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ORIGINAL ARTICLE

Prevalence and factors associated with sleep disturbance in adult patients with psoriasis

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Abstract

Background Sleep, which is crucial for restoring of physiological functions and health, is reportedly impaired in psoriasis. The role of different potential sleep confounding factors, including detailed pruritus characteristics, and the complex interplay between psychological variables (anxiety and depression), pruritus and sleep disturbance in psoriasis remain insufficiently investigated.

Objectives To investigate sleep characteristics and to identify clinical, demographic and psychological factors associated with sleep disturbance in psoriasis.

Methods This cross-sectional study included 334 psoriasis patients (response rate 86%) and 126 control subjects (response rate 82%). Measures included sleep quality [Pittsburgh Sleep Quality Index (PSQI)], psoriasis severity, pruritus characteristics, including average pruritus intensity [visual analogue scale (VAS)], severity of comorbidities, anxiety and depression (Hospital Anxiety and Depression Scale – HADS) and quality of life (Dermatology Life Quality Index – DLQI, and Short Form 12 – SF12).

Results Fifty-nine per cent of patients and 34% of control subjects ($P < 0.001$) suffered from sleep disturbance (PSQI > 5). Patients slept 1 h less than control subjects (median 6 vs. 7 h, $P < 0.001$). Patients without pruritus had less impaired sleep (global PSQI) than patients with strong ($P < 0.001$) and very strong pruritus ($P < 0.001$). Anxiety (HADS-A) and depression (HADS-D) levels were the strongest predictors of sleep impairment, followed by pruritus exacerbation at night, age, female sex, pruritus exacerbation in the morning, average pruritus intensity (VAS), diagnosed depression and gastroesophageal reflux disease, altogether explaining 32%–37% of the variance in global sleep quality. Both anxiety (HADS-A) and depression (HADS-D) were significant mediators explaining the association between pruritus intensity (VAS) and sleep impairment in 42% and 37% respectively.

Conclusions Sleep disturbance in patients with psoriasis is highly prevalent. Patients with psoriasis should be assessed for sleep impairment, pruritus, anxiety and depression. Reduction in pruritus should be considered as an important therapeutic goal, along with therapies aimed at reducing anxiety and depression.

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Conflict of interest

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Introduction

Psoriasis is a chronic inflammatory disease, primarily affecting the skin, with a prevalence of 2%–3% of the population worldwide.[1] The impact of psoriasis extends far beyond the skin, and psoriasis exerts considerable burden in many areas of patients' functioning, which increases in patients with comorbidities and pruritus.[2]

Sleep is crucial to restore and maintain physiological functions and health.[3,4] Sleep disturbance has adverse effects on numerous physiological processes,[5] health status,[5,6] functioning[7] and quality of life (QoL).[8] Short sleep duration is linked with negative health consequences, e.g. obesity,[5] diabetes,[9,10] hypertension[6,11] and depression,[12] which are also associated with psoriasis.[13] Sleep disturbances in psoriasis increase the risks of ischaemic heart disease and stroke.[14]

Sleep impairment in psoriasis was reported starting from the late eighties in studies aimed primarily at investigating QoL and disease burden.[15–17] Recent research (58–179 patients included per study) focusing on sleep and employing validated questionnaires reported higher prevalence of sleep disturbance in psoriasis as compared to control subjects.[18–21] Depending on the employed methodology and assessed parameters, different variables associated with poor sleep were identified, such as severity of pruritus,[21,22] depression,[19,22] anxiety[22] and female sex.[20]

Pruritus is the most consistently analysed and reported sleep confounder in psoriasis[23]; however, contradictory findings exist regarding the association of its intensity with sleep disturbance.[21,22,24–26] Also, the role of further sleep confounders, and detailed pruritus characteristics, such as nocturnal exacerbation, remain to be elucidated. It still remains unclear, whether or to what extent pruritus leads to a direct sleep disruption (e.g. due to its nocturnal exacerbation), or – as previously suggested – impairs sleep indirectly through stress and depression.[27]

The aim of the present study was to investigate sleep characteristics and quality and to identify clinical, demographic and psychological factors associated with sleep disturbance in patients with psoriasis.

Material and methods

Study population and procedures

This cross-sectional, questionnaire-based study including clinical interview and assessment of disease severity was performed as a part of an international project for investigation of characteristics of pruritus and disease burden in patients with psoriasis (ChIP – characterization of disease burden and itch in psoriasis) performed in Germany, Poland, Russia and Turkey. Sleep quality was assessed using a validated sleep questionnaire only in Berlin (Germany). Here, we present data of the German patients and control subjects. The ethics committee of the Charité-Universitätsmedizin Berlin approved the study (EA1/263/15). Consecutive, adult German-speaking patients with psoriasis were recruited between December 2015 and February 2017, from in- and out-patient clinics and the day-care unit of the dermatology department in a tertiary care university hospital (Charité-Universitätsmedizin Berlin, Germany). Patients with dermatologist-diagnosed psoriasis with psoriatic lesions and without active psoriasis arthropathica (i.e. without indication for intensification of therapy due to psoriasis arthropathica) were included. Three hundred thirty-four patients were recruited (three further patients declined participation), interviewed, examined (on the day of the visit for the out-patients or within three days following admission in in-patients and patients of the day-care unit) and received self-reported questionnaires, of whom 286 patients returned questionnaires (response rate 85.6%). One hundred twenty-six control subjects without chronic skin diseases or pruritus were recruited and interviewed, of whom 103 returned self-reported questionnaires (response rate 81.8%, age- and gender-matched). Valid global Pittsburgh Sleep Quality Index (PSQI)[28] scores could be obtained for 258 patients and 98 control subjects (Table 1).

