Sleep Problems in Patients with Rheumatoid Arthritis

René Westhovens, Kristien Van der Elst, Ann Matthys, Michelle Tran, and Isabelle Gilloteau

ABSTRACT. ***Objective.*** To investigate sleep problems, and the relationship between sleep and disease activity, in Belgian patients with established rheumatoid arthritis (RA).

Methods. This cross-sectional, observational, multicenter study assessed sleep quality using the Athens Insomnia Scale (AIS) and Pittsburgh Sleep Quality Index (PSQI), and daytime sleepiness using the Epworth Sleepiness Scale (ESS). Additional patient-reported outcomes included visual analog scales (VAS) for fatigue and pain, the Medical Outcomes Study Short Form-36 Health Survey, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Positive and Negative Affect Schedule. Multivariate regression and structural equation modeling identified factors associated with sleep quality, with the 28-joint Disease Activity Score [DAS28-C-reactive protein (CRP)] as a continuous or categorical variable. Analyses were performed on the total population and on patients stratified by disease activity status: remission/low (DAS28-CRP ≤ 3.2) or moderate to high (DAS28-CRP > 3.2).

Results. Among 305 patients, mean (SD) age was 57.00 (12.38) years and mean (SD) disease duration was 11.77 (9.94) years. Mean (SD) AIS, PSQI, and ESS scores were 6.8 (4.79), 7.8 (4.30), and 7.3 (4.67), respectively. Mean (SD) VAS fatigue, VAS pain, and HAQ-DI were 45.22 (26.29), 39.04 (26.21), and 1.08 (0.75), respectively. There were significant positive relationships between DAS28-CRP and AIS/PSQI, but a significant negative relationship between DAS28-CRP and ESS. Several potentially confounding factors were identified.

Conclusions. Poor control of RA is associated with a reduction in sleep quality and decreased daytime sleepiness, which is likely explained by pain-related alertness. Future prospective studies are needed to confirm potential relationships between sleep quality, sleepiness, and RA treatment. (J Rheumatol First Release Dec 1 2013; doi:10.3899/jrheum.130430)

Key Indexing Terms:
SLEEP RHEUMATOID ARTHRITIS FATIGUE PAIN QUESTIONNAIRE

The primary goal of treatment of rheumatoid arthritis (RA) with disease-modifying antirheumatic drugs (DMARD) is to achieve and maintain remission or low disease activity (LDA)[1]. In RA, the effect of persistent synovitis on joint destruction and ultimately on a patient's mobility and capacity to fulfill daily activities is easily understood. However, RA may also affect other areas of a patient's life. For example, sleep disturbances are frequently reported in adults with RA[2,3]. Impaired sleep, including excessive daytime sleepiness, may lead to fatigue, which in turn may reduce work productivity, the ability to accomplish daily activities, and social functioning in patients with RA[4,5,6,7,8].

Sleep quality and daytime sleepiness are important and meaningful patient-reported outcomes (PRO)[2,3,9] that can be measured using specific, validated tools[10]. Quality of sleep, in particular, is a complex, multidimensional outcome that can be associated with 1 or more of the following components: prolonged sleep latency, lower sleep efficiency and/or an increase in the number of awakenings during the night, arousals, or wake time after sleep onset[2].

It is hypothesized that RA disease activity may be a common factor in sleep disturbances by eliciting pain and the release of cytokines that affect many neurobiologic factors[11]. Sleep disruption in RA may also be associated with other factors not related to disease activity, such as fatigue and depression[4,5,6,7,8,12,13,14,15].

The availability of biologic DMARD has improved prospects for patients with established RA, by allowing better control of pain and disease activity[16]. Further, biologic DMARD have been reported to positively influence fatigue and sleep quality in patients with RA[17,18].

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Wells, *et al*[19] applied the 12-item Medical Outcomes Study (MOS) Sleep Questionnaire in 2 abatacept trials [Abatacept in Inadequate responders to Methotrexate (AIM)[20] and Abatacept Trial in Treatment of Antitumor necrosis factor IN adequate responders (ATTAIN)[21]] to assess sleep disturbance, snoring, awakening with shortness of breath or headache, sleep adequacy, and somnolence. Across both trials, the greatest magnitude of sleep improvement occurred within the sleep disturbance domain that includes sleep initiation and sleep maintenance, factors that have been ranked as highly important by both patients and researchers[10].

However, the exact nature of the relationship between disease activity and sleep quality is not completely understood. To improve the design of future prospective studies for evaluation of sleep quality in patients with RA, a better understanding of the relationship between sleep quality and daytime sleepiness, as measured by validated tools, with disease-related aspects of RA, is needed.

Our main objective was to describe the relationship between RA disease activity and aspects of sleep quality, and to explore other potential factors associated with sleep quality. An additional objective was to assess the burden of disease in patients with RA as observed in daily clinical practice.

MATERIALS AND METHODS

Study design and recruitment. This was an observational, cross-sectional, multicenter study in a population of Belgian patients with established RA. Rheumatology clinics were invited to participate if their treatment protocols included conventional and biologic DMARD. To study a representative sample, academic, as well as nonacademic, RA clinics were invited to participate. Further, participants were categorized according to baseline disease activity level into remission/LDA [28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP) ≤ 3.2] or moderate to high disease activity (DAS28-CRP > 3.2). Next, each site was asked to include a predefined proportion of patients according to the distribution of disease activity levels, as observed in a previous Belgian population-based study — that is, 50.6% patients in remission/LDA, 35.8% with moderate disease activity (3.2 < DAS28-CRP < 5.1), and 13.6% with high disease activity (DAS28-CRP ≥ 5.1)[22].

