CHAPTER 5

Sleep duration, but not insomnia, predicts the 2-year course of depressive and anxiety disorders

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Abstract

Objective

To examine the predictive role of insomnia and sleep duration on the 2-year course of depressive and anxiety disorders.

Method

This study is a secondary data analysis based on data from the baseline (2004-2007) and two-year assessment of the Netherlands Study of Depression and Anxiety. Participants were 1069 individuals with DSM-IV based depressive and/or anxiety disorders at baseline. Sleep measures included insomnia (assessed with the Women's Health Initiative Insomnia Rating Scale, score ≥9) and sleep duration (categorized as short (≤6 hours), normal (7-9 hours) or long (≥10 hours)). Outcome measures were persistence of DSM-IV depressive and anxiety disorders (current diagnosis at two-year follow-up), time-to-remission and clinical course trajectory of symptoms (early sustained remission, late remission/recurrence and chronic course). Logistic regression analyses were adjusted for sociodemographics and chronic medical disorders, psychotropics, and severity of depressive and anxiety symptoms.

Results

The effect of insomnia on persistence of depressive and/or anxiety disorders (OR=1.50, 95%CI=1.16-1.94) was explained for by severity of baseline depressive/anxiety symptoms (adjusted OR with severity=1.04, 95%CI=0.79-1.37). Long sleep duration was independently associated with persistence of depression/anxiety even after adjusting for severity of psychiatric symptoms (OR=2.52, 95%CI=1.27-4.99). For short sleep duration, the independent association with persistence of combined depression/anxiety showed a trend towards significance (OR=1.32, 95%CI=0.98-1.78), and a significant association for the persistence of depressive disorders (OR=1.49, 95%CI=1.11-2.00). Both short and long sleep duration were independently associated with a chronic course trajectory (OR short sleep=1.50, 95%CI=1.04-2.16; OR long sleep=2.91, 95%CI=1.22-6.93).

Discussion

Both short and long sleep duration – but not insomnia – are important predictors of a chronic course, independent of symptom severity. It is to be determined whether treating these sleep conditions results in more favorable outcomes of depression and anxiety.

Introduction

The course of depressive and anxiety disorders is often chronic, or with episodes of both remission and recurrence (1,2). Depression and anxiety disorders are associated with a significant comorbidity (3), impaired occupational functioning (4,5) and diminished quality of life (6,7), thus, it is of great importance to identify factors which determine its course.

Sleep may impact the course of depressive and anxiety disorders, given the intricate relationship between sleep disturbances and mood (8). Sleep can be disturbed in terms of subjective quality (insomnia) and duration. Many studies have examined the role of insomnia on the outcome of depression. Nowadays, the term insomnia is usually reserved for a disorder in which subjects experience problems falling asleep combined with impairments in daytime functioning.

In individuals with major depression (n=1801, one year follow-up), remission rates were lower in those with insomnia (9). Depressed adolescents with insomnia (n=309, nine weeks follow-up) responded slower to antidepressants than adolescents without insomnia (10). For anxiety disorders, few studies have examined the impact of sleep on its course. One study (n=533, five-year follow-up) found no effect of insomnia on generalized anxiety disorder, panic disorder or social phobia (11). In contrast, another study found that insomnia was associated with a better outcome in subjects with generalized anxiety disorder treated with venlafaxine (12). To our knowledge, no studies have examined sleep duration as predictor of course of depressive or anxiety disorders.

However, not all aspects of the relationship between sleep disturbances and the course of depressive/ anxiety disorders have been studied extensively. In particular, the following factors need to be addressed. Firstly, depressive and anxiety disorders should be studied simultaneously, because of frequent comorbidity between these disorders (13). Secondly, severity of psychopathology should be considered when studying the impact of sleep disturbances, because sleep disturbances can be a symptom of psychopathology. Thirdly, the effects of insomnia and sleep duration need to be examined separately, because of differential associations with psychopathology (14, 8). Finally, sleep is also influenced by other factors, such as age, gender, chronic medical disorders and use of (psychotropic) medication (15). Many studies include some of the above-mentioned characteristics, but most include only individuals with major depression (10, 16). For anxiety disorders, there are only a few studies available on the impact of sleep disturbances on course (11). Also, there is a very limited number of studies which includes data on both insomnia and sleep duration (16).

In this study we examined, we examined the predictive role of sleep disturbances (both insomnia and duration) on the 2-year course of depressive and/or anxiety disorders in

a sample of currently depressed and/or anxious patients, taking into account the effect of chronic medical disorders, psychotropic medication and severity of psychopathology.