Clinical interview and examination

Clinical characteristics were recorded based on a clinical interview and medical records. Severity of comorbidities was assessed using the Cumulative Illness Rating Scale (CIRS).[29] Psoriasis severity was assessed using Psoriasis Area and Severity Index (PASI), and the body surface area (BSA).

Self-reported questionnaires

Pruritus intensity during the last week was assessed using the 5-point Likert scale, ranging from absent to very strong and the visual analogue scale (VAS), ranging from 0 (no pruritus) to 10 (worst pruritus imaginable), both for average and maximum pruritus intensity. *Current pruritus* was defined as reporting of at least mild average pruritus intensity on the Likert scale. Patients were asked whether their pruritus intensity fluctuated throughout the day, and if yes, at which time of the day pruritus exacerbated (multiple answers possible).

We used the PSQI to assess sleep disturbance and sleep quality impairment over the past four weeks. The PSQI consists of 19 items grouped into 7 components: *subjective sleep quality*, *sleep latency*, *sleep duration*, *habitual sleep efficiency*, *sleep disturbances*, *use of sleeping medication* and *daytime dysfunction*. Each item and each component are scored from 0 to 3, building up to a global score, referred to as *global sleep quality*, ranging from 0 to 21. A score >5 is indicating poor sleep, referred to as *sleep disturbance*.[28]

The Hospital Anxiety and Depression Scale (HADS) is comprised of two subscales assessing anxiety (HADS-A) and depression (HADS-D).[30,31] The 12-item Short Form Survey (SF-12) was used to assess generic health-related quality of life

Table 1 Sociodemographic, clinical characteristics and disease burden of good (global PSQI score ≤ 5) and poor sleepers (global PSQI score > 5)

Numerical variable		**All patients, *N* = 258**			**Control subjects, *N* = 98**		
		Good sleepers, *N* = 106	**Poor sleepers, *N* = 152**	**Good vs. poor sleepers**	**Good sleepers, *N* = 65**	**Poor sleepers, *N* = 33**	**Good vs. poor sleepers**
		Median (IQR)		***P*, Mann–Whitney**	**Median (IQR)**		***P*, Mann–Whitney**
Age (years)		52.0 (41.0–64.0)	55.0 (47.0–65.0)	0.128	55.0 (41.0–63.0)	53.0 (43.5–60.0)	0.769
Disease duration (years)		20.0 (8.0–32.5)	21.0 (12.0–35.0)	0.425	-	-	-
Last remission (years)		2.0 (1.0–6.0)	3.0 (1.0–6.0)	0.754	-	-	-
Duration of pruritus (years)		17.5 (5.0–30.0)	19.0 (8.0–30.0)	0.580	-	-	-
Pruritus intensity during the last week (VAS 0-10)	Average	2.2 (0.6–5.1)	3.5 (0.8–6.4)	**0.033**	-	-	-
	Maximum	2.7 (0.5–5.8)	4.3 (1.0–7.4)	**0.049**	-	-	-
Body mass index (kg/m^2)		27.5 (24.3–31.4)	28.1 (24.2–33.3)	0.628	24.7 (22.2–26.7)	26.0 (21.8–30.8)	0.314
Severity of comorbidities	CIRiS score	1.0 (0–4.0)	3.0 (0.3–5.0)	**0.001**	0 (0–1.0)	1.0 (0–3.0)	**0.020**
Number of medications		0 (0–2.0)	2.0 (0–3.0)	**<0.001**	0 (0–1.0)	0 (0–1.5)	**0.037**
HADS	HADS–A	4.0 (3.0–7.0)	8.0 (5.0–11.0)	**<0.001**	4.0 (1.0–6.0)	5.0 (4.0–7.5)	**0.011**
	HADS–D	4.0 (1.3–5.0)	7.0 (4.0–11.0)	**<0.001**	2.0 (1.0–3.0)	3.0 (2.0–6.0)	**0.026**
SF-12	PCS	51.0 (39.6–54.4)	38.9 (29.4–49.5)	**<0.001**	54.4 (50.0–55.9)	51.9 (45.3–53.9)	**0.009**
	MCS	50.0 (44.1–52.3)	38.8 (31.2–49.2)	**<0.001**	49.6 (46.9–51.6)	46.9 (44.0–50.0)	0.080
DLQI-score		2.0 (1.0–7.0)	7.0 (3.0–12.8)	**<0.001**	-	-	-
		Mean ± SD		***P*, *t* test**			
Psoriasis severity	PASI	6.7 ± 6.3	6.5 ± 6.3	0.851	-	-	-
	BSA (%)	8.8 ± 11.8	7.8 ± 8.7	0.427	-	-	-
Categorical variable		***n* (%)**		***P*, χ^2**	***n* (%)**		***P*, χ^2**
Sex	Male	72 (67.9)	72 (47.4)	**0.001**	38 (58.5)	16 (48.5)	0.348
	Female	34 (32.1)	80 (52.6)		27 (41.5)	17 (51.5)	
Age (years)	<65	81 (76.4)	113 (74.3)	0.704	53 (81.5)	26 (78.8)	0.745
	≥65	25 (23.6)	39 (25.7)		12 (18.5)	7 (21.2)	
Body mass index (kg/m^2)	<20 (underweight)	2 (2.2)	5 (3.7)	0.774†	4 (6.5)	4 (12.9)	**0.005**†
	20–25 (normal weight)	27 (29.7)	40 (29.6)		28 (45.2)	10 (32.3)	
	25–30 (overweight)	32 (35.2)	43 (31.9)		26 (41.9)	8 (25.8)	
	≥30 (obesity)	30 (33.0)	47 (34.8)		4 (6.5)	9 (29.0)	
Recruitment from	Outpatient clinic	68 (64.2)	103 (67.8)	0.136	-	-	-
	Day–care unit	27 (25.5)	25 (16.4)		-	-	-
	Ward	11 (10.4)	24 (15.8)		-	-	-
Clinical type of psoriasis	Chronic plaque	103 (97.2)	145 (95.4)	0.625	-	-	-
	Guttate	2 (1.9)	6 (3.9)		-	-	-
	Psoriatic erythroderma	1 (0.9)	1 (0.7)		-	-	-
Inactive psoriasis arthropathica		26 (24.5)	53 (34.9)	0.076	-	-	-
Psoriasis severity (PASI)	Mild (≤10)	88 (83.0)	120 (78.9)	0.416	-	-	-
	Moderate to severe (>10)	18 (17.0)	32 (21.1)		-	-	-
Sleeping medication		***n* (%)**		***P*, χ^2**	***n* (%)**		***P*, Fisher's exact test**
Sleeping pills‡		2 (1.9)	24 (15.8)	**<0.001**	0	3 (9.1)	**0.036**

