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Psychological (co)morbidity in patients with psoriasis: the impact of pruritus and anogenital involvement on symptoms of depression and anxiety and on body dysmorphic concerns – a cross-sectional study

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ABSTRACT

Objectives While stress plays a paramount role on the onset/exacerbation of psoriasis, via overactivation of the hypothalamic–pituitary–adrenal axis and increased release of pro-inflammatory cytokines, cutaneous inflammatory response induces, in turn, anxiety/depression symptoms, via body disfigurement and stigmatisation. The intensity of pruritus and anogenital involvement are additional risk factors for psychological comorbidity.Aims were to (1) examine the effects of intensity of pruritus and anogenital psoriasis on disease burden and psychological comorbidity and (2) identify the variables associated with the presence of clinically significant depression, anxiety, and dysmorphic concerns.

Design Cross-sectional study.

Setting Conducted at the University Medical Center Hamburg-Eppendorf (UKE).

Participants 107 patients with psoriasis (mean age = 46.3, SD = 14.6 years; 53.3% male): 64 with none/mild pruritus; 43 with moderate/severe pruritus; 31 with anogenital psoriasis; 76 not affected in the anogenital area.

Primary/secondary outcomes measures Disease severity was assessed with Psoriasis Area and Severity Index and intensity of pruritus was rated by patients. Patient-reported outcomes included the Dermatology Life Quality Index, ItchyQoL, Patient Benefit Index, Perceived Stigmatisation Questionnaire, and Relationship and Sexuality Scale. Psychological morbidity was assessed with the Patient Health Questionnaire, Generalised Anxiety Disorder, and Dysmorphic Concern Questionnaire.

Results Patients with moderate/severe pruritus reported more quality of life impairments, depression, anxiety and dysmorphic concerns, and less treatment benefits than those with none/mild pruritus. Moderate/severe pruritus had a deleterious effect on depression and stigmatisation for patients without anogenital involvement. Less patient benefits were associated with a higher likelihood of clinically significant depression/anxiety.

Conclusion Pruritus induces significant burden and psychological morbidity, particularly for patients without anogenital involvement. However, coping strategies used by patients with anogenital psoriasis might be dysfunctional for overall psychosocial adaptation. Patient-centred healthcare might be the best way to prevent psychological comorbidity.

Ethics approval Ethics Committee of the Medical Association of Hamburg (process number PV6083, 28 May 2019).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was innovative in its comprehensive approach to psychological comorbidity in patients with psoriasis, by examining not only the effects of clinical variables but also a wide range of patient-reported outcomes.
⇒ Another foremost contribution was the testing of interaction effects between two of the most burdensome features of psoriasis on mental health outcomes.
⇒ Additional methodological strengths were the assessment of quality of life impairments at both the skin-generic and pruritus-specific levels and the use of a high-resolution grid to document the topology of psoriasis that enabled the patients to disclose the anogenital involvement regardless of whether they have previously discussed this sensitive topic with their physicians.
⇒ This study strengthens the importance of a person-centred model of care for psoriasis, by identifying patient-defined treatment benefits as the best predictor of positive mental health outcomes.
⇒ The study had a cross-sectional design and bidirectional associations cannot be ruled out.
⇒ The small sample size diminished the statistical power of analyses and limited the generalisability of results.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that appears in a large variety of phenotypes and body locations, affecting

approximately 2.5% of the German population.[1] According to a classification of psychodermatological disorders,[2] psoriasis can be considered both as a psychophysiological condition and as a dermatological disorder with secondary psychiatric symptoms. On the one hand, psychological stressors play an instrumental role on the aetiology and exacerbation of psoriasis, via overactivation of the hypothalamic–pituitary–adrenal axis and consequent increased release of pro-inflammatory cytokines.[3] On the other hand, the cutaneous inflammatory response may induce anxiety and depression symptoms,[4] via body disfigurement and perceived stigmatisation.[5] Considering the well-established evidence on these complex neuro-immuno-cutaneous associations, the WHO recommends a comprehensive individually adapted treatment of psoriasis and its comorbidities, taking into account the patient's needs and by coordinating multidisciplinary teams of specialists, including mental health professionals.[6]

The prevalence of comorbid clinical depression (12–19%) and anxiety (7–16%) among patients with psoriasis is significantly higher than among healthy controls, and yet the proportion of patients presenting clinically significant symptoms of depression and anxiety, as assessed by questionnaire screening and requiring further evaluation, ascend to 28% and 20–50%, respectively.[7 8] In addition, disturbances in body image are also very common and a prevalence of body dysmorphic disorder (BDD) of 11.3% was estimated in general dermatology outpatients.[9]

Noteworthy, risk factors for psychological comorbidity in patients with psoriasis are a greater intensity of pruritus[10] and the location of psoriasis lesions in sexually sensitive body areas.[11 12] Itching is one of the most bothersome symptoms of psoriasis and it can be both aggravated by and the cause for psychological stress.[13 14] Indeed, greater intensity of pruritus and resulting scratching behaviours have been associated with more quality of life (QoL) impairments, anxiety and depression symptoms, sleep disturbances, increased stigmatisation, and impaired sexual relations.[10 14 15] Likewise, patients with anogenital involvement present higher risk for experiencing significant QoL impairments, stigmatisation experiences, and sexual dysfunction,[16–18] compared with those with psoriasis affecting other body regions. In addition, anogenital location of psoriasis has been associated with more depressive symptoms and body dysmorphic concerns.[11 12]

However, these studies focus on the main effects of specific risk factors and less is known about the interaction effects of anogenital involvement and intensity of pruritus, despite evidence that itching is the most frequently reported symptom in patients with genital psoriasis.[19] In addition, the majority of research addresses risk factors for developing mental health problems, and patient-centred resources that can be fostered in real-world conditions to prevent and/or reduce psychological symptoms, such as the formulation of therapy goals on the basis of patient needs, are often neglected in psychodermatology. Therefore, this study aimed to: (1) test the main and interaction effects of anogenital involvement and intensity of pruritus on disease/treatment burden and mental health outcomes; (2) examine the associations between sociodemographic, clinical and patient-reported outcomes (PROs) of disease/treatment burden and the presence of clinically significant symptoms of depression, anxiety, and body dysmorphic concerns.

