Sleep disturbance in patients with rheumatoid arthritis is related to fatigue, disease activity, and other patient-reported outcomes

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Objectives: To explore factors related to sleep disturbance in patients with rheumatoid arthritis (RA).

Method: Cross-sectional data from 986 patients in the Oslo RA Register (ORAR) collected in 2009 were included. Sleep problems were assessed by four measures: the Medical Outcomes Study (MOS) sleep disturbance scale, and the sleep components of the Rheumatoid Arthritis Impact of Disease (RAID) score, the Multi-Dimensional Health Assessment Questionnaire (MDHAQ), and the 15-dimensional quality of life questionnaire (15D). Patient-reported outcomes (PROs) were recorded using standard questionnaires for physical and mental function [the HAQ and the MOS 36-item Short-Form Health Survey (SF-36), disease activity (the RA Disease Activity Index, RADAI), utility (SF-6D), and visual analogue scales (VAS) for pain, fatigue, and disease activity]. Demographics including comorbidity were collected. Information on use of medication for RA and sleep disturbance was obtained using checklists. Multivariate analyses were used to identify factors independently associated with sleep problems by four different measures.

Results: The mean (standard deviation, SD) age of the patients was 59.4 (12.5) years, 76.9% were females, and the mean (SD) disease duration was 13.7 (10.7) years. The correlation between the various sleep measures was high (r² = 0.71–0.78). Sleep disturbance was moderately correlated to pain (r² = 0.41–0.61), fatigue (r² = 0.44–0.58), physical function (r² = 0.33–0.48), RADAI (r² = 0.42–0.55), and utility (r² = 0.49–0.61). RAID sleep demonstrated the highest correlation with other PROs. RADAI, fatigue, the mental component score of SF-36, physical function, body mass index (BMI), and use of Z-drugs/benzodiazepines were independently associated with two or more measures of sleep problems (all p < 0.001).

Conclusions: Sleep disturbance measured by four different measures was independently related to other PROs including fatigue, pain, and disease activity in RA patients.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease of the joints with synovitis, joint pain, joint swelling, and disability (1, 2). The Outcome Measures in Rheumatology (OMERACT) has identified sleep as one of the key outcomes important to RA patients (3–6). Sleep loss may exacerbate fatigue and pain in RA (7, 8), and pain may cause sleep disturbance (8–11). Sleep disturbance is a disruption or deviation from a normal sleep pattern that may include difficulty falling asleep, poor quality sleep, non-restorative sleep, numerous nightly awakenings, early morning awakening, excessive daytime sleepiness, and fatigue (12). Fatigue may be physical (physical exhaustion or reduced energy) or cognitive (problems with thinking, concentration, or memory) (13). Sleep disturbance has been reported in a number of rheumatic diseases including RA (12), and a bidirectional relationship between sleep disturbance and fatigue has been demonstrated (10). There are studies demonstrating that depression and anxiety are the strongest correlates with fatigue (p < 0.001), with no significant associations with pain, Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire (HAQ) score, or radiographic damage (14). Other studies have demonstrated impaired sleep quality by pain, disease activity, fatigue, and depression (15, 16). Poor RA disease control has been associated with reduced sleep quality and daytime sleepiness (17). Patients with various immune-mediated inflammatory diseases, including RA, have reported disturbed sleep and fatigue further adding to disease burden (7, 18).

As a consequence of these factors, patients may enter into a vicious circle of pain, sleep disturbance, and fatigue with resultant reduced quality of life. Despite being important to these patients, sleep has been infrequently reported in results from clinical trials in RA (19). The Medical Outcomes Study (MOS) sleep disturbance scale has been validated for use in RA (20); however, this is not the case for the sleep components of some of the...
questionnaires used to measure patient-reported outcomes (PROs) in RA patients, for example the RA Impact of Disease (RAID) score, the Multi-Dimensional Health Assessment Questionnaire (MDHAQ), and the 15-dimensional quality of life questionnaire (15D). RAID takes into account seven aspects of RA considered important by the patients, one of these aspects being sleep quality (21). The MDHAQ, a modification of the Health Assessment Questionnaire (HAQ), includes one question to assess sleep (22), and 15D contains one question regarding sleep (23). There is a lack of knowledge with respect to how these four different measures of sleep disturbance correlate, and whether or not the association between PROs and sleep disturbance in RA is consistent. The Oslo RA register (ORAR) offered the opportunity to perform these investigations in a large patient population and add valuable knowledge about a patient group representative of the issues clinicians face in daily clinical practice (19).

