REVIEW ARTICLE

Prevalence and Odds of Anxiety Disorders and Anxiety Symptoms in Children and Adults with Psoriasis: Systematic Review and Meta-analysis

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The magnitude of the association between psoriasis and depression has been evaluated, but not that between psoriasis and anxiety. The aim of this systematic review and meta-analysis was to examine the prevalence and odds of anxiety disorders and symptoms in patients with psoriasis. Five medical databases (Cochrane Database, EMBASE, PubMed, PsychINFO, ScienceDirect) were searched for relevant literature. A total of 101 eligible articles were identified. Meta-analysis revealed different prevalence rates depending on the type of anxiety disorder: 15% [95% confidence interval [CI] 9–21] for social anxiety disorder, 11% [9–14] for generalized anxiety disorder, and 9% [95% CI 8–10] for unspecified anxiety disorder. There were insufficient studies assessing other anxiety disorders to be able to draw any conclusions on their true prevalence. Meta-analysis also showed a high prevalence of anxiety symptoms (34% [95% CI 32–37]). Case-control studies showed a positive association between psoriasis and unspecified anxiety disorder (odds ratio 1.48 [1.18; 1.85]) and between psoriasis and anxiety symptoms (odds ratio 2.51 [2.02; 3.12]). All meta-analyses revealed an important heterogeneity, which could be explained in each case by methodological factors. The results of this study raise the necessity of screening for the presence of anxiety disorders, as previously recommended for depressive disorders, in patients with psoriasis and, if necessary, to refer such patients for evaluation by a mental health professional and appropriate treatment.

Key words: psoriasis; anxiety disorders; anxiety symptoms; systematic review; meta-analysis.

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SIGNIFICANCE

In addition to physical symptoms, psoriasis is associated with psychological symptoms, such as anxiety. The term "anxiety" is very often used without distinguishing disorders from symptoms, whereas their monitoring and treatment should be different. This systematic review and meta-analysis of 101 articles describes the prevalence of each anxiety disorder and anxiety symptoms separately. Meta-analysis revealed different prevalence rates depending on the type of anxiety disorder: 15% [95% confidence interval 9–21] for social anxiety disorder, 11% [95% confidence interval 9–14] for generalized anxiety disorder, 9% [95% confidence interval 8–10] for unspecified anxiety disorder and a high prevalence of anxiety symptoms (34% [95% confidence interval 32–37]).

The association between certain chronic inflammatory skin diseases and anxiety has been studied widely. Systematic reviews or meta-analyses have been performed in alopecia areata (1, 2), atopic dermatitis (3), hidradenitis suppurativa (4–6) and chronic urticaria (7), studying anxiety symptoms (3, 5) or anxiety disorders (4, 7) or both (1, 2, 6). In the last case, the meta-analyses evidenced global prevalence rates and odds, without distinguishing anxiety disorders from anxiety symptoms, while this is essential for evaluation and treatment. Anxiety can manifest as a symptom (anxious emotions, cognitions and behaviours, which can be pathological due to their intensity, repercussions or poor control) in various diseases; or anxiety can manifest as a specific diagnosis belonging to the category of "anxiety disorders" as defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM5) (8) or International Classification of Diseases 10 (9). Not all patients with anxiety symptoms have an anxiety disorder; however, they should undergo specific evaluation and monitoring because symptoms can evolve into a disorder and patients with an established anxiety disorder should receive care from mental health professionals.

Prevalence rates of psoriasis range from 0.5% to 11.4% in adults, and up to 1.37% in children (10, 11). Physical symptoms include pain and pruritus in areas with thick, dry, red skin lesions covered with silvery scales. One meta-analysis showed a positive significant association between psoriasis and depressive symptoms, depression and antidepressant use (12). Another, in contrast, found no such association between psoriasis and

suicidal thought and behaviour (13). Previous studies on the prevalence of anxiety in patients with psoriasis yielded divergent results (14, 15). To the best of our knowledge, the exact magnitude of the association between psoriasis and anxiety disorders/anxiety symptoms is unknown. The aims of this study were therefore to make a pooled estimate of their prevalence and odds, distinguishing anxiety symptoms and anxiety disorders in patients with psoriasis by meta-analysis, and to study the relationship between variations in prevalence and study characteristics.

