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Title page**Itch and mental health in dermatological patients across Europe: a cross sectional study in 13 countries**

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Abstract

Itch is a highly prevalent and multi-dimensional symptom. We aimed to analyze the association between itch and mental health in dermatological patients. This multi-center study is observational cross-sectional conducted in dermatological clinics across 13 European countries. A total of 3530 patients and 1094 healthy controls were included. Patients examined clinically. Outcome measures were itch (presence, chronicity and intensity), the Hospital Anxiety and Depression Scale, EQ5D-VAS and Dermatology Life Quality Index, sociodemographics, suicidal ideation, stress (negative life events and economic difficulties). Ethical approval was obtained. Results showed significant association between itch and depression, anxiety, suicidal ideation and economic difficulties (odds ratios respectively OR 2.62, 95% CI 2.04–3.37, OR 1.98, 95% CI 1.64-2.40, OR 1.86, 95% CI 1.51-2.31, OR 1.56 95% CI 1.34- 1.82). The mean scores of EQ5D were 65.9 (SD=20.1) and 9.1 (SD=7.0) for DLQI in patients with itch, compared to 74.7 (SD=18.0) and 4.1 (SD=5.4) in patients without itch. EQ5D was significantly lower for patients with itch (β -coefficient 8.69, 95% CI -11.25-(-4.45)) and controls with itch (β -coefficient 7.85, 95% CI 9.98-7.39) compared to patients and controls without itch. Itch contributes substantially to the disease burden in dermatological patients and the management of patients should include access to multidisciplinary care.

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.*, 2010; Reich *et al.*, 2016; Zachariae *et al.*, 2012), prurigo nodularis (Brenaut *et al.*, 2018; Konda *et al.*, 2015), among hemodialysis patients (Susel *et al.*, 2014; Weiss *et al.*, 2016; Yamamoto *et al.*, 2009), hidradenitis suppurativa (Kaaz *et al.*, 2018) and in chronic itch patients (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 pruritus patients (Wang *et al.*, 2018) .

The multidimensional nature of pruritus and the quality of life impairment of patients with pruritus were demonstrated 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; Dalgard *et al.*, 2004) and among adolescents the severity of itch was shown to increase with symptoms of depression among adolescents (Halvorsen *et al.*, 2009). The pathophysiological mechanism might be the production and interaction of neuropeptides such as, for example, serotonin (Zhao *et al.*, 2013).

Data on the epidemiology of itch in dermatological patients in comparison to healthy skin controls were recently published (Schut *et al.*, 2018). The present itch study is based on the same dataset and is part of a large European multi-center study conducted by the European Society for Dermatology and Psychiatry (ESDaP) which aimed to better document the psychological burden of patients with skin diseases (Dalgard *et al.*, 2015). The aim of the present study is therefore 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 3635 patients and 1359 controls were examined with a participation rate of 79.5%. 3530 patients (97.1% of all examined patients) and 1094 controls (80.5% of all controls) responded to the question on the experience of itch. This group of 4624 subjects constitutes our study population. The characteristics of participants with itch were described in a recently published article (Schut *et al.*, 2018).

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

The prevalence of depression is 14.1%, 95% CI 12.5-15.7 in patients with itch, 5.7%, 95% CI 4.5-6.9 in patients without itch and 3.4%, 95% CI 2.4; 4.5 in controls. The prevalence of anxiety in patients with itch is 21.4%, 95% CI 19.6- 23.3 and 12.3%, 95% CI 10.5-13.9 in patients without itch and 8.7 %, 95% CI 7.1; 10.5 among controls (Table 1). The prevalence of suicidal ideation is 15.7%, 95% CI 14.0-17.3 in patients with itch, 9.1 %, 95% CI 7.7-10.6 in patients without itch and 8.6%, 95% CI 6.9-10.4 in controls. Patients with itch reported that they had experienced more negative life events than controls (38.2%, 95% CI 36.1-40.5 vs. 31.4%, 95% CI 28.7- 4.3).

The mean score of reported generic health status assessed by the EQ5D-VAS was 65.9 (SD=20.1) in patients with itch, compared to 82.3 (SD=15.7) in controls. The mean score of the dermatological-specific quality of life instrument (the DLQI) was 9.1 (SD=7.0) in patients with itch compared to 4.1 (SD=5.4) in patients without itch (Table 1).

