CHAPTER 7

General discussion

In this chapter, the main findings of the present thesis will be summarized and discussed in the context of the current scientific literature in order to present a more comprehensive view of the link between sleep disturbances and depressive and anxiety disorders. Finally, methodological considerations, strengths and limitations and directions for future research as well as clinical implications will be discussed.

Summary of main findings

An integration of the main findings of this thesis is presented below in Table 1.

Table 1: Summary of findings: links between sleep variables and psychopathology

Sleep	Link with depressive and anxiety disorders (cross-sectional)	Link with work functioning in depressive and anxiety disorders (cross-sectional)	Prediction of onset of depressive and anxiety disorders	Prediction of course of depressive and anxiety disorders
Insomnia	+	+	+	-
Short sleep duration	+	+	+	+
Long sleep duration	+	-	-	+
Late chronotype	+	N.E[1]	N.E	N.E

[1] N.E= not examined

+ = a positive association, – = no significant association

Using cross-sectional data from the NESDA study, we found that current depressive and/ or anxiety disorders were associated with more insomnia and with both a short and a long sleep duration. Also persons with remitted depressive disorders, but not those with anxiety disorders, reported more insomnia and a shorter sleep duration (**Chapter 2**). With regard to the consequences of sleep disturbances, this thesis found that, in subjects with current depressive and/ or anxiety disorders, insomnia and short sleep duration – independent of other clinical characteristics – were cross-sectionally associated with decreased work functioning (**Chapter 3**). No consistent associations between sleep measures (insomnia/ sleep duration) and work functioning were found in subjects without current depressive and/ or anxiety disorders. Subsequent longitudinal analyses confirmed that both insomnia and a short sleep duration prospectively predicted the onset of depressive and/ or anxiety disorders in subjects who had never suffered from depressive and/ or anxiety disorders before ('healthy controls') (**Chapter 4**). In addition, independent of other clinical characteristics, both short and long sleep duration, but not insomnia, were predictive of a poorer 2-year course outcome in subjects with depressive and/ or anxiety disorders (**Chapter 5**). Finally, this thesis showed that persons with

current depressive and/ or anxiety disorders reported a later chronotype (**Chapter 6**). In the paragraphs below, we will elaborate on these main findings in the context of the recent literature.

Associations between insomnia, sleep duration, chronotype and current depressive and/ or anxiety disorders

From the current scientific literature, it is clear that sleep and psychiatric disorders are tightly linked (1-3). Depending on what definition is used, prevalence rates for 'insomnia' vary greatly. The spectrum 'insomnia' ranges from only insomnia symptoms (with a prevalence of 30-48% in the general population), insomnia symptoms plus daytime consequences (9-15% of the general population), dissatisfaction with sleep quality or quantity (8-18% of the general population) or an insomnia diagnosis (according to the DSM-IV, with a prevalence of 6%) (2). In one study, it was estimated that up to 90% of patients suffering from a depressive disorder complain of their sleep (4). Another study found that nearly 80% of individuals with a current major depressive disorder complained of insomnia symptoms. If an anxiety disorders was also present, almost 90% complained of insomnia symptoms (5). Individuals with a generalized anxiety disorder in primary care complain in 74% of cases of sleep disturbances (6) and 68% of individuals with a panic disorder, complain of difficulties of falling asleep (7). Looking at it the other way around, 52.5% of subjects referred to an insomnia clinic suffers from a (DSM-IV based) psychiatric disorder, with the most common disorders being generalized anxiety disorder, obsessive-compulsive disorder or major depressive disorder/ dysthymia (8). Thus, it is clear that insomnia and psychiatric disorders are frequently diagnosed in each others presence.

Our results in **Chapter 2** confirm that sleep and depressive and anxiety disorders are strongly connected. Subjects with current depressive and current anxiety disorders reported significantly higher insomnia scores than subjects without these disorders. Short sleep duration (defined as sleeping on average less than 6 hours per night) was common in depressed and/ or anxious patients (31.1% of subjects with major depressive disorder, and 25.3 % of subjects with current anxiety disorders in our study). However, a substantial percentage of depressed and/ or anxious patients did report the contrary: a long sleep duration (10 or more hours/ night) (6% of subjects with major depressive disorder reported long sleep duration , 3% of subjects with anxiety disorder, and 8.8 % of subjects with both depressive and anxiety disorders). Our findings are in line with other studies, which also find a strong connection between (for example) insomnia and depressive and anxiety disorders (4).

The association between depressive disorders with both extremes of the sleep continuum (both short and long sleep duration) is well known in clinical practice. Subjects who are depressed can present with either 'vital symptoms' (which includes shorter sleep), but also with 'atypical symptoms' (which includes hypersomnia). The mechanism behind this association can be either psychologically, environmentally, genetic, or a combination of (all) these factors. In rats, a one week sleep restriction leads to alterations in neurotransmitter receptor systems (such as a reduced sensitivity of the serotonin 1A receptor for corticotropin- releasing hormone) and changes in the HPA-system (such as a blunted ACTH pituitary response). Alterations in these systems have also been associated with depression in humans (9). In addition, both short as well as increased sleep duration has been associated with an increase in inflammatory markers (C- reactive protein and interleukin-6) (10, 11). Depression has been associated with elevated levels of interleukin-6 itself (12), which suggests that inflammation may be an underlying mechanism, possibly underlying both depression and the extremes of short and long sleep duration.

