians in child and adolescent mental health service (CAMHS) need to be aware of sleep problems and

include assessment and targeted intervention towards sleep problems when treating children with anxiety disorders and/or ADHD.

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List of papers

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Comparison of sleep problems in children with anxiety and attention deficit disorders

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II Hansen BH, Skirbekk B, Oerbeck B, Wentzel-Larsen T, Kristensen H

Associations between Sleep Problems and Attentional and Behavioral Functioning in Children with Anxiety Disorders and ADHD

Submitted

III Hansen BH, Skirbekk B, Oerbeck B, Wentzel-Larsen T, Kristensen H

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List of abbreviations

ADHD – Attention Deficit/Hyperactivity Disorder, IA : inattentive subtype, HI: hyperactive/impulsive subtype, C: combined subtype

ANT – Attention Network Test

ANX – Anxiety Disorders

ASEBA TRF – Achenbach System of Empirically Based Assessment, Teacher Report Form

Brief FAM – Brief Family Assessment Measure

CAMHS – Child and Adolescent Mental Health Service

CD – Conduct Disorder

CGAS – Child Global Assessment Scale

CSHQ – Children's Sleep Habit Questionnaire

CTRL – controls

DBRS – Disruptive Behavior Rating Scale

DSM-IV TR – Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision

DSPS – Delayed Sleep Phase Syndrome

EEG – Electroencephalogram

GAD – Generalized Anxiety Disorder

ICC – Intraclass Correlation Coefficient

ICSD-2 – International Classification of Sleep Disorders, 2nd edition

IQ – Intelligence Quotient

Kiddie-SADS-PL – Kaufman Schedule for Affective Disorders and Schizophrenia Present and Lifetime version

MDD – Major Depressive Disorder

MSLT – Multiple Sleep Latency Test

NREM – Non Rapid Eye Movement

OCD – Obsessive Compulsive Disorder

ODD – Oppositional Defiant Disorder

OR – Odds Ratio

OSAS – Obstructive Sleep Apnea Syndrome

PLMD – Periodic Limb Movement Disorder

PSG – Polysomnography

PPT – School Psychological Service

RC – Regression Coefficient

REK – Regional Committee for Medical and Health Research Ethics

REM – Rapid Eye Movement

RLS – Restless Leg Syndrome

SD – Standard Deviation

SDB – Sleep Disordered Breathing

SES – Socio Economic Status

VIF – Variance Inflating Factor

WASI – Wechsler Abbreviated Scale of Intelligence

INTRODUCTION

The importance of sleep for emotional well-being has been recognized across cultures since early ages, and anyone who has had trouble sleeping or has travelled across time zones will recognize the influence of sleep deprivation, reduced sleep quality, or disturbed diurnal rhythms on cognitive functions such as attention or memory. The importance of sleep for healthy development in children and adolescents has been focused in later years. Our parents' statements of the necessity of getting enough sleep for proper growth and development, and their comforting words in times of misery: "you will feel better in the morning after a good night's sleep" are receiving increasing scientific support.

In my work as a physician at psychiatric clinics, I have met many patients who have trouble sleeping. Among children, adolescents, and adults sleep problems are a frequent concern; for many patients it is as if an indistinguishable part of their psychiatric disorder. Sleep disorders are associated with a range of unfavourable outcomes in typically developing children, including emotional and behavioural problems and impaired cognitive functioning (1, 2), and have implications for choice of treatment, for instance what medication to use when treating patients with ADHD (3). Despite this, knowledge about sleep in child and adolescent psychiatric populations is limited. Research examining sleep problems in children with psychiatric disorders has primarily focused on children with depression, and in the last two decades, on sleep in children with ADHD (4). Sleep problems in other childhood psychiatric disorders such as anxiety disorders, have received little attention (5).

Advances in sleep research, notably contributions from experimental sleep deprivation studies (mainly with adults), and from studies in children treated for sleep disorders, have increased our knowledge of the importance of sleep for daytime function. For instance, studies before and after adenotonsillectomy in children with sleep disordered breathing demonstrated the negative influence of sleep disruption on cognitive function and behavioural/emotional problems in children (6). Several studies have later reported associations between other types of sleep disturbances and impairments in academic function and emotional and behavioural problems in typically developing children (for review see (1)). The question then is – are sleep disturbances related to impairment in daytime functioning in children with psychiatric disorders? While some researchers suggest that insufficient sleep will exacerbate the

symptoms and cognitive impairments in children with psychiatric disorders (7-9), other researchers claim that the empirical support for such an assumption is limited (1, 10).

On a group level, sleep problems decline across childhood (11), while individual sleep problems have been demonstrated to be relatively stable (12-14). Longitudinal studies on the persistence of sleep problems in children with psychiatric disorders are however limited. The reason for this may be that when sleep problems accompany psychiatric disorders, the sleep problems have been conceptualized as part of the disorder, not needing any special assessment or monitoring. However, there is a shift in this conceptualization, towards a view of the sleep problem being a comorbid condition of its own (15, 16). So, what is the course of this comorbid condition among children with psychiatric disorders?

The three main aims of this study are to 1) examine and compare the frequency of sleep problems, 2) explore possible associations between sleep problems and attentional, emotional, and behavioural function, and 3) examine the persistence of the sleep problems over time, in referred children with anxiety disorders, ADHD or both anxiety disorders and ADHD. These are important issues for the clinician when deciding what focus to have on sleep problems when treating children referred to CAMHS.

Participating in the clinical research project titled "Anxiety disorders in children aged 7-13 years – association with neurodevelopmental delays/disorders and temperament/personality. A clinical case-control and prospective study." gave me an opportunity to look at this prevalent clinical phenomenon with a researcher's approach. During the spring of 2007 a pilot study was undertaken to ascertain feasibility of the procedure for the planned study. As part of the assessment sleep problems in the child were systematically asked for during the interview with parents, and this was frequently reported. A literature search revealed the several gaps of knowledge in this field, and we decided to include a sleep measure to the research protocol.

1 GENERAL BACKGROUND

1.1 Sleep disorders and sleep problems

Sleep disorders are disorders of sleep described and defined by diagnostic manuals such as the International Classification of Sleep Disorders, second edition (ICSD-2) (17), and the Diagnostic and Statistical Manual of Mental Disorders 4th version (DSM-IV) (18). Table 1 gives a description of selected sleep disorders relevant to this thesis.

Table 1 Description of selected sleep disorders

Insomnias	Group of sleep disorders characterized by repeated difficulty with sleep initiation, maintenance or quality. Includes: Insomnia Due to Mental Disorder and Behavioural Insomnia of Childhood.
Circadian Rhythm Sleep Disorders	Group of sleep disorders characterized by sleep disturbance due to alterations of the circadian timekeeping system or misalignment between the endogenous circadian rhythm and exogenous factors.
Narcolepsy	Excessive daytime sleepiness with recurrent daytime naps or lapses into sleep. Occurring with or without cataplexy: sudden muscle weakness or sudden bilateral loss of postural muscle tone in association with intense emotion.
Sleep Disordered Breathing Disorders	Group of sleep disorders characterized by disordered respiration during sleep. Includes: Obstructive Sleep Apnoea Syndromes (OSAS).
Sleep Related Movement Disorders	Group of sleep disorders characterized by stereotyped movements or sleep related leg cramps. Includes: Restless Leg Syndrome (RLS): unpleasant sensation in the legs during rest which is relieved by movements of the limb; Periodic Limb Movement Disorder (PLMD): Repetitive highly stereotyped limb muscle movements during sleep.
Parasomnias	Group of sleep disorders characterized by undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep. Includes: Sleepwalking, Somniloquy: sleeptalking Bruxism: tooth-grinding or tooth clenching during sleep; Sleep terrors: sudden arousal from deep sleep beginning with a panicky scream accompanied by manifestations of intense fear, with amnesia for the episode; Nightmares: awakening with recall of intensely disturbing dream with dysphoric emotional content; Enuresis: bedwetting.

This thesis is concerned with the frequency, associated features and persistence of *sleep problems* as they present in CAMHS, and the review of previous literature in this thesis will mainly focus on results from studies on sleep problems, and only to some extent on studies regarding sleep disorders in children. Table 2 gives a description of the sleep problems described in this thesis. These are sleep problems commonly reported in children, both in clinical (19, 20) and nonclinical (21, 22) samples, and may or may not be symptoms of a sleep disorder. The concept of *sleep problems* will be used interchangeably with *sleep disturbances*.

Table 2 Description of sleep problems and potential corresponding sleep disorders

SLEEP PROBLEM	SYMPTOMS	SLEEP DISORDER
Bedtime resistance	Irregular bedtime, falls asleep in other's bed, afraid to sleep alone, requires parents to be present at bedtime, refuses to get ready for bed, refuse to remain in bed.	Insomnias, Circadian Rhythm Sleep Disorders, Restless Legs Syndrome, Periodic Limb Movement Disorder.
Sleep onset difficulties	Difficulties falling asleep	Insomnias, Circadian Rhythm Sleep Disorders, Restless Legs Syndrome, Sleep Related Breathing Disorders.
Sleep duration	Reduced or variable duration of total sleep time as perceived by parents or child.	Insomnias, Circadian Rhythm Sleep Disorders, Restless Legs Syndrome, Sleep Related Breathing Disorders, Periodic Limb Movement Disorder.
Sleep anxiety	Requiring parents to be present, afraid to sleep alone or afraid of the dark, afraid to sleep away from home.	Insomnias.
Night wakings	Night wakings.	Insomnias, Restless Leg Syndrome, Periodic Limb Movement Disorder, Sleep Related Breathing Disorders.
Parasomnias	Sleep talking, sleep walking, bruxism, sleep enuresis, sleep terrors, nightmares, restless sleep	Sleep Talking, Sleep Walking, Bruxism, Sleep Enuresis, Sleep Terrors, Nightmares, Periodic Limb Movement Disorder.
Sleep Disordered Breathing	Snoring, gasping, snorting, pauses in breathing during sleep (sleep apnea).	Sleep Related Breathing Disorders.

1.2 Sleep regulation and physiology

Sleep and wakefulness are regulated by two processes operating simultaneously: the homeostatic process basically regulating the length and depth of sleep, and the circadian rhythm (biological time clocks) which influences the timing of wakefulness and sleep. The homeostatic pressure (or sleep drive) builds up during wake time, and is dissipated during sleep, while the circadian rhythm are synchronized to the 24-hour day cycle by external cues called zeitgebers, such as light and activity.

On a neurobiological level, wakefulness is mediated by ascending neurons from the brainstem and hypothalamus sending excitatory projections to thalamus, activating the thalamo-cortical projections. These ascending neurons comprise different arousal systems using different neurotransmitters, and coordinated activity in all these systems is required for complete alertness. Sleep initiation depends on a coordinated activity in hypothalamic inhibitory neurons which regulate these arousal regions. These arousal and sleep promoting systems are thought to mutually balance each other, and the rising homeostatic pressure throughout the wake state gradually shifts this balance towards sleep (23). This activation/deactivation cycle is reflected in brain electric activity as measured on electroencephalogram recordings (EEG). The wake state and the five sleep stages (Non Rapid Eye Movement (NREM) sleep stages 1–4, and the Rapid Eye Movement (REM) sleep stage) are defined based on characteristics of the EEG (23). In the wake state, brain electric activity displays a rapid, random and low voltage pattern (alpha- and beta waves). As we get drowsier, the waves become more synchronized but are still rapid (8– 12 Hz alfa waves). Sleep stage 1 is initiated when the waves become slower and the 3–7 Hz theta waves dominate the EEG pattern, while sleep stage 2 is dominated by rapid 12–14 Hz waves. In sleep stage 3 and 4, deep sleep or slow-wave sleep, slow high-voltage (delta) waves are the predominant EEG pattern. These NREM sleep stages occur in periods lasting 90–120 minutes throughout the night. In the end of one such NREM sleep cycle, the sleep becomes gradually lighter, and REM sleep is initiated. In the REM sleep, the EEG pattern resembles that of the wake state, with predominantly alpha- and beta waves. During REM sleep, motor neuron activation is blocked and neuron activity inhibited, both contributing to the muscle atonia associated with REM sleep. The deep NREM sleep stages dominate the first half of the night, while

REM sleep is more abundant during the second half. The amount of NREM deep sleep increases after sleep deprivation. The new born exhibits an even distribution of waking, REM sleep, and slow wave sleep, spending about 8 hours in each state, with a gradual decrease of REM sleep to about 1 hour a day and of slow wave sleep to 6–7 hours a day at 15 years of age (24).

1.3 Sleep deprivation/restriction, emotions and cognition.

The precise functions of sleep are still not fully understood, but we do know that sleep has an important role in many cognitive and psychological processes. On a neurobiological basis, inadequate sleep during brain development has been hypothesized to cause aberrant neural connections that may cause disruption in cognitive and psychological development (1, 25). Experimental sleep deprivation/restriction studies, mostly with adults, have provided information of the effects of insufficient sleep and have formed the basis for theories of the functions of sleep. In the following some of the findings from experimental sleep deprivation/restriction studies and theories regarding the function of sleep relevant to this thesis will be briefly described.

1.3.1 Sleep, emotional processing and emotional reactivity

Sleep is important for emotional processing, and enhances both the encoding and the consolidation of emotional memories (26). This is of potential clinical importance; for instance sleep deprivation after exposure to trauma has been suggested to reduce memory of the traumatic experience and hence reduce the risk of developing post-traumatic stress syndrome (PTSD) (27). In contrast, memory processes of importance to recover from fear such as extinction of fear, and generalization of the extinction, are enhanced by sleep (28, 29). This effect on fear extinction processes is at least partly attributable to the amount of REM sleep (26, 29). According to one theory the replay of autobiographical memories during sleep dependent memory consolidation is disconnected from the emotional marker during REM sleep, allowing for a modification of the memory without the fearful emotional experience attached to it (26).

Sleep also plays a role in in modulating the reactive states of the affective brain networks. An MRI study in healthy adults demonstrated that after sleep deprivation the prefrontal inhibitory control on

amygdalae was reduced and the amygdala activity increased as response to an emotionally stimulus (30). Sleep compared to equivalent time awake was followed by decreased amygdala activation on fMRI and a reduction in the subjective ratings of emotional intensity in response affective stimuli (31). Equivalent results have been demonstrated in healthy adolescents; sleep restriction, compared to a sleep extension condition was followed by larger pupil dilatation (a physiological measure of emotional reactivity) as response to negative auditory stimuli, and a display of more negative affect during peer interaction (32).

1.3.2 Sleep, attention and executive function

In adults, attention is the cognitive capacity most consistently impacted by sleep deprivation, with deficits in sustained attention detectable after one night without sleep (33). The homeostatic sleep drive that builds up during wake represents an increasing pressure towards sleep. According to the wake-state instability hypothesis this sleep pressure will lead to instability in the sleep-wake regulation after extended periods of wakefulness. As a consequence, periods of sleep-like brain activity may interrupt on-going wakefulness (34), leading to intrusive and unwanted lapses of attention, evident as longer reaction times and increased number of errors on attention tests in adults (35). In children however, findings diverge as to the effects of sleep deprivation on attentional functioning measured by formal tests: in one study, one hour of sleep expansion versus one hour of sleep restriction did lead to improved performance on a sustained attention task (decrease in commission errors) (36), while other studies have failed to find an impact of sleep restriction/deprivation on formal tests of attention (for review see (1)). A recently published meta-analysis on the association between sleep duration/sleep efficiency and sustained attention did not find any significant associations, however the fraction of experimental studies included in this analysis was low as the majority of studies included were of correlative nature (2).

Executive functions comprises functions such as inhibition, set shifting, planning, fluency and working memory, and rely on coordinated interaction of different cortical and subcortical networks (37). Neuroimaging studies have shown reduced activity in brain structures subserving executive functions such as the prefrontal cortex after sleep deprivation (38). On formal tests of executive

functions, divergent findings are reported in adult studies, however, and at present which types of executive function tasks are consistently affected by sleep loss in adults remain unclear (39). In children, a meta-analysis concluded that impairment in executive functions was associated with reduced sleep duration (both experimental and correlative studies included) in typically developing school children (2). A review based on experimental studies only, concluded that studies are too few to draw any conclusions regarding the influence of sleep deprivation or restriction towards executive functions in children (1).

1.4 Assessment of sleep

Because sleep may be measured in different ways a short description of the various methods available for assessing sleep will be given.

1.4.1 Subjective measures

Subjective measures in pediatric sleep medicine are questionnaires, interviews or sleep diaries, and these are either parental reports or self-report. Sleep diaries are sleep logs, typically kept for 2 weeks, where parents or the child itself note time for bed, light out, time for sleep onset, night waking and time for waking in the morning. Sleep diaries are considered helpful in addition to interviews and retrospective questionnaires to detect variations in, and to give more accurate measures of sleep onset and sleep duration, for instance to compare weekday and weekend sleep schedules (40).

1.4.2 Objective measures

Objective measures of sleep include polysomnography (PSG), multiple sleep latency test (MSLT) and actigraphy.

PSG, most commonly performed in sleep laboratories, is regarded the gold standard of sleep assessment. This is a comprehensive evaluation, measuring brain electrical activity (EEG), muscle tone activity and respiratory parameters. Deviations in sleep architecture, i.e. the structure and pattern of brain electric activity and the distribution of the different sleep stages, are only detected by PSG. PSG is the method of choice for the assessment of sleep disorders such as sleep related movement disorders, e.g. PLMD, and sleep disordered breathing disorders, e.g. OSAS. MSLT is a measure of

physiological tendency to fall asleep, and comprises a series of five scheduled 20-min daytime opportunities to nap. MSLT in combination with PSG is the gold standard of diagnosing narcolepsy (17).

Actigraphy is a small and simple device attached to the child's wrist or ankle and is well suitable for home based studies. It will continuously registers physical motion per unit of time that can be translated to estimates of sleep onset, night waking, and sleep efficiency (= percentage of time spent in bed actually sleeping) (40).

1.5 Children and sleep

1.5.1 Sleep problems in children

Sleep problems are commonly reported among typically developing children. In cross-sectional epidemiological studies sleep disturbances are reported in 25–45% of school-aged children (22, 41). Bedtime resistance, sleep related anxiety, sleep initiation problems, insufficient hours of sleep, night waking and daytime fatigue and tiredness are sleep problems frequently reported in school aged children (42, 43). Parasomnias (Table 1) are also common phenomena in children; sleepwalking was reported to have occurred in 13.8 %, somnoloquy (sleeptalking) in 55.5%, and bruxism (teeth grinding) in 28.1% in children aged 3–13 years (44). Nightmares were reported to occur often in 2.5% and sometimes in 27.1% of children aged 8–11 years (45).

