Sleep, depression and anxiety: an epidemiological perspective

van Mill, J.G.

2013

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
van Mill, J. G. (2013). *Sleep, depression and anxiety: an epidemiological perspective*.

CHAPTER 4

Insomnia, sleep duration and incidence of depressive and anxiety disorders results from a large cohort study

Josine G. van Mill
Nicole Vogelzangs
Witte J.G. Hoogendijk
Brenda W.J.H. Penninx

Abstract

Background
Sleep disturbances are thought to increase the risk of developing depressive and anxiety disorders. However, evidence up until now is not conclusive.

Objective
To determine associations between insomnia and sleep duration at baseline and the incidence of depressive and anxiety disorder during two year follow-up in a sample free of lifetime depressive and anxiety disorders at baseline, while adjusting for the effect of subclinical depressive symptoms, sociodemographics and somatic health indicators.

Methods
Data are from the Netherlands Study of Depressive and Anxiety Disorders, a longitudinal cohort study. Subjects without lifetime depressive and anxiety disorders at baseline (n=565) were selected for the current study. Incidence of depressive and anxiety disorders over two years of follow-up according to the Composite International Diagnostic Interview based on DSM-IV criteria.

Results
Insomnia and short sleep duration at baseline were significantly associated with 2-year incidence of depressive and anxiety disorders (OR Insomnia=4.23, 95% CI=2.15-8.33, OR short sleep duration=2.70, 95% CI= 1.35-5.48). Associations remained present after considering baseline subclinical depressive symptoms, sociodemographics and somatic health indicators.

Limitations
Sleep measures were based on self-report only.

Conclusions
Both insomnia and short sleep duration are independent risk factors for incident depressive and anxiety disorders. Future research is needed to determine if interventions directed at improving sleep are effective in preventing these disorders.

Introduction

Depressive and anxiety disorders are common disorders, with an estimated lifetime prevalence of approximately 16 % for major depressive disorder and 28% for anxiety disorders (1). These disorders have a considerable impact on both individuals and society: they often run a chronic course (2), are associated with a diminished quality of life (3) and impact on work productivity and absenteeism (4). Given the enormous consequences, knowledge of risk factors is of particular importance in order to develop preventative strategies for these disorders.

Sleep disturbances, such as insomnia, may be one of the risk factors for depressive and anxiety disorders and various epidemiological studies have tried to unravel the link between sleep disturbances and subsequent depressive and anxiety disorders (5-8). A major difficulty in investigating this link is the fact that a variety of factors need to be considered. Firstly, because sleep disturbances are one of the most common residual symptoms of a depressive episode (9), subjects with a lifetime diagnosis of a depressive or anxiety disorder should be excluded from the sample. Ford and Kamerow were one of the first to report on the relationship between insomnia and subsequent depression, but they did not investigate a sample free of lifetime disorders (7). Also when Breslau et al. investigated the association between prior insomnia and subsequent first onset depressive or anxiety disorders, they did not use a restrictive sample free of all investigated (depressive and anxiety) disorders (5).

Also, not all studies investigating the predictive role of sleep disturbances rely on psychiatric diagnoses to assess depressive and anxiety disorders, but some rely on symptom questionnaires instead (6, 10, 11). Secondly, because other subclinical depressive symptoms have been reported to be an important confounder in the relationship between insomnia and the onset of depressive and anxiety disorders (5), its effect should not be overlooked. In addition, also other potential confounders such as health indicators (alcohol intake, body mass index, somatic diseases, and pain scores should be considered (12), which has not always been dealt with in previous research. Finally, when investigating sleep disturbances, it is interesting to examine both insomnia and sleep duration since recent research has found these to be differentially associated with psychopathology (13).

Previous studies have only partly addressed all these abovementioned issues. In this study, we want to extend current knowledge of sleep disturbances as a predictor of depressive and anxiety disorders. Therefore, the aim of the current study is to describe the longitudinal association between sleep disturbances at baseline (both insomnia and sleep duration) and the incidence of depressive and anxiety disorders during follow-up, in a sample never diagnosed with lifetime depressive or anxiety disorders,

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while adjusting for the effect of other subclinical depressive symptoms, relevant socio-demographics and somatic health indicators.