Study population. Participants were recruited during their routine outpatient visits and were eligible if they met the following criteria: aged 18–75 years, a diagnosis of RA according to the revised 1987 criteria of the American College of Rheumatology[23], currently receiving conventional and/or biologic DMARD, fulfilled the center's predefined disease activity criteria, and able to provide written informed consent. Exclusion criteria were a past history of major depressive disorder, psychiatric illness, or substance abuse; a concurrent diagnosis of fibromyalgia (FM); a lifestyle that placed the patient at serious risk of sleep disturbances (i.e., shift work or night work); traveling through more than 3 time zones during the week before screening or during the study; a body mass index > 35 kg/m^2; sleep-related breathing disorders; restless legs syndrome; and/or periodic limb movement disorder.

This study was approved by the Medical Ethics Committee of the UZ KU Leuven.

Sociodemographic and clinical status assessment. Data were collected on the year of RA diagnosis, socioeconomic and demographic status, past and current pharmacological treatment for RA, concurrent medications (including sleep medication), medical history, and comorbidities that were recorded according to the body system affected.

RA disease activity assessment. The level of RA disease activity was assessed according to the DAS28-CRP European League Against Rheumatism response criteria[24].

Patient-reported sleep measures assessment. The Athens Insomnia Scale (AIS) is an 8-item questionnaire designed to measure sleep difficulty based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems criteria for insomnia. The first 4 items assess difficulty with sleep quantity, including sleep induction, nighttime awakenings, early morning awakenings, and total sleep duration. The fifth item relates to overall sleep quality, and the last 3 items refer to the effect of nocturnal sleep disturbance on daytime performance. Each item is scored from 0 (no problem) to 3 (very serious problem), corresponding with the experience of sleep difficulty in each item for at least 3 times a week, during the last month. Total scores range from 0 (absence of any sleep-related problem) to 24 (the most severe degree of insomnia), with a cutoff score of ≥ 6 for a diagnosis of insomnia[25,26].

The Pittsburgh Sleep Quality Index (PSQI) measures sleep quality over the past 4 weeks, using 19 of the overall 24 items. Good sleepers can be distinguished from poor sleepers through the measurement of 7 subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances (i.e., number of awakenings during the night and number of arousals), use of sleep medication, and daytime dysfunction. Each subscale is rated from 0 to 3, where 3 reflects a more severe sleep complaint. A total PSQI score ≥ 5 is indicative of a poor sleeper[27].

The Epworth Sleepiness Scale (ESS) measures excessive daytime sleepiness over the past 2 weeks. Respondents are asked how likely they are to doze in the following situations: sitting and reading, watching television, sitting inactive in a public place (e.g., a meeting), as a passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after a lunch without alcohol, and in a car while stopped for a few minutes in traffic. Each situation is scored from 0 (would never doze) to 3 (high chance of dozing). The commonly applied cutoff score of ≥ 9 was used to indicate excessive daytime sleepiness and reflects "very sleepy and should seek medical advice"[28].

Other PRO assessment. Additional PRO were measured to explore the overall burden of RA disease and their possible influence on aspects of sleep. All PRO scales included had been validated for use in the Belgian population.

Visual analog scales (VAS) were used to assess fatigue and pain. Patients were asked to rate their experience of fatigue and pain during the last week, each on a VAS of 0–100, with a higher score indicating more severe fatigue or pain[29].

Health status was assessed using the Medical Outcomes Study Short Form-36 (SF-36), a generic instrument comprising 8 dimensions: limitations in physical functioning because of health problems, limitations in social functioning because of physical or mental health problems, role limitations caused by physical health problems, role limitations caused by personal or emotional problems, bodily pain, general mental health, vitality, and general health perception[30,31].

The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used to evaluate patients' functional disability status, measuring the ability to perform daily functional activities in 8 categories: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities[32].

The Positive and Negative Affect Schedule measures respondents' experience of positive and negative emotions during the past 4 weeks. The 10-item positive affect subscale reflects emotions such as interest, determination, enthusiasm, and pride. The 10-item negative affect subscale reflects emotions such as fear, distress, hostility, and shame. Items are scored using a 5-point Likert scale (1 = very slightly or not at all, 5 = extremely)[33].

Coping with pain, defined as patients' behavioral and cognitive attempts to manage or tolerate pain, was assessed with a Coping Strategies

Questionnaire. Two global questions were answered: "having control on pain", scored between 0 (absence of control) and 6 (total control), and "ability to decrease pain", scored between 0 (cannot reduce pain) and 6 (can totally reduce pain).

Data analysis. Data were analyzed using statistical software (SAS, version 9.1; SAS Institute Inc.). Descriptive analyses are reported for all sleep quality dimensions, as well as for all PRO. Chi-squared and t tests were used to compare DAS28-CRP and sleep scale scores. A consistency check was also conducted for sleepiness as recorded by sleepiness-related questions of the AIS and PSQI (question 9 "sleepiness during the day", and question 8 "difficulty to stay awake", respectively), and each of the 8 questions/variables of the ESS. Pearson's correlation coefficients were obtained to measure the strength of the association between DAS28-CRP and each sleep quality score. Searching for outliers was performed for all variables and then values were corrected before incorporation into the regression models. Covariates listed in Table 1 were explored in the different models.