MATERIALS AND METHODS

Study design and participants

This study is part of the broader research project 'Significance of chronic pruritus for social stress and disfigurement in psoriasis—healthcare study to characterise the need for action and awareness' (Pruri-Impact), which had a cross-sectional design and was conducted at the Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf (UKE), in compliance with the Declaration of Helsinki (1964, as revised in 2013).

Data collection took place between February 2019 and March 2020. Patients were consecutively recruited, according to the following inclusion criteria: (1) aged ≥ 18 years; (2) clinical diagnosis of psoriasis vulgaris; (3) ability to answer the questionnaires in German language; and (4) written informed consent form. Patients were excluded if they presented any condition, including other inflammatory diseases or dermatological conditions (eg, xerosis cutis, eczema, chronic spontaneous urticaria), which would place them at unacceptable risk due to participation in the study or would confound the interpretation of the results because of the inherent pruritus. However, psoriasis is recognised as a multisystemic disease[20] and, thus, patients with common comorbid conditions to psoriasis, such as cardiovascular diseases, diabetes, psoriatic arthritis, and depression, were included.

Outcome measures

A set of questionnaires were completed by the physician (belonging to the clinical team caring for the patient and specifically assigned for this study) and by the patient. The physician questionnaire included the assessment of clinical characteristics of psoriasis, current treatment (or last to date of assessment), comorbidities, disease severity (Psoriasis Area and Severity Index, PASI)[21] and body surface area (BSA).[22]

The patient questionnaire included a sociodemographic and clinical datasheet and the German versions of several standardised PROs, namely the Dermatology Life Quality Index (DLQI),[23] the ItchyQoL,[24] the Patient Benefit Index (PBI),[25] the two-item Patient Health Questionnaire (PHQ-2)[26] and Generalised Anxiety Disorder (GAD-2),[27] the Dysmorphic Concern Questionnaire (DCQ),[28] the Perceived Stigmatisation Questionnaire (PSQ),[29] and the Relationship and Sexuality Scale (RSS).[30] A more detailed description of the PRO measures was published elsewhere[31] and is provided in the online supplemental material.

Table 1 Sociodemographic and clinical characteristics of patients with none/mild pruritus (NRS ≤ 3) and with moderate/severe (NRS ≥ 4), with and without anogenital involvement

	None/mild pruritus		Moderate/severe pruritus		Comparison between groups	
	No anogenital involvement (n=52)	Anogenital psoriasis (n=12)	No anogenital involvement (n=24)	Anogenital psoriasis (n=19)	F/χ^2	p value
Sociodemographic characteristics						
Age, M (SD)	44.98 (14.02)	49.83 (12.41)	48.38 (17.23)	44.95 (14.49)	0.58	0.628
Gender, n (%)						
Male	33 (63.5)	6 (50.0)	8 (33.3)	10 (52.6)	6.06	0.109
Female	19 (36.5)	6 (50.0)	16 (66.7)	9 (47.4)		
Marital status, n (%)						
Single	15 (28.8)	2 (16.7)	3 (12.5)	5 (26.3)	8.30	0.504
Married/partnership	29 (55.8)	8 (66.7)	16 (66.7)	12 (63.2)		
Divorced/separated	6 (11.5)	0 (0.0)	5 (20.8)	1 (5.3)		
Widowed	2 (3.8)	1 (8.3)	0 (0.0)	1 (5.3)		
Missing	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)		
Clinical characteristics						
Type of psoriasis, n (%)*						
Plaque-type	48 (92.3)	9 (75.0)	19 (79.2)	16 (84.2)	3.90	0.272
Guttate	7 (13.5)	3 (25.0)	4 (16.7)	7 (36.8)	5.18	0.159
Intertriginous	2 (3.8)	4 (33.3)	4 (16.7)	6 (31.6)	12.42	0.006
Pustular	2 (3.8)	1 (8.3)	1 (4.2)	2 (10.5)	1.44	0.697
Psoriatic arthritis	3 (5.8)	3 (25.0)	4 (16.7)	2 (10.5)	4.56	0.207
Disease duration, M (SD)	19.65 (14.61)	13.55 (12.65)	15.64 (14.91)	14.88 (15.36)	0.88	0.454
Missing, n (%)	6 (11.5)	1 (8.3)	2 (8.3)	3 (15.8)		
Treatment, n (%)*						
Biological systemic	40 (76.9)	6 (50.0)	12 (50.0)	8 (42.1)	10.27	0.016
Conventional systemic	5 (9.6)	4 (33.3)	4 (16.7)	2 (10.5)	4.88	0.181
Topical	17 (32.7)	5 (41.7)	10 (41.7)	9 (47.4)	1.53	0.676
Other	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.07	0.785
None	1 (1.9)	0 (0.0)	1 (4.2)	2 (10.5)	3.87	0.336
Comorbidities, n (%)						
Yes	21 (40.4)	7 (58.3)	17 (70.8)	12 (63.2)	7.31	0.063
No	31 (59.6)	5 (41.7)	7 (29.2)	7 (36.8)		
PASI, M (SD)	1.73 (2.87)	1.87 (1.52)	4.66 (3.35)	7.50 (8.96)	8.49	<0.001
%BSA, M (SD)	2.11 (3.89)	1.65 (1.53)	7.18 (4.93)	16.63 (24.97)	7.97	<0.001
Missing, n (%)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)		

*Multiple answers were possible and, thus, no cumulative % can be calculated.
BSA, body surface area (range 0%-100%); M, mean; n, number of cases; NRS, Numeric Rating Scale; PASI, Psoriasis Area and Severity Index (range 0–72, with higher values indicating greater disease severity); SD, standard deviation.