Total number of patients and control subjects was 334 and 126 respectively. Data presented in the table are declared for 258 patients and 98 control subjects with valid PSQI, divided in good and poor sleepers according to the PSQI cut off > 5. The reported percentage values refer to valid data only (excluding missing data). Difference in group sizes (258 patients and 98 control subjects) may lead to less power in statistical analyses for control group. Bold font indicates statistical significance at $P < 0.05$.

BMI, body mass index; BSA, body surface area; CIRS, Cumulative Illness Rating Scale; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; HADS-A, Anxiety subscale; HADS-D, Depression subscale; IQR, interquartile range; MCS, mental component summary; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SF-12, 12-item Short Form Survey; VAS, visual analogue scale.

†*P* value of the chi-squared test for comparison between obese patients [body mass index (BMI) ≥ 30] and non-obese patients (BMI < 30).

‡Obtained from the PSQI (use of sleep medication at least once weekly in the last 4 weeks).

(HR-QoL) in two components: physical component summary (PCS) and mental component summary (MCS) score.[32] Skin disease-specific HR-QoL was assessed using the Dermatology Life Quality Index (DLQI).[33]

Statistical analysis

Differences in distribution of categorical variables were tested using chi-squared test or the Fisher's exact test, where appropriate. Differences between two independent categories of parametric and non-parametric variables were tested using the two-sample *t* test or Mann–Whitney *U* test, respectively, and for three independent categories one-way analysis of variance (ANOVA) was employed, with Fisher's least significant difference (LSD) used as a post-test. Linear relationships were analysed using Spearman's correlation, and ρ coefficients <0.2 were considered as negligible. To investigate factors independently predicting sleep impairment, multiple linear regression was used. The variable selection was supported by the forward selection method. To investigate mediation effects of psychological variables (anxiety and depression) between pruritus intensity and sleep, we employed the bootstrap method.[34] Statistical significance was set at $P < 0.05$.

Results

The prevalence of sleep disturbance is higher, and sleep is more impaired in psoriasis patients than in control subjects

Poor sleep (PSQI-global > 5) was more prevalent in psoriasis patients as compared to control subjects (58.9% vs. 33.7%, $P < 0.001$, Table 2). Seventy-nine per cent of patients (219/277, 9 data missing) reported having current pruritus. Patients with current pruritus had more impaired components of subjective sleep quality, sleep latency, sleep disturbances and daytime dysfunction than patients without current pruritus (Table 2).

Patients reported shorter sleep duration than control subjects [median (IQR): 6 (5–7) vs. 7 (6–7.5) h, $P < 0.001$], and they slept more frequently shorter than 6 and 5 h, and less frequently 7–8 h/day ($P = 0.003$, $P = 0.012$ and $P = 0.003$, respectively, Fig. 1).

