Itch and Mental Health in Dermatological Patients across Europe: A Cross-Sectional Study in 13 Countries

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Itch is a highly prevalent and multidimensional symptom. We aimed to analyze the association between itch and mental health in dermatological patients. This multicenter study is observational and cross-sectional and was conducted in dermatological clinics across 13 European countries. A total of 3,530 patients and 1,094 healthy controls were included. Patients were examined clinically. Outcome measures were itch (presence, chronicity, and intensity), the Hospital Anxiety and Depression Scale, EQ-5D visual analogue scale, socio-demographics, suicidal ideation, and stress (negative life events and economic difficulties). Ethical approval was obtained. Results showed significant association between the presence of itch in patients and clinical depression (odds ratio, 1.53; 95% confidence interval, 1.15−2.02), suicidal ideation (odds ratio, 1.27; 95% confidence interval, 1.01−1.60), and economic difficulties (odds ratio, 1.24; 95% confidence interval, 1.10−1.50). The mean score of reported generic health status assessed by the EQ-5D visual analogue scale was 65.9 (standard deviation = 20.1) in patients with itch, compared with 74.7 (standard deviation = 18.0) in patients without itch ($P < 0.001$) and 74.9 (standard deviation = 15.7) in controls with itch compared with 82.9 (standard deviation = 15.6) in controls without itch ($P < 0.001$). Itch contributes substantially to the psychological disease burden in dermatological patients, and the management of patients should include access to multidisciplinary care.

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INTRODUCTION

The burden of itch has been described for specific skin diseases such as hand eczema (Boehm et al., 2012), atopic dermatitis (Chrostowska-Plak et al., 2013; Simpson et al., 2018), psoriasis (Chrostowska-Plak et al., 2013; Reich et al., 2016, 2010; Zachariae et al., 2012), prurigo nodularis (Brenaut et al., 2019; Konda et al., 2015), and hidradenitis suppurativa (Kaaz et al., 2018); among hemodialysis patients (Suseł et al., 2014; Weiss et al., 2016; Yamamoto et al., 2009); and in chronic itch patients in general (Schneider et al., 2006; Steinke et al., 2018; Stumpf et al., 2015). The cross-aggravation of pruritus and depression was demonstrated to give important implications for the treatment of depression in patients with pruritus (Wang et al., 2018). Although there are already studies showing evidence of correlation between itch and mental health problems in general (Caccavale et al., 2016) and in specific skin disorders, there is a lack of a cross-sectional study across chronic skin diseases demonstrating the correlations between itch and mental health problems.

The multidimensional nature of pruritus and the quality of life impairment of patients with pruritus were demonstrated

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Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; VAS, visual analogue scale

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in a Danish study (Zachariae et al., 2012). The association of itch, depression, and quality of life has been described in the general population among adults (Dalgard et al., 2007 , 2004); and among adolescents the severity of itch was shown to increase with symptoms of depression (Halvorsen et al., 2009). The pathophysiological mechanism might be the production and interaction of neuropeptides such as serotonin (Zhao et al., 2013). Itch as a demonstration of a neurogenic inflammation has been described by several authors in recent years, highlighting the interaction between nerve endings in the skin and brain activation (Choi and Di Nardo, 2018; Gupta and Harvima, 2018).

Data on the epidemiology of itch in dermatological patients in comparison to healthy skin controls were recently published (Schut et al., 2019). This itch study is based on the same data set and is part of a large European multicenter study conducted by the European Society for Dermatology and Psychiatry that aimed to better document the psychological burden of patients with skin diseases (Dalgard et al., 2015). The aim of this study is to compare the psychological burden of disease and the health-related quality of life between dermatological patients with itch and dermatological patients without itch as well as with healthy controls.

