A sad day's night

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CHAPTER 6

Bidirectionality between sleep symptoms and core depressive symptoms and their long-term course in major depression

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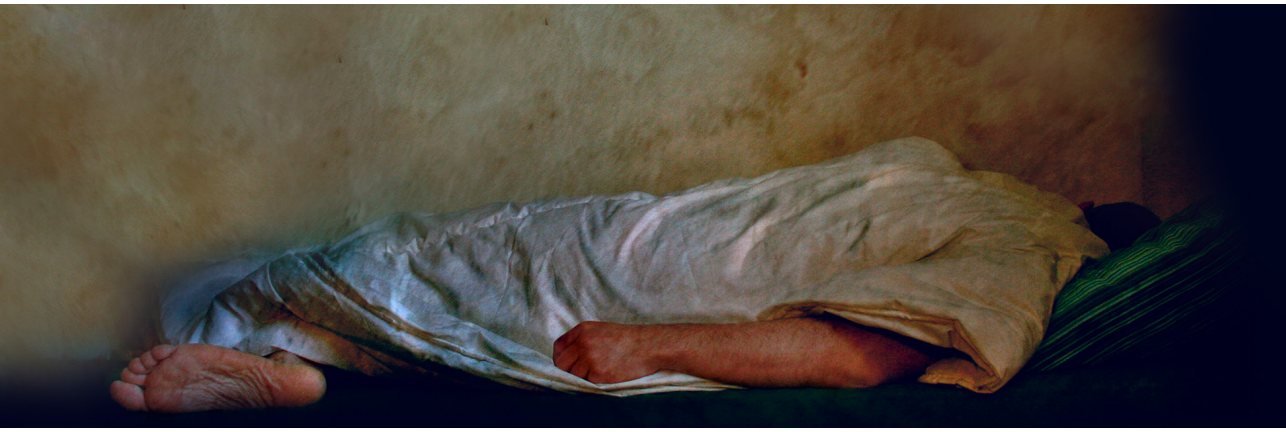

Abstract

The objective of this study was to investigate the bidirectional dynamic relationship between sleep symptoms and core depressive symptoms and to identify subgroups differing with respect to their course.

The weekly state of depressive symptoms in depressed primary care patients (N=267) was assessed retrospectively every 3 months for 3 consecutive years. The bidirectional relationship between sleep and core symptoms was estimated by means of manifest Markov modeling. Data-driven subgroups were estimated with parallel processes – latent class growth analyses to identify differences in courses of sleep and core symptoms.

In total, core symptoms were associated with next-week development (odds=1.42, 95% CI 1.20 to 1.67, p<.001) and remission of sleep symptoms (odds=0.86, 95% CI 0.75 to 0.99, p=.033). Vice versa sleep symptoms were associated with the development (odds=1.26, 95% CI 1.05 to 1.50, p=.012) and remission of core symptoms (odds=0.87, 95% CI 0.76 to 0.99, p=.038). Three classes with different 3-year courses were derived. In class 1 the likelihood that core symptoms remitted was reduced if sleep symptoms were present, and symptoms remained present over 3 years. In class 2 symptoms were bidirectionally related, and remitted over 3 years. In class 3 symptoms were not associated, and sleep symptoms declined less steeply than core depressive symptoms.

The results suggest that sleep symptoms should be treated alongside core depressive symptoms in patients with an a-synchronic decrease of sleep and core symptoms and in patients that do not respond to treatment in order to increase the chance of complete remission.

Introduction

Sleep disturbances are considered as a transdiagnostic condition, because their presence has been found to predict the onset of several psychiatric disorders[1,2]. Sleep disturbances can be seen as a key course modifier in the context of major depressive disorder (MDD). They are an independent risk factor for MDD[3], and they play an important role in the maintenance and exacerbation of the disorder[4,5]. Non-depressed people with insomnia have a twofold risk to develop depression compared to people without sleep problems[6]. A lifetime history of hypersomnia, insomnia, or both, is significantly related to future development of depression[7]. Besides, insomnia and hypersomnia belong to the symptoms of MDD[8], and are present in approximately 70% of depressed patients[9,10]. Further, sleep disturbances often remain as a residual symptom in patients in remission[6,10-12]. Thus, sleep disturbances and depression are clearly associated with each other. However, it remains unclear how they interact over time within depressed patients.

A limitation of previous studies is that the relationship between sleep disturbances and depression over time has been examined mostly in the general population[6,12] and rarely in clinical populations[6]. Furthermore, Baglioni and colleagues[6] and Skapinakis et al.[12] examined whether sleep disturbances were a predictor of depressive episodes at least 12 months later. This long time lag precludes a fine-grained insight into the interaction between sleep disturbances and depression over time. Moreover, because sleep disturbances can be part of MDD diagnosis[13], this approach could have resulted in an artificial overlap between the predictor and outcome variable, thereby possibly overestimating the predictive effect of sleep disturbances[12]. In the present study, core symptoms of depression (low mood and/or anhedonia) were used instead of depression diagnosis as outcome to overcome the latter problem[12].

Overcoming these limitations is needed to develop a better understanding of the exact nature of sleep disturbances in recurrent depression. This may provide targets for treatment and prevention. Therefore, in the present study, we examined the bidirectional relationship between sleep disturbances and core symptoms of depression, in a longitudinal study with repeated weekly measurements for three consecutive years in a clinical sample of recurrent depressed primary care patients.