The aims of our study were to describe sleep disturbance in patients with RA, examine correlations between different measures of sleep disturbance in RA, explore disease-specific and generic measures to identify factors independently associated with sleep disturbance, and investigate whether the four sleep measures used in this study were consistently related to other measures of disease burden in RA.

Method

Study population

Patients with RA living in Oslo were included in ORAR, a large, representative and community-based register estimated 85% complete for patients with RA in the Oslo area (24, 25). Data on a number of PROs were collected in this RA population displaying the broad spectrum of disease seen in daily clinical practice, thus providing an ideal opportunity to investigate sleep disturbance and identify factors associated with sleep disturbance in RA. The present cross-sectional study includes 986 (76.9% females, response rate 59.7%) RA patients responding to a postal survey in 2009 (26).

Patient demographics

Information on age, gender, disease duration [years since fulfilment of 1987 American College of Rheumatology (ACR) criteria] (27), and seropositivity for rheumatoid factor (RF)/anti-cyclic citrullinated peptide (anti-CCP) antibodies was extracted from the database. Patients were asked about education (range 7–17 years), and body mass index (BMI) was calculated from height and weight (kg/m²). Comorbidity was recorded from one item of the Arthritis Impact Measurement Scales 2 (AIMS2) (28) and for the purpose of this study coded present or absent. Smoking was recorded as current smoker yes/no.

PRO measures

In the context of OMERACT, four sleep questionnaires applicable for use in RA (MOS sleep measure, the Pittsburgh Sleep Diary, the Athens Insomnia Scale, and the Women’s Health Insomnia Rating Scale) were found feasible, reliable, valid, and responsive (29). The MOS sleep measure scored high on truth and feasibility and was found to display good psychometric properties in assessing sleep disturbance in RA (29). The sleep disturbance subscale of MOS sleep was found to be valid, reliable, and sensitive to change in RA when used by Wells et al to investigate sleep quality in RA patients (20). After being validated for use in RA, the sleep disturbance scale was included in the ORAR questionnaire.

Questions on sleep disturbance are included in some of the questionnaires already in use in studies of PROs, such as the MDHAQ, RAID, and 15D. The sleep measures are further described under the appropriate sections of the questionnaires they originated from.

The MOS 36-item Short-Form Health Survey (SF-36) is a generic measure of eight health dimensions (physical and social functioning, role-physical, bodily pain, general health, vitality, role-emotional, and mental health), range 0–100 (0 = worst possible health state, 100 = perfect health) (30). Mental (MCS) and physical (PCS) component summary scores were calculated from SF-36. Utility (SF-6D) was derived from SF-36 (31), range 0.29–1, where a living person will obtain a score between ≥ 0.29 and 1.00 (1.00 denotes perfect health) (32). MOS-Sleep consists of 12 questions (six-point Likert scale) from which the sleep disturbance subscale was calculated using four of the 12 questions (range 0–100, 100 = worst) (33).

RAID is a seven-item RA-specific questionnaire capturing pain, quality of sleep, fatigue, physical and emotional well-being, functional capacity, and coping (range 0–10, 0 = no pain/difficulty, 10 = extreme pain/difficulty) (21, 34, 35). An overall RAID score was computed using standard weight of domains: pain 0.21, functional disability 0.16, fatigue 0.15, sleep difficulties 0.12, emotional well-being 0.12, physical well-being 0.12, and coping 0.12 (21). Minimum Clinically Important Improvement (MCII) for RAID has been suggested (36), and a maximal value of 2 has been suggested as defining acceptable status (36).

The HAQ is an extensive measure of physical function with 20 questions across eight categories of activities of daily living (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and ‘common daily activities’) (37). The modified HAQ (MHAQ) and MDHAQ are shortened versions of the HAQ with one question from each of the eight categories (37, 38).
Box 1. Outcome variables measuring sleep disturbance in the Oslo Rheumatoid Arthritis Register (ORAR).

### MOS sleep disturbance scale
How long did it usually take for you to fall asleep during the past 4 weeks?
Circle one of the options: 1) 0–15 minutes, 2) 16–30 minutes, 3) 31–45 minutes, 4) 46–60 minutes, 5) more than 60 minutes
How often during the past week did you...
- Feel that your sleep was not quiet (e.g. moving restlessly, feeling tense, speaking while sleeping)?
- Have trouble falling asleep?
- Awaken during your sleep time and have trouble falling asleep again?
For each question circle one option: 1) all of the time, 2) most of the time, 3) a good bit of the time, 4) some of the time, 5) a little of the time, and 6) none of the time.