RESULTS

A total of 3,635 patients and 1,359 controls were examined with a participation rate of 79.5%. Of all examined participants, 3,530 patients (97.1% of all patients) and 1,094 controls (80.5% of all controls) responded to the question on the experience of itch. This group of 4,624 subjects constitutes our study population. Among itchy patients, 56.3% were females compared with 64.6% of the controls, and the mean age was 47.2 years (standard deviation [SD] = 17.5) compared with 40.5 years (SD = 13.3) among the controls. The prevalence of itch in dermatological conditions was 88.9% in prurigo and related conditions, 86.0% in atopic dermatitis, 82.3% in hand eczema, 77.7% in other eczema, 75.9% in urticarial, and 70.4% in psoriasis. Other characteristics of the population are described in a recently published article (Schut et al., 2019).

Prevalence of mood disorders and quality of life impairment in patients with itch

The prevalence of depression was 14.1% (95% confidence interval [CI] = 12.5−15.7%) in patients with itch, 5.7% (95% CI = 4.5−6.9%) in patients without itch, 5.7% (95% CI = 0.8−10.7%) in controls with itch, and 3.2% (95% CI = 2.1−4.3%) in controls without itch. The prevalence of anxiety in patients with itch was 21.4% (95% CI = 19.6−23.3) and 12.3% (95% CI = 10.5−13.9%) in patients without itch, 8.1% (95% CI = 2.2−13.9%) in controls with itch, and 8.8% (95% CI = 7.0−10.5) in controls without itch (Table 1). The prevalence of suicidal ideation was 15.7% (95% CI = 14.0−17.3%) in patients with itch, 9.1% (95% CI = 7.7−10.6%) in patients without itch, 18.6% (95% CI = 10.2−27.0%) in controls with itch, and 8.6% (95% CI = 6.9−10.4%) in controls without itch. Patients with itch reported that they had experienced more negative life events than patients without itch (38.2%, 95% CI 36.1−40.5% vs. 32.4%, 95% CI 29.9−34.7%; $P < 0.001$).

The mean score of reported generic health status assessed by the EQ-5D visual analogue scale (VAS) was 65.9 (SD = 20.1) in patients with itch compared with 74.7 (SD = 18.0) in patients without itch ($P < 0.001$) and 74.9 (SD = 15.7) in controls with itch compared with 82.9 (SD = 15.6) in controls without itch ($P < 0.001$).

Association of presence, chronicity, and intensity of itch with mood disorders, stressful life events, and quality of life in dermatological patients

Table 2 shows a significant association between the presence of itch in patients and clinical depression (odds ratio [OR], 1.53; 95% CI, 1.15−2.02), suicidal ideation (OR, 1.27; 95% CI, 1.01−1.60), and economic difficulties (OR, 1.24; 95% CI, 1.10−1.50), but no significant association with anxiety and negative life events within the last 6 months. There was no significant association for chronicity and intensity of itch with psychosocial factors, and there was no significant association between presence, chronicity, and intensity of itch and general quality of life assessed with EQ-5D-VAS. There was a weak significance with health state (EQ-5D-VAS) and presence and chronicity of itch (OR, 0.97, 95% CI, 0.97−0.98 and OR, 0.99, 95% CI, 0.98−0.99, respectively).

DISCUSSION

Our major findings were that depression and suicidal ideation showed a strong association with the presence of itch in dermatological patients compared with patients without itch. This suggests that mental health problems in patients with skin diseases are greatly related to itch. This was confirmed also by other single center studies (Stumpf et al., 2018). A speculative reason for this correlation is that itch correlates with skin inflammation and skin inflammation induces the serotonin network in the brain, leading to depression and anxiety (Yosipovitch et al., 2008; Zhao et al., 2018).

This study is the second part of a European study on itch; in the first part, it was demonstrated that itch was a very frequent symptom among dermatological patients in general outpatient clinics with a prevalence of 54% (Schut et al., 2019), highlighting the importance of focusing on this symptom. The increased prevalence of mental health problems in dermatological patients has been documented previously for single diseases and in clinical samples. In this study, this association is demonstrated in a large sample of dermatological outpatients, and it is shown that the association between mental health problems and skin disease is even stronger if the skin disease is itchy.