Method

Sample

Data were analyzed from the baseline and two-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study investigating the course of depressive and anxiety disorders (n=2981.) Subjects were recruited from the general population (n=564), primary health care (n=1610) and secondary mental health care (n=807) in order to represent various care settings and psychopathology. Exclusion criteria for the NESDA study were not speaking the Dutch language or a known primary clinical diagnosis of bipolar disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A detailed description of the study's rationales, methods and recruitment strategy is described elsewhere (13). The research protocol was approved by the ethical committees of participating universities, and all respondents provided written informed consent. Our sample was restricted to subjects with baseline depressive (major depressive disorder and dysthymia) and/or anxiety disorders (panic disorder, agoraphobia, social phobia and generalized anxiety disorder), according to the Composite Interview Diagnostic Instrument (CIDI version 2.1). The standardized diagnostic CIDI interview uses the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria to establish diagnoses (17,18). A baseline disorder was defined as a 6-month CIDI depressive and/or anxiety diagnosis while confirming symptoms in the last month, at either the CIDI recency questions or the Life Chart Interview (see below) (19). Of the 1456 baseline depressed or anxious individuals, 1209 participated in the follow-up interview (83.0%). Non-response was higher in those with younger age, lower education, or depressive disorder (20). Subsequently, 140 individuals were excluded because of missing data on sleep measures (=124) or on outcome measures (n=16) , resulting in a final sample size of 1069. Excluded individuals were more often males (p-value=.04), but did not differ in age (p-value=.09), education-level (p-value=.33) or presence of depressive, anxiety or co-morbid disorder.

Measurements

The baseline interview was conducted between 2004 and 2007, with follow up interviews two years later.

Insomnia and sleep duration

Sleep was measured at baseline. *Insomnia* was measured with the Women's Health Initiative Insomnia Rating Scale (IRS, 21), which consists of five questions concerning sleep in the past four weeks (trouble falling asleep, waking up during the night, early morning awakenings, getting back to sleep after waking up and sleep quality). Answers are on a four-point scale, with a maximum score of 20. A higher score indicates more insomnia. In our study sample Cronbach's α was .83. Scores were dichotomized at a cut-off point of 9 or higher, which indicates clinically significant insomnia (22). We also used the total continuous score (range 0-20). *Sleep duration* (in full hours, regarding the past four weeks) was estimated by the subjects. It was used as a categorical measure (short sleep duration (≤6 hours), normal sleep duration (7-9 hours) and long sleep duration (≥10 hours)), and as a continuous measure (8).

Course outcomes

Three course outcome measures were used: (1) persistence of diagnosis, (2) time-to-remission and (3) clinical course trajectories of symptoms. *Persistence of depressive/ anxiety disorders* was defined as a CIDI 6-month diagnosis of depressive and/ or anxiety disorder at follow-up. To define time-to-remission and clinical course trajectory of symptoms over the two years, the Life Chart Interview (LCI, 19) was completed for individuals with detected symptoms at the 2-year CIDI-interview. Using a calendar method, life events were recalled to refresh memory, after which presence of depressive and anxiety symptoms was determined for each month during the previous two years. For each month with reported symptoms, severity was assessed (no or minimal, mild, moderate, severe, or very severe). Symptoms on LCI were considered to be present when at least of mild severity. *Time-to-remission* of the index disorder was defined as the first point in time (calculated in months) at which no symptoms of the disorder were reported over three consecutive months, based on the LCI. Using both the CIDI and the LCI, we defined three *clinical course trajectories:* (1) early sustained remission (remission within six months, no recurrence of symptoms during follow-up; (2) late remission/ recurrence (remission after six months without recurrence, or remission with recurrence of depressive/ anxiety symptoms after initial remission) and (3) chronic course (no remission, depressive/ anxiety symptoms of at least mild severity during the whole follow-up period). Remission was defined as reporting no symptoms on the LCI for three consecutive months (23).

Baseline covariates

Sociodemographics and chronic medical disorders

Sociodemographic characteristics included age, gender and education (in years). Selected chronic medical disorders were based on our previous study on the association between sleep disturbances and psychopathology (8). Alcohol intake was categorized into none (less than 1 drink per week), moderate (males: 1-21, females 1-14 drinks per week) or heavy (males >21, females > 14 drinks per week). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A total count of the following self-reported chronic diseases was made: lung disease, cancer, osteoarthritis, intestinal disorders, liver disease, epilepsy, chronic fatigue syndrome, thyroid gland disease, cardiovascular disease and diabetes.

Psychotropic medication

Psychotropic medication influences sleep and the persistence of depressive and anxiety disorders. Antidepressant and benzodiazepine use in the past month was classified according to the World Health Association's ATC classification (24). Antidepressants were categorized as selective serotonin reuptake inhibitors (SSRIs) (ATC code NO6AB), tricyclic antidepressants (TCAs) (ATC code NO6AA) and other antidepressants (ATC codes N06AF and N06AX). For benzodiazepines ATC codes NO5BA, NO5CF, NO5CD and NO3AE were included.

