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ORIGINAL RESEARCH

Objective and Subjective Sleep in Rheumatoid Arthritis and Severe Seasonal Allergy: Preliminary Assessments of the Role of Sickness, Central and Peripheral Inflammation

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Introduction: Disturbed sleep in inflammatory disorders such as allergy and rheumatoid arthritis (RA) is common and may be directly or indirectly related to disease processes, but has not been well characterized in these patient groups, especially not with objective methods.

Aim: The present study aimed to characterize objective and subjective sleep in patients with allergy or RA using sleep diaries, one-channel EEG and actigraphy. It also aimed to investigate if sleep measures were associated with central immune activation, assessed using translocator protein (TSPO) positron emission tomography, as well as cytokine markers of peripheral inflammation and disease-specific symptoms or general symptoms of sickness.

Methods: In total, 18 patients with seasonal pollen allergy, 18 patients with RA and 26 healthy controls were included in the study. Allergy patients and matched controls were assessed twice, in and out of pollen season, and RA patients and controls were assessed once. Sleep was recorded for approximately 1 week at each occasion.

Results: Patients with allergy had increased levels of slow-wave sleep during pollen season. In contrast, patients with RA had less SWS compared to healthy controls, while no differences were observed in sleep duration or subjective sleep quality. Across groups, neither proinflammatory cytokines, grey matter TSPO levels nor general sickness symptoms were associated with objective or subjective measures of sleep. Rhinitis, but not conjunctivitis, was correlated to worse subjective sleep and more slow wave sleep in allergy. Functional status, but not disease activity, predicted lower subjective sleep in RA.

Conclusion: This study tentatively indicates that both patients with allergy and RA display sleep alterations but does not support inflammation as an independent predictor of the sleep disturbance across these patient groups.

Keywords: sleep, inflammation, allergy, rheumatoid arthritis

Background

The global prevalence of seasonal allergic rhinoconjunctivitis is estimated to be between 10% and 40%[1] and the global prevalence of rheumatoid arthritis (RA) about 0.25%.[2] Despite effective symptom-specific treatments for both seasonal allergic rhinoconjunctivitis and rheumatoid arthritis (RA), levels of non-specific sickness symptoms, including depressed mood, anxiety and fatigue, are high.[3–8]

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Poor subjective sleep is commonly also reported in both conditions.[5,9–13] The pathophysiology of both allergy and RA involves systemic inflammation, and inflammatory cytokines can be related to sleep disturbances and fatigue and are involved in regulation of sleep.[14,15] In addition to the acute symptoms of allergy and RA, such as rhinitis and pain, it is therefore likely that underlying inflammatory processes can interfere with sleep in these conditions.[9,16] However, sleep disturbances in these inflammatory disorders and their relationship to immunological markers are still poorly characterized.

We have previously shown that subjective sleep quality was decreased during pollen season in severe seasonal allergy and that patients with allergy had a shorter total sleep time (TST) compared to controls.[6] Similarly, self-reported sleep quality has by others been reported to be lower in RA,[17] and studies with objective measures of sleep showed more sleep fragmentation and more sleep apnea in RA patients compared to healthy controls.[16,18,19] Disturbed sleep has also been shown to covary with pain in patients with RA,[16] and similarly, apnea and nasal congestion in allergy might impair sleep.[9,16]

Across a number of different patient and healthy populations, subjective sleep disturbances as well as long and short sleep durations, compared to normal, are associated with higher levels of interleukin (IL)-6 and C-reactive protein.[14,20] These markers of systemic inflammation are also related to sleepiness and fatigue.[21] Sleep disturbances have also been shown to occur in response to vaccination,[22] high doses of lipopolysaccharide[23] as well as during acute respiratory infections.[24,25] Specifically, proinflammatory cytokines, eg IL-6 and tumor necrosis factor (TNF)-α, are implicated in sleep regulation.[26] Furthermore, a specific link between these proinflammatory cytokines and slow wave sleep (SWS) is indicated by observations in animals, where TNF-α or IL-1 beta injections enhance non-rapid eye movement (NREM) sleep, and plasma levels of TNF-α covary with electroencephalography (EEG) slow-wave activity and sleep propensity.[27] Likewise, animal studies suggest that sleep disturbance is associated with increased pro-inflammatory cytokine IL-6 levels and microglia activation in the brain.[28]

Beyond increased levels of type 2 helper (Th2)-associated cytokines such as IL-4, IL-5 and IL-13, allergy has been associated with increases in pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α,[6,29,30] ie, those implicated in sleep regulation. Correspondingly, RA is associated with RA-specific immunological markers, such as the rheumatoid factor and anti-citrullinated protein antibodies, but also a general proinflammatory response involving IL-1 beta, IL-6, IL-8 and TNF-α.[31] A testable hypothesis is thus that sleep in both allergy and RA is associated with levels of pro-inflammatory cytokines and brain markers of neuroinflammation.

We have previously investigated glial activation as measured with positron emission tomography (PET) and the translocator protein (TSPO) radioligand [^{11}C]PBR28 in small samples of patients with allergy[6] and RA.[32] Here, we aim to specifically characterize the objective and subjective sleep problems in both these patient samples, and to investigate their relationship to TSPO and peripheral inflammatory markers, as well as disease-specific symptoms and general sickness symptoms. Given that RA and allergy patients show similarities in non-specific symptoms and partly overlapping immunological profiles, data from both samples were pooled in order to increase statistical power for the analyses of sleep and inflammation and sickness. Because of the need to study sleep at home in clinical populations over longer time periods, an additional exploratory aim was to test whether an ambulatory one-channel EEG in combination with a sleep diary could be a feasible method to study sleep in patients with inflammatory disease. The following specific research questions were investigated:

1. Do allergic and RA patients show disturbed subjective and objective sleep compared to controls and are these changes potentiated during pollen season for the allergic patients? Note that this question has been partly investigated in our previous analysis for the allergic sample (6). 1
2. Are higher levels of pro-inflammatory cytokines in peripheral blood and the glial marker translocator protein (TSPO) as measured with PET, across both RA and allergy associated with worse subjective sleep quality and objective measures of sleep (SWS and TST)?
3. Are measures of subjective sleep quality, SWS and TST associated with more symptoms of disease severity, ie, rhinitis symptoms in allergy and disease activity score (DAS-28) and functional status (measured with the Health Assessment Questionnaire (HAQ)[33,34]) in RA? (Analyses of the Health Assessment Questionnaire were added during the review process.) Furthermore, are more general sickness symptoms as measured with the Sickness Questionnaire significantly associated with poorer subjective sleep quality, less SWS and shorter TST?

