**Title:** The relationship between sleep disturbance, symptoms and daytime functioning in psoriasis: a prospective study integrating actigraphy and experience sampling methodology.

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**Abstract
Objective/Background:** Sleep disturbance is common in individuals with psoriasis and appears to be related to both physical and psychological factors. We sought to examine whether psoriasis symptoms, night-time arousal and low mood predicted subsequent objective and self-reported sleep; and whether objective and self-reported sleep predicted next-day psoriasis symptoms and day-time functioning.

**Participants:** Nineteen individuals (Female: 11 [59.7%], median age: 39 years) with chronic plaque psoriasis and poor sleep quality (mean Pittsburgh Sleep Quality Index = 9.11).

**Methods:** Momentary assessments of psoriasis symptoms, mood and daytime functioning were completed at five pseudo-random intervals each day for 15 days using time-stamped digital diary entry. Objective sleep was estimated using wrist-worn actigraphy. Self-reported sleep and night-time arousal were assessed each morning using validated measures.

**Results:** Two-level random intercept models showed that increased night-time arousal was associated with poorer diary-reported sleep. Neither self-reported nor objective sleep parameters were associated with daytime psoriasis symptoms in bi-directional analyses. Diary-reported sleep predicted next-day functioning, specifically sleepiness, concentration, and fatigue. Actigraphy-defined total sleep time predicted next-day fatigue**.**

**Conclusions:** Night-time arousal is associated with poorer self-reported sleep in people with psoriasis, and sleep predicts next-day functioning. Contrary to our hypothesis, sleep disturbance does not appear to be associated with momentary assessments of psoriasis symptoms.

**Keywords:** sleep disturbance, psoriasis, actigraphy

**Introduction**

 Although psoriasis is a dermatological disorder, its impact extends beyond the skin. In addition to the characteristic dermatological sequelae, psoriasis is associated with significant physical and psychological morbidity (Kurd, Troxel, Crits-Christoph, & Gelfand, 2010; Takeshita et al., 2017). It is not surprising, therefore, that patients with psoriasis experience low health-related quality of life and high disease burden (Meyer et al., 2010; Obradors, Blanch, Comellas, Figueras, & Lizan, 2016).

Accumulating evidence shows that sleep disturbance is common in psoriasis (Henry, Kyle, Chisholm, Griffiths, & Bundy, 2017; Jensen, Zachariae, Skov & Zachariae., 2018). A factors may contribute to sleep disturbance in this population, including itch (Amatya, Wennersten, & Nordlind, 2008; Duffin, Wong, Horn, & Krueger, 2009; Henry et al., 2017; Henry et al. 2019; Jensen et al., 2018; Wong, Chandran, Li & Gladman., 2017) pre-sleep cognitive arousal (Henry et al., 2019), and low mood (Henry et al., 2017). Recent qualitative data also indicate that sleep disturbance has a substantial impact on the daily lives of people with psoriasis, negatively impacting daytime functioning as well as psoriasis symptoms; suggesting a potential bi-directional relationship (Henry et al., 2019). Despite increased interest in the relationship between sleep disturbance and psoriasis, research has predominantly comprised retrospective examinations using self-reported measures of sleep, with limited appraisal of the putative bi-directional relationship between sleep and day-time variables over time.

We aimed to examine the bi-directional associations between the daytime experience of psoriasis and sleep. We used experience sampling methodology (ESM), a prospective daily-diary methodology whereby experiences (e.g. mood, cognitions, behaviours, symptoms) are sampled, in the moment, over multiple time-points in the participants’ everyday surroundings (Larson & Csikszentmihalyi, 1983). This method permits examination of sequential relationships, overcoming limitations associated with retrospective assessments (Csikszentmihalyi & Larson, 2014; Shiffman, Stone, & Hufford, 2008). Recent studies using ESM have incorporated actigraphic measurement of sleep in a range of health conditions, revealing important associations between daytime experiences, symptoms and sleep disturbance (Littlewood, Kyle, Carter, Peters, Pratt & Gooding, 2018; Mulligan, Haddock, Emsley, Neil, & Kyle, 2016; Russell, Wearden, Fairclough, Emsley, & Kyle, 2016; Tang, Goodchild, Sanborn, Howard, & Salkovskis, 2012). Our study had three specific aims:

1. To examine whether psoriasis symptoms, arousal, and low mood predict sleep disturbance, hypothesizing that greater symptoms, night-time arousal and lower mood would all predict greater levels of sleep disturbance.
2. Examine the relationship between sleep and next-day psoriasis symptoms, hypothesizing that greater sleep disturbance would predict greater symptom severity the following day.
3. Examine whether sleep disturbance predicts next-day functional impairments, hypothesizing that greater sleep disturbance would be associated with greater functional impairment the following day.