Table 2 Prevalence of sleep disturbance (global PSQI score >5) is higher, and sleep quality (PSQI) is reduced in its all components in patients as compared to control subjects

PSQI components and global score	Psoriasis patients			Control subjects	Total patients vs. control subjects	Patients with vs. without current pruritus
	Total	With current pruritus	Without current pruritus			
	Mean ± SD				*P*, *t* test	*P*, Fisher's least significant difference (LSD)†
Subjective sleep quality	1.41 ± 0.84	1.47 ± 0.85	1.17 ± 0.81	0.98 ± 0.68	**<0.001**	**0.019**
Sleep latency	1.43 ± 0.96	1.50 ± 0.94	1.21 ± 1.02	0.97 ± 0.82	**<0.001**	**0.048**
Sleep duration	0.92 ± 1.01	0.96 ± 1.04	0.75 ± 0.88	0.46 ± 0.70	**<0.001**	0.155
Habitual sleep efficiency	0.97 ± 1.16	0.99 ± 1.16	0.98 ± 1.16	0.50 ± 0.76	**<0.001**	0.953
Sleep disturbances	1.38 ± 0.62	1.45 ± 0.64	1.11 ± 0.47	1.10 ± 0.50	**<0.001**	**<0.001**
Use of sleeping medication	0.33 ± 0.86	0.33 ± 0.86	0.36 ± 0.90	0.10 ± 0.41	**<0.001**	0.821
Daytime dysfunction	1.18 ± 0.84	1.24 ± 0.86	0.98 ± 0.75	0.81 ± 0.70	**<0.001**	**0.039**
Global sleep quality (global PSQI score)	7.38 ± 4.27	7.65 ± 4.31	6.56 ± 4.14	4.92 ± 2.83	**<0.001**	0.081
	n (%)				*P*, χ^2	*P*, χ^2
Good sleepers (global PSQI score ≤ 5)	106 (41.1)	77 (38.9)	24 (48.0)	65 (66.3)	**<0.001**	0.241
Poor sleepers (global PSQI score > 5)	152 (58.9)	121 (61.1)	26 (52.0)	33 (33.7)		

Number of analysed total psoriasis patients, patients with current pruritus, patients without current pruritus and control subjects for *subjective sleep quality*: *N* = 278, 215, 52 and 102, respectively; *sleep latency*: *N* = 270, 208, 52 and 101, respectively; *sleep duration*: *N* = 280, 217, 53 and 102, respectively; *habitual sleep efficiency*: *N* = 274, 212, 52 and 102, respectively; *sleep disturbances*: *N* = 272, 209, 53 and 101, respectively; *use of sleeping medication*: *N* = 281, 217, 53 and 102, respectively; *daytime dysfunction*: *N* = 279, 215, 53 and 102, respectively; *global PSQI score*: *N* = 258, 198, 50 and 98, respectively. Bold font indicates statistical significance at $P < 0.05$. Presence of current pruritus was defined as reporting of at least mild average pruritus intensity in the last week on the Likert scale.

PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

†Differences between patients with and without current pruritus and control subjects were tested using one-way analysis of variance (ANOVA, $P < 0.001$ for all PSQI components, except *habitual sleep efficiency*, and *use of sleeping medication*: $P = 0.001$ and $P = 0.028$, respectively), with Fisher's least significant difference (LSD) used as a post-test for comparisons between patients with and without current pruritus.

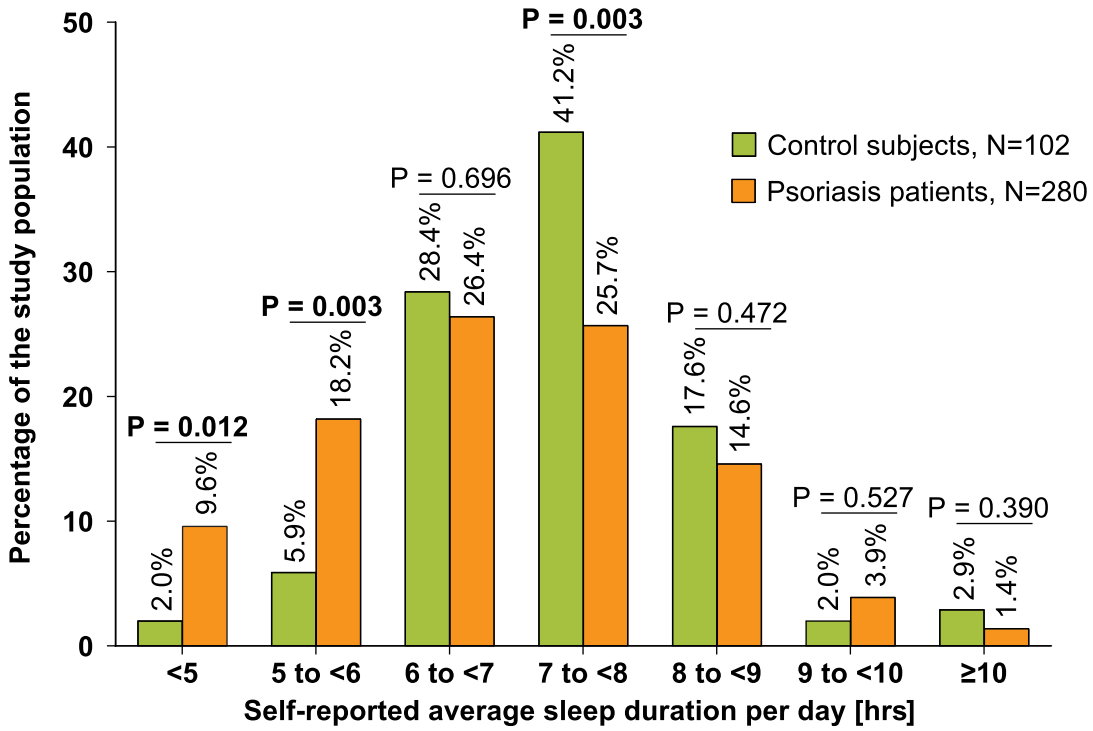

Figure 1 Psoriasis patients sleep shorter than control subjects. Comparison of self-reported average sleep duration (for the last month) per day, obtained from the Pittsburgh Sleep Quality Index (PSQI) in psoriasis patients and control subjects. *P* values on the figure declared for χ^2 or Fisher`s exact test, where appropriate. PSQI, Pittsburgh Sleep Quality Index.