The first aim of this study was to investigate the bidirectional relationship between sleep disturbances and core depressive symptoms, i.e. whether the presence of sleep symptoms was associated with the appearance and disappearance of core symptoms and vice versa, whether the presence of core symptoms was associated with next-moment changes in sleep symptoms. It is plausible that the course of sleep symptoms and core depressive symptoms over time differs between patients. Therefore, our second aim was to construct data-driven subgroups based on the 3-year course of these symptoms. This enabled us to investigate whether sleep symptoms and core depressive symptoms were associated with each other differently within these groups. Third, we examined whether demographic characteristics differed between the classified subgroups.

Materials and Methods

Participants and design

We used data from a randomized-controlled trial (RCT) that was carried out from 1998 to 2003 in the Northern part of the Netherlands. The RCT aimed to investigate the effectiveness of four treatments for primary care patients with a major depressive disorder (MDD)[14].

Patients who were currently treated for a major depressive episode by their general practitioner, had suffered one or more previous depressive episodes, and were aged 18-70 were referred by their general practitioner to participate in the study. Referred patients were provided with detailed verbal and written information on the study and screened by telephone. After that, patients were interviewed by means of the Composite International Diagnostic Interview (CIDI)[15] by an experienced research assistant, in order to examine the presence of a major depressive disorder (MDD). The CIDI has shown good reliability and validity[16,17]. Diagnostic criteria for major depression had to be met at the time of the interview (baseline measurement) or in the 3 months prior to the interview for patients to be included in the study. Exclusion criteria were: the presence of a psychotic disorder, bipolar disorder, dementia, primary alcohol or drug dependence or abuse, pregnancy, and receiving treatment for depression in a specialty mental health setting. Of the 397 referred patients, 267 met the inclusion criteria. These patients were stratified according to antidepressant usage at baseline and randomly assigned to one of the four treatment groups: (1) care as usual (CAU); (2) CAU enhanced by a psycho-educational prevention program (PEP); (3) psychiatric consultation and PEP (PC + PEP); or (4) cognitive behavioral therapy and PEP (CBT + PEP) in ratio 2:3:1:1. The PEP program was developed to enhance self-management and self-efficacy by means of psycho-educational techniques in order to decrease the chance of depression recurrence. Patients in the PC + PEP program had an appointment with one or two psychiatrists prior to the start of the PEP program. The aim of the CBT + PEP program was behavioral activation and restructuring of dysfunctional cognitions in 10-12 sessions of 45 minutes prior to the PEP program[14]. Specific sleep-focused components were not incorporated in any of the programs. All participants gave informed consent prior to inclusion in the study[18]. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen (no: MEC 96/02/028). Please note that no differential effects of the four treatments were found in the RCT regarding CIDI-based outcome measures[14].

Measurements

Symptoms of depression and sleep

During the study period, in which patients were followed for a maximum of 173 consecutive weeks, patients were interviewed by telephone every 3 months with an adapted CIDI depression section to assess the weekly presence or absence of all nine DSM-IV symptoms of major depression during that period. In order to prevent recall problems the interviewers reminded the patients of their symptom state at the time of the previous telephone interview. Then patients were asked whether the symptoms that were present

three months earlier persisted or remitted, and how many weeks ago a possible change occurred. If a symptom was absent three months earlier, patients were asked whether the symptom remained absent or developed, how many weeks ago this change occurred, and if it remained present or remitted again. Besides, interviewers were extensively trained and supervised each three months during the entire follow-up period of the study. Supervisors were trained at the official WHO-CIDI Training and Reference Center (Academic Medical Center, Amsterdam).

The two core symptoms, (1) depressed mood or irritability most of the day, nearly every day; and (2) decreased interest or pleasure in most activities most of each day, nearly every day, were selected for the analyses. We did not focus on onset or remission of MDD, because the criteria for this diagnosis include sleep problems[12]. To represent the absence or presence of the core symptoms of depression, a dichotomous variable was created with values 0 = no core symptoms this week, and 1 = one or two core symptoms this week.

Weekly sleep symptoms were assessed in the same way as the core symptoms, i.e. by means of the adapted CIDI depression section every 3 months. Sleep symptoms ((1) insomnia nearly every day; or (2) hypersomnia nearly every day) were available as 0 = no sleep symptoms this week, and 1 = one or two sleep symptoms this week. Independent insomnia and hypersomnia ratings were not available.

Statistical analyses

The temporal relationship between sleep symptoms and core depressive symptoms Manifest Markov modeling was used to investigate the (bidirectional) temporal relationship between sleep symptoms and core depressive symptoms over time. This method allows to investigate the chance that a next-week change (=manifest) in core depressive symptoms (i.e., onset or decline) is associated with the state (i.e., present or absent) of sleep symptoms in the current week[19]. Contrariwise, we investigated the association of the state of core depressive symptoms this week with a manifest in sleep symptoms next week. A graphical representation of the Manifest Markov model is presented in Figure S1, Supplemental Content. The software Latent GOLD® 5.0 (Statistical Innovations Inc, Belmont, MA) was used to search for the a priori defined manifests and to perform simultaneous multiple logistic regression analyses to estimate the chance that these manifests were significantly associated with the state of the previous weeks' sleep symptoms or previous weeks' MDD core symptoms. This means that measurement points in which no manifests occurred were discarded from analyses. Two continuous covariates (start counting at '0' after a change in state occurred) were computed to control for the duration of the state of sleep symptoms and core depressive symptoms (i.e., no symptoms versus symptoms). A covariate for time was included to account for the possibility that the measurements of sleep symptoms and MDD core symptoms were time dependent. Adding a constant covariate to the models would not change unique individual patterns over time, therefore we could not control for suggested variables such as depression severity at baseline. Not everybody participated an equal amount of weeks; the maximum amount (=173 weeks) was used for all participants, as full-information estimates could be computed with missing data[20]. Therefore, missing data were not imputed. The best-fitting and simplest model was estimated and selected according to information criteria[21]. The

Bayesian Information Criterion (BIC) and the modified Akaike Information Criterion (AIC3) were compared and the model with the smallest values of these information criteria was selected. The syntax of the generic final model is added as an Appendix. The hypothesis examined was that manifests in both core symptoms and sleep symptoms could be explained significantly with the state of previous weeks' sleep symptoms and core depressive symptoms, respectively.