In earlier studies, long sleepers have also been reported to worry more (13, 14). However, potentially complicating the interpretation of these results is the fact that these studies did not use a validated assessment of worry (15). A more recent study, which assessed worrying with a validated instrument, found that worrying is negatively associated with sleep length, which means that short sleepers worry more than long sleepers (15), and suggests that increased worrying might not be the underlying mechanism for a longer sleep duration.

In **Chapter 6**, we examined whether current depressive and/ or anxiety disorders were associated with chronotype. We found that a later chronotype was associated with both current depressive and/ or anxiety disorders. We found no differences in chronotypes between subjects with remitted depressive and/ or anxiety disorders or in healthy controls. Clinical characteristics such as type of disorder, severity of psychiatric symptoms and use of medication did not contribute to this association. This points to the fact that a later chronotype is independently associated with current depressive and/ or anxiety disorders. Because our analyses are based on cross-sectional analyses, it is possible that psychopathology leads to a later chronotype, but it is also possible that a later chronotype is a risk factor for developing depressive and/ or anxiety disorders. Underlying genetic factors, such as clock genes, causing both mood symptoms and differences in chronotype could be responsible for this association. This has been reported before: circadian clock-related polymorphisms have been associated both with seasonal affective disorder and diurnal preference (16). It is also possible that environmental factors, such as bright light, are responsible for the association between chronotype and psychopathology. Bright light is one of the best known 'Zeitgebers' of

the biological clock, and a lack of bright light might affect both circadian rhythmicity and mood (17).

Primary versus secondary/ comorbid insomnia

It is not yet clear how insomnia in the context of depressive and anxiety disorders must be ultimately viewed, since insomnia or sleep disturbances are also a diagnostic criterion of major depressive disorder and generalized anxiety disorders. In the older literature, there were two different viewpoints: (1) sleep disturbances were an indicator of severity of the underlying psychiatric condition, and (2) sleep disturbances were a condition which existed on its own (labelled as a 'separate entity'), next to or comorbid to the depressive and anxiety disorders (18). The International Classification of Sleep Disorders (19) followed this abovementioned distinction, and subsequently distinguished two types of insomnia: *primary insomnia* and *secondary insomnia*. Primary insomnia was diagnosed in the absence of an underlying psychiatric or other medical cause. Secondary insomnia was thought to result from an underlying psychiatric or medical cause (19). More recent literature actually favours the term 'comorbid insomnia' instead of 'secondary insomnia' (20). Comorbid insomnia implies that the insomnia is viewed as a separate condition with a need for treatment aimed specifically at the insomnia. As for the second explanation which views sleep as an indicator of underlying severity, this makes sense from a clinical point of view. As we have stated before, sleep disturbances, such as insomnia, are one of the diagnostic criteria of a major depressive disorder and are also included in the definition of generalized anxiety disorder. Sleep disturbances are also included in symptom severity checklists for depression (21). To illustrate this further: in a sample which compared majorly depressed individuals based on the presence/ absence of insomnia, it was found that subjects with insomnia reported an increased severity of psychiatric symptoms and that also the duration of the depressive episode was longer (22). This was also found in a large sample (n=3743) of non-psychotic majorly depressed outpatients: symptoms of insomnia were indicative of a more severe depression (23). But, as stated before, insomnia can also be viewed as a separate, independent condition.

Suggestions that sleep disturbances are an indicator of severity of psychopathology

In **Chapter 2** we found increased insomnia scores in subjects with current depressive and/ or anxiety disorders, with subjects suffering from both conditions (i.e., the most severely affected) reporting the highest insomnia scores. These findings were not altered

by adjusting for a large set of confounders known to influence sleep (such as somatic health, severity of mood symptoms or use of psychotropic medication). In addition, in **Chapter 5** it was shown that insomnia (and a short sleep duration) was associated with a worse course (i.e., persistence of diagnosis or chronic course trajectory) of depressive and/ or anxiety disorders. However, we found that the effect of insomnia on persistence of a depressive and/ or anxiety disorder was (entirely) attributed to symptom severity, since associations disappeared after adjusting for severity of psychiatric symptoms. This could suggest that – with respect to course of depressive and/ or anxiety disorders – insomnia is an indicator of more severe psychopathology.

Suggestions that sleep disturbances are independent of severity of psychopathology

In line with the indication of primary insomnia in which the insomnia is an important phenomenon independent of an underlying cause, in **Chapters 4** and **5**, rather independent associations between sleep disturbances and the onset and course of depressive and/ or anxiety disorders were found. In **Chapter 4**, we found that both insomnia and short sleep duration were associated with incident depressive and/ or anxiety disorders. It is of course also possible that subjects who experience insomnia prior to a clinical diagnosis of a depressive or anxiety disorder, already experience subsyndromal psychiatric symptoms. Therefore, we adjusted our results for severity of (subsyndromal) depressive symptoms, in order to examine the independent effect of insomnia on the onset of these disorders. After adjustment, we still found that insomnia was predictive of the onset of these disorders.

These findings are in line with the suggestion of 'primary insomnia', because the insomnia was present before the onset of the disorder. This suggests that primary insomnia is on the causal pathway of developing depressive and anxiety disorders. How insomnia contributes to the onset of depressive and/ or anxiety disorders remains not fully understood. Most research has focussed on insomnia and the onset of depression. Less research has been conducted in order to explore whether insomnia leads to incident anxiety disorders. In adolescents, it has been found that in 73% of the studied sample the anxiety disorder precedes the insomnia and prior insomnia was not significantly associated with onset of anxiety disorders (16), which is in contrast with our study.