Age, sex, socioeconomic status (SES), family function and life events may influence the prevalence rates of sleep problems. At a group level sleep problems decrease throughout childhood (11), and the types of reported sleep problems vary with age. Bedtime resistance, sleep terrors, nightmares and night waking are more common among younger children, while difficulties falling asleep, insufficient sleep duration and excessive daytime sleepiness are sleep problems more commonly reported among older children (13, 22). As to sex differences reports are inconsistent. A higher frequency of parent reported sleep problems was reported in girls in an epidemiological survey among children 2 to 14 years of age (22), and adolescent girls had more complaints about their sleep quality than boys in a Dutch study (46). Other studies report no sex difference in the prevalence of sleep problems in prepubertal children

(13, 47). In one study a higher prevalence of insomnia in girls compared to boys emerged after onset of puberty (48). Environmental factors such as parental education level (41, 48), parental psychopathology (49), family conflict, marital discord and divorced parents (41, 50), and stressful life events (51, 52) have all been associated with increased frequency of sleep problems in children and adolescents.

1.5.2 Sleep, health and daytime functioning

Inadequate sleep is associated with a broad range of unfavourable outcomes in the child as well as the family. Sleep disturbances in children have been associated with increased risk for injuries (53), and in adolescents chronic insomnia predicted negative somatic health outcome (54), was associated with increased propensity for substance abuse (55), and increased suicidality (56). The relationship between child sleep and family function is most probably bidirectional (50), and several studies have also described this relationship with the premise that sleep problems in the child disrupt parent's sleep (57, 58), increase parental stress (59), and negatively influences family functioning (60).

Of special relevance for this thesis is the relationship between sleep problems and internalizing and externalizing symptoms, and impairments in cognitive functions. An association between inadequate sleep and internalizing symptoms has been documented in both cross sectional (61-63) and longitudinal studies (64-66), and in sleep restriction studies in adolescents (67). In children with chronic diseases sleep problems were associated with co-occurring emotional problems (68). Sleep problems have been associated with externalizing behaviour problems such as hyperactivity and impulsivity both in cross-sectional (61, 69) and longitudinal studies (11), although findings are not unequivocal (70). Children and adolescents display increased inattentive behaviour after sleep restriction (71, 72), whereas increased hyperactive/impulsive behaviour after experimental sleep restriction has not been demonstrated in children (1).

Subjective sleepiness, impaired sleep quality, and to a lesser degree sleep duration are associated with impaired academic achievement in children (73). Reduced sleep duration is associated with impairments in cognitive function, in particular executive functions and on performance on tasks that

address multiple cognitive domains (such as WISC block design) (2). Persistent sleep problems during early childhood predicted impairments on neurocognitive tests at school entry (74) and in adolescence (75). The course of sleep problems across childhood seems to be of importance; in 8–9 year olds an increase in self-report of sleepiness over 3 years compared to decrease was associated with reduced development of verbal comprehension skills (76), and one study found that sleep problems in early childhood were not associated with later impairment in cognitive function unless the sleep problems persisted across childhood (77).

1.5.3 Persistence of sleep problems in children

The percentages of the child population presenting with persistent sleep problems vary across studies from 0.3% (78) to 12–14% (12, 64), depending on definitions of what constitutes a sleep problem and length of follow up time. Sleep problems display a moderate stability in children with persistence rates varying from 30 % to 60% (12, 14) over the course of one year. A Finnish study recently reported a high continuity of both subjectively reported and actigraphically measured sleep disturbances from childhood to preadolescence (79). In contrast a Chinese study found a persistence rate of 14.9% of insomnia over the course of 5 years (80). The reasons for the lower figures in this latter study may be a stricter definition of a sleep problem. As to predictors of persistence having internalizing problems predicted persistence of sleep problems (64), stressful life events were related to persistent sleep problems among pre-schoolers (81), and in adolescents psychiatric disorders and school stress was associated with chronic insomnia (48, 82).

2 SLEEP PROBLEMS IN CHILDREN WITH ANXIETY DISORDERS AND IN CHILDREN WITH ADHD

Parents of children with psychiatric disorders report high prevalences of sleep problems in their child (83, 84). In virtually all psychiatric disorders and neurodevelopmental disorders of childhood, some forms of associated sleep disruption have been described (for review see (85)). The types of sleep problems most often reported are typically bedtime resistance, sleep onset and maintenance

difficulties, parasomnias, and tiredness during the day (83, 86). The relationship between sleep problems and psychiatric disorders may be explained by factors associated with both psychiatric disorders in general and sleep problems (e.g parental psychopathology, family dysfunction or life events) (49, 81). Alternatively the sleep problems may be more specifically related to one or more psychiatric disorder.

2.1 Sleep problems in children with anxiety disorders

Although sleep disturbances can comprise core features of anxiety disorders, such as worry at bedtime, research that focuses on sleep disturbances in clinical samples of children with anxiety disorders is quite limited. The data that exist, report high prevalence rates of sleep problems in children with anxiety disorders. In a group of children with anxiety disorders parents reported clinically significant sleep problems in 85% (19), and in approximately 90% of children with anxiety disorders parents or the child themselves reported one or more sleep related problem (87, 88). However, none of these studies used clinical or nonclinical control groups, or controlled for comorbidity with other axis I disorders. One study that compared sleep problems in children with anxiety or depression (considered as one group) to controls did not find increased parental reported sleep problems in the children with anxiety or depression (89).

As to types of sleep problems in children with anxiety disorders bedtime resistance, refusal to sleep alone, difficulties with initiating and/or maintaining sleep, and nightmares are commonly reported (19, 88). One study reported nightmares, fatigue, and feeling tired as common sleep problems among anxious children (87), however bed time struggles, sleep onset delay, night waking, parasomnias other than nightmares, or sleep disordered breathing symptoms were not assessed in this study.

Some data suggest that children with anxiety disorders may underreport their sleep problems. Compared to the parental-reported rate of 85% with a sleep problem, 54% of the children themselves reported having a sleep problem (19). In another study among anxious adolescents self- reported sleep onset delay or sleep maintenance difficulties were no higher compared to controls. In the discussion of

this finding, the authors pointed to the possibility that this is caused by reluctance of anxious youths to report on their sleep problems (90). In a study comparing self-reported sleep problems and PSG recordings in children with anxiety disorders, children with major depressive disorder (MDD), and healthy controls the children with anxiety disorders reported less sleep problems but showed more evidence of objective sleep disturbances on PSG recordings than the other groups (91).

The objective sleep disturbances in children with anxiety disorders in the above mentioned study were longer sleep onset latency and less slow-wave sleep (91). Other objective sleep disturbances described are abnormalities in REM sleep and more frequent limb movements in adolescents with anxiety disorders compared to controls (92), and increased sleep latency, reduced sleep efficiency, and shorter REM latency in children with obsessive compulsive disorders (OCD) compared to controls (93).

Results are somewhat inconsistent regarding whether types of anxiety disorders are of importance. Sleep problems were reported to be present in equal percentages in children with separation anxiety disorder, generalized anxiety disorder (GAD), social phobia and OCD (87). In children with OCD, sleep problems were reported in equal frequencies compared to a group of children with other anxiety disorders (94), and in a Swedish study the sleep related problems in children with OCD were considered mainly associated with anxiety symptoms in general rather than to the obsessive compulsive symptoms (95). In contrast, in one study sleep problems were reported to be more prevalent in children with GAD compared to children with other anxiety disorders (considered as one group) (88).

The role of comorbidity for anxious children's sleep problems has not been investigated thoroughly. One study compared sleep problems between children with mood/anxiety disorders and children with mood/anxiety disorders and comorbid ADHD. The group of children with mood/anxiety disorders and ADHD displayed more frequent bedtime struggles and leg jerks during sleep compared to the mood/anxiety group alone. The use of stimulant medication was not controlled for, however (83).

Some findings suggest a specific link between anxiety disorders and sleep disturbances; in a longitudinal study involving a large community sample persistent sleep problems reported during

childhood significantly predicted anxiety disorders at age 26, while no such association was found between childhood sleep problems and adult depression (64). There are different views as to what came first however, the anxiety disorder or the sleep problem. Although present evidence rules in favour of sleep problems to predate anxiety disorders (96), findings are supportive of both views; the same way sleep problems in childhood predicted anxiety disorders in adulthood, internalizing problems in childhood predicted insomnia in adulthood (65) and prior anxiety disorders were associated with an increased risk of later insomnia in adolescents (97). Correspondingly, the same way as sleep insufficiency may lead to impaired emotional processing and poorer emotional regulation (26) troubled rumination and feeling of anxiety may activate stress responses that can override the normal sleep wake regulation and lead to difficulties with initiation and maintenance of sleep (98, 99). Thus a bidirectional influence is apparent; sleep and anxiety may negatively influence each other (9). Finally, shared genetic contributions to both sleep problems and anxiety disorders have been described (100), as well as shared brain structures influencing both emotional regulation and sleep (38, 101, 102).

2.2 Sleep problems in children with ADHD

Estimates of parent-reported sleep problems in school aged children with ADHD range from 25 to 55% (103), with a two-to-three fold prevalence rate to that of controls (7). A meta-analysis published in 2009 concluded that children with ADHD are reported to have significantly higher bedtime resistance, more sleep onset difficulties, night waking, difficulties with morning awakenings, and display more daytime sleepiness compared to controls (20). One Danish study reported higher frequency of restless sleep in children with ADHD compared to healthy controls (104).

Studies using objective measures such as PSG or actigraphy have resulted in variable findings; increased sleep onset latency (105), shorter actual sleep time, and more total interrupted sleep time (106), increased nocturnal movements (107), REM sleep alterations (108) and increased daytime sleepiness (109) have been described in children with ADHD, however inconsistently across studies. One study described mainly intra-individual day-to-day variability of the objective sleep variables in children with ADHD (110). Cortese (2009) concluded from findings in his meta-analysis of both PSG and actigraphic studies that children with ADHD had longer sleep onset latency, higher number of

sleep stage shifts, higher apnoe/hypopnoa index, and lower sleep efficiency compared to controls (20), while Sadeh (2006) in a meta-analysis of PSG findings concluded that children with ADHD had higher frequencies of periodic limb movements in sleep (111).

Studies comparing parental reports with objective measures do not consistently confirm parental complaints of sleep problems in their child with ADHD. For instance parental reports of sleep onset delay, sleep duration problems, night waking and parasomnias could not be corroborated by PSG (112), and in a comparison of actigraphy and subjective reports (parent and child sleep diaries) no clinical meaningful correlations were found (106). It has been suggested that the disconnect between parental reports and objective measures may be that parents of children with ADHD overestimate their children's sleep problems (105), or that parental reports are sensitive to problems not normally detected by objective sleep measures such as day-to-day variability or difficulties with the downregulation of activity necessary to initiate sleep because of hyperactivity, restlessness and distractability (113).

With regard to comorbidity, some studies find that the sleep problems in ADHD children are accounted for by comorbid oppositional defiant disorder (ODD), medication status or comorbid anxiety disorders (114, 115). Other studies find that even if having comorbid anxiety disorders and using stimulants are indeed associated with more sleep problems in children with ADHD, the association between sleep problems and ADHD remains significant also after accounting for these factors (116, 117). The role of stimulant medication for sleep disturbances in ADHD remains unsettled. One study found that after adjusting for ADHD severity stimulant medication was associated with increased sleep onset difficulties, but no other sleep problems (118). Other studies report that stimulant medication adversely influenced sleep duration and quality, while some studies demonstrated no adverse effect of stimulant medication on sleep, and even beneficial effect of stimulant medication on sleep related movements have been reported (for review see (119)).

Several possible explanations for the association between ADHD/ADHD symptoms and sleep disturbances have been suggested. First, sleep disorders such as sleep disordered breathing (SDB),

periodic limb movement disorder (PLMD), restless leg syndrome (RLS) and delayed sleep phase syndrome (DSPS) occur more frequently in children with ADHD than in controls (for review see (120)). ADHD and sleep disorders may share pathophysiology: both ADHD and RLS/PLMD have been associated with lower ferritin level known to be involved in dopamine system regulation, and children with ADHD were found to have delayed salivary melatonin increase, an indicator of circadian phase delay as in delayed sleep phase syndrome (DSPS). Children with narcolepsy and children with ADHD both display increased daytime sleepiness and increased sleep propensity on MSLT, suggesting that both groups have abnormalities with the sleep-wake and arousal regulation (for review see (121)).

Primary sleep disorders also give rise to symptoms mimicking ADHD, which may lead to misdiagnosing children as having ADHD who actually have a primary sleep disorder. For instance in a study among children scheduled for clinically-indicated adenotonsillectomi (usually sleep disordered breathing) 28% fulfilled the diagnostic criteria of ADHD before surgery, and 50% of these did no longer qualify for the diagnosis one year after surgery (6).

Furthermore, sleep insufficiency may partly cause or exacerbate both the cognitive and behavioral impairments associated with ADHD such as attention deficits and/or executive function dysfunction (122), and externalizing symptoms (112). Sleep restriction has been associated with impaired performance on tests measuring sustained attention (36), executive function (123), and subjectively reported sleep problems has been associated with externalizing behavior (69) in typically developing children. In children with ADHD, one hour of sleep restriction over a course of 6 days led to impaired performance on a sustained attention task, where the mean scores of four of six outcome measures deteriorated from subclinical to clinical levels (124), and parent reported sleep problems correlated significantly with both attention problems and externalizing problems (112). The association between sleep insufficiency and impairments associated with ADHD may go the other way round as well; the hyperactivity, restlessness, and distractibility of ADHD, and the impaired self-regulatory skills which is regarded a core feature of ADHD (125), may compromise the down regulation of activity that is mandatory for sleep initiation and maintenance (126).

2. 3 Cognitive, emotional and behavioural correlates of sleep problems in children with anxiety disorders and in children with ADHD

Empirical evidence for an association between sleep disturbance and exacerbation of emotional, behavioral and cognitive problems in children with psychiatric disorders is limited. In a mixed clinical group of children parental reported sleep problems correlated with parental reported behavioural and emotional problems (83). In children with anxiety disorders sleep problems correlated with the severity of anxiety symptoms and at-home impairment, but not out-of home impairment, as rated by the clinician using the Pediatric Anxiety Rating Scale (88). In another study in children with anxiety disorders parent- and child reported sleep problems correlated with child report of anxiety (87). In children with ADHD studies report somewhat differently; as mentioned in the previous section, one study reported impaired performance on a sustained attention task following experimental sleep restriction (124), another reported positive correlations between parent reported sleep problems and parent reported internalizing and externalizing problems (112). ADHD children with a self-reported sleep problem were more distractable compared to ADHD children without (127). In contrast, one study failed to demonstrate a correlation between actigraphically measured sleep quality and performance on a range of neurocognitive measures in children with ADHD (109), and another failed to demonstrate an association between actigraphically measured sleep onset latency and severity of ADHD symptoms (105). A recently published review on research in sleep and ADHD concluded that evidence to date is insufficient as to conclude whether sleep disturbances affects cognitive performance in children with ADHD (10).

2.4 Persistence of sleep problems in children with anxiety disorders and in children with ADHD

Regarding the persistence of sleep problems in children with anxiety disorders and/or ADHD, present knowledge is limited. In children with anxiety disorders about 30% of the children treated with fluvoxamine reported mild insomnia after eight weeks of treatment, compared to 88% at baseline. Corresponding figures for the placebo group were unfortunately not reported (5). In a longitudinal

population based cohort study investigating sleep patterns in children with ADHD compared to children without ADHD, the children with ADHD had significantly shorter sleep duration and more night wakings compared to controls during preadolescence (128). The persistence of sleep problems was not reported in this study, and we have failed to find any longitudinal study of persistence of sleep problems in clinical samples of children with ADHD. Given the chronicity of the disorder and the frequent use of medication with a potential negative influence on sleep (119), one would assume that the sleep problems might be persistent. On the other hand, the aetiology of sleep problems in ADHD is most probably multifactorial, and may also be related to extrinsic factors associated with ADHD (129), and these factors need not be as persistent as the disorder itself.

Our knowledge is also limited regarding the persistence of sleep problems in children with other psychiatric disorders. In children with depression, sleep problems persisted in about one fourth of the children who had recovered from their depression (130). Children with autism spectrum problems had significantly higher prevalence of chronic sleep initiation and/or sleep maintenance problems (39.3%) across four years compared to children without autism spectrum problems (3.6%) (131).

In typically developing children, reported persistence rates of sleep problems vary from 14.9% (80) to 60% (12), dependent on age, follow-up period, and definition of sleep problem. Among children 6 to 8 years of age the persistence rates of the various sleep problems over 14 months varied from 30 to 46% (14). One third of children reporting sleep problems at age 8 still had this at age 12 (132). Sleep initiation problems persisted in about 60% over one year in a population survey of 9–11 year-olds, while about 40% had a persistent sleep problem spanning more than two years (12). Among Chinese children followed from age 9 to 14, persistence rate of insomnia was 14.9% using an insomnia criterion of three times or more a week, rising to 27.4% when more than once a week was the criterion (80). In adolescents insomnia persisted in over 50% of cases across one year (82). As to persistence of the various types of sleep problems; sleep initiation, night waking, snoring, parasomnias, and nightmares persisted in a substantial percentage of children (12-14, 44, 49) but conflicting results have been reported regarding both sleep initiation and night waking problems (12, 13). Bedtime resistance has been described as a transient sleep problem in childhood (13).

The limited amount of studies of persistence of sleep problems in children with psychiatric disorders, gives little indication as to what may represent risk factors for chronicity of sleep problems in this population. Leaning on knowledge from studies in typically developing children and childhood risk factors for adult insomnia one may hypothesize that impaired family functioning and negative life events influence the risk of persistence of sleep problems. In pre-schoolers, negative life events were significantly related to persistent sleep problems (81). In Swedish pre-schoolers being rated as consistently good sleepers was associated with lower prevalence rates of parents with psychiatric problems, marital discord or alcoholic problems compared to children being rated as poor sleepers (49). A study among adolescents suggested that school stress may pose a risk factor for persistence of insomnia (82)**.** In adults with chronic sleep problems childhood adversities (133) and family conflict (134) were childhood factors associated with increased risk for adult insomnia.

2.5 Summary and rationale for the thesis' research questions

In children with anxiety disorders, clinical studies on sleep problems are sparse and there is a lack of studies using controls or studies who adjust for comorbid conditions. Anxiety disorders and ADHD are common comorbid conditions in CAMHS (135), but the role of comorbid ADHD for sleep problems in children with anxiety disorders has not been reported in unmedicated clinical populations. Thus we do not know whether the increased frequency of sleep problems reported in children with both ADHD and anxiety disorders compared to children with anxiety disorders only (83) is associated with the comorbid ADHD per se or is related to an association between stimulant medication and poor sleep. There are only a few clinical studies who have investigated the prevalence of the various types of sleep problems in children with anxiety disorders. The association between sleep problems and emotional/ behavioral problems in children with anxiety disorders has been investigated using parents or self-report of both sleep and emotional/behavioral problems (87, 88, 112). Thus we do not know whether this reported positive association may be partly caused by rater bias, and whether the associated emotional and behavioral problems will display themselves also in out-of-home settings. Despite a known association between insufficient sleep and cognitive functioning in children in general (1), such an association has not been investigated in children with anxiety disorders. Follow-

up studies of sleep problems in children with anxiety disorders are limited to one eight week follow-up study being part of a medication trial (88), thus knowledge of the course and potential predictors of persistence of sleep problems in this population is lacking.