Methods

Sample

For this study, data were analyzed from the baseline measurement and the two-year follow-up from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is an ongoing eight-year longitudinal cohort study designed to investigate the long term course of depressive and anxiety disorders in individuals aged 18 through 65 years. NESDA includes both persons with depression and anxiety disorders and healthy controls. NESDA respondents were recruited from three different settings: the general population, primary health care and secondary mental health care. Exclusion criteria for the NESDA study were not speaking Dutch and a known primary clinical diagnosis of bipolar disorder, obsessive compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. A more detailed description about the study's sampling procedures is described elsewhere (14).

The final sample size of the NESDA study consisted of 2981 subjects. For the purpose of the current study 652 subjects without lifetime Composite International Diagnostic Interview (CIDI; 15) depressive or anxiety disorders at baseline were selected. Of this sample, 44 subjects had no data available on sleep measures and 43 subjects did not participate in the follow-up, leaving 565 persons for the present study. Excluded subjects did not differ in age, gender and educational level, compared to subjects who were included in the study.

Measurements

Between September 2004 and February 2007, participating individuals visited one of the seven interview locations for the baseline measurement. Follow-up assessments (face-to-face) were conducted two years later. Both the baseline and the follow-up measurement consisted (amongst others) of a standardized diagnostic psychiatric interview, a medical assessment, drawing of a blood sample, computer tasks and two fill out questionnaires (one before and one after the interview).

Insomnia and sleep duration

Sleep disturbances were assessed by insomnia and sleep duration. Both insomnia and sleep duration were part of a questionnaire which subjects filled out at the end

of the baseline interview or at home afterwards (median time log for returning the questionnaire was four days). Insomnia was assessed with the Women's Health Initiative Insomnia Rating Scale (IRS). This scale was developed by Levine et al. (2003) and consists of five questions concerning sleep in the past month (16). The five items address trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up and sleep quality. Scores on the first four items range from 0 "no" to 4 " ≥5 times a week", whereas the fifth item of sleep quality ranges from 0 "very sound or restful" to 4 "very restless". The total summary score ranged from 0 (no insomnia) to 20 (severe insomnia). Validity of the IRS has been evaluated in a study of 66269 post menopausal women: reported test-retest reliability was 0.96 (same day) and 0.66 (one year later) (17). IRS correlated with other actigraphy derived sleep measures (sleep efficiency, sleep latency, wakefulness after sleep onset) (17), implying that the IRS is capable of signalling differences in these more objective measures. In our study the Cronbach's alpha was 0.76. Next to the continuous score, scores on the IRS were dichotomized at a cut off point of nine, which has shown to indicate clinical significant insomnia (17).

Sleep duration was assessed by asking subjects to estimate the average hours of sleep per night during the past month, ranging from less than five hours to more than ten hours. Next to this continuous measure, answers were categorized in sleep duration of ≤6 hours (short sleep duration), 7-9 hours (normal sleep duration), or ≥10 hours (long sleep duration). Because both short and long sleep duration are associated with psychopathology (18) including only a continuous sleep duration measure may not be sufficient. Sleep duration and IRS score were only mildly correlated (r= -0.33, p= <.001), confirming that sleep duration and sleep complaints are separate concepts.

Incidence of depressive and anxiety disorders
Subjects were only included in the present study if a lifetime diagnosis of depressive or anxiety disorders had been ruled out at baseline, using the Composite International Diagnostic Interview (CIDI). The CIDI is a standardized diagnostic psychiatric interview which uses DSM-IV criteria to establish diagnoses and was administered by trained research staff (19). The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders (20). At follow-up, the incidence of a depressive or anxiety disorder between the baseline interview and 2-year follow-up was assessed. Depressive disorders included major depressive disorder and dysthymia. Anxiety disorders included panic disorder, agoraphobia, generalized anxiety disorder and social phobia.