In the literature, there is general consensus on the model of 'hyperarousal'. Every individual experiences life stressors which can result in insomnia. In some individuals (for whatever cause), the insomnia does not resolve after the stressor disappears, resulting in a state of 'hyperarousal' (24). Instead of becoming relaxed and preparing to fall asleep, these individuals are aroused, and there is increased cortical activation as a

result of classical conditioning. There is increased sensory and information processing, and enhanced memory formation. Each of these processes might have a negative effect on sleeping. For instance, it is thought that an increased level of cortical activation makes it difficult for subject to distinguish between sleep and wakefulness. Enhanced memory formation might interfere with one's ability to experience uninterrupted sleep. A hyperarousal state is associated with a diminished amount of Rapid Eye Movement sleep, which is associated with altered emotional responses, different functioning of the cognitive system – including cognitions about one self and the environment and ultimately to depression (24). From a psychological perspective, this can be explained by the model of 'learned helplessness', in which negative cognitions about one's ability to function lead/ contribute to the onset of depression.

Another underlying mechanism could be that insomnia and depressive or anxiety disorders share a genetic basis. Certain genes may contribute independently to insomnia and to mood disorders. A variation in the serotonin transporter gene (one or two copies of the polymorphism in the promotor region) has been associated with more depressive symptoms (25). In another study, a variation in the serotonin transporter gene (two short alleles) was associated with primary insomnia (26). Thus, there is evidence (be it little) that such genetic variations are possibly associated with both mood disorders and insomnia.

The explanation for the predictive role of insomnia could also be neuro-endocrine. There has been been quite some research linking hypercortisolism to major depression (27). Some studies have also found increased cortisol excretion in insomniacs (28), and this finding was replicated in another study (29). However, another study was not able to replicate this finding (30), and a recent review states that the research on the relationship between cortisol and insomnia has not been studied extensively enough to draw conclusions on the direction of the association (24).

In **Chapter 5**, we found that both short and long sleep duration were associated with a chronic course, independent of severity of baseline symptoms. Possibly, short sleep duration increases daytime fatigue, which has been predictive of poor outcome of depression (31). Theoretically subjects with short sleep duration may suffer from a biologically different type of depression or anxiety, thus contributing to a poorer course. A shared genetic background for mood disorders and short sleep duration has recently been proposed, because genetic variation previously linked to depression (GRIA3-polymorphism) has also been linked to shorter sleep duration (32). Short sleepers might also just have more 'time' for pessimistic thoughts, thus contributing to poor outcome in depression (15). The fact that long sleep duration contributes to poorer outcome, might be based on the fact that depressed/ anxious individuals spend more time in bed, dissatisfied with the fact that they can not get out of bed.

Sleep disturbances: indicative of severity of psychopathology, or independent of psychopathology?

Summarizing, our results suggest that sleep disturbances can likely reflect an indication of (current) severity as well as an independent comorbid condition. It is not easy to discriminate between these two mechanisms, and the results of this study suggest that both may be partly true. We provide evidence that sleep disturbances are indicative of major depressive disorder severity, but our study also provides evidence that insomnia and sleep duration add predictive value in onset and course of depression and anxiety disorders, next to the standard clinical severity indicators. A recent study investigated the presence of 'primary' and 'secondary' insomnia in depressed subjects: 40.7% reported primary insomnia, 58.8% reported secondary insomnia, and 33.3% reported both types of insomnia (18). This suggests that it is important to distinguish between these two types of insomnia, but given the fact that more than one third suffers from both types of insomnia, the distinction may not be that relevant. From a scientific point of view, it is important to differentiate between these forms of insomnia (18). But from a clinical point of view, it is probably not always possible to rely on individuals' perceptions in diagnosing at which point in time the insomnia was first present (either before of during the disorder) (33).

Sleep and remitted depressive disorders

In **Chapter 2** we found that insomnia and short sleep duration were associated with *remitted* depressive disorders. This suggests that sleep disturbances are not only an indicator of *current* severity, but could also be a 'residual symptom' of a depressive disorder. It has been reported before that sleep disturbances are one of the most common residual symptoms after a major depressive episode (34). In unipolar depressive disorder, there is evidence that the first episodes of the disorder are associated with a considerable amount of stressors (such as life events), but this is less pronounced in subsequent episodes of the disease, in which the relapses occur much easier. This phenomenon is also called 'kindling' (35). The mind is then 'predisposed' to the development of a new episode (35). Possibly the sleep disturbances after a remitted diagnosis of major depressive disorder are a manifestation of this 'kindling' effect, making subjects more vulnerable for a new episode.

Our results are also in line with other studies. Sleep disturbances in remitted depressed individuals have previously been found not to be related to baseline severity and duration of depression, subtypes of depression or comorbid somatic diseases (36). The results of this study were similar to an earlier study which also explored residual rates of

insomnia after treatment for major depressive disorder (37). The results of our study and previous studies thus support the idea that sleep disturbances may also be considered a 'separate entity' (18), a condition which does not necessarily improve after the depressive disorder has remitted.

Consequences of sleep disturbances

In **Chapter 3,** we found that insomnia and short sleep duration were significantly associated with decreased work performance and absenteeism in subjects with current psychopathology, also after adjusting for symptom severity and use of psychotropic medication. This suggests that insomnia and short sleep duration have independent effects on work performance, and is not simply a manifestation of severity of the underlying psychopathological disorder. We did not find these associations in subjects without current psychopathology. An explanation for the fact that the association between sleep disturbances and work functioning almost exclusively occurred in subjects with psychopathology, may be that subjects with psychopathology call in sick earlier, because they find it harder to cope with their sleep disturbances. This might be a decreased (psychological) 'flexibility' due to their underlying depressive or anxiety disorder. Also, it is possible that sleep in depressed/ anxious individuals is a different phenomenon, with, for instance, a larger role for ruminating/ worrying subjects with psychopathology (38), thus having a different effect on work functioning.