In children with ADHD there are few studies investigating sleep problems before treatment with medication have started. Previous reports of less sleep problems in unmedicated children with ADHD may be biased as the more severe conditions are more likely to have started medication before referral to clinics, making interpretations of findings difficult (118). The influence of comorbid psychiatric conditions on the frequency of sleep problems remains unsettled**.** Both ODD and anxiety disorders are frequently occurring comorbid conditions in ADHD (136) and have both been associated with increased frequency of sleep problems (20). Findings are however divergent with regard to comorbid ODD (118). The assumption that the prevalence of sleep problems is higher in children with ADHD compared to children with other psychiatric conditions (127) has not been confirmed; one study did report higher prevalences of sleep problems in children with ADHD compared to clinical controls (83), but the clinical controls were not children with well-defined psychiatric disorders. The notion that sleep disturbances may exacerbate internalizing and externalizing problems in children with ADHD lacks empirical support. Findings are divergent in clinical samples with regard to this association (105, 112, 137), and no study have used teachers as informants for the behavioral and emotional problems. The association between sleep problems and cognitive function in children with ADHD is unclear (10), with divergent results reported even for attentional functioning, the cognitive function considered most vulnerable towards the effects of sleep insufficiency (33). Investigating the relationship between sleep problems and a neurocognitive test measuring different aspects of attention may add to present knowledge in this regard. And finally, the course and predictors of persistence of sleep problems in ADHD children have, to the best of my knowledge, not previously been reported in clinical samples.

3 AIM AND RESEARCH QUESTIONS

The aim of this thesis is to examine the frequency, associations with behavioural, emotional and attentional functioning, and persistence of sleep problems in a clinical sample of children aged 7 to 13 years of age with anxiety disorders, ADHD or both. We also compare the prevalence and persistence of sleep problems to a group of nonreferred children of similar age and sex. The research questions in the three papers are:

1. What are the frequencies of total and types of sleep problems in children with anxiety disorders and/or ADHD (paper I)?
2. What is the influence of comorbidity on the frequency of sleep problems in children with anxiety disorders and/or ADHD? (paper I)?
3. Is impairment of attentional functioning associated with sleep problems in children with anxiety disorders and/or ADHD? (paper II)?
4. Are teacher ratings of internalizing and externalizing problems associated with sleep problems in children with anxiety disorders and/or ADHD? (paper II)?
5. What is the persistence of total and types sleep problems in children with anxiety disorders and/or ADHD (paper III)?
6. What are the possible predictors of persistence of sleep problems in children with anxiety disorders and/or ADHD (paper III)?

4 MATERIAL AND METHODS

This thesis was part of a larger study focusing on developmental delays/disorders in children with anxiety disorders and ADHD. The Centre for Child and Adolescent Mental Health, Eastern and Southern Norway had the administrative responsibilities for the project. The study and the data collection were performed in collaboration with Lovisenberg Diakonale Hospital and Akershus University Hospital, in that two CAMHS outpatient clinics participated in the study; Nic Waals Institute, and BUP Lillestrøm (now BUP Nedre Romerike). Nic Waals Institute is located in the capital city of Oslo, serving a district of approximately 27 500 children aged 0–18 years, and

Lillestrøm BUP, located in the neighbouring town of Lillestrøm, is serving approximately 35.000 children aged 0–18 years in eight municipalities, both urban and rural areas.

The research group consisted of : Hanne Kristensen, Child and Adolescent Psychiatrist, PhD (project leader); Beate Ørbeck, Neuropsychologist, PhD.; Benedicte Skirbekk MD, PhD fellow; Berit Hjelde Hansen, Child and Adolescent Psychiatrist, PhD fellow.

4.1 Participants

Figure 1 illustrates the recruitment of patients and controls into the study, both initially (T1) and the follow-up assessment (T2).

4.1.1 Inclusion and exclusion criteria at T1

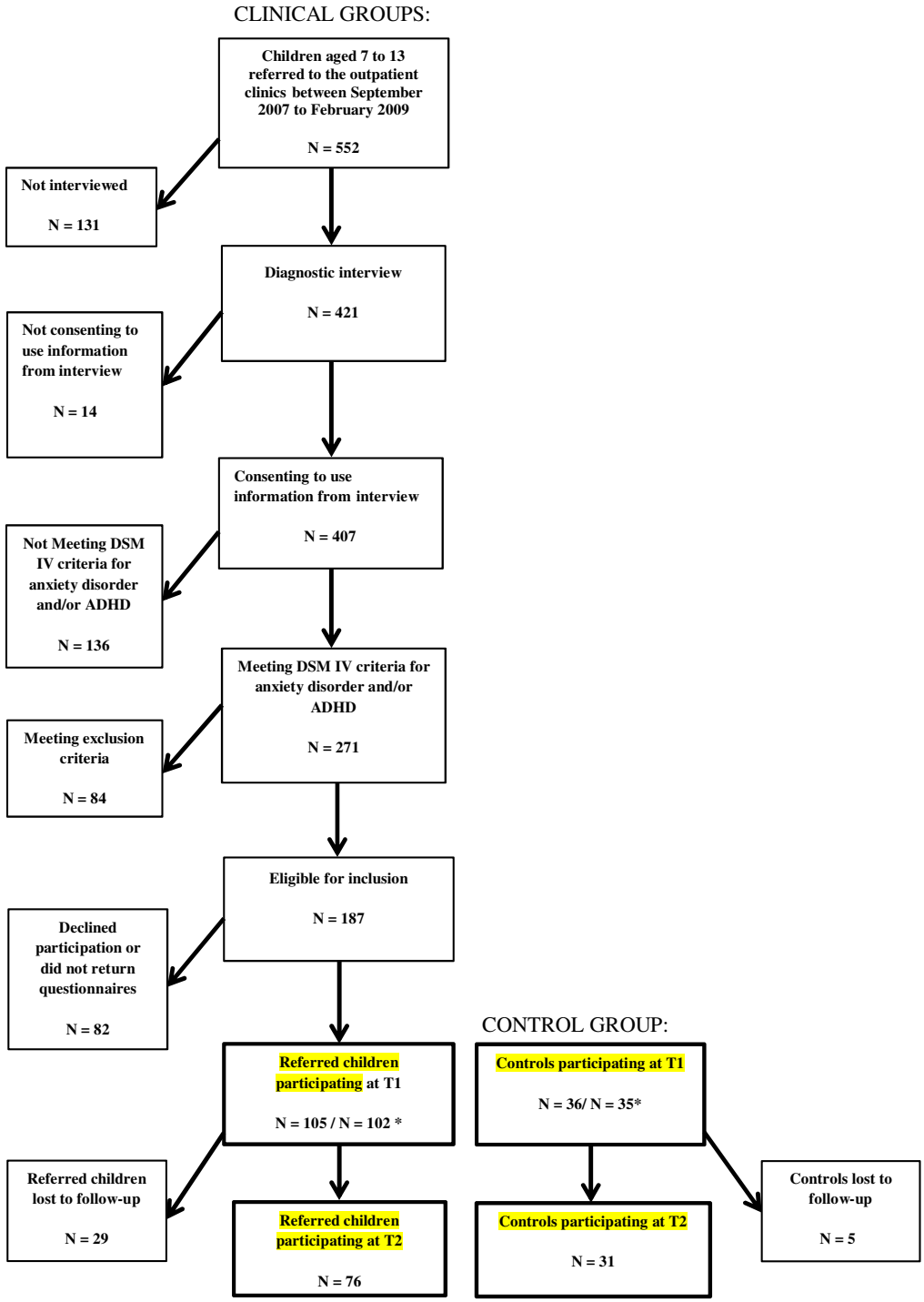
Inclusion criteria for the clinical groups were having turned 7 but not 14 years at time of inclusion and that the parents described symptoms meeting the DSM-IV criteria for any anxiety disorder, ADHD or both according to Kiddie-SADS-PL.

The exclusion criteria were:

- Asperger's disorder, n = 12
- Having ADHD and taking ADHD medication at time of assessment, n = 16
- Having ADHD and subthreshold/lifetime, but not present anxiety disorders, n = 8
- Known neurological disease, n = 4
- Full-scale IQ below 70, n = 9
- Biological mother not available or did not speak Norwegian sufficiently to answer questionnaires, n = 35

Children were included as controls given they had turned 7 and not 14 years at time of inclusion, and that they had not been referred to CAMHS or school psychological service (PPT). Exclusion criteria for the controls were the same as for the clinical group, with the added criterion: meeting diagnostic

Figure 1 Flowchart illustrating recruitment of clinical groups and controls into study



* paper II sample as teacher questionnaires were not returned for 4 children

criteria for any lifetime or present anxiety disorders or ADHD according to DSM-IV after Kiddie-SADS-PL interview with parents.

4.1.2 Participants at T1 (paper I and II)

Paper I sample

Table 3 displays demographic and clinical characteristics for the T1 sample in paper I. Age, sex distribution, family structure, or parental educational level did not differ significantly between the three clinical groups or between clinical groups and controls. There were no significant differences between the clinical groups regarding scores on the Child Global Assessment Scale (CGAS), but the clinical groups scored significantly lower than the controls, which was to be expected. Of the 407 parents of referred children who were interviewed (and gave permission to the use of information from the interview for research purposes, see figure 1) 271 parents (66.6%) described symptoms in their child meeting DSM-IV criteria for either an anxiety disorder, ADHD or both. Among these 271 children, exclusion criteria (see above) applied for 84 children (31.0%). Thus 187 children were eligible for participation in the study, of which 105 children (56.1%) agreed to participate and were included at T1. The group of eligible children included did not differ from eligible children not included in mean age; mean score on the CGAS, sex ratio, any anxiety disorder, ADHD, comorbid anxiety and ADHD, comorbid affective disorder, comorbid ODD/CD, comorbid enuresis/encopresis, or comorbid tics/Tourette's disorder. The 105 referred children included in the study were grouped as follows based on the description by parents given in the Kiddie-SADS PL interview:

- Children with any anxiety disorder and no ADHD, (ANX), n = 41
- Children with ADHD, but no anxiety disorders or sub threshold anxiety disorders, (ADHD), n = 39
- Children with both anxiety disorders and ADHD, (ANX+ADHD), n = 25

Children with ADHD Combined (C) and ADHD Hyperactive/Impulsive (HI) subtype were grouped together, due to a small number of children with the ADHD HI subtype. The distribution of ADHD IA

Table 3 Demographic and clinical characteristics for 141 children participating at T1 and constituting sample for paper I. Complete dataset except where indicated.

	ANX N = 41	ADHD N = 39	ANX+ADHD N = 25	CTRL N = 36
Age mean (SD)	10.9 (2.0)	9.8 (1.6)	10.1 (1.9)	10.7 (2.3)
Gender distribution, n (%)				
Girls	14 (34.1)	9 (23.1)	13 (52.0)	15 (41.7)
Boys	27 (65.9)	30 (76.9)	12 (48.0)	21 (58.3)
Family structure n (%)				
Living with both biological parents	25 (61.0)	20 (51.3)	14 (56.0)	26 (72.2)
Other	16 (39.0)	19 (48.7)	11 (44.0)	10 (27.8)
Parental educational level n (%)				
Mother > 12 years of education	20 (48.8)	26 (66.7)	12 (48.0)	21 (58.3)
Mother 12 years or less	21 (51.2)	13 (33.3)	13 (52.0)	15 (41.7)
Father(n = 133) > 12 years of education	13 (36.1)	19 (50.0)	9 (37.5)	21 (60.0)
Fathers 12 years or less	23 (63.9)	19 (50.0)	15 (62.5)	14 (40.0)
CGAS mean (range)	51.3 (40-65)	52.6 (41-63)	49.9 (41-60)	89.0 (72-97)
Type of anxiety disorder n (%)				0
Separation anxiety	15 (36.6)	0	12 (48.0)	0
Social phobia	16 (39.0)	0	3 (12.0)	0
Specific phobia	10 (24.4)	0	10 (40.0)	0
Generalized anxiety disorder	6 (14.6)	0	2 (8.0)	0
Obsessive Compulsive disorder	10 (24.4)	0	4 (16.0)	0
Agoraphobia	2 (4.9)	0	1 (4.0)	0
Panic Disorder	2 (4.9)	0	0	0
ADHD subtype n (%)				
ADHD IA	0	17 (43.6)	12 (48.0)	0
ADHD C and H/I	0	22 (56.4)	13 (52.0)	0
Other axis I disorders n (%)				
Affective disorder	5 (12.2)	4 (10.3)	2 (8.0)	0
ODD/CD	6 (14.6)	11 (28.8)	7 (28.0)	0
Enuresis/encopresis	3 (7.3)	7 (17.9)	2 (8.0)	0
Tourette's Disorder/tics	7 (17.1)	9 (23.1)	5 (20.0)	1 (2.8)

ANX anxiety disorder ; ANX+ADHD anxiety disorder and comorbid ADHD; CTRL nonreferred controls; SD standard deviation; CGAS Child Global Assessment Scale; IA Inattentive subtype; C Combined subtype; H/I Hyperactive/Impulsive subtype; ODD oppositional defiant disorder; CD conduct disorder

subtype and ADHD C/HI subtypes did not differ significantly between the ADHD and the ANX+ADHD groups.

At time of assessment at T1, none of the children received any psychopharmacological treatment or any specific treatment for their sleep problems.

Thirty-six children were recruited as controls from neighbouring schools. Further description of the recruitment procedure of the controls is given in section 4.2.1. The control group (CTRL) was a convenient sample of typically developing children who had not been referred to CAMHS or PPT. The controls were matched at group level on age, sex ratio, and socio-economic status (SES) measured by parent education level.

Paper II sample

Teachers of four children (3 referred and 1 nonreferred controls) did not return the questionnaires, and these children were excluded for analyses in paper II. Thus 137 children constitute the sample in paper II; 39 children with anxiety disorders and no ADHD (ANX), 38 children with ADHD and no anxiety disorders (ADHD), 25 children with anxiety disorders and comorbid ADHD (ANX+ADHD), and 35 nonreferred controls (CTRL).

4.1.3 Participants at follow-up (paper III)

At the follow-up assessment (T2) after about 18 months, 76 of the 105 (72.4%) referred children agreed to participate: 30 children from the ANX group, 27 from the ADHD group and 19 from the ANX+ADHD group. Thirty-one of the 36 (86.1%) nonreferred children (CTRL), agreed to participate. Thus the follow-up sample consists of 107 children (76 referred children and 31 nonreferred controls), giving an overall follow-up rate of 75.9%. Due to the small sample size, the referred children were considered as one group (CLIN) in the main analyses.

During the follow-up period, the 76 children in the CLIN group had received treatment as usual at the clinics. At T2, 25 children had finished their treatments at the clinics; none of these children were receiving psychopharmacological treatment. Fifty-one children were still receiving treatment at their

clinics; 25 children were receiving psychopharmacological treatment (methylphenidate: n = 18 (23.7%), melatonin: n = 9 (11.8%), selective serotonin reuptake inhibitor (SSRI) n = 2 (2.6%)) in addition to other types of treatment (psychotherapy, family counselling, school counselling), while 26 children were receiving the other types of treatment but no medication.

The referred children who agreed to participate at T2 and the referred children lost to follow-up did not differ on the following variables: mean age, sex ratio, mean score on the CGAS, clinical group (belonging to the ANX, ADHD, or ANX+ADHD group), or other comorbid axis I disorders. Referred children participating at T2 had higher scores at T1 on the Day Time Sleepiness subscale than children lost to follow-up (participants 14.01 (SD 3.39); children lost to follow-up 11.83 (SD 2.89), p = 0.003).

4.2 Procedure

4.2.1 Procedures at T1

The T1data for the clinical groups were collected from September 2007 to February 2009. In this period the two participating clinics implemented a routine to use a diagnostic interview (Kiddie-SADS-PL) when interviewing all parents of children between 7 and 14 years being admitted to the clinics. Exceptions to this rule were some few emergency referrals and children who had recently been assessed at other institutions and according to this assessment either was not meeting inclusion criteria, or was meeting exclusion criteria. Together with a letter informing the family that they were admitted the parents were invited to come in for the interview. One reminder was sent out in case the parents did not show up. A total of 552 children between 7 and 14 years of age were referred to the two CAMHS clinics in the inclusion period, and parents of 421 children (76.3%) were interviewed, while parents of 131 children were not (23.7%), mostly because they did not turn up despite one reminder. All interviewed parents were asked to give a written consent to use information regarding age, sex, reason for referral, and information from the interview for research purposes. Parents of 14 children who were interviewed did not give a written consent to use this information and in addition declined participation in the study. Thus we have no information of a total of 145 children.

All interviews were performed at the clinics by one of the three physicians in the research group.

If the child met criteria for any anxiety disorder or ADHD, and none of the exclusion criteria were applicable, the families were invited to participate in the study. A leaflet with information of the study's purpose and the assessment procedure, including a consent form, was provided for both parents and children. An appointment for the T1 assessment was made after the interview. The assessment took place before the treatment started, and all assessments were performed at the clinics by one member of the research group. The mothers were answering the questionnaires while the child was tested in an adjacent room. A letter was sent to the child's main teacher with information of the research project and questionnaires to be filled out regarding behavioural and emotional problems of the child, including the ASEBA TRF and the Disruptive Behavior Rating Scale (DBRS). Two reminders were sent to the teachers if questionnaires were not returned.

Data from controls were collected between April 2009 and December 2009. Controls were recruited from neighbouring schools. The Regional Committee for Medical and Health Research Ethics (REK) set restrictions to the recruitment procedure for the controls. The invitation to participate had to be conveyed via the teachers who were informed of the study's objectives, and that suitable controls would be typically developing children who had not been referred to CAMHS or PPT. The teachers were asked to contact parents of children they considered suitable by means of an information leaflet and consent form provided by the research group. If the parents returned the consent form and thus agreed to participate, one member of the research group contacted the families and made an appointment for both the interview of the mother and the assessment of the child. The children recruited as controls and their mothers underwent the same procedures as the referred children, and the teachers were given the same questionnaires as the teachers of the referred children. All interviews and assessments were performed by one member of the research group, and scoring of the neuropsychological tests were done by the research group's neuropsychologist. The assessments took place at school during school hours, while the interviews were performed at the family's home, the workplace, by telephone or at the research institution.

4.2.2 Procedures at T2

The written consent given by parents and children at T1 included a permission to be contacted and asked to participate in the follow-up assessment. The T2 assessments took place between 18 and 19 months after the T1 assessments (mean 18.6 months, SD = 1.4).

4.4 Measurements

Instruments used for research purposes should ideally be internationally recognized, standardized instruments with official translations, with known and acceptable psychometric properties and applicable to the study's age group. The instruments in this study were chosen based on to what extent these criteria were met.

4.4.1 The Kaufman Schedule for Affective Disorders and Schizophrenia, present and lifetime version (Kiddie-SADS-PL)

The Kiddie-SADS-PL is a semistructured diagnostic interview for the age group 6–18. It provides DSM-IV Axis 1 present and lifetime psychiatric diagnoses (138). Several revisions of this questionnaire exist; we used a version revised by Birmaher in 2007, which also covered the pervasive developmental disorders. Whenever there was any doubt of a diagnose after the interview, consensus was obtained after a discussion in the research group. Interrater reliability in terms of kappa was 0.88 for any anxiety disorder and 0.90 for ADHD, based on rescoring of audiotapes from 39 randomly selected interviews.