The primary analysis model consisted of the dependent variable sleep quality (operationalized as the aggregate PSQI, AIS, or ESS score) and the independent variable disease activity (measured by DAS28-CRP as a continuous or a categorical variable). Analyses were performed on the overall RA sample, as well as by disease activity status: remission/LDA (DAS28-CRP ≤ 3.2) and moderate to high (DAS28-CRP > 3.2). Variables that, in the univariate analysis, showed an association with sleep quality with a p- or F-value of ≤ 0.1 for continuous and categorical covariates, respectively, were entered separately in the multivariate models. The DAS28-CRP covariate was "forced" into multivariate models (i.e., included in the model even if p or F was > 0.1) to determine the best models (i.e., the ones with significant relationships between DAS28-CRP and sleep scores), together with the maximum number of significant additional covariates. Only covariates with at least 5% observations not equal to zero were considered for entry in the multivariate models. The strengths of the associations in logistic models were expressed using OR with 95% CI calculated for all potential factors associated with sleep quality and sleepiness. In the logistic regression models, the odds for success were determined using the following cutoffs: PSQI > 5 (vs ≤ 5), AIS ≥ 6 (median; vs < 6), and ESS ≥ 9 (vs < 9). The fit of each model was also considered for the selection of best association models (Model R^2 and p value for linear models and likelihood ratio, score, and Wald for logistic models). Collinearity between variables was assessed for the overall RA sample and each sleep questionnaire, and structural equation modeling (SEM) was performed to test the hypothesis about a relationship between the observed covariates with sleep quality scores, and to check for correlations among the study covariates. SEM was run with path analyses to achieve the best models in both significant associations and model fit compared with all other models. LINEQS was used in the models for the direct and indirect effects of the observed covariates on sleep quality scores. The findings with DAS28-CRP as a continuous variable are reported here.

Table 1. List of candidate variables in multivariate models.

Category	Variable	Measure
RA severity/disease activity	Disease duration	Mean (2008 minus year of RA + 1)
	DAS28-CRP score	Mean
	DAS28-CRP category	≤ 3.2 versus > 3.2
RA treatment characteristics	Type of RA treatment	Conventional versus biologic treatment
	DMARD treatment	Abatacept, adalimumab, etanercept, infliximab, leflunomide, methotrexate, rituximab, sulfasalazine, DMARD other 1, DMARD other 2
	DMARD treatment duration	Mean, in years
Demographic characteristics	Sex	Male versus female
	Age	Mean, ≥ 55 versus < 55 years
	BMI	Mean
	Employment status	Active, incapacitated, retired, other
	Living circumstances	Living with partner, with child, alone
	Comorbidities	1 (when patients have any) versus 0
	Concomitant medication: antidepressants, antihypertensive drugs, antiallergic drugs, glucocorticoids, pain medication, sleep medication, glucocorticoid dose	1 (patients currently taking the drugs) versus 0 (not treated + previously treated)
		None, < 5 mg, 5-10 mg, > 10 mg
	Consumption: caffeinated drinks, alcohol use, caffeinated units, alcohol units	1 (when patients have any) versus 0
		0, 1–2, 4–6, 7+
Sleep characteristics	Frequency of sleep medication (from PSQI)	Reference: 3 or more times a week versus less than once a week, not during the past month, once or twice a week
	Type of sleep complaint (from PSQI): Wake up in the middle of the night/too early, cannot get to sleep	Reference: 3 or more times a week versus less than once a week, not during the past month, once or twice a week
Patient-reported outcomes	SF-36: bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning, vitality	Mean
	HAQ-DI, VAS Pain, VAS Fatigue, PANAS P and N	Mean
	Coping control and decrease	0–2, 3, and 4–6

Antidepressant type and sleep medication type: because of the small sample size, these variables were not expected to have an effect in regression models and therefore have not been considered in the regression models. BMI: body mass index; DAS28-CRP: 28-joint Disease Activity Score (C-reactive protein); DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; PANAS P and N: Positive and Negative Affect Schedule positive and negative emotions; PSQI: Pittsburgh Sleep Quality Index; RA: rheumatoid arthritis; SF-36: Medical Outcomes Study Short Form-36 Health Survey; VAS: visual analog scale.

RESULTS

Characteristics of the study sample. A total of 307 patients from 10 Belgian sites were enrolled between June and November 2008. Two patients were not eligible for analysis because of missing data, so analyses were performed on data from 305 patients. Study population demographic and clinical characteristics at baseline are summarized in Table 2.

Table 2. Study population demographic and clinical characteristics at baseline.