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Method

Overall Study Design

The present study is part of a project investigating central and peripheral immune alterations as a potential mechanism underlying nonspecific symptoms in seasonal allergy and rheumatoid arthritis. As previously described,[6] 18 patients with seasonal allergy and 13 matched healthy controls were investigated in and out of pollen season in a counter-balanced design. Similarly, 18 patients with RA and 19 matched controls were investigated once in an otherwise identical design.[32] Six of the controls were used as controls for both allergy patients and RA patients resulting in 26 healthy controls in total. At each occasion, participants recorded their sleep for approximately 7 days (see below) in their homes, followed by two testing days (study visits). On the first testing day, participants filled in questionnaires, provided blood samples and underwent a PET examination. On the second testing day, participants underwent pain testing and a battery of cognitive tasks (reported elsewhere). Some data concerning sleep and its relation to inflammation for the allergic group have been reported in a previous publication,[6] see below for details. In a small number of cases, the testing had to be rescheduled after participants received the sleep equipment, which resulted in more recordings or in some cases a delay between the sleep recordings and PET imaging/blood sampling. The study was performed in accordance with the Helsinki declaration and was approved by The Regional Ethical Review Board of Stockholm (no: 2011/1846-31/1). All participants were informed about the purpose of the study and provided written and oral consent.

Participants

Patients with severe seasonal allergic rhinoconjunctivitis, with or without asthma, fulfilling criteria to start allergen-specific immunotherapy, were recruited from allergy clinics in Stockholm, Sweden.[6] Allergy was confirmed through skin prick tests and specific immunoglobulin E. Patients with RA were recruited from the rheumatology clinic at the Karolinska University Hospital in Stockholm, Sweden.[32] All RA patients were anti-citrullinated protein antibodies positive and fulfilled the 1987 Rheumatoid Arthritis Classification criteria for RA.[35] Detailed disease characteristics and disease-modifying medication/biologics in RA patients have been previously published.[35] Healthy participants were recruited through advertisements (on university campus and on public notice-boards across Stockholm). Patients and healthy subjects were matched on age, sex and for the genetic polymorphism rs6971 which affects binding to TSPO radioligands.[36] The data collection for allergics was interrupted after planned interim analyses.[6] RA patients and controls were recruited to yield a sample of 15 patients and controls with complete data. However here, we used all available data, with six individuals as controls for both allergy and RA, explaining why the sample sizes are not equal (Table 1). To be eligible, participants were to be healthy with no chronic disease (except allergy or RA for patients, well-controlled hypothyroidism or hypertension), no regular medication (except for allergy, RA, hypothyroidism or hypertension), no chronic pain (except RA-related pain in RA patients) or mental or neurological illness, BMI < 29 kg/m^2, fluent in Swedish, right-handed and 20–70 years of age. The following exclusion criteria also applied: pregnancy, self-reported use of estrogen containing hormonal contraceptives and ongoing infection.

All participants were instructed to refrain from alcohol and hard physical activity and to sleep regularly 2 days before the first study visit (ie, the 2 last days of the sleep recording for most participants). Allergic patients did not use any inhaled, nasal or systemic steroids or leukotriene antagonists 10 days before the 1st study visit and were instructed not to use any antihistamines 5 days before study visits, which coincided with the days when sleep was recorded. No RA patient had any treatment with oral steroids, and RA patients were instructed to avoid non-steroid anti-inflammatory drugs 2 days before the first study visit, but no other medication change was allowed for these patients the preceding week (ie, during the time when sleep was recorded). Participants were instructed to avoid travel across more than 2 time zones and shift work (nights) 3 weeks before the study visits. An overview of participants' demographics are presented in Table 1, and further clinical details have been reported before.[6,32]

Sleep Measures

As reported in Tamm et al,[6] participants filled out sleep diaries daily[37] and used an ambulatory single frontal EEG electrode (MyZeo, Zeo Inc., Boston MA, USA) to measure sleep duration and sleep stages[38] in their homes for approximately a week. For a subset (n = 38, due to technical circumstances) of the participants, data from actigraphs (Actiwatch Spectrum, Philips Respironics) were available. Participants were sent the sleep equipment 6 days prior to the first study visit, but recorded sleep for

Table 1 Demographical information.

	Allergy	Allergy Controls	RA	RA Controls
Sample				
Number of subjects	18	13	18	19
Demographics				
Age (median, interquartile range)	34.0 (30.2–44.2)	34.0 (27.0–46.0)	53.0 (48.5–58.5)	49.0 (45.5–54.0)
Sex (females)	8 (44.4%)	5 (38.5%)	15 (83.3%)	16 (84.2%)
BMI (mean and sd)	25.4 (±4.5)	22.6 (±3.0)	24.1 (±3.7)	23.1 (±3.5)
Education				
College graduate	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (6.2%)
Elementary/High school	0 (0.0%)	1 (10.0%)	4 (26.7%)	1 (6.2%)
Other	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (6.2%)
Some college	5 (27.8%)	1 (10.0%)	2 (13.3%)	2 (12.5%)
Some university	2 (11.1%)	5 (50.0%)	2 (13.3%)	2 (12.5%)
University graduate	9 (50.0%)	3 (30.0%)	7 (46.7%)	9 (56.2%)

Note: Note that 6 of the controls were used as controls for both RA patients and patients with allergy and the total number of controls was 26.