Symptom severity

Severity of depressive symptoms was measured with the Inventory of Depressive Symptomatology (IDS, 25). Because of overlap with our predictor variables, we excluded the four sleep-related items from the IDS, resulting in a maximum score of 72. The Cronbach's alpha for this adjusted IDS scale was .83. Severity of anxiety symptoms was measured with the Beck Anxiety Inventory (BAI, 26). The Cronbach's alpha for the BAI was .90, and correlation between BAI and IDS was .61.

Statistical analyses

Data were analyzed using SPSS 15.0 (SPSS Inc, Chicago, Illinois). Baseline characteristics were calculated for the total sample and according to our main outcome measure, persistence of diagnosis. Differences between groups were compared based on independent t-tests for continuous variables and chi-square statistics for dichotomous/ categorical variables. The cumulative probability of remission was estimated with Kaplan-Meier product limit. Subjects with a duration of symptoms greater than

24 months were censored at 24 months. Survival curves were compared across insomnia categories (y/n) and sleep duration categories with the log-rank test.

Logistic regression analyses were performed with sleep measures as the predictor and persistence of depressive and/ or anxiety disorders as the outcome variable. First, analyses were adjusted for sociodemographics and chronic medical disorders (age, gender, education, alcohol intake, BMI, number of chronic medical disorders). Second, we also adjusted for psychotropic medication (antidepressants, benzodiazepines). Finally, we adjusted for all before mentioned covariates (age, gender, education, alcohol intake, BMI, number of chronic medical disorders) and for severity of depressive (IDS) and anxiety symptoms (BAI). In order to check whether the continuous measurement for sleep duration indeed showed a non-linear association with course of depression/ anxiety disorder, we performed an analysis while adding a sleep duration squared term (sleep duration* sleep duration) to the linear term. We also added both insomnia (categorical) and sleep duration (categorical) simultaneously to our first model (adjusting for age, gender, education, alcohol intake, BMI, and number of chronic medical disorders) in order to check if insomnia and sleep duration are independent predictors of course outcome. Finally, to rule out that insomnia and sleep duration may have an interacting effect, we tested whether an interaction term insomnia (categorical)*sleep duration (categorical) did significantly predict persistence of diagnosis, adjusting for sociodemographics and chronic medical disorders.

Multinomial logistic regression analyses were performed with clinical course trajectories of symptoms as the outcome in which late remission/ recurrence and chronic course were compared to 'early sustained remission'. Analyses were also firstly adjusted for sociodemographics and chronic medical disorders, subsequently for psychotropic medication, and finally for severity of depressive (IDS) and severity of anxiety (BAI) symptoms. Also, additional fully adjusted (multinomial) logistic regression analyses were conducted, to examine the association between sleep measures and persistence and the clinical course trajectories of depressive disorders and of anxiety disorders separately, in order to investigate whether associations were consistent across depressive and anxiety disorder course. Again, analyses were conducted with both insomnia and sleep duration simultaneously in the fully adjusted model to check whether their effects were independent, and with an interaction term for insomnia*sleep duration to check for potential interacting effects.

Finally, additional fully adjusted (multinomial) logistic regression analyses were conducted, to examine the association between sleep measures and persistence and the clinical course trajectories of depressive disorders and of anxiety disorders separately, in order to investigate whether associations were consistent across depressive and anxiety disorder course.

Table 1: Baseline characteristics of depressed and anxious subjects (n=1069)