Characteristic	Total, n = 305
Mean (SD) age, yrs	57.00 (12.38)
Male, n (%)	87 (28.5)
Mean (SD) BMI, kg/m^2	25.09 (4.1)*
Comorbidities, n (%)	46 (15.1)
Employment status†, n (%)	
Active	90 (29.8)
Incapacitated	84 (27.8)
Retired	64 (21.2)
Other	64 (21.2)
Mean (SD) RA disease duration, yrs	11.77 (9.94)‡
Mean (SD) DAS28-CRP	3.54 (1.5)§
DAS28-CRP categorization, n (%)	
Remission/LDA	138 (44.4)§
Moderate to high	173 (55.6)§
Current RA treatment, n (%)	
Conventional DMARD only	171 (56.4)#
Biologic DMARD¶	132 (43.6)#
Glucocorticoids	138 (45.8)††
Sleep medication, n (%)	
Never	217 (71.1)
Currently	58 (19.0)
Concurrent medication, n (%)	
Antidepressants	37 (12.1)
Antidepressant type: sedative	13 (35.1)‡‡
Antiallergy medication	11 (3.6)
Analgesia	149 (48.9)
Antihypertensives	74 (24.3)
Concurrent consumption, n (%)	
Caffeinated drinks	245 (84.2)§§
Alcohol	148 (50.2)‡

* n = 293. † Incapacitated included sick leave, early retirement, permanently invalid, n = 302. Other includes unemployed, at home, not known. ‡ n = 295. § n = 311. ¶ Biologic DMARD includes abatacept, adalimumab, etanercept, infliximab, and rituximab. # n = 303. †† n = 301. ‡‡ n = 37 (current antidepressant users only). §§ n = 291. BMI: body mass index; DAS28-CRP: 28-joint Disease Activity Score (C-reactive protein); DMARD: disease-modifying antirheumatic drug; LDA: low disease activity; RA: rheumatoid arthritis.

Sleep quality and its relationship with disease activity. Mean (SD) sleep quality scores were PSQI 7.8 (4.30), AIS 6.8 (4.79), and ESS 7.3 (4.67).

Correlation analysis. Pearson correlation revealed a statistically significant correlation between DAS28-CRP and AIS, as well as between DAS28-CRP and PSQI (Table 3), but no correlation between DAS28-CRP and ESS.

Consistency of questionnaires for sleepiness results. The cross-check of sleepiness items between the 3 sleep questionnaires confirmed the accuracy of the results. Table 4 shows an example of this consistency check for the ESS variable "sitting quietly after a lunch without alcohol". The higher the chance of dozing as measured on the ESS, the higher the frequency of daytime sleepiness and the greater the difficulty of staying awake as reported in the AIS and PSQI questionnaires, respectively.

Regression analysis. Using the AIS and PSQI scales, DAS28-CRP was significantly associated with poor sleep quality in univariate (Table 5A and B) and adjusted multivariate (Table 5C and D) linear and logistic regression analyses. DAS28-CRP and sleep quality were inversely related: as DAS28-CRP increased, AIS and PSQI scores worsened. Using the ESS, DAS28-CRP did not have a significant association with daytime sleepiness in univariate analyses, but had a significant inverse effect on excessive sleepiness in both multivariate linear and logistic regression models. As DAS28-CRP increased, level of excessive daytime sleepiness decreased.

DAS28-CRP was significantly associated with sleep quality after excluding from the multivariate models the covariates of AIS and PSQI that were highly suspected of collinearity (pain and all SF-36 variables for AIS; fatigue and all SF-36 variables for PSQI). Conversely, the full models, including all ESS covariates, provided the strongest association between DAS28-CRP and excessive sleepiness.

Other factors associated with sleep quality and excessive daytime sleepiness included positive and negative affect, comorbidities, caffeinated drinks, glucocorticoids, sleep medication, and some subdomains of the SF-36 (general health, mental health, role physical, and vitality; Table 5C and D). Negative affect was found to be positively associated with excessive sleepiness and poor sleep quality with DAS28-CRP, indicating that an increase in negative

Table 3. Correlation between Disease Activity Score 28-joint C-reactive protein and sleep quality scores.

Scale	No. Patients	Pearson Correlation Coefficient (95% CI)	p
AIS	294	0.277 (0.168 to 0.380)	< 0.0001
PSQI	278	0.241 (0.127 to 0.349)	< 0.0001
ESS	291	0.047 (–0.068 to 0.161)	0.4214

AIS: Athens Insomnia Scale; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index.

Table 4. Consistency between Epworth Sleepiness Scale (ESS) variables and Athens Insomnia Scale (AIS; question 9)/ Pittsburgh Sleep Quality Index (PSQI; question 8) for sleepiness items. Example: sitting quietly after a lunch without alcohol.

ESS Chance of Dozing	AIS Q9 (Sleepiness Frequency)	Frequency	Percentage	PSQI Q8 (Sleepiness Frequency)	Frequency	Percentage
No chance,	—	2	1.4	—	2	1.4
n = 143	None	65	45.5	No difficulty	105	73.4
	Mild	68	47.6	Some difficulty	22	15.4
	Considerable	7	4.9	Much difficulty	9	6.3
	Intense	1	0.7	Unable to do	5	3.5
Slight chance,	—	2	2.3	—		
n = 89	None	23	25.8	No difficulty	43	48.3
	Mild	55	61.8	Some difficulty	29	32.6
	Considerable	8	9.0	Much difficulty	12	13.5
	Intense	1	1.1	Unable to do	5	5.6
Moderate chance,	—	1	2.6	—		
n = 38	None	9	23.7	No difficulty	15	39.5
	Mild	15	39.5	Some difficulty	11	29.0
	Considerable	10	26.3	Much difficulty	10	26.3
	Intense	3	7.9	Unable to do	2	5.3
High chance,	None	2	9.5	No difficulty	8	38.1
n = 21	Mild	6	28.6	Some difficulty	3	14.3
	Considerable	9	42.9	Much difficulty	3	14.3
	Intense	4	19.1	Unable to do	7	33.3