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a mean of 6.8 days (range 1–14) for logistic reasons, such as rescheduling of study visits.

Subjective sleep quality was based on sleep diary data.[37] As described in Tamm et al,[6] an index based on four questions ("Did you have difficulties falling asleep?" (1 = very much to 5 = not at all), "How did you sleep?" (1 = very poorly to 5 = very well), "Did you have a restless sleep?" (1 = very much to 5 = not at all), and "Did you wake up very early without being able to fall asleep?" (1 = very much too early to 5 = no)) was computed. Self-reported bed- and rise times were used to calculate time in bed. Karolinska Sleepiness Scale (KSS) was used to measure sleepiness (1 = alert to 9 = very sleepy, great effort keeping awake, fighting sleep) every morning and evening.

Data from MyZeo were first inspected and then manually exported using Zeo Sleep Viewer (version 0.2.9). As described in Tamm et al,[6] we removed recordings where participants reported that the electrode fell off, and in cases where it was judged obvious that most of the recording was missing. Participants were instructed to use the EEG while in bed, and hence, time in bed (TIB) based on MyZeo is defined as the automatically generated "total duration". Two criteria were used to remove data with poor recording quality. First, only recordings with less than 5% missing data were used. Secondly, recordings where the TIB based on MyZeo was less than 75% of the TIB estimated from sleep diaries for the specific night, were discarded. Criterion two was applied because the first criterion would not find cases where the electrode fell off completely and not reattached. Of 478 recordings, 169 were excluded based on these criteria. The measures exported were TST, no of awakenings, deep sleep (corresponding to N3/N4 or SWS), light sleep (corresponding to N1 and N2) and REM sleep. Actigraph data were automatically scored and exported through Actiware software (Philips Respironics) and we used the measure of TST.

Measures of Disease Activity and Sickness

As reported in Tamm et al[6] and Forsberg et al,[32] participants filled out a number of validated questionnaires on the first testing day. General sickness was measured using the 10 items of the Sickness Questionnaire,[39] here rated as part of a larger pool of 36 items evaluated during the validation of the questionnaire. Nine common allergic symptoms (runny nose, itching nose, sneezing, nasal congestion, loss of smell, runny eyes, itching eyes, eye redness and swollen eyes) were reported each evening during the week leading up to the testing days, from 0 (no symptoms) to 10 (maximal symptoms). Asthma symptoms were measured on the first testing day using the Asthma Control Test (ACT).[40] RA disease activity was assessed through the disease-activity score based on 28 joint count (DAS28)[41] and functional status was measured using the Health Assessment Questionnaire (HAQ).[33,34]

PET

Participants underwent a PET examination at the PET center at Karolinska Institutet, Stockholm, using a High-Resolution Research Tomograph (Siemens Molecular Imaging,

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Knoxville, TN) on the first testing day. The procedures for [^{11}C]PBR28 preparation, injection and PET data acquisition and processing and results have been described in detail previously.[6,32] The radioligand was injected through a vein catheter and arterial blood was sampled using an automated system for the first 5 min and manual samples were drawn at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 70 and 90 min. Preprocessing of arterial blood data was performed using Kaleidagraph 4.1 software (Synergy Software) as described in detail before.[42] Correction for radioligand metabolism was performed in PMOD v3.3 (pixel-wise modelling software; PMOD Technologies Ltd., Zurich, Switzerland) using individual parent fraction data fitted using a 3-exponential model. Image processing and the definition of ROIs using T1 MR images were performed as described previously.[6,32,42,43] The primary ROI was brain grey matter (GM). Quantification of [^{11}C]PRB28 binding was performed using Logan graphical analysis with a metabolite corrected plasma input function to fit the TAC data and estimate total distribution volume (VT).[6,32]

Cytokines

As described in Tamm et al and Forsberg et al,[6,32] venous blood was collected on the first testing day before the PET examination. Serum concentration of cytokines were analyzed using sandwich immunoassays: multispot V-PLEX Proinflammatory panel 1, human, K15049D (IFN-c, IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4, IL-6, IL-8, TNF-a), single spot V-PLEX Human IL-5 Kit, K151QSD (IL-5) and single spot V-PLEX Human MCP-1 K151NND (MCP-1) from Meso Scale Diagnostics (www.mesoscale.com). Cytokines were log-transformed to better correspond to a normal distribution. A composite measure of proinflammatory cytokines was calculated as the sum of log (TNF-α), log (IL-6) and log (IL-8) concentrations. Exploratory analyses of the separate cytokines were also performed.

Data Loss and Final Sample

For the present study, we used all available data from the different assessments. Because of previously described data loss, technical problems and missing data on individual variables[6,32] the number of measurements for each variable is presented in Table 2 which for some variables differs from the two earlier main publications.[6,32]

Statistical Analyses

The effects of group (allergy/RA patient vs healthy subjects) and pollen season (for allergy) on sleep duration, sleep stages, awakenings, sleepiness and sleep quality were investigated using mixed effects models, with a random intercept for each subject and a second random intercept for each matched pair (patient and control). These analyses were carried out for allergic patients and matched controls and RA patients and matched controls separately. Significant interactions were followed-up with similar mixed effects models investigating one predictor (group or pollen season) at a time. Controls and outside pollen season (for analyses including allergics) were always considered reference levels in the models. All models are presented as effect estimates in original units, ie, minutes, numbers, points on a rating scale, etc., with 95% CI.

To investigate associations between cytokines, sickness, PET measures and sleep measures across patient groups, linear mixed effects models were used, across the full sample. The specific predictor was allowed to interact with group (ie, RA, allergy, control) and the data for all patients and controls were fitted in the same model. Disease-specific predictors were investigated in models with only the relevant patient group included, ie, RA patients for DAS-28 and HAQ and allergy patients for rhinitis symptoms.