Sensitivity analysis: the temporal relationship between other depressive symptoms and core symptoms

For sake of comparison we investigated whether the remaining depressive symptoms were of similar importance as sleep symptoms with regard to the likelihood of changes in core depressive symptoms. Again we used Manifest Markov analyses, this time for each of the remaining six symptoms of MDD. The remaining symptoms included (1) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day; (2) psychomotor agitation or retardation nearly every day; (3) fatigue or loss of energy nearly every day; (4) feelings of worthlessness or excessive or inappropriate guilt nearly every day; (5) diminished ability to think or concentrate, or indecisiveness, nearly every day; and (6) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Again, for each symptom a dichotomous variable was created to represent its weekly absence or presence, with 0 = not reported this week, and 1 = reported this week.

Data-driven subgroups of the 3-year course of sleep symptoms and core depressive symptoms

To establish latent classes representing meaningful differences in course over time of both sleep disturbances and core depressive symptoms, a parallel processes – latent class growth analysis (PP-LCGA) was performed by means of Mplus (Muthén and Muthén, Los Angeles, CA). PP-LCGA is a technique that allows to model multiple data-driven processes (in this case sleep symptoms and core symptoms) simultaneously[22]. PP-LCGA results in a distribution of the data in an optimal amount of classes, whereby each class represents a substantially different group of patients. Patients are allocated to a class based on how well their individual course of sleep symptoms and core depressive symptoms over time is alike in these classes[23].

We used PP-LCGA to estimate classes for core symptoms and sleep symptoms simultaneously. As PP-LCGA is not suitable for dichotomous variables, the proportion of the weekly presence of the variable over the past 3 months was computed for respectively core symptoms and sleep symptoms (with 0 = 'not present', up to 100 = 'always present'). The timespan of 3 months was chosen as the telephonic CIDI was administered every 3 months. This means that this part of the analyses focuses on the 3-monthly averages and not on week-to-week transitions. The best-fitting model with an optimal amount of classes was selected based on the Akaike Information Criterion and the Bayesian Information Criterion. The Bootstrapped Likelihood Ratio Test (BLRT) as well as the Lo-Mendell-Rubin Likelihood Ratio Test (MLR) were used to end up with the best-fitting model. Both BLRT and MLR had to be insignificant to make sure the kth classes' model

outperformed the k-1 classes' model[24]. Additional criteria were taken into account to find the best solution: successful convergence (replication of the same output by choosing the first two seeds that give the best log likelihood output); a high entropy value (near 1.0); more than 1% of total N in one class; and average latent class probabilities for most likely latent class membership by latent class (posterior probabilities) near 1.0[23].

The PP-LCGA analyses were used to differentiate between latent classes based on the course of both symptoms over time. After these classes were estimated, we determined if there was a difference between these classes in how sleep and core depressive symptoms were associated with each other over time. Therefore we investigated whether the estimated classes showed similar or different bidirectionality between sleep and core depressive symptoms by means of the Manifest Markov analyses as mentioned above.

Predictors of data-driven subgroups of the 3-year course of sleep and core depressive symptoms

To conclude, an analysis of variance (ANOVA) or chi-square test was performed with IBM SPSS Statistics 22 (IBM, SPSS Inc., Chicago, IL) to compare classes with regard to baseline predictors. Tukey's test and Bonferroni adjusted tests was used for post-hoc comparison of significant class differences after ANOVA and Chi-square tests, respectively. Based on earlier research on sleeping problems and depression[12], treatment, proportion of time that antidepressant medication was used during the study period, amount of symptoms at baseline as assessed by the CIDI, age, gender, marital status, occupational status (Are you: employed (employed or independent entrepreneur) = '1', homemaker = '2', other (student, unemployed, retired, or unable to work) = '3'), education level ('What is the highest level of education you have completed?' with answering categories: low (primary school, lower vocational education, pre-vocational education, general secondary education) = '1', middle (vocational education, senior general secondary education, pre-university education) = '2', high (higher vocational education, academic education) = '3'), depression severity, the amount of previous episodes of depression (≤ 3 episodes = '0', > 3 episodes = '1') 25, age of first episode, antidepressant use at baseline, and additional use of psychological therapy during the study period were used as predictor of class membership.

Results

Data characteristics

Table 1 shows sociodemographic and clinical characteristics of the sample. Patients participated for a maximum of 173 weeks. With 267 participating patients this resulted in 46,191 measurement occasions. Not all patients completed every measurement. In total 16,860 measurement occasions had to be treated as missing, leaving 29,331 measurement occasions left for analysis. The mean duration of participation was 132.2 (SD=45.7) weeks. Sleep symptoms were reported at almost half of the completed measurements (46.6%), and core symptoms of depression in one-third (35.3%). At 44.9% of the measurements occasions, neither sleep symptoms nor core symptoms of depression were reported, and at 26.8% of the measurement occasions patients reported the presence of both sleep symptoms and core symptoms.