**Methods**

**Participants**

Participants were recruited from psoriasis clinics at a tertiary referral dermatology centre in a large teaching hospital in the UK, a participant research database, and through social media. All participants self-reported a diagnosis of chronic plaque psoriasis, were ≥18 years old, had a sufficient understanding of English to complete measures and scored ≥6 on the Pittsburgh Sleep Quality Index (PSQI) indicating poor sleep (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Individuals were excluded if they were currently receiving in-patient treatment, met criteria for a sleep disorder other than insomnia (Brief Screen for Sleep Disorders; Wilson et al., 2010), reported a primary organic disorder responsible for sleep disturbances (e.g. hyperthyroidism, neurological disorders) or were using central nervous system altering medications that interact with sleep. Ethical approval was obtained from the Health Research Authority North East Ethics Committee (REC ref: 16/NE/0338).

**Screening measures**

Two screening measures (Brief Screen for Sleep Disorders (Wilson et al. 2010) and the Pittsburgh Sleep Quality Index [PSQI]; 19 items, range 0-21) were administered via telephone to assess the eligibility of all participants alongside collecting demographic information (age, sex, duration of psoriasis).

**Baseline Measures**

Four baseline measures were administered prior to the ESM procedure to fully describe the sample in terms of sleep (Dysfunctional Beliefs and Attitudes about Sleep Scale [DBAS-16]; scale 0-10; averaged to produce a total score; Morin, Vallières & Ivers., 2007), mood (Hospital Anxiety and Depression Scale [HADS]; scale 0-3; total score calculated for depression and anxiety subscales [range 0-21]; Zigmond & Snaith., 1983), psoriasis (Simplified Psoriasis Index Severity Scale [SPI-S]; range 0-50; Chularojanamontri et al. 2013) and stress (Perceived Stress Scale [PSS]; scale 0-4; range: 0-40; Cohen, Kamarck & Mermelstein., 1983).

**Daily Sleep Measures**

Objective sleep-wake patterns were estimated using a wrist-worn CamNtech Patient Reported Outcomes (PRO) Diary actigraph with an integrated electronic diary (CamNtech Ltd., Cambridge, UK) allowing the wearer to respond to momentary questions and has been validated previously (Jungquist, Pender, Klingman, & Mund., 2015). Data were extracted and analysed using Motionware 1.1.20 software (CamNtech Ltd., Cambridge, UK). For each night we extracted the following variables: total sleep time (TST; the total time spent asleep according to the epoch-by-epoch wake/sleep categorisation), sleep efficiency (SE: the proportion of time in bed spent asleep relative to time spent in bed expressed as a percentage) and sleep fragmentation index (the sum of time spent mobile and immobile bouts lasting ≤1 minute, with a higher score reflecting greater sleep fragmentation expressed as a percentage). Participants were instructed to wear the actigraph continuously from 18:00 on the day of administration and for fifteen days consecutively, except during wet activities.

Self-reported sleep was recorded each morning upon waking using the Consensus Sleep Diary (CSD) (Carney et al. 2012). The variables extracted for this study were (i) TST, (ii) SE [TST/ TIB (Time elapsed between when sleep was attempted and rise time) x 100], (iii) sleep quality [rated on a 5-point Likert scale (1 – very poor to 5 - very good)]. The variables used to calculate self-reported TIB were also used to set TIB for actigraphy analysis.

Night time arousal was assessed using the 9-item Sleep Interference Rating Scale (SIRS)(Bernstein, Gellis, Nau & Fichten, 2015)which captures aspects of night-time arousal (including cognitive, emotional, somatic factors) that may disturb sleep continuity and quality. Items are rated on a scale from 0 (did not occur) to 10 (interfered with sleeping very much) and are summed to yield a total daily score ranging from 0 to 90.

**ESM diary questions**

Participants were asked about their experience of psoriasis symptoms, mood, and daytime functioning using the PRO-Diary display. Questions asked participants to answer these questions based on their experience at that specific moment in time. To ensure their face validity and clarity all items were piloted with the IMPACT Psoriasis (www.impactpsoriasis.org.uk) research user group. All items were scored on seven-point Likert scales.

*Physical symptoms of psoriasis*

Psoriasis symptoms were assessed using nine items based upon symptoms reported in the Patient Reported Outcomes Measure for Psoriasis Treatment Study (PROMPT) (Kitchen, Cordingley, Young, Griffiths, & Bundy, 2015) including: *itching, soreness, pain, cracking, dry/flaking, burning, stinging, bleeding* and *hot.* Scores for each item were combined to create a global score representing *psoriasis symptoms* which could range from 9 to 63.