In addition, patients reported on the presence of pruritus within the last 24 hours using a dichotomous response scale (yes/no), and those reporting itching also assessed its intensity ('How strong was the average itching during the last 24 hours?') using a Numeric Rating Scale (NRS) from 0 to 10. For comparative analysis, two groups were considered: patients with none/mild pruritus (NRS ≤ 3) and patients with moderate/severe pruritus (NRS ≥ 4).[32]

Anogenital involvement was assessed by the patients, based on a high-resolution grid scheme on topology of psoriasis with 1424 small squares.[33] For analysis, two groups were considered: anogenital psoriasis, when at least one square in the genital area or anal area was marked, and no anogenital involvement, when no squares in the anogenital area were marked.

Statistical analyses

The statistical analyses were conducted using IBM SPSS Statistics (SPSS, V.23.0, IBM). For all statistical tests, p values < 0.05 were considered as statistically significant. Descriptive statistics (absolute/relative frequencies for categorical variables; mean (M) and standard deviation (SD) for continuous variables) were obtained for

Table 2 Comparative analyses of patient-reported outcomes of disease and treatment burden across patients with none/mild pruritus (NRS ≤ 3) and with moderate/severe pruritus (NRS ≥ 4), with and without anogenital involvement

	None/mild pruritus		Moderate/severe pruritus		Main effects				Interaction effects	
	No anogenital involvement	Anogenital psoriasis	No anogenital involvement	Anogenital psoriasis	Pruritus		Anogenital involvement		Pruritus* anogenital	
Intrapersonal burden	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	**F**	**η_p2**	**F**	**η_p^2**	**F**	**η_p^2**
Skin-generic QoL (DLQI)	2.92 (4.37)	5.92 (5.42)	11.13 (7.19)	11.79 (5.56)	21.46***	0.18	0.36	0.00	0.71	0.01
Pruritus-specific QoL (Itchy-QoL)	1.73 (0.73)	1.98 (0.90)	3.09 (0.84)	2.83 (0.72)	32.93***	0.26	0.45	0.01	1.09	0.01
Patient benefits (PBI)	3.08 (1.05)	2.29 (1.25)	1.47 (1.10)	1.75 (1.12)	12.65***	0.13	0.02	0.00	3.47	0.04
Depression (PHQ-2)	0.48 (0.98)	1.30 (1.83)	2.38 (2.12)	1.72 (1.71)	5.61*	0.06	0.04	0.00	4.20*	0.04
Anxiety (GAD-2)	0.65 (1.25)	1.17 (1.70)	2.13 (2.07)	1.56 (1.25)	5.60*	0.06	0.28	0.00	1.76	0.02
Dysmorphic concerns (DCQ)	6.12 (4.31)	5.50 (5.50)	9.79 (6.36)	7.89 (4.00)	6.08*	0.06	1.46	0.02	0.18	0.00
Frequency of scratching†	1.23 (1.85)	1.64 (2.01)	7.00 (2.25)	9.63 (14.87)	12.67***	0.11	0.50	0.01	0.33	0.00
	n (%)	**n (%)**	**n (%)**	**n (%)**	**χ^2**		**χ^2**		**–**	
Sleeping problems‡	21 (40.4)	5 (41.7)	24 (100.0)	18 (94.7)	21.64***		7.43**		–	
Interpersonal burden	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	**F**	**η_p^2**	**F**	**η_p^2**	**F**	**η_p^2**
Perceived stigmatisation (PSQ)	1.76 (0.41)	1.79 (0.50)	2.06 (0.56)	1.74 (0.32)	0.14	0.00	2.78	0.03	3.86*	0.04
Sexual dysfunction (RSS)	15.04 (5.90)	18.83 (8.21)	16.77 (5.53)	20.67 (6.16)	0.16	0.00	3.30	0.03	0.01	0.00

The presence of intertriginous psoriasis, biological treatment and Psoriasis Area and Severity Index were included in the models as covariates.
*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, two tailed.
†Assessed by the patients through the questions 'Did you have to scratch yourself within the last 24 hours?' and 'How often have you had to scratch within the last 24 hours?', using a yes/no and a 0–10 NRS, respectively, whereby patients reporting no pruritus and/or no scratching in the last 24 hours were assumed as NRS = 0.
‡Assessed by the patients through the question 'Did you have any sleeping problems within the last 24 hours because of the itching?', using a yes/no response scale, whereby patients reporting no pruritus (not applicable) were assumed as having no sleeping problems.
DCQ, Dysmorphic Concerns Questionnaire (range 0–21, whereby higher values indicate higher dysmorphic concerns and scores ≥ 11 represent significant concerns in bodily appearance); DLQI, Dermatology Life Quality Index (range 0–30, with higher values indicating more QoL impairments); F, two-way univariate analysis of covariance; GAD-2, Generalised Anxiety Disorder (range 0–6, with cut-off scores of ≥ 3 as indicators of clinically significant symptoms of anxiety); ItchyQoL, (range 1–5, with higher scores representing more QoL impairments); M, mean; NRS, Numeric Rating Scale; PBI, Patient Benefit Index (range from 0 = "no benefit" to 4 = "maximal benefit"); PHQ-2, Patient Health Questionnaire (range 0–6, with cut-off scores of ≥ 3 as indicators of clinically significant symptoms of depression); PSQ, Perceived Stigmatisation Questionnaire (range 1–5, with higher scores indicating higher levels of perceived stigmatisation); QoL, quality of life; RSS, Relationship and Sexuality Scale (range 0–36, whereby a higher score indicates higher problem level); SD, standard deviation.

sociodemographic and clinical variables, and the homogeneity of sample characteristics between the groups with none/mild versus moderate/severe pruritus, and with versus without anogenital involvement, was examined by one-way analyses of variance (ANOVA) with post hoc tests with Bonferroni correction (continuous variables) or χ^2 tests with post hoc pairwise comparisons (categorical variables). The sociodemographic and clinical variables that significantly differed between the groups were controlled in the subsequent analyses.