4.4.2 Child Global Assessment Scale (CGAS)

The CGAS represents an assessment of the child's overall severity of disturbance with scores ranging from 1 (lowest functioning) to 100 (excellent functioning) (139). The clinician performing the Kiddie-SADS-PL interview rated the child's level of functioning based on information from parents and referral papers.

4.4.3 The Disruptive Behavior Rating Scale (DBRS)

The DBRS, Teacher Form is a questionnaire completed by the child's teacher which contains the 18 items corresponding to the DSM-IV symptoms of ADHD (140). Teacher rates the occurrence of the

behaviors on a four-point scale: 0 = never, 1 = sometimes, 2 = often and 3 = very often. The questionnaire yields a total score and three subscale scores: hyperactive/impulsive, inattentive and combined subscales corresponding to the DSM-IV ADHD subtypes. High internal reliability values have been demonstrated (141), and in our material, the internal reliability in terms of Cronbachs alfa was 0.94 and 0.92 for the inattentive and the hyperactive/impulsive subscale respectively. This scale was used as an additional instrument to classify ADHD into the different subtypes, in that a symptom was defined as present if described by parents in the Kiddie-SADS-PL interview or endorsed on the DBRS by the teacher. Data were missing for one child with ADHD; in this case ADHD subtyping was based on information from the Kiddie-SADS-PL interview with the parents only.

4.4.4 The Children's Sleep Habit Questionnaire (CSHQ)

This questionnaire was developed as a screening tool for school aged children in order to identify children with sleep disturbances. The design of the questionnaire is based on common clinical symptom presentations of the most prevalent pediatric ICSD-2 diagnoses (142). Parents are asked to recall sleep behaviour occurring over a "typical" week and rate the occurrence of 33 sleep behaviours as occurring "usually" (5–7times/week), "sometimes" (2–4 times/week), or "rarely" (0–1 times/week) on a 1 to 3 scale. Two items are scored on a 0 to 2 scale (tired or falling asleep when watching TV or riding a car). The total score is calculated by summing up the 33 items. Higher scores are indicative of more disturbed sleep. In addition to a total score, the questionnaire provides eight subscale scores: The Bedtime Resistance, the Sleep Onset Delay, the Sleep Duration, the Sleep Anxiety, the Night Wakings, the Parasomnias, the Sleep Disordered Breathing and the Daytime Sleepiness subscale scores. The items of the Daytime Sleepiness subscale do not map onto a specific sleep disorder, but are considered the consequences of either insufficient amount of sleep, or fragmented/disrupted sleep. In a survey of psychometric properties of the CSHQ comparing typically developing children and children with sleep disorders (Behavioural Insomnias, Parasomnias or Sleep Disordered Breathing), internal consistencies in terms of Cronbachs alfa were near or at acceptable level for total score (0.68 and 0.78) and subscale scores (range 0.63 – 0.90), with the exception for poor levels of internal consistencies reported for the Night Wakings (0.44 and 0.54) and Parasomnias subscales (0.36 and

0.56) in both groups, and the Sleep Disordered Breathing subscale (0.51) in the group of typically developing children (142). In this survey, a total score above 41 yielded sensitivity (0.80) and specificity (0.72) which was considered adequate for differentiating between children with and without clinical sleep disturbances. The total CSHQ scores for children with Parasomnias or Sleep Disordered Breathing Disorders were lower than for children with Behavioral Insomnias, reflecting that the total CSHQ score is weighted towards items pertaining to difficulties with initiating and maintaining sleep (142).

The CSHQ has been used in both epidemiological and a variety of clinical populations (143, 144), and in different countries (21, 22). In an evidence-based psychometric assessment of subjective pediatric sleep measures, the CSHQ was considered as "well established" (145). Although the psychometric properties have been reported for the age range 4 to10 only (142), the questionnaire has been used in older children (143). The lack of standardization and norms for the total score and the subscales has been criticized (146).

In this study, the total CSHQ score and the subscale scores were used as both continuous and categorical variables. As a categorical variable, a total CSHQ score above 41 was used as cut off value for having a sleep problem in a clinical range, in accordance with previous studies in both epidemiological (21, 147) and clinical samples (19, 148). When the subscale scores were used as categorical variables and dichotomized, we defined a sleep problem as present if the child was reported to have at least one symptom of the sleep problem subscale occurring at least twice a week.

In our material the internal consistency in terms of Cronbach alfa's were 0.88 for the T1 CSHQ total scores and 0.83 for the T2 CSHQ total scores. Internal consistency for the subscale scores varied from poor level for the Sleep Disordered Breathing subscale (T 1 : 0.26, T2: zero variance items, negative value), the T1 Parasomnias subscale (0.58), the T2 Sleep Anxiety subscale (0.59), the T2 Night Waking subscale (0.49), and acceptable or near acceptable levels for the rest of the subscale scores (0.64 - 0.79).

Three of the CSHQ questionnaires had a total of five missing items at T1, and four of the questionnaires had a total of four missing items at T2. In paper I, the missing values were replaced by

the *median* score of the corresponding subscale, and in paper II and III by the *mean* score of the corresponding subscale when calculating the scale scores.

The questionnaire was downloaded from the official website of the author (JudithOwens: www.kidzzzleep.org), and translated to Norwegian by three separate clinicians: Ståle Pallesen and Ingvild Danielsen at the University of Bergen, and the author of this thesis, then back translated to English and the final version was approved by all three translators. The use of the questionnaire in this research project was approved by the original author.

We used the CSHQ total and subscale scores as outcome variables in paper I and III, and as predictor variables in paper II.

4.4.5 The Attention Network Test for children (ANT)

The ANT is based on a model of attention developed by Posner (149). According to this model, attention consists of 3 anatomically and functionally separate networks each subserving an attention domain: alerting, orienting, and executive control (149, 150). The alerting network provides the capacity to maintain an alert state (tonic alertness) and to increase response readiness to a target subsequent to an external warning stimulus (phasic alertness). The orienting network is involved in the selection of information among multiple inputs, and consists of three operations: disengaging attention from the present focus, moving attention to a new focus, and re-engaging attention to the new focus. The executive control network is engaged in detecting and resolving conflict among responses. Supportive evidence for the relative independence of these networks has been reported (149, 151, 152).

The ANT is a computer based test, developed by Posner and his research group (153), and has been adapted for children (149). No norms are available and some concern has been raised regarding the test-retest reliability of the different networks (154, 155). The test has been widely used in both typically developing children and in clinical populations (149, 154, 156).

The test combines a flanker and cued reaction time test. The target stimulus is a fish presented on the computer screen, and the child is invited to “feed the fish” as quickly as possible by pressing a button

indicating to which direction the fish's mouth is pointing. The different flanker conditions are: *neutral*: the fish is presented alone; *congruent*: target fish presented with other fish swimming in the same direction; *incongruent*: target fish presented with other fish swimming in the opposite direction. The cues are visual warning signals presented before the target stimuli (the fish), and function to inform the child about *when* the fish will be presented or *where* the fish will be presented. The different cue conditions are: *no-cue*; *temporal* and *spatial.* The efficiency of the alerting network is measured as the size of the reduction in the reaction time that accompanies temporally informative cues indicating when the target will occur. The alerting score (ANT Alert) is calculated by subtracting the reaction time after temporally informative cues are given (ANT Double Cue Reaction Time; RT) from the reaction time when no warning signal is given (ANT No Cue RT). The efficiency of the orienting network is measured as the size of the reduction in the reaction time that accompanies spatially informative cues indicating where the target will occur. The orienting score (ANT Orient) is obtained by subtracting the reaction time for the spatial cue condition from the reaction time for the central cue condition (which gives temporally but not spatially informative cue).The efficiency of the executive control network is the size of reduction in reaction time going from incongruent to congruent condition. It is measured by the conflict score (ANT Conflict), which is calculated by subtracting the reaction time in the congruent condition from the reaction time in the incongruent condition. The alerting, orienting, and conflict scores (ANT Alert, ANT Orient, and ANT Conflict) were the main outcome variables in this study, but we also reported the total reaction time (total RT). The results of the ANT at the T1 assessment were used as outcome variables in paper II.

4.4.6 The Achenbach System of Empirically Based Assessment, Teacher Report Form (ASEBA TRF)

The ASEBA TRF is a questionnaire completed by the child's teacher, and consists of 120 problem statements rated on a three-point scale based on the child's behaviour the past two months. In our study the questionnaires were scored using the Achenbach scoring program. Three empirically based broadband symptom scales for Total, Internalizing, and Externalizing Problems were computed in addition to eight narrowband symptom scales: Anxious/Depressed, Withdrawn/Depressed, Somatic

Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behaviour, and Aggressive Behaviour (157). The ASEBA is a standardized and well-documented questionnaire on children's behaviour and mental health, and has demonstrated excellent psychometric properties (157). Higher scores indicate more problems. In our sample the Chronbach alfas for the broad-band symptom scales (raw scores) were: Internalizing Problems 0.92, Externalizing Problems 0.96 and Total Problems 0.97. The raw scores of the broad-band symptom scales reported at T1 were used as outcome variable in paper II.

4.4.7 Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI (158) was used to assess the intelligence quotient (IQ). WASI provides a brief assessment of IQ and has been shown to have high internal and external validity (159). The results of the WASI at the T1 assessment were used as a covariate in paper I and II.

4.4.8 Family structure

At T1, the mothers gave information regarding family structure. The response choices were: child living with both biological parents, with mother or father, with mother and partner, or father and partner, with grandparents, or other. In the analyses, this variable was dichotomized into living with both biological parents, or not. Family structure as reported by the mother at T1 was used as covariates in paper I and III.

4.4.9 Parent educational level

At T1, the mothers gave information on the educational level of both herself and the child's father. In the analyses this variable was dichotomized into having education beyond higher secondary school or not, and labelled as more than 12 years of education versus having 12 years or less. In paper 1, the educational level of each parent was used separately as a predictor in the regression analysis, while in paper III this variable was dichotomized into at least one parent having 12 years or more versus no parent having 12 years or more. This simplification was done in order to reduce the number of variables entered into the regression analysis. Parent education level as reported by the mother at T1 was used as covariate in paper I and III.

Information of educational level was missing for the fathers of 5 children.

4.4.10 Brief Family Assessment Measure (Brief FAM)

The Brief Family Assessment Measure–III (Brief FAM) is a parent- or child-report instrument that provides quantitative indices of family functioning (160). The questionnaire comprises 14 statements about family function, with response alternatives on a 4-point scale from "strongly disagree" to "strongly agree". The higher score is indicative of more difficulties in functioning. We used the raw scores in analysis. The internal consistency for the current sample was acceptable (Cronbach's alpha = 0.80). Two items were missing, and these were replaced by the total score mean value when computing the sum score. Brief FAM total score reported by the mother at T1 was used as predictor variables in paper III.

4.4.11 Life Events

We used a modified version of the Life Events Questionnaire for Adolescents (LEQ-A) (161, 162) to measure life events that occurred between T1 and T2. The questionnaire comprises 37 statements about life events, 25 of which are considered negative life events and the rest positive or ambiguous. At T2, the mothers were asked to indicate whether the event stated had occurred or not the last year, and to indicate the overall impact of the reported events. In our analysis, the total number of life events was used as a variable, but we also analyzed the predictive effect of the items assigned as negative on persistence of sleep problems. The overall internal consistency in our sample was near acceptable (Cronbach's alpha = 0.63). The total number of life events reported by mother at T2 was used as predictor variable in paper III.

4.6 Statistics

4.6.1 Paper I

Non-parametric tests were used to compare total CSHQ scores and CSHQ subscale scores due to non-normality of distribution and presence of outliers. The CSHQ subscale Sleep Onset Delay consists of only one item, and the subscale Sleep Disordered Breathing had low internal consistency (Cronbach's alfa 0.26), thus these subscales were analysed at item level. The categorical subscale variables were

dichotomized by defining a sleep problem as present if reported to occur at least twice a week. Bonferroni corrections were made for multiple comparisons. A hierarchical regression analysis was used to calculate possible predictors of total sleep problem score. The assumption of normality of distribution of the residuals was checked by visual inspection of graphs. The SPSS for Windows Version 15.0 (SPSS Inc.) was used for all data analyses.

4.6.2 Paper II

In this paper multiple linear regression analyses adjusting for age, sex, full-scale IQ and group status (belonging to the ANX, ADHD, ANX+ADHD or CTRL group) were used to explore associations between sleep problems, and performance on the ANT and teacher ratings on the ASEBA TRF. Holm corrections (163) were made for multiple comparisons. The assumption of normality of distribution of the residuals was checked by visual inspection of graphs. All statistical analyses were performed with SPSS version 18.0 for Windows (IBM SPSS) and R (The R Foundation for Statistical Computing, Vienna, Austria). R was used for the Holm correction and to draw the figures.

4.6.3 Paper III

Persistence of both total sleep problems and types of sleep problems from T1 to T2 was analysed. Persistence of sleep problems was analysed as 1) persistence rates of sleep problems; i.e the proportion of the children with a sleep problem at T1 who also had a sleep problem at T2, 2) stability of the CSHQ scores from T1 to T2 by means of Intra Class Correlation Coefficient (ICC), and 3) prevalence of a persistent sleep problem; i.e. the proportion of children having a sleep problem at both T1 and T2. The ICC analysis was not suitable for the Sleep Onset Delay subscale, the Night Wakings subscale, and the Sleep Disordered Breathing subscale, which all had few possible values. A hierarchical linear regression analysis in two steps was used to identify possible predictors of the total CSHQ score at T2. The assumption of normality of distribution of the residuals was checked by visual inspection of graphs, and multicollinearity of the predictor variables was checked by calculating the variance inflating factor (VIF). All statistical analyses were performed with SPSS version 18.0 for Windows

(IBM SPSS) and R (The R Foundation for Statistical Computing). R was used for to calculate the ICC's and confidence intervals (CI) using the bootstrap technique.

4.7 Ethics

Both parents and participants, if eligible, were given written information about the study and were informed that participation was voluntarily, and that they could withdraw from the study at any point. Participation in the study did not preclude or delay start of treatment at the clinics. Written consents from both parents, and the child if 12 years or older, needed to be present before assessments took place. The research group offered to summarize the findings from assessment and enter this in the child's case sheet at the clinic, in case the parents wanted to.

The study was approved by the Regional Committee for Medical and Health Research Ethics. General ethical guidelines for research have been followed. Analyses have been conducted on anonymous data.

5 SUMMARIES OF RESULTS

5.1 Paper I

In this paper we examined and compared the mother's report of sleep problems at T1, both total and types of sleep problems, in referred children with anxiety disorders (ANX), ADHD, combined anxiety disorders and ADHD (ANX+ADHD), and in nonreferred controls (CTRL). We also explored the association between sleep problems and comorbidity with other axis I disorders in the clinical groups.

The total CSHQ score was significantly higher in the referred children compared to nonreferred children (ANX+ADHD median = 53, ANX median = 47, ADHD median = 42, and CTRL median = 37, each clinical group versus CTRL, $p < 0.001$). Children in the ANX and the ANX+ADHD groups had significantly higher total CSHQ score than children in the ADHD group

Sleep problems in a clinical range (total CSHQ score above 41) were reported in 81.8% of children with any anxiety disorder (the ANX and the ANX+ADHD groups combined), significantly higher than in children in ADHD children with no comorbid anxiety disorder (53.8%). Children in the clinical

groups had a significantly higher frequency of having sleep problems in a clinical range than children in the CTRL group (25.0%).

Regarding the various sleep problem types, children in the ANX group were reported to have more bedtime resistance, sleep onset delay, sleep anxiety, sleep duration problems, and parasomnias than the nonreferred controls. Children in the ANX+ADHD group had more sleep onset delay, sleep anxiety, sleep duration variation, night wakings and parasomnias than the nonreferred controls, while children in the ADHD group had more sleep disordered breathing problems than controls. All clinical groups displayed more daytime sleepiness compared to the controls. There were five significant differences between the clinical groups relating to types of sleep problems: the ANX group had more bedtime resistance than the ADHD group, the ANX and ANX+ADHD group had more sleep anxiety than the ADHD group, and the ANX+ADHD group had more night wakings than the ADHD or ANX group.

The total CSHQ score was not significantly correlated with comorbid affective disorder, enuresis/encopresis, or tics/Tourette's disorder, and comorbid ODD/ conduct disorder (CD) did not explain any significant additional variance in total CSHQ score after clinical group status was accounted for.

5.2 Paper II

In this paper we examined the associations between mother reported sleep problems (total and subscale scores of CSHQ), attentional functioning (ANT), and teacher ratings of behavioral and emotional problems (ASEBA TRF) at T1.

The total CSHQ score was significantly associated with attentional functioning in the whole sample, in that the higher CSHQ total score, the lower ANT Alert score in a regression analysis adjusting for age, sex, full-scale IQ and group status (belonging to the ANX, the ADHD, the ANX+ADHD or the CTRL group) (regression coefficient, RC = - 1.85, p = 0.012).

In similar regression analyses with the different CSHQ subscale scores as predictor variables, the Bedtime Resistance and the Sleep Onset Delay subscale scores were significantly associated with a

lower ANT Alert score, and the Sleep Anxiety subscale score was significantly associated with an *increase* in ANT Conflict scores. However, these predictions were nonsignificant after Holm correction.

A series of linear regression analyses was performed to investigate possible associations between sleep problems and teacher ratings on the ASEBA TRF of total problems, internalizing or externalizing problems. No such association was found. However, the Daytime Sleepiness score was significantly associated with the ASEBA TRF broadband scale internalizing problems scores in children in the ANX group (RC = 1.16, Holm adjusted p = 0.011).

5.3 Paper III

In this paper we examined the persistence of sleep problems by means of the mother's report on the CSHQ at both T1 and T2 (after about 18 months). The persistence of both total sleep problems and types of sleep problem across the follow-up period was examined for all groups of children, and the predictive effects of family function, family structure, parent educational level, and stressful life events on sleep problems at follow-up were investigated in the group of referred children. Due to the small sample size, the referred children were considered as one (CLIN) in the main analyses.

Persistence rate of total sleep problems in a clinical range was 72.4 % in the group of referred children. The persistence rates did not differ significantly between children with a T1 diagnosis of anxiety disorder (76.0 %), ADHD (70.6 %), anxiety disorder and ADHD (68.8 %), or the nonreferred controls (50.0 %). Of the referred children who had completed treatment at their clinics, 60.0% had sleep problems in a clinical range at T2, and 44.0% had a persistent sleep problem at T2. Of the referred children who still were receiving treatment, 70.6% had sleep problems in a clinical range at T2, and 60.8% had a persistent sleep problem.

The persistence rates for the different sleep problem types ranged between 56.3% (Bedtime Resistance) and 86% (Parasomnias) in the CLIN group, and between 30.8% (Bedtime Resistance) and 100% (Sleep Onset Delay, Sleep Duration and Sleep Disordered Breathing) in the CTRL group.