The association between depression and suicidal ideation was significant only for the presence of itch, not for chronicity and intensity. In comparison, in a study including 89 patients with atopic dermatitis, depression was significantly associated with itch severity, but in that study depression was assessed with a different questionnaire (Chrostowska-Plak et al., 2013). In a large study among adolescents with eczema, the crude OR for having suicidal ideation was more than threefold higher for those with itch than those without itch (Halvorsen et al., 2014).

The reported occurrence of stressful life events was higher in individuals with itch than in those without itch. The clinical relevance of this difference should be explored further, although the association of itch and stressful life events has

Table 1. Prevalence of Psychological Comorbidities and Stress and Health-Related Quality of Life in Patients and Controls with and without Itch

Outcome	Patients with itch (n = 1,917)		Patients without itch (n = 1,613)			Controls with itch (n = 88)		Controls without itch (n = 1,006)		
	n; % (95% CI)	Md	n; % (95% CI)	Md	P-value	n; % (95% CI)	Md	n; % (95% CI)	Md	P-value
Clinical depression HADS-D ≥11	266; 14.1% (12.5–15.7)	25	90; 5.7% (4.5–6.9)	35	<0.001[1]	5; 5.7% (0.8–10.7)	1	32; 3.2% (2.1–4.3)	2	ns[1]
Clinical anxiety HADS-A ≥11	405; 21.4% (19.6–23.3)	28	193; 12.3% (10.5–13.9)	39	<0.001[1]	7; 8.1% (2.2–13.9)	1	88; 8.8% (7.0–10.5)	3	ns[1]
Suicidal ideation	297; 15.7% (14.0–17.3)	21	146; 9.1% (7.7–10.6)	13	<0.001[1]	16; 18.6% (10.2–27.0)	2	72; 7.6% (5.9–9.3)	63	<0.001[1]
Stressful life events	724; 38.2% (36.1–40.5)	23	516; 32.4% (29.9–34.7)	21	<0.001[1]	35; 40.7% (30.1–51.3)	2	306; 30.6% (27.7–33.4)	5	ns[1]
Economic difficulties (stress)	623; 33.0% (30.9–35.1)	30	381; 24.9% (22.0–26.2)	28	<0.001[1]	27; 31.0% (21.1–41.0)	1	265; 26.7% (23.9–29.4)	12	ns[1]
EQ-5D-VAS, mean (SD) (0 worst–100 best)	65.9 (20.1)	106	74.7 (18.0)	87	0.001[2]	74.9 (15.7)	3	82.9 (15.6)	18	<0.001[2]

Abbreviations: CI, confidence interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; Md, missing data; ns, not significant; SD, standard deviation; VAS, visual analogue scale.
[1]Chi-square test was performed.
[2]t-test was performed.

been demonstrated previously in large community samples (Dalgard et al., 2015; Yamamoto et al., 2009). The report of economic difficulties is a more specific assessment of stress related to financial hardship and has been shown to be relevant in stress assessment in patients with various conditions; our findings confirm this association for dermatological patients with itch (Levenstein et al., 1995; Perrone et al., 2016; Richardson et al., 2017).

Our results show that in patients with itchy skin diseases, health-related quality of life was more impaired than in dermatological patients without itch and healthy controls. This finding is in accordance with that of several studies investigating single skin diseases (Leader et al., 2015). The use of the EQ-5D in patients with itchy skin diseases has shown that patients with itchy skin diseases carry a disease burden similar to patients with chronic diseases such as diabetes (mean EQ-5D = 68.8, SD = 18.3) (Matza et al., 2007). Detailed comparisons with other medical conditions from our data set were performed recently (Balieva et al., 2017).