MATERIALS AND METHODS

In France, ethics approval is not required for this type of research. Recommendations of the Preferred Items for the Reporting of Systematic Reviews and Meta-Analysis (PRISMA) were followed (16). The protocol for this meta-analysis is registered in PROSPERO (CRD42020158948).

Literature search

The search for, and extraction of, relevant literature from 5 medical databases (Cochrane Database, EMBASE, PubMed, PsychINFO, Science Direct) were performed by 2 of the authors (IJ and FR) from inception to 31 December 2019, using the following search terms: *psoriasis* AND *anxiety* OR *generalized anxiety disorder* OR *phobia* OR *panic disorder* OR *panic* OR *obsessive compulsive disorder (OCD)* OR *obsession* OR *compulsion* OR *OCD*. Studies exclusively including patients with psoriatic arthritis were excluded. Cohort follow-up studies were usually excluded, since results were presented as incidence and hazard ratio (not as prevalence and odds ratio (OR)): only cohorts with baseline description and prevalence were included. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM5) no longer classifies OCDs among anxiety disorders, but it was nevertheless decided to include in the current analysis studies that used previous versions of the DSM. Studies had to be primary research. No limits were set on language, year of publication, age of study participants, or study size. All articles were independently screened according to title and abstract by 2 of the authors (IJ and FR). Relevant studies were also retrieved by screening reference lists of previous key or review articles.

Only articles with full-text access were retained: those with access solely to an abstract were excluded. If necessary, the articles were requested from the authors. The full-text articles were independently assessed for inclusion by 3 of the authors (FB, EM and FR). If several papers analysed data from the same cohort, the article with the most complete data was selected.

Any disagreements between the reviewers were adjudicated by consensus between 3 of the authors (FR, FB and IJ).

Data extraction

Three of the authors extracted and tabulated data and checked for accuracy (FB, EM and FR). The data collected were sociodemographic (proportion of females included, mean age), medical (mean age of diagnosis of psoriasis, mean duration of psoriasis, Psoriasis Area and Severity Index (PASI) score, proportion of psoriatic arthritis, proportion of smokers, number of patients/controls with anxiety), and methodological (prospective or retrospective study, number of patients included, method of anxiety assessment, presence of healthy controls).

Risk of bias

The risk of bias was assessed with a specific instrument for estimating risk of bias in studies measuring disease prevalence that has high inter-rater agreement (17). This tool includes several items mainly evaluating the representativeness of the population and how was defined and collected the prevalence. Disagreements between the reviewers were adjudicated by consensus between 3 of the authors. All studies were included irrespective of their low, moderate or high risk of bias.

Statistical analysis

Statistical analysis was performed with Stata software (version 13, StataCorp, College Station, TX, USA).

Proportion meta-analysis was conducted using the "metaprop" command of Stata. This routine provides procedures for pooling proportions in a meta-analysis of multiple studies and displays the results in a forest plot. The confidence intervals are based on score (Wilson) or exact binomial (Clopper-Pearson) procedures (18). Then, the meta-analysis took account of between- and within-study variability. To address the non-independence of data due to study effect, random-effects models were preferred to the usual statistical tests to assess the prevalence of anxiety, using the method of DerSimonian & Laird with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model (19). A test of whether the summary effect measure is equal to the zero is given, as well as a test for heterogeneity, i.e. whether the true effect in all studies is the same. For stratified analyses (according to the assessment method used or to diagnosis) and for comparison of cases and controls, the same statistical approach was adapted. Results were expressed as prevalence and 95% confidence intervals (CI) and results concerning case-controls comparisons were expressed as odds ratios (OR) and 95% CI. Heterogeneity in the study results was also assessed by forest plots and the I^2 statistic, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically considered low for 25%, modest for 25–50%, and high for 50% (20). Publication bias was assessed by funnel plots and confidence intervals and Egger's test (21, 22) for anxiety symptoms and for each anxiety disorder one at a time, owing to their great effect on heterogeneity. When possible (sufficient sample size), meta-regression analysis was used to study the relationship between variations in prevalence and study characteristics, such as assessment method, risk of bias, number and age of patients included, proportion of smokers and obese patients included, body mass index (BMI), PASI score, and study design (prospective or retrospective). Results were expressed as regression coefficients (estimated coefficient (EC) and 95% CI).