Table 1. *Sociodemographic and clinical characteristics of the participants at baseline*

	Total (N = 267)	
	%	n
Age, years	42.8 (11.3)	
Female	65.0	174
Marital status		
Married/cohabiting	64.8	173
Not married	19.1	51
Divorced	12.7	34
Widowed	3.4	9
Education		
Low	43.8	117
Middle	36.3	97
High	19.9	53
Primary occupation		
Employed	60.3	161
Unemployed	19.1	51
Other	20.6	55
Treatment group		
CAU	27.0	72
PEP	41.9	112
PEP + PC	14.6	39
PEP + CBT	16.5	83
Antidepressant use	74.2	198
CIDI depressive symptoms at baseline, #	6.0 (2.1)	
> 3 previous episodes	36.8	98
Age at first depression onset, years	31.3 (19.9)	

Note. N = number of participants; CAU = Care As Usual; PEP = Psycho-Educational Prevention; PC = Psychiatric Consultation; CBT = Cognitive Behavioral Therapy. If not otherwise specified, mean and standard deviation (in parentheses) are given.

The bidirectional relationship between sleep symptoms and core depressive symptoms

Sleep symptoms

The odds to develop current sleep symptoms was 1.42 larger when core symptoms of depression were present the previous week compared with the absence of core symptoms the previous week (95% CI 1.20 to 1.67, $p<.001$). The odds for sleep symptoms to disappear was 0.86 smaller when core symptoms were present instead of absent the week before the manifest occurred (95% CI 0.75 to 0.99, $p=.033$). The covariate for the duration of core symptoms did not add significant information to the model (Wald's statistic = 1.73, $p=.42$). The covariate for the duration of sleep symptoms did add significant information to the model (odds = 0.99, $p<.001$), indicating that the prolonged presence or absence decreased the chance of a transition.

Core depressive symptoms

The odds to develop current core symptoms was 1.26 larger when sleep symptoms were present the week before compared with the absence of sleep symptoms in the previous week (95% CI 1.05 to 1.50, $p=.012$). The odds for core symptoms to disappear was 0.87 smaller when sleep symptoms were present instead of absent the week before the manifest occurred (95% CI 0.76 to 0.99, $p=.038$). The covariate for the duration of sleep symptoms did not add significant information to the model (Wald's statistic=0.17, $p=.92$). The covariate for the duration of core symptoms did add significant information to the model (odds = 0.99, $p<.001$), indicating that the prolonged presence or absence decreased the chance of a transition.

Sensitivity analysis: the temporal relationship between other depressive symptoms and core symptoms

The odds to develop core symptoms given the presence instead of the absence of each of the remaining symptoms last week was significant for all six symptoms ($p\leq.003$), and the odds for core depressive symptoms to disappear when each of the other symptoms was absent instead of present the previous week was significant for each symptom as well ($p<.001$). The odds to develop each of the six remaining symptoms given the presence of core symptoms in the previous week was significant in all cases ($p<.001$). The odds that each of the six symptoms disappeared given the presence of core symptoms last week was significant for 3 out of 6 symptoms ($p\leq.003$), namely fatigue or loss of energy, diminished ability to think or concentrate, and recurrent thoughts of death, but not for eating problem, feelings of worthlessness and guilt and psychomotor problems (see table 2 for detailed information).

Table 2. *Bidirectional relationship between remaining six symptoms and core symptoms*

Manifest	OR	95% CI	*p*-value
Given presence core symptom$_{t-1}$:			
Weight symptom$_t$ develops	2.17	1.73 – 2.71	<0.001
Weight symptom$_t$ disappears	0.89	0.73 – 1.10	0.28
Given presence weight symptom$_{t-1}$:			
Core symptom$_t$ develops	1.60	1.20 – 2.13	0.002
Core symptom$_t$ disappears	0.67	0.55 – 0.82	<0.001
Given presence core symptom$_{t-1}$:			
Motor symptom$_t$ develops	3.14	2.34 – 4.21	<0.001
Motor symptom$_t$ disappears	0.99	0.74 – 1.33	0.97
Given presence motor symptom$_{t-1}$:			
Core symptom$_t$ develops	2.17	1.92 – 3.56	<0.001
Core symptom$_t$ disappears	0.51	0.40 – 0.64	<0.001
Given presence core symptom$_{t-1}$:			
Energy symptom$_t$ develops	3.12	2.36 – 4.13	<0.001
Energy symptom$_t$ disappears	0.63	0.52 – 0.78	<0.001
Given presence energy symptom$_{t-1}$:			
Core symptom$_t$ develops	2.23	1.74 – 2.87	<0.001
Core symptom$_t$ disappears	0.61	0.48 – 0.77	<0.001
Given presence core symptom$_{t-1}$:			
Guilt symptom$_t$ develops	2.63	2.04 – 3.40	<0.001
Guilt symptom$_t$ disappears	0.96	0.75 – 1.21	0.70
Given presence guilt symptom$_{t-1}$:			
Core symptom$_t$ develops	2.12	1.60 – 2.81	<0.001
Core symptom$_t$ disappears	0.58	0.48 - 0.71	<0.001
Given presence core symptom$_{t-1}$:			
Cognitive symptom$_t$ develops	3.37	2.48 – 4.58	<0.001
Cognitive symptom$_t$ disappears	0.56	0.45 – 0.69	<0.001
Given presence cognitive symptom$_{t-1}$:			
Core symptom$_t$ develops	2.22	1.74 – 2.84	<0.001
Core symptom$_t$ disappears	0.54	0.42 – 0.69	<0.001

Given presence core symptom$_{t-1}$:			
Suicide symptom$_t$ develops	2.13	1.59 – 2.85	<0.001
Suicide symptom$_t$ disappears	0.67	0.51 – 0.88	0.003
Given presence suicide symptom$_{t-1}$:			
Core symptom$_t$ develops	1.77	1.21 – 2.59	0.003
Core symptom$_t$ disappears	0.48	0.38 – 0.61	<0.001

Note. Manifest Markov modeling was used to investigate the temporal relationship between symptoms over time; OR = Odds Ratio; CI = Confidence Interval.