Depressive versus anxiety disorders: does type of disorder matter in the association with sleep disturbances?

In some chapters of this thesis, we found that sleep disturbances (insomnia/ sleep duration) are more associated with depressive than with anxiety disorders. In **Chapter 2,** we found that the odds ratios associating major depressive disorder with insomnia/ short sleep duration were respectively 3.12 (95%CI=2.51-3.89) and 2.26 (95%CI=1.78-2.87). For anxiety disorders, the odds ratios for insomnia and short sleep duration were 1.84 (95%CI=1.51-2.24) and 1.33 (95%CI=1.07-1.65). This may be partially because of the fact that insomnia is included in the definition of major depressive disorder. However, adjusting our findings for severity of depression did not significantly alter most of our findings, suggesting the association of insomnia with depressive disorders is truly stronger than the association with anxiety disorders. In **Chapter 2**, we also found an association between sleep disturbances (insomnia/ short sleep duration) and remitted depressive disorders. For remitted anxiety disorders, we found no associations for insomnia and sleep duration. In **Chapter 4**, the odds ratios for short

sleep duration predicting depressive versus anxiety disorders, were different (odds ratio for the incidence of depression=1.64, 95%CI=0.68-3.96; odds ratio for the incidence of anxiety=4.05, 95%CI=1.73-9.46), suggesting that the effect of short sleep duration on the incidence of anxiety appears more pronounced than the effect on the incidence of depressive disorders. In **Chapter 6,** we found that compared to anxious subjects, depressed subjects reported a significantly later chronotype. Possibly the explanation for the stronger associations for depression, is the fact that a disturbed biological clock has more impact in depressed subjects than in anxious subjects. Life events can trigger a disruption in social and biological rhythms, affecting both circadian rhythmicity (the biological clock) and mood in vulnerable subjects (39).

In other chapters, our results point to comparable effects of sleep on depressive and/or anxiety disorders. For instance, in **Chapter 4,** we found that the odds ratios for insomnia in predicting the onset of depressive and anxiety disorders were relatively comparable (depressive disorders: OR=3.04, 95% CI=1.36-6.80) (anxiety disorders: OR= 3.39 (95% CI=1.45-7.94). In conclusion, although for some results the link with depressive disorders was slightly stronger and for other results the link with anxiety disorders was stronger, it becomes clear from our study that sleep disturbances are associated with both depressive AND anxiety disorders.

Methodological considerations, strengths and limitations

We have discussed specific limitations in each individual chapter. Overall, the most important general limitation throughout this thesis and the current literature is the absence of a uniformly accepted definition of insomnia. Depending on what instrument is used, prevalence rates for insomnia vary considerably. For instance, in a population-based study insomnia was defined as 'difficulty sleeping' with approximately one-third of the subjects complaining about this (40). However, if a criterion is included which states that the insomnia symptoms must result in day-time consequences or impairments, the prevalence rate of insomnia is only 10% (40). This implies that insomnia is not one concept that is uniformly defined and, therefore, it is not easy to generalize findings across studies. For our study we have used the Insomnia Rating Scale, which has been validated against actigraphy measures (41). However, the Insomnia Rating Scale has only been validated for (post-menopausal) women and possibly cut-off values are different for men. After all, insomnia has frequently been associated with female gender (2). Menopause in itself has been associated with insomnia (42) and possibly cut-off values are different for premenopausal and postmenopausal women. Furthermore, the Insomnia Rating Scale has not frequently been used in research, making it more

difficult to compare our results with other studies. Nevertheless, many of our results are comparable to other studies and in line with our a priori hypotheses.

Another limitation is that individuals with psychopathological conditions might wrongly assess the degree of their insomnia or sleep duration. For instance, depressed patients have been reported to both over- as well as underestimate their amount of sleep time (43). In a study including bipolar patients, depressive symptomatology was associated with a greater degree of underestimation of total sleep time, whereas manic symptoms had little impact on estimating total sleep time (44). These results suggest that estimating sleep time may not be accurate enough in subjects with psychopathology. More objective measurements, used to estimate aspects of sleep, consist for instance of actigraphy and polysomnography. Actigraphy makes use of a special watch-like device that records movement over time. Actigraphy has been shown to adequately measure sleep (45), and a recent study showed that actigraphy is more reliable than a sleep diary (46) in estimating sleep time. The so-called polysomnography (PSG) is considered the 'gold standard' in diagnosing clinical sleep disorders. However, this is invasive since it involves recording an electroencefalogram (EEG; the measurement of electrical impulses produced by brain activity), an electro-oculogram (EOG; the measurement of eye movement), electromyogram (EMG; the measurement of muscle tone) and an electrocardiogram (ECG; the measurement of heart rate). The American Academy of Sleep Medicine (AASM) views depression with insomnia as an indication for PSG. There are however no specific characteristics on a PSG which uniquely indicate depression. Also, a recent study found that there are no PSG criteria which differentiate subjects with primary insomnia from good sleepers (47), which basically means that this is not an instrument which can be used to diagnose insomnia in research. Moreover, for circadian rhytmn sleep disorders, the AASM recommends that PSG should not be routinely used (48). Moreover, in a study which compared women with and without chronic insomnia, there were unexpectedly no differences in PSG results (49). Taken together, this suggests it is complicated to find an instrument or measurement which can reliably distinguish between good sleepers and subjects who suffer from insomnia, and it is even more difficult to find an instrument or measurement which measures this non-invasively. Actigraphy, however, can reliably be used to estimate sleep duration.