Strengths and limitations

A strength of the study is the inclusion of healthy controls. Data from this study have enabled us to demonstrate the occurrence of psychological burden in dermatological patients with and without itch, as well as in healthy skin controls. As the study was cross-sectional, nothing can be inferred about causation. Mental health suffering possibly may cause itch to some degree; however, it is much more likely that the skin disease is the cause of itch. We can speculate that if better itch-specific treatment had been made available, this association would have been weaker. In psoriasis, itch has been shown to be an important mediator of the association between improvement in disease severity and health-related quality of life (Zhu et al., 2014). The selection of patients may have been biased, as mainly university clinics participated, and so the sample may not have fully reflected patients in other settings. Most of the data are self-reported. The healthy controls were mainly employees at hospitals, a well-known possible cause of bias. All patients observed in the study were living in countries with easy access to medical care and may have had contact with physicians before their visit to the dermatologist; the findings remain representative for European dermatological patients in an urban setting. Another limitation of this study was that stress was assessed by the question, "Have you had any stressful life events during the last 6 months?"; the binary answer would not accurately capture the presence of chronic stress in a subject's life. That is, maybe nothing unusual happened over the last 6 months because the individual is under continuous stress, or maybe there was a significant life event to which the subject was resilient. Other limitations have been described previously (Dalgard et al., 2015; Schut et al., 2019).

Our findings demonstrate that the presence of itch in dermatological patients is significantly associated with clinical depression, suicidal ideation, and stress. The study reveals that itch contributes substantially to the psychological burden of dermatological patients and confirms the multidimensional suffering of dermatological patients with itch. The management of patients with itch should involve access to a

Table 2. Multiple Logistic Regression Analysis for Presence and Chronicity of Itch and Linear Regression Analysis for Intensity of Itch

	Itch presence (n = 4,141)	Itch chronicity (n = 1,600)	Itch intensity (n = 1,767)	
Variable	Adjusted OR[1] (95% CI)	Adjusted OR[1] (95% CI)	Unstandardized Coefficient b (95% CI)	Standardized Coefficient β
Control (0)	1.0 (ref)	1.0 (ref)	1.63 (1.07–2.19)	0.132
Patient (1)	11.12 (8.70–14.21)	0.78 (0.43–1.39)		
No depression (0)	1.0 (ref)	1.0 (ref)	0.35 (−0.02 to 0.73)	0.048
Clinical depression (1)	1.53 (1.15–2.02)	0.75 (0.53–1.07)		
No anxiety (0)	1.0 (ref)	1.0 (ref)	0.37 (0.05–0.69)	0.060
Clinical anxiety (1)	1.07 (0.86–1.33)	0.93 (0.69–1.26)		
No suicidal ideation (0)	1.0 (ref)	1.0 (ref)	0.20 (−0.14 to 0.54)	0.029
Suicidal ideation (1)	1.27 (1.01–1.60)	1.32 (0.95–1.85)		
No stressful live events (0)	1.0 (ref)	1.0 (ref)	−0.22 (−0.47 to 0.03)	−0.043
Stressful live events (1)	0.95 (0.81–1.10)	0.98 (0.77–1.24)		
No economic difficulties (0)	1.0 (ref)	1.0 (ref)	0.34 (0.08–0.59)	0.063
Economic difficulties (1)	1.24 (1.05–1.45)	0.82 (0.65–1.04)		
Health state (EQ-5D) 0 = bad; 100 =best	0.97 (0.97–0.98)	0.99 (0.98–0.99)	−0.02 (−0.03 to −0.12)	−0.145

Abbreviations: CI, confidence interval; OR, odds ratio.
[1]Odds ratios are adjusted for age and sex.

multidisciplinary team when necessary. Additionally, preventive programs might also be useful, such as psoriasis education programs or targeted Web-based information. In many chronic inflammatory skin disorders, early aggressive treatment tailored specifically for the patient might help to reduce itch at this earliest possible opportunity and prevent the development of mental health problems. Anti-itch interventions that are already developed should be implemented more frequently into the routine care of those patients (Evers et al., 2009).

MATERIALS AND METHODS

Study design

This investigation was an observational cross-sectional multicenter study with sites in dermatological outpatient clinics in 13 European countries. The study was questionnaire-based, and the collection of data took place from November 2011 to February 2013. For details, see the earlier publication in this journal (Dalgard et al., 2015).

Assessments

Assessments were self-reported, including information on socioeconomic background. Information about itch was obtained by the following items: "Does your skin itch now?" (possible answers, "yes" or "no"); if yes, "For how long?" (possible answers, "under 6 weeks" or "over 6 weeks"); and "How intense is your itching?" with answers given on a VAS from 0 ("none") to 10 ("worst imaginable") (Ständer et al., 2010).

Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale, a validated instrument assessing symptom severity and caseness of anxiety disorders and depression in somatic patients in hospital settings as well as in the general population (Bjelland et al., 2002; Zigmond and Snaith, 1983). It includes seven items assessing anxiety and seven for depression, each with four possible answers. For each dimension of anxiety and depression, a score from 0–7 is considered normal; from 8–10, borderline case; and from 11–21 indicating clinical case in need for further examination or treatment. Suicidal ideation was assessed with the item "Have you ever thought of committing suicide?" (possible answers, "yes" or "no"). The socioeconomic level was self-reported and assessed in the sociodemographic section with the item: "On which socioeconomical level are you?" with possible answers "low", "middle", and "high". Economic difficulties, as a measure of stress over time, were assessed with the question: "Did you experience serious economic difficulties in the last 5 years?" with possible answers "yes" or "no". Stress within the last 6 months was assessed with the occurrence of negative life events question: "Have you had any stressful life events during the last 6 months?" (possible answers "yes" or "no"). Health-related quality of life was assessed with the generic instrument EQ-5D-VAS, a standardized generic instrument assessing the general health state from "worst" to "best imaginable health state" (values from 0 to 100). This scale is described in different medical conditions, and there are existing population norms in many countries (https://euroqol.org) where this instrument is used by health economists (Coons et al., 2000).

Settings

At each clinic, consecutive patients were invited to participate in the study until 250 patients were included. The following inclusion criteria were used: age over 18 years, being able to read and write the local language, and not suffering from severe psychosis. The controls were recruited by advertisement among hospital employees at the same institution, but not from the dermatological department. Employees with a skin condition were excluded.

Each participant completed the same questionnaire including sociodemographic background, Hospital Anxiety and Depression Scale, and EQ-5D. The patients handed it to the consultant before being examined clinically by the consultant who recorded the diagnosis. It was possible to record one, two, or more diagnoses. If there were doubts as to whether a skin disease was present (e.g., no diagnosis, no flares, and no itch), the patient was not included. The presence of other physical conditions was recorded by asking the patient or by reviewing the patient's file. The controls were not examined clinically.

Ethics

The study protocol was approved by the Regional Committee for Medical Research Ethics in Norway REK 2011/1087. Local ethical approval was obtained where necessary. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The data were entered into a database on each site and sent to the Statistical Center in Giessen, Germany, then merged to a single file. SPSS, version 24 software (IBM, released 2016; IBM SPSS statistics for Windows) was used to analyze the data. For details, see a previous publication (Schut et al., 2019). We described the prevalence of depression, anxiety, suicidal ideation, physical comorbidities, and stress with percentages and numbers and EQ-5D-VAS with mean values and standard deviation.

Multiple logistic regression analyses were performed to identify predictors of the presence and the chronicity of itch. A linear regression analysis was performed to identify predictors of the intensity of itch. The independent variables entered into all three analyses were group (controls vs. patients), depression (Hospital Anxiety and Depression Scale-Depression), anxiety (Hospital Anxiety and Depression Scale-Anxiety), suicidal ideation, occurrence of stressful life events, economic difficulties, and health state (EQ-5D). All three regression models were adjusted for the covariates sex and age. The ORs for the multiple regression models were calculated as the exponential of the estimated regression coefficients β from the logistic regression models.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author FJD. The data are not publicly available because of restrictions, such as their containing information that could compromise the privacy of research participants.