Data-driven subgroups of the 3-year course of sleep symptoms and core depressive symptoms

The optimal model estimated by means of PP-LCGA consisted of 3 classes (table 3). BLRT and MLR criteria were used to choose the best model. Even in the 6-class model, the BLRT did not become insignificant, although errors occurred and likelihood ratio tests could not be computed anymore. Because BLRT did not provide useful information, it was decided to choose the best model fit based on MLR statistics. The 3-class model was the most parsimonious model with good fit. Visual inspection of the growth models (Figure 1) shows that in class 1 (N=61) the proportion of sleep symptoms and core symptoms changed simultaneously over time but remained as high as 76% and 72%, respectively, after 3 years. A similar pattern is visible in class 2 (N=127), albeit with a much steeper decrease in proportion of both symptoms over time (with proportions around 12% after 3 years). Class 3 (N=79) differs from class 1 and 2 in that sleep symptoms seem to be more persistent in this group (mean proportion of 47% after 3 years) than core symptoms (approximately 10% after 3 years).

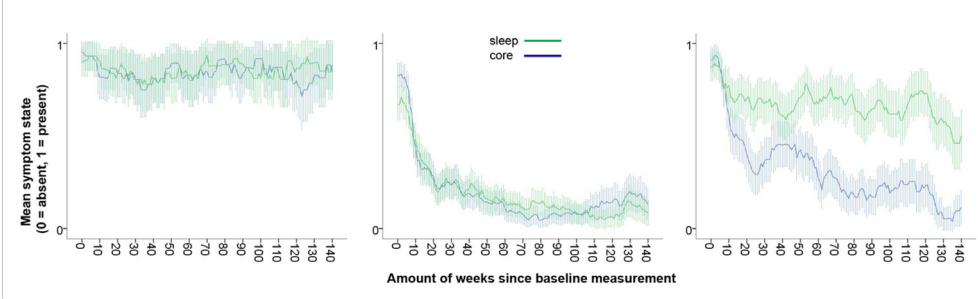

Figure 1. *Observed growth trajectories for each of the PP-LCGA classes*
PP-LCGA = Parallel Processes – Latent Class Growth Analysis; the lines represent fractions of the class having the symptom; the shaded area around the mean represents the 95% CI.

Table 3. *Parameter comparison of PP-LCGA*

Number of classes	Df	AIC	BIC	BLRT, p-value	LMR, p-value	Smallest class, n (%)
1	32	55738	55852	-	-	-
2	39	54262	54402	<0.001	0.03	109 (40.8%)
3	**46**	**53680**	**53845**	**<0.001**	**0.03**	**61 (22.8%)**
4	53	53384	53574	<0.001	0.12	27 (10.1%)
5	60	53129	53344	<0.001	0.33	26 (9.7%)
6	67	52984	53225	<0.001	0.39	18 (6.7%)

Note. AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = Bootstrap Likelihood Ratio Test; LMR = Lo-Mendell-Rubin likelihood ratio test; n = number of participants within class; PP-LCGA = Parallel Processes – Latent Class Growth Analysis. Bold refers to the most parsimonious model with good fit.

The three classes differed significantly regarding age, occupational status and educational level (p<.050, table 4) in baseline clinical characteristics (p<.001), and in the amount of missingness (p<.001). In class 1, the amount of missing data (51%) was higher than class 2 (33%) and class 3 (31%). Patients in class 1 reported significantly more CIDI symptoms at baseline compared with patients in class 2 (mean difference = 1.4, SD = 0.3, p<.001), and patients in class 3 also reported significantly more CIDI symptoms at baseline compared with patients in class 2 (mean difference = 0.9, SD = 0.3, p=.007). Patients in class 1 were significantly older (mean age = 46.2 years), were more often unemployed, and had a lower level of education compared with patients in the other two classes. Patients in class 2 were the youngest (mean age = 40.8 years) and had the highest education level. Class 3 consisted of people who obtained a medium level of education and mean age (mean age = 43.3 years) compared to the other classes. Patients in class 3 were more often employed compared with patients in the other two classes (p=.034, table 4), and used antidepressant medication a larger proportion of time in comparison with patients in class 2 (mean difference = 0.16, p=.009, main effects table 4). This difference in proportion of 0.16 equals 21 weeks, at a mean study participation of 132 weeks. In other words, patients in class 3 used antidepressant medication on average 21 weeks longer compared to patients in class 2.

Results of the Manifest Markov modeling showed substantial differences between the classes regarding the association of changes in core symptoms with the presence or absence of sleep symptoms, and vice versa. A graphical representation of the final Manifest Markov model per class is presented in Figure S2, Supplemental Content. A summary of the prevalence of sleep and core symptoms throughout the study period, and of the prevalence of the possible transitions across and within the classes is available in Tables S1 and S2, Supplemental Content.