Intense pruritus and pruritus fluctuating throughout the day, with exacerbations occurring around normal bedtime is associated with impaired sleep

Psoriasis patients, regardless of the presence and intensity of pruritus (Likert scale for average pruritus), had worse global sleep quality as compared to control subjects ($P < 0.001$ to $P = 0.012$), but only patients with strong and very strong pruritus had worse global sleep quality than patients without pruritus ($P < 0.001$ for both, Fig. 2).

Patients with poor sleep reported more intense pruritus (average pruritus VAS: 3.5 vs. 2.2, $P = 0.033$, maximum pruritus VAS: 4.3 vs. 2.7, $P = 0.049$, Table 1). Pruritus intensity, both average and maximum (VAS), correlated negligibly with global sleep quality impairment ($\rho = 0.196$, $P = 0.002$; $\rho = 0.189$, $P = 0.003$, respectively).

Of patients with current pruritus, 45.7% (100/219) reported daily fluctuation of its intensity, with exacerbations occurring in this group in the evening (75.0%) and/or at night (48.0%), but rarely in the morning (15.0%) and/or in the afternoon (13.0%).

Fluctuation of pruritus throughout the day was associated with worse global sleep quality [median global PSQI (IQR): 9.0 (5.0–11.0) vs. 5.0 (4.0–9.0), $P < 0.001$]. Especially, if the pruritus exacerbated at night [10.0 (6.0–13.5) vs. 6.0 (4.0–9.0), $P < 0.001$], followed by its exacerbation in the morning [10.0 (6.0–13.0) vs. 6.0 (4.75–10.0), $P = 0.038$], and in the evening [8.0 (5.0–11.0) vs. 6.0 (4.0–10.0), $P = 0.027$], global sleep quality was worse.

There were no differences between poor and good sleepers in psoriasis severity, neither for PASI ($P = 0.851$) nor for BSA ($P = 0.427$, Table 1), and the global sleep quality did not correlate with psoriasis severity, neither PASI ($\rho = 0.019$, $P = 0.762$) nor BSA ($\rho = 0.041$, $P = 0.510$).

Female patients, but not control subjects, more frequently have sleep disturbance

Poor sleep was more prevalent in female patients, but not female control subjects ($P = 0.001$ and $P = 0.348$, respectively, Table 1). Similarly, anxiety levels (but not depression – data not shown) were higher in female patients as compared to males, but not in female control subjects, [median HADS-A (IQR): 7.0 (4.0–10.5) vs. 5.0 (3.0–8.5), $P < 0.001$; 5.0 (3.0–8.0) vs. 4.0 (2.0–6.0), $P = 0.056$, respectively].