In the CLIN group the total CSHQ score at T1 significantly predicted the total sleep problems score at T2 (RC = 0.48, $p < 0.001$), whereas age, sex, parent education level and total number of life events did not. Family function in terms of total score on the Brief FAM and clinical group status at T1 was of borderline significance in predicting total CSHQ at T2.

6 DISCUSSION

6.1 Sleep problems in children with anxiety disorders

The high frequency of sleep problems in children with anxiety disorders in our study corresponds well with previously reported figures (19, 87), however our study is the first to use controls when examining the sleep problems of children with anxiety disorders. The frequency of sleep problems in the children with anxiety disorders was significantly higher than in the nonreferred controls. The frequencies of sleep problems in the nonreferred control group match those of previous population studies (21, 22, 142). The vast majority of the referred children with an anxiety disorder was reported to have a sleep problem in a clinical range. We found that both insomnia and parasomnia symptoms were more frequently reported in children with anxiety disorders compared to nonreferred controls, consistent with results from previous studies (19). This suggests that several aspects of sleep are disturbed in children with anxiety disorders, and that a broad range of sleep behaviors needs to be assessed when treating children with anxiety disorders.

An association between sleep disturbances and emotional problems has previously been described in children with anxiety disorders (e.g. (85)), but has not previously been reported using teachers as informants for the emotional problems. Thus reporter bias caused by using parents as informants for both sleep and emotional problems do not explain the association described in our study, and our findings also demonstrate that the associated increase in internalizing problems applies to out-of-home settings.

Our findings lend support to a hypothesis of a specific association between sleep disturbances and anxiety: The frequency of reported sleep problems in children with anxiety disorders were 3 to 4 times

that of the nonreferred controls, and significantly higher than reported for the children with ADHD. Comorbid disorders such as ADHD, ODD/CD or affective disorders did not explain the higher sleep problem scores. Having a comorbid anxiety disorder was associated with a significant increase of the total sleep problems score in children with ADHD, but not the other way round. A specific association between sleep disturbances and anxiety disorders has previously been suggested based on findings from the Dunedin cohort. In this study an increased risk for adult anxiety disorder but not depression, was found in children reported to have persistent sleep problems in childhood (64). The interrelated mechanisms underlying the relationship between sleep problems and anxiety is poorly understood (96). A strong genetic overlap between anxiety and sleep disturbances has been demonstrated (164), and shared brain structures are involved in both emotional and sleep regulation (38, 101, 102). The bidirectional influence between sleep and anxiety, that is the role of sleep in emotional processing and regulation (165), and that anxiety can interrupt sleep wake regulation mechanisms (99) may be one psychobiological mechanism behind a specific association between anxiety disorders and sleep problems.

In our sample the sleep problems of children with anxiety disorders were associated with impairments in both behavioural and cognitive domains. Children with anxiety disorders were reported by their mothers to display more daytime sleepiness symptoms compared to controls, which is suggestive of daytime consequences of the sleep problems (142). The sleep problems reported by the mother were associated with increased teacher ratings of internalizing problems, and the sleep problems were associated with impaired performance on a test of attentional functioning.

The demonstration of an association between parent reported sleep problems and performance on a formal test of attentional functioning in children with anxiety disorders is novel. Studies in typically developing children and adolescents have reported an association between self-reported sleep problems and an inattentive cognitive profile (127), and in healthy young adults an association between self- reported sleep quality and performance on neuropsycholgical tests (166). The association between sleep problems and impaired alerting functioning in our sample was mainly driven by the effect of bedtime resistance and sleep onset delay problems. These sleep problems may

be symptoms of a variety of sleep disorders in children (Table 1), however most often they are symptoms of insomnia (42). Thus our results may also be compared with results from studies in adults with primary insomnia: these studies demonstrated associations between insomnia and reduced performance on sustained attention tasks that required a response choice (for review see (167)).

The relationships between sleep, attention and anxiety are complex and probably multidirectional: both emotional regulation and attentional functioning are vulnerable towards the effect of insufficient sleep (30, 35)**;** anxiety may impair sleep initiation and maintenance (19, 126), and impairments in attentional functioning have been associated with state anxiety in adults (168); and finally, impaired attentional control and attention bias towards threat are associated with anxiety disorders in children (169), and with insomnia in adults (170)**.**

In accordance with our finding in this respect, future studies of attention function in children with anxiety disorders should consider to control for sleep status, as is suggested for studies on the cognitive function of children with ADHD (124).

6.2 Sleep problems in children with ADHD

The children with ADHD were reported to have more sleep problems than controls, also when controlling for comorbid anxiety disorders, affective disorders, and ODD/CD. The frequency of mother-reported sleep problems in children with ADHD in our study is comparable to previous studies reporting a two to three fold frequency of sleep problems compared to controls (7, 103), and our figures corresponds well with other reports of sleep problems in children with ADHD using the same sleep questionnaire as we did (116). As all the ADHD children in our study were assessed before start of medication our results are not confounded by the effect of stimulant medication on sleep, or by a possible greater severity of the ADHD condition in medicated children. Our findings thus add to existing knowledge on the frequency of sleep problems in children with ADHD.

Comorbid anxiety disorders influenced the frequency of sleep problems in children with ADHD, while comorbid ODD/CD and comorbid affective disorder did not. The finding of increased frequency of sleep problems associated with comorbid anxiety disorder but not with comorbid affective disorder in

children with ADHD is consistent with previous reports (116-118). Our findings underline the importance to systematically look for and treat comorbid anxiety disorders in children with ADHD and sleep problems. Previous studies have reported inconsistent results regarding the role of comorbid ODD/CD for sleep problems in children with ADHD (104, 118, 171). Our findings do not support the assumption that comorbid ODD/CD is associated with an increased frequency of sleep problem in children with ADHD.

Except for daytime sleepiness and sleep disordered breathing, no sleep problem type was reported to occur significantly more often among ADHD children without comorbid anxiety disorder compared to the controls. There was a nonsignificant trend of a longer sleep onset delay among the children in the ADHD group. Our results are partly in contrast with the findings from the meta analysis by Cortese (2009) reporting that children with ADHD and no comorbid anxiety disorder had more daytime sleepiness, sleep disordered breathing problems, more bedtime resistance problems, longer sleep onset delay and increased occurrence of night waking compared to typically developing children (20). The exclusion of ADHD children with sub threshold anxiety disorders in our study may offer one explanation for some of these discrepancies. Although not specifically investigated, a reported clinical impression is that even sub threshold anxiety symptoms may be of importance for bedtime resistance problems and sleep onset difficulties in children with ADHD (4). An implication of such an interpretation is to carefully assess for anxiety symptoms when children with ADHD are reported to have bedtime resistance problems or sleep onset difficulties, even in the absence of a frank anxiety disorder. As for the lack of significant difference in night wakings between ADHD children and nonreferred controls in our study this may be due to the small sample size and hence lack of power to detect the difference as significant.

Regarding associated daytime impairments, we found an association between mother-reported sleep problems and reduced performance on a test of attentional functioning in children with ADHD. Previous studies on the association between sleep and cognition in children with ADHD have yielded contrasting results (10)**.** We investigated the association between sleep problems and the alerting, the orienting and the executive attention network separately, which has previously not been reported. In

our material the total sleep problem score significantly predicted alerting network efficiency. If this finding is replicated, it may offer an explanation for the variability of results when not investigating these different aspects of attentional functioning separately.

We found a reduction in the alerting score (lower ANT Alert score) associated with sleep problems, i.e a reduction of the ability to increase response speed following an external stimulus, reduced *phasic alertness* (150). In our sample ADHD per se was associated with increased phasic alertness (higher ANT alert score) but also an impairment in the *tonic alertness* (higher ANT No Cue RT); that is the ability to maintain alertness when no external stimulus is given (150). This pattern of attentional functioning in children with ADHD is consistent with a theory that suggests that ADHD children have difficulties with arousal regulation in the absence of an alerting cue (150). This could imply that in children with ADHD, sleep insufficiency compromises the effect of the external signals used to compensate for the arousal regulation difficulties.

Our results do not support an assumption of sleep problems to increase behavioural or emotional problems in children with ADHD. Maternal reports of sleep problems did not predict an increase in the teacher's reports of internalizing or externalizing problems in children with ADHD. This is in contrast with one study who reported an association between parental reports of sleep problems and parental reports of behavioural and emotional problems in ADHD children (112). One explanation for this discrepancy may be due to reporter bias as this latter study used parental reports to assess both sleep problems and behavioural problems. Our findings are more in concert with another study reporting no association between actigraphically measured sleep problems and ADHD symptoms in children with ADHD (105).

6.3 Persistence of sleep problems in children with anxiety disorders and/or ADHD

About three quarters of the referred children who had sleep problems in a clinical range at T1 had sleep problems of this magnitude also at T2. The course of sleep problems in children with anxiety disorders and/or ADHD has previously been described over just a few weeks, thus this study represents novel results. The persistence rates and the prevalences of persistent sleep problems in the

nonreferred children in our study are comparable to previously reported rates in community samples (12, 64), validating our findings.

One study reported from an 8 week placebo controlled study of SSRI treatment in children with anxiety disorders; the reported post treatment prevalence rates for the different sleep problems varied between 11% and 27% in the treatment group, and between 41 and 44% in the placebo group (88). These are lower than our figures. Comparisons are difficult, however, as both sleep measurement, study design and the length of follow up period differed.

As to types of sleep problems, persistence rates in our material were high for all types of sleep problems among the referred children (from 56.3% to 86.0%) as well as among the nonreferred children (from 30.8% to 100%). The large majority of the children who had one sleep problem type at initial assessment had the same problem at follow-up 18 months later. Compared to previous findings in typically developing children, we report higher persistence rate of bedtime resistance problems and comparable results regarding the other sleep problem types (12, 13, 44). Sleep problems were persistent in children who were still under treatment as well as in children who had completed treatment at the clinics.

The high rates of persisting sleep problems indicate that sleep problems are not addressed sufficiently in CAMHS. This is problematic, as insufficient sleep is associated with a range of unfavourable outcomes in children as well as their families (172-174), and may lead to poorer prognosis of the disorder itself. Indeed, inadequate sleep during brain development has been hypothesized to cause aberrant neural connections resulting in disruption of cognitive, behavioural or emotional functioning (1, 25).

We did not demonstrate any predictive effect of life events occurring between T1 and T2, family functioning, family structure, parent education level, or diagnostic status at T1 on frequency of sleep problems at T2. As to the role of family functioning, previous results have been inconsistent; in one community based study family conflict during childhood significantly predicted insomnia 18 years later (134), while in another perceived parental support did not predict persistence of insomnia among

adolescents (82). These discrepancies may be because family functioning influences incidence of insomnia but not the persistence of pre-existing insomnia problems, or that the nature of the family dysfunction is of importance. Family conflict may influence persistence of sleep problems while the child's perceived lack of parental support do not.

7 METHODOLOGICAL CONSIDERATIONS

7.1 Study design, sample size and statistical methods

The design and sample size used in this study were originally planned and calculated for examining developmental delays and disorders in children with anxiety disorders. Thus an important question was whether the design and sample size would be appropriate for studying sleep problems in children with anxiety disorders and/or ADHD.

The design of the study is a cross-sectional and prospective case-control study in that cases (children with anxiety disorders and/or ADHD) were compared to controls with regard to a concurrent attribute or characteristic (sleep problems). This design enabled a description of the point prevalence of an important comorbidity in children with two commonly occurring psychiatric disorders in CAMHS. Sleep problems are frequently occurring in typically developing children as well, thus comparison of sleep problems with a nonreferred control group was necessary in order to describe to what degree sleep problems are more frequent among children with psychiatric disorders. The inclusion of children with two different clinical diagnoses enabled a comparison between the groups and hence whether the sleep problems are more specifically associated with children with anxiety disorders or to children with ADHD. The cross sectional design allowed for studying the association between sleep problems and daytime functioning in two major areas: cognitive and behavioral, but did not allow for any interpretations as to direction of influence. The prospective design enabled us to investigate the persistence of the sleep problems in a naturalistic treatment setting.

Calculation of the study's power to detect differences in sleep problems of potential clinical relevance had to be done in retrospect. Although the importance of doing a power analysis before beginning a

study is universally accepted, the role of retrospective power analysis is more controversial, and several approaches have been described (175). One approach is to determine the size of the difference of the measured variables one wants to detect, and then estimate the power of the study to detect a difference of such magnitude. The size of the difference one wants to detect may be based on previously reported differences in the literature, by a pilot study, or by clinical judgement (176, 177). Alternatively one may estimate the study's power to detect as significant the observed difference as found in the study (175). Estimation of a study's power may be done by use of standardized differences and Altman normograms or by statistical programs such as the SPSS (175, 177).

Our results regarding sleep problem types in the children with ADHD was not fully according to our initial hypothesis and previous findings (20), and this may have been caused by the small sample size in our study. To estimate the power to detect as significant the differences in sleep problems between children in the ADHD group (without comorbid anxiety disorder) and nonreferred controls we used standardized differences previously reported in a meta-analysis (20) applied to an Altman normogram. This revealed the study had acceptable power to detect differences of the same magnitude as found in the meta-analysis regarding sleep onset delay (power 0.83), bedtime resistance (power 0.92), but not night wakings (power 0.12).

No such standardized differences had been reported for persistence rates in clinical samples, so for the paper III analyses we used clinical judgement and decided that a difference in persistence rates of 20% or higher might be of potential clinical relevance, and calculated the study's power to detect the observed differences at least as large as this. These retrospective power analyses were done by the SPSS two sample proportion comparison procedure. This revealed that the study was underpowered in order to report as significant the difference in persistence rate of having a sleep problem in a clinical range between the referred and the nonreferred children (persistence rate referred children: 0.72; persistence rate nonreferred children 0.50, power 0.22) and the difference in prevalence of a persistent sleep problem between children still in treatment and children who had completed treatment (prevalence of persistence children still in treatment: 0.71, prevalence of persistence in children completed treatment: 0.44, power 0.66). Further the study was underpowered in order to report as

significant differences in persistence rates between the referred and nonreferred children of the sleep problem types bedtime resistance, sleep duration, sleep anxiety, and sleep disordered breathing (power ranging from 0.24 to 0.46).

As to choice of statistical methods, the continuous sleep problem variables were not normally distributed in our material, and several of the CSHQ subscale variables had outliers. When dealing with outliers or nonnormality of distributions three options are possible: to transform the variable into a more normally distributed variable, to exclude the outliers, or to use statistical methods robust for nonnormality of distribution (176). An attempt to transform variables was not successful in achieving satisfactory normality of the distribution, and given the limited sample size exclusion of outliers would impair the power of our findings. We therefore chose to apply nonparametric tests in our main analyses with the exception of the regression analyses. Regression analyses may be applied when the variables are nonnormally distributed, given the standardized residuals are normally distributed, and this condition was checked by visual inspection of the graphs in cooperation with a statistician. Also, linear regressions are to some extent robust for moderate nonnormality (178).

7.2 Validity

The validity of a study may be split into internal and external validity. Internal validity means that we measure what is intended in the study, and external validity is the extent to which the results of the study can be generalized to other groups (179).

7.2.1 Internal validity

Two types of errors may threaten the internal validity: systematic and random errors. Systematic errors are often grouped into three general categories: selection bias, information bias and confounding bias (179).

Selection bias

In this study a selection bias means the groups compared differ in important aspects (the investigated variables or confounders) as a result of the selection of participants into the study (179).

The children admitted having anxiety disorders may have been more seriously impaired than children admitted having ADHD. Findings from a community based study in Norway suggested that children with anxiety disorders were being admitted to CAMHS at a lower rate than were children with ADHD (180). However, CGAS (global functioning measure) and number of comorbid disorders did not differ significantly between the groups of referred children in our study (Table 3).

A selection bias may have been introduced as children of parents who were not interviewed, or the eligible children who declined participation, or the patients lost to follow-up differed substantially in important aspects.

Parents of 76.3% of the children in the age group admitted to the clinics were interviewed with the Kiddie-SADS-PL. The families not interviewed were some few emergency referrals and children assessed recently at other clinics, but mostly they were parents who did not turn up for the interview. We did not have permission to gather information for these children and their families, thus we cannot exclude that some important aspects of functioning were different in the families not being interviewed; such as socioeconomic status, family functioning or parent psychopathology.

A total of 187 referred children were eligible for inclusion, and 105 children (56.2%) agreed to participate. The group of eligible children included did not differ significantly from eligible children not included in mean age, sex ratio; mean score on the CGAS, clinical group status (belonging to the ANX, ADHD, or ANX+ADHD group) or other comorbid psychiatric disorders.

Of 105 children participating at T1, 76 (75.6%) agreed to participate at T2. The referred children who agreed to participate at T2 and the referred children lost to follow-up did not differ significantly on the following: mean age, sex ratio, mean score on the CGAS, clinical group status (belonging to the ANX, ADHD, or ANX+ADHD group), other comorbid psychiatric disorders, on the total CSHQ score or seven of eight subscale scores at T1. Children participating at T2 had higher scores at T1 on the CSHQ subscale Day Time Sleepiness subscale than nonparticipants which may have introduced a bias in that the slightly more sleep impaired children participated at T2. However, we have no reason to believe this could introduce spurious associations between groups we compare, but it may threaten the external validity of our findings.

The recruitment procedure of the controls may have introduced a bias. Initially we wanted to invite as controls all children in the appropriate age group at the participating schools. This was not approved of due to ethical considerations. Instead we informed the teachers that we wanted to include typically developing children that had not been referred to CAMHS or PPT. The teachers made the initial contact with parents of children considered appropriate. These children may have been especially well-functioning children, and the teacher ratings on the ASEBA TRF broad-band scales in our control sample (see table 2 in paper II) were lower compared to results from a population study in Norwegian children (181). However, the controls were matched on SES and the prevalence of sleep problems in our control group corresponded well with prevalences described in other community samples (22, 142).

Information bias

Information bias may occur as a result of how the information is collected, and whether the information is gathered in the same way across the groups to be compared (179).

The use of parents only as informants for diagnostic assessment may have introduced a bias. Multi informant approaches are generally recommended in child psychiatry (182), and the teachers' information is especially valuable when assessing disorders that may express themselves at school, such as ADHD. The children having anxiety disorders and subthreshold ADHD were included in the anxiety disorders only group in our study; we cannot rule out the possibility that a few of these children could have met criteria for comorbid ADHD had teacher information been included.

The study was not blinded, which may have introduced biased information gathering. This may apply for the diagnostic assessment of the controls; the researchers performing the diagnostic interviews at T1 were not blind to the child being recruited as control. Also the researcher performing the T1 assessments were not blind to the child's diagnostic status.

