CHAPTER 2

Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders

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Abstract

Objective

Disturbed sleep has a high impact on daily functioning and has been correlated with psychopathology. We investigated the extent to which insomnia and sleep duration were associated with both current and remitted depressive and anxiety disorders in a large scale epidemiological study, taking sociodemographics, health factors and medication use into account.

Method

Data of 2619 individuals from the Netherlands Study of Depression and Anxiety (NESDA) were analyzed. Psychopathology was classified as no, current or remitted DSM-IV based diagnosis of major depressive or anxiety disorder. Outcome measures were insomnia (Women's Health Initiative Insomnia Rating Scale ≥9) and sleep duration (≤6, 7-9, ≥10 hours).

Results

Both current and remitted depressive disorder as current anxiety disorder were associated with insomnia and short sleep duration with Odds Ratios (ORs) for insomnia ranging from 1.42 to 3.23, and for short sleep duration ranging from 1.41 to 2.53. Associations were stronger for current than for remitted diagnoses and stronger for depressive than for anxiety disorders. Also long sleep duration was associated with current depressive disorder and anxiety disorders (OR range: 1.53-2.66). Sociodemographics, health indicators and psychotropic medication did contribute to sleep outcomes, but could not explain much of the psychopathology and sleep associations.

Conclusion

Depressive disorder – but also anxiety disorder – is strongly associated with sleep disturbances. Insomnia and short sleep duration persist after remittance of these disorders, suggesting these are residual symptoms or possibly a trait marker. Also long sleep duration is associated with current depressive or anxiety disorders.

Introduction

Humans spend approximately one third of their lives sleeping. Although at first glance sleeping may seem a passive process, the brain is in a highly active state and various important processes take place during the night, such as the secretion of neuro-endocrine hormones (1) and the facilitation of memory consolidation (2,3). The restorative function of sleep is essential for maintaining both physical and mental health, and over the past years there has been a vested interest in sleep related research. Sleeping well is not only crucial for optimal functioning of an individual, but also for society as a whole: sleep disturbances increase risks of accidents, rates of absenteeism at work and health care costs (4).

Psychopathology has been found to be strongly associated with sleep disturbances (5). This seems to be especially true for major depressive disorders (5), but has been shown for anxiety disorders as well (6,7). In individuals referred to an insomnia clinic, 40% is diagnosed with a primary psychiatric disorder (8). Moreover, persistent insomnia is associated with the development of a new episode of a major depressive disorder (9, 10). Depressive and anxiety disorders share a high degree of co-morbidity between them (11), complicating the investigation of the link between psychopathology and sleep disturbances, and leaving some questions whether anxiety disorders really show sleep disturbances independent of co morbid depressive disorder. In addition, some studies found past psychiatric disorders also to be associated with sleep complaints (12), possibly reflecting either a "scar" effect of the disease or a trait of the formerly depressed or anxious persons (13). This illustrates that not only current psychiatric diagnoses are important in investigating the link between psychopathology and sleep disturbances, but also remitted diagnoses. Finally, sleep disturbances cover a broad spectrum of complaints and can range from problems with falling asleep, frequent nocturnal awakenings, early morning awakenings or a disturbed sleep duration (either too short or too long). Recent research has pointed out that subjective sleep assessment and sleep duration are not equally associated with psychopathology and should be analyzed separately (14). It is important to explore not only the relationship between psychopathology and short sleep duration but to also focus on a long sleep duration, since hypersomnia is a common complaint in depression, and subjects with anxiety disorders have been shown also to report an extended sleep duration (15).

Epidemiological studies have investigated sleep in psychopathology, but most large scale studies do not rely on standardized psychiatric interviews in diagnosing both current and remitted psychopathology, do not study depression and anxiety in concert or do not have data on a large set of possible confounders. The latter is important since – besides psychopathology – sleep is also influenced by factors such as sociodemographics (age,

gender, marital status, life events), somatic health (chronic diseases, pain conditions) and use of medication (antidepressants, benzodiazepines) (5, 16, 10, 17, 18). Therefore, the aim of this study is to describe the association between both insomnia and sleep duration with current and remitted depressive and anxiety disorders in a large cohort study, taking sociodemographics, somatic health and medication use into account.