### RAID sleep
Select the number that best describes the sleep difficulties (i.e. resting at night) you felt due to your rheumatoid arthritis during the last week
[Numeric rating scale (NRS) 0–10; 0 = no difficulty, 10 = extreme difficulty]

### MDHAQ sleep
Within the last week were you able to get a good night’s sleep?
Circle one of the options: 0) without problems; 1) with some problems; 2) with major problems; 3) unable to)

### 15D sleep
Which statement describes your current state best?
I am able to sleep normally, i.e. I have no problems with sleeping
I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night
I have moderate problems with sleeping, e.g. disturbed sleep or feeling I have not slept enough
I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning
I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night

MDHAQ contains five additional questions including one on sleep (Box 1) (39). The HAQ and MDHAQ have been validated in Swedish, which is similar to Norwegian (40, 41). The HAQ, MHAQ, and MDHAQ are scored on a scale from 0 to 3 (0 = no problems, 3 = unable to do).

The 15D is a generic, standardized, comprehensive, 15-dimensional [breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression], self-administered measure of health-related quality of life (HRQoL) that can be used both as a profile and as a single index score measure (23). Each dimension is divided into five levels (1 = no problem/normal function, 5 = unbearable symptoms/unable to do). The single index score (0–1 scale) represents the overall HRQoL with the maximum score 1 (best) and minimum score 0 (worst).

Pain, fatigue, and patient global assessment of disease (PtGA) were recorded using 100-mm visual analogue scales (VAS), range 0–100 (0 = no symptoms, 100 = worst possible symptom).

The RA Disease Activity Index (RADAI) is a patient-reported measure of disease activity without the need for clinical examination or blood tests (42). The RADAI contains questions on disease activity, joint tenderness and pain, duration of morning stiffness, and area of pain. RADAI has been found to correlate significantly to the HAQ score and the Disease Activity Score with 28-joint counts (DAS28) (42, 43). The DAS28 includes 28 tender and swollen joint counts, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and PtGA on a 0–100 VAS. DAS28 calculators can be found at [www.das-score.nl](http://www.das-score.nl).

The EuroQol measure EQ-5D provides a single index value for the five health dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the present study we used the three-level version (EQ-5D-3L), scale 0–1 (0 = death, 1 = full health), which has been validated in RA patients (44).

Alphabetical checklists queried the use of synthetic (sDMARDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs), glucocorticosteroids, benzodiazepines, and non-benzodiazepine hypnotic drugs (Z-drugs). The use of benzodiazepines and Z-drugs was combined into one variable for the purpose of multivariate analyses because of the small numbers and some overlap in use.

### Statistics
Descriptive statistics present continuous variables as means with standard deviations (SD) or medians with 25th–75th percentiles. Categorical variables are presented as counts and percentages. To test for group differences we used the two-sample independent t-test for continuous variables, and the χ² test for proportions. Pearson correlation coefficients were calculated within the four outcome variables measuring sleep as well as between-sleep variables and the other PROs.

We used univariate linear regression analysis to identify variables associated with sleep disturbance (sleep disturbance scale, MDHAQ sleep, RAID sleep, and 15D sleep). Candidate variables (p < 0.20) were then entered into multivariate general linear models together with the prespecified exogenous confounding factors age, gender, and disease duration. Further selection of...
variables was performed using forward and backwards selection, with the robustness of the final models checked by reintroduction of dropped variables. When more than one variable measuring the same domain was available (e.g. physical function with HAQ, MHAQ, and PCS), we performed separate analyses with each of the variables. The variable contributing the most to the final models was kept (e.g. MHAQ for physical function).

We used adjusted R², the proportion of variance in the dependent variable explained by the final model, as a measure of goodness of fit. The model assumptions were assessed using residual plots. The amount of missing data was low (less than 5%). Missing data were assessed as missing completely at random (MCAR), and no further adjustments were made. SPSS version 21 (IBM SPSS, Chicago, IL, USA) was used for the analyses, and two-tailed p < 0.05 was regarded as statistically significant.

Results

For all 986 patients, demographics and disease characteristics are presented in Table 1. The patients were predominantly females (76.9%) with a mean (SD) age of 59.4 (12.5) years and disease duration of 13.7 (10.7) years. Self-reported disease activity (PfGA VAS and RADAI) and the use of prednisolone, sDMARDs, and bDMARDs were similar between genders and in the two groups. We enquired about use of medication in the questionnaire. The mean (median, 25th–75th percentiles) values for MOS sleep disturbance scale, RAID sleep, MDHAQ sleep, and 15D sleep were 32.3 (27.5, 10.0–50.0), 2.97 (2.0, 0.0–5.0), 0.76 (1.0, 0.0–1.0), and 2.1 (2.0, 1.0–3.0), respectively (Table 1).