To examine the main and interaction effects of intensity of pruritus and anogenital involvement on PROs of disease/treatment burden, two-way univariate analyses of covariance (ANCOVA) were performed, including presence of intertriginous psoriasis, biological treatment and PASI as covariates. Partial eta squared (η^2_p), calculated from the sum of squares of the effect in relation to the sum of squares of the effect and the sum of squares of the error associated with the effect, were presented as measures of effect sizes for the comparison analyses, considering $\eta_p^2 \geq 0.01$, $\eta_p^2 \geq 0.06$ and $\eta_p^2 \geq 0.14$ as small, medium, and large effects, respectively. For the nominal scale of presence of sleeping problems, χ^2 tests were performed.

Logistic regressions were used to identify the sociodemographic variables, clinical features and PROs of disease/treatment burden associated with the presence of clinically significant symptoms of depression (PHQ-2 ≥ 3), anxiety (GAD-2 ≥ 3), and dysmorphic concerns (DCQ ≥ 11). Only variables that were significant ($p < 0.05$) in preliminary univariable analysis were included in the multivariable models. Variance inflation factors (VIF) were examined to diagnose potential multicollinearity problems in the multivariable models, considering VIF > 5 as cause for concern and VIF ≥ 10 as indicator of severe problems.[34] The goodness of fit of the overall model was evaluated using the Hosmer-Lemeshow test, with lower values (and non-significance) indicating a better fit to the data. The statistical significance of individual variables was evaluated by calculating the Wald statistic and the odds ratio (OR), with a 95% confidence interval (CI).

RESULTS

Sample characteristics

A total of 132 patients with psoriasis vulgaris were recruited. After excluding 22 patients (16.7%) who did not return the completed questionnaires and three patients (2.3%) because of missing information on the questions related to the presence/intensity of pruritus, the sample was composed of 107 patients (mean age = 46.28, SD = 14.63 years; 52.3% male). The descriptive statistics for clinical characteristics and PROs of disease and treatment burden in the total sample were presented in a previous

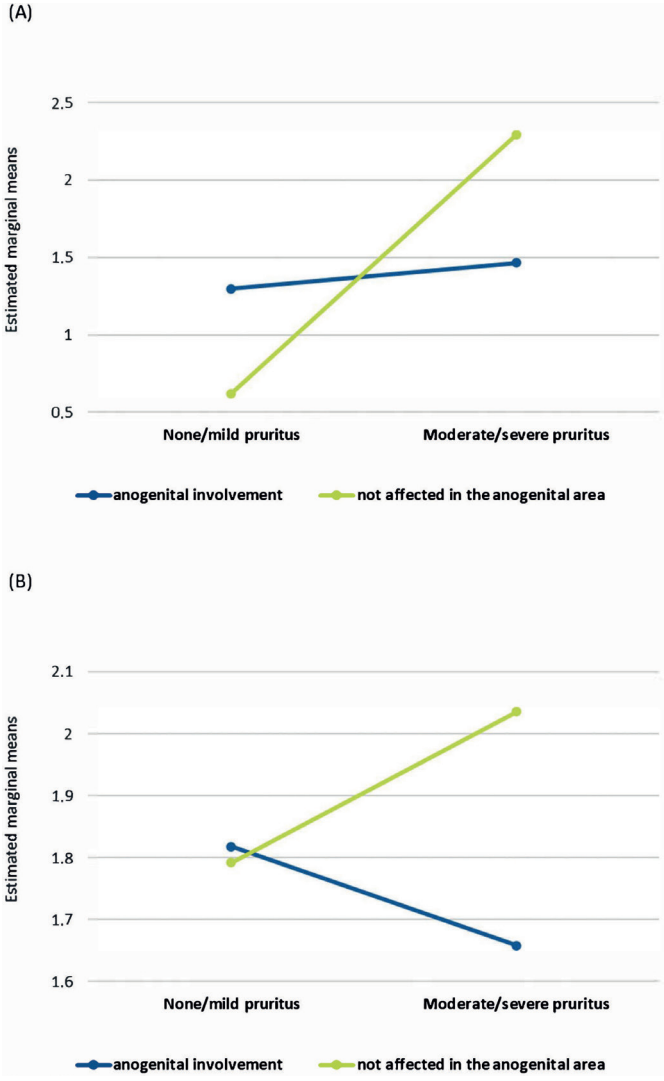

Figure 1 Interaction effects of intensity of pruritus and anogenital involvement on (A) depression symptoms and (B) stigmatisation experiences. For differences in depression symptoms (Patient Health Questionnaire-2), covariates appearing in the model were evaluated at the following values: intertriginous psoriasis = 0.16; biological treatment = 0.59; Psoriasis Area and Severity Index (PASI) = 3.44. For differences in perceived stigmatisation (Perceived Stigmatisation Questionnaire), covariates appearing in the model were evaluated at the following values: intertriginous psoriasis = 0.14; biological treatment = 0.62; PASI = 3.53.

publication.[31] Succinctly, most patients presented plaque-type psoriasis (86.0 %), with mean PASI = 3.43 (SD = 5.03; 5.6% of patients presenting moderate to severe psoriasis (PASI ≥ 10)) and mean DLQI = 6.67 (SD = 6.70; 26.2% of patients presenting very/extremely large impairments (DLQI > 10)) and were treated with biological systemic therapy (61.7%), with mean PBI = 2.39 (SD = 1.29; 69.2% of patients reporting at least minimum patient-relevant treatment benefit (PBI ≥ 1)).