Methods

Sample

For this study, data were analyzed from the baseline measurement of the NESDA study (Netherlands Study of Depression and Anxiety). The NESDA study is an ongoing eight-year longitudinal cohort study designed to investigate the long term course of depressive and anxiety disorders in individuals ranging from 18 through 65 years. The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent. NESDA respondents were recruited from three different settings: the general population, primary health care and secondary mental health care. Individuals from the general population had previously participated in the NEMESIS study (Netherlands Mental Health Survey and Incidence Study) (19) or the ARIADNE study (Adolescents at Risk for Anxiety and Depression) (20). Individuals from primary care were recruited through a three-stage screening procedure, including the Kessler-10 (21) and a short-form Composite International Diagnostic Interview phone interview (CIDI) (22). Individuals from secondary care were recruited after they were newly enrolled for anxiety or depressive disorders at one of the participating mental health clinics. 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. A more detailed description about the study's sampling procedures is described elsewhere (23). The final sample size of the NESDA study consisted of 2981 subjects (18.9% from the community, 54.0% from primary care and 27.0% from secondary mental health care). Of these participants, 362 (12.2%) had missing data on the questionnaire concerning sleep and were excluded from the current study, resulting in a sample size of 2619 persons. Excluded individuals were significantly younger (37.9 versus 42.4 years, $p<.001$), more often female (67.1% versus 61.0%, $p=.02$) and suffered more frequently from a current major depressive disorder (53.3% versus 35.3%, $p=<.001$) or anxiety disorder (57.7% versus 41.8%, $p= <.001$) than included individuals.

Measurements

Between September 2004 and February 2007, participating individuals visited one of the seven interview locations for the baseline measurement. This measurement consisted amongst others of a standardized diagnostic psychiatric interview, drawing of a blood sample, a medical assessment, computer tasks and two fill out questionnaires (one before and one after the interview).

Insomnia and sleep duration

Sleep was assessed by insomnia and sleep duration. Both insomnia and sleep duration were part of a questionnaire which subjects filled out after the interview or at home (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 (24). 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) (25). IRS correlated with other actigraphy derived sleep measures (sleep efficiency, sleep latency, wakefulness after sleep onset (25), implying that the IRS is capable of signalling differences in these more objective measures. In our study Cronbach's alpha was 0.83. Scores on the IRS were dichotomized at a cut off point of nine, which has shown to indicate clinical significant insomnia (25). 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. Answers were categorized in sleep duration of ≤6 hours (short sleep duration), 7-9 hours or ≥10 hours (long sleep duration). Sleep duration and IRS score were only mildly correlated (r= -0.45, p= <.001) confirming that sleep duration and sleep complaints are separate concepts.

Psychopathology

The presence of psychiatric disorders was determined using the CIDI . The CIDI is a standardized diagnostic psychiatric interview which uses DSM-IV criteria to establish diagnoses (22). Major depressive disorder status was categorized as follows: current diagnosis (i.e. in the past six months), remitted diagnosis (lifetime diagnosis, but not in the past six months) or controls (no lifetime diagnosis). Assessed anxiety disorders

included panic disorder, agoraphobia, generalized anxiety disorder and social phobia and was categorized similarly as current diagnosis, remitted diagnosis or controls.

Covariates

Socio-demographics

Socio-demographic characteristics that could possibly affect sleep included age (in years), gender, current partner status, education (in years) and working status. A total count of negative life events in the past year was made through Brughas List of Threatening Experiences (26).

Health indicators

A number of health factors that have been associated with both sleep as well as psychopathology were assessed. Smoking was categorized as "current smoker", "former smoker" or "non smoker". Alcohol intake was calculated by categorizing the number of alcoholic drinks per week in none (less than one per week), moderate (for males: 1-21, for females 1-14 per week) and heavy (for males > 21 per week and for females > 14 per week). Hypertension was defined as a mean systolic blood pressure ≥140 mmHg, a mean diastolic blood pressure ≥90 mmHg or the reported use of antihypertensive drugs (based on drug container inspection and categorized according to Anatomical Therapeutic Chemical Classification (codes CO2, CO3, CO7- CO9). Body Mass Index (BMI) was computed by weight in kilograms divided by height in meters squared. Diabetes was defined as either a fasting blood glucose level >7 mmol/ L (126 mg/ dL) or use of anti-diabetic drugs (ATC code A10). Cardiovascular disease (including myocardial infarction, angina pectoris, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting or cerebrovascular accidents) was adjudicated using standardized algorithms considering self-report and medication use. A total count of the following other (chronic) diseases was made, based on self report: lung disease, cancer, osteoarthritis, intestinal disorders, liver disease, epilepsy, chronic fatigue syndrome, thyroid gland disease and intestinal ulcers. The intensity of chronic pain was measured with the Graded Chronic Pain Scale (27).

Psychotropic medication

Sleep can be influenced by psychotropic medication, which can therefore confound the association between psychopathology and sleep outcomes. Based on drug container inspection of all drugs used in the past month, medication use was classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification (28). Psychotropic medication included antidepressants and benzodiazepines, and was considered present

if subjects reported use of >50% of the time. Antidepressants were categorized as selective serotonin reuptake inhibitors (SSRI, NO6AB), tricyclic antidepressants (TCA, NO6AA) and other antidepressants (N05BA, N05CF, N05CD, N03AE). Benzodiazepines included ATC- codes NO5BA, NO5CF, NO5CD, NO3AE.

