

CHAPTER 1

General introduction

General introduction

The theme sleep has inspired many individuals: varying from artists, writers and scientists. The ancient Greek had a god which was a symbol of sleep. He was named Hypnos, and is often pictured with wings on his temple bones, nowadays called 'sleep bones'. Vincent van Gogh's painting 'the bedroom' is well known to most people – but fewer people are aware of the fact that Vincent van Gogh soaked his pillowcase in chamfer every night to relieve his insomnia (he suffered from manic-depressive disorder which possibly explains his sleep disturbances). Sleep has also interested scientists. Eugene Aserinsky – a graduate student with initially absolute no interest in sleep – discovered 'REM (Rapid Eye Movement) sleep'. This turned out to be one of the most important discoveries in sleep research. At night, Aserinsky wired his eight-year-old son to his home-made and self-invented machine which registered movements of the eyes during sleep. He then made his great discovery: during sleep there are certain periods in which the eyes move very quickly (Rapid Eye Movement). The periods of REM-sleep were found to be associated with a recollection of vivid dreaming, but Eugene Aserinsky was not a man who favored Freudian explanations. He viewed his discovery as a sign that sleep reflects an active state of the brain, in contrast to the presumed 'passive' state of sleeping. Aserinsky turned his back on sleep research for quite some years and studied electrical currents in salmons instead, returning to sleep research only years later. He died at the age of 77 and it is still not clear if his car accident was the result of a lack of sleep (1).

Ultimately, humans cannot function without sleep. Even Randy Gardner – who holds the world record of voluntarily sleep deprivation – needed some sleep after staying awake for 11 day (2). His attempt was scientifically documented in one of the most important psychiatric journals, Archives of General Psychiatry, and carried the title *Psychiatric and EEG observations on a case of prolonged (264 hours) wakefulness* (3). Interestingly, the first word of this title already refers to something intuitively known to most individuals: there is a relationship between sleep and mental well-being.

This thesis will examine the relationship between sleep and depressive and anxiety disorders, from an epidemiological perspective. The present chapter will first provide some general information on sleep, then take a closer look at both depressive and anxiety disorders, followed by what is known about sleep in relationship to depressive and anxiety disorders, and finally addresses the general aim and outline of this thesis.

Sleep

Despite the fact that humans spend approximately one third of their lives asleep (4), the exact function of sleep remains essentially unknown (5). Various hypotheses about why humans sleep exist. These hypotheses fall into one of the following three categories: (1) sleep plays a role in energy metabolism, (2) sleep plays a role in neural plasticity and (3) sleep plays a role in cellular defense. As for *energy metabolism*: neurons in the brain consume a lot of energy, and sleep is thought to prevent energy depletion of the brain, which is considered a serious threat to the human body (5). This has also been called the 'adenosine theory': in subjects who are awake, the concentration of adenosine rises because of energy depletion caused by neuronal activity. As a result of the increase in adenosine, wake-active neurons decrease in activity and sleep is induced (5). Second, the function of sleep may be explained for by the 'neural plasticity theory'. According to this theory, synapses are formed during wakefulness. Necessary repolarizations of these neurons will cost the brain a large amount of energy. Therefore, according to the 'neural plasticity theory', weakening of these synapses during sleep (also called 'downscaling of synapses') will result in a energy-efficient state of the brain (5,6). Third, there is the theory of sleep in 'cellular defense'. If subjects are awake for a long period, their immune system is activated. For instance, in waking there is an increase in cytokine expression, CRP and also in numbers of white blood cells. This is explained for by the fact that a long period of waking might constitute a threat to the individual, because energy supplies are depleted (6). Sleep is therefore needed to keep energy levels up.

Sleep disturbances: definition and associated factors

Sleep can be disturbed in various ways. It can manifest itself as a condition in which subjects are dissatisfied with the quality of their sleep, also referred to as insomnia. Subjects can also be dissatisfied with the duration of their sleep, complaining of a shortened sleep duration. In addition, prolonged sleep duration can be regarded as a sleep disturbance.

One of the major difficulties in insomnia research is the definition of insomnia itself, because "insomnia is often a poorly defined term" (7). Clinicians working in the psychiatric field define insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (8). According to the DSM-IV, insomnia is a condition in which subjects have difficulties initiating or maintaining sleep for at least one month. Also, the sleep disturbance must cause significant distress or impairment in social, occupational or other important areas of functioning. Clinicians in sleep clinics use a different definition of insomnia, and sometimes also rely on electro-encephalic

measurements to diagnose conditions such as sleep apnea which can also present with insomnia (9). Population-based studies often use self-report questionnaires to estimate insomnia. In the present thesis, insomnia was measured with the self-report Women's Health Initiative Insomnia Rating Scale (IRS) (10), which addresses trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up and sleep quality.