A further limitation in our study is the absence of data on the effects of insomnia on day-time functioning (such as daytime naps, difficulties in concentrations etc.), which are nowadays included in the DSM-IV definition of insomnia. We also had no data available on the duration of the insomnia. If these pieces of information had been present, we would have been able to diagnose insomnia according to DSM-criteria, making it easier to compare insomnia across psychiatric diagnoses ('primary' versus 'comorbid' insomnia). Furthermore, we have no information available on other sleep disorders,

such as narcolepsy, snoring, sleep apnoea and restless legs syndrome. These syndromes are common (50), and symptomatology may overlap partially, posing difficulties for clinicians. In a recent study, e.g., the prevalence of depression was 53% in individuals who were referred to a sleep clinic because of snoring (51).

Another important limitation is that part of the studies in this thesis rely on cross-sectional analyses only (**Chapters 2, 3 and 6**), which makes it impossible to draw definite conclusions on the direction of the associations that we found. Sleep can impact on psychiatric symptoms, and psychiatric symptoms can impact on sleep. However, we have used longitudinal analyses in **Chapters 4** and **5** in order to specifically examine what the effect of a disturbed sleep is on the onset and course of depressive and anxiety disorders.

However, our study also has a considerable number of strengths. First of all, we had the opportunity to assess depressive and anxiety disorders according to DSM-IV criteria in a large cohort instead of relying on disorder specific symptom severity checklists. Previous studies have used symptom severity checklists (52), which makes it more difficult to state whether the psychiatric symptoms are present in the context of a psychiatric disorder or not. Second, we assessed sleep quality, short and long sleep duration, as well as chronotype, which enabled us to look at the concept sleep from different perspectives. We found differential associations for different predictors (e.g., insomnia did not predict course of depressive and anxiety disorders, while sleep duration did) which clearly shows that it is important to differentiate between these concepts. Third, because sleep is influenced by many factors, such as sociodemographic, somatic health and psychotropic medication, it is important to incorporate all these in an epidemiological sleep study. Because of our reasonable large sample size, we were statistically able to include a large set of confounders or covariates. Finally, the longitudinal design of part of this thesis made it possible to further disentangle the effect of sleep disturbances on the onset and course of depressive and anxiety disorders.

Future research

Future research should investigate how to measure insomnia and sleep duration in an epidemiological setting most reliable, and yet the least invasive for the subjects involved. We only used self-reported information, but information with more objective sleep information will learn us more about the adequacy of self-reported sleep data, and whether objective sleep data, such as actigraphy data, does further add predictive information for e.g., the onset and course of depressive and/ or anxiety disorders.

Furthermore, our many cross-sectional and longitudinal findings that linked sleep variables – both insomnia and sleep duration – with depressive and anxiety disorders,

suggest that it is worthwhile to intervene on these outcomes. Therefore, additional research should investigate whether interventions directed at improving sleep in subjects who complain of sleep disturbances and who have never suffered from depressive and anxiety disorders, reduce the risk of developing these disorders. Also, it should be investigated whether this leads to improved course outcomes in depressed and/ or anxious subject. Ideally, interventions aimed at improving sleep, such as cognitive-behavioural therapy (CBT) or physical exercise should consist of a treatment with little side-effects and positive long term effects. CBT has been shown to be both effective and cost-effective (53). CBT for insomnia has also been shown to be effective regardless of baseline depression levels (54). Also, CBT has been shown to be effective in both uncomplicated as well as 'comorbid' insomnia (insomnia associated with medical disorders) (55), which makes it also suitable for individuals who already suffer from a depressive and/ or anxiety disorder. This makes it an ideal 'candidate' for future research. However, it is not yet known whether CBT targeted at insomnia will also reduce for instance costs associated with work absenteeism or decreased productivity (55). Furthermore, it should be investigated whether adding for instance physical exercise – a treatment with few side effects – has a favourable outcome on sleep as well as on depressive or anxiety disorders. For depressive disorders, it has been shown that antidepressant treatment which is 'enriched' with physical exercise, improves self-reported sleep quality (56).

Interventions involving CBT or physical exercise would be preferable above the use of benzodiazepines. Benzodiazepines are frequently prescribed in clinical practice to improve sleep, however, they are only to be presribed on a short term basis (ideally with a maximum duration of two weeks). They also carry the risk of 'tolerance', which means that the dosage of the benzodiazepine gradually needs to be increased in order to produce the same effect. Another negative side effect of benzodiazepines is that they can result in (too much) daytime sedation and psychomotor and cognitive and psychomotor impairment (57). Given these side-effects, benzodiazepines are generally not considered the first choice in treating sleep disturbances on the long term. Antidepressant medication does not carry the risk of tolerance and has less daytime sedation. However, it is still not clear which antidepressant medication improves the long term outcomes of patients with insomnia the most. Further research should investigate which antidepressant medication best targets insomnia. Recently, it has been found that quetiapine monotherapy in a dosage of 50-300 mg improves symptoms of sleep disturbance in subjects with a diagnosis of major depressive disorder (58). The antidepressant mirtazepine is also frequently prescribed in clinical practice because of its sleep-promoting properties in subjects with major depressive disorder (59). It has been found that mirtazepine also promotes sleep in individuals suffering from post traumatic

stress disorder (60). But it is to be determined whether mirtazepine also specifically targets sleep disturbances in the anxiety disorders we studied in this thesis. Until now, mirtazapine has been found effective in treating panic disorder in general (61), but in social anxiety disorder no positive effect was found (62).
Finally, future research should address the direction in the relationship between chronotype and depressive and/ or anxiety disorders. It is to be determined whether a late chronotype is a cause or a consequence of psychopathology. Also, it should be examined whether 'treating' chronotype with sleep deprivation or chronotherapeutics has a favourable outcome on the course of depressive and/ or anxiety disorders.