Correlations between different sleep measures were investigated using mixed effects models across groups (with same random effects as above), where group (allergy, RA, controls) was treated as a covariate of no interest.

In light of the study's exploratory nature, alpha was considered 0.05 throughout and no correction for multiple comparisons was performed. All analyses were performed in R,[44] and the scripts can be found at https://doi.org/10.5281/zenodo.4584690.

Data Availability

Because of the small sample of patients and a risk of identification of individual responses, the full data set has not been published online, but is available upon request.

Results

A Summary of Previously Reported Sleep Changes in the Allergic Sample

Some of the sleep measures from the allergic sample have been reported previously.[6] In short, allergic patients had shorter TST based on EEG than healthy controls across seasons, and the allergic patients also showed an increase in SWS percentage during pollen season. As also reported,[6] there was a significant interaction in self-reported sleep quality for groupx season, with allergic

Table 2 No of observations for all variables of interest in the present study.

Variable	Allergy Patients (Observations)	RA Patients (Observations)	Controls (Observations)
Sleep diaries	18 (239)	17 (101)	25 (237)
Single electrode EEG	15 (105)	15 (65)	23 (161)
Actigraphs	14 (141)	9 (56)	15 (123)
Sickness questionnaire	18 (35)	18 (18)	24 (37)
Rhinitis symptom scoring	18 (209)	NA	13 (156)
DAS 28	NA	15 (15)	NA
Cytokines	18 (34)	17 (17)	25 (38)
PET	15 (28)	16 (16)	23 (35)

Notes: Allergy patients and 13 controls were assessed both in and out of pollen season while RA patients and 13 controls were assessed only during one test period. Numbers corresponding to total number of participants in each group and total number of observations per group is shown in brackets.

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patients, but not controls, showing worse sleep quality during pollen season. Furthermore, morning sleepiness was increased in allergic patients during pollen season.[6]

Additional Sleep Measures in the Allergic Sample

Total sleep time based on sleep diaries did not differ between groups (Table 3) or seasons.

In line with the group x season interaction for SWS percentage, SWS in absolute terms increased in patients but not controls during pollen season, as demonstrated by a significant group x season interaction (Table 3 and Figure 1A). When decomposed, allergic patients showed an increase in absolute SWS time during pollen season (+8.79 min [2.13, 15.45], $p = 0.01$), whereas controls did not (−2.42 [−7.79, 2.95], $p = 0.34$). None of the other measured sleep stages showed an effect of group or season (Table 3 and Figure 1B and C). Neither sleep efficiency, number of awakenings nor subjective evening sleepiness differed between allergic patients and controls nor between seasons (Table 3 and Figure 1D). For descriptive purposes, all variables from the sleep diaries are plotted in the Supplementary Figure 1.

Sleep Findings in the RA Sample

TST did not differ between RA patients and controls, neither for diaries nor the one-channel EEG, see Table 4. Amount of deep sleep, light sleep and REM for RA patients compared to controls are presented in Figure 2A–C and Table 4. RA patients had significantly shorter deep sleep compared to controls, but none of the other stages differed between RA patients and controls. Neither sleep efficiency nor number of awakenings differed significantly between patients and controls (Figure 2D and Table 4).

Subjective sleep quality from the sleep diaries is presented in Table 4. There was no significant difference in subjective sleep quality between patients with RA and matched controls. For descriptive purposes, all other variables from the sleep diaries are plotted in the Supplementary Figure 2. Furthermore, subjective sleepiness did not differ between RA patients and controls (Table 4).

Sleep and Inflammation

We have previously reported that allergic subjects had elevated levels of TNF-α (and IL-5) during pollen season compared to controls[6] and that RA patients had elevated levels of both TNF-α, IFN-γ and IL-6 compared to controls.[32] Here, the composite of pro-inflammatory cytokines did not significantly predict TST, amount of deep sleep or sleep quality (Table 4) across groups. Neither was [^{11}C]PBR28 V_T significantly associated with TST, deep sleep or subjective sleep quality across patient groups (Table 5). In addition, none of the exploratory analyses between specific cytokines and sleep measures were significant (data not shown).

Sickness and Disease-Specific Symptoms

Allergic patients compared to controls did not have significantly higher levels of sickness symptoms (0.06 CI [−3.28, 3.40], $p = 0.970$) and the interaction with pollen season was not significant (3.42 CI[−0.55, 7.39], $p = 0.089$). RA patients reported higher levels of sickness symptoms compared to controls (4.02 CI[1.10, 6.94], $p =$

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Table 3 Sleep in allergy and controls.

Variable	Intercept	Group (Allergic vs Controls)		Season (In vs Out)		GroupxSeason	
	Estimate (95% CI)	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
Sleep							
Sleep quality	4.23 (4.02–4.44)	−0.19 (−0.48–0.1)	0.189	−0.02 (−0.23–0.19)	0.881	−0.28 (−0.55–0)	0.047
Total sleep time (EEG)	435.79 (413.58–458)	−37.77 (−72.79–2.75)	0.036	−9.99 (−35.51–15.52)	0.441	10.81 (−26.45–48.08)	0.568
Total sleep time (Diary)	417.59 (392.43–442.74)	−1.7 (−36.46–33.07)	0.921	−5.66 (−29.14–17.83)	0.636	−10.14 (−40.69–20.42)	0.515
No of awakenings (EEG)	2.37 (1.42–3.33)	0.4 (−1.02–1.83)	0.567	0.12 (−0.56–0.8)	0.731	−0.19 (−1.18–0.8)	0.702
No of awakenings (diary)	1.6 (1.04–2.17)	−0.13 (−0.91–0.65)	0.73	0.12 (−0.22–0.47)	0.486	0.22 (−0.24–0.67)	0.348
Deep sleep (abs)	66.61 (54.2–79.02)	−8.55 (−26.59–9.48)	0.339	−2.24 (−7.99–3.51)	0.444	11.08 (2.69–19.48)	0.01
Light sleep (abs)	229.75 (213.21–246.29)	−25.98 (−60.46–8.5)	0.133	−3.2 (−14.42–8.02)	0.575	2.2 (−20.25–24.65)	0.847
REM sleep (abs)	124.77 (108.9–140.63)	−4.09 (−28.11–19.94)	0.729	−4.83 (−18.26–8.59)	0.478	1.96 (−17.61–21.54)	0.843
Sleep efficiency	98.21 (96.58–99.84)	−1.36 (−3.87–1.15)	0.277	−0.64 (−2.25–0.98)	0.438	1.4 (−0.96–3.76)	0.243
Sleepiness							
Morning sleepiness (KSS)	4.85 (4.15–5.56)	0.17 (−0.79–1.14)	0.716	0.14 (−0.33–0.62)	0.56	0.76 (0.14–1.38)	0.017
Evening sleepiness (KSS)	6.51 (5.98–7.05)	−0.07 (−0.82–0.67)	0.84	0.05 (−0.4–0.51)	0.812	−0.36 (−0.96–0.23)	0.232