Finally, to check the robustness of the results, sensitivity analyses were performed, which excluded studies that were not evenly distributed around the base of the funnel. The results of the sensitivity analyses (before and after, and the funnel plots of each meta-analysis) are presented in Table SI and Figs S1–S5. Results presented in this paper are those obtained after sensitivity analyses. A sensitivity analysis was also made to study the prevalence estimate only for those studies for which a case-control comparison was possible, so as to ensure representativeness in terms of prevalence of this subsample.

RESULTS

A total of 3,612 articles on psoriasis and anxiety were identified. After screening the titles and abstracts and

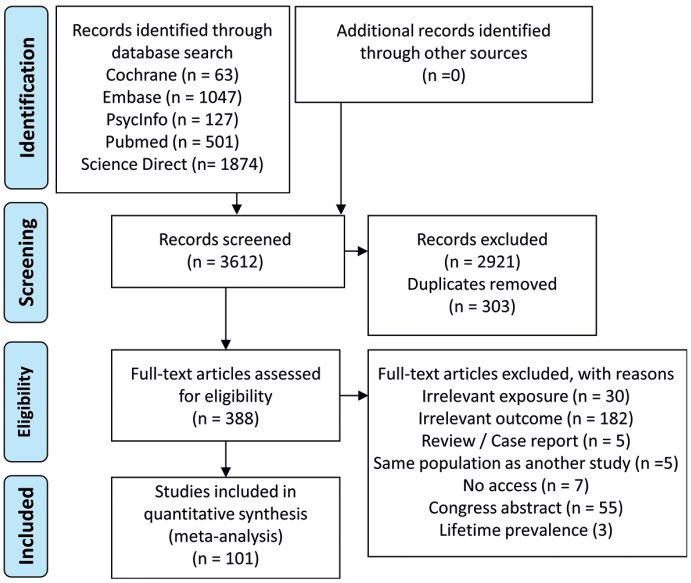

Fig. 1. Flow diagram of article selection for the meta-analysis (Preferred Items for the Reporting of Systematic Reviews and Meta-Analysis (PRISMA) 2009). The numbers correspond to the number of articles. Studies with irrelevant exposure are studies without data on psoriasis and those with irrelevant outcomes present no data on anxiety prevalence.

removal of duplicates, 388 articles remained and were submitted for full-text review. Of these articles, 287 were excluded. A total of 101 articles were included in the meta-analysis (**Fig. 1**).

Three studies assessing lifetime prevalence of anxiety were not included in the meta-analysis (23–25). The studies selected for the meta-analysis of the prevalence of anxiety are listed in Table SII (26–126). The studies excluded from the meta-analysis because of heterogeneity and risk of publication bias are signalled in Tables SI–SII.

Too few studies assessed separation anxiety disorder, specific phobia, agoraphobia, panic disorder and obsessive compulsive disorder to conclude on their true prevalence (**Fig. 2**). The global prevalence of anxiety disorders (all diagnoses) was 9% [95% confidence interval [95% CI] 8–10] with wide variations.

Social anxiety disorder

Nine studies assessed the presence of social anxiety disorder (26, 29–36), 6 by interview, 3 with self-administered questionnaires and 1 with medical records. Meta-analysis showed a high prevalence of social anxiety disorder in patients with psoriasis (15% [95% CI 9–21]) with very wide heterogeneity (I^2=97.2%) and risk of publication bias (Egger's test, p=0.016) (Fig. 2). The meta-regression analysis revealed that the prevalence varied according to the method of assessment (self-administered questionnaire EC +37% [95% CI 20; 53], p=0.001 vs interview), the risk of bias (EC +33% [95% CI 05; 61], p=0.029 for high risk) and the number of included patients (EC –29% [95% CI–52; –6], p=0.030 for studies including fewer than 100 patients. Thus, the prevalence was 3% [95% CI 1–5] in studies using interview and 42% [95% CI 32–51] in studies with self-administered questionnaires. In addition, women more often have social anxiety disorder since for each additional percentage of women included, the prevalence increases by 1.7% [0.7; 2.6] (p=0.007).