Correlations between the different sleep measures were high (r = 0.71–0.78) (Table 2). We did not observe any correlations between the four sleep measures and age, disease duration, education, or BMI (r ≤ 0.20); there were low correlations (r = 0.2–0.5) to most of the other PROs while correlation with RAID total was moderate (r = 0.55–0.60). RAID sleep demonstrated a slightly higher correlation to all PROs than the other sleep measures in this study (Table 2). Correlation between RAID total and RADAI was 0.82 (p < 0.001; data not included).

Table 3 presents factors independently associated with different sleep measures in RA. The results are presented separately for univariate and multivariate analyses. RADAI, fatigue, MCS, and use of Z-drugs + benzodiazepines (Z+benzo) were significant contributors in all multivariate models, while other variables [e.g. BMI, MHAQ, VAS for pain (VAS Pain), patient global VAS, and utility] did not contribute in all models. Repeating the univariate and multivariate analyses with the combined Z+benzo variable vs. using Z-drugs or benzodiazepines as separate variables made no, or only marginal, changes to the overall regression models (e.g. adjusted R² was unchanged for MOS sleep disturbance and MDHAQ sleep). The four separate models in Table 3 list factors independently associated with sleep disturbance in RA. R² was 0.53 for RAID sleep, 0.41 of MOS sleep disturbance, 0.40 for 15D sleep, and 0.38 for MDHAQ sleep disturbance.

A robustness analysis was performed for the multivariate model with RAID sleep with and without the inclusion of VAS Pain. There were only minor changes in parameter coefficients except for RADAI, which changed from 0.41 to 0.55. The final multivariate models for RAID sleep with and without VAS Pain retained the same significant independent variables and the adjusted R² differed by 0.3% (data included in online Supplementary Table S1).

Discussion

Sleep disturbance is important to patients and sleep quality and fatigue were early identified by OMERACT as important aspects of health and well-being to patients with RA (3, 4, 6). The bidirectionality between disturbed sleep and other PROs has been documented; however, the results are somewhat divergent and the direction of association may be difficult to determine because of the cross-sectional design of the studies.

Four sleep questionnaires have been identified as applicable for use in RA (29). In the present study with RA patients, we included the MOS sleep disturbance scale and the sleep questions from frequently used PRO questionnaires, to investigate whether there were consistent associations between the different sleep measures and other PROs.

The MOS sleep disturbance scale has been validated for use in RA (20). RAID, MDHAQ, and 15D have been used in many clinical trials with RA but the sleep components of these questionnaires have, to our knowledge, not previously been explored together with MOS sleep disturbance. Threshold values for the MOS sleep disturbance scale and the sleep questions from RAID, MDHAQ, and 15D have not been set, and thus it is impossible to determine the exact level of sleep disturbance our patients experience. However, an overall maximal RAID value of 2 was proposed as the optimal threshold (36). Our patients report a mean (SD) RAID
Sleep disturbance in RA

Table 1. Demographics and disease characteristics of patients in the Oslo Rheumatoid Arthritis Register (ORAR),