	Total sample	Persistence of diagnosis		p-value[a]
	n=1069	*No (n=416)*	*Yes (n=653)*	
Sociodemographics				
Age (mean years ± SD)	42.7±12.3	42.0±12.7	43.2±12.0	.08
Female, %	66.7	67.1	66.5	.84
Education (mean years ± SD)	11.9±3.2	12.0±3.1	11.8±3.3	.31
Chronic medical disorders				
Alcohol intake, %				
– *none*	20.8	20.2	21.1	.92
– *moderate*	66.9	67.5	66.5	
– *heavy*	12.3	12.3	12.4	
BMI (mean ± SD)	25.8±5.2	25.6±5.0	25.9±5.3	.19
BMI (categories)%				
– underweight	2.4	2.2	2.6	
– normal weight	49.5	50.7	48.7	.21
– overweight	29.0	31.0	27.7	
– obese	19.1	16.1	21.0	
Chronic diseases (mean number ± SD)	1.5±1.4	1.3±1.3	1.6±1.4	.02
Psychiatric characteristics				
Major depression%	63.3	56.0	68.0	<.001
Dysthymia%	19.3	12.5	23.8	<.001
Agoraphobia%	12.9	13.9	12.3	.42
Panic disorder%	39.9	32.9	44.3	<.001
Generalized anxiety disorder%	27.6	21.2	31.7	<.001
Social phobia%	42.5	35.1	47.2	<.001
Antidepressant use, %				
– *no*	61.4	66.1	58.3	
– *SSRI*	24.6	22.6	25.9	.07
– *TCA*	3.9	3.1	4.4	
– *other antidepressants*	10.1	8.2	11.3	
Benzodiazepine use, %	12.5	9.9	14.2	.04
IDS, range2-59 (mean score ± SD)	26.2±11.0	22.2±10.0	28.8±10.9	.17
BAI, range 0-61 (mean score ± SD)	17.5±10.3	14.4±9.0	19.4±10.6	<.001
Sleep measures				
Presence of insomnia, %	59.0	52.4	63.2	<.001
Insomnia score, range 0-20 (mean ± SD)	10.0±5.2	9.3±5.0	10.4±5.3	.34
Sleep duration, %				
– *short sleep duration*	33.6	27.4	37.5	
– *normal sleep duration*	60.5	69.7	54.7	<.001
– *long sleep duration*	5.9	2.9	7.8	
Sleep duration (mean hours ± SD)	7.2±1.4	7.3±1.3	7.1±1.5	.002

a Based on chi-square tests (dichotomous and categorical variables) and independent t-tests (continuous variables).

BAI = Beck Anxiety Inventory; BMI = body mass index; IDS = Inventory of Depressive Symptomatology; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Results

Table 1 shows baseline characteristics of the study sample (n=1069). Mean age was 42.7 years (SD=12.3) and 59% of subjects reported insomnia. Mean sleep duration was 7.2 hours (SD=1.4). Subjects with a persistent depressive/ anxiety diagnosis reported more insomnia (63.2%) compared to subjects with no persistent disorder (52.4%, p<.001). Subjects with a persistent diagnosis also reported a shorter sleep duration (7.1 hours, SD=1.5) compared to subjects with no persistent diagnosis (7.3 hours, SD=1.3, p=.002), although both short and long sleep duration was more prevalent among the persistent group (p<.001). Figure 1 shows Kaplan-Meier survival curves for time-to-remission based on insomnia status and sleep duration. No differences in time-to-remission were found based on insomnia status (p=.18), but significant differences were found according to sleep duration status (p<.001). Subjects with a long sleep duration appeared to have the longest time-to-remission.

Persistence of depressive and anxiety disorders over 2 years

Associations between sleep measures and persistence of depressive and/ or anxiety disorders are described in Table 2. At follow-up, 61.1% (n=653) of the sample had a persistent diagnosis of depressive and/ or anxiety disorder. Both insomnia and the continuous insomnia score were associated with persistence of depressive and/or anxiety disorders, after adjusting for sociodemographics, chronic medical disorders, and psychotropic medication (OR insomnia=1.48, 95%CI=1.14-1.92, OR continuous score=1.04, 95%CI=1.02-1.07). However, associations disappeared after adjusting for severity of depressive and anxiety symptoms.

Short sleep duration (as compared to normal sleep duration) was also associated with persistence of diagnosis after adjusting for sociodemographics, chronic medical disorders, and psychotropics (OR=1.66, 95%CI=1.25-2.21). After adjusting for severity of symptoms, this association was only borderline significant (OR=1.32, 95%CI=0.98-1.78). Also, long sleep duration (as compared to normal sleep duration) was associated with persistence of depressive and/ or anxiety disorders, independent of sociodemographics, chronic medical disorders, and psychotropics (OR=3.08, 95%CI=1.59-5.95) and of severity of depressive and anxiety symptoms (OR=2.52, 95%CI=1.27-4.99). To determine whether the association between sleep duration and course outcome is indeed non-linear, we checked both the linear and the squared term for sleep duration in our analyses. The linear term was not, but the squared term of sleep duration was associated with persistence of depressive and/or anxiety disorders (p=.02, after full adjustment), indicating a non-linear association.