Clinical implications

Clinicians should give more attention to short sleep duration and long sleep duration in individuals suffering from depressive or anxiety disorders, given the fact that these were both associated with a more unfavourable course. Especially the impact of long sleep duration and the occurrence of sleep problems along with anxiety disorders has until now been under-recognized by many psychiatrists and psychologists. Although it is to be determined whether 'treating' sleep duration will result in a more favourable outcome, it is evident that sleep should be a specific item of concern when treating depressed or anxious individuals. At the very least, the results of this thesis suggest that clinicians have to monitor sleep explicitly during the treatment of their depressed and anxious patients. A recent study in which subjects (either currently on antidepressant medication or in the past, n=227) were asked to rate hypothetical outcomes of depression, revealed that these subjects rated the absence of sleep disturbances (next to the absence of side effects, pain related to depression and feelings of guilt) more important than a depressed mood (63). These results are surprising, since a depressed mood is one of the core symptoms of major depressive disorder, and antidepressant treatments are generally aimed at – at least – the improvement of mood. The authors also found that patients value the ability to cope with everyday living the most important (63). Perhaps clinicians need to more explicitly discuss with their patients which symptoms should be targeted primarily. In other words, sleep should be a more explicit focus in the treatment of depressive and anxiety disorders. However, it is to be determined whether the results of this one study are generalizable to the heterogeneous population of depressed subjects (inpatients/ outpatients), that clinicians treat in their daily practice.
Furthermore, the results of this thesis suggest that clinicians, such as general practitioners, who treat patients complaining of sleep disturbances – but have never suffered from depressive and or anxiety disorders – should be aware of the fact that sleep disturbances can lead to the development of a first episode of an depressive and/ or

an anxiety disorder. Although it is yet to be determined whether treating the insomnia can prevent the transition to a depressive or anxiety disorder, referral to a cognitive behavioural therapist for an insomnia treatment (CBT-I: Cognitive Behavioural Therapy for Insomnia) should be considered, since this is an effective treatment for insomnia (64). Moreover, CBT seems to have effect also after discontinuation of the treatment (65), which is in contrast to pharmacological agents such as benzodiazepines. CBT can even be administered via internet (with mild/ moderate effect), thus making the treatment available for almost everyone having access to a computer (66).

Also, it should be recognized that insomnia and a short sleep duration have an effect on work functioning in depressed and anxious subjects. Possibly, CBT, delivered either via internet or face-to-face, results in more favourable work outcomes in depressed and anxious subjects. CBT has been administered in certain work fields before, but has not been tested with work absenteeism or work functioning as outcome. For shift work, CBT has been found to be effective in treating the insomnia (67) and also employees in Occupational Health Services have been shown to benefit from CBT directed at their insomnia (68). However, as in all treatments, patients differ in adhering to the treatment. Unfortunately, there are few studies available on adherence/ attrition and sleep outcomes in CBT for insomnia (69), which complicates identifying which subjects may benefit from the treatment. In the current health system in the Netherlands, large adjustments are made for the mental health budget, and this warrants careful identification of effectiveness and efficacy of any treatment in order to justify spending the health care budget on them.

In conclusion

The main aim of this thesis was to examine the role of sleep (insomnia/ duration/ chronotype) in depressive and anxiety disorders on several outcomes, i.e., the prevalence, onset and course of depressive and anxiety disorders and work functioning. Not only current depressive, but also current anxiety disorders are associated with insomnia and both short and long sleep duration. Moreover, sleep disturbances, i.e., insomnia and short sleep duration, may have a scarring impact, since they are still significantly more common among persons with remitted depressive disorders.

Sleep should be an explicit focus in the treatment of depressive and anxiety disorders, given its association with work functioning, the fact that a disturbed sleep predicts the onset of depressive and anxiety disorders, and the fact that a disturbed sleep is associated with a more unfavourable outcome of depressive and anxiety disorders. Clinicians should not only consider insomnia and a short sleep duration, but also a long sleep duration, since we found that a long sleep duration predicts a more unfavourable course of depressive and/ or anxiety disorders.