Generalized anxiety disorder

After selection (Table SI and Fig. S1), 12 studies, all prospective, assessed the prevalence of generalized anxiety disorder (GAD) (26–31, 35, 37, 39–42). The meta-analysis revealed a prevalence of 11% [95% CI 9–14]

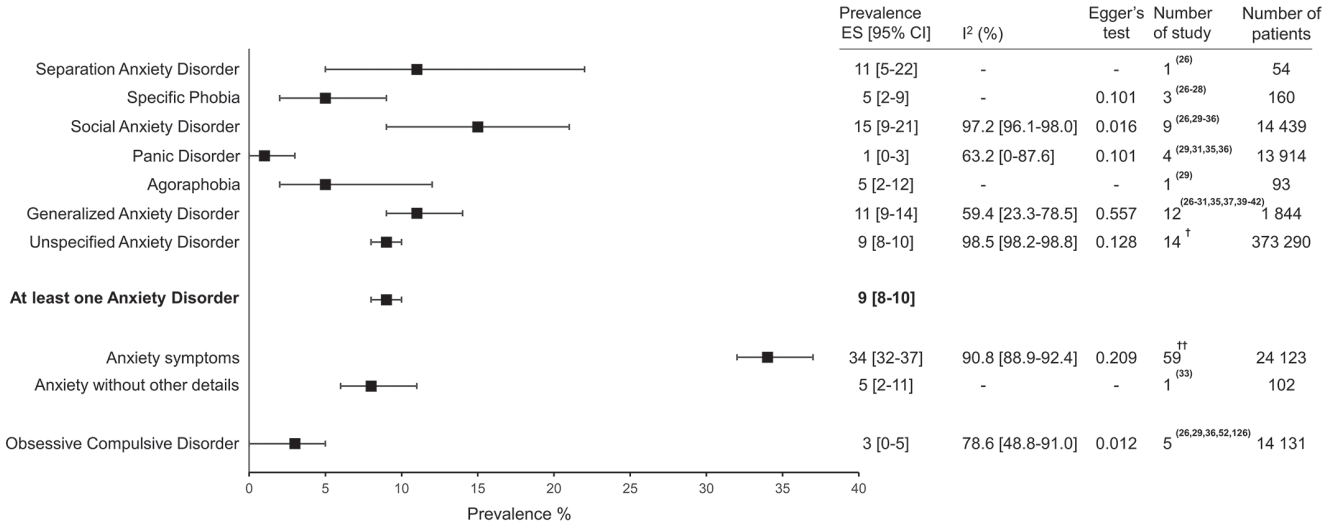

Fig. 2. Meta-analysis of the prevalence of anxiety disorders and anxiety symptoms in psoriasis patients. ES: effect size (estimated prevalence); 95% CI: 95% confidence interval. †References 28, 43, 45–53, 55, 56, 60. ††References 32, 62–81, 83–92, 94–97, 99–110, 112–117, 119, 121–125.

(Fig. 2). None of the factors tested in the meta-regression analysis had any effect on the prevalence of GAD.

Unspecified anxiety disorder

Of the 21 studies assessing anxiety disorder without specification of the disorder (unspecified anxiety disorder), 14 were retained for the meta-analysis (Table SI and Fig. S2) (28, 43, 45–53, 55, 56, 60). Seven were prospective (5 interview, 1 based on medical record and 1 other on report by the investigator) and 7 retrospective (all based on medical records). The meta-analysis showed a prevalence of 9% [95% CI 8–10] with very wide heterogeneity (98.5%) (Fig. 2). The meta-regression analyses showed that prevalence significantly diminished in studies including more than 500 patients (EC –16% [–25; –07], $p=0.003$), in studies based on medical records (EC –8% [OR –14; –3], $p=0.006$) and in retrospective studies (EC –8% [OR –12; –4], $p=0.001$). The psoriasis duration, the PASI score, the proportion of psoriatic arthritis patients, the proportion of obese patients, and the mean BMI did not influence the prevalence of anxiety disorders.