The possible misclassification of referred children because of lack of multi informant diagnostic assessment could obscure differences between anxious children with and without comorbid ADHD, and the lack of blinding when diagnosing the controls could obscure differences between referred

children and controls. The magnitude of a potential information bias in diagnostic grouping is limited, however, as other measures of emotional and behavioural problems, for instance the teacher ratings on the ASEBA TRF questionnaire differentiated children in the ANX, the ADHD, the ANX+ADHD, and the CTRL groups (see table 2 paper II). As for the lack of blinding of the clinician performing the assessments at T1, it is unlikely that this would introduce considerable bias in this study. This because the assessment results used in this thesis were results from questionnaires answered by the mothers and the teachers, and an objective measure of attentional functioning.

The reliance on a parent questionnaire to assess sleep problems may have introduced a bias. Generally, parents are considered poor reporters of their child's sleep problems (12), while parents of children having anxiety disorders or ADHD may be more aware of their child's sleep problems than are parents of typically developing children (19, 183). These potential reporter biases may have led to an inflation of the difference in sleep problems between referred children and the controls.

The psychometric properties of the CSHQ, and the sensitivity and specificity of the cut off value used to categorize children into having or not having sleep problems in a clinical range, are estimated for American children up to 10 years of age, and not for Norwegian children, or older children. This may have led to misclassification (wrongfully classifying children as having sleep problems in a clinical range, or wrongfully classifying children as not having sleep problems in a clinical range). Using a sleep onset delay of 20 minutes in classifying children into having a sleep onset delay problem might be overly liberal (142), also leading to misclassification. However, the magnitude of a possible misclassification is limited; the 25% point prevalence of sleep problems in a clinical range in the group of nonreferred children in our study corresponds well with findings from larger epidemiological studies (12, 184).

The CSHQ lacks standardization and norms, thus we had to define what may constitute a sleep problem. Our definition of a sleep problem and a persistent sleep problem in paper III may have been overly inclusive. We defined a sleep problem as having at least one symptom of the sleep problem subscale occurring at least twice a week, and a persistent sleep problem was defined as having the same symptom at both T1 and T2. For instance, if a child was reported to "Struggle at bedtime" (one

of six items comprising the Bedtime Resistance subscale) occurring at least twice a week at both T1 and T2, the child was categorized as having a persistent bedtime resistance problem. This procedure was chosen to allow for a better comparison with epidemiological longitudinal studies using the same frequency criteria and definition of persistence of a sleep problem (e.g. (12)).

Regarding the test we used to assess attentional functioning – the ANT for children – there is no agreement as to what constitutes clinically meaningful cut off values, and no norms are available. The ability of the ANT to assess attention has not been questioned; the two subcomponents comprising the ANT (flanker and cued reaction time tests) are well established tests of attention. The test-retest reliability and the ability of the test to separately assess the three attentional networks have however raised some concerns (155).

Confounders

A confounder is a characteristic which is unevenly distributed between the groups of children we compare, and who influences the outcome variables in question, in this thesis the outcome variables sleep problems, behavioural problems, or measures of attention.

In our study, we used different methods to control for confounders. One was the restriction approach, in which predefined exclusion criteria reduced possible confounding effects. Another was application of multivariate regression analysis adjusting for possible relevant confounders.

To adjust for all possible confounders is not possible, however. A too harsh restriction by extensive exclusion criteria may increase internal validity, but as a result, the group of included children may be different from the target population reducing the external validity. The numbers of variables one may include in a regression analysis are restricted by the numbers of participants in the study. And finally, one can only control for the known confounders; as research progresses, we will know of other confounders in the future not controlled for today.

Random errors

Random errors are errors arising purely by chance, and will always be present in measurements. Type I errors are false-positive results; that is the difference or association found in the sample does not

exist in the population (falsely rejecting the null hypothesis), and type II errors occur when true differences or associations in the population are not significant in the sample (falsely failing to reject the null hypothesis) (176).

The p-value is the probability of obtaining a test statistic (a standardized expression of the observation) at least as extreme as the one observed, assuming the null hypothesis is true (185). Thus there is an inherent chance of committing a type I error (falsely rejecting the null hypothesis) when interpreting results based on the level of significance chosen. In addition, when multiple comparisons are made, the chance that one of the significant findings is due to chance increases (176). In this thesis, adjustment for multiple analyses by either the Bonferroni or the Holm method has been applied in order to reduce the risk of type I errors.

The most common reason for type II errors is inadequate sample size; clinically meaningful differences are there but the groups being compared are too small for the difference to reach statistical significance. The best way to avoid this is to perform sample size calculations at the design stage of a study based on knowledge of prevalence, variability and what are clinically important differences of the variable in question, to ensure the sample sizes are adequate to find such a difference (179). In this study, however, the sample sizes were estimated based on knowledge of developmental delay/disorders, and not sleep problems, because the primary focus of the main study was developmental delay/disorders in anxiety disorders. As discussed in section 6.1 retrospective power analyses were performed to ascertain no major type II errors were committed when interpreting the findings from our study.

7.2.2 External validity

External validity regards the applicability of the findings to a larger group than the study sample, in this study to children referred to CAMHS having anxiety disorders and/or ADHD

Parents of 23.7 % of children referred to the two clinics were not interviewed, the main reason being that the parents did not meet for interview after a second reminder, in addition to some to some few emergency referrals. We did not have permission to gather information from this group of patients or

their families. Previous studies have demonstrated that participants and non-participants in clinical studies may differ on important variables (e.g. (186)). We cannot exclude the possibility that important aspects, for instance family function, socioeconomic status or parental psychopathology differed between the families that did meet for interview and those who did not.

The children participating at T1 (56.2% of eligible) did not differ significantly from the ones who did not participate on characteristics such as age, sex ratio, CGAS or comorbid axis I diagnoses. Of the children participating at T1, 27.6% were lost to follow-up at T2. The referred children who agreed to participate at T2 and the referred children who declined did not differ significantly on the following: mean age, sex ratio, mean score on the CGAS, clinical group status (belonging to the ANX, ADHD, or ANX+ADHD group), other comorbid axis I disorders, total sleep problems or sleep problem types at T1 except that the referred children participating at T2 had higher scores at T1 on the CSHQ Day Time Sleepiness subscale than the children lost to follow-up.

The exclusion criteria applied may limit the generalizability of our findings. Twenty-four children with ADHD were excluded because they were taking medication for their ADHD (n = 16), or had subthreshold or lifetime anxiety disorders (n = 8). This constitutes a substantial number of children with ADHD otherwise being eligible. The children who were excluded because they were receiving stimulant medication may be children having a more severe condition. The group of children with ADHD who were excluded because of subthreshold anxiety disorders may have had more sleep problems than the children constituting the ADHD group included (4). Thus, the children with ADHD in our study, and especially the group without comorbid anxiety disorders, may have less sleep problems than children with ADHD attending outpatient clinics in general. However, the frequencies of sleep problems in the ADHD group found in our study correspond with findings in other studies from clinical samples (103, 116, 183). The exclusion criterion of mother's insufficient language skills reduces the generalizability of our findings towards children with mothers not having Norwegian as their native language.

7.3 Strengths and limitation of the study

A major strength of the study is that it provides new information in an understudied field of clinical relevance. The prospective designs allowed reporting novel findings regarding the course of sleep problems in a clinical child psychiatric sample. Other strengths are having well-defined and thoroughly assessed clinical groups and control group, and that the same protocol was followed for cases and controls, as well as the use of a limited number of experienced clinicians both as interviewers and when assessing the children.

We made an effort to interview parents of all children in the age group referred to the participating clinics, regardless of reason for referral, and the clinics represent the treatment option for the large majority of children in the cover area.

We used a multiassessment design in that interviews, questionnaires and objective tests were used to assess the children. We also a multiinformant design to assess associations between sleep problems and behavioral and emotional functioning.

Well established instruments with known and acceptable psychometric properties were used for diagnostic assessment (Kiddie-SADS-PL), ratings of emotional/behavorial problems (ASEBA TRF), and sleep problems (CSHQ). The assessment followed the same written protocol for both referred children and the children recruited as controls. Three experienced clinicians performed all the Kiddie-SADS-PL interviews at T1, and the inter-rater reliability scores were acceptable. The cognitive tests were administered by specially trained experienced clinicians. The WASI was scored by an experienced neuropsychologist, and the ANT scored by the ANT computerized scoring program. The Kiddie-SADS-PL and the ASEBA TRF are available in official Norwegian translations. The CSHQ were translated into Norwegian prior to initialisation of this study by three professionals, and the translation procedure included translation back to English by an independent translator.

One major limitation of the study is the small sample size, which reduced the statistical power of our analyses. Thus nonsignificant findings need to be interpreted with caution in order to avoid type II errors. This applies in particular for the lack of significant difference between children with ADHD

and nonreferred controls on frequency of night wakings, the lack of significant difference in overall persistence rate between referred and nonreferred children, and on the lack of difference in prevalence of a persistent sleep problem between referred children completed treatment and referred children still in treatment.

There are also major limitations regarding the assessment of sleep problems. The lack of standardization and norms is a limitation of the CSHQ (187). The use of only parent reports to assess sleep problems in the child poses a limitation as well. Including self-report or sleep diary could reduce reporter or recall bias, and a sleep diary could have given information on day to day variation and more accurate figures on sleep onset delay and sleep duration. Although the use of objective methods to assess for some primary sleep disorders would have imposed a too costly assessment procedure, an interview of parents and/or child on symptoms of primary sleep disorders could have increased the study's validity and relevance.

8 SUMMARY, CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Our findings demonstrate that children referred to CAMHS who are diagnosed with anxiety disorders and/or ADHD have high frequencies of sleep problems. About three quarters of the referred children have sleep problems in a clinical range. Children with anxiety disorders have more sleep problems compared to children with ADHD. Bedtime resistance symptoms, sleep anxiety, sleep onset delay, sleep duration, parasomnias and daytime sleepiness are problems reported to occur more frequently in children having any anxiety disorder compared to nonreferred children, while sleep disordered breathing and daytime sleepiness are the only specific sleep problems reported to occur more often among children with ADHD and no comorbid anxiety disorders. The reported sleep problems are associated with impaired daytime functioning; impaired attentional functioning for all children and increased internalizing problems for children with anxiety disorders and no comorbid ADHD. The sleep problems are persistent; of the referred children having sleep problems in a clinical range at initial assessment, the sleep problems remained in this range at follow-up in about three quarters of the children.

Our findings stress the need to be more aware of sleep problems in child psychiatric practice. In children having an anxiety disorder, by definition already impaired by their emotional problems, having sleep problems was associated with an increase of internalizing symptoms as observed and rated by their teachers, and for children in general, mother reports of sleep problems were associated with impaired performance on a test of attentional functioning.

The sleep problems are frequent, they are associated with impairments in daytime functioning, and they are persistent. Thus there is a need to properly assess for sleep problems, implement targeted interventions strategies as well as monitor the sleep problems during the course of treatment in CAMHS. In contrast to this, available guidelines for treating both anxiety disorders and ADHD include no recommendation for assessing and treating comorbid sleep problems (188-190). This may be due to lack of awareness of the importance of sleep in CAMHS, or because sleep problems are being conceived as secondary or intrinsic to psychiatric disorder, and are consequently anticipated to remit in parallel with the primary disorder. And finally, the lack of evidence based treatments for sleep problems comorbid to psychiatric disorders in children may also be of concern.

There is a need for more research in both developing and implementing efficient treatment strategies for sleep problems in children with anxiety disorders and/or ADHD. We need to know what may be efficient strategies for alleviating sleep problems in children with psychiatric disorders, general sleep problem interventions or specifically tailored to the psychiatric disorder. Previous studies have demonstrated short term efficiency of SSRIs for comorbid sleep problems in children with anxiety disorders, in that fluvoxamine reduced insomnia and reluctance to sleep alone to a higher degree than did placebo (88). But the efficiency of non-pharmacological treatments of sleep problems in anxious youths has not been investigated. In children with ADHD, some promising findings suggest that even brief behavioural interventions significantly reduce the sleep problems in children with ADHD (191).

We also need to know whether there are gains in treatment efficiency for both the ADHD and the anxiety disorders if the comorbid sleep problems are successfully treated. In children with ADHD and sleep disorders (sleep disordered breathing) treating the sleep disorder also reduced the ADHD

symptoms (6). However, we do not know whether this will apply when treating other sleep problems or sleep disorders in children with ADHD, or whether treating sleep problems or sleep disorders in children with anxiety disorders will reduce anxiety symptoms.

We also need to know to what degree to which treating sleep problems in children having psychiatric disorders will improve other areas of functioning. Sleep problems are just one of many problems facing patients and their families in CAMHS, leading clinicians to prioritize other problems. However, sleep problem interventions have the potential of improving habits and interactions influencing other areas, such as home routines and parental behaviour regulating skills, and self-regulating skills in the child. In addition, improved sleep in the child has the potential to improve quality of life and psychosocial functioning for the parents and the family (192, 193).

Prospective studies are needed to clarify to what degree sleep problems persist despite remittance of the psychiatric disorder, and to what degree persistence of sleep problems predicts outcome of the disorder itself or functional outcome. Finally we need to know whether treating sleep problems in children with psychiatric disorders will reduce the risk sleep problems continuing into adulthood.

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Appendix: Children's Sleep Habit Questionnaire – Norwegian Version

Søvnvaner hos barn (4-12 år)

Påstandene under er om ditt barns søvnvaner og mulige søvnproblemer. Tenk på den siste uka i barnets liv når du svarer på spørsmålene. Dersom den siste uken var uvanlig av en eller annen grunn (som for eksempel at barnet var sykt og derfor sov dårlig eller at TV var gått i stykker), tenk da tilbake på uka nærmest i tid som var en vanlig uke. Svar VANLIGVIS dersom noe inntreffer **5 ganger eller oftere** i løpet av en uke; svar NOEN GANGER, dersom det inntreffer **2-4 ganger** i en uke; svar SJELDEN om noe inntreffer **aldri eller 1 gang** i løpet av en uke. Vær vennlig også å oppgi om søvnvanen er et problem ved å sette ring rundt "Ja", "Nei" eller ikke aktuelt "IA".

Leggetidspunkt
Skriv tidspunktet for når barnet går til sengs: _____

		Vanligvis (5-7)	Noen ganger (2-4)	Sjelden (0-1)	Problem?		
1)	Barnet legger seg til samme tid hver kveld	☐	☐	☐	Ja	Nei	IA
2)	Barnet sovner innen 20 minutter etter at det har lagt seg	☐	☐	☐	Ja	Nei	IA
3)	Barnet sovner inn alene i sin egen seng	☐	☐	☐	Ja	Nei	IA
4)	Barnet sovner inn i sengen til foreldre eller søsken	☐	☐	☐	Ja	Nei	IA
5)	Barnet trenger å ha en av foreldrene til stede i rommet for å sovne inn	☐	☐	☐	Ja	Nei	IA
6)	Barnet protesterer mot å legge seg (gråter, nekter å være i sengen etc.)	☐	☐	☐	Ja	Nei	IA
7)	Barnet er redd for å sove i mørket	☐	☐	☐	Ja	Nei	IA
8)	Barnet er redd for å sove alene	☐	☐	☐	Ja	Nei	IA

Søvnatferd
Barnes vanlige mengde søvn oppnådd per døgn: _____timer og _____ minutter (sum av nattesøvn og blunder på dagtid)

		Vanligvis (5-7)	Noen ganger (2-4)	Sjelden (0-1)	Problem?		
9)	Barnet sover for lite	☐	☐	☐	Ja	Nei	IA
10)	Barnet får tilstrekkelig mengde søvn	☐	☐	☐	Ja	Nei	IA
11)	Barnet sover omtrent like mye hvert døgn	☐	☐	☐	Ja	Nei	IA
12)	Barnet tisser i sengen om natten	☐	☐	☐	Ja	Nei	IA
13)	Barnet snakker i søvne	☐	☐	☐	Ja	Nei	IA
14)	Barnet er urolig og beveger seg mye mens det sover	☐	☐	☐	Ja	Nei	IA
15)	Barnet går i søvne om natten	☐	☐	☐	Ja	Nei	IA
16)	Barnet flytter seg til en annens seng i løpet av natten (foreldre, bror, søster, etc.)	☐	☐	☐	Ja	Nei	IA
17)	Barnet skjærer tenner når det sover (tannlegen kan ha informert deg om dette)	☐	☐	☐	Ja	Nei	IA
18)	Barnet snorker høyt	☐	☐	☐	Ja	Nei	IA

Søvnatferd (fortsettelse)

		Vanligvis (5-7)	Noen ganger (2-4)	Sjelden (0-1)	Problem?		
19)	Barnet ser ut til å stoppe å puste under søvn	☐	☐	☐	Ja	Nei	IA
20)	Barnet pruster og/eller gisper etter luft under søvn	☐	☐	☐	Ja	Nei	IA
21)	Barnet har vansker med å sove når det er borte fra hjemmet (besøke slektninger, ferier)	☐	☐	☐	Ja	Nei	IA
22)	Barnet våkner skrikende om natten, svetter og er vanskelig å roe ned/trøste	☐	☐	☐	Ja	Nei	IA
23)	Barnet våker redd pga en skremmende drøm	☐	☐	☐	Ja	Nei	IA

Nattlige oppvåkninger

24)	Barnet våkner en gang i løpet av natten	☐	☐	☐	Ja	Nei	IA
25)	Barnet våkner mer enn en gang i løpet av natten	☐	☐	☐	Ja	Nei	IA

Skriv ned hvor mange minutter en nattlig oppvåkning vanligvis varer: _____

Oppvåkning om morgenen/søvnighet på dagtid

Skriv ned tidspunktet for når barnet vanligvis våkner om morgenen: _____

		Vanligvis (5-7)	Noen ganger (2-4)	Sjelden (0-1)	Problem?		
26)	Barnet våkner av seg selv	☐	☐	☐	Ja	Nei	IA
27)	Barnet er i dårlig humør når det våkner	☐	☐	☐	Ja	Nei	IA
28)	Voksne eller søsken vekker barnet	☐	☐	☐	Ja	Nei	IA
29)	Barnet har vansker med å komme seg opp av sengen om morgenen	☐	☐	☐	Ja	Nei	IA
30)	Barnet bruker lang tid på å bli ordentlig våken om morgenen	☐	☐	☐	Ja	Nei	IA
31)	Barnet virker trett	☐	☐	☐	Ja	Nei	IA

Barnet har virket veldig søvnig eller har sovnet i disse situasjonene (kryss av for det som passer):

		Ikke søvnig	Veldig søvnig	Faller i søvn
32)	Se på TV	☐	☐	☐
33)	Passasjer i bil	☐	☐	☐

Kilde: Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1-9. Til norsk ved Yngvild Sørebø Danielsen, Berit Hjelde Hansen og Ståle Pallesen.

I

II

Associations between Sleep Problems and Attentional and Behavioral Functioning in Children with Anxiety Disorders and ADHD

Running head: Associations of sleep problems in anxiety disorders and ADHD

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Berit Hjelde Hansen, Benedicte Skirbekk, Beate Oerbeck, Tore Wentzel-Larsen, and Hanne Kristensen declare no conflicts of interest.