|                                | All patients (n = 986) |
|--------------------------------|------------------------|
|                                | n (all responders)     | Mean ± SD or n (%) | Median (IQR) |
| Age (years)                    | 986                    | 59.4 ± 12.5        | 61.0 (51.0–69.0) |
| Gender, females                | 758                    | 758 (76.9)         |               |
| Disease duration (years)       | 962                    | 13.7 ± 10.7        | 11.0 (5.0–20.0) |
| Seropositive*                  | 957                    | 549 (55.7)         |               |
| Comorbidity                    | 986                    | 560 (56.8)         |               |
| Current smokers                | 976                    | 223 (22.8)         |               |
| Education (years)              | 967                    | 12.9 ± 3.3         | 12.0 (10.0–17.0) |
| BMI (kg/m²)                    | 963                    | 25.3 ± 4.6         | 24.7 (22.0–27.9) |
| HAQ (0–3)                      | 983                    | 0.88 ± 0.71        | 0.86 (0.29–1.43) |
| MHAQ (0–3)                     | 965                    | 0.43 ± 0.46        | 0.25 (0.00–0.63) |
| SF-36 PCS (0–100)              | 954                    | 36.4 ± 11.6        | 35.7 (28.1–45.2) |
| SF-36 MCS (0–100)              | 941                    | 47.3 ± 11.6        | 49.9 (38.7–56.6) |
| VAS Pain (0–100)               | 973                    | 34.0 ± 24.2        | 30.0 (13.0–52.0) |
| VAS PtGA (0–100)               | 973                    | 36.7 ± 24.7        | 32.0 (16.0–55.5) |
| VAS Fatigue (0–100)            | 969                    | 44.1 ± 28.6        | 44.0 (18.0–69.0) |
| RAID (0–10)                    | 954                    | 3.31 ± 2.14        | 3.1 (1.5–5.0)   |
| RADAII (0–10)                  | 977                    | 3.18 ± 1.70        | 3.0 (1.8–4.5)   |
| SF-6D (0.29–1.00)              | 934                    | 0.67 ± 0.14        | 0.65 (0.58–0.77) |
| EQ-5D-3L                       | 959                    | 0.86 ± 0.25        | 0.69 (0.62–0.80) |
| MOS sleep disturbance scale (0–100) | 914             | 32.3 ± 25.7        | 27.5 (10.0–50.0) |
| RAID sleep (0–10)              | 963                    | 2.97 ± 2.78        | 2.0 (0.0–5.0)   |
| MDHAQ sleep (0–3)              | 960                    | 0.76 ± 0.79        | 1.0 (0.0–1.0)   |
| 15D sleep (1–5)                | 958                    | 2.1 ± 1.0          | 2.0 (1.0–3.0)   |
| Z-drugs                        | 184                    | 104 (18.7)         |               |
| Benzodiazepines                | 84                     | 84 (8.5)           |               |
| Prednisolone                   | 247                    | 247 (25.1)         |               |
| sDMARDs                        | 586                    | 586 (59.4)         |               |
| bDMARDs                        | 202                    | 202 (20.5)         |               |

BMI, Body mass index; HAQ, Health Assessment Questionnaire; MHAQ, modified HAQ; SF-36 PCS and MCS, 36-item Medical Outcomes Study (MOS) Short-Form Health Survey, Physical and Mental Component Scores; VAS, visual analogue scale; PtGA, patient global assessment of disease; RAID, Rheumatoid Arthritis Impact of Disease; RADAII, RA Disease Activity Index; SF-6D, utility measure derived from the MOS SF-36 (score 0.29–1, a living person will obtain a value of at least 0.29, 1.00 = best health state); EQ-5D, EuroQol 5-dimensional self-reported measure of health with three levels of severity; 15D, 15-dimensional quality of life questionnaire with one question on sleep; Z+benzo, Z-drugs + benzodiazepines; bDMARD, biological disease-modifying anti-rheumatic drug; sDMARD, synthetic DMARD; IQR, interquartile range (25th–75th percentile).

* Presence of rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, or both.

score of 3.31 (2.14) and RAID sleep score of 2.97 (2.78), suggesting that they experience not only a high impact of disease but also a high level of sleep disturbance. The correlations between the different sleep measures were high (0.71–0.78).

We found sleep disturbance to be independently related to a number of generic and RA-specific PROs, including fatigue, SF-36 MCS, and patient global disease activity (RADAII). It is interesting that these factors were not only bivariately but also independently related to sleep disturbance in multivariate analyses. Being consistent across all four measures of sleep disturbance further strengthens the validity of these findings. Thus, our study contributes to research on sleep disturbance in RA, which is considered important by patients (3).

Early studies of sleep disturbance in RA demonstrated conflicting evidence of association with disease activity (45, 46); however, the numbers of patients were small. Several studies have since demonstrated an association between sleep disturbance and RA disease activity, although these were trials of various medications used in RA (20, 47, 48). Our study supports the association between disease activity and sleep disturbance in RA as we find RADAII to be independently associated with sleep disturbance across all four models. Sleep disturbance in fibromyalgia has been associated with negative mood, psychological distress, pain, and fatigue (49, 50). Similarities between sleep disturbance in RA and fibromyalgia have been described (15), as well as the effect of pain, fatigue, depression, and disease activity on sleep quality in RA patients (15). Overall, later studies and more recent reviews suggest associations between sleep disturbance and pain, fatigue, female gender, depressed mood, and overall well-being (8, 10, 51). Our findings further support the association between fatigue and mental components in models for all four measures of sleep disturbance in RA. We found VAS pain to be associated with sleep disturbance in only one of the four models.
Table 2. Correlation between sleep measures and important patient-reported outcomes (PROs) in the Oslo Rheumatoid Arthritis Register (ORAR).