Moderate/severe pruritus was reported by 43 patients (40.2%) versus 64 patients (59.8%) with none/mild pruritus, and anogenital involvement was observed in 31 patients (29.0%) versus 76 patients (71.0%) with psoriasis not affecting the anal or genital areas. The patients' sociodemographic and clinical characteristics by intensity of pruritus and anogenital involvement are displayed in table 1.

Comparative analyses revealed a lower frequency of intertriginous psoriasis among patients with none/mild pruritus and no anogenital psoriasis, compared with those with none/mild pruritus and anogenital involvement (χ^2 = 9.98, p = 0.009) and to those with moderate/severe pruritus and anogenital involvement (χ^2 = 10.71, p = 0.004). Patients with none/mild pruritus and no anogenital psoriasis were more often treated with biologics, compared with patients with moderate/severe pruritus and no anogenital psoriasis (χ^2 = 5.51, p = 0.020) or those with moderate/severe pruritus and anogenital involvement (χ^2 = 7.70, p = 0.007). Moreover, patients with moderate/severe pruritus and with anogenital involvement presented higher PASI and larger %BSA than those with none/mild pruritus and no anogenital involvement (mean difference (MD) = 5.77, 95 % CI = 2.48, 9.07, p <0.001 for PASI and MD = 14.52, 95 % CI = 6.22, 22.82, p < 0.001 for %BSA) and those with none/mild pruritus and anogenital psoriasis (MD = 5.63, 95 % CI = 1.10, 10.16, p = 0.007 for PASI and MD = 14.98, 95 % CI = 2.98, 26.98, p = 0.007 for %BSA). Thus, intertriginous psoriasis, biological treatment and PASI were controlled in subsequent analyses. Although there were also significant differences in %BSA, this measure of severity overlaps with PASI and, thus, was excluded as covariate to avoid multicollinearity problems.

PROs of disease and treatment burden

Descriptive statistics for PROs of disease/treatment burden by intensity of pruritus and anogenital involvement are presented in table 2.

Significant main effects of intensity of pruritus were found for all PROs of intrapersonal disease burden. Specifically, patients with moderate/severe pruritus reported more skin-generic and pruritus-specific QoL impairments, less treatment benefits, more depression and anxiety symptoms, more dysmorphic concerns, higher frequency of scratching behaviours and more sleeping problems than those with none/mild pruritus. Although no significant main effects of anogenital involvement were found, its interaction effects with intensity of pruritus were significant for depression symptoms and perceived stigmatisation.

Specifically, for depression symptoms (figure 1A), the deleterious effect of moderate/severe pruritus was stronger when the anogenital areas were not affected by psoriasis, while for patients with anogenital involvement the intensity of pruritus played a less relevant role. Moreover, when there was no anogenital involvement, the intensity of pruritus was positively associated with increased stigmatisation. Conversely, when the anogenital area was affected, the intensity of pruritus was negatively associated with perceived stigmatisation (figure 1B).

Table 3 Univariable and multivariable logistic regression analysis for clinically significant depression (PHQ-2 ≥ 3)

	Univariable analysis			Multivariable analysis			
	B (SE)	Wald	OR (95% CI)	*B* (SE)	Wald	OR (95% CI)	VIF
Sociodemographic characteristics							
Age	−0.01 (0.02)	0.43	0.99 (0.95, 1.03)	–	–	–	–
Gender (0 = male vs 1 = female)†	0.58 (0.54)	1.15	1.79 (0.62, 5.16)	–	–	–	–
Clinical characteristics							
Pruritus (0 = none/mild vs 1 = moderate/severe)†	1.76 (0.62)	8.16**	5.83 (1.74, 19.53)	−0.12 (1.42)	0.01	0.89 (0.06, 14.41)	2.11
Anogenital involvement (0 = no vs 1 = yes)†	0.69 (0.55)	1.56	2.00 (0.68, 5.93)	–	–	–	–
Intertriginous psoriasis (0 = no vs 1 = yes)†	0.98 (0.62)	2.45	2.65 (0.78, 9.00)	–	–	–	–
Disease duration	−0.06 (0.03)	4.43*	0.95 (0.90, 0.99)	−0.02 (0.04)	0.20	0.98 (0.91, 1.06)	1.15
Biological treatment (0 = no vs 1 = yes)†	−1.19 (0.56)	4.55*	0.30 (0.10, 0.91)	4.39 (2.10)	4.35*	80.30 (1.30, 4950.81)	1.85
Comorbidities (0 = no vs 1 = yes)†	0.23 (0.54)	0.19	1.26 (0.44, 3.64)	–	–	–	–
PASI	0.13 (0.06)	4.88*	1.13 (1.01, 1.27)	0.25 (0.13)	3.61	1.28 (0.99, 1.65)	1.70
PROs of disease/treatment burden							
Skin-generic QoL (DLQI)	0.18 (0.05)	14.64***	1.19 (1.09, 1.31)	−0.10 (0.12)	0.68	0.90 (0.71, 1.15)	3.29
Pruritus-specific QoL (ItchyQoL)	1.22 (0.36)	11.46***	3.40 (1.68, 6.91)	−0.25 (1.05)	0.06	0.78 (0.10, 6.08)	2.88
Patient benefit (PBI)	−1.44 (0.38)	14.38***	0.24 (0.11, 0.50)	−3.08 (1.31)	5.50*	0.05 (0.01, 0.60)	2.57
Frequency of scratching	0.03 (0.03)	0.94	1.03 (0.97, 1.09)	–	–	–	–
Sleeping problems (0 = no vs 1 = yes)†	1.69 (0.62)	7.43**	5.42 (1.61, 18.26)	0.83 (1.42)	0.34	2.29 (0.14, 37.31)	1.71
Perceived stigmatisation (PSQ)	2.24 (0.64)	12.20***	9.40 (2.67, 33.03)	2.14 (1.62)	1.76	8.52 (0.36, 202.47)	1.41
Sexual dysfunction (RSS)	0.18 (0.05)	12.56***	1.19 (1.08, 1.31)	−0.05 (0.12)	0.14	0.96 (0.75, 1.22)	1.73

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, two tailed.
†The reference category was the first, that is, scored as 0.
B, regression coefficient; CI, confidence interval; DLQI, Dermatology Life Quality Index; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBI, Patient Benefit Index; PHQ-2, Patient Health Questionnaire; PROs, patient-reported outcomes; PSQ, Perceived Stigmatisation Questionnaire; QoL, quality of life; RSS, Relationship and Sexuality Scale; SE, standard error; VIF, variance inflation factor.