Because of the differences in defining insomnia, prevalence rates of insomnia vary greatly across fields and studies. Most definitions of insomnia include one or more of the following 'core' symptoms: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early morning awakenings (EMA) or non restorative sleep (NRS) (11). Prevalence rates for insomnia in the general population vary from (for instance) 9.5% (12) to 23.6% (11) and some even consider prevalence rates for insomnia to vary between 10 and 50% (13). Given the fact that there is no single (uniform) definition of insomnia, it makes comparison of studies on insomnia difficult. Despite the heterogeneity in defining insomnia, most epidemiological studies find more insomnia in elderly subjects and in females (14, 13). Also, insomnia is more present in subjects experiencing painful conditions (15), as well as in subjects with hypertension and type II diabetes (16). Furthermore, although subjects with insomnia frequently use alcohol to promote sleep, alcohol ultimately disrupts the sleep cycle (17). Finally, insomnia can be influenced by the use of medication, such as antidepressants (18) (both sedation and insomnia are associated with the use of antidepressants) and benzodiazepines (9).

Next to insomnia, sleep duration can also reflect sleep disturbances. Normal sleep duration ranges between 7 and 9 hours per night, with 6 or less hours representing short sleep duration and 10 or more hours indicating long sleep duration. In modern society, the amount of sleep per night has slowly declined over the past decades (19), but other studies challenge this belief (20). In population-based studies, like in this thesis, sleep duration is often assessed by self-report. Like insomnia, sleep duration has been associated with age, gender, somatic conditions (chronic diseases, pain conditions) and the use of medications (21-23). In addition, it has been reported that both short and long sleep are associated with more mortality (24). The biological mechanism remains unclear however. In experiments, it has been shown that voluntarily sleep restriction is associated with a decrease in glucose tolerance (25), possibly in this way contributing to the development of factors or diseases known to impact on cardiovascular disease, which impacts on mortality. In line with this theory, short sleep has also been associated with pre-diabetes (26). The fact that long sleep is associated with increased mortality is possibly explained by the fact that these individuals already suffer from major health problems and need more sleep.

Insomnia and short sleep duration seem intuitively connected, but this does not necessarily have to be the case. Some individuals are perfectly happy with sleeping only four hours per night (such as Thomas Edison, inventor of the light bulb (27), while others need excessive amounts of sleep (such as Albert Einstein who slept for more than 10 hours per night) (28). Most epidemiological studies focussing on sleep consider insomnia only, but leave out sleep duration. However, there may actually be different patterns in associating both insomnia and sleep duration with different health outcomes. A recent review found that insomnia combined with short sleep duration is more likely to be associated with an anxious-ruminative profile, and that insomnia combined with a normal sleep duration is more likely to be associated with an increased risk of cardio-metabolic abnormalities (16).

Summarizing, sleep and sleep disturbances can be influenced by a variety of factors which need to be taken into account when evaluating sleep. Furthermore, it is important to assess both sleep quality (insomnia) as well as sleep duration. The present thesis will be able to address these points.

Chronotype

Another concept closely related to sleep is chronotype. Most individuals are well aware of their chronotype, or put otherwise: their preference for being a morning- or an eveningness type. In research, like in this thesis, chronotype is often defined as the mid-point in time between falling asleep and waking up. Chronotype depends on both genetic and other factors, such as gender and age (29). Children are generally early chronotypes, adolescents tend to delay their chronotype and elderly subjects shift towards early chronotypes again (29). Individuals with late chronotypes have reported more smoking and drinking behavior and more novelty seeking (30, 31) indicating that lifestyle and personality have been linked to chronotype. Consistently, a late chronotype has been associated with more unhealthy dietary habits (32), type 2 diabetes and arterial hypertension (33). The later findings could be due to the fact that evening chronotypes may suffer more from sleep problems, which could mediate the association with type II diabetes and hypertension (33). It seems therefore important to also consider chronotype in sleep research and will therefore be included in the present thesis.

Depressive and anxiety disorders

A depressive disorder (as diagnosed by the DMS-IV) (8) is a syndrome characterized by at least one of the two following core symptoms: (a) experiencing a low mood or (b) having a diminished interest in activities which were viewed as enjoyable before

the onset of symptoms. Furthermore, at least four of the following other symptoms need to accompany the low mood or diminished interest in activities (or three if subjects experience both core symptoms): difficulty concentrating, less appetite (or more), psychomotor agitation (or retardation), fatigue (or loss of energy), feelings of worthlessness or inappropriate guilt, recurrent thoughts about death and insomnia (or hypersomnia). Depressive disorders are common mental disorders: the lifetime prevalence of depressive disorders in the general population is estimated at 16.6% (34). The 1-year prevalence of the more narrow concept of a major depressive disorder is estimated at 4.1% and the lifetime prevalence at 6.7% (35). Prevalence rates of depressive disorders are higher among women than among men (34). In the present thesis we will focus on the major depressive disorder.