Statistical analyses

Data were analyzed using SPSS 15.0. Mean (unadjusted) IRS scores and sleep duration were calculated according to psychopathology status. To compare characteristics across insomnia and sleep duration categories, analysis of variance (ANOVA), t-tests, chi-square statistics or Fisher's exact test were used. Subsequently logistic regression analyses were performed with insomnia (yes versus no IRS ≥9) as the outcome, first unadjusted, followed by adjustment for sociodemographics and health factors, and finally adjusted for all covariates. Similarly, multinomial logistic regression analyses were performed for sleep duration categories in which short- and long-duration outcomes were compared to normal duration as the reference group. We directly compared current major depressive disorder and current anxiety disorder in a sub sample analysis, adjusting for sociodemographics and somatic health factors. Interaction effects between current major depression and current anxiety disorder were tested in order to explore whether co morbidity of these conditions had multiplicative effects on sleep outcomes. Finally, within currently anxious individuals, we tested whether associations with sleep outcomes were consistent across anxiety subtypes by testing specific indicators for anxiety subtypes in logistic and multinomial regression analyses.

Results

The mean age of the study sample (n=2619) was 42.4 years (SD=13.1), 67.1% was female and 61.9% was currently working. Mean sleep duration was 7.2 hours (SD=1.3) and mean IRS score was 8.1 (SD=5.1). Almost half of the individuals (43.7%) had an IRS score ≥9, indicating clinically significant insomnia.

Table 1 shows that more insomnia was found for subjects with current depressive and anxiety disorders, and those with a higher age, less education, both no alcohol intake or heavy alcohol intake, a higher BMI, more hypertension, more cardiovascular disease or other diseases, a higher pain intensity and more psychotropic medication and benzodiazepine use. For sleep duration, additional differences were found for female gender, more recent life events and current smoking.

Table 1: Psychopathology and confounding variables across insomnia and sleep duration[a]

	Insomnia			Sleep duration			
	IRS < 9	*IRS ≥ 9*		*≤ 6 hours*	*7-9 hours*	*> 10 hours*	
	n=1473	*n=1146*	*p**	*n=733*	*n=1777*	*n=109*	*p**
Psychopathology							
Major depressive disorder %							
Never	46.9	24.2	<.001	25.4	42.8	19.3	<.001
Remitted	29.7	25.4		26.7	29.0	14.7	
Current	23.4	50.4		47.9	28.1	66.1	
Anxiety disorder %							
Never	51.1	30.8	<.001	33.7	46.9	23.9	<.001
Remitted	16.8	14.7		15.0	16.3	14.7	
Current	32.1	54.5		51.3	36.8	61.5	
Sociodemographic							
Age (years), mean±SD	40.4±13.3	45.1 ± 12.4	<.001	46.9±11.4	40.9±13.3	36.8±13.4	<.001
Female %	66.3	68.1	.35	62.9	67.9	81.7	<.001
Partner %	71.9	68.5	.06	68.3	71.7	63.3	.06
Education (years), mean±SD	12.6±3.2	11.9 ± 3.3	<.001	11.5±3.2	12.7±3.2	11.7±3.3	<.001
Currently working %	66.4	56.0	<.001	57.6	65.3	34.9	<.001
Nr of life events, mean±SD	0.59±0.93	0.62±0.92	.40	0.68±1.02	0.57±0.88	0.79±1.04	.002
Somatic health							
Smoking %							
Never	30.3	27.7		25.0	30.8	31.2	
Former	33.7	36.5	.24	36.4	34.9	23.9	.003
Current	36.0	35.8		38.6	34.3	45	
Alcohol intake %							
None	14.5	19.5		19.6	15.3	20.2	
Moderate	75.9	66.6	<.001	67.4	73.8	68.8	.02
Heavy	9.6	13.9		13.0	10.9	11	
BMI, mean ± SD	25.2±4.8	26.0±5.0	<.001	26.6±5.2	25.1±4.6	25.4±6.1	<.001
Hypertension %	37.3	46.3	<.001	47.6	39.2	32.1	<.001
Diabetes %	4.3	5.6	.12	7.8	3.6	5.5	<.001
Cardiovascular disease %	4.7	7.9	0.001	10.0	4.5	5.5	<.001
Nr. of other diseases, mean±SD	0.60±0.88	0.97±1.07	<.001	0.98±1.06	0.65±0.91	1.09±1.25	<.001
Pain intensity, mean±SD	1.37±0.92	1.85±1.08	<.001	1.86±1.12	1.44±0.95	1.98±1.10	<.001
Psychotropic medication							
Antidepressants							
No antidepressants %	80.4	70.4		74.5	78.2	50.5	
TCA %[b]	2.0	3.2	<.001	2.9	2.1	6.4	<.001
SSRI %[c]	13.4	18.9		16.1	14.3	39.4	
Other antidepressants %	4.2	7.4		6.5	5.3	3.7	
Benzodiazepines %	3.3	12.2	<.001	12.3	5.1	8.3	<.001