Dashes indicate missing data.

affect worsens sleepiness and sleep quality. Both duration of RA disease and type of RA treatment (conventional vs biologic DMARD) were not associated with sleep quality or excessive sleepiness. Interestingly, coping with pain and HAQ-DI were significantly associated with sleep quality in univariate analyses but not in the multivariate models with ESS, AIS, and PSQI. DAS28-CRP as a categorical variable was also found to be associated with sleep quality, with patients achieving remission/LDA status presenting significantly better sleep quality scores and higher levels of daytime sleepiness than patients with moderate to high disease activity status. Results of the multivariate models were confirmed using SEM (Appendix 1,2,3). Pain had a significant indirect effect, through disease activity, on sleep quality as assessed using the PSQI, and on daytime sleepiness assessed using the ESS. This was not observed in the multivariate analyses.

Burden of disease. Data for non-sleep PRO are presented in Table 6. Additional analyses by DAS status showed a significant increase in burden with moderate to high disease activity versus remission/LDA for all PRO (data not shown).

DISCUSSION

The results of our study indicate a positive and independent association between disease activity and sleep quality in patients with established RA representative of those routinely attending rheumatology clinics in Belgium. The relatively high use of biologic drugs indicates a patient population with severe RA that was regularly followed up by a rheumatologist. An inverse relationship between disease activity and daytime sleepiness was also observed.

Mean sleep quality scores indicated notable sleep disturbances in this population, and crossed threshold scores for "poor sleeper" (PSQI) and "insomnia" (AIS). However, despite bad nighttime sleep, these patients did not seem to experience daytime sleepiness (ESS). All demographic variables were modeled for their relationship with sleep quality. Sex, employment status, DMARD treatment, caffeine or alcohol, and concurrent medication were significantly associated with sleep quality in univariate models, but not in multivariate models.

Consistent with the literature[34], our study has identified factors in addition to disease activity that may influence sleep in patients with RA, such as the experience of positive/negative emotions, general health, mental health, and vitality, which could also be included in future prospective studies to evaluate the effect of RA treatment on sleep problems in such patients.

While biologic DMARD may have similar effects on disease control[35], different results for PRO may occur. Studies on the effects of biologics on aspects of sleep in patients with RA include patients treated with abatacept (as discussed earlier[18,19]), infliximab[36,37], and tocilizumab[38]; such studies may also aid our understanding of the pathophysiologic mechanisms contributing to sleep disturbance in patients with RA. Zamarrón, *et al*[36] evaluated the effect of infliximab on sleep and alertness in 6 patients with active

Table 5. Linear associations between sleep quality scores and covariates.

(A) Univariate linear regression models between sleep quality scores and DAS28-CRP as a continuous variable.

	ESS			AIS			PSQI		
	Estimate	p	Model R^2	Estimate	p	Model R^2	Estimate	p	Model R^2
DAS28	Relationship not statistically significant			0.898	< 0.0001	0.0769	0.69459	< 0.0001	0.0580

(B) Univariate logistic regression models between sleep quality scores and DAS28-CRP as a continuous variable.

	ESS		AIS		PSQI	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
DAS28	Relationship not statistically significant		1.300 (1.104–1.530)	0.0016	1.409 (1.173–1.692)	0.0002

(C) Multivariate linear regression models by sleep scale with DAS28-CRP as a continuous variable.

ESS	Estimate R^2 = 0.235 p < 0.0001 n = 264	p	AIS	Estimate R^2 = 0.437 p < 0.0001 n = 286	p	PSQI	Estimate R^2 = 0.391 p < 0.0001 n = 274	p
DAS28	–0.507	0.0248	DAS28	0.478	0.0034	DAS28	0.336	0.0269
PANAS Score N	0.144	0.0084	Concurrent medication: glucocorticoids	0.976	0.0417	Sleep medication	3.245	< 0.0001
SF-36 General Health	0.220	0.0213	Comorbidities	1.588	0.0152	Living with partner	–1.017	0.0376
SF-36 Mental Health	0.238	0.0499	PANAS Score N	0.224	< 0.0001	PANAS Score N	0.182	< 0.0001
SF-36 Vitality	–0.283	0.0478	PANAS Score P	–0.096	0.0028	PANAS Score P	–0.069	0.0250

(D) Multivariate logistic regression models by sleep scale with DAS28-CRP as a continuous variable.