Table 4. *Comparison of baseline predictors between classes*

Predictor	Total	Class 1	Class 2	Class 3	Class-comparison		
	N = 267	N = 61	N = 127	N = 79	*F*	p-value	η^2
Age, years	42.8 (11.3)	46.2 (10.4)	40.8 (12.1)	43.3 (10.0)	4.90	.008	.04
Age at first depression onset, years	31.3	31.3 (13.8)	31.2 (13.0)	31.5 (13.1)	0.01	.99	<.001
Proportion time of medication use, 0 - 1	0.44 (0.37)	0.48 (0.37)	0.37 (0.36)	0.53 (0.37)	4.67	0.010	.04
Baseline CIDI total, 1 – 9	6.0 (2.1)	6.8 (1.7)	5.4 (2.3)	6.3 (1.9)	10.67	<.001	.07
					X^2	p-value	η^2
Female, %	64.0	59.0	66.1	64.6	.92	.63	.06
Marital status, %					5.1	.52	.10
Married/cohabiting	64.8	62.3	63.0	69.6			
Not married	19.1	16.4	22.8	15.2			
Divorced	12.7	16.4	10.2	13.9			
Widowed	3.4	4.9	3.9	1.3			
Primary occupation, %					10.4	.034	.14
Employed	60.3	55.7	59.1	65.8			
Homemaker	19.1	29.5	20.5	8.9			
Other	20.6	14.8	20.5	25.3			
Education, %					17.3	.002	.18
Low	43.8	57.4	39.4	40.5			
Middle	36.3	36.1	31.5	44.3			
High	19.9	6.6	29.1	15.2			
Treatment group, %					2.4	.88	.07
UC	27.0	24.6	26.8	29.1			
PEP	41.9	49.2	39.4	40.5			
PEP + PC	14.6	13.1	16.5	12.7			
PEP + CBT	16.5	13.1	17.3	17.7			
> 3 previous episodes, %	36.8	39.3	33.3	40.5	1.29	.53	.07
Antidepressant use, %	77.2	73.8	75.6	82.3	1.7	.42	.08
Additional psychological therapy, %	38.0	46.2	37.1	34.2	1.98	.37	.09

Note. An analysis of variance (ANOVA) or chi-square test was performed to compare classes. Tukey's test or Bonferroni adjusted test was used for post-hoc comparison of significant class differences; N = number of participants. CAU = Care As Usual; PEP = Psycho-Educational Prevention; PC = Psychiatric Consultation; CBT = Cognitive Behavioral Therapy; if not otherwise specified, mean and standard deviation (in parentheses) are given.

In class 1, the odds for core symptoms to disappear was 0.43 smaller when sleep symptoms were present instead of absent the week before the manifest occurred (95% CI 0.22 to 0.81, p=.009). The odds for core symptoms to develop given previous' weeks sleep symptoms was not significant (95% CI 0.50 to 1.76, p=.83). The presence or absence of core depressive symptoms did not add significant predictive value to changes in sleep symptoms (Wald's statistic = 1.00, p=.61). Altogether this means that in class 1 the state of sleep symptoms was significantly associated with subsequent manifests in core symptoms, but not the other way around. More specifically, the likelihood of remission of core symptoms was reduced in case of presence of sleep symptoms.

In class 2, the odds to develop current sleep symptoms was 2.78 larger when core symptoms of depression were present the previous week compared with the absence of core symptoms (95% CI 1.85 to 4.17, p<.001). The odds that sleep symptoms disappeared was not significantly different due to the absence or presence of previous week's core symptoms (95% CI 0.56 to 1.01, p=.055). In total, core symptoms were significantly associated with changes in sleep symptoms (Wald's statistic = 28.09, p<.001). The odds to develop current core symptoms was 2.39 larger when sleep symptoms were present the previous week compared with the absence of sleep symptoms the previous week (95% CI 1.54 to 3.71, p<.001). The odds that core symptoms disappeared was not significantly different due to the absence or presence of previous sleep symptoms (95% CI 0.74 to 1.31, p=.92). Sleep symptoms did contribute significantly to the model (Wald's statistic = 15.09, p<.001). In summary, in class 2, the presence of core symptoms increased the chance of developing subsequent sleep symptoms, and the presence of sleep symptoms increased the chance to develop subsequent core symptoms. The state of both symptoms was not associated with next-week remission of one another.

Finally, in class 3 the odds for sleep symptoms to either develop or disappear given previous' weeks core symptoms did not add significant value to the model (Wald's statistic = 2.87, p=.24). Also, the odds for core symptoms to either develop or disappear given previous' weeks sleep symptoms did not add significant value to the model (Wald's statistic = 2.81, p=.25). To summarize, in class 3, the state of sleep symptoms and core symptoms were not significantly associated with manifests in one another.

Discussion

This study was the first to assess the bidirectional relationship between sleep and core depressive symptoms by means of multiple repeated assessments in major depressed primary care patients. Sleep symptoms were found to be associated with changes in core symptoms, and vice versa. Parallel processes – latent class growth analysis showed that three latent classes could be identified which differed substantially in the 3-year course, the strength, and the direction of the relationship between sleep and core symptoms.