[a] Based on ANOVA, t- test and chi-square statistics

[b] TCA= tricyclic antidepressants

[c] SSRI= selective serotonin reuptake inhibitors

Insomnia analyses

Figure 1 shows mean IRS scores according to psychopathology status. Of all subjects, 23.5% never had a diagnosis of major depression or anxiety disorders, 22.3% had a remitted major depressive or anxiety disorder but no current disorder, 12.6% had a current major depressive but no current anxiety disorder, 19.3% had a current anxiety disorder but no current major depressive disorder (MDD), and 22.6% suffered from both current disorders. Table 2 shows that both current (OR=3.29, 95% CI= 2.69-4.03) and remitted major depressive disorder (OR= 1.49, 95% CI= 1.20-1.84), as well as current (OR= 1.99, 95% CI= 1.65-2.40) and remitted anxiety disorder (OR=1.30, 95%CI=1.02-1.67) were associated with insomnia. Except for remitted anxiety disorder, this association could not be explained by sociodemographics or somatic health factors, since ORs remained significant when adding these factors to the model (OR current MDD= 3.11, 95%CI= 2.51-3.87, OR current anxiety disorder= 1.84, 95%CI= 1.51-2.24, OR remitted MDD= 1.39, 95% CI= 1.12-1.74, model 2). In multivariable analyses, independent of psychopathology, also higher age, current smoking, heavy alcohol intake, more chronic diseases and a higher pain intensity were independently associated with insomnia. Even after adding

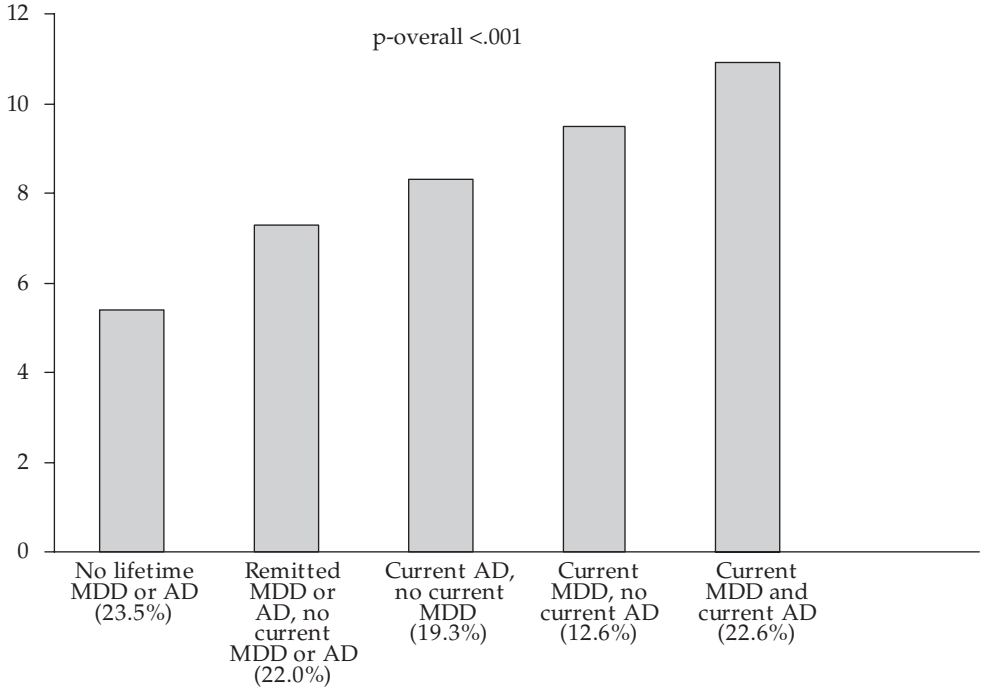

Figure 1: Mean score on IRS according to psychopathology status

psychotropic medication to the model, associations with psychopathology remained (model 3). Use of SSRIs was associated with less insomnia (OR=0.75, 95% CI=0.58-0.96) and use of benzodiazepines with more insomnia (OR=1.79, 95%CI=1.23-2.59).

When we directly compared currently depressed individuals with currently anxious individuals (n=1427), associations for major depressive disorder appeared to be stronger than for anxiety disorder (OR major depressive disorder=1.98, p <.001). To determine if comorbid depressive and anxiety disorders were more associated with insomnia complaints than the sum of the single diagnoses, interaction effects were tested, revealing that there was no significant multiplicative interaction effect (p>.10).