Variables associated with psychological comorbidity

The mean PHQ-2 in the total sample was 1.26 (SD = 1.73), with 17 patients (15.9%) presenting clinically significant symptoms of depression (PHQ-2 ≥ 3). Univariable analyses (table 3) revealed that patients with moderate/severe pruritus, shorter disease duration, not prescribed with biological treatment, higher PASI, more skin-generic and pruritus-specific QoL impairments, less patient benefits, sleeping problems, more stigmatisation experiences, and greater sexual dysfunction were more likely to present clinically significant symptoms of depression. The final multivariable logistic regression model was significant, $\chi^2_{(10)} = 34.03$, $p < 0.001$, and explained approximately 37.7% (Cox and Snell R^2) to 65.5% (Nagelkerke R^2) of the variation in the presence of clinically significant depression. The results of the Hosmer-Lemeshow goodness of fit test indicated that the multivariable model fit the data well, $\chi^2_{(8)} = 5.16$, $p = 0.740$. In the multivariable model, patients prescribed with biological treatment and reporting less patient benefits were more likely to present clinically significant symptoms of depression (table 3). However, the significance of biological treatment should be interpreted with caution because of the extremely wide 95% CI.

The mean GAD-2 was 1.21 (SD = 1.62), with 16 patients (15.0%) presenting clinically significant symptoms of anxiety (GAD-2 ≥ 3). A greater likelihood of having clinically significant symptoms of anxiety was observed in univariable analyses for female patients, with moderate/severe pruritus, with more DLQI and ItchyQoL impairments, less treatment benefits, experiencing sleeping problems, perceiving higher levels of stigmatisation, and having more sexual problems (table 4). The multivariable logistic regression model was significant, $\chi^2_{(8)} = 35.57$, $p < 0.001$, and showed a good fit to the data, as indicated by the Hosmer-Lemeshow test, $\chi^2_{(8)} = 2.19$, $p = 0.975$. The model explained approximately 36.6% (Cox and Snell R^2) to 65.8% (Nagelkerke R^2) of the variation in the presence of clinically significant anxiety. The multivariable analysis showed that the presence of clinical anxiety was less likely in patients with more patient-defined treatment benefits (table 4).

In addition, the mean DCQ was 7.23 (SD = 5.10), with 25 patients (23.4%) reporting significant concerns in bodily appearance (DCQ ≥ 11). Univariable analyses (table 5) showed that females, patients with moderate/severe pruritus, with comorbidities, more skin-generic and pruritus-specific QoL impairments, less patient benefits, and with higher levels of perceived stigmatisation were more likely to report significant concerns in bodily appearance. The multivariable model was significant, $\chi^2_{(7)} = 18.37$, $p = 0.010$, fitted the data well as indicated by

Table 4 Univariable and multivariable logistic regression analysis for clinically significant anxiety (GAD-2 ≥ 3)

	Univariable analysis			Multivariable analysis			
	B (SE)	Wald	OR (95% CI)	*B* (SE)	Wald	OR (95% CI)	VIF
Sociodemographic characteristics							
Age	< 0.01 (0.02)	0.04	1.00 (0.97, 1.04)	–	–	–	–
Gender (0 = male vs 1 = female)†	1.50 (0.62)	5.92*	4.50 (1.34, 15.12)	0.69 (1.47)	0.22	2.00 (0.11, 35.25)	1.22
Clinical characteristics							
Pruritus (0 = none/mild vs 1 = moderate/severe)†	1.40 (0.59)	5.68*	4.03 (1.28, 12.70)	0.11 (1.29)	0.01	1.11 (0.09, 13.96)	1.74
Anogenital involvement (0 = no vs 1 = yes)	0.42 (0.57)	0.55	1.53 (0.50, 4.66)	–	–	–	–
Intertriginous psoriasis (0 = no vs 1 = yes)†	0.71 (0.66)	1.16	2.03 (0.56, 7.34)	–	–	–	–
Disease duration	−0.04 (0.03)	2.46	0.96 (0.92, 1.01)	–	–	–	–
Biological treatment (0 = no vs 1 = yes)†	−1.07 (0.56)	3.58	0.34 (0.11, 1.04)	–	–	–	–
Comorbidities (0 = no vs 1 = yes)†	0.18 (0.55)	0.11	1.20 (0.41, 3.51)	–	–	–	–
PASI	0.04 (0.05)	0.64	1.04 (0.95, 1.14)	–	–	–	–
PROs of disease/treatment burden							
Skin-generic QoL (DLQI)	0.19 (0.05)	15.83***	1.21 (1.10, 1.34)	0.10 (0.14)	0.56	1.11 (0.85, 1.46)	2.87
Pruritus-specific QoL (ItchyQoL)	1.41 (0.40)	12.59***	4.09 (1.88, 8.91)	−0.39 (0.99)	0.16	0.68 (0.10, 4.67)	2.74
Patient benefit (PBI)	−2.18 (0.62)	12.30***	0.11 (0.03, 0.38)	−2.22 (0.93)	5.77*	0.11 (0.02, 0.66)	1.88
Frequency of scratching	0.03 (0.03)	0.92	1.03 (0.97, 1.09)	–	–	–	–
Sleeping problems (0 = no vs 1 = yes)†	1.90 (0.64)	8.89**	6.71 (1.92, 23.44)	−0.19 (1.39)	0.02	0.83 (0.05, 12.70)	1.55
Perceived stigmatisation (PSQ)	2.12 (0.61)	11.94***	8.31 (2.50, 27.59)	1.94 (1.48)	1.72	6.98 (0.38, 127.24)	1.30
Sexual dysfunction (RSS)	0.15 (0.05)	10.16***	1.16 (1.06, 1.28)	−0.03 (0.12)	0.05	0.98 (0.77, 1.23)	1.43