Anxiety disorders consist of different types of specific disorders. The most prevalent and impairing anxiety disorders are studied within this thesis and include panic disorder, agoraphobia, generalized anxiety disorder and social phobia. A *panic disorder* is characterized by recurrent panic attacks, mostly provoked by specific triggers, such as standing in line in the supermarket or sitting on a bus. Some individuals explicitly avoid these situations (for instance by staying at home), making sure they experience no panic attacks any more, but this limits their daily functioning severely. *Agoraphobia* is fear about being in spaces (such as shopping centers) from which one can not easily 'escape'. Agoraphobia is usually present in combination with a panic disorder. *Generalized anxiety disorder (GAD)* is an anxiety disorder in which subjects worry excessively about everyday life (such as worrying about money, health etc). A *social phobia* is characterized by a fear of doing something which will be viewed by others as humiliating (8). Lifetime prevalence of panic disorder is estimated at 5.1% (with a 1-year prevalence of 2.1% (36). Agoraphobia has a lifetime and 1-year prevalence of 1.7% and 0.8%, respectively (34, 37). Lifetime and 1-year prevalence of GAD are estimated at 2.0 % and 3.1% (34, 37). Social phobia has a lifetime prevalence of 12.1% and a 1-year prevalence of 7.1% (38). Also for anxiety disorders, prevalence rates are higher among women than among men (34).

It is actually not only the high prevalence that make depressive and anxiety disorders important for our society, but it are also the many (personal) impairments associated with these disorders. Both depressive and anxiety disorders have e.g. a significant unfavorable impact on quality of life, work productivity, work absenteeism, general health and societal costs (39, 40). For instance, depressive disorders are associated with an increased odds of work absenteeism, and also with impaired work performance (39). To a lesser degree, anxiety disorders have also been associated with absenteeism and impaired work performance (39). In addition, comorbid depressive and anxiety disorders are associated with more impairment at work (39). To illustrate the impact of depressive and anxiety on our society even more: depressive and anxiety disorders

are often chronic conditions, which frequently relapse (41-43) or are associated with residual symptoms (44), thus impacting on daily life. Sleep could be one of the psychiatric symptoms (partially) responsible for the association between depressive and anxiety disorders and work functioning, because insomnia itself has also been found to be associated with absenteeism and work performance (45). The impact of sleep disturbances in depressive and anxiety disorders on work functioning will therefore also be a topic of this thesis.

Sleep disturbances in depressive and anxiety disorders

Sleep disturbances in depressive disorders are very common, and up to 90% of patients complain of disturbed sleep (46). Some individuals do not complain of insomnia, but rather sleep too much, a symptom which is called hypersomnia and is considered an 'atypical' symptom of a depression (47). The relationship between sleep and depressive disorders is complex. One of the most striking examples of this relationship is the fact that total sleep deprivation (i.e. a whole night without sleep) actually relieves depressive symptoms. Around 60% of depressed subjects treated with sleep deprivation show a positive response, but this response lasts only short and the effect usually disappears after a following normal night of sleep (48). The underlying biological mechanism remains largely unknown (48). Not only do sleep disturbances usually accommodate depressive disorders, they are also one of the most common residual symptoms after remission of a depression (44). Remission rates of depression are lower in subjects who suffer from insomnia (49). Also, insomnia has been reported to predict depression in adults (50, 14). Sleep seems to play a role before, during and after a depressive disorder. Because sleep is a symptom of depression, it can also be viewed as an indicator of severity. Questions on sleep are present in scales assessing severity of a depressive disorder, such as the Inventory of Depressive Symptoms (51). Residual symptoms, occurring frequently after suffering from a depressive disorder (52), can constitute of sleep disturbances. Furthermore, many factors that influence sleep are also associated with depressive states, such as age, gender, marital status, somatic conditions (chronic diseases, pain conditions) and use of medications (such as antidepressants and benzodiazepines (53, 14, 54, 55)). Given these facts, it is difficult how one must view sleep disturbances in the context of a depressive disorder: are they (only) a diagnostic symptom, an indicator of severity, or do they persist after remission of the psychopathological disorder? Are they an independent risk factor for depressive disorders? And also, what is the role of other factors contributing to sleep disturbances, such as socio-demographics and somatic health indicators, and the impact of sleep on daily functioning, such as work? The present thesis will address these questions from an epidemiological perspective.