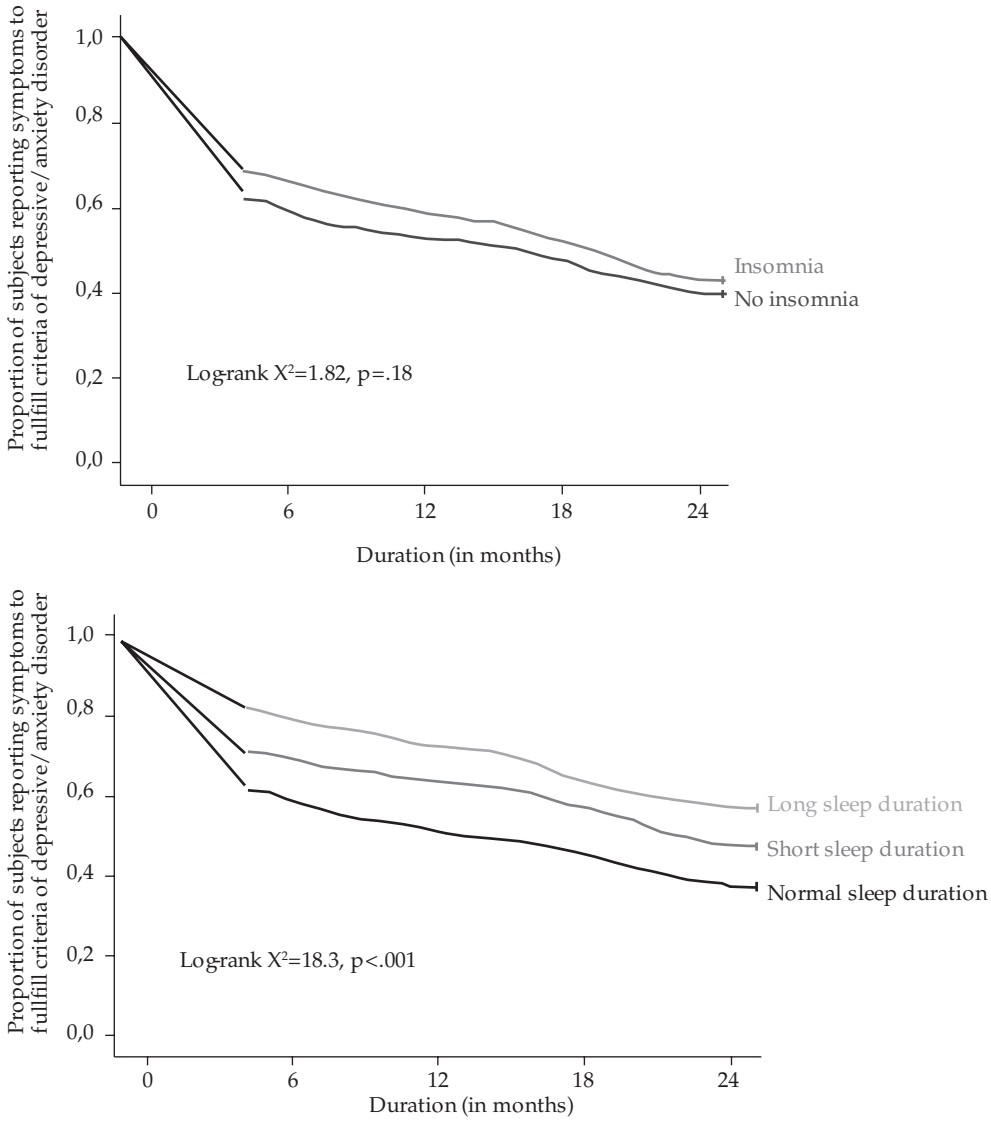

Figure 1: Survival curve illustrating time until remission for depressive/ and or anxiety disorder, according to insomnia status and sleep duration (n=1066)*

* Black lines are projected lines, since by definition no remission could have occurred within the first 3-month period.

Three subjects were excluded because of missing data

Table 2: Odds Ratios for associating sleep measures with 2-year persistence and clinical course trajectories in depressed/ anxious subjects (n=1069)