ESS	OR (95% CI) n = 261 LR < 0.0001 Score < 0.0001 Wald = 0.0021	p	AIS	OR (95% CI) n = 286 LR < 0.0001 Score < 0.0001 Wald = 0.0001	p	PSQI	OR (95% CI) n = 270 LR < 0.0001 Score < 0.0001 Wald = 0.0003	p
DAS28	2.388 (1.142–4.993)	0.0207	DAS28	1.229 (1.002–1.508)	0.0483	DAS28	1.348 (1.058–1.718)	0.0157
PANAS Score N	1.105 (1.035–1.180)	0.0029	Comorbidities	2.324 (1.023–5.277)	0.0439	Sleep medication	16.741 (3.607–77.700)	0.0003
SF-36 General Health	1.154 (1.025–1.298)	0.0174	Caffeinated drinks	2.297 (1.017–5.183)	0.0453	PANAS Score N	1.106 (1.049–1.166)	0.0002
SF-36 Mental Health	1.205 (1.034–1.403)	0.0167	PANAS Score N	1.097 (1.050–1.146)	< 0.001			
SF-36 Role Physical	0.865 (0.759–0.984)	0.0280	PANAS Score P	0.961 (0.924–0.999)	0.0466			
SF-36 Vitality	0.813 (0.679–0.972)	0.0234						

For multivariate linear and logistic regression models, only factors found to be significantly associated with sleep quality are presented. For multivariate linear regression models: covariate estimate > 0: increase of the covariate leads to an increase of sleep quality score (worsens sleepiness); covariate estimate < 0: increase of the covariate leads to a decrease of sleep quality score (improves sleepiness). For multivariate logistic regression models: OR < 1: means that the variable reduces the risk of having poor sleep quality and denotes a negative relationship of the covariate with the risk of having excessive daytime sleepiness; OR > 1: means that the variable increases the risk of having poor sleep quality and denotes a positive relationship of the covariate with the risk of having excessive daytime sleepiness. AIS: Athens Insomnia Scale; DAS28-CRP: 28-joint Disease Activity Score (C-reactive protein); ESS: Epworth Sleepiness Scale; LR: likelihood ratio; PANAS P and N: Positive and Negative Affect Schedule positive and negative emotions; PSQI: Pittsburgh Sleep Quality Index; SF-36: Medical Outcomes Study Short Form-36 Health Survey.

RA. Abnormalities in sleep and alertness improved the day after the first infusion of infliximab. This prompt response, not related to amelioration of joint discomfort, suggests a key role for tumor necrosis factor-α in sleep disturbance[36]. Further, an increased number of apneic events was reported following infliximab treatment in a patient with obstructive

Table 6. Burden of RA: non-sleep patient-reported outcomes. Data are mean (SD) unless otherwise indicated.

Instrument		Measure of Burden
HAQ-DI score*		1.08 (0.75)
PANAS negative†		19.40 (7.79)
PANAS positive†		31.65 (7.80)
VAS fatigue‡		45.22 (26.29)
VAS pain‡		39.04 (26.21)
SF-36	Bodily pain§	6.96 (2.19)
	General health†	14.75 (3.89)
	Mental health†	17.45 (4.30)
	Physical function†	21.29 (5.10)
	Vitality†	12.31 (3.39)
	Role physical¶	12.23 (4.11)
	Social functioning†	7.50 (2.13)
	Role emotional¶	10.96 (3.41)
Coping with pain, n (%)	0–2	43 (14.4)
(0: absence of control; 3: average	3	110 (36.8)
control; 6: total control)#	4–6	146 (46.8)
Ability to decrease pain, n (%)	0–2	62 (20.9)
(0: can't reduce pain; 3: in certain way;	3	131 (44.1)
6: can totally reduce pain)††	4–6	104 (35.0)

* n = 303. † n = 302. ‡ n = 294. § n = 301. ¶ n = 300. # n = 299. †† n = 297. HAQ-DI: Health Assessment Questionnaire-Disability Index; PANAS: Positive and Negative Affect Schedule; RA: rheumatoid arthritis; SF-36: Medical Outcomes Study Short Form-36 Health Survey; VAS: visual analog scale.

sleep apnea[37]. In a tocilizumab study of 15 patients with RA experiencing sleep disturbances, improvement in sleep quality and reduction in daytime sleepiness were reported[38]. The changes in PSQI score over time were not associated with changes in disease activity, suggesting a direct influence of interleukin 6 on sleep disturbance.

Sleep disturbances are common and occur frequently in a number of chronic diseases, as well as in the general population. This study excluded patients with sleep problems inherent to specific comorbidities or patients at risk of sleep troubles for known reasons other than RA. However, it cannot be discounted that sleep quality in patients with RA may be affected by causes that also affect sleep in a healthy population, such as non-RA-related stress. Although sleep results may have been biased by patients taking sleep medication or sedative antidepressants, only small numbers of patients taking such drugs were included in the study population.

Instruments for assessing sleep quality in RA have previously been tested, for example the MOS Sleep Measure, the Pittsburgh Sleep Diary, and the Women's Health Insomnia Rating Scale[10]. These instruments were identified by OMERACT (Outcome Measures in Rheumatology) as being potentially applicable to patients with RA[10,39]. Both the AIS and the MOS Sleep Measure scored high on truth (content validity) and feasibility (administrative burden and applicability)[10]. Here, we tested 3 validated, non-disease-specific, patient-reported sleep questionnaires frequently used in clinical trials. Our study findings support the use of the PSQI and AIS as tools to assess sleep quality in patients with RA. In contrast to the PSQI and AIS, the ESS did not discriminate between patients with high versus low DAS28-CRP. One potential explanation for this is that patients in remission/LDA had limited sleep problems at night, making them less likely to be sleepy during the day, while patients with moderate to high disease activity experienced the same local and systemic inflammation during the day that disturbed their sleep at night. The measurement of specific aspects of sleep and the fact that different instruments may measure different aspects of sleep may also help explain these differences in discrimination. Analyses with DAS28-CRP as either a continuous or categorical variable were very consistent, confirming the robustness of the study findings.