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, two tailed.
†The reference category was the first, that is, scored as 0.
B, regression coefficient; CI, confidence interval; DLQI, Dermatology Life Quality Index; GAD-2, General Anxiety Disorder; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBI, Patient Benefit Index; PROs, patient-reported outcomes; PSQ, Perceived Stigmatisation Questionnaire; QoL, quality of life; RSS, Relationship and Sexuality Scale; SE, standard error; VIF, variance inflation factor.

the Hosmer-Lemeshow test, $\chi^2_{(8)} = 14.66$, p = 0.066, and explained approximately 19.2% (Cox and Snell R^2) to 28.3% (Nagelkerke R^2) of the variation in the presence of dysmorphic concerns. However, none of the isolated independent variables was significantly associated with the likelihood of dysmorphic concerns in the multivariable logistic regression model (table 5).

DISCUSSION/CONCLUSION

This study was innovative in its comprehensive approach to psychological comorbidity in patients with psoriasis, by examining not only the effects of clinical variables but also a wide range of PROs, including intrapersonal and interpersonal burden of psoriasis. Another foremost contribution was the testing of interaction effects between two of the most burdensome features of psoriasis, that is, intensity of pruritus[14] and anogenital location,[18] on mental health outcomes. In addition, this was the first study examining patient-defined treatment benefits and how they operate as a resource factor to prevent/reduce psychological symptoms. Additional methodological strengths were the assessment of QoL impairments at both the skin-generic and pruritus-specific levels and the use of a high-resolution grid to document the topology of psoriasis[33] that enabled the patients to disclose the anogenital involvement regardless of whether they have previously discussed this sensitive topic with their physicians.

While the higher intrapersonal disease burden (ie, lower QoL, more psychological symptoms and less treatment benefits) among patients with more intense pruritus was predictable, the interaction effects of anogenital involvement and intensity of pruritus on depression and stigmatisation are worth of further discussion. Previous studies have found positive associations between intensity of pruritus and levels of depression[10 14] as well as intensity of pruritus and stigmatisation,[14 15] which was confirmed in our study, but only for the group of patients without anogenital involvement. However, when the anogenital area was affected, the impact of moderate/severe pruritus on depression symptoms became negligible, and it even decreased the levels of perceived stigmatisation. At the first glimpse, this result contradicts the literature advocating that pruritus is one of the most frequent and debilitating symptoms of genital psoriasis,[19] but an alternative interpretation suggests that the accumulative burden of anogenital psoriasis and moderate/severe pruritus may trigger avoidance coping strategies (eg, mental disengagement; social withdrawal) that have a protective effect on the patients' mental health, on the short term. Nevertheless, the long-term efficacy of such avoidance coping

Table 5 Univariable and multivariable logistic regression analysis for significant dysmorphic concerns (DCQ ≥ 11)

	Univariable analysis			Multivariable analysis			
	B (SE)	Wald	OR (95% CI)	*B* (*SE*)	Wald	OR (95% CI)	VIF
Sociodemographic characteristics							
Age	−0.01 (0.02)	0.47	0.99 (0.96, 1.02)	–	–	–	–
Gender (0 = male vs 1 = female)†	1.19 (0.49)	5.99*	3.29 (1.27, 8.54)	0.50 (0.62)	0.66	1.65 (0.49, 5.54)	1.21
Clinical characteristics							
Pruritus (0 = none/mild vs 1 = moderate/severe)†	1.47 (0.49)	8.91**	4.33 (1.65, 11.34)	0.71 (0.69)	1.05	2.03 (0.53, 7.81)	1.80
Anogenital involvement (0 = no vs 1 = yes)†	0.01 (0.51)	0.00	1.01 (0.37, 2.75)	–	–	–	–
Intertriginous psoriasis (0 = no vs 1 = yes)†	0.78 (0.58)	1.82	2.18 (0.70, 6.76)	–	–	–	–
Disease duration	< −0.01 (0.02)	0.01	1.00 (0.97, 1.03)	–	–	–	–
Biological treatment (0 = no vs 1 = yes)†	−0.52 (0.46)	1.25	0.60 (0.24, 1.48)	–	–	–	–
Comorbidities (0 = no vs 1 = yes)†	1.07 (0.50)	4.60*	2.92 (1.10, 7.77)	0.91 (0.60)	2.32	2.48 (0.77, 8.02)	1.07
PASI	0.04 (0.04)	0.83	1.04 (0.96, 1.13)	–	–	–	–
PROs of disease/treatment burden							
Skin-generic QoL (DLQI)	0.07 (0.03)	4.90*	1.08 (1.01, 1.15)	−0.11 (0.07)	2.68	0.89 (0.78, 1.02)	3.11
Pruritus-specific QoL (ItchyQoL)	0.97 (0.28)	11.76***	2.64 (1.52, 4.59)	0.84 (0.49)	2.93	2.30 (0.89, 5.99)	3.17
Patient benefit (PBI)	−0.50 (0.20)	6.47*	0.61 (0.42, 0.89)	−0.30 (0.28)	1.15	0.74 (0.43, 1.28)	1.98
Frequency of scratching	0.02 (0.03)	0.47	1.02 (0.97, 1.08)	–	–	–	–
Sleeping problems (0 = no vs 1 = yes)†	1.05 (0.57)	3.45	2.86 (0.94, 8.69)	–	–	–	–
Perceived stigmatisation (PSQ)	1.27 (0.50)	6.48*	3.55 (1.34, 9.40)	0.70 (0.76)	0.86	2.02 (0.46, 8.95)	1.33
Sexual dysfunction (RSS)	0.06 (0.04)	2.40	1.06 (0.99, 1.14)	–	–	–	–