Notes: Effect estimates correspond to minutes for sleep parameters, percentages for sleep efficiency and ratings on the Karolinska Sleepiness Scale (KSS). The intercept represents the estimate for the control group outside pollen season, the group effect represents the difference between allergic patients and controls outside pollen season, the main effect of season represents the difference between controls for outside respective during pollen season and the group*season term represents the difference between (controls in – controls out) and (-) (allergics in - allergics out). Green shaded cells have been reported in (6) but are displayed for completeness. Abbreviations: EEG, single channel electroencephalography; abs, absolute values; CI, confidence interval; REM, rapid eye movement.

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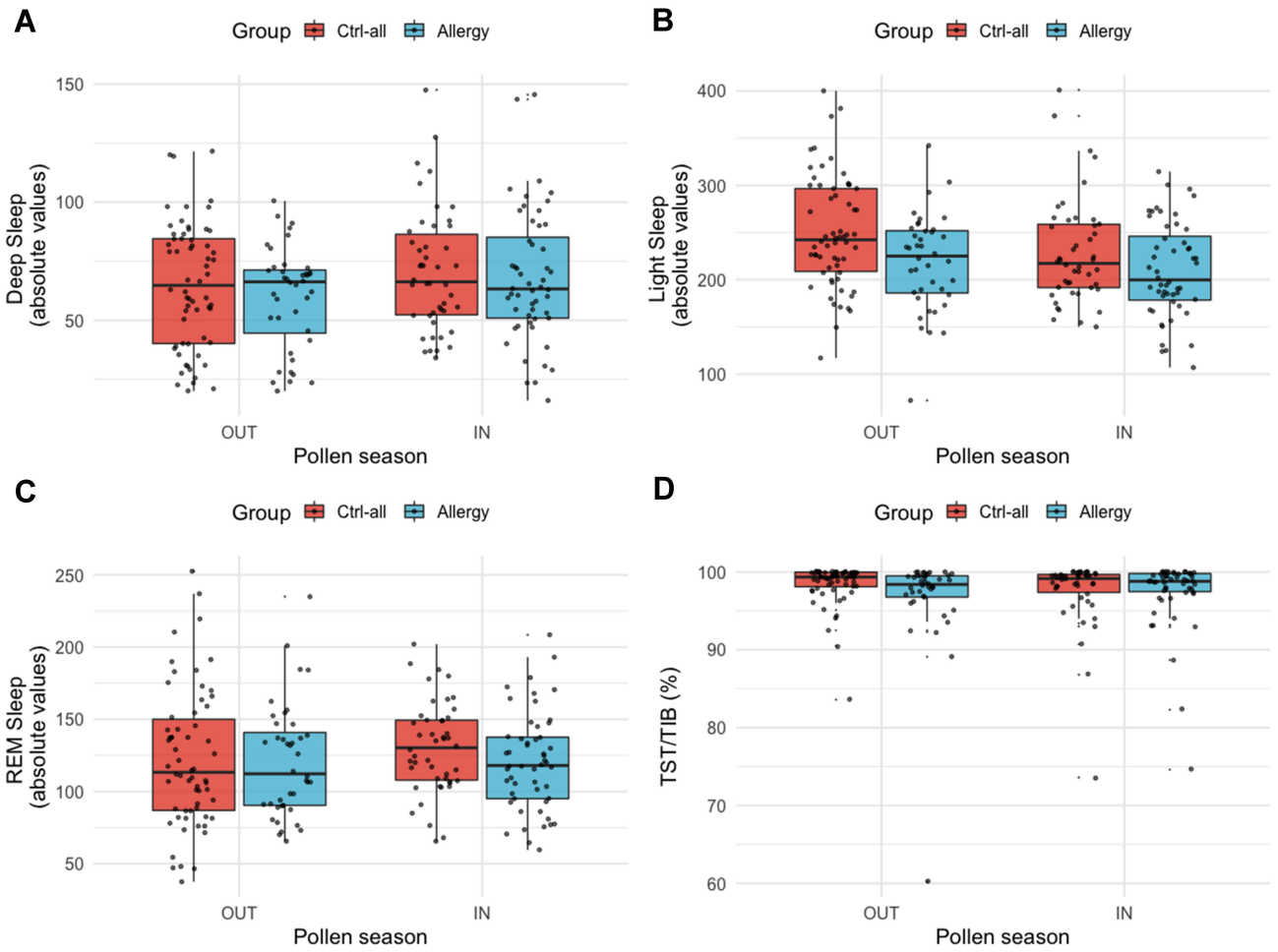

Figure 1 Objective sleep parameters based on the one-channel EEG for allergy patients and healthy controls. All box plots show median values, 25th and 75th percentile and whiskers show 95% CI. Individual data points represent single nights. Ctrl-all = allergy control subjects. (**A**). Deep sleep (SWS). (**B**). Light sleep. (**C**). REM sleep. (**D**). Sleep efficiency, calculated as the percentage of sleep (TST) out of the time the electrode was used (time in bed, TIB). Y-axis truncated for visualization.