ABSTRACT

This study examined associations between sleep problems and attentional and behavioral functioning in 137 children aged 7-13 years with anxiety disorders (n = 39), ADHD (n = 38), combined anxiety disorder and ADHD (n = 25) and 35 controls. Diagnoses were made using the semistructured diagnostic interview Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version. Sleep problems were assessed using the Children's Sleep Habits Questionnaire; attention was measured by the Attention Network Test and behavioral problems by teacher ratings on the Achenbach System of Empirically Based Assessment, Teacher Report Form. Sleep problems were associated with reduced efficiency of the alerting attention system for all children, and with increased internalizing problems in children with anxiety disorders.

Accumulating evidence indicates that inadequate sleep is associated with behavioral and emotional problems and impairments in cognitive functions in children (Beebe, 2011). Cross sectional studies in typically developing children have reported associations between sleep disturbances and internalizing problems (Alfano, Zakem, Costa, Taylor, & Weems, 2009), externalizing problems (Aronen, Paavonen, Fjallberg, Soininen, & Torronen, 2000), and impairments in neurocognitive functions such as working memory (Steenari et al., 2003) and attention (Sawyer et al., 2009). Longitudinal studies have demonstrated that sleep problems in preschool predict emotional and externalizing behavioral problems (Gregory & O'Connor, 2002), as well as impaired performance on neurocognitive tests (Gregory, Caspi, Moffitt, & Poulton, 2009) in adolescents.

Knowledge of how sleep problems may influence the daytime functioning in children with psychiatric disorders is limited, however, despite the high prevalence of sleep problems in this population (Ivanenko, Crabtree, O'Brien, & Gozal, 2006). Anxiety disorders and ADHD represent two of the most prevalent childhood psychiatric disorders (Costello, Egger, & Angold, 2005) and the frequencies of sleep problems in these populations are high (Alfano, Pina, Zerr, & Villalta, 2010; Cortese, Faraone, Konofal, & Lecendreux, 2009; Hansen, Skirbekk, Oerbeck, Richter, & Kristensen, 2011). Thus more knowledge is needed regarding the association between sleep problems and daytime functioning in these diagnostic groups.

In children with anxiety disorders, one study reported that parent/clinician-rated sleep problems correlated with the severity of anxiety symptoms and at-home impairment, but not out-of- home impairment, as rated by a clinician using the Pediatric Anxiety Rating Scale (Alfano, Ginsburg, & Kingery, 2007). Another study found that parent- and child- reported sleep problems correlated with child- reported anxiety (Chase & Pincus, 2011). In a study of a

mixed clinical group of children (including those with anxiety disorders and ADHD) parent-reported sleep problems correlated with the severity of parent-reported internalizing and externalizing behavioral problems (Ivanenko, et al., 2006).

Regarding neurocognitive functions, the relationship between sleep problems and performance on formal tests of cognitive functions has, to the best of our knowledge, not been investigated in children with anxiety disorders. Impairment in different aspects of attentional functioning has been demonstrated in anxious children (Britton et al., 2012; White, McDermott, Degnan, Henderson, & Fox, 2011), but how attentional functioning is associated with sleep problems in children with anxiety disorders has not been investigated.

In children with ADHD insufficient sleep is assumed to exacerbate both behavioral and emotional problems (Owens, 2005), but findings are divergent. Parent-reported sleep problems in children with ADHD correlated with parent-rated externalizing and internalizing symptoms (Choi, Yoon, Kim, Chung, & Yoo, 2010), while another study failed to find significant associations between actigraphically measured sleep onset delay and parent ratings of ADHD symptoms (Hvolby, Jorgensen, & Bilenberg, 2008).

Studies examining the relationship between sleep and performance on tests of attentional functioning in children with ADHD have yielded conflicting results. Subjectively reported sleep problems were associated with increased distractibility, but not inattention or impulsivity (Sawyer, et al., 2009), and sleep restriction was associated with impaired sustained attention (Gruber et al., 2011) in children with ADHD. In contrast, actigraphically measured sleep quality was not associated with reduced performance in a range of neurocognitive tasks (including attention) in boys with ADHD (Gruber & Sadeh, 2004). How sleep problems are related to functioning of the different attentional networks as described by Fan & Posner (2004) has not been reported in children with ADHD. Findings from sleep deprivation studies in healthy adults suggest that these networks are differently affected by

sleep insufficiency. One study found that sleep deprivation can affect the orienting and executive control domains (Martella, Casagrande, & Lupianez, 2011), whereas another study suggested that it may only be executive control domain that is impacted (Jugovac & Cavallero, 2012). Caution is however called for when comparing results from experimental sleep deprivation studies to associations with subjectively reported sleep problems.

In the present study, we examined the relationships between sleep problems, attentional functioning and internalizing and externalizing problems, in a clinical sample of children with anxiety disorder and/or ADHD and nonreferred controls. More specifically, we explored the associations between sleep problems reported by the mother, and 1) performance on a test measuring various aspects of attention and 2) teacher ratings of internalizing and externalizing problems. Based on research with adults, we hypothesized that the executive control attention network would be negatively influenced by sleep problems. Based on previous research with children, we hypothesized that sleep problems would be associated with an increase in internalizing problems in children with anxiety disorders and with increases in both internalizing and externalizing problems in children with ADHD.

METHOD

Participants

The sample consisted of 137 children aged between 7 and 13 years (87 boys, 50 girls), comprising 102 referrals to two outpatient mental health clinics in Norway and 35 children recruited as controls. The clinical sample was recruited from 421 children referred to the clinics from primary health care for evaluation, diagnosis and management of their behavioral and emotional problems, and all children were undiagnosed at time of referral. They were eligible for inclusion in the study if they met the diagnostic criteria for any anxiety disorder or

ADHD after the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version (K-SADS-PL) interview with the parents. Of 271 children with anxiety disorder and/or ADHD, a total of 84 children (31.0%) were excluded because they met the diagnostic criteria for Asperger's disorder or autism (n = 12, 14.3%), had ADHD in combination with lifetime anxiety disorder or present subthreshold anxiety disorder (n = 8, 9.5%), known neurological disease according to their referral papers or parent information (n = 4, 4.8%), full-scale intelligence quotient (IQ) below 70 according to their referral papers or based on the assessment results (n = 9, 10.7%), had started medication for ADHD before referral to the clinics (n = 16, 19.0%), or the biological mother was not available or did not speak Norwegian sufficiently well to answer the questionnaires (n = 35, 41.7%). Eighty-two families (43.9% of eligible) declined participation, and the teachers of three children did not return the questionnaires. The group of eligible children participating in the study did not differ from the eligible children who did not participate in terms of their mean age, mean score on the Children's Global Assessment Scale (CGAS), or sex ratio.

The controls were children recruited from nearby schools with no history of referral to school psychology services or mental health services. We used the same exclusion criteria for the controls, with the additional proviso that they had not been diagnosed with any present or lifetime anxiety disorder, or ADHD.

Based on their diagnoses after the K-SADS-PL interviews with their parents, the referred children were grouped as follows: 39 children with anxiety disorders and no ADHD (ANX); 38 children with ADHD with no comorbid anxiety disorder (ADHD); and 25 children with comorbid anxiety disorder and ADHD (ANX+ADHD). The types of anxiety disorders in the ANX and the ANX+ADHD groups (n = 64) were: separation anxiety disorder, 26 (40.6%); specific phobia, 20 (31.3%); social anxiety disorder, 19 (29.7 %); obsessive compulsive disorder (OCD), 13 (20.3%); generalized anxiety disorder, 8 (12.5%); agoraphobia; 3 (4.7%);

and panic disorder, 2 (3.1%). None of the participating children was receiving psychopharmacological treatment at the time of assessment, including anti-anxiety medication.

Measures

The K-SADS-PL is a semi-structured interview that provides axis 1 psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (Kaufman et al., 1997). Three of the authors, all of whom are experienced clinicians, performed the interviews. In this study, interrater reliability in terms of kappa was 0.88 for any anxiety disorder and 0.90 for ADHD, based on the rescored audiotapes from 39 randomly selected interviews.

The Children's Global Assessment Scale (CGAS) assesses a child's overall severity of disturbance, with scores ranging from 1 (lowest functioning) to 100 (excellent functioning) (Shaffer et al., 1983). The K-SADS-PL interviewer rated the child's overall functioning based on parental descriptions immediately after the interview was completed.

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to assess IQ. The WASI provides a brief assessment of IQ and has been shown to have high internal and external validity (Canivez, Konold, Collins, & Wilson, 2009).

The Children's Sleep Habits Questionnaire (CSHQ) is a parental questionnaire that was developed as a screening instrument for schoolchildren. Parents rate 33 sleep habits or sleep problems as occurring "usually" (5 - 7 times/week), "sometimes" (2 - 4 times/week), or "rarely" (0 - 1 times/week) in the most recent typical week. Parents are also asked to supply information on bedtime schedules and estimated nightly sleep times. The questionnaire provides a total sleep problems score (total CSHQ score) and eight subscale scores. Seven subscales reflect the symptoms of common sleep disorders in childhood: the Bedtime

Resistance (6 items), Sleep Onset Delay (1 item), Sleep Duration (3 items), Sleep Anxiety (4 items), Nighttime Wakings (3 items), Parasomnias (7 items), and Sleep Disordered Breathing (3 items) subscales. The eighth subscale is the Daytime Sleepiness subscale (8 items), which describes behavior upon getting up in the morning and tiredness during the day, which are considered to be consequences of inadequate sleep. A higher score indicates more sleep problems. Acceptable test-retest reliability and validity have been reported for the CSHQ (Owens, Spirito, & McGuinn, 2000). The total CSHQ score and the eight subscale scores were used as predictor variables in our analyses.

The Achenbach System of Empirically Based Assessment, Teacher Report Form (ASEBA TRF) is a teacher-rated questionnaire consisting of 120 problem statements that are rated on a three-point scale: not true (0), somewhat or sometimes true (1) and very or often true (2) during the preceding two months. The scores are grouped into eight syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior and aggressive behavior. The eight syndrome scales are in turn grouped into broadband scales: the *internalizing problems* score (anxious/depressed, withdrawn/depressed, and somatic complaints), the *externalizing problems* score (rule-breaking behavior and aggressive behavior), and the *total problems score* (all eight syndrome scales). The ASEBA TRF is a standardized and well-documented questionnaire that is used to assess children's behavior and mental health, and has excellent psychometric properties (Achenbach & Rescorla, 2001). We scored the questionnaire using the Achenbach scoring program. The unadjusted raw scores of the total problem score, the internalizing problem score and the externalizing problem score were used as outcome variables. Higher scores on the ASEBA TRF indicate more problems.

The Attention Network Test (ANT) for children is a computer-based test to assess the efficiency of three attention networks: alerting, orienting and executive control (Rueda et al.,

2004). The alerting network provides the capacity to achieve and maintain a state of high sensitivity to incoming stimuli. The orienting network is involved in the selection of information from multiple inputs, and consists of three operations: disengaging attention from the present focus, moving attention to a new focus, and reengaging attention with the new focus. The executive control network is involved in detecting and resolving conflicts between responses. The ANT combines a flanker task and a cued reaction time task. The target is a fish, that is presented either alone (neutral flanker condition), with other fish swimming in the same direction (congruent flanker condition) or with other fish swimming in the opposite direction (incongruent flanker condition). The cues are visual warning signals presented before the target stimulus and function to inform the participant of the spatial location of the target stimulus (i.e., *where* the target will be presented), and/or the timing of the target presentation (i.e., *when* the target will be presented). There is also a no- cue condition (no warning signal). The efficiency of the alerting network is measured as the reduction in reaction time associated with the temporal warning signal. The alerting score (ANT Alert) is calculated by subtracting the reaction time after temporally informative cues are given (ANT Double Cue Reaction Time, RT) from the reaction time when no warning signal is given (ANT No Cue RT). The efficiency of the orienting network is measured as the reduction in reaction time associated with the spatial warning signal, and the orienting score (ANT Orient) is obtained by subtracting the reaction time for the spatial cue condition from the reaction time for the central cue condition (temporally but not spatially informative cue). The efficiency of the executive control network is measured by the conflict score (ANT Conflict), which is calculated by subtracting the reaction time in the congruent condition from the reaction time in the incongruent condition. The alerting, orienting and conflict scores (ANT Alert, ANT Orient and ANT Conflict) were the main outcome variables in our analysis, but we also report the total reaction time (total RT).

Procedure

Parents of children aged between 7 and 13 years consecutively referred to two outpatient clinics in the Oslo area of Norway between September 2007 and February 2009 were interviewed using the K-SADS-PL. The families were asked to participate if the child's symptoms met the criteria for an anxiety disorder or ADHD, and none of the exclusion criteria applied. Of the 421 parents interviewed, 271 (64.4%) described symptoms in their children that met the criteria for an anxiety disorder or ADHD: of these, 84 children (31.0%) were excluded from participation because they met one or more of the exclusion criteria. Of the remaining 187 eligible children, 102 families (54.5%) consented to participate and had the questionnaires returned by the child's teacher. After the families gave their consent to participate, an appointment was made for the assessment, which took place within 1 - 4 weeks, and a letter was sent to the child's main teacher with a questionnaire about the child's internalizing and externalizing behavioral problems (the ASEBA TRF). The referred and nonreferred children underwent the same assessments and diagnostic procedures, with the assessments being carried out during the morning hours for the large majority of children (n = 120, 87.6%). While the mothers completed the questionnaires and gave information on parental education level, the children were tested in an adjacent room. All assessments were performed by the first, second, third or last author.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The parents, and the children 12 years and older, gave their written consent to participate in the study.

Statistical Analysis

The groups were compared with the χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Associations between the sleep variables as predictors and the ANT outcome variables were investigated with a linear regression model adjusting for age, sex, full-scale IQ, and clinical group status. One regression analysis was performed for each sleep variable (the total CSHQ score and eight CSHQ subscale scores) as predictor variable. We used the Holm correction method (Aickin & Gensler, 1996) to control the family-wise error rate across the multiple regression analyses with sleep subscale scores as predictors. We used the same linear regression model to examine associations between the sleep variables (predictors) and the ASEBA TRF broadband scales (outcome variables), with the addition of a second step to include the interactions between clinical groups and sleep variables. Holm adjustments were made for multiple analyses in the final step of the analysis where sleep subscales were predictors for the different clinical groups. All probabilities reported are two-tailed. A total of five items was missing in four sleep questionnaires. These were replaced with the mean score of the corresponding subscale when computing the sum scores. Estimated sleep time was available for 127 children, and information regarding the father's education level was available for 129 children. These missing values were not replaced. All other dataset were complete, including results of the WASI.

All statistical analyses were performed with SPSS version 18.0 for Windows (IBM SPSS) and R (The R Foundation for Statistical Computing, Vienna, Austria). R was used for the Holm correction and to draw the figures.

RESULTS

The distribution in the four groups of children of demographics, sleep problems, parents' estimate of sleep time, teacher ratings of total problems, internalizing and externalizing problems, and ANT variables are displayed in Tables 1 and 2.

Children with ADHD (with and without comorbid ANX) had slower reaction times than nonreferred controls when no warning signal was given prior to the target stimulus (higher ANT No Cue RT). Children with ADHD only (without comorbid ANX) had higher ANT Alert scores than nonreferred controls, that is, the warning signal reduced the ADHD children's response times more than it reduced the response times of the nonreferred control children (see Fig. 1).

Performance on the Attention Test Predicted by Sleep Variables

The total CSHQ score significantly predicted the ANT Alert score in the whole sample (Table 3). An *increase* in total sleep problems (higher total CSHQ score) predicted *lower* alerting scores; that is, the warning signals had less effect in reducing reaction time. No significant associations were found between the total CSHQ score and the ANT Orient score (*Regression Coefficient, RC* = 1.10, p = .169), the ANT Conflict score (*RC* = 1.29, p = .088) or the total RT (*RC* = 1.78, p = .144).

In similar regression models, the CSHQ subscale scores for Bedtime Resistance and Sleep Onset Delay significantly predicted lower ANT Alert scores (Bedtime Resistance: *RC* = -4.91, p = .034, Sleep Onset Delay: *RC* = -15.12, p = .022). The Sleep Anxiety subscale score also predicted lower ANT Alert scores, albeit with borderline significance (*RC* = -5.28, p = .066), and it significantly predicted an *increase* in the ANT Conflict scores (*RC* = 5.80,

p = .049). However, these predictions were nonsignificant after Holm correction. Parents' estimate of sleep time (available for 127 children) did not significantly predict performance on any of the ANT variables.

Teacher Ratings Predicted by Sleep Variables

There was no main predictive effect of the total CSHQ score or CSHQ subscale scores in the linear regression models with the ASEBA TRF broadband symptom scales (total problems, internalizing and externalizing problems) as dependent variables. The interaction between clinical group and the total CSHQ score was significant for the internalizing problems broadband scale (p = .041), but not for the externalizing problems broadband scale (p = .249) or the total problems scale (p = .072). The total CSHQ score significantly predicted internalizing problems scores in the ANX group (p = .034).

The interaction between clinical group and Daytime Sleepiness score was significant for the internalizing problems scores (p = .019) and the total problems scores (p = .010). However, after using the Holm correction to adjust for multiple analyses, only one prediction remained significant: the Daytime Sleepiness score significantly predicted the internalizing problems scores in children with an anxiety disorder and no comorbid ADHD (RC = 1.16, adjusted p = .011: see Fig. 2). No interaction between clinical group and other subscale scores were significant for any TRF broadband symptom scales. Parents' estimate of sleep time (available for 127 children) did not significantly predict performances on the ASEBA TRF internalizing, externalizing or total problems scores for any group of children.

DISCUSSION

In this study of children with anxiety disorders and/or ADHD, and in nonreferred controls we investigated associations between sleep problems and attentional functioning, externalizing

problems and internalizing problems. We found significant associations between parental reports of sleep problems and performance on a test of attentional functioning for all groups of children, as well as a significant association between daytime sleepiness and increased teacher-reported internalizing problems in children with anxiety disorders only (i.e., without comorbid ADHD).

Performance on Attention Tests Predicted by Sleep Variables

We have failed to find any previous study reporting on the association between parent-reported sleep problems and objectively measured attentional functioning in children in general. Our findings suggest that symptoms of childhood insomnia such as bedtime resistance, sleep onset delay and sleep anxiety are associated with impairment in attentional functioning. Although our study is cross-sectional, and allows for no interpretation as to the direction of influence, our findings are comparable with the results from studies in adults with primary insomnia, which indicate that sustained attention is the most consistently affected neurocognitive function, although more subtly so than with other sleep disorders (for a review, see (Shekleton, et al., 2010). Given the prevalence of these insomnia symptoms in children in general (Owens & Mindell, 2011) and in children with psychiatric disorders in particular (Ivanenko, et al., 2006), findings of possible consequences for daytime attentional function are important.

Mothers' reports of total sleep problems significantly predicted the alerting network efficiency, whereas the orienting and the executive control networks were not significantly predicted by the total sleep problems score. This selective association between sleep disturbance and one domain of attention (rather than with global attentional functioning) is interesting considered previous findings in adults, that attentional networks are differently

vulnerable towards the effects of sleep deprivation (Jugovac & Cavallero, 2012; Martella, et al., 2011). If this specificity is replicated, it may offer one explanation for the inconsistent results from previous studies of the association between sleep disturbance and attentional functioning in children, as these studies have not investigated domains of attention separately (for a review, see (Beebe, 2011).