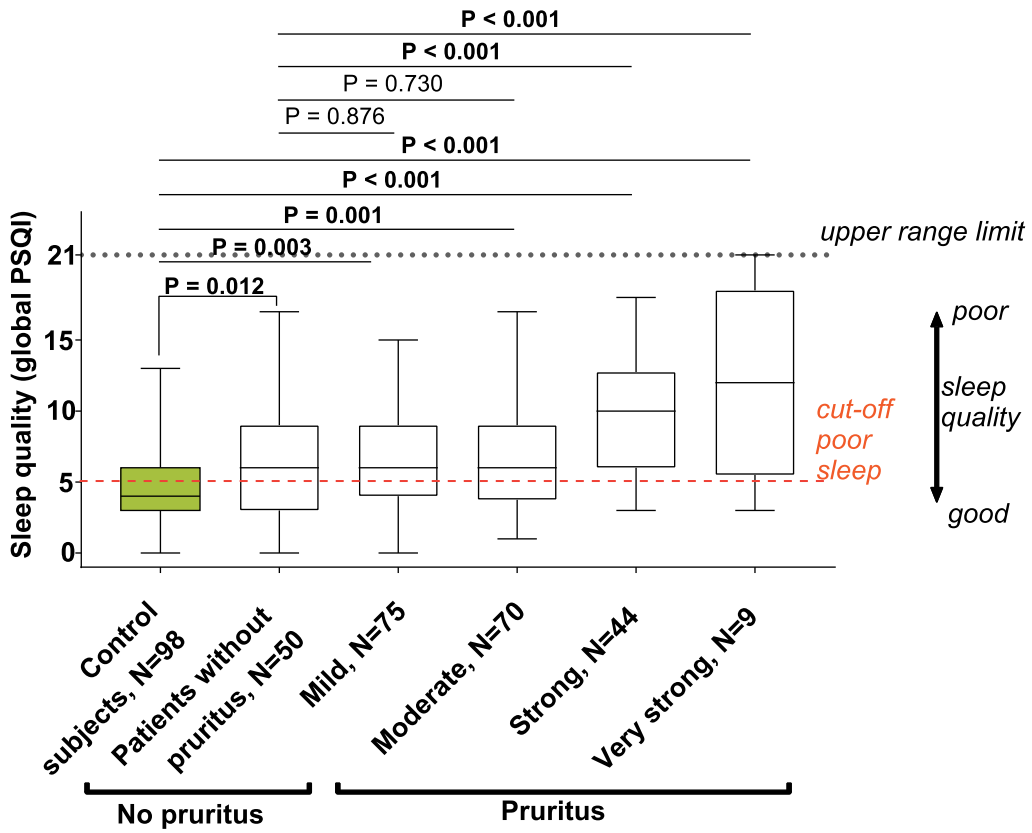

Figure 2 Psoriasis patients have more impaired sleep than control subjects, and patients with strong and very strong pruritus have more impaired sleep than patients without pruritus. ANOVA, $P < 0.001$. P values declared for Fisher's least significant difference (LSD). Horizontal lines represent median values, boxes represent interquartile ranges, and whiskers represent ranges. Only patients who provided complete responses to the PSQI and the Likert scale for pruritus were included, $N = 248$. PSQI, Pittsburgh Sleep Quality Index; LSD, Fisher's least significant difference.

Morbidity and use of sleeping pills are associated with sleep disturbance

Patients and control subjects with poor sleep had more severe comorbidities (CIRS, $P = 0.001$, and $P = 0.020$, respectively) and took more medications ($P < 0.001$ and $P = 0.037$, respectively, Table 1).

Poor sleep was associated with regular use of sleeping pills, which was reported by 16% of patients and 9% of control subjects with poor sleep ($P < 0.001$ and $P = 0.036$, respectively, Table 1).

Sleep disturbance is associated with anxiety, depression and diminished HR-QoL

Patients with sleep disturbance had more depressed mood (HADS-D), were more anxious (HADS-A) and had more impaired generic QoL [physical health domain (SF-12-PCS) and mental health domain (SF-12-MCS)], and skin disease-specific QoL (DLQI, $P < 0.001$ for all, Table 1).

Anxiety and depression are the main predictors of sleep impairment, and they mediate the link between pruritus intensity and sleep impairment

We used multiple regression modelling to investigate the complex relationship between sleep and different clinical, demographic and psychological variables. Anxiety (HADS-A) and depression (HADS-D) levels were the strongest predictors of sleep impairment in patients and control subjects, followed in patients by pruritus exacerbation at night, age, female sex, average pruritus intensity (VAS), pruritus exacerbation in the morning, diagnosed depression and GERD altogether explaining 32%–36% of variance (adjusted $R^2 = 0.320$ and $R^2 = 0.369$ for the regression models including depression and

anxiety, respectively) in global sleep quality impairment (Table 3).

Mediation analysis indicated that anxiety (ß = 0.106, 95% CI [0.049, 0.175]) and depression (ß = 0.094, 95% CI [0.038, 0.155]) are significant mediators explaining more than one-third (HADS-A: 42%, P_M = 0.416 and HADS-D: 37%, P_M = 0.369) of the association between average pruritus intensity (VAS) and global sleep quality impairment (Fig. 3a,b).

Discussion

Our cross-sectional study, using a validated sleep questionnaire, performed in the largest cohort of psoriasis patients until now, demonstrated high prevalence and relevant burden of sleep disturbance and revealed clinical and demographic variables associated with poor sleep.

Six of 10 patients (61%) with and 52% of patients without pruritus suffered from sleep disturbance. These rates are higher than in our control group (34%) and in a large community-based sample in Germany (36%),[35] and they are similar (54%–60%)[18,19] or lower (76%–80%)[21,22] than previously reported in psoriasis, using the same criteria. Of note, the prevalence of sleep disturbance in our patients was high although psoriasis in most of them was mild.

Median sleep duration of 6 h in patients was 1 h shorter than in control subjects, which confirms previous data.[19] Sleep shorter than 7 h is considered insufficient,[36] and shortened sleep

Table 3 Anxiety (HADS-A) and depression (HADS-D) are the main predictors of sleep quality impairment (global PSQI)

Predicted variable	Predictors in the model	Coefficients			R^2 change	Significant *F* change	Model summary	
		Unstandardized		Standardized			Adjusted R^2	*P*
		B	SE	Beta				
(a)								
Global sleep quality in psoriasis patients	Anxiety (HADS-A)	0.430	0.065	0.415	0.257	<0.001	0.369	**<0.001**
	Exacerbation of pruritus intensity at night	2.532	0.622	0.239	0.054	<0.001		
	Age	0.045	0.018	0.151	0.026	0.008		
	Exacerbation of pruritus intensity in the morning	2.161	0.994	0.128	0.023	0.012		
	Comorbid depression	1.652	0.773	0.133	0.015	0.035		
	Comorbid GERD	1.808	0.890	0.121	0.014	0.044		
Global sleep quality in control subjects	Anxiety (HADS-A)	0.178	0.079	0.221	0.098	0.002	0.186	**<0.001**
	Comorbid GERD	3.134	1.183	0.257	0.056	0.017		
	Comorbid depression	6.556	2.538	0.246	0.059	0.011		
Predicted variable	**Predictors in the model**	**Coefficients**			**R^2 change**	**Significant *F* change**	**Model summary**	
		Unstandardized		**Standardized**			**Adjusted R^2**	***P***
		B	**SE**	**Beta**				
(b)								
Global sleep quality in psoriasis patients	Depression (HADS-D)	0.415	0.063	0.413	0.244	<0.001	0.320	**<0.001**
	Exacerbation of pruritus intensity at night	1.914	0.661	0.181	0.044	0.001		
	Female sex	−1.276	0.526	−0.148	0.027	0.008		
	Average pruritus intensity (VAS)	0.022	0.009	0.147	0.020	0.021		
Global sleep quality in control subjects	Depression (HADS-D)	0.196	0.103	0.203	0.119	0.001	0.173	**<0.001**
	Comorbid depression	6.122	2.616	0.229	0.039	0.044		
	Comorbid GERD	2.757	1.274	0.226	0.042	0.033		