Table 1. Prevalence of psychological comorbidities and stress (in percentage and confidence intervals) and health-related quality of life (in mean with SD) in patients with itch, without itch and healthy controls.

	Patients with itch		Patients without itch		Controls	
	(N=1917)		(N=1613)		(N=1094)	
	N, %, (CI 95%)	Missing	N, %, (CI 95%)	Missing	N, % (CI 95%)	Missing
Clinical depression	266, 14.1% (12.5-15.7)	25	90, 5.7% (4.5- 6.9)	35	37 , 3.4 % (2.4-4.5)	3
HADS-D >=11						
Clinical anxiety	405, 21.4% (19.6- 23.3)	28	193, 12.3% (10.5-13.9)	39	95,8.7% (7.1-10.5)	4
HADS-A >=11						
Suicidal ideation	297, 15.7% (14.0-17.3)	21	146, 9.1% (7.7- 10.6)	13	88, 8.6% (6.9- 10.4)	65
Stressful life events	724, 38.2% (36.1-40.5)	23	516, 32.4% (29.9-34.7)	21	341, 31.4% (28.7-4.3)	7
Economic difficulties	623, 33.0% (30.9- 35.1)	30	381, 24.9% (22.0-26.2	28	292, 27.0% (24.2- 29.7)	13
(stress)						
	Mean (SD)		Mean (SD)		Mean (SD)	
EQ-5D-VAS	65.9 (20.1)	106	74.7 (18.0)	87	82.3 (15.7)	21
(0 worst-100 best)						

DLQI	9.1 (7.0)	28	4.1 (5.4)	43	-	-
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(0 best-30 worst)

Association of presence, chronicity and intensity of itch and 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, clinical anxiety, suicidal ideation, economic difficulties and the occurrence of stressful life events respectively (OR 2.62, 95% CI 2.04-3.37, OR 1.98, 95% CI 1.64-2.40, OR 1.86 95% CI 1.51-2.31, OR 1.56, 95% CI 1.34-1.82, OR 1.31, 95% CI 1.13-1.51), but not for chronicity and hardly for intensity of itch. The association was significant between presence of itch and suicidal ideation and the occurrence of life events in the control group (OR 2.71, 95% CI 1.47-5.01, OR 1.63, 95% CI 1.03-2.57). There was no significant association between the chronicity of itch and psychological variables, either among itchy patients or itchy controls. There were significant associations between the intensity of itch and clinical depression, clinical anxiety, suicidal ideation and economic difficulties among patients (respectively OR 1.17, 95% CI 1.11-1.24, OR 1.14, 95% CI 1.09-1.20, OR 1.11, 95% CI 1.05-1.17, OR

1.07, 95% CI 1.03-1.11) and clinical anxiety, occurrence of life events and economic difficulties among controls (OR 1.38, 95% CI 1.01- 1.89, OR 1.25, 95% CI 1.01-1.53, OR 1.58, 95% CI 1.22-2.04).

Table 2. Crude and adjusted (for age and gender) odds ratios (with 95% confidence interval) for the association between the presence, chronicity and intensity of itch as independent variables and psycho-social variables, among patients (N=3530) and controls (N=1094) with itch

	Itch presence		Itch chronicity		Itch intensity	
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Patients	Controls	Patients	Controls	Patients	Controls
Depression (HADS-D)						
Crude	2.70 (2.10- 3.47)	1.85 (0.70-4.88)	0.92 (0.68- 1.24)	1.08 (0.10-11.15)	1.18 (1.12-1.24)	1.22 (0.87- 1.71)
Adjusted	2.62 (2.04- 3.37)	1.48 (0.51- 4.29)	0.90 (0.67-1.22)	1.20 (0.10-13.78)	1.18 (1.11- 1.24)	1.42 (0.94- 2.13)
Anxiety (HADS-A)						
Crude	1.95 (1.62- 2.35)	0.91 (0.40-2.03)	0.95 (0.74-1.23)	-	1.15 (1.10- 1.20)	1.28 (0.95- 1.71)
Adjusted	1.98 (1.64- 2.40)	0.79 (0.33-1.87)	0.96 (0.74-1.24)	-	1.14 (1.09- 1.20)	1.38 (1.01- 1.89)
Suicidal ideation						
Crude	1.85 (1.49; 2.28)	2.76 (1.52; 5.00)	1.23 (0.91; 1.66)	0.87 (0.23; 3.24)	1.11 (1.05-1.16)	1.04 (0.83- 1.31)
Adjusted	1.86 (1.51;2.31)	2.71 (1.47;5.01)	1.30 (0.96; 1.77)	0.82 (0.20; 3.24)	1.11 (1.05- 1.17)	1.08 (0.84-1.38)