0.008). No significant associations were found between sickness symptoms and TST, amount of deep sleep or subjective sleep quality (Table 4).

Rhinoconjunctivitis symptoms were highly correlated with pollen season in allergic subjects, introducing multicollinearity. In a model with both pollen season and rhinoconjunctivitis symptoms, more rhinoconjunctivitis symptoms were associated with worse subjective sleep quality (−0.01 CI[−0.02, −0.00], p = 0.005), rendering pollen season no longer significant (−0.07 CI[−0.41, 0.27], p = 0.69). In a model without pollen season, more rhinoconjunctivitis symptoms were also associated with greater amount of deep sleep (0.16 CI[0.01, 0.31], p = 0.04), but not with TST (0.26 CI[−0.34, 0.86], p = 0.39). Additional analyses showed that the effect on worse subjective sleep quality was primarily driven by rhinitis rather than conjunctivitis symptoms (data not shown).

Additional analyses of the association between asthma symptoms, measured using the Asthma Control Test and subjective sleep quality showed a significant association for ACT and subjective sleep quality in a model without pollen season. However, the association was not significant when including pollen season. Neither the association between ACT and SWS or ACT and TST was significant.

DAS28 in RA patients was not associated with TST (6.55 min, CI[−4.22, 17.29], p = 0.21), subjective sleep quality (−0.10 CI[−0.37, 0.17, p = 0.44) or amount of deep sleep (−1.04 CI[−12.29, 10.20], p = 0.84). Higher HAQ in RA patients was associated with lower subjective sleep quality (−0.99 CI[−1.52, −0.46], p = 0.002), but not with TST (−5.36 min CI[−38.86, 28.14], p = 0.73) or deep sleep (7.50 min CI[−24.47, 39.47], p = 0.61).

Table 4 Sleep parameters in RA patients.

Variable	Intercept	Group (RA vs Controls)	
	Estimate (95% CI)	Estimate (95% CI)	*p*
Sleep			
Sleep quality	4.08 (3.86–4.29)	−0.14 (−0.46–0.18)	0.375
Total sleep time (EEG)	420.91 (403.82–438)	−14.93 (−41.46–11.6)	0.259
Total sleep time (Diary)	409.35 (386.52–432.19)	16.78 (−17.81–51.38)	0.331
No of awakenings (EEG)	3.68 (2.58–4.78)	1.56 (−0.1–3.23)	0.064
No of awakenings (diary)	1.59 (1.19–1.98)	0.19 (−0.42–0.79)	0.534
Deep sleep (abs)	63.49 (52.42–74.56)	−18.53 (−35.1–1.97)	0.03
Light sleep (abs)	246.08 (224.21–267.96)	9.55 (−23.4–42.49)	0.558
REM sleep (abs)	110.08 (91.19–128.98)	−2.9 (−31.34–25.54)	0.836
Sleep efficiency	96.28 (94.41–98.15)	−1.39 (−4.23–1.44)	0.323
Sleepiness			
Morning sleepiness (KSS)	4.74 (4.15–5.32)	0.37 (−0.51–1.24)	0.4
Evening sleepiness (KSS)	6.43 (5.97–6.9)	0.23 (−0.46–0.92)	0.502

Notes: Effect estimates correspond to minutes for sleep parameters, percentages for sleep efficiency and ratings on the Karolinska Sleepiness Scale (KSS). The intercept represents the estimate for the control group.
Abbreviations: EEG, single channel electroencephalography; abs, absolute values; CI, confidence interval; REM, rapid eye movement.

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Associations Between Different Types of Sleep Measures

Associations between measures of TST from the one-channel EEG, actigraphy and sleep diaries are presented in Supplementary Figure 3A–C. The association between number of awakenings measured with EEG and reported in diaries is presented in Supplementary Figure 3D. The associations between sleep diaries and the one-channel EEG for TST, actigraphy and sleep diaries for TST, actigraphy and the one-channel EEG for TST and number of awakenings measured with one-channel EEG and sleep diaries were all highly significant ($p < 0.001$).

Discussion

This exploratory study aimed at investigating objective and subjective sleep disturbances in allergy and RA and their association with markers of inflammation. Although preliminary in nature, the results do not support inflammation as a potential common mechanism for sleep problems across patient groups. Neither peripheral measures of inflammation, ie, proinflammatory cytokines, nor grey matter TSPO levels in the brain, were significantly associated with objective or subjective measures of sleep. Both patient groups, however, differed in sleep compared to controls. In addition to shorter TST (across seasons), more morning sleepiness, lower sleep quality and higher percentage of SWS during pollen season that we reported previously,[6] we here report that allergics also showed a higher absolute amount of deep sleep. RA patients had significantly less SWS than controls, while their subjective sleep quality did not differ significantly. Neither was the degree of general sickness symptoms associated with measures of sleep across groups. Instead, rhinitis symptoms in allergy were correlated to worse subjective sleep quality, but more SWS, and higher HAQ in RA was associated to lower sleep quality. Thus, the results suggest that specific measures of disease severity, such as rhinitis symptoms in allergy and functional status in RA, are better predictors of disturbed sleep than inflammatory markers or a global sickness measure.