Results of multiple linear regression analysis investigating clinical, demographic and psychological variables [(a) anxiety – Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A), and (b) depression – Hospital Anxiety and Depression Scale – Depression subscale (HADS-D)] as predictors of sleep quality [global Pittsburgh Sleep Quality Index (PSQI)] in psoriasis patients and control subjects. Anxiety (HADS-A) and depression (HADS-D) levels were strongly interrelated (patients: $r = 0.684$, $P < 0.001$; control subjects: $r = 0.573$, $P < 0.001$). Therefore, two separate regression models were performed for each of these two variables. Tested variables: Comorbidities more prevalent than 3.5% [high blood pressure, diabetes mellitus type 2, depression, gastroesophageal reflux disease (GERD), hypothyroidism, dyslipidemia, osteoarthritis and herniated disc], body mass index (BMI), Psoriasis Area and Severity Index (PASI), psoriasis arthropathica, average pruritus intensity during the last week on the visual analogue scale (VAS), pruritus exacerbation in the morning/ evening/ afternoon/ at night, age, sex, Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale – Depression subscale (HADS-D). Bold font indicates statistical significance at $P < 0.05$.

BMI, body mass index; GERD, gastroesophageal reflux disease; HADS, Hospital Anxiety and Depression Scale; PASI, Psoriasis Area and Severity Index; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; VAS, visual analogue scale.

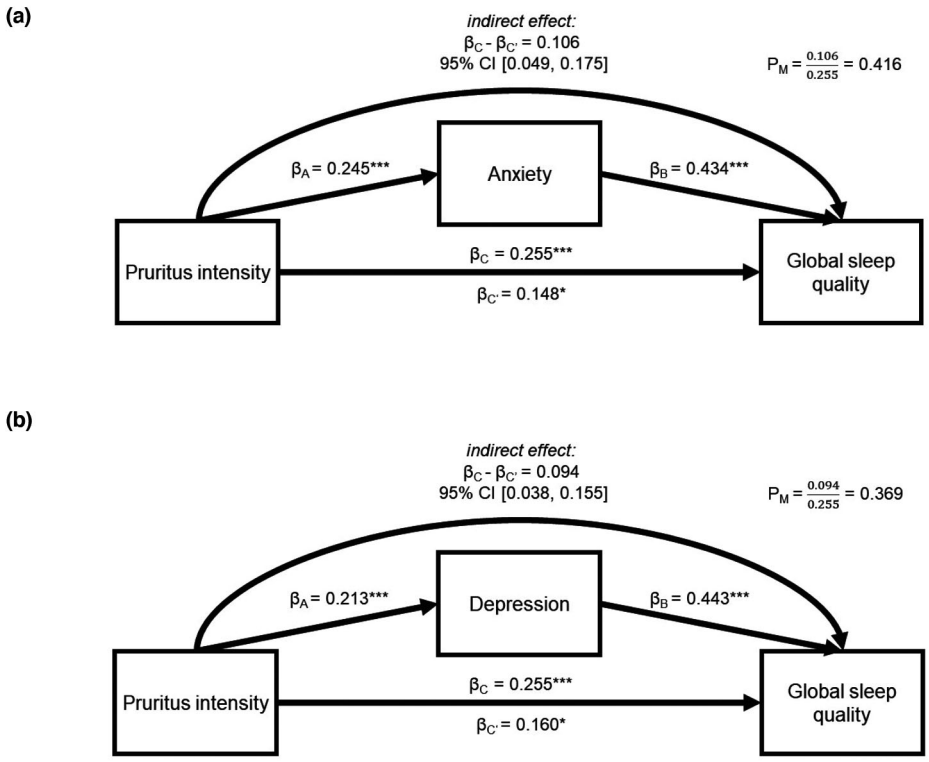

Figure 3 Anxiety and depression mediate the link between pruritus intensity and sleep impairment. (a) Anxiety [Hospital Anxiety and Depression Scale (HADS) -A] and (b) depression (HADS-D) were analysed as mediators of the relationship between pruritus intensity [average pruritus intensity in the last week on the visual analogue scale (VAS)] and sleep quality impairment [global Pittsburgh Sleep Quality Index (PSQI)]. Univariate regression was used to test direct relationships between pruritus and psychological variables (anxiety and depression levels, tested separately) (β_A), psychological variables and sleep quality (β_B), and pruritus and sleep quality (β_C). Partial mediation by psychological variables was indicated by the reduced association between pruritus and sleep quality ($\beta_{C'}$), after inclusion of psychological variables to a bivariate regression model.[50] Significance of the indirect effect mediated by psychological variables ($\beta_C - \beta_{C'}$) was confirmed using confidence intervals (CI) (the PROCESS macro for SPSS, version 3.4; model 4).[34] Confidence intervals that do not cross zero indicate significant mediation. The number of bootstrap samples for confidence intervals (95%) was set 10000. Effect size of mediation is referred to as mediation proportion (P_M) defined as ratio of the mediated effect ($\beta_C - \beta_{C'}$) to the total effect (β_C).[51] The mediation analysis showed that 42% and 37% (P_M) of the relationship between pruritus intensity and global sleep quality impairment were indirect and mediated by anxiety and depression respectively. $^{***}P < 0.001$; $^{*}P < 0.05$; ß, standardized coefficient; CI, confidence interval; P_M, mediation proportion; VAS, visual analogue scale; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