			Course trajectories of symptoms[b]			
	Persistence of diagnosis[a] (n cases=653)		**Late remission/ recurrence (n cases=344)**		**Chronic course (n cases=459)**	
	OR (95%CI)	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*
Insomnia (yes/no)						
sociodemographics +CMD [c] adjusted	1.50 (1.16-1.94)	.002	1.16 (0.83-1.62)	.38	1.25 (0.91-1.71)	.17
+ psychotropics adjusted	1.48 (1.14-1.92)	.003	1.14 (0.82-1.59)	.44	1.22 (0.89-1.67)	.22
+ severity adjusted	1.04 (0.79-1.37)	.79	0.87 (0.61-1.24)	.44	0.80 (0.57-1.13)	.21
Insomnia (continuous)						
sociodemographics +CMD adjusted	1.04 (1.02-1.07)	.002	1.03 (1.00-1.06)	.09	1.03 (1.00-1.06)	.07
+ psychotropics adjusted	1.04 (1.02-1.07)	.003	1.03 (0.99-1.06)	.11	1.03 (1.00-1.06)	.10
+ severity adjusted	1.01 (0.97-1.03)	.96	0.99 (0.96-1.04)	.96	0.98 (0.95-1.02)	.29
Sleep duration (categories)						
sociodemographics +CMD adjusted						
– *short sleep duration*	1.64 (1.24-2.17)	.001	1.48 (1.02-2.15)	.04	1.85 (1.31-2.62)	.001
– *normal sleep duration*	REF.	REF.	REF.	REF.	REF.	REF.
– *long sleep duration*	3.31 (1.72-6.37)	<.001	2.04 (0.83-5.00)	.12	3.85 (1.66-8.91)	.002
+ psychotropics adjusted						
– *short sleep duration*	1.66 (1.25-2.21)	<.001	1.50 (1.03-2.18)	.03	1.88 (1.33-2.67)	<.001
– *normal sleep duration*	REF.	REF.	REF.	REF.	REF.	REF.
– *long sleep duration*	3.08 (1.59-5.95)	.001	1.91 (0.77-4.71)	.16	3.53 (1.52-8.23)	.003
+ severity adjusted						
– *short sleep duration*	1.32 (0.98-1.78)	.06	1.28 (0.87-1.88)	.20	1.50 (1.04-2.16)	.03
– *normal sleep duration*	REF.	REF.	REF.	REF.	REF.	REF.
– *long sleep duration*	2.52 (1.27-4.99)	.008	1.64 (0.66-4.10)	.29	2.91 (1.22-6.93)	.02
Sleep duration (continuous)						
sociodemographics +CMD adjusted						
Linear duration[d]	0.92 (0.84-1.01	.09	0.99 (0.88-1.12)	.92	0.92 (0.82-1.03)	.17
Squared duration[e]	1.15 (1.08-1.22)	<.001	1.13 (1.03-1.23)	.006	1.18 (1.09-1.28)	<.001
+ psychotropics adjusted						
Linear duration[d]	0.91 (0.82-1.00)	.04	0.98 (0.87-1.11)	.76	0.90 (0.81-1.02)	.09
Squared duration[e]	1.14 (1.07-1.21)	<.001	1.12 (1.03-1.22)	.009	1.17 (1.08-1.27)	<.001
+ severity adjusted						
Linear duration[d]	0.97 (0.87-1.07)	.49	1.03 (0.91-1.17)	.66	0.97 (0.86-1.10)	.66
Squared duration[e]	1.09 (1.02-1.16)	.02	1.09 (1.00-1.19)	.07	1.12 (1.03-1.22)	.008

[a] Based on logistic regression analyses, adjusted for sociodemographics and chronic medical disorders (age, gender, education, alcohol intake, BMI, number of chronic medical disorders), psychotropics (antidepressants, benzodiazepines) and severity of symptoms (IDS and BAI).

[b] Based on multinomial logistic regression analyses, reference category= 'early sustained remission' (n cases=266), adjusted for sociodemographics and health (age, gender, education, alcohol intake, BMI, number of chronic medical disorders), psychotropics (antidepressants, benzodiazepines) and severity of symptoms (IDS and BAI).

[c] CMD= chronic medical disorders. [d] Only linear sleep duration term included. [e] Includes both linear sleep duration term as well as squared sleep duration term.

When adding insomnia (categorical) and sleep duration (categorical) simultaneously to our model (adjusting for age, gender, education, alcohol intake, BMI, number of chronic medical disorders), we found both insomnia (OR=1.38, 95% CI=1.04-1.82) as well as short and long sleep duration (as compared to normal sleep duration, OR short sleep duration=1.44, 95% CI=1.06-1.95, OR long sleep duration= 3.37, 95% CI=1.75-6.51) to be independently associated with 'persistence of diagnosis'. These analyses indicate that insomnia and sleep duration have independent effects on the outcome measures). Also, there was no significant interaction effect of the insomnia (categorical)* sleep duration (categorical) term (p-value .34).

Course trajectories of symptoms over 2 years

Associations between sleep measures and clinical course trajectories of symptoms are described in Table 2. Insomnia was not associated with late remission/ recurrence or a chronic course (as compared to early sustained remission) after adjusting for sociodemographics and chronic medical disorders (OR late remission/recurrence=1.14, 95%CI=0.82-1.59; OR chronic course=1.22, 95%CI=0.89-1.67). Compared to normal sleep duration, both short and long sleep were associated with a chronic course after full adjustment (OR short sleep duration=1.50, 95%CI=1.04-2.16; OR long sleep duration=2.91, 95%CI=1.22-6.93). A non-linear association between sleep duration and chronic course was confirmed by the significant association between the squared sleep duration term and chronic course of symptoms (p=.008 after full adjustment). In order to check if effects of insomnia (categorical) and sleep duration (categorical) are independent of each other, we added them simultaneously to our model (adjusting for age, gender, education, alcohol intake, BMI, number of chronic medical disorders). We found that insomnia was not (OR=1.05, 95% CI=0.75-1.49) but both short and long sleep duration (as compared to normal sleep duration, OR short sleep duration=1.81, 95% CI=1.24-2.64, OR long sleep duration= 3.86, 95% CI=1.67-8.94) were associated with 'chronic course'. Additional adjusting for severity of psychiatric symptoms did not significantly change these results (OR insomnia=0.70, 95%CI=0.49-1.02, OR short sleep duration=1.69, 95%CI=1.14-2.50, OR long sleep duration=2.84, 95%CI=1.20-6.75). These analyses suggest that insomnia and sleep duration can be considered separate concepts (with different effects on the outcome measures). No significant interaction between insomnia and sleep duration was found (p interaction chronic course=.85 for insomnia*long sleep duration and .07 for insomnia*short sleep duration).