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Covariates

Other characteristics assessed that possibly affect sleep and the incidence of depressive and anxiety disorders, included age (in years), gender, current partner status (yes/no), education (in years), currently smoking (yes/ no), alcohol intake (none= less than one per week, moderate=1-21 per week for males, 1-14 for females, severe= >21 per week for males, >14 for females), body mass index (BMI, weight in kg divided by height in m^2), a total count of self-reported somatic diseases for which participants received treatment (including lung disease, diabetes, cardiovascular disease, cancer, osteoarthritis, intestinal disorders, liver disease, epilepsy, chronic fatigue syndrome and thyroid gland disease), and pain during the past 6 months. The conceptualization of the pain score was based on earlier work by von Korff and classified as grade 0 (pain free), grade 1 (low pain intensity-low disability), grade 2 (high intensity-low disability) grade 3 (high disability-moderately limiting) or grade 4 (high disability-severely limiting) (21). Severity of baseline (subclinical) depressive symptoms was measured with the Inventory of Depressive Symptoms (IDS) (22). The IDS contains four sleep related items, which were excluded in order to prevent overadjustment.

Statistical analyses

Baseline characteristics were calculated and compared across individuals who did and did not develop depressive or anxiety disorders during follow-up, using chi-square statistics for categorical variables and t-tests for continuous variables. Logistic regression analyses were performed with depressive or anxiety disorders (yes/no) during follow-up as the outcome and sleep variables (insomnia/ sleep duration) as the predictors. Odds Ratios (ORs) are reported for two different models: first adjusted for age, gender, education, partner, smoking, alcohol intake, BMI, number of somatic diseases and pain score (model 1) and adjusted for all before mentioned variables plus the severity of subclinical depressive symptoms at baseline (model 2). For each sleep measure, the percentage of change in the natural logarithm of the Odds Ratios (ln OR) between model 1 and model 2 was calculated.

Results

Table 1 shows baseline characteristics of persons who did and did not develop depressive or anxiety disorders over two years. Of the sample, 9.2% (n=52) developed a depressive or anxiety disorder during follow up. Subjects who developed a disorder were significantly younger, had less often a partner, were more often current smokers, reported higher insomnia scores, shorter sleep duration and a higher IDS score. Because

of low frequencies, long sleepers were excluded from subsequent analyses with the categorical sleep duration variable.

Table 1: Baseline sample characteristics (n=565)

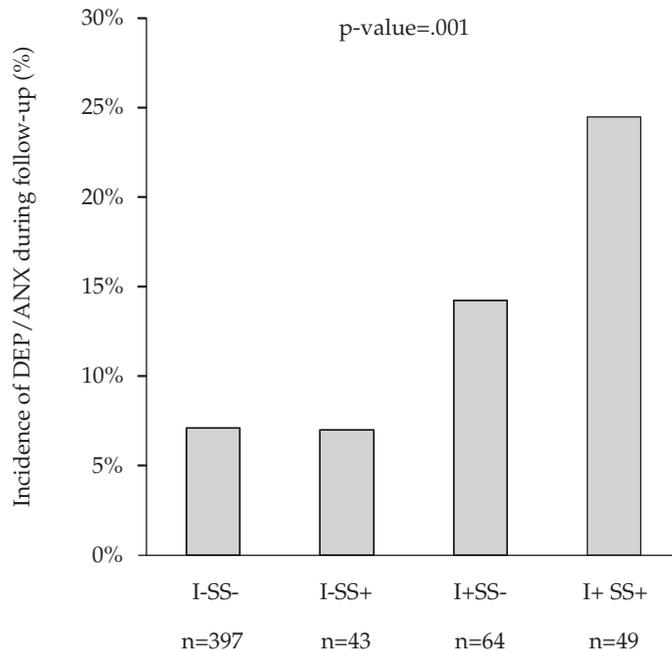|	No incidence of DEP/ ANX (n=513)	Incidence of DEP/ ANX (n=52)	p-value[a]
Age (mean±SD)	41.6±14.6	37.1±14.6	.03
Female (%)	61.0	61.5	.94
Partner (%)	77.0	63.5	.03
Education (years,mean±SD)	12.9±3.2	12.8±3.0	.68
Current smoker (%)	23.8	44.2	.001
Alcohol intake (%)			
– none	10.7	7.7	
– moderate	78.6	78.8	.69
– severe	10.7	13.5	
BMI (mean±SD)	25.0±4.6	24.7±4.3	.68
Number of somatic diseases (mean±SD)	0.6±0.9	0.8±.1.1	.12
Pain score (mean±SD)	1.1±0.8	1.3±0.9	.12
Insomnia (%)	17.9	40.4	<.001
Insomnia, continuous score (mean±SD)	5.1±3.7	7.3±4.6	.001
Sleep duration (%)			
– short	15.0	28.8	
– normal	82.7	71.2	.02
– long	2.3	0	
Sleep duration, continuous (mean±SD)	7.4±1.0	7.2±0.9	.16
IDS score (mean±SD)	5.7±6.1	12.9±7.7	<.001