References

1. Riemann D. Insomnia and comorbid psychiatric disorders. *Sleep Med* 2007; 8; Suppl 4:S15-20.
2. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev 2002*; 6(2): 97-111.
3. Ohayon MM, Caulet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry* 1998; 39(4): 185-197.
4. Tsuno N, Besset A, Ritchie K. Sleep and Depression. *Sleep* 2005; 66(10): 1254-1269.
5. Ohayon MM, Shapiro CM, Kennedy SH. Differentiating DSM-IV anxiety and depressive disorders in the general population: comorbidity and treatment consequences. *Can J Psychiatry* 2000; 45(2): 166-172.
6. Marcks BA, Weisberg RB, Edelen MO, Keller MB. The relationship between sleep disturbances and the course of anxiety disorders in primary care patients. *Psychiatry Res* 2010; 178(3): 487-492.
7. Sheehan DV, Ballenger J, Jacobsen G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch Gen Psychiatry* 1980; 37(1): 51-59.
8. Mahendran R, Subramaniam M, Chan YH. Psychiatric morbidity in patients referred to an insomnia clinic. *Singapore Med J* 2007; 48(2): 163-165.
9. Novati A, Roman V, Cetin T, Hagewoud R, den Boer JA, Luiten PG *et al*. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. *Sleep* 2008; 31(11): 1579-1585.
10. Patel SR, Zhu X, Storffer-Isser A, Mehra R, Jenny NS, Tracy R *et al*. Sleep duration and biomarkers of inflammation. *Sleep* 2009 Feb; 32(2): 200-204.
11. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep and fatigue. *Ann N Y Acad Sci* 2012; 1261: 88-896.
12. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK *et al*. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010; 67(5): 446-457.
13. McCann SJ, Stewin LL. Worry, anxiety and preferred length of sleep. *J Genet Psychol* 1988; 149(3): 413-418.
14. Hartmann E, Baekemann F, Zwilling GR. Psychological differences between long and short sleepers. *Arch Gen Psychiatry* 1972; 26(5): 463-468.
15. Kelly WE. Worry and sleep length revisited: worry, sleep length and sleep disturbances ascribed to worry. *J Genet Psychol* 2002; 163(3): 296-304.
16. Johansson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kiesseppä T *et al*. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 2003; 28(4): 734-739.

17. Okawa M, Uchiyama M. Circadian rhythm sleep disorders: characteristics and entrainment pathology in delayed sleep phase and non-24-h sleep-wake syndrome. *Sleep Med Rev* 2007; 11(6): 485-496
18. Gupta R, Lahan V. Insomnia associated with depressive disorder: primary, secondary or mixed. *Indian J Psychol Med* 2011; 33(2): 123-128.
19. International classification of sleep disorders. 2nd ed. Westchester: AASM; 2005.
20. National Institutes of health. NIH state of the science conference statement manifestations and management of chronic insomnia in adults. *J Clin Sleep Med* 2005; 1(4): 412-421.
21. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 1996; 26(3): 477-486.
22. O'Brien EM, Chelminski I, Young D, Dalrymple K, Hrabosky J, Zimmerman M. Severe insomnia is associated with more severe presentation and greater functional deficits in depression. *J Psychiatr Res* 2011; 45(8): 1101-1105.
23. Sunderajan P, Gaynes BN, Wisniewski SR, Miyahara S, Fava M, Akingbala F *et al*. Insomnia in patients with depression: a STAR*D report. *CNS Spectr* 2010; 15(6): 394-404.
24. Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. *Curr Psychiatry Rep* 2012; 14(5): 511-518.
25. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H *et al.* Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003; 301(5631): 386-389.
26. Deuschle M. Schredl M, Schilling C, Wüst S, Frank J, Witt SH *et al*. Association between a serotonin transporter length polymorphism and primary insomnia. *Sleep* 2010; 33(3): 343-347.
27. Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depressoion: implications for therapy. *J Affect Disord* 2001; 62(1-2): 77-91.
28. Vgontzas AN, Tsigos C, Bixler EO, Stratakis CA, Zachman K, Kales A *et al*. Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res* 1998; 45(1): 21-31.
29. Rodenbeck A, Huether G, Rüther E, Hajak G. Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett* 2002; 324(2): 159-63.
30. Riemann D, Klein T, Rodenbeck A, Feige B, Horny A, Hummel R *et al*. Nocturnal cortisol and melatonin secretion in primary insomnia. *Psychiatry Res* 2002; 113(1-2): 17-27.
31. Van Noorden MS, van Fenema EM, van der Wee NJ, Zitman FG, Giltay EJ. Predicting outcome of depression using the depressive symptoms profile: the Leiden Routine Outcome Monitoring Study. *Depress Anxiety* 2012; 29(6): 523-530.
32. Utge S, Kronholm E, Partonen T, Soronen P, Ollila HM, Loukola A *et al*. Shared genetic background for regulation of mood and sleep: association of GRIA3 with sleep duration in healthy Finnish women. *Sleep* 2011; 34(10): 1309-1316.

33. Sanchez-Ortuño MM, Edinger JD. Cognitive-behavioral therapy for the management of insomnia comorbid with mental disorders. *Curr Psychiatry Rep* 2012; 14(5): 519-28.
34. Nierenberg AA, Hussain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR *et al*. Residual symptoms after remission of major depressive disorders with citalopram and risk of relapse: a STAR*D report. *Psychol Med* 2010; 40(1): 41-50.
35. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *Am J Psychiatry* 2001; 158(4): 582-586.
36. Li SX, Lam SP, Chan JW, Yu MW, Wing YK. Residual sleep disturbances in patients remitted from major depressive disorder: a 4-year naturalistic cohort study. *Sleep* 2012; 35(8): 1153-1161.
37. Carney CE, Segal ZV, Edinger JD, Krystal AD. A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *J Clin Psychiatry* 2007; 68(2): 254–260
38. Roelofs J, Huibers M, Peeters F, Arntz A, van Os J. Rumination and worrying as possible mediators in the relation between neuroticism and symptoms of depression and anxiety in clinically depressed individuals. *Behav Res Ther* 2008; 46(12): 1283-1289.
39. Grandin LD, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhtythms and mood disorders: review and evaluation. *Clin Psychol Rev* 2006; 26(6): 679-694.
40. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. *Sleep* 1999; 22 Supl: S347-453.
41. Levine DW, Dailey ME, Rockhill B, Tipping D, Naughton MJ, Shumaker SA. Validation of the Women's Health Initiative Insomnia Rating Scale in a multicenter controlled clinical trial. *Psychosom Med* 2005; 67(1): 98-104.
42. Guidozzi F. Sleep and sleep disorders in menopausal women. *Climacteric* 2013; 16(2): 214-219.
43. Rotenberg VS, Indursky P, Kayumov L, Sirota P, Melamed Y. The relationship between subjective sleep estimation and objective sleep variables in depressed patients. *Int J Psychophysiol* 2000; 37(3): 291-297.
44. Gonzalez R, Tamminga C, Tohen M, Suppes T. Comparison of objective and subjective assessments of sleep time in subjects with bipolar disorder. *J Affect Disord* 2013; 149(1-3): 363-366.
45. Tyron WW. Issues of validity in actigraphic sleep measurement. *Sleep* 2004; 27(1): 158-165.
46. McCall C, McCall WV. Comparison of actigraphy with polysomnography and sleep logs in depressed patients. *J Sleep Res* 2012; 21(1): 122-127.
47. Edinger JD, Ulmer CS, Means MK. Sensitivity and specificity of polysomnographic criteria for defining insomnia. *J Clin Sleep Med* 2013; 19(5): 481-91.

48. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J Jr *et al*. Practice parameters for the indications of polysomnography and related procedures: an update for 2005. *Sleep* 2005; 28(4): 499-521.
49. Seelig E, Keller U, Klarhofer M, Scheffler K, Brand S, Holsboer-Trachsler E. Neuroendocrine regulation and metabolism of glucose and lipids in primary chronic insomnia: a prospective case-control study. *PLos One* 2013; 8(4): e61780.
50. Juuti AK, Hiltunen L, Rajala U, Laakso M, Härkönen P, Keinänen-Kiukaanniemi S *et al*. *Sleep Breath* 2012; 16(3): 639-648.
51. Douglas N, Young A, Roebuck T, Ho S, Miller BR, Kee K *et al*. Prevalence of depression in patients referred with snoring and obstructive sleep apnoea. *Intern Med J* 2013; 43(6): 630-634.
52. Szklo-Coxe M, Young T, Peppard PE, Finn LA, Benca RM. Prospective associations of insomnia markers and symptoms with depression. *Am J Epidemiol* 2010; 171(6): 709-720.
53. Sharma MP, Andrade C. Behavioural interventions for insomnia: theory and practice. *Indian J Psychiatry* 2012; 43(4): 359-366.
54. Lancee J, van den Bout J, van Straten A, Spoormaker VI. Baseline depression levels do not affect efficacy of cognitive-behavioral self-help treatment for insomnia. *Depress Anxiety* 2013; 39(2): 149-156.
55. Vitiello MV, McCurry SM, Rybarczyk BD. The future of cognitive behavioral therapy for insomnia: what important research remains to be done? *J Clin Psychol* 2013 (epub ahead of print) doi: 10.1002/jclp.21948
56. Rethorst CD, Sunderajan P, Greer TL, Grannemann BD, Nakonezny PA, Carmody TJ *et al*. Does exercise improve self-reported sleep quality in non-remitted major depressive disorder? *Psychol Med* 2013; 43(4): 699-709.
57. Lader M. Benzodiazepine harm: how can it be reduced. *Br J Clin Psychopharm* 2012; (epub ahead of print) doi:10.1111/j.1365-2125.2012.04418.x.
58. Trivedi MH, Bandelow B, Demyttenaere K, Papakosts GI, Szamosi J, Earley W *et al*. Evaluation of the effects of extended release quetiapine fumarate monotherapy on sleep disturbance in patients with major depressive disorder: a pooled analysis of four randomized acute studies. *Int J Neuropsychopharmacol* 2013; 16(8): 1733-1744.
59. Dolder CR, Nelson MH, Iler CA. The effects of mirtazapine on sleep in patients with major depressive disorder. *Ann Clin Psychiatry* 2012; 24(3): 215-224.
60. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to treatment. *CNS Drugs* 2006; 20(7): 567-590.
61. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol* 2013; 28(1): 33-45.

62. Schutters SI, Van Megen HJ, Van Veen JF, Denys DA, Westenberg HG. Mirtazapine in generalized anxiety disorder: a randomized, double blind, placebo-controlled study. *Int Clin Psychopharmacol* 2010; 25(5): 302-304.
63. Zimmermann TM, Clouth J, Elosge M, Heurich M, Schneider E, Wilhelm S et al. Patient preferences for outcomes of depression in Germany: a choice-based conjoint analysis study. *J Affect Disord* 2013; 148(2-3): 210-219.
64. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy. *Cognit Ther Res* 2012; 36(5): 427-440.
65. Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev* 2009; 13(3): 205-214.
66. Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother Psychosom* 2012; 81(4): 206-216.
67. Jaärnefelt H, Lagerstedt R, Kajaste S, Sallinen M, Savolainen A, Hublin C. Cognitive behavioral therapy for shift workers with chronic insomnia. *Sleep Med* 2012; 13(10): 1238-1246.
68. Järnefelt H, Lagerstedt R, Kajaste S, Sallinen M, Savolainen A, Hublin C. Cognitive behavioral therapy for chronic insomnia in occupational health services. *J Occup Rehabil* 2012; 22(4): 511-21.
69. Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS. Adherence to cognitive behavioral therapy for insomnia: a systematic review. *Sleep Med Rev* 2013; epub ahead of print: doi.10.1016/j.smrv.2013.01.001.