| MOS sleep disturbance | RAID sleep | MDHAQ sleep | 15D sleep |
|-----------------------|------------|-------------|-----------|
| RAID sleep            | 0.78***    | 1           |           |
| MDHAQ sleep           | 0.73***    | 0.77***     | 1         |
| QoL 15D sleep         | 0.75***    | 0.73***     | 0.71***   |
| Age                   | 0.11**     | 0.15***     | 0.12***   |
| Disease duration      | 0.03 (p = 0.35) | 0.09*** | 0.11** | 0.07* |
| Education             | -0.18***   | -0.20***    | -0.14***  |
| BMI                   | 0.15***    | 0.14***     | 0.09**    |
| VAS Pain              | 0.44***    | 0.61***     | 0.45***   |
| VAS PtGA              | 0.44***    | 0.61***     | 0.45***   |
| VAS Fatigue           | 0.51***    | 0.58***     | 0.47***   |
| HAQ                   | 0.36***    | 0.51***     | 0.42***   |
| MHAQ                  | 0.34***    | 0.48***     | 0.41***   |
| SF-36 PCS             | -0.57***   | -0.52****   | -0.39***  |
| SF-36 MCS             | -0.51****  | -0.47****   | -0.41***  |
| RAID total            | 0.60***    | na          | 0.60***   |
| RAID total            | 0.47***    | 0.63***     | 0.49***   |
| SF-6D                 | -0.54***   | -0.61***    | -0.50***  |
| EQ-5D-3L              | -0.45***   | -0.55***    | -0.47***  |

MOS, Medical Outcomes Study; RAID, Rheumatoid Arthritis Impact of Disease; MDHAQ, Multi-Dimensional Health Assessment Questionnaire; 15D, 15-dimensional quality of life (QoL) questionnaire with one question on sleep; BMI, body mass index; VAS, visual analogue scale; PtGA, patient global assessment of disease; SF-36 MCS and PCS, 36-item MOS Short-Form Health Survey Mental and Physical Component Scores; RADAI, Rheumatoid Arthritis Disease Activity Index; SF-6D, utility measure derived from the MOS SF-36; EQ-5D, EuroQol, 5-dimensional self-reported measure of health with three levels of severity; na, not applicable.

Values given are Pearson correlation coefficients. * p < 0.05, ** p < 0.01, *** p < 0.001.

(RAID sleep). However, pain is included in the RADAI score, which was significantly associated with all four sleep measures. These findings support previous studies that describe an association between pain and sleep disturbance (8, 13, 52). We did not further investigate whether some of the RADAI components contributed more than others, but a robustness analysis with and without VAS pain included in the multivariate model for RAID sleep indicated contributions of the pain domain within RADAI. However, we decided to keep pain in the model because it made a contribution, together with the other variables. Our findings suggest that pain is associated with sleep disturbance in RA, both separately and as a component of other measures such as RADAI. Sleep apnoea and depression have also been associated with sleep disturbance in patients with rheumatic diseases (52, 53) and it would have been of interest to explore this in our study. However, we were not able to include the entire MOS sleep questionnaire or a depression questionnaire because of space limitations.

Few earlier studies have examined the prevalence of sleep disturbance and the associations between sleep disturbance and clinical variables in RA patients seen in daily practice. In RA there are many studies reporting sleep disturbance from single questionnaires, but none have compared the MOS sleep disturbance scale with other measures of sleep disturbance as part of other questionnaires commonly used in RA. In clinical trials, and to some extent in daily clinical practice, these questionnaires are used (e.g. RAID, MDHAQ, and 15D).

Westhovens et al identified an association between poor RA disease control and sleep disturbance using some of the above-mentioned questionnaires (17). The patient population in our study and in that of Westhovens et al display similar demographics and patient characteristics, both representing unslected patient material not subject to stringent inclusion and exclusion criteria. The sleep questionnaires applicable to RA have been used in studies that identify associations between sleep disturbance and SF-36 (subscales or component summaries), disease activity (DAS28 or PtGA), use of sleep medication, and mental factors (negative emotions or SF-36 MCS) in multivariate analyses (17, 29).

Fatigue may be a prominent symptom in many rheumatic diseases (54). A number of factors may contribute to fatigue, and the relationship between pain, fatigue, and sleep disturbance has been described previously (7, 11, 54, 55). In our study fatigue is significantly associated with all measures of sleep in multivariate models, further strengthening previous studies reporting that fatigue and sleep disturbance are associated in RA.