However, the pattern of affected attention networks reported here is not consistent with the findings from adult sleep deprivation studies. The associations we found were primarily with the alerting network score. In the adult studies, the orienting (Martella, et al., 2011) and the executive control network (Jugovac & Cavallero, in press; Martella, et al., 2011) were impaired following sleep deprivation, but not the alerting network. This discrepancy may be explained by two differences in these research designs. First, we found an association between subjectively measured sleep problems (specifically, insomnia symptoms such as bedtime resistance, sleep onset delay, and sleep anxiety) and attentional functioning, whereas the adult studies examined the effect of sleep deprivation on attentional functioning. Insomnia and sleep deprivation may well influence daytime attentional functioning differently. Second, given the developmental differences between children and adults in these three attention networks (Posner, 2008), the effects of sleep disturbances on attention may well be different for these two populations.

Sleep problems were associated with a *lower* alerting score in our study, indicating a diminished ability to fully use the information from external signals to accelerate response speed. Although our findings relate to associations with subjectively reported sleep problems and are not directly comparable to experimental studies, our findings are consistent with the observed reduced responsiveness of children after sleep deprivation (Beebe, 2011), and are also consistent with a discussion in the adult literature suggesting that sleep loss alters the

functioning of the attention network by disengaging attentional functioning from external sensory input (Killgore, 2010).

It is also noteworthy that sleep problems but *not* IQ were significantly associated with the functioning of the alerting network. This supports the view that sleep status should be considered in future studies of attentional functioning in children (Gruber, et al., 2011), at least in populations with a high rate of sleep problems.

An association between sleep problems and impairment in attentional functioning in children with anxiety disorders has, as far as we know, not previously been reported. The relationships between sleep, attention and anxiety are complex and probably multidirectional. Sleep problems may be an underlying factor for both the impairments in attentional functioning and anxiety as both attentional functioning and emotional regulation are vulnerable towards the effect of insufficient sleep (Lim & Dinges, 2008; Yoo, Gujar, Hu, Jolesz, & Walker, 2007). On the other hand, anxiety may be a common factor underlying both the sleep problems and the attentional problems; heightened cognitive and physiological arousal may impair sleep initiation and maintenance in children with anxiety disorders (Alfano, et al., 2010; Dahl, 1996), and in adults state anxiety is associated with impairments in attentional functioning (Pacheco-Unguetti, Acosta, Callejas, & Lupianez, 2010). Finally, impaired attentional control and attention bias towards threat are associated with anxiety disorders in children (Britton, et al., 2012), and with insomnia in adults (Harvey & Tang, 2012).

Associations between parental reports of sleep problems and performance on a formal test of attention has not previously been reported in children with ADHD. Our finding of a lower alerting score associated with sleep problems in children with ADHD may be consistent with the results from a previous study who found an increased number of omission errors on a

continuous performance test following one week of sleep restriction in children with ADHD (Gruber, et al., 2011). However, another study reported increased distractability, but not inattention, in children with ADHD and sleep problems (Sawyer, et al., 2009).

Interestingly, having ADHD and having sleep problems were associated with impairments in different aspects of alerting functioning in our sample**.** While sleep problems were associated with a *lower* alerting score, having ADHD was associated with *higher* alerting scores and *longer reaction times* when no warning cue was given prior to the target stimulus. This suggests that ADHD children have an intact ability to use cues to improve performance, but they need external signals to maintain alertness. This is consistent with a theory that suggests that ADHD children have difficulties with arousal regulation in the absence of an alerting cue (Posner, 2008), and is also consistent with previous reports of deficits in the alerting functions in children with ADHD (Johnson et al., 2008; Mullane, Corkum, Klein, McLaughlin, & Lawrence, 2011).

Teacher Ratings Predicted by Sleep Variables

We did not find a main predictive effect of the mother's reports of sleep problems on teacher ratings of the children's internalizing or externalizing behavioral problems. We did, however, find a predictive effect of daytime sleepiness on internalizing problems in the group of children with anxiety disorders and no comorbid ADHD. The association between sleep disturbances and emotional problems is well recognized in children and adolescents (Dahl & Harvey, 2007), and a possible mechanism for this association is the importance of sleep for emotional processing and regulation (Walker, 2008).

Contrary to our hypothesis, the CSHQ total or subscale scores were *not* associated with increased teacher-reported internalizing problems or externalizing behaviors in children with ADHD. Our findings do not support the commonly held assumption that sleep problems

exacerbate behavioral symptoms in children with ADHD. In our study, the children with ADHD were indeed rated by their teachers as having both more internalizing and more externalizing behavioral problems than the nonreferred controls, but having sleep problems was not associated with an increase in their symptom loads. The discrepancy between our findings and previously reported associations between sleep problems and behavior problems in children with ADHD (Choi, et al., 2010) may be due to methodological issues such as rater bias because parents were reporters of both the sleep problems and the behavior problems. Our findings are more in concert with a previous study that found no association between actigraphically measured sleep onset latency and ADHD symptoms in children with ADHD (Hvolby, et al., 2008). It may be that sleep problems in children with ADHD are primarily associated with impairments in attentional functioning, and not with observed behavior. Another explanation may be that teachers fail to notice subtle behavioral changes in the internalizing or externalizing functions of children who are hyperactive and restless.

Limitations

Our findings should be considered within the context of the study's limitations. The CSHQ is a screening instrument and not a diagnostic tool for sleep disorders. We did not have any objective measure of sleep, and we did not assess for primary sleep disorders. These are important limitations of our study. Another limitation is the low specificity of the sleep questionnaire (CSHQ), which may have diluted the predictive value of insufficient sleep for daytime functioning. A third limitation concerns our diagnostic assessments, which were based on parent information only, with no input from the children or their teachers. The small sample size did not allow enough statistical power to identify what may be subtle relationships between sleep problems and daytime functioning. The generalizability of our findings is limited because of the small sample size, because the clinical sample included

children with a full-scale IQ in the borderline range, and because the group of children with anxiety disorders was a clinical sample with a mixture of anxiety disorders including OCD.

Clinical Implications

Sleep problems in general, and bedtime resistance and sleep onset delay in particular, are common sleep complaints reported in children with psychiatric disorders (Alfano & Gamble, 2009). We demonstrated that there is an association with these sleep problems and impairment in daytime attentional functioning. Daytime sleepiness, considered a consequence of insufficient sleep, was associated with increased internalizing problems in children with anxiety disorders. Our findings stress the need to address sleep problems when treating children with psychiatric disorders, and to develop efficient treatment strategies for sleep problems in children with psychiatric disorders.

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TABLE 1

Demographic, Clinical and Sleep Variables in Children with Anxiety Disorders (ANX), ADHD, or Comorbid Anxiety Disorder and ADHD (ANX+ADHD), and in Nonreferred Controls (CTRL)

	ANX	ADHD	ANX+ADHD	CTRL	*p*	*Post hoc*
	(*n* = 39)	(*n* = 38)	(*n* = 25)	(*n* = 35)		
Age, mean (SD)	10.8 (2.0)	9.8 (1.5)	10.1 (1.9)	10.7 (2.4)	.074[a]	
Sex (girls), n (%)	13 (33.3)	9 (23.7)	13 (52.0)	15 (42.9)	.109[b]	
Parental education, *n* (%)						
Mother						
> 12 years	19 (48.7)	26 (68.4)	12 (48.0)	21 (60.0)		
≤ 12 years	20 (51.3)	12 (31.6)	13 (52.0)	14 (40.0)	.259[b]	
Father (*n* = 129)						
> 12 years	12 (35.3)	18 (48.6)	9 (37.5)	21 (61.8)		
≤ 12 years	22 (64.7)	19 (51.4)	15 (62.5)	13 (38.2)	.126[b]	
CGAS, mean (SD)	51.0 (6.2)	52.5 (5.2)	49.9 (5.6)	88.8 (6.2)	<.001[a]	All patient groups < CTRL
WASI FIQ, mean (SD)	97.2 (12.2)	100.4 (15.7)	96.3 (11.6)	108.9 (12.3)	<.001[a]	All patient groups < CTRL
CSHQ scores, mean (SD)						
Total CSHQ score	48.6 (8.1)	43.0 (6.4)	51.7 (9.7)	38.1 (4.6)	<.001[a]	All patient groups > CTRL
						ANX > ADHD, ANX+ADHD > ADHD
Bedtime Resistance	8.6 (3.0)	7.1 (1.6)	8.9 (2.9)	6.7 (1.5)	<.001[a]	ANX > CTRL, ANX+ADHD > CTRL,
						ANX > ADHD, ANX+ADHD > ADHD

TABLE 1 continued

	ANX (n = 39)	ADHD (n = 38)	ANX+ADHD (n = 25)	CTRL (n = 35)	*p*	*Post hoc*
Sleep Onset Delay	1.9 (0.8)	1.6 (0.8)	2.0 (0.9)	1.3 (0.7)	.004[a]	ANX > CTRL, ANX+ADHD > CTRL
Sleep Duration	4.6 (1.5)	4.0 (1.4)	4.8 (1.6)	3.5 (1.1)	.002[a]	ANX > CTRL, ANX+ADHD > CTRL
Sleep Anxiety	6.6 (2.5)	5.0 (1.4)	7.2 (2.3)	4.4 (0.8)	<.001[a]	ANX > CTRL, ANX+ADHD > CTRL, ANX > ADHD, ANX+ADHD > ADHD
Night Wakings	3.5 (0.9)	3.6 (1.1)	4.4 (1.4)	3.2 (0.5)	<.001[a]	ANX+ADHD > CTRL, ANX+ADHD > ANX, ANX+ADHD > ADHD
Parasomnias	9.0 (1.8)	8.5 (1.5)	10.0 (2.5)	7.9 (1.3)	<.001[a]	ANX > CTRL, ANX+ADHD > CTRL, ANX+ADHD > ADHD
Sleep Disordered Breathing	3.2 (0.5)	3.4 (0.7)	3.3 (0.6)	3.1 (0.2)	.033[a]	ADHD > CTRL
Daytime Sleepiness	14.1 (3.1)	12.3 (3.4)	14.2 (3.5)	10.0 (2.7)	<.001[a]	All patient groups > CTRL, ANX > ADHD, ANX+ADHD > ADHD
Estimated sleep time, minutes, mean (SD)	541.8 (57.9)	569.1 (59.2)	545.0 (53.9)	565.0 (60.6)	.138[a]	

[a]ANOVA; [b]χ^2 df = 3. *Post hoc* comparisons with the Holm correction, significance set at the .05 level.
SD = standard deviation; CGAS= Children's Global Assessment Scale; WASI FIQ = Wechsler Abbreviated Scale of Intelligence Full-Scale IQ; CSHQ = Children's Sleep Habit Questionnaire. Complete dataset except where indicated.

TABLE 2

Teacher Ratings of Total Problems, Internalizing and Externalizing Problems (ASEBA TRF Broadband Symptom Scales), and Performance on Attention Test (Attention Network Test, ANT) in Children with Anxiety Disorders (ANX), ADHD, or Comorbid Anxiety Disorder and ADHD (ANX+ADHD), and in Nonreferred Controls (CTRL)

	ANX	ADHD	ANX+ADHD	CTRL	*p*	*Post hoc*
	(*n* = 39)	(*n* = 38)	(*n* = 25)	(*n*= 35)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
ASEBA TRF raw scores						
Total problems	37.77 (25.35)	55.79 (33.26)	42.88 (25.58)	4.37 (7.56)	<.001	All patient groups > CTRL, ADHD > ANX
Internalizing problems	13.59 (10.26)	7.29 (6.96)	10.00 (8.76)	1.40 (2.20)	<.001	All patient groups > CTRL, ANX > ADHD
Externalizing problems	5.49 (7.70)	16.53 (13.88)	10.16 (11.36)	0.46 (1.20)	<.001	ADHD > CTRL, ADHD > ANX, ADHD > ANX+ADHD, ANX+ADHD > CTRL
ANT variables						
Total RT, ms	757.08 (126.86)	799.32 (132.90)	807.72 (118.08)	718.17 (145.71)	.025	n.s.
Alert score	72.87 (59.71)	105.04 (65.51)	98.00 (74.63)	65.29 (55.94)	.022	ADHD > CTRL
Orient score	33.62 (67.20)	32.41 (61.55)	62.59 (75.08)	27.27 (61.39)	.189	
Conflict score	84.44 (68.87)	70.04 (62.35)	74.92 (49.38)	85.17 (65.77)	.684	

One-way ANOVA with *post hoc* comparisons and the Holm correction, with significance set at the.05 level.
SD = standard deviation; ASEBA TRF = Achenbach System of Empirically Based Assessment, Teacher Report Form; RT = reaction time; n.s. = nonsignificant

TABLE 3

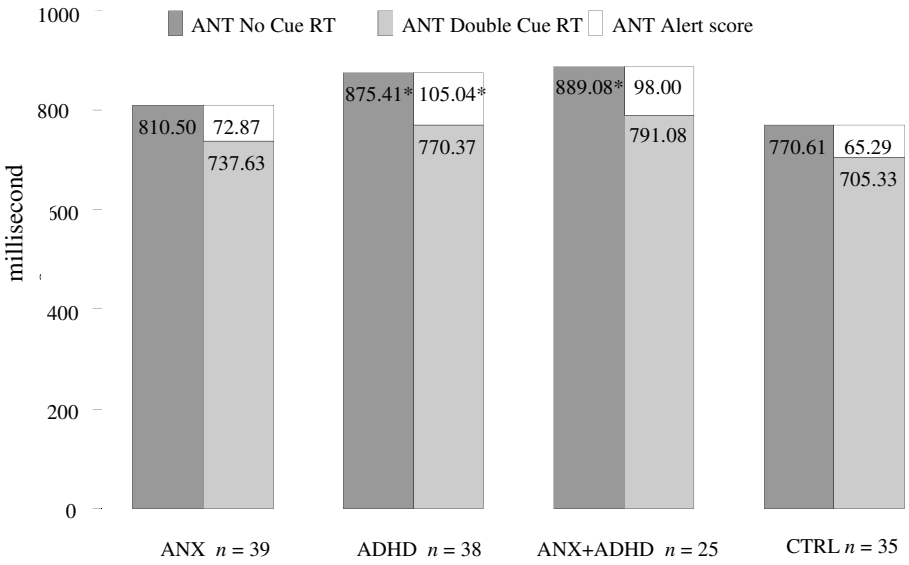
Linear Regression (Model 3) Showing Predictors of ANT Alert Score (Reduction in Reaction Time in Cued Versus Noncued Condition) in Children with Anxiety Disorders (ANX), ADHD, or Comorbid Anxiety Disorders and ADHD (ANX+ADHD), and in Nonreferred Controls (CTRL)

			95% CI *RC*	
	RC	*p*	Lower bound	Upper bound
Female sex	- 6.36	.564	- 28.11	15.39
Age (years)	- 6.50	**.015**	- 11.73	- 1.27
WASI FIQ	- 0.36	.373	- 1.14	0.43
ANX vs. CTRL	23.63	.159	- 9.40	56.67
ADHD vs. CTRL	40.52	**.010**	10.02	71.03
ANX+ADHD vs. CTRL	48.60	**.013**	10.26	86.95
CSHQ score	- 1.84	**.012**	- 3.28	- 0.41

Significant coefficients marked in bold. Significance set at the.05 level.
ANT = Attention Network Test; *RC* = regression coefficient; CI = confidence interval, WASI FIQ = Wechsler Abbreviated Scale of Intelligence Full-Scale IQ; CSHQ = Children's Sleep Habit Questionnaire

FIGURE 1

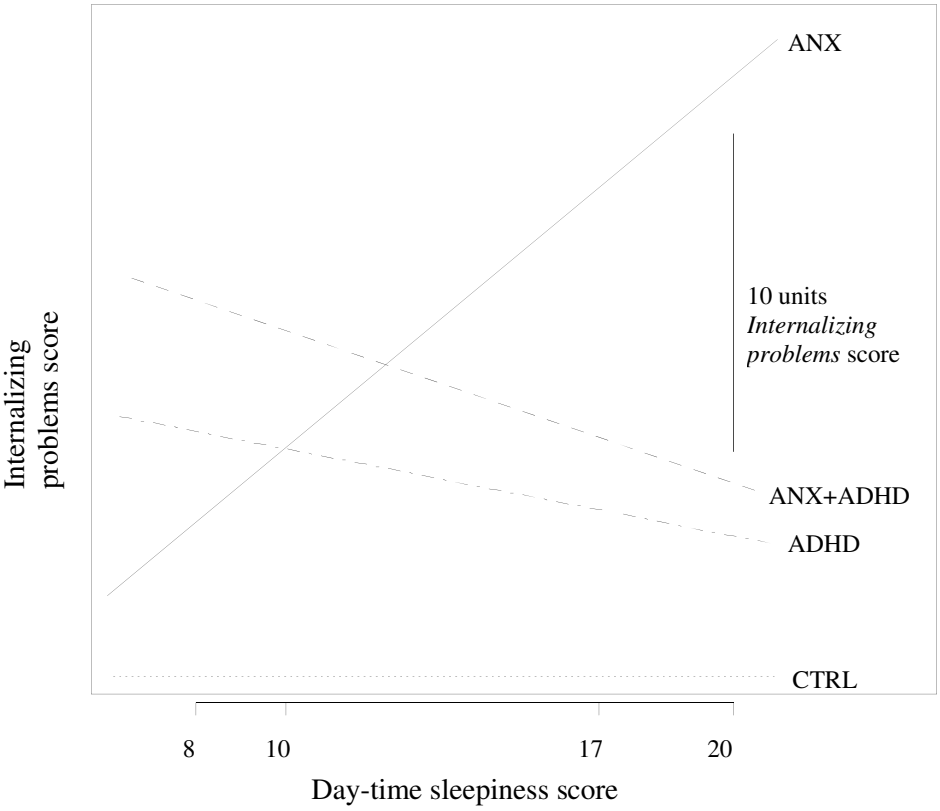
Mean Attention Network Test reaction times (ms) and alerting score in children with anxiety disorders (ANX), ADHD, comorbid anxiety disorders and ADHD (ANX+ADHD), and nonreferred controls (CTRL), showing the reaction time without warning signals (ANT No Cue RT), the reaction time after warning signals (ANT Double Cue RT), and the ANT Alert score.



One way ANOVA with post hoc comparisons and Holm correction; significance was set at the 0.05 level.
*p < 0.05 after Holm correction: ADHD and ANX + ADHD > CTRL.

FIGURE 2

Graph of the linear regression: ASEBA TRF *internalizing problems* score by day-time sleepiness score and diagnostic group, showing different relationships in each group; anxiety disorder (ANX, n = 39), ADHD (n = 38), comorbid anxiety disorders and ADHD (ANX+ADHD, n = 25), and nonreferred controls (CTRL, n = 35). Adjusted for age, sex and full-scale IQ.



The exact position of the *internalizing problems* axis on the diagram depends on the values of the adjustment variables, and is therefore not shown.

III