DEP/ANX = depressive or anxiety disorder;

BMI = body mass index;

IDS = Inventory of depressive symptoms.

[a] Based on chi-square statistics (categorical variables) and t-tests (continuous variables)

Figure 1 illustrates the unadjusted incidence of depressive/ anxiety disorders across different sleep categories. Subjects who reported only short sleep duration did not differ in incidence of depression and anxiety at follow up, compared to subjects without insomnia and short sleep duration. Higher incidence rates were found for subjects with insomnia only, and for subjects reporting both insomnia and short sleep duration. The last category reported the highest incidence, suggesting a cumulative effect of sleep disturbances on the incidence of depressive and anxiety disorders.

Figure 1: Incidence of depressive/ anxiety disorders during 2 year follow-up according to insomnia and short sleep duration (n=553)[a]

I = Insomnia, SS = short sleep duration; DEP/ANX = depressive or anxiety disorder

[a] Subjects with long sleep were excluded because of low frequencies (n=12)

Table 2 shows adjusted associations between sleep disturbances and incidence of depressive and anxiety disorders during the 2 year follow-up. All baseline sleep measures were significantly associated (model 1) with the incidence of depressive and anxiety disorders. After adjusting for severity of subclinical depressive symptoms at baseline (model 2), the associations for insomnia (OR= 2.65, 95%CI=1.29-5.41), insomnia continuous score (OR=1.11, 95%CI=1.03-1.20), and short sleep duration (OR=2.27, 95% CI=1.07-4.80) declined, but remained statistically significant. The difference in ln OR between model 1 and model 2 was -32.4% for insomnia, -35.2% for insomnia continuous score and -17.4% for short sleep duration. This suggests that the severity of subclinical depressive symptoms plays an important role in the association between sleep measures and the incidence of depressive and anxiety disorders, but does not fully explain this association.

Table 2: Associations between sleep disturbances at baseline and incidence of depressive and anxiety disorder during follow-up in subjects without lifetime depressive or anxiety disorder at baseline (n=565)

	Model 1[a]		Model 2[b]		
	OR (95% CI)	p-value	OR (95% CI)	p-value	% Change in ln (OR) between model 1 and 2
Insomnia	4.23 (2.15-8.33)	<.001	2.65 (1.29-5.41)	0.008	-32.4
Insomnia, continuous score	1.18 (1.10-1.27)	<.001	1.11 (1.03-1.20)	0.008	-35.2
Short sleep duration [c]	2.70 (1.33-5.48)	.006	2.27 (1.07-4.80)	0.03	-17.4
Sleep duration, continuous	0.71 (0.51-0.97)	.03	0.77 (0.56-1.07)	0.12	-26.4

[a] Logistic regression analyses, adjusted for age, gender, partner, education, smoking, alcohol intake, BMI, number of somatic diseases and pain score (one analysis per row)

[b] Logistic regression analyses, adjusted for age, gender, partner, education, smoking, alcohol intake, BMI, number of somatic diseases, pain score and IDS (one analysis per row)

[c] Reference group = normal sleep duration; long sleepers (n=12) were excluded from this analysis because of low frequencies.

For the continuous measure of sleep duration, we found an association in model 1 (OR=0.71, 95%CI=0.51-0.97), but not after adding severity of subclinical depressive symptoms (model 2). Change in ln OR was -26.4%.