A national health survey from the USA suggests that RA patients are more likely to experience sleep disturbance than non-RA patients, mainly due to joint pain and limitations related to joint pain (56). In our study we find a high correlation between sleep disturbance by four different measures and worse PROs and moderate correlations for RAID sleep to pain measured by VAS and through RADAI. RAID sleep demonstrates the highest correlation with other PROs of the four sleep measures.
Table 3. Variables associated with measures of sleep disturbance in patients with rheumatoid arthritis (RA).

| Variable                     | MOS sleep disturbance scale (0–100) | RAID sleep (0–10) | MDHAQ sleep (0–3) | 15D sleep (1–5) |
|------------------------------|-------------------------------------|-------------------|--------------------|-----------------|
|                              | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
| Age                          | 0.23 (0.001) | -0.04 (0.46) | 0.03* | -0.05 (0.35) | 0.01* | -0.003 (0.14) | 0.01* | 0.00 (0.995) |
| Gender                       | 3.91 (0.05) | 2.10 (0.20) | 0.72 (0.001) | 0.35 (0.03) | 0.13 (0.03) | 0.03 (0.61) | 0.22 (0.005) | 0.10 (0.14) |
| Disease duration             | 0.08 (0.35) | -0.04 (0.20) | 0.02 (0.006) | -0.01 (0.26) | 0.01 (0.001) | 0.001 (0.49) | 0.01 (0.04) | -0.002 (0.51) |
| Seropositive§                | -1.91 (0.27) | -0.11 (0.54) | -0.09 (0.09) | -0.09 (0.20) | -0.09 (0.09) | -0.09 (0.20) | -0.09 (0.20) | -0.09 (0.20) |
| Comorbidity                  | 9.37* | 1.07* | 0.20* | 0.40* | -0.05* | 0.03 (0.18) | -0.05* | 0.03 (0.18) |
| Smoking                      | 0.91 (0.09) | 0.09 (0.14) | 0.01 (0.47) | 0.03 (0.18) | 0.01 (0.47) | 0.03 (0.18) | 0.01 (0.47) | 0.03 (0.18) |
| Education†                   | -1.35* | -0.17* | -0.03* | -0.05* | -0.03* | -0.05* | -0.03* | -0.05* |
| BMI                          | 0.89* | 0.44 (0.003) | 0.08* | 0.04 (0.007) | 0.02 (0.009) | 0.02 (0.001) | 0.02 (0.001) | 0.02 (0.001) |
| VAS Pain                     | 0.47* | 0.07* | 0.01* | 0.02* | 0.01* | 0.04 (0.04) | 0.02* | 0.04 (0.04) |
| VAS Fatigue                  | 0.45* | 0.17* | 0.06* | 0.02* | 0.01* | 0.005* | 0.02* | 0.005* |
| VAS PtGA                     | 101 | 0.07* | 0.02 (0.004) | 0.01* | 0.02* | 0.04 (0.04) | 0.02* | 0.04 (0.04) |
| VAS Pain                     | 0.46* | 0.07* | 0.01* | -0.004 (0.04) | 0.02* | 0.04 (0.04) | 0.02* | 0.04 (0.04) |
| HAQ                          | 13.1* | 2.0* | 0.47* | 0.50* | 0.47* | 0.50* | 0.47* | 0.50* |
| MHAQ                         | 19.1* | 2.9* | 0.70* | 0.74* | 0.70* | 0.74* | 0.70* | 0.74* |
| PCS                          | -0.81* | -0.12* | -0.03* | -0.03* | -0.03* | -0.03* | -0.03* | -0.03* |
| MCS                          | -1.1* | -0.63* | -0.11* | -0.04* | -0.03* | -0.01* | -0.04* | -0.01 (0.02) |
| RADAI                        | 7.0* | 3.09* | 1.02* | 0.41* | 0.23* | 0.13* | 0.25* | 0.08* |
| SF-6D                        | -98.4* | -121.1* | -2.8* | -3.6* | -3.6* | -3.6* | -3.6* | -3.6* |
| EQ-5D-3L                     | -46.4* | -6.2* | -1.5* | -1.7* | -1.5* | -1.7* | -1.5* | -1.7* |
| Z-drugs                      | 21.5* | 2.5* | 0.69* | 1.2* | 0.69* | 1.2* | 0.69* | 1.2* |
| Benzodiazepines              | 16.4* | 1.7* | 0.49* | 0.68* | 0.49* | 0.68* | 0.49* | 0.68* |
| Z+benzo                      | 21.3* | 10.60* | 2.4* | 1.16* | 0.68* | 0.40* | 1.1* | 0.79* |
| Prednisolone                 | 4.0 (0.03) | 0.83* | 0.18 (0.001) | 0.16 (0.03) | 0.16 (0.03) | 0.16 (0.03) | 0.16 (0.03) | 0.16 (0.03) |
| sDMARD                       | -1.3 (0.45) | 0.02 (0.93) | -0.09 (0.07) | -0.11 (0.11) | -0.11 (0.11) | -0.11 (0.11) | -0.11 (0.11) | -0.11 (0.11) |
| bDMARD§                      | -1.5 (0.15) | -0.24 (0.29) | -0.09 (0.15) | -0.01 (0.23) | -0.01 (0.23) | -0.01 (0.23) | -0.01 (0.23) | -0.01 (0.23) |
| Intercept                    | 45.1* | 2.46* | 1.15* | 3.32* | 1.15* | 3.32* | 1.15* | 3.32* |
| Adjusted R²                  | 0.413 | 0.534 | 0.378 | 0.399 | 0.378 | 0.399 | 0.378 | 0.399 |