Ten case-control studies (8 based on medical records and 2 on interviews) were retained (Table SI and Fig. S3) for the analysis of an association between psoriasis and unspecified anxiety disorder (43, 44, 48, 49, 53–55, 59–61). The results showed a positive association between this anxiety disorder and psoriasis (OR 1.48 [1.18; 1.85]) with a high heterogeneity (I^2=99.6%) (**Fig. 3**). The meta-regression analyses showed that the association was stronger in prospective studies, based on interview than in retrospective studies based on medical records (EC –0.79 [OR –1.71; 0.14], $p=0.085$). Sensitivity analysis showed that the prevalence of unspecified anxiety disorder in patients from the case-control studies was similar to that observed in the meta-analysis (9% [6–11]).

Symptoms of anxiety

Of the 66 articles assessing symptoms of anxiety, 59 were retained for the meta-analysis after risk of bias of publication and heterogeneity evaluation (Table SI and Fig. S4) (32, 62–81, 83–92, 94–97, 99–110, 112–117, 119, 121–125). These articles assessed anxiety symptoms mainly by self-administered questionnaires ($n=52$), like Hospital Anxiety and Depression Scale (HADS) (45/52), by researcher-administered questionnaires ($n=2$) and by patients self-report ($n=5$). The prevalence of symptoms of anxiety was 34% [95% CI 32–37] with high heterogeneity (I^2=90.8%) (Fig. 2). Meta-regression analysis showed that the prevalence of anxiety symptoms varied with the questionnaire and the cut-off score used: studies with the Zung self-rating anxiety scale (SAS) and those with a HADS cut-off equal to 8 showed significantly higher prevalence (EC +30% [OR 16; 43], $p<0.001$ and EC +8% [2; 14], $p=0.009$, respectively). Prevalence of anxiety symptoms decreased with age (EC –0.6% [OR –1.2; –0.03], $p=0.041$ for each additional year).

Nine case-control studies (all with self-administered questionnaires) were retained for the analysis of an association between psoriasis and anxiety symptoms (Table SI and Fig. S5) (32, 73, 88, 97, 99, 103, 112, 115, 116). The result presented a strong association (2.51 [2.02–3.12]) without heterogeneity (Fig. 3). Sensitivity analysis showed that the prevalence of anxiety symptoms in patients from the case-control studies was close to that observed in the meta-analysis (37% [95% CI 27–47]). None of the factors tested in the meta-regression analysis had any effect on this association.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis assessing the prevalence rates and odd ratio (OR) for anxiety disorders and anxiety symptoms in psoriasis. The study evidences high prevalence rates of anxiety symptoms and some anxiety disorders in patients with psoriasis and a positive and significant association between psoriasis and anxiety symptoms and unspecified anxiety disorder. In addition, it shows that the prevalence of anxiety symptoms and some anxiety disorders varies notably according to methodological factors.

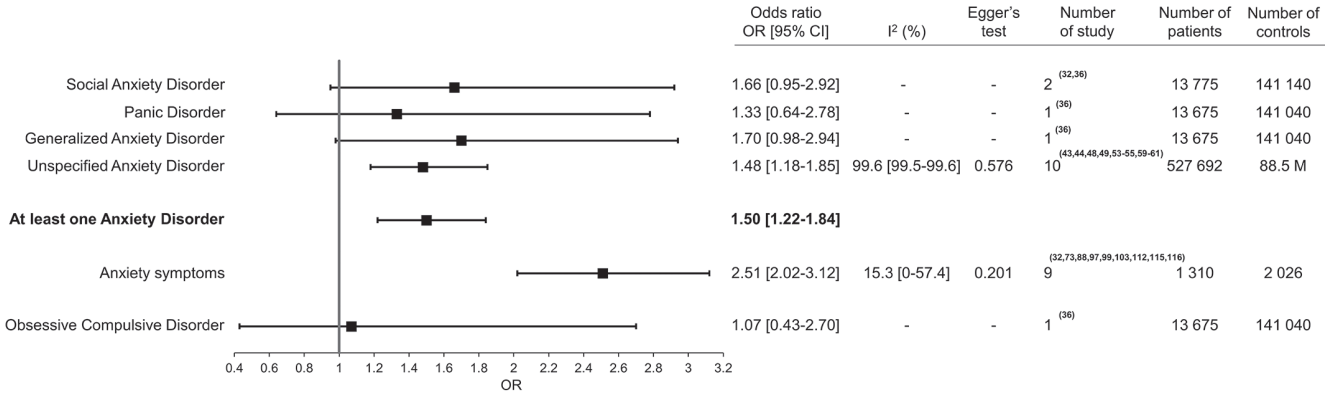

Fig. 3. Odds ratio (OR) meta-analysis of the association between anxiety disorders, anxiety symptoms and psoriasis. CI: confidence interval.