The negative association between DAS28-CRP and daytime sleepiness may also be explained by an increased level of pain in RA leading to increased alertness. SEM was performed to enhance the multivariate regression models, as well as to identify potential indirect effects that may explain the relationship between disease activity and sleep quality, and revealed that, while pain did not have a significant direct effect on sleep quality or sleepiness, it did have an indirect effect through disease activity. This reinforces our potential explanation on the negative relationship between disease activity and sleepiness. We found that the more active the disease, the less sleepy the patients were, certainly

because of increased alertness due to pain. However, in other chronic pain conditions, such as FM, patients also experience daytime sleepiness[40]. This is an interesting finding that suggests that there may be differential associations between sleep problems and complaints of fatigue in different conditions associated with chronic pain.

Potential confounding factors in the association between disease activity and sleep components identified in this exploratory study may be important to consider in future prospective investigations. For instance, significant relationships between disease activity and non-sleep covariates (e.g., pain, fatigue, some domains of the SF-36 or HAQ-DI) in univariate models (data not shown) disappeared when adjusting for covariates in multivariate models, suggesting potential overlap between the different PRO used in the models or between PRO and DAS28-CRP.

The strengths of our study were the multiple variables tested in the different models, the use of a representative real-world population, the use of several validated and commonly used sleep questionnaires, and the multiple statistical tests performed, including SEM. Limitations include possible bias in the selection of the variables in the models and the cross-sectional design of the study, which make it impossible to establish cause and effect in the associations examined. Also, the study was not designed to make comparative analyses across RA treatments, something that should be investigated. An extensive validation of the content of the different sleep measurements to be used in RA studies would also be of value in further research, to help select the most appropriate tool.

Our study in patients with established RA undergoing treatment in routine clinical practice in Belgium suggests that poor control of disease activity alters sleep quality. A negative association between DAS28-CRP and excessive daytime sleepiness is probably explained by an increased level of pain and inflammation leading to increased alertness. These findings support the use of the PSQI and AIS as valid tools to assess sleep quality in patients with RA; however, the ESS requires further investigation. Possible patient-related confounders have been identified and need to be explored in prospective research. Our study provides data to inform the design of such future studies to evaluate the effect of different treatments for RA on sleep.

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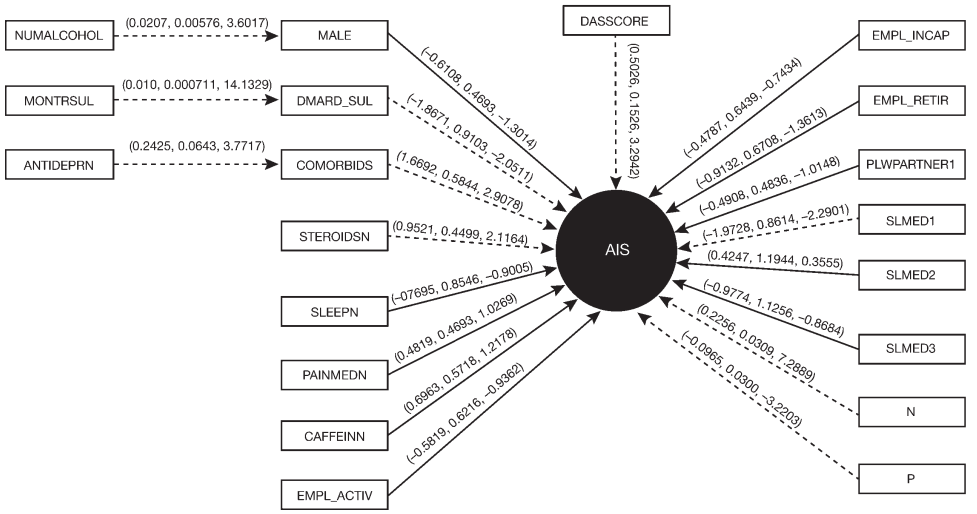
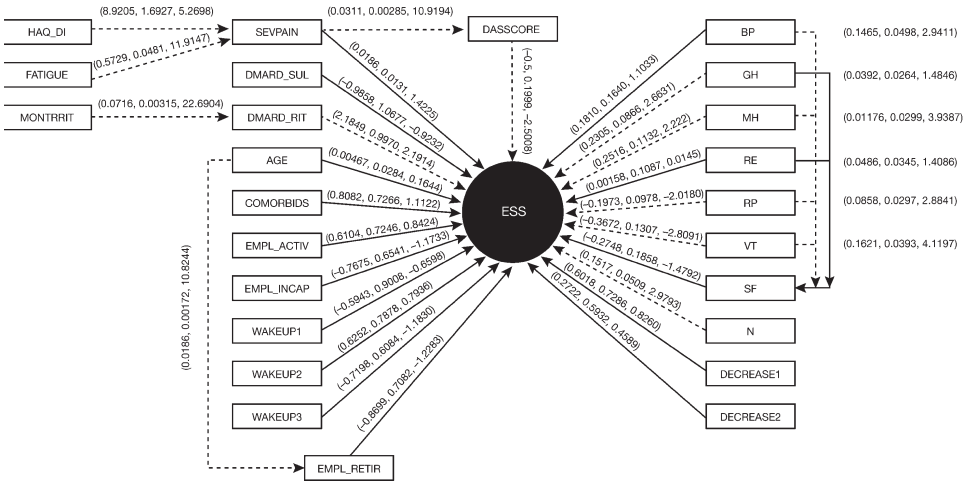
APPENDIX 1. Best structural equation models with 28-joint Disease Activity Score-C-reactive protein (DAS28-CRP) as a significant predictor. Athens Insomnia Scale (AIS).