In a subset of currently anxious individuals (n=1097), we explored whether associations with insomnia were consistent for the specific anxiety subtypes using a logistic regression analysis adjusted for age and gender. Within the anxiety group it appeared that especially those with generalized anxiety disorder had a higher odds of insomnia compared to subjects with social phobia and panic disorder (OR generalized anxiety disorder=1.74, 95%CI=1.34-2.26).

Table 2: Results of multivariable analyses of psychopathology and confounding variables on insomnia[a]

	Odds ratios for insomnia complaints (IRS ≥ 9)		**Odds ratios for insomnia complaints (IRS ≥ 9)**		**Odds ratios for insomnia complaints (IRS ≥ 9)**	
	Model 1		*Model 2*		*Model 3*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Psychopathology						
MDD[b]						
Never	Ref.		Ref.		Ref.	
Remitted	1.49	1.20-1. 84**[c]	1.39	1.12-1.74 *	1.43	1.15-1.79*
Current	3.29	2.69-4.03**	3.11	2.51-3.87 **	3.23	2.57-4.05 *
AD[d]						
Never	Ref.		Ref.		Ref.	
Remitted	1.30	1.02-1.67*[e]	1.18	0.92-1.52	1.21	0.94-1.56
Current	1.99	1.65-2.40**	1.84	1.51-2.24**	1.88	1.53-2.30**
Sociodemographic						
Age (years)			1.03	1.02-1.04**	1.03	1.02-1.04**
Female gender			1.03	0.85-1.25	1.04	0.86-1.26
Education (years)			0.98	0.95-1.01	0.98	0.95-1.01
Currently working			0.95	0.79-1.13	0.95	0.79-1.15
Partner			0.87	0.72-1.05	0.88	0.73-1.06
No. of recent life events (per increase)			0.99	0.90-1.08	0.98	0.90-1.08

	Odds ratios for insomnia complaints (IRS ≥ 9)		Odds ratios for insomnia complaints (IRS ≥ 9)	
Health indicators				
Smoking				
Never	Ref.		Ref.	
Former	0.98	0.79-1.22	0.98	0.78-1.22
Current	0.79	0.63-0.98*	0.79	0.63-0.98*
Alcohol intake				
None	Ref.		Ref.	
Moderate	0.96	0.75-1.21	0.95	0.75-1.21
Heavy	1.40	1.01-1.96*	1.38	0.99-1.94
BMI (per kg/ m^2 increase)	1.00	0.98-1.02	1.00	0.98-1.02
Hypertension	1.03	0.85-1.26	1.04	0.85-1.27
Diabetes	0.84	0.55-1.26	0.83	0.55-1.25
Cardiovascular disease	0.98	0.67-1.43	0.97	0.66-1.42
Nr. of other diseases	1.14	1.03-1.25*	1.13	1.02-1.24*
Pain intensity (per point increase)	1.28	1.16-1.40**	1.27	1.15-1.39**
Medication				
No antidepressant			Ref.	
TCA[f]			0.72	0.42-1.23
SSRI[g]			0.75	0.58-0.96*
Other antidepressants			0.85	0.58-1.25
Benzodiazepines			1.79	1.23-2.59*

[a] Based on multivariable logistic regression analyses, 1 analysis per column

[b] MDD= Major depressive disorder

[c] **= p-value <.001

[d] AD= Anxiety disorder

[e] * = p-value ≤ 0.05 and >.001

[f] TCA= Tricyclic antidepressants

[g] SSRI= Selective serotonin reuptake inhibitors

Sleep duration analyses

Figure 2 shows differences in sleep duration categories (short, normal, long) according to psychopathology status. Of individuals with remitted major depressive or anxiety disorder, but no current disorder 27.1% slept ≤6 hours and 1.7% slept ≥10 hours. Of individuals suffering from a current major depressive disorder only, 31.1% slept ≤ 6 hours and 6.0% slept ≥ 10 hours per night. In the case of a current anxiety disorder, 25.3% slept ≤ 6 hours and 3.0 % slept ≥10 hours per night. When both disorders were present, 41.8% slept ≤6 hours and 8.8% slept ≥10 hours per night.