Course outcomes for depressive versus anxiety disorders

To compare whether effects were comparable for depressive and anxiety disorders, we repeated the analyses for course outcomes for both disorders separately (Table 3).

Table 3: Odds Ratios for associating sleep measures with persistence of diagnosis and chronic course of symptoms for depressive and anxiety disorders separately (n=1069)

	Persistence of diagnosis[a]				**Chronic course of symptoms[b]**			
	Persistent depressive disorder (n cases=424)		*Persistent anxiety disorder (n cases=492)*		*Chronic depressive symptoms (n cases=279)*		*Chronic anxiety symptoms (n cases=401)*	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Sleep measures								
Insomnia (yes/no)	1.27 (0.95-1.70)	.10	1.07 (0.81-1.41)	.64	1.30 (0.80-2.10)	.29	0.69 (0.45-1.03)	.07
Insomnia (continuous)	1.02 (1.00-1.05)	.11	1.01 (0.98-1.03)	.60	1.02 (0.97-1.06)	.46	0.96 (0.92-1.00)	.07
Sleep duration (categories)								
– *short sleep duration*	1.49 (1.11-2.00)	.008	1.21 (0.91-1.61)	.20	2.03 (1.21-3.39)	.007	1.62 (1.05-2.50)	.03
– *normal sleep duration*	REF.	REF.	REF.	REF.	REF.	REF.	REF.	REF.
– *long sleep duration*	2.52 (1.40-4.54)	.002	1.30 (0.74-2.28)	.37	4.34 (1.51-12.46)	.006	7.73 (1.76-33.95)	.007
Sleep duration (continuous)								
Linear duration[c]	0.98 (0.88-1.08)	.62	0.92 (0.84-1.02)	.10	0.96 (0.81-1.13)	.59	0.97 (0.84-1.13)	.73
Squared duration[d]	1.11 (1.04-1.18)	.002	1.03 (0.97-1.10)	.33	1.17 (1.0 5-1.30)	.004	1.19 (1.07-1.32)	.001

[a] Based on logistic regression analyses, adjusted for age, gender, education, alcohol intake, BMI, number of chronic medical disorders, antidepressants, benzodiazepines, and severity of symptoms (IDS and BAI).

[b] Based on multinomial logistic regression analyses comparing 'chronic course' versus 'early sustained remission', adjusted for age, gender, education, alcohol intake, BMI, number of chronic medical disorders, antidepressants, benzodiazepines, and severity of symptoms (IDS and BAI).

[c] Only linear sleep duration term included.

[d] Included both linear sleep duration term as well as squared sleep duration term.

In our sample, 424 subjects had a persistent depressive disorder (with or without an anxiety disorder) and 492 subjects had a persistent anxiety disorder (with or without a depressive disorder). Insomnia (both dichotomous and continuous) was not associated with persistent depressive disorder, nor with persistent anxiety disorder. Both short and long sleep duration were independently associated with persistent depressive disorder after full adjustment (including severity of symptoms) (OR short sleep duration=1.49, 95%CI=1.11-2.00; OR long sleep duration=2.52, 95%CI=1.40-4.54). For anxiety disorders, we found no significant associations between sleep duration and persistence.

Furthermore, we explored the association of sleep measures with clinical course trajectories of depressive symptoms and of anxiety symptoms separately. Only results

for 'chronic course' are presented because the results for associating sleep measures with course of symptoms were not significantly different between 'early remission' and 'remission/ recurrence' in our previous analyses (Table 2). Both insomnia and the insomnia continuous score were not associated with a chronic course of depressive symptoms, nor with a chronic course of anxiety symptoms. However, both short and long sleep duration were associated with a chronic course of depressive symptoms (OR short sleep duration=2.03, 95%CI= 1.21-3.39; OR long sleep duration=4.34, 95%CI=1.51-12.46) as well as a chronic course of anxiety symptoms (OR short sleep duration=1.62, 95%CI=1.05-2.50; OR long sleep duration=7.73, 95%CI=1.76-33.95). A non-linear association between sleep duration and chronic course of depressive as well as of anxiety symptoms was again confirmed by significant associations between the squared sleep duration term and chronic course of symptoms (depressive symptoms: p=.004; anxiety symptoms: p=.001).