Additional analyses separately for the incidence of depressive disorders as outcome measure and the incidence of anxiety disorders , showed that ORs for insomnia in both analyses were comparable to each other, and comparable to the ones reported in Table 2: OR for depressive disorder=3.04 (95% CI=1.36-6.80). OR for anxiety disorders=3.39 (95% CI=1.45-7.94). This indicates that insomnia appears to be equally predictive of depressive and anxiety disorders. The ORs for short sleep duration, however, were different for the incidence of depressive versus anxiety disorders (OR for the incidence of depression=1.64, 95%CI=0.68-3.96), OR for the incidence of anxiety=4.05, 95%CI=1.73-9.46), suggesting that the effect of short sleep on the incidence of anxiety appears more pronounced than the effect on the incidence of depressive disorders.

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Discussion

Our results showed that in a sample of subjects free of lifetime depressive or anxiety disorders, both insomnia and short sleep duration are associated with the incidence of these disorders during two years of follow-up. These associations remained after adjusting for severity of subclinical depressive symptoms at baseline, suggesting that both insomnia and short sleep duration are risk factors for first-onset depressive and anxiety disorders.

Our results are in line with previous research, which has shown that insomnia is a predictor of depressive and/or anxiety disorders (7, 23, 24), even when subclinical depressive symptoms are controlled for (25). However, in our study we were able to exclude subjects with lifetime depressive or anxiety diagnoses. We can therefore rule out the possibility that sleep disturbances at baseline were a residual symptom of an earlier disorder. So sleep disturbances do really seem to be on the causal trajectory to depressive and anxiety disorders.

Our results were also adjusted for the effect of (possible present) subclinical depressive symptoms, because this was found to be an important confounder in the relationship between sleep disturbances and the onset of depressive and anxiety disorders (5). Although we have attempted to investigate the independent role of sleep disturbances in first onset depressive or anxiety disorders, and have adjusted our results for subclinical depressive symptoms, it is possible that sleep disturbances are in fact a prodromal state of depressive and anxiety disorders, and adjusting for its effect is a form of overcorrection. Insomnia and sleep duration were our main predictors. However, it is also possible that not the sleep disturbances itself are responsible for the found associations, but that they are the reflection of another process which predisposes subjects to depressive and anxiety disorders. In addition, although exact mechanisms through which sleep deprivation leads to depressive or anxiety disorders remain unclear, experimental sleep deprivation studies have indicated various physiological mechanisms that could lead to depressive and anxiety symptoms (26). E.g. induced sleep deprivation has shown to result in increased activation of the amygdala if negative stimuli are presented (27). Sleep disturbances have also been associated with increased levels of inflammation (28), which have been associated with depressive disorders (29).

Strengths and limitations

Our study has some important strengths. It uses a sample of subjects in which lifetime depressive and anxiety disorders were ruled out at baseline, using a diagnostic interview based on DSM-IV criteria and we were able to adjust for the presence of possible subclinical depressive symptoms. In addition, we had the opportunity to adjust for many

factors known to influence sleep as well as depressive and anxiety disorders, such as sociodemographics, chronic diseases and experienced pain. However, some limitations of our study have to be acknowledged. Our sleep measures (both insomnia and sleep duration) are based on self-report. Subjects may have over- or underestimated insomnia complaints or sleep duration. Because the sleep-items referred to sleeping in the past four weeks, we do not have information on the duration of the period of insomnia or altered sleep duration. Possibly a longer period of insomnia/ altered sleep duration leads to a higher risk for depression or anxiety than a shorter period of symptoms, in a dose-response relationship. Also, because our follow-up duration was two years, the number of incident depressive and anxiety disorder cases was rather small. A longer follow-up could provide a larger number of incident cases and strengthen associations between sleep measures and the incidence of depressive and anxiety disorders. Previous studies reported that insomnia is associated with a greater risk for depression even up to 30 years after the insomnia was measured (30).

In conclusion, our results confirm that sleep disturbances, such as insomnia and short sleep duration are risk factors for developing depressive and anxiety disorders in subjects without lifetime depressive and anxiety disorders. This is not explained for by sociodemographics, somatic health or subclinical depressive symptoms. From a clinical point of view, physicians should be aware of the increased risk of developing a first-episode of depressive and anxiety disorders in subjects complaining of insomnia and shortened sleep duration. Future research is needed to determine if interventions directed at improving sleep (such as sleep hygiene measures or cognitive behavioural therapy) are effective in preventing these disorders.

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