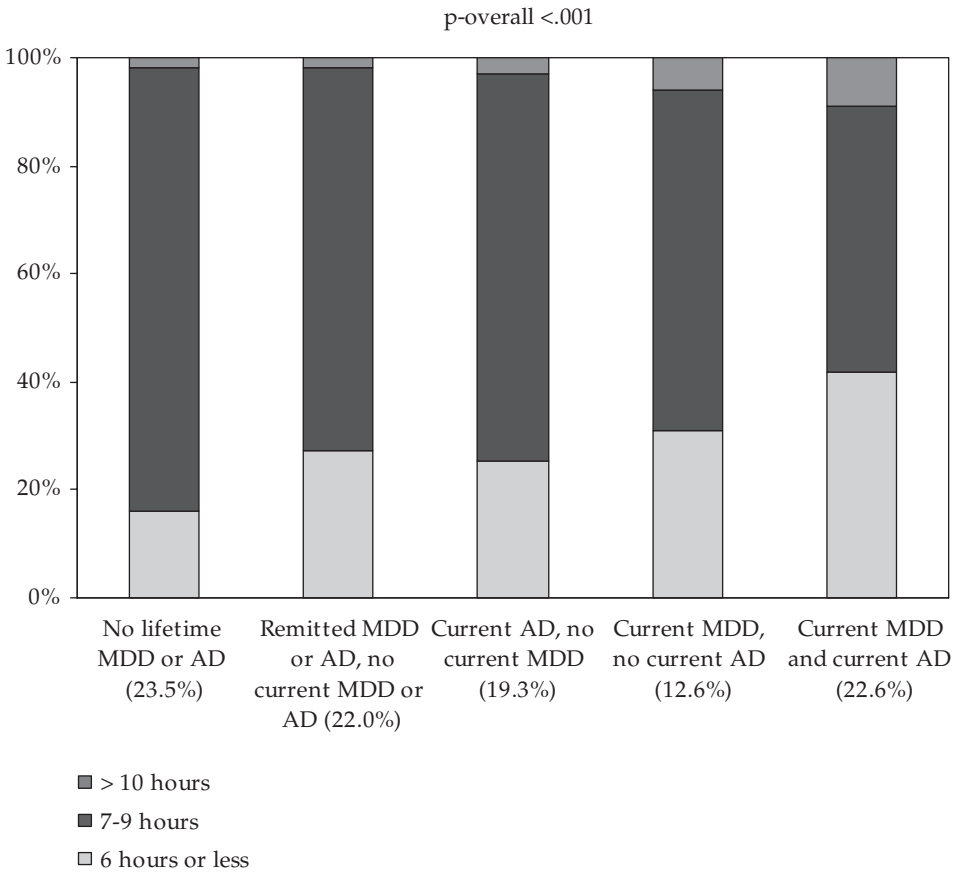

Figure 2: Sleep duration according to psychopathology status

Table 3 shows that a short sleep duration (≤6 hours) was associated with current major depressive disorder and anxiety disorder (OR=2.50, 95%CI=2.00-3.12; OR=1.46, 95% CI: 1.19-1.79, respectively) as well as with remitted major depressive disorder (OR=1.46, OR:1.15-1.82), but not with remitted anxiety disorder. Even after adding covariates to the model, associations remained (OR current major depressive disorder=2.26, 95% CI=1.78-2.87, OR remitted major depressive disorder=1.34, 95%CI=1.05-1.72, OR current anxiety disorder=1.33, 95%CI=1.07-1.65). Also higher age, less education, male gender, more recent life events, higher BMI, no hypertension and higher pain intensity were independently associated with short sleep duration. The use of SSRIs and other antidepressants was independently associated with a significantly lower risk of reporting a short sleep duration (OR=0.62, 95% CI=0.47-0.82, OR=0.62. 95%CI=0.41-0.93 respectively), but benzodiazepine use was not significantly associated with short sleep duration (model 3). Additional adjustment for psychotropic medication did not largely change the short sleep duration risks for depressive and anxiety disorders.

Long sleep duration was also associated with current major depressive disorder and anxiety disorder (OR current major depressive disorder=4.03, 95%CI=2.38-6.81, OR current anxiety disorder=2.09, 95%CI=1.27-3.41, model 1) and these associations remained significant after adding covariates (OR current major depressive disorder=3.08, 95%CI=1.79-5.30, OR current anxiety disorder=1.72, 95%CI=1.03-2.86, model 2), but a lower age, female gender, not currently working and more chronic diseases also contributed to long sleep duration. No associations were found for remitted disorders (model 2). In line with a lower risk for short sleep duration, the use of antidepressants (TCAs and SSRIs) did significantly increase the risk for long sleep duration (OR= 2.88, 95%CI=1.12-7.39, OR=2.35, 95%CI=1.45-3.81 respectively). After adding psychotropic medication to the model, associations remained for current major depressive disorder, but not for current anxiety disorder (model 3). When we directly compared currently depressed individuals with currently anxious individuals (n=1427), associations for major depressive disorder appeared to be stronger than for anxiety disorder, both for short sleep duration (OR=2.03, 95%CI= 1.55-2.65) and long sleep duration (OR= 2.72, 95%CI=1.50-4.93). To determine if co-morbid depressive and anxiety disorders were more strongly associated with short or long sleep duration than the sum of single diagnoses interaction effects were tested, but not found to be present (both p>.10).