Discussion

Our results clearly indicate that insomnia doest not predict the course of depressive and/ or anxiety disorders. However, both short and long sleep duration do predict a poorer course of depressive and/ or anxiety disorders. Our findings for insomnia are partially in line with earlier research. A large study (n=1801), which controlled for severity of symptoms, found that subjects with insomnia were more likely to remain depressed (9). However, these were elderly primary care patients. Another study found that insomnia alone was not predictive of non-remission in major depression, but the combination of insomnia and increased sleep latency was (while controlling for severity) (16). In subjects with generalized anxiety disorder, treated with venlafaxine or placebo, insomnia has been found to be predictive of a good outcome (12). In general, results on the impact of insomnia on the persistence of depression/ anxiety appear conflicting. One of the reasons may be the lack of a general definition of insomnia. All studies use different instruments in diagnosing insomnia, which hampers comparison. Also, insomnia may actually be an indicator of the underlying severity of psychiatric symptoms, with more severe psychopathology leading to more insomnia. Poor mental health has been shown to predict insomnia (27, 28). Moreover, insomnia has been shown to predict incident depression (29). But it is also possible that it is the other way around, and that more insomnia leads to more severe psychopathology. Because insomnia and psychopathology were measured at the same time, we cannot draw any causal conclusions on the link between insomnia and psychopathology.

Sleep duration showed a curvi-linear association to course of psychopathology, with both short and long sleep duration being predictive of unfavorable course outcomes.

Short sleep duration may increase daytime tiredness, which has been predictive of poor outcome of depression (30). It is also possible that subjects reporting short sleep suffer from a biologically different type of depression or anxiety, which might have a poorer course. A shared genetic background for mood disorders and short sleep has recently been proposed, because genetic variation previously linked to depression (GRIA3-polymorphism) has also been linked to shorter sleep duration (31). Or, short sleepers might simply have more 'time' for pessimistic thoughts, thus contributing to poor outcome in depression (30). Interestingly, also long sleep duration was predictive of a chronic course of depressive and anxiety disorders. Long sleep duration can be an atypical symptom of depression. Especially in atypical depression, a different psychopathology may exist with more metabolic abnormalities and inflammation than in non-atypical depression (32), which in turn could unfavorably impact on course of disorders (33). Several studies have indeed indicated that underlying pathophysiology of inflammation may be more strongly involved than in the more typical (melancholic) depression (34). Furthermore, higher levels of inflammation have also been associated with longer sleep duration itself (35). It could well be that inflammation may be an underlying common pathophysiological mechanism leading to both increase in sleep duration and detrimental effects on course of depression/anxiety disorders. The same might hold true for anxiety disorders. Long sleep duration has also been correlated to low physical activity (36). Individuals who spend many hours in their bed sleeping, may be unsatisfied with being unable to activate themselves, resulting in increased feelings of depression and hopelessness, which may contribute to a poorer outcome.

Sleep duration, however, was a significant predictor of course of psychopathology even after taking symptom severity into account. In a previous study, an interaction effect between insomnia and short sleep duration predicted non-remission of depression (16). Interaction effects between insomnia and sleep duration have also been found to predict deficits in neuropsychological functioning (37), hypertension (38), type II diabetes (39), and in men, even with increased mortality (40) suggesting that interaction effects between insomnia and sleep duration lead to adverse outcomes on multiple domains of health. However, our study could not confirm interaction effects between insomnia and sleep duration on the outcome of psychopathology.

Our results also show that it is important to differentiate between insomnia and sleep duration, since there was no interaction effect between insomnia and sleep duration. This is in line with previous research (14), suggesting that psychopathology is differentially associated with insomnia and sleep duration. The predictive effect of insomnia on course of psychopathology can possibly be attributed to higher symptom severity. But, it is also possible that more severe psychopathology causes more severe insomnia.

Strengths of our study are the longitudinal data on sleep disturbances and psychopathology, making it possible to draw conclusions on the predictive role of sleep disturbances on course. Furthermore, diagnoses were based on DSM-IV criteria, and we adjusted our results for psychotropics and severity of psychopathology. However, there are some limitations. Both insomnia and sleep duration were self-reported, and subjects with psychopathology may over- or underestimate their sleep. We did not use objective measures of sleep such as polysomnography or actigraphy. Finally, the subgroup of 'long sleepers' was not a large group (n=64).

To conclude, our study adds significant information on the impact of sleep disturbances on the course of psychopathology. Both short and long sleep duration – but not insomnia – are predictors of a chronic course, independent of disorder symptom severity. In clinical practice, routinely asking for sleep duration might identify subjects at risk for a chronic course.

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