Occurrence of
stressful life events

Crude	1.29 (1.12-1.48)	1.55 (0.99- 2.44)	0.96 (0.77-1.19)	1.50 (0.50- 4.53)	1.02 (0.98- 1.06)	1.26 (1.03-1.54)
Adjusted	1.31 (1.13- 1.51)	1.63 (1.03- 2.57)	0.97 (0.78- 1.21)	1.45 (0.46- 4.58)	1.01 (0.97- 1.05)	1.25 (1.01- 1.53)

Economic**difficulties (Stress)**

Crude	1.55 (1.24- 1.80)	1.23 (0.76-1.99)	0.86 (0.69- 1.08)	1.08 (0.34- 3.42)	1.07 (1.03- 1.11)	1.48 (1.18- 1.86)
Adjusted	1.56 (1.34- 1.82)	1.22; 0.75- 1.99)	0.86 (0.69- 1.08)	0.99 (0.29- 3.35)	1.07 (1.03 -1.11)	1.58 (1.22- 2.04)

 “-“ not defined in the regression model

Significant association of presence of itch and health-related quality of life impairment in patients and controls with itch

Table 3 shows the association between the presence, chronicity and intensity of itch and general and dermatological quality of life impairment in patients and controls with itch, compared to patients and controls without itch, in a linear model adjusting for age and gender. The general self-rated health state was significantly lower for patients with itch (β coefficient 8.69 95% CI 9.98-7.39) and controls with itch (β -coefficient 7.85, 95% CI -11.25-(-4.45)) compared to patients and controls without itch. The dermatology-specific quality of life impairment was significantly higher for patients with itch compared to patients without itch (β -coefficient 5.02, 95% CI 4.60-5.44).

Table 3. Association between presence, chronicity and intensity of itch and generic quality of life measured by the EQ5D-VAS in the whole European sample (N=4624), and dermatology-specific quality of life (DLQI) among patients (N=3485). Crude and adjusted β coefficients from linear regression models with itch variables as independent variables are presented.

	Generic quality of life (EQ5D-VAS)	Generic quality of life (EQ5D-VAS)	Dermatological quality of life (DLQI)	Dermatological quality of life (DLQI)
	Crude β coefficient (95% CI)	Adjusted β coefficient (95% CI) ¹	Crude β coefficient (95% CI)	Adjusted β coefficient (95% CI)*
Itch presence				
Controls	-7.96 (-11.42- 4.51)	-7.85 (-11.25- 4,45)		
Patients	-8.84 (-10.14- 7.53)	-8.69 (-9.98-7.39)	5.00 (4.58-5.42)	5.02 (4.60- 5.44)
Chronicity				
Controls	-1.86 (-10.99- 7.26)	-1.30 (-10.81- 8.19)		

Patients	-3.31 (-5.49-1.13)	-2.62 (-4.80-0.44)	0.88 (0.15- 1.62)	1.02 (0.27- 1.77)
Intensity				
Controls	-2.31 (-3.75-0.87)	-2.30 (-3.77-0.83)		
Patients	-1.45 (-1.82-1.08)	-1.46 (-1.83-1.10)	1.09 (0.97- 1.21)	1.10 (0.98- 1.22)

¹adjusted for age and gender

DISCUSSION

Our major findings were that depression, anxiety and suicidal ideation showed a strong association with the presence of itch in dermatological patients compared to patients without itch. This suggests that mental health problems in patients with skin diseases are for a great part related to itch.