As noted above, inflammation was not associated with measures of sleep. The literature on sleep and inflammation support a role of pro-inflammatory cytokines in sleep regulation.[15,45,46] In the present study, factors such as large

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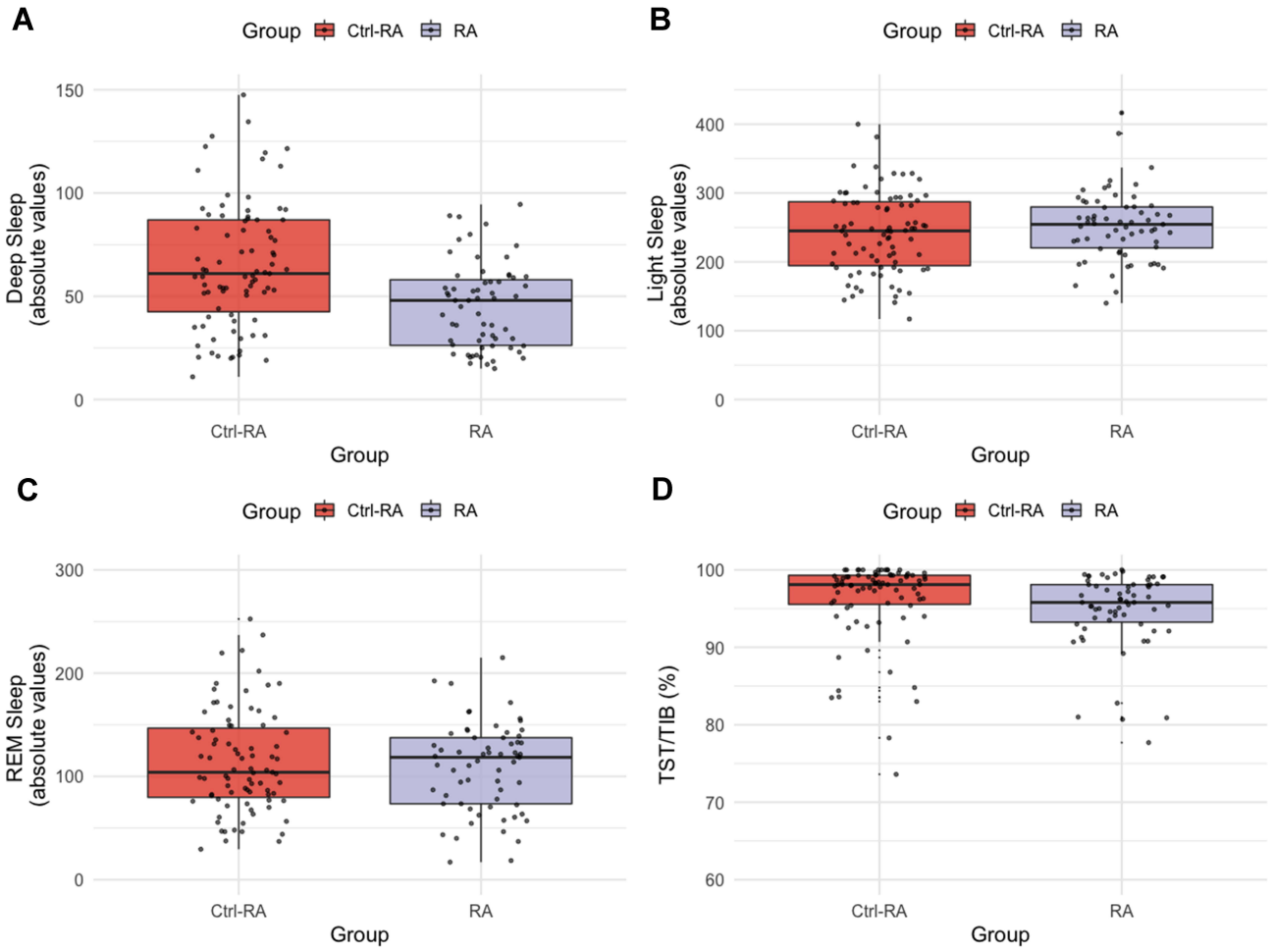

Figure 2 Objective sleep parameters based on the EEG for RA patients and healthy controls. All box plots show median values, 25th and 75th percentile and whiskers show 95% CI. Individual data points represent single nights. Ctrl-RA = RA control subjects. (**A**). Deep sleep (SWS). (**B**). Light sleep. (**C**). REM sleep. (**D**). Sleep efficiency, calculated as the percentage of sleep (TST) out of the time the electrode was used (time in bed, TIB). Y-axis truncated for visualization.

time-dependent and between-subject variation in inflammatory measures in combination with one-shot measurement potentially led to risk for Type II-error and lower sensitivity to detect subtle true effects, if present. Although this study increased power for the investigation of sleep in relation to inflammation through pooling data from two patient groups, this may not have compensated fully for these factors. While SWS was not associated with pro-inflammatory markers, pollen season was associated with both an increase in SWS and an increase in proinflammatory cytokines, potentially in line with animal studies showing that TNF-α or IL-1 beta injections enhance SWS and that plasma levels of TNF alpha covary with SWS.[27] However, these relationships seem to be less stable in humans.[22,24] Furthermore, patients with RA also showed an increase in proinflammatory cytokines, but had *less* SWS, compared to healthy.

We observed no association for sickness ratings and sleep measures across groups. The sickness questionnaire has been shown to be a sensitive measure of general disease and to be sensitive to inflammatory activation.[47] Here we wanted to test whether the concept of *feeling sick*, ie, diagnosis-independent behavior which is sensitive to inflammation, itself could be a predictor of poor sleep, which was not the case. Rather, specific symptoms of allergy (eg, rhinitis) showed associations with poorer sleep quality, but more SWS, and worse functional status in RA correlated with lower sleep quality. Even though the results do not rule out common mechanistic routes for sleep disturbances in different types of inflammatory diseases, the present findings highlight the importance of an individualized and symptom-based approach when dealing with comorbid sleep problems in a clinical setting.

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Table 5 Possible predictors of sleep variables across allergy patients, RA patients and healthy controls, investigated in a linear mixed effects model. For deep sleep and TST, effect estimates correspond to minutes. Sickness and RA significantly interacted for sleep quality, whereas no other predictor was significantly associated to sleep parameters or interacted significantly with the sleep parameters. All numbers derive from linear mixed effects models. See supplementary table 1 for analyses controlled for sex and age.