The current study showed that for participants diagnosed with major depression at baseline a bidirectional relationship existed between sleep symptoms and core depressive symptoms. This bidirectionality was also found in longitudinal studies that were performed during a longer period of time (differing from 12 months up to > 10 years between

baseline and follow-up) with regard to major depression[5,6,12,26,27]. Insomnia is associated with the development of depression; non-depressed people with insomnia have a twofold risk of developing depression[6]. Interestingly, the three classes that were identified based on the course of symptoms over time differed significantly in direction and strength of this bidirectional relationship. In class 1, wherein people were on average older, less educated and more often unemployed, the presence of sleep symptoms was significantly associated with changes in core symptoms, but not the other way around. In class 2 people were on average the youngest and highest educated. In this class the presence of both symptoms was only associated with the onset of the other symptom, and not the remission of the symptoms. This suggests that the presence of each symptom sustains the emergence of the other symptom, but that the disappearance of the symptoms is regulated by another factor. Lastly, in class 3, which consisted of the highest proportion of employed people, both symptoms showed relatively separate courses and acted rather independently from each other. This suggests that in this class the course of both symptoms is influenced by or associated with separate processes. Therefore, the results of this study implicate the presence of (1) sleep being imbedded within depression, in which a change of sleep is associated with a small decrease (class 1) or increase (class 2) of sleep and core depressive symptoms; and (2) sleep being part of a construct independent of the depression, as represented in class 3. Sleep appears to have an independent status in the latter class with the highest rate of employment. This suggests that sleep symptoms in this class might be associated with external factors, for example related to work (i.e., high workload, stress), instead of being a part of MDD. An alternative explanation can be found in the use of antidepressants. In class 3, patients reported antidepressant use on average 21 extra weeks in comparison with patients in class 2. It is common knowledge that not sleeping well or feeling very sleepy can be a side effect of antidepressant use[28]. Possibly, the use of antidepressants prolonged the continuation of sleep problems in this class. Obviously it cannot be ruled out that unmeasured confounding variables underlie the observed associations.

Several methodological limitations should be mentioned. First, data on insomnia and hypersomnia were only available in a combined measure of sleep problems in this study. This might be suboptimal because insomnia and hypersomnia may be differentially related to core depressive symptoms. However, insomnia and hypersomnia regularly co-occur in patients with MDD, with more than 25% of patients who suffered from MDD in the past year reporting both insomnia and hypersomnia symptoms[29]. The overall course of MDD in these patients did not differ compared to patients who reported only hypersomnia symptoms (5.9%) or insomnia symptoms (59.1%). Nevertheless, future studies should preferably use separate measures for in- versus hypersomnia. The same holds for the other bidirectional symptoms of MDD: change in activity and change in weight; we could not differentiate between patients with increased or decreased psychomotor activity, and weight gain or weight loss. This is a major limitation, as recent studies suggest that these phenotypes of depression may be driven by different processes. Second, Manifest Markov modeling was used to estimate reciprocity between sleep and core symptoms. The type of interviewing used in the study (3-monthly, retrospectively over the past 12 weeks) may have resulted in a biased representation of the presence of symptoms that is not accounted for in

the statistical model. Findings could be partly explained by shared method variance. Both sleep and core symptoms were assessed with the same instrument designed to evaluate the symptoms of depression. Other methods of assessing sleep that do not rely on the same interview (e.g. sleep diaries[30], actigraphy) are less likely to be confounded with depressive symptoms. Still, this is the only study in which multiple repeated assessments were used, in contrast with earlier studies in which only two assessments were used to examine the bidirectional relationship between sleep symptoms and depression[6,12]. A third limitation is the fact that Manifest Markov modeling only uses previous measurements in association to current measurements[31] while earlier measurements are not taken into account. The duration of the presence of a symptom can be important in predicting changes, therefore two covariates were created to account for earlier measurements. The additional effects of these covariates were, however, found to be non-significant. At last, the sensitivity analyses revealed that the importance of sleep symptoms should be considered in a realistic perspective, as most of the other symptoms showed significant associations with the (dis)appearance of core symptoms as well. This indicates that though the impact of sleep symptoms on onset or remission of core depressive symptoms and vice versa is substantial, it is probably not unique. Another point of interest is that the amount of missingness could have influenced the class membership of the participants. Missingness may depend on class membership or the growth trajectory over time (in our case, reaching remission). Possibly, the non-remitters had the highest missingness due to severity of their depression. Unfortunately, there is not much literature available about the effects of data missing not at random in growth models[32], and it is mere speculation whether this affected class membership in this study.

The results of the present study hold some important clinical implications, especially with regard to the sequencing and selection of depression treatment. The key difference between classes was in the degree of remission; class 1 consisted of non-remitters, class 2 of remitters, and class 3 of partial remitters. Imaginably, patients in class 1 need more intensive treatment because their symptoms did not improve during the study period of 3 years. Treatment of depression resulted in a lasting decline of core symptoms in class 2 and class 3, and also resulted in a decline of sleep symptoms in class 2. In class 3, treatment of the persistent sleep disturbances following depression treatment may ultimately be helpful to establish more complete and sustained remission. In particular because sleeping problems may trigger core symptoms while core symptoms in their turn are identified as risk factors for of depression relapse[33]. In class 1, the non-responders, joint treatment of sleep and depression treatment may be a key to remission, especially because present results showed that changes in sleep were associated with changes in core symptoms in this class. Monitoring changes in symptoms over the first months during depression treatment could suggest a direction for treatment sequencing and focus that might enhance the treatment success.

In this study the bidirectional relationship between sleep and core symptoms in depressed primary care patients with multiple repeated assessments was examined for the first time. Different classes of patients were found, namely a class of patients in which core symptoms changed independently of sleep symptoms, and two classes in which core symptoms changed simultaneously with sleep symptoms. This indicates that depressed

primary care patients who do not remit should receive more intensive and/or more specifically targeted treatment. Second, patients whose core symptoms but not sleep symptoms remit should not only be treated for depression but for their sleep disturbances as well to enhance the chance of complete remission.