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, two tailed.
†The reference category was the first, that is, scored as 0.
B, regression coefficient; CI, confidence interval; DCQ, Dysmorphic Concern Questionnaire; DLQI, Dermatology Life Quality Index; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBI, Patient Benefit Index; PROs, patient-reported outcomes; PSQ, Perceived Stigmatisation Questionnaire; QoL, quality of life; RSS, Relationship and Sexuality Scale; SE, standard error; VIF, variance inflation factor.

strategies should be addressed in further research and in clinical practice, as a decreased level of perceived external stigmatisation may indicate reduced opportunities for social interactions derived from avoidance coping mechanisms.

With regard to the second aim of the study, several isolated factors associated with depression, anxiety, and dysmorphic concerns were identified, although only decreased patient benefits remained significantly associated with a higher likelihood of having clinically significant symptoms of depression and anxiety in the multivariable models, together with biological treatment in the case of depression. The negative associations between the PBI and the higher likelihood of clinically significant symptoms of depression and anxiety indicate that treatment choices that address the specific patient needs are the best predictors of positive mental health outcomes and strengthen the importance of a person-centred model of care for psoriasis. With regard to the association between being prescribed with biological treatment and being more prone to present clinically significant symptoms of depression, the results should be interpreted with caution, because of the instability of the direction of this association in the univariable (patients not prescribed with biologics were more likely to present clinical symptoms of depression) versus multivariable analyses (prescription of biologics was associated with higher likelihood of depression) and because of the extremely wide 95% CI in the multivariable regression. Increased risk of depression has been also found among patients receiving topical, conventional systemic or biological therapy, with the highest risk for those aged 40–50 years and treated with biologics.[35] Contrariwise, three randomised control trials showed a significant reduction of depression symptoms in patients treated with adalimumab, etanercept or ustekinumab, compared with placebo groups.[36] Considering that biologics are not the first-line treatment for psoriasis, a higher disease severity and higher disease burden, which qualifies the patients for biological treatment, could be the explanatory factors for the higher likelihood of depression (confounding by indication). The univariable associations between higher PASI and clinical depression, as well as between more DLQI impairments and clinical depression, corroborate this hypothesis. Although

the independent variable 'biological treatment' did not present high multicollinearity with the other predictors, the confounded inter-relationships between biological treatment, PASI and DLQI impairments might have influenced significantly the regression model results, namely the wide range of the 95% CI.[37]

Some limitations should be taken into account in the interpretation of results. First, the study had a cross-sectional design and bidirectional associations cannot be ruled out, for example, depression and anxiety symptoms exacerbating the severity of psoriasis,[3 4] the intensity of pruritus[13] or the QoL impairments.[11] Second, the small sample size diminished the statistical power of analyses and resulted in wide CIs, particularly in multivariable analyses. Consequently, conclusions based on effect estimates are unreliable and the results must be interpreted only qualitatively, in terms of positive/negative associations between the variables. Third, the convenience sampling method in a single dermatology outpatient clinic based in an university hospital limits the generalisability of results, for example, to other geographical areas or to patients being cared by office-based dermatologists. A fourth limitation refers to the absence of detailed information on the previous psychiatric history. Only the presence of comorbid depression was inquired to the physicians, but no information was recorded regarding anxiety and BDD or whether the diagnosis of depression was primary or secondary to psoriasis. Finally, the inadequacy of PASI to capture the involvement and severity of anogenital psoriasis should be also acknowledged as a limitation, even if significant convergent validity between the patient-reported grid of topical distribution of psoriasis and the clinical outcomes was previously demonstrated.[33]

Despite the aforementioned limitations, this study has important implications for clinical practice. While the percentage of patients scoring above the cut-off points for clinically significant depression and anxiety resembled the prevalence rates reported in literature,[7 8] the portion of patients presenting significant dysmorphic concerns in our study was double the prevalence of BDD in general dermatology outpatients.[9] This disparity might be due to the use of a cut-off point ≥ 11, which ensured maximal sensitivity but may have compromised specificity.[38] Even keeping this limitation in mind, the frequency of subclinical symptoms of BDD secondary to a visible skin condition calls for further evaluation in clinical practice, as they may significantly impair the patients' health outcomes. Indeed, screening for psychological symptoms, even when subclinical, is crucial to prevent non-adherence to treatments.[39 40] The clinical decisions based on patient needs might be the best way to prevent or reduce psychological problems. In-depth evaluation of patient needs, particularly related to sexually sensitive issues, and avoidance coping mechanisms is paramount,[18] because their apparent protective role can disguise a maximal impact of psoriasis in patients' intrapersonal experiences and mental health.

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Contributors NdS contributed for conceptualisation, methodology, data curation, formal analysis, discussion of results and writing of the manuscript (original draft). MA contributed for conceptualisation, funding acquisition, investigation, methodology, project administration, supervision, discussion of results and writing of the manuscript (critical review and editing). CH contributed to conceptualisation, investigation, methodology, data acquisition, discussion of results, and writing of the manuscript (critical review and editing). CCvS contributed for conceptualisation, methodology, validation of analysis, discussion of results, and writing of the manuscript (critical review and editing). RS contributed for conceptualisation, funding acquisition, methodology, project administration, supervision, discussion of results and writing of the manuscript (critical review and editing). NdS, MA, and RS accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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