This study is the second part of a European study on itch: in the first part it was demonstrated that itch was the most frequently encountered symptom among dermatological patients in general out-patient clinics, with a prevalence of 54% (Schut *et al.*, 2018), highlighting the importance of focusing on this symptom. The increased prevalence of mental health problems in dermatological patients has previously been documented for single diseases and in clinical samples. However, the originality of this report is the demonstration in a large sample of dermatological out-patients

that the association of mental health problems and skin disease is even stronger if the skin disease is itchy. In fact, in our sample the odds ratio (OR) for having depression between dermatological patients and controls reported previously by our group (Dalgard *et al.*, 2015) was OR 2.40, 95% CI 1.67-3.47, which is a little bit lower than that between dermatological patients with itch and without itch and controls reported in the present study with OR 2.62, 95% CI 2.04 -3.37.

The association between depression, anxiety and suicidal ideation was only highly significant for the presence of itch, not for chronicity and weak for itch 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 compared to those without itch (Halvorsen *et al.*, 2014).

The reported occurrence of stressful life events was higher in dermatological patients with itch than in the other groups. The clinical relevance of this difference should be explored further, although the association of itch and stressful life events has 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 different 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 in healthy controls. This finding is in accordance with that of several studies investigating single skin diseases (Leader *et al.*, 2015). The

use of the EQ5D 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 EQ5D=68.8, SD=18.3) (Matza *et al.*, 2007). Detailed comparisons with other medical conditions from our dataset were performed recently (Balieva *et al.*, 2017). The average DLQI score for dermatological patients with itch reflected a moderate effect on patient's life compared to a small effect on patient's life for dermatological patients without itch; this highlights the impact of the symptom itch on a patient's life (Finlay and Khan, 1994; Hongbo *et al.*, 2005). The symptoms and feelings subscale of the DLQI, including the question about itch, is antecedent to a latent variable (factor) representing the remaining five subscales of the DLQI (Stull *et al.*, 2018). This accords with the score influence of pruritus on overall quality of life impairment.

Strengths and limitations

A strength of the study is the inclusion of healthy controls which is novel. Data from this study has 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 may possibly 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 to physicians prior to their visit to the dermatologist, the findings remain representative for European dermatological patients in an urban setting. Other limitations have been described previously (Dalgard *et al.*, 2015; Schut *et al.*, 2018).

Conclusions

Our findings demonstrate that the presence of itch in dermatological patients is significantly associated with clinical depression, anxiety, suicidal ideation and stress. The study reveals that itch contributes substantially to the psychological burden of dermatological patients and confirms the multi-dimensional suffering of dermatological patients with itch; the management of patients with itch should involve access to a multidisciplinary team when necessary.

MATERIALS AND METHODS

Study design

This investigation was an observational cross-sectional multi-center study with sites in dermatological out-patients 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 concerning socio-economic 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 visual analog scale (VAS) from 0 (“none”) to 10 (“worst imaginable”) (Stander *et al.*, 2010). Possible presence of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Suicidal ideation was assessed with the items “Have you ever thought of committing suicide?”. Stress was assessed with the occurrence of negative life events “Have you had any stressful life events during the last 6 months?” (possible answers “yes” or “no”) and the presence of economic difficulties “did you experience economic difficulties the last 5 years?” (possible answers “yes” or “no”). Health-related quality of life (HRQoL) was assessed with the generic instrument EQ5D (<https://euroqol.org>) and the skin-specific questionnaire the Dermatological Life Quality Index (DLQI) (Finlay and Khan, 1994).

Settings

At each clinic, consecutive patients were invited to participate in the study until 250 patients were included. The inclusion criteria were: age over 18 years, being able to read and write the local language and to not suffer 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, HADS and EQ5D. 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 Crop, released 2016. IBM SPSS statistics for Windows) was used to analyze the data. For details see previous publication (Schut

et al., 2018). We describe the prevalence of depression, anxiety, suicidal ideation, physical comorbidities and stress with percentages and numbers and EQ-5D and DLQI with mean values and standard deviation.

Multivariate logistic regression analysis were performed with depression (HADS-D), anxiety (HADS-A), suicidal ideation, occurrence of stressful life events or economic difficulties as dependent variables. Linear regression models with EQ-5D and DLQI as dependent variables were tested to study the associations between itch variables (presence, chronicity and intensity) and quality of life in dermatological patients with or without itch and skin healthy controls, adjusting for gender and age. The odds ratios (ORs) were calculated as the exponential of the estimated regression coefficients β from the logistic regression models.

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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. AYF is joint copyright owner of the DLQI: Cardiff University and AYF receive royalties. AYF is a paid member of a Novartis Advisory Board.

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