In the subset of currently anxious individuals (n=1097), we found no significant differences across anxiety subtypes in their association with short sleep duration (all p>.10 for contrasts between subtypes). For long sleep duration, we found that GAD was associated with a significant higher odds compared to the other anxiety disorders (OR=1.70, 95% CI= 1.02-2.84).

Table 3: Results of multinomial regression analyses of psychopathology and confounding variables on sleep duration[a]

	Odds Ratio for short sleep duration (≤6 hours)						Odds ratio for long sleep duration (≥10 hours)					
	Model 1		*Model 2*		*Model 3*		*Model 1*		*Model 2*		*Model 3*	
	OR	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Psychopathology												
MDD[b]												
Never	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Remitted	1.46	1.15-1.85*[c]	1.34	1.05-1.72*	1.42	1.10-1.82*	0.95	0.49-1.87	0.91	0.46-1.81	0.86	0.43-1.73
Current	2.50	2.00-3.12**[e]	2.26	1.78-2.87**	2.53	1.97-3.25**	4.03	2.38-6.81**	3.08	1.79-5.30**	2.66	1.52-4.65*
AD[d]												
Never	Ref.		Ref.		Ref.		Ref.		Ref.			
Remitted	1.15	0.88-1.51	1.05	0.79-1.40	1.09	0.82-1.45	1.73	0.90-3.32	1.81	0.92-3.53	1.66	0.84-3.29
Current	1.46	1.19-1.79**	1.33	1.07-1.65*	1.41	1.13-1.77 *	2.09	1.27-3.41*	1.72	1.03-2.86*	1.53	0.91-2.58
Sociodemographic												
Age (per year increase)			1.04	1.03-1.05**	1.04	1.03-1.05**			0.97	0.95-0.99*	0.97	0.95-0.99*
Female gender			0.80	0.65-0.98	0.80	0.65-0.98*			1.79	1.06-3.02*	1.70	1.00-2.88*
Education (per year increase)			0.93	0.90-0.96**	0.93	0.91-0.96**			0.96	0.90-1.03	0.96	0.90-1.03
Currently working			1.10	0.90-1.34	1.08	0.89-1.32			0.39	0.25-0.60**	0.40	0.26-0.62**
Partner			0.82	0.67-1.00*	0.83	0.67-1.02			0.88	0.57-1.35	0.89	0.58-1.38
Nr life events (per event increase)			1.15	1.04-1.27 *	1.15	1.04-1.27*			1.04	0.86-1.26	1.04	0.85-1.27
Health hindicators												
Smoking												
Never			Ref.		Ref.				Ref.		Ref.	
Former			0.99	0.77-1.26	0.98	0.77-1.26			0.86	0.49-1.50	0.87	0.49-1.53
Current			1.06	0.83-1.35	1.08	0.84-1.37			1.16	0.71-1.90	1.15	0.70-1.88

	Odds Ratio for short sleep duration (≤6 hours)				Odds ratio for long sleep duration (≥10 hours)			
Alcohol intake								
None			Ref.		Ref.			
Moderate	1.00	0.78-1.29	0.95	0.74-1.24	1.21	0.71-2.05	1.28	0.75-2.20
Heavy	1.09	0.77-1.56	1.04	0.73-1.49	1.32	0.60-2.90	1.35	0.61-2.98
BMI (per kg/ m^2 increase)	1.03	1.01-1.05*	1.03	1.01-1.05*	1.01	0.97-1.05	1.00	0.96-1.04
Hypertension	0.74	0.59-0.92*	0.74	0.59-0.92*	0.88	0.53-1.47	0.92	0.55-1.54
Diabetes	1.24	0.83-1.88	1.26	0.83-1.90	1.66	0.63-4.36	1.50	0.56-3.96
Cardiovascular disease	1.29	0.89-1.87	1.27	0.87-1.84	1.14	0.44-2.99	1.25	0.47-3.30
Number of other chronic diseases	1.06	0.96-1.17	1.05	0.95-1.16	1.32	1.08-1.61*	1.31	1.07-1.60*
Pain intensity (per score increase)	1.19	1.08-1.31*	1.19	1.08-1.31*	1.15	0.94-1.42	1.16	0.94-1.43
Psychotropic medication								
Antidepressants								
No medication			Ref.				Ref.	
TCA[f]			0.61	0.34-1.11			2.88	1.12-7.39*
SSRI[g]			0.62	0.47-.082*			2.35	1.45-3.81*
Other antidepressants			0.62	0.41-0.93*			0.61	0.21-1.81
Benzodiazepines			1.32	0.93-1.86			0.65	0.30-1.43