Predictor	**Allergy**		**RA**		**Cytokine Composite**		**Allergy*Cytokine Composite**		**RA*Cytokine Composite**	
	Estimate (95% CI)	***p***	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***
Cytokines										
Deep sleep	−19.17 (−41.44–3.09)	0.09	−19.13 (−45.6–7.34)	0.153	−9.31 (−21.85–3.23)	0.145	16.67 (−0.84–34.18)	0.062	2.97 (−14.89–20.84)	0.739
Total sleep time (EEG)	−24.36 (−87.36–38.64)	0.441	−5.21 (−66.44–56.03)	0.865	12.49 (−26.7–51.69)	0.531	−4.39 (−63.15–54.36)	0.883	−18.64 (−67.68–30.4)	0.448
Sleep quality	−0.19 (−0.79–0.4)	0.513	0.06 (−0.54–0.66)	0.845	0 (−0.41–0.4)	0.987	−0.06 (−0.59–0.48)	0.837	−0.15 (−0.62–0.31)	0.516
	Allergy		RA		PBR-28 binding		Allergy*PBR28 binding		RA*PBR-28 binding	
[11C]PBR28 binding	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
Deep sleep	−6.16 (−32.78–20.46)	0.643	−14.2 (−49.27–20.86)	0.418	2.88 (−0.82–6.59)	0.127	1.9 (−4.81–8.6)	0.578	−1.2 (−10.82–8.41)	0.802
Total sleep time (EEG)	−35.26 (−105.67–35.16)	0.318	−30.78 (−101.54–39.98)	0.385	−2.35 (−13.35–8.65)	0.674	−0.6 (−21.17–19.97)	0.954	2.11 (−17.85–22.06)	0.832
Sleep quality	−0.36 (−1.03–0.31)	0.283	−0.33 (−1–0.35)	0.334	−0.05 (−0.15–0.05)	0.324	0.04 (−0.15–0.23)	0.672	0.05 (−0.13–0.24)	0.575
	Allergy		RA		Sickness Q		Allergy*Sickness Q		RA*Sickness Q	
Sickness Q	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
Deep sleep	−9.82 (−26.44–6.81)	0.241	−28.03 (−49.99–6.08)	0.013	−1.45 (−3.15–0.24)	0.093	1.93 (−0.08–3.93)	0.059	2.32 (−0.61–5.26)	0.118
Total sleep time (EEG)	−49.14 (−85.08–13.19)	0.008	−27.08 (−68.81–14.64)	0.198	−1.67 (−6.41–3.08)	0.49	4.77 (−1.31–10.84)	0.123	1.52 (−5.07–8.11)	0.644
Sleep quality	−0.19 (−0.48–0.1)	0.193	0.33 (−0.03–0.68)	0.069	0.03 (−0.01–0.07)	0.18	−0.03 (−0.08–0.02)	0.189	−0.12 (−0.18–0.06)	<0.001

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A striking difference between RA patients and allergy patients was the discrepancy between objective and subjective sleep measures. RA patients, despite changes in objective sleep quality, ie, less SWS, did not differ in their subjective sleep quality compared to healthy controls, while allergy patients showed a decrease in subjective sleep quality during symptomatic seasons, in parallel with changes in objectively measured SWS. It is also notable that these changes included an increase in SWS, which is considered most important for recovery. These findings bring the question of what constitutes subjective good sleep, and the relation between objective and subjective sleep measures to the fore. One explanation could be that patients with allergy, due to disease activity and symptoms, display a higher homeostatic sleep pressure as reflected in more sleepiness, resulting in more SWS.

Participants were instructed to avoid antihistamines during the 5 days before the study visit, which approximately coincided with the sleep measurements, but an effect of prior medication use could not be completely ruled out. The observed pattern potentially indicates that subjective sleep is dependent on previous experiences of sleep and expectations. Thus, in line with previous studies showing that RA patients tend to underestimate their sleep problems,[16] RA patients may habituate to a poorer sleep quality and display a response shift, adapting sleep appraisal according to life circumstances.[48] Along the same line of reasoning, patients with seasonal allergy and recurring predictable changes in disease activity across the year would not habituate to poor sleep quality. Measures of subjective sleep quality might therefore be considered more sensitive to short time than long-time variations in sleep.

In the present study, sleep was measured using a one-channel EEG, which has previously been validated against polysomnography.[38] However, this EEG-device has not been validated in clinical populations. In this patient sample, a substantial number of recordings had to be discarded because of poor quality (36% loss), mainly because of the electrode falling off during the night. This loss of data was to some extent compensated for by the fact that participants could tolerate the measurements well and the possibility to have multiple recordings in participants' homes without assistance of research personnel. The one-channel EEG showed a high convergence with actigraphy-derived measures of sleep and self-rated sleep length, supporting the reliability of the EEG method and its usefulness in a clinical population.

The main limitation in the present study is the relatively small sample size. Although power is larger in within-subject designs compared to between-subject designs, it still might not have been sufficient to detect clinically meaningful effects. The use of within-subject changes in allergy patients and matched controls for both patient groups potentially mitigated some of this weakness. In contrast to single measurements of inflammation at the day of each PET examination, sleep was recorded in a mean of 6.8 nights at each occasion, leading to a fairly large accumulated number of total recorded nights. Thus, internal validity is more strongly supported for sleep measurements than for measures of inflammation, which were limited to single measurements, with possibly lower reliability. Furthermore, sleep measurements in the present study took place mainly after medication withdrawal in allergic patients, and further studies need to investigate how treatments, including antihistaminergic medication with a clear effect on sleepiness,[49] affect sleep patterns in allergy. In all, the findings should be regarded as preliminary and further investigation is warranted.

Conclusion

This study corroborates earlier findings that both patients with seasonal allergy and RA suffer from sleep alterations in addition to their primary symptomatology. Allergy patients reported decreased sleep quality during pollen season, whereas RA patients had objectively, but not subjectively affected sleep patterns. Daily measurements of disease-specific symptoms in allergy and functional status in RA, rather than single measures of inflammation, measured in blood as well as brain, or general sickness was indicated to be of stronger importance to explain poor sleep.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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