Sleep disturbances have also been found in anxiety disorders, but this has been less examined. Although a disturbed sleep is not a diagnostic symptom of anxiety disorders, except for GAD, panic disorders and social phobia have been associated with sleep disturbances (56). Patients suffering from panic disorder often (18-45%) report nocturnal panic attacks (57) and subjects with social phobia often complain of insomnia (56). Losing sleep may even exacerbate these anxiety disorders (56). The hyperarousal state associated with anxiety disorders, may also contribute to sleep disturbances in anxiety disorders (56). In addition, sleep disturbances might be prevalent in anxiety disorders through their high comorbidity with depressive disorders. On the other hand, sleep disturbances have been shown not to predict course of anxiety disorders (58), but this study only included primary care patients. Interestingly, anxiety disorders do not respond positively to sleep deprivation (59), which may differentiate them from depressive disorders. When evaluating sleep disturbances it seems therefore important to consider both depressive and anxiety disorders.

Next to sleep disturbances, also chronotype might be linked with depressive and anxiety disorders. A later chronotype as well as eveningness has been associated with increased depressive symptomatology (60, 61). Less research is available on the relationship of chronotype with anxiety, but eveningness has been associated with more trait anxiety (62) and with being increasingly 'emotionally upset' (63).

Summarizing, there is a complex relationship between sleep and depressive and anxiety disorders, which is difficult to disentangle. Most previous studies investigating the relationship between sleep and depressive and anxiety disorders do not have information available on both disorders (50), do not have information available on severity of the underlying psychiatric disorder (64) or do not have information on both sleep duration as well as insomnia (50). Moreover, some studies do not rely on DSM-IV based psychiatric diagnoses, but rely on symptom checklists (65, 66). None of these studies have had the advantage to incorporate all these factors to investigate how the relationship between sleep with depressive and anxiety disorders must be viewed. Therefore, in the present thesis we choose to take all these factors into account / study all these factors in concert. Knowledge about the link between sleep and depressive and anxiety disorders may have clinically relevant implications. Identifying subjects at risk for a prolonged course of the disorder could, for instance, imply that these subjects can be monitored more strictly, in order to reduce an unfavorable outcome of their disorder. Knowledge of chronotype might be important to identify subgroups of patients that may benefit from chronotherapeutical interventions.

Netherlands Study of Depression and Anxiety (NESDA)

The Netherlands Study of Depression and Anxiety (www.nesda.nl) is an ongoing longitudinal epidemiological cohort study, designed to investigate the long-term course of depressive and anxiety disorders. For this thesis, we used data from the baseline measurement and the two-year follow up. The main aim of the NESDA-study is to integrate knowledge on (the course) of depressive and anxiety disorders from various perspectives. These perspectives vary from psychological, psychiatric, behavioral, somatic to genetic and are embedded in an epidemiological structure. NESDA-respondents were recruited from three different settings: the general population, general practices and mental health organizations. This recruiting strategy ensures a large variety in psychiatric symptoms and disorders- ranging from none (healthy controls), subjects with subthreshold disorders, subjects with remitted disorders and subjects with current depressive and/ or anxiety disorders.

A few of the advantages of the NESDA study are the large sample size ($n=2981$), its detailed clinical assessments (including both psychiatric DSM-IV diagnoses information as well as self-report instruments regarding symptom severity, duration and symptom profiles), and the assessment of many environmental, psychological or somatic risk factors. Sleep within this study is measured with the Women's Health Initiative Insomnia Rating Scale and by asking subjects to estimate their sleep duration. This study allows us to address both insomnia and sleep duration and its relationship to depressive and anxiety disorders, in various points in time. In this way, longitudinal analyses can be conducted, to assess the impact of sleep disturbances on outcomes.

General aim of the thesis

The general aim of this thesis is to describe the relationship between sleep and depressive and anxiety disorders, using an epidemiological approach. Sleep indicators will be assessed by means of sleep quality (insomnia), sleep duration and chronotype. The following research questions will be addressed:

- (1) To what extent are sleep characteristics (insomnia, sleep duration) independent risk factors for current or remitting episodes of depressive and anxiety disorders?
- (2) To what extent do sleep indicators (insomnia, sleep duration) impact on work functioning and the course of depressive and anxiety disorders?
- (3) To what extent is chronotype associated with depressive and anxiety disorders?

Thesis outline

The general aim of this thesis is to investigate the association between sleep and depressive and anxiety disorders. In **Chapter 2**, we will describe the cross-sectional association between sleep and current as well as remitted depressive and anxiety disorders. In **Chapter 3**, we will describe the cross-sectional association between sleep and work functioning, both for subjects with current depressive and anxiety disorder, as for subjects without these disorders. In **Chapter 4**, we will zoom in on the predictive role of sleep for the incidence of depressive and anxiety disorders, using a longitudinal approach. In **Chapter 5**, the role of sleep in the course of depressive and anxiety disorders will be examined. **Chapter 6** will describe the association between chronotype and depressive and anxiety disorders. Finally, in **Chapter 7** overall findings from this thesis will be summarized and discussed.

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