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Appendix

Model Specification

The generic Manifest Markov model was estimated in Latent GOLD® (Statistical Innovations, Belmont, MA) with the following syntax:

```
variables
     caseid id1;
     dependent sla_d_w1_173, krn_d_w1_173;
     independent teller_sla_lag, teller_krn_lag;
     latent
     sla dynamic nominal 2, dep dynamic nominal 2;

equations
     sla <- (b1~tra) 1 | sla[-1] + (b2~tra) dep[-1] | sla[-1] + (b3~tra)
     teller_sla_lag | sla[-1] + (b4~tra) teller_krn_lag | dep[-1] sla[-1];

     dep <- (c1~tra) 1 | dep[-1] + (c2~tra) sla[-1] | dep[-1] + (c3~tra)
     teller_krn_lag | dep[-1] + (c4~tra) teller_sla_lag | sla[-1] dep[-1];

     sla_d_w1_173 <- (a~err) 1 | sla;
     krn_d_w1_173 <- (a~err) 1 | dep;
     a = -100;
```

In the `variables` section we define the `caseid` variable "`id1`" connecting the multiple records of a person, the `latent`, `dependent`, and `independent` variables to be used in the analysis, as well as various attributes of these variables, such as their scale types. The term "`dynamic nominal 2`" indicates that the nominal variables for sleep and core symptom may change their values over time, in two possible states. The `equations` section contains five equations. The first two equations represent each response variable. "`sla`" refers to sleep symptom and "`dep`" refers to core symptom. The logit models for both "`sla`" and "`dep`" contain an intercept (the term "`(b1~tra) 1`"), an effect of previous core symptom state (the term "`(b2~tra) dep[-1]`"), an effect of the amount of weeks the dependent symptom has been in the same state (the term "`(b3~tra) teller_sla_lag`"), and an effect of the amount of weeks the independent symptom has been in the same state (the term "`teller_krn_lag`"), all conditional on the state of sleep at the previous measurement (the term "`| sla[-1]`"). The third and fourth equation contain the term "`(a~err) 1`" which in combination with "`a = -100;`" in equation five fixes the logit parameters in the model for the response variables to -100. This yields a perfect relationship between "`sla`" and "`sla_d_w1_173`", and between "`dep`" and "`krn_d_w1_173`", assuming that no measurement error was observed.

Table S1. *Prevalence of sleep and core symptoms throughout study period*

	Core symptom present	Core symptom absent
Total (N=267)		
Sleep symptom present	7862	5804
Sleep symptom absent	2510	13155
Class 1 'the non-remitters' (N=61)		
Sleep symptom present	3846	557
Sleep symptom absent	488	256
Class 2 'the remitters' (N=127)		
Sleep symptom present	1643	1301
Sleep symptom absent	1321	10520
Class 3 'the partial remitters' (N=79)		
Sleep symptom present	2373	3946
Sleep symptom absent	701	2379

Note. N = number of participants.

Table S2. *Prevalence of the possible transitions*

	Total	Class 1	Class 2	Class 3
Sleep symptom develops	305	43	123	139
Sleep symptom disappears	398	50	187	161
Core symptom develops	257	41	114	102
Core symptom disappears	404	48	198	158

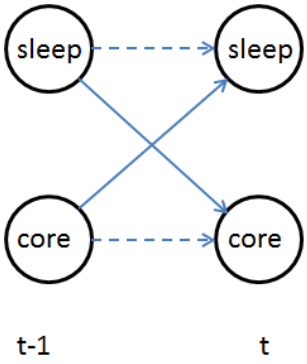

Figure S1. *Graphical representation Manifest Markov Model*

Note. Manifest Markov models were used to examine if the state of one symptom (i.e., sleep symptoms, with state 0 = absent, and state 1 = present) at time t-1 was associated with a transition in the other symptom (i.e. core symptoms, with transition possibilities from '0 = absent' to '1 = present', and from '1 = present' to '0 = absent') at time t and vice versa. Dotted lines represent transition, solid lines represent association with the transition.

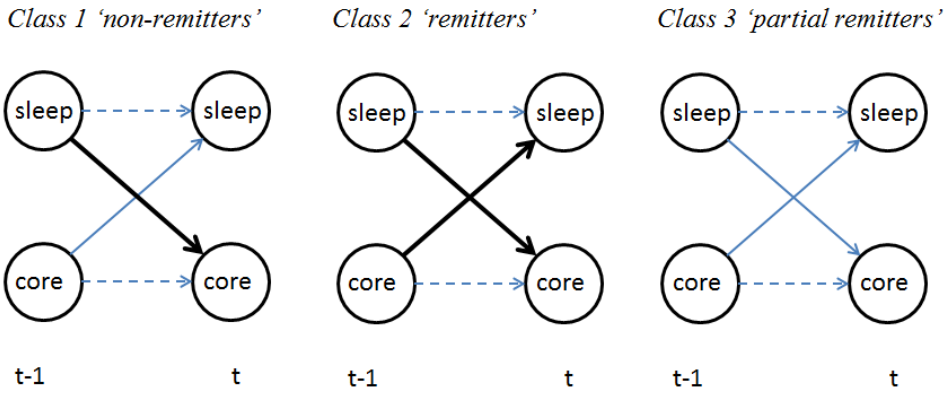

Figure S2. *Graphical representation Manifest Markov Models per class*

Note. Bold lines represent significant associations with transitions. This means that in class 1, a transition in core symptoms this week (time t) was associated with the state of sleep symptoms the previous week (t-1). In class 2, next to that, a transition in sleep symptoms this week was associated with the state of core symptoms the previous week. In class 3, no significant association with a transition was found.