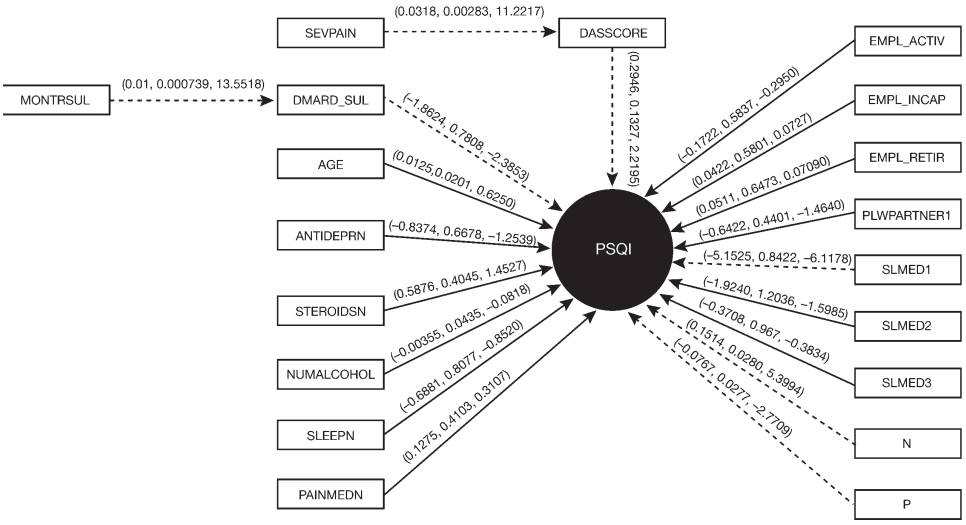
Goodness-of-fit index = 0.9773 (> 0.95 good fit), chi-square = 75.90 with degrees of freedom = 54 and p = 0.0263 rejected at 0.01 level only, not 0.05 level; root mean square error of approximation = 0.0374 (< 0.05 good fit). The best model for AIS has DAS28 score (DASSCORE), sulfasalazine treatment (DMARD_SUL), comorbidities (COMORBIDS), steroids (STEROIDSN), use of sleep medication less than once a week during the past 30 days to help sleep (SLMED1), PANAS N (N) and PANAS P (P; Positive and Negative Affect Schedule positive and negative emotions) as significant predictors for AIS. The model also contains indirect effects of duration of sulfasalazine treatment (MONTRSUL) to sulfasalazine treatment (DMARD_SUL), antidepressant use (ANTIDEPRN) to comorbidities (COMORBIDS), and frequency of alcohol consumption (NUMALCOHOL) to sex (MALE).

APPENDIX 2. Best structural equation models with 28-joint Disease Activity Score-C-reactive protein (DAS28-CRP) as a significant predictor. Epworth Sleepiness Scale (ESS).



Goodness-of-fit index = 0.9284 (acceptable fit), chi-square = 321.57 with degrees of freedom = 102 and p < 0.0001 (not acceptable fit), root mean square error of approximation 0.0893 (just acceptable fit). The best model for ESS has DAS28 score (DASSCORE) as significant predictor, along with rituximab treatment (DMARD_RIT), Medical Outcomes Study Short Form (SF-36) General Health (GH), SF-36 Mental Health (MH), SF-36 Role Physical (RP), SF-36 Vitality (VT), SF-36 Social Functioning (SF), and PANAS N (Positive and Negative Affect Schedule positive and negative emotions). The model also contains indirect effects of pain (SEVPAIN) to DAS28 score (DASSCORE), duration of rituximab treatment (MONTRRIT) to rituximab treatment (DMARD_RIT), Health Assessment Questionnaire-Disability Index (HAQ_DI), and fatigue (FATIGUE) to pain (SEVPAIN), age (AGE) on retirement from work (EMPL_RETIR), as well as SF-36 Bodily Pain (BP), SF-36 Role Physical (RP), and SF-36 Vitality (VT) to SF-36 Social Functioning (SF).

APPENDIX 3. Best structural equation models with 28-joint Disease Activity Score-C-reactive protein (DAS28-CRP) as a significant predictor. Pittsburgh Sleep Quality Index (PSQI).



Goodness-of-fit = 0.9848 (good fit), chi-square = 42.4024 with degrees of freedom = 35 and p = 0.1821 (good fit), root mean square error of approximation = 0.0281 (good fit). The best SEM model also has DAS28 score (DASSCORE) as significant predictor for PSQI, along with sulfasalazine treatment (DMARD_SUL), use of sleep medication less than once a week during the past 30 days to help sleep (SLMED1), PANAS N (N), and PANAS P (P; Positive and Negative Affect Schedule positive and negative emotions). The model also contains indirect effects of pain (SEVPAIN) to DAS28 score (DASSCORE) and duration of sulfasalazine (MONTRSUL) to sulfasalazine treatment (DMARD_SUL).

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