*Mood*

Items assessed negative mood (*sad, anxious, and irritable)*. All items were combined to create a total score ranging from 3 to 21. These items have been used to assess mood in previous ESM studies (Mulligan et al., 2016; Palmier-Claus, Dunn, & Lewis, 2012).

*Daytime Functioning*

 Sleepiness, fatigue and concentration were assessed using three questions. Items were treated as individual items in analyses.

**ESM and Sampling procedure**

Momentary assessments were programmed, administered and recorded using the PRO-Diary actigraph watch. Assessments were at 5 quasi-random time points each day for 15 days and were personalized for each participant, occurring within 1 hour of their habitual rise-time and bedtime and at three random intervals between these times. This sampling strategy was used to maximise adherence to the ESM procedure and to reduce the likelihood of anticipatory responses and reactivity (Palmier‐Claus et al., 2011; Verhagen, Hasmi, Drukker, van Os, & Delespaul, 2016). A 15-day sampling period was chosen to maximise opportunity to detect variation in both sleep and psoriasis symptoms and to enhance statistical power through increased sampling of predictor and outcome observations. A schematic of this can be seen in Figure 1.

[Insert Figure 1 about here]

**Procedure**

*Recruitment/screening phase*

Fully informed participants gave verbal consent and were screened for eligibility by telephone. Approximate bedtime and rise-times were established based upon PSQI responses to allow personalisation of ESM schedules for each participant.

*Baseline phase*

All eligible participants met with the researcher and, once written consent was obtained, baseline assessments were conducted. Following this, participants were briefed on the sleep/ESM phase and familiarized with the PRO-Diary watch, ESM procedure and completion of the paper CSD and SIRS measures.

*Sleep/ESM phase*

Participants were contacted by either phone or email on the first, fourth and eighth days of the study to check for difficulties with the watch and to remind them to complete assessments and wear the actigraphy watch. This also provided an opportunity to check that participants were still happy to continue with study participation.

 *Post-sleep/ESM phase*

On the fifteenth day participants returned the PRO-Diary and paper questionnaires. All participants were given a small cash token of appreciation for their involvement.

**Statistical Analysis**

Analyses were conducted using Stata version 14.0 (Stata Corporation, 2016, Texas, USA). Descriptive data were calculated for baseline demographic characteristics. ESM typically elicits a three-level structure, with momentary assessments nested within days nested within individuals, however, as sleep was only sampled once per day a two-level structure was required. Mean day-level aggregate scores were calculated for each dependent variable (psoriasis, mood, fatigue, sleepiness and concentration) for each participant. To limit multiple and redundant testing, SOL and WASO were not included in analyses as these contribute to and are therefore highly correlated with SE. All analyses used objective and self-reported TST, objective and self-reported SE, self-reported sleep quality and objective sleep fragmentation. Two-level random intercept models were estimated to address each research question. Following modelling analyses, residuals were calculated; all of which were normally distributed. For all models, baseline psoriasis severity was included as a covariate. Intra-class correlations (ICC) were calculated to examine between-subject variability for each model. Three participants’ assessments crossed over the beginning of daylight savings time, therefore a sensitivity analysis was conducted to examine any effect of clock change on results by removing one-week of data following on from daylight savings to account for any influence on sleep-wake patterns. No substantial changes were observed in coefficients, confidence intervals or significance, therefore we report results on the complete dataset.

**Results**

**Sample Characteristics**

Initial interest was expressed by 56 individuals, with 15 not responding to further contact, leading to 41 individuals who were screened for eligibility. Nineteen were excluded as they did not fulfil inclusion criteria (10 due to medication, 6 not meeting PSQI cut-off, 3 presenting with probable comorbid sleep conditions). Scheduling/location issues prevented two individuals from participating and one individual had to withdraw prior to starting for personal reasons. The final sample comprised 19 participants (Median age = 39; IQR = 31-55). Demographic and baseline data for all participants are displayed in Table 1. Of 1364 possible time points, participants completed 1031 (75.4%). The ICC for day-level mean aggregated psoriasis symptoms was .80, indicating low within-subject variability. Mean day-level psoriasis symptoms for the sample was 19.67 (SD=11.05) out of a possible range of 0-70.

 [Insert Table 1 about here]

**Sleep variables**

Mean scores, standard deviations, range and ICC of actigraphy and sleep diary data for all participants are shown in Table 2. Actigraphy-defined TST indicated that 78.9% of participants slept <7 hrs, 19.5% 7-9 hrs and 1.6% >9 hrs. Average values for both objective and self-reported sleep efficiency indicated poor sleep (<85%).