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CONFLICT OF INTEREST

The corresponding author has no conflict of interest. All authors are members of the European Society for Dermatology and Psychiatry. GBEJ has received honoraria from AbbVie, Janssen-Cilag, Novartis, Leo pharma, Pierre Fabre, and UCB for participation on advisory boards, and grants from Abbvie, Janssen-Cilag, Leo Pharma, Novartis, Regeneron, and Serono for participation as an investigator, and received speaker honoraria from AbbVie, Galderma, Leo Pharma, and MSD. He has furthermore received unrestricted research grants from AbbVie, Leo Pharma and Novartis. AYF is joint copyright holder of the Dermatology Quality Life Index. Cardiff University and AYF receive royalties. AYF is on a Novartis advisory board. SS has received educational grants from Sanofi, Novartis, BMS, Celgene, and Agios. The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: FJD, JK, JAH, UG; Data Curation: JK,UG, FJD; Formal Analysis: FJD, JK, JAH, UG; Funding Acquisition: UG, FJD, LL, ÅS; Investigation: UG, FJD, JK; Methodology: UG, FJD, JK; Project Administration: FJD, UG, JK; Resources: UG, JK; Software: JK; Supervision: FJD, UG, JK; Validation: JK, CS; Visualization: FJD, JAH, UG, JK; Writing - Original Draft Preparation: FJD, JAH, JK, UG, CS; Writing - Review and Editing: FJD, JAH, LTA, FP, GBEJ, LM, CS, DL, FS, SSK, FB, JCS, AL, SEM, IKA, SS, AYF, LL, ÅS.

REFERENCES

Balieva F, Kupfer J, Lien L, Gieler U, Finlay AY, Tomás-Aragonés L, et al. The burden of common skin diseases assessed with the EQ5D: a European multicentre study in 13 countries. Br J Dermatol 2017;176:1170–8.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002;52:69–77.

Boehm D, Schmid-Ott G, Finkeldey F, John SM, Dwinger C, Werfel T, et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. Contact Dermatitis 2012;67:184–92.

Brenaut E, Halvorsen JA, Dalgard FJ, Lien L, Balieva F, Sampogna F, et al. The self-assessed psychological comorbidities of prurigo in European patients: a multicentre study in 13 countries. J Eur Acad Dermatol Venereol 2019;33:157–62.

Caccavale S, Bove D, Bove RM, LA Montagna M. Skin and brain: itch and psychiatric disorders. G Ital Dermatol Venereol 2016;151:525–9.

Choi JE, Di Nardo A. Skin neurogenic inflammation. Semin Immunopathol 2018;40:249–59.

Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol 2013;27:e239–42.

Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics 2000;17:13–35.

Dalgard F, Lien L, Dalen I. Itch in the community: associations with psychosocial factors among adults. J Eur Acad Dermatol Venereol 2007;21:1215–9.

Dalgard F, Svensson A, Holm JØ, Sundby J. Self-reported skin morbidity among adults: associations with quality of life and general health in a Norwegian survey. J Investig Dermatol Symp Proc 2004;9:120–5.

Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol 2015;135:984–91.

Evers AW, Duller P, de Jong EM, Otero ME, Verhaak CM, van der Valk PG, et al. Effectiveness of a multidisciplinary itch-coping training programme in adults with atopic dermatitis. Acta Derm Venereol 2009;89:57–63.

Gupta K, Harvima IT. Mast cell-neural interactions contribute to pain and itch. Immunol Rev 2018;282:168–87.

Halvorsen JA, Dalgard F, Thoresen M, Thoresen M, Bjertness E, Lien L. Itch and mental distress: a cross-sectional study among late adolescents. Acta Derm Venereol 2009;89:39–44.

Halvorsen JA, Lien L, Dalgard F, Bjertness E, Stern RS. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. J Invest Dermatol 2014;134:1847–54.

Kaaz K, Szepietowski JC, Matusiak Ł. Influence of itch and pain on sleep quality in patients with hidradenitis suppurativa. Acta Derm Venereol 2018;98:757–61.

Konda D, Chandrashekar L, Rajappa M, Kattimani S, Thappa DM, Ananthanarayanan PH. Serotonin and interleukin-6: association with

pruritus severity, sleep quality and depression severity in Prurigo Nodularis. Asian J Psychiatry 2015;17:24–8.

Leader B, Carr CW, Chen SC. Pruritus epidemiology and quality of life. Handb Exp Pharmacol 2015;226:15–38.

Levenstein S, Kaplan GA, Smith M. Sociodemographic characteristics, life stressors, and peptic ulcer. A prospective study. J Clin Gastroenterol 1995;21:185–92.