MOS, Medical Outcomes Study; RAID, Rheumatoid Arthritis Impact of Disease (0 = no symptoms, 10 = worst possible symptoms); MDHAQ, Multi-Dimensional Health Assessment Questionnaire; 15D, 15-dimensional quality of life questionnaire; BMI, body mass index; bDMARD, biological disease-modifying anti-rheumatic drug; sDMARD, synthetic DMARD; VAS, visual analogue scale (0 = no symptoms/problems, 100 = worst possible symptoms/problems); PtGA, patient global assessment of disease; MHAQ, modified HAQ; MCS and PCS, Mental and Physical Component Scores from the 36-item MOS Short-Form Health Survey (SF-36); RADAI, Rheumatoid Arthritis Disease Activity Index (0 = no symptoms, 10 = worst possible symptoms); SF-6D, utility measure derived from MOS SF-36 (1 = best health state, any living person will obtain a value of at least 0.29); EQ-5D-3L, EuroQol 5-dimensional 3-level self-reported measure of health; Z-drugs, use of zopiclone or zolpidem; Z+benzo, use of Z-drugs and/or benzodiazepines.

§ Presence of rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, or both.
† Range 7–17 years.

All values for univariate and multivariate analyses used general linear models and are given as beta (p-value). Multivariate analyses adjusted for all variables in the models.

Categorical variables: gender (male = reference); seropositive (seronegative = reference); comorbidity (none = reference); smoking (no smoking = reference); use of medication (no use = reference).

* p < 0.001.

Z-drugs are considered safer and with fewer side-effects and lower risk of abuse than benzodiazepines for use in insomnia (57). Sleep disturbance is reported to be more common in the elderly (51). In the present study, use of Z-drugs was associated with sleep disturbance, was more common in females, and increased with advancing age.

The strengths of our study include the large number of RA patients, reflecting the range of disease activity and disease consequences seen in clinical practice. We address sleep disturbance as an issue suggested by patients for further research in OMERACT (3, 4). Multivariate analyses with four different measures of sleep were consistent for fatigue, disease activity (RADAI), MCS, and use of sleep medication, while MHAQ and BMI were important in at least two models. These findings indicate the robustness of our study. Possible weaknesses include the use of self-reported data, which may introduce reporting bias. It is difficult to account for all possible confounders in cross-sectional studies, and although a wide range of variables was studied, it would have been valuable to also have information on, for example, sleep apnoea and depression. Our findings are consistent across different measures of sleep and we do not believe there are any major confounders in this study. We have previously studied the ORAR data with a 15-year perspective and did not identify any significant problems with reporting bias (26). This study is the first.
to broadly address sleep disturbance in RA using four different measures. It is a hypothesis-generating study where we look at factors independently associated with the different measures of sleep disturbance to investigate whether there are any common factors. Because of the cross-sectional study design, we cannot draw any conclusions with respect to possible causality. We find that sleep disturbance is independently associated with fatigue, disease activity, and pain (RADAI), mental health (SF-36 MCS), and use of sleep medication. The findings in the present study suggest that the sleep components of already commonly used PRO instruments, including RAID and the MOS sleep disturbance scale, may be used to investigate sleep disturbance in RA patients.

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Supporting Information
Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Multivariate models for RAID sleep presented with and without VAS Pain.

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