 [Insert Table 2 about here]

**Aim 1: Do psoriasis symptoms, night-time arousal and mood predict objective/self-reported sleep parameters?**

Daytime psoriasis symptoms and mood did not significantly predict any objective or self-reported sleep parameter (all p≥0.05). Increased night-time arousal predicted lower self-reported TST and SE, and poorer self-reported sleep quality but not objective sleep parameters (Table 3).

 [Insert Table 3 about here]

**Aim 2: Do self-reported and objective sleep parameters predict next-day psoriasis symptoms?**

Objective and self-reported sleep parameters did not predict next-day psoriasis symptoms (p>0.05) (Table 4).

 [Insert Table 4 about here]

**Aim 3: Do sleep parameters predict next day functioning (sleepiness, fatigue and concentration)?**

Lower objective and self-reported TST, and poorer self-reported sleep quality, significantly predicted higher levels of next-day fatigue. Thus, for a one hour decrease in objective TST, self-reported TST fatigue scores increased by 0.151 and 0.113 respectively. Lower self-reported TST, SE and poorer self-reported sleep quality significantly predicted increased next-day sleepiness. Finally, poorer self-reported sleep quality significantly predicted reduced concentration the following day (Table 5).

 [Insert Table 5 about here]

**Discussion**

To our knowledge, this is the first study to examine the prospective associations between the daytime experience of psoriasis and self-reported and objective indicators of sleep. Our findings reveal a link between perceptions of sleep and night-time arousal; specifically, we found that increased thoughts and worries during the night were consistently associated with poorer self-reported sleep, including lower TST, SE and sleep quality. Contrary to our hypothesis and previous research (Henry et al., 2019; Henry et al., 2017), psoriasis symptoms were not associated with night-time sleep, and we did not observe exacerbation of psoriasis symptoms following poor sleep. The lack of relationship may represent a true finding, or there may be relevant methodological factors to consider. For example, the 2-week study period may have been too short to observe significant changes in skin expression and resultant symptoms; or variations in sleep may have been too small to manifest in significant symptom changes. Sleep curtailment in causal designs has been linked to upregulated immune activity in healthy individuals (Irwin, 2015; Irwin, Olmstead, & Carroll, 2015) and exacerbation of psoriasis in murine models of psoriasis (Hirotsu, Rydlewski, Araujo, Tufik, & Andersen, 2012). Observable changes in symptoms may require greater manipulation of sleep. A related point is that our sample reported mild and well-controlled psoriasis, with stable symptoms throughout the study period, indicating a possible ‘floor effect’ in symptoms. Recruitment of participants with greater disease activity, or those who make causal attributions between sleep and psoriasis symptoms, may have delivered different results.

Both objective and self-reported measures of sleep were associated with next-day sleepiness, fatigue and concentration; all of which are known to negatively affect the daily lives of people with psoriasis (Henry, Bundy, et al., 2017; Skoie et al., 2017; Verhoeven et al., 2007). Similar findings have been documented in other chronic disease populations (Russell et al., 2016). Indeed, the negative impact of sleep disturbance on daytime functioning may increase disease burden and further contribute to impaired quality of life and therefore result in increased help-seeking behaviour due to reduced ability to cope (Kyle, Morgan, & Espie, 2010; Morin et al., 2016). This would be worth examining in future research.

A key strength of this study was the integration of actigraphy and ESM, allowing the 24-hour experience to be captured in a sequential and ecologically-valid manner. However, a number of limitations must be considered. First, although sequential associations were established, no causal inferences can be made between variables. Moreover, as night-time arousal was examined retrospectively due to concerns about reactivity, caution should be exercised when inferring prospective associations. Second, while high-frequency assessment with ESM enhances statistical power to observe relationships, the sample only consisted of 19 participants with limited variation in psoriasis severity. Third, indirectly estimating sleep using actigraphy did not permit examination of sleep staging or architecture, which may be altered due to itch and subsequent scratching (Aoki et al., 1991) or inflammatory processes (Thomas, Motivala, Olmstead, & Irwin, 2011). Finally, multiple statistical tests were performed, thus increasing the risk of Type 1 error, however we chose to report exact *p* values rather than adjusted values which is supported in clinical research as adjustment methods can increase risk for Type 2 error (Perneger, 1998). Despite these limitations, we believe this to be the first prospective examination of the reciprocal relationship between sleep and daytime variables in people with psoriasis and the first examination of objective sleep and psoriasis symptoms over multiple days. We hope this work stimulates interest in the common comorbidity between psoriasis and sleep disturbance.

We found that night-time arousal is an important correlate of disturbance in self-reported sleep parameters and that sleep significantly predicts next-day functioning in people with psoriasis. We posit that existing sleep interventions may be effective at improving sleep in individuals with psoriasis. Building upon this work, an important next-step would be to examine the acceptability and effectiveness of CBT for insomnia in patients with psoriasis.

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