Matza LS, Boye KS, Yurgin N. Validation of two generic patient-reported outcome measures in patients with type 2 diabetes. Health Qual Life Outcomes 2007;5:47.

Perrone F, Jommi C, Di Maio M, Gimigliano A, Gridelli C, Pignata S, et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. Ann Oncol 2016;27:2224–9.

Reich A, Hrehorów E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. Acta Derm Venereol 2010;90:257–63.

Reich A, Mędrek K, Szepietowski JC. Interplay of itch and psyche in psoriasis: an update. Acta Derm Venereol 2016;96:55–7.

Richardson T, Elliott P, Roberts R, Jansen M. A longitudinal study of financial difficulties and mental health in a national sample of British undergraduate students. Commun Ment Health J 2017;53:344–52.

Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Ständer S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol 2006;31:762–7.

Schut C, Dalgard FJ, Halvorsen JA, Gieler U, Lien L, Aragones LT, et al. Occurrence, chronicity and intensity of itch in a clinical consecutive sample of patients with skin diseases: a multi-centre study in 13 European countries. Acta Derm Venereol 2019;99:146–51.

Simpson EL, Guttman-Yassky E, Margolis DJ, Feldman SR, Qureshi A, Hata T, et al. Association of Inadequately Controlled Disease and Disease Severity with Patient-Reported Disease Burden in adults with atopic dermatitis. JAMA Dermatol 2018;154:903–12.

Ständer S, Schäfer I, Phan NQ, Blome C, Herberger K, Heigel H, et al. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. Dermatol 2010;221:229–35.

Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: Results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. J Am Acad Dermatol 2018;79:457–63.e5.

Stumpf A, Schneider G, Ständer S. Psychosomatic and psychiatric disorders and psychologic factors in pruritus. Clin Dermatol 2018;36:704–8.

Stumpf A, Ständer S, Warlich B, Fritz F, Bruland P, Pfleiderer B, et al. Relations between the characteristics and psychological comorbidities of chronic pruritus differ between men and women: women are more anxious than men. Br J Dermatol 2015;172:1323–8.

Suseł J, Batycka-Baran A, Reich A, Szepietowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. Acta Derm Venereol 2014;94:276–81.

Wang XD, Yang G, Bai Y, Feng YP, Li H. The behavioral study on the interactive aggravation between pruritus and depression. Brain Behav 2018;8:e00964.

Weiss M, Mettang T, Tschulena U, Weisshaar E. Health-related quality of life in haemodialysis patients suffering from chronic itch: results from GEHIS (German Epidemiology Haemodialysis Itch Study). Qual Life Res 2016;25:3097–106.

Yamamoto Y, Yamazaki S, Hayashino Y, Takahashi O, Tokuda Y, Shimbo T, et al. Association between frequency of pruritic symptoms and perceived psychological stress: a Japanese population-based study. Arch Dermatol 2009;145:1384–8.

Yosipovitch G, Ishiuji Y, Patel TS, Hicks MI, Oshiro Y, Kraft RA, et al. The brain processing of scratching. J Invest Dermatol 2008;128:1806–11.

Zachariae R, Lei U, Haedersdal M, Zachariae C. Itch severity and quality of life in patients with pruritus: preliminary validity of a Danish adaptation of the itch severity scale. Acta Derm Venereol 2012;92:508–14.

Zhao X, Yu C, Ye F, Wang YG, Mei QY, Ma Q, et al. Chronic itch impairs mood and HPA axis function in mice: modulation by CRFR1 antagonist. Pain 2018;159:2201–13.

Zhao ZQ, Huo FQ, Jeffry J, Hampton L, Demehri S, Kim S, et al. Chronic itch development in sensory neurons requires BRAF signaling pathways. J Clin Invest 2013;123:4769–80.

Zhu B, Edson-Heredia E, Guo J, Maeda-Chubachi T, Shen W, Kimball AB. Itching is a significant problem and a mediator between disease severity and quality of life for patients with psoriasis: results from a randomized controlled trial. Br J Dermatol 2014;171:1215–9.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.