is associated with increased risk of metabolic syndrome,[37] obesity,[5] diabetes[9,10] and hypertension,[6] which are frequent comorbidities in psoriasis.[13]

Pruritus intensity in almost half of patients fluctuated throughout the day, worsening most frequently in the evening and at night, a pattern we recently described in a wide spectrum of different dermatoses.[38] Fluctuation of pruritus and its exacerbation around normal bedtime was associated with sleep impairment, probably due to a direct interference with sleep. Here, we confirmed in a large cohort of patients with psoriasis our recent finding in patients with different pruritic dermatoses, that exacerbation of pruritus around normal bedtime, and especially at night is an important predictor of sleep impairment, independent from pruritus intensity.[38]

Patients with disturbed sleep reported more intense pruritus, but linear correlation between sleep impairment and pruritus intensity was negligible. Previous studies reported none-to-moderate correlations between pruritus intensity and sleep impairment.[21,22,24–26] This may be so, because the relationship between sleep and pruritus seems not to be linear for the whole range of pruritus intensity. We observed that only strong and very strong pruritus interfere with sleep, which supports our previous finding in a large cohort of dermatologic patients.[39] Recently, we demonstrated that patients with pruritus exceeding

5 and 6.5 points on the VAS for average and maximum intensity, respectively, are likely to suffer sleep disturbance due to pruritus.[38] Our results suggest, that in patients who suffer strong pruritus, or pruritus exacerbating at night or in the morning (around normal bedtime), its reduction should be considered as an important therapeutic goal. In line with previous findings, we found no association between sleep disturbance and psoriasis severity.[21,40]

Female patients suffered more frequently sleep disturbance, which supports some previous reports,[19,20] but not the other.[21] Our observation can be explained by the fact that female patients suffer more psoriasis-related psychological burden and distress,[41] e.g. due to being more vulnerable to stigmatization,[42] which may further lead to sleep disturbance. Higher anxiety levels reported by our female patients may support this notion.

Patients and control subjects with sleep disturbance suffered more severe comorbidities. Impaired health, resulting in more physical complaints and psychological problems, leads to impaired sleep[43] and opposite, impaired sleep may exacerbate comorbidities[5,6] and impair health status.[7]

Sixteen per cent of our patients and 9% of control subjects with sleep disturbance reported regularly taking sleeping pills. Previously, even 16.5% of all psoriasis patients with chronic pruritus reported taking sleeping pills.[44] The long-term use of sedative-hypnotics has serious adverse effects and is associated with increased risk of mortality.[45] Therefore, our results indicate the need for effective treatment of the underlying factors causing sleep disturbance, such as anxiety, depression and pruritus, to improve sleep and limit consumption of sedative-hypnotics.

Age was an independent predictor of sleep impairment in psoriasis, which was previously reported.[46] Jensen et al. did not observe this relationship; however, their patients were younger.[19]

Increased levels of anxiety and depression appeared to be the main predictors of sleep impairment in our patients and control subjects. In patients, higher levels of anxiety and depression predicted sleep impairment better than pruritus parameters altogether (exacerbation at night, in the morning and pruritus intensity). As much as 37%–42% of the relationship between sleep and pruritus intensity (VAS average) was mediated by depression or anxiety, which proves that in psoriasis, depression and anxiety caused by pruritus have comparable impact on sleep as direct sleep disruption by pruritus.

It must be noted that anxiety and depression levels, as measured using HADS, were strongly interrelated, and therefore, regression modelling and mediation analyses were performed independently for these both variables. Recently, HADS-total score was proposed as a measure of psychological distress.[47–49] It is also possible that anxiety and depression result from psychological distress (e.g. caused by pruritus), which leads to sleep problems.

The cross-sectional study design does not allow for definite conclusions about causal relationships between sleep disturbances and identified associated factors. However, due to our large sample size, we can provide precise estimates of relevant associations.

To our knowledge, this is the most comprehensive study on sleep in patients with psoriasis, including clinical interview, examination and using validated questionnaires. We reveal an alarmingly high prevalence of sleep disturbance in a population of patients with prevailingly well-controlled psoriasis. Patients with psoriasis should be assessed for sleep impairment, pruritus, anxiety and depression. Our results indicate that especially in patients with strong and very strong pruritus or pruritus exacerbating at night or in the morning, its reduction should be considered as an important therapeutic goal. Providing complementary psychotherapy aimed at reducing anxiety, depression and psychological distress may help to improve sleep in patients with psoriasis.

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Data availability statement

Data are available on request due to privacy/ethical restrictions.

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