[a] Based on multivariable multinomial logistic regression analyses, reference category is 7-8 hours sleep, 1 analysis per column

[b] MDD=Major depressive disorder

[c] * = p-value ≤ 0.05 and >.001

[d] AD= Anxiety disorder

[e] **= p-value <.001

[f] TCA= Tricyclic antidepressant

[g] SSRI= Selective serotonin reuptake inhibitors

Discussion

Our findings indicate that both current and remitted major depressive disorder as well as current anxiety disorders are associated with insomnia and short sleep duration. Long sleep duration is associated with current major depressive and anxiety disorders. Associations were stronger for depressive than for anxiety disorders and were independent of socio-demographics, health factors or psychotropic medication use. Associations were also stronger for current than for remitted depressive diagnoses, although the latter still had a significant impact on sleep, suggesting sleep disturbances are possibly a trait marker or a residual symptom of major depression. After adjusting for confounding variables anxiety disorders were only associated with insomnia and short and long sleep duration in the case of current disorders, suggesting that these sleep disturbances resolve after recovery from the disorder. Figure 1 clearly illustrates that insomnia scores differed according to psychopathology: individuals with no lifetime diagnosis had the lowest scores, followed by individuals with remitted disorders, whereas the highest scores were found in subjects suffering from both disorders.

As expected, the strongest associations for both insomnia and sleep duration were found for depressive disorder, which is in line with other studies (5), but we also found an independent association with anxiety disorders. Interestingly, not only current major depressive disorder, but also remitted disorders are associated with insomnia and short sleep duration. In previous studies, sleep complaints were found to be one of the most common residual symptoms after achieving remission from a major depressive episode, next to fatigue and loss of interest. This finding was irrespective of the subjects' baseline severity depression, length of the episode, age, gender or marital status (29). Residual depressive symptoms are also associated with a significant earlier relapse rate than asymptomatic recovery (30). Some studies suggest a more vigorous approach of treating major depressive disorder resulting in as few residual symptoms as possible (31), although this enhances the risk of side-effects and non-compliance. The literature is inconsistent on sleep disturbances being a trait marker for depression: some studies find persistent EEG-changes in remitted depressed individuals (32), whereas other do not find these differences (33). This may be due to methodological differences, but possibly certain subgroups of depressed individuals are more prone to relapse of the disorder and display such trait markers, whereas others recover from these abnormalities (33).

The association between psychopathology and insomnia and sleep duration was not altered significantly by adding covariates to the model. However, in addition to psychopathology, some of these factors such as higher pain intensity, do independently contribute to sleep disturbances. Other factors contributing to the association, such as

chronic diseases are a known risk factor for sleep disturbances, not only because of the disease itself, but also because of side effects of related medications (17).

The use of benzodiazepines was associated with more insomnia, which is likely due to indication-bias, since benzodiazepines are most likely to be used by subjects who experience the most severe insomnia. Strikingly, although benzodiazepine use was associated with more insomnia, the use of certain antidepressants was associated with less insomnia and longer sleep duration. This opposite effect of antidepressants could potentially reflect efficacious effects of antidepressants: randomized controlled trials testing TCAs have shown sleep complaints to diminish and sleep duration to increase among antidepressants users (34).

Interestingly, current depressive and anxiety disorders were associated with not only shorter sleep duration but also with longer sleep duration. For depressive disorders, this may have to do with the fact that depressive disorders can present with both melancholic as atypical symptoms, resulting in both a short sleep duration as a long sleep duration. As for subtypes of current anxiety disorders, in our study GAD was most prominently associated with insomnia and long sleep duration. GAD has in previous studies been found to be associated with a sleep maintenance insomnia (35), but an association with long sleep duration has not been reported before.

Although this study had the advantage to use a large psychiatric sample and could adjust for a large set of possible confounders in investigating the relationship between psychopathology and sleep disturbances, there are a few limitations to be mentioned. First, because the data in this study are cross-sectional it is impossible to draw conclusions on causality regarding sleep disturbances and psychopathology. Therefore, future longitudinal research is needed. Second, sleep outcomes (both insomnia complaints and sleep duration) were based on self-reported measures. Over- and underestimation of sleep complaints and sleep duration could have been influenced by psychopathological status. Third, the IRS has been validated for women only. In spite of these limitations, our study stresses the importance of addressing sleep disturbances in psychopathology, not only in current diagnoses but also in remitted disorders.

To conclude, subjects with depressive and anxiety disorders disorder may experience insomnia and altered sleep duration, even after remittance of the disorder. Inquiring about a short sleep duration only may not be sufficient, as our study clearly shows that both extremes of the sleep duration spectrum are associated with both depressive and anxiety disorders. Clinicians should actively ask about insomnia and sleep duration, not only in depressive disorders, but also in anxiety disorders.

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