Social anxiety disorder and GAD emerge as the 2 most common anxiety disorders in patients with psoriasis. The meta-analysis of 12 studies, of which 8 were based on interviews and 4 on self-administered questionnaires, showed a GAD prevalence in patients with psoriasis 2–3-fold higher than in the general population independent of the methodological factors (8, 127, 128). The meta-analysis showed a social anxiety disorder prevalence in patients with psoriasis with a high heterogeneity for which meta-regression analyses suggest several explanations. Figures concerning other types of anxiety disorder should be treated with caution for there are very few studies of each disorder among patients with psoriasis. Finally, the studies assessing unspecified anxiety disorder do not detail results of the various types of anxiety disorders and do not specify if they have assessed them.

Meta-regression analyses showed that variations can be attributed to methodological factors, i.e. the manner in which this disorder was evaluated, the number of patients included in the studies, the study design and the risk of bias in studies included. It should be noted that all these factors are closely related: (*i*) retrospective studies, generally based on medical records and including more patients, produce lower prevalence rates than studies using interview due to false-negatives (patients who are not assessed for anxiety are recorded as negative); (*ii*) interview-based studies included fewer patients; the risk of bias could therefore be increased. This risk could also be increased by the fact that psoriasis is a visible dermatosis; (*iii*) studies based on self-administered questionnaires show higher prevalence rates of anxiety and allow inclusion of more patients than the interview-based studies. The inconsistent level of psychometric properties of some of the self-administered questionnaires could have contributed to the wide variations. While none of the dermatological factors tested (duration and severity of psoriasis, and proportion of patients with psoriatic arthritis) in meta-regression can explain prevalence variations, 2 demographic factors can do it: (*i*) the prevalence of social anxiety disorder was more important in studies including more women, which is consistent with higher prevalence of social anxiety disorder among females in the general adult population (8); (*ii*) the prevalence of anxiety symptoms decreased as age increased, as it does in the general adult population (8, 127, 128). Similarly, older patients with psoriasis tend to report less impairment in quality of life (75).

The overall prevalence of anxiety symptoms in psoriasis is close to that obtained in meta-analyses of anxiety symptoms among patients with alopecia areata (27% (1)) and chronic urticaria (30.6% (7)). We determined a pooled OR for anxiety symptoms (2.51) that was also close to that obtained among patients with alopecia areata (2.00 (1); 2.50 (2)). The HADS was by far the most widely used (45/52) self-report instrument to assess anxiety symptoms in the studies in the current meta-analysis. Meta-regression analysis showed that the prevalence of anxiety symptoms assessed with the HADS was higher when a low cut-off score (≥ 8) was used compared with a more conservative one (≥ 11). The HADS has very few questions on somatic symptoms, has good feasibility and is the most commonly used anxiety-screening instrument in psoriasis. In addition, no validation studies of HADS in psoriasis have been performed (56) and to determine a definitive cut-off point it could therefore be beneficial to have a full assessment of the disorder. However, screening tools can only reveal anxiety symptoms or possible/probable anxiety disorder, whereas a structured clinical psychiatric interview is the gold standard to establish a formal diagnosis of anxiety disorder (129).

Strength and limitations

The major strength of this meta-analysis is to evidence specific prevalence rates and OR of anxiety disorders on the one hand and anxiety symptoms on the other. The other strengths of this meta-analysis are the large number of studies included, the large sample size, the inclusion of subjects from various geographical areas, the use of a specific instrument for estimating risk of bias in studies included that has high interrater agreement and the elimination of studies responsible for a risk of publication bias and high heterogeneity. In addition, sensitivity analysis showed that the prevalence of anxiety symptoms and unspecified anxiety disorder in patients from the case-control studies were close to that observed in the current meta-analysis.

Our meta-analysis was influenced by the limitations of the studies included. Most of the studies did not provide sufficient details about the patients enrolled, such as the severity of psoriasis (only 27 of the 101 studies mentioned the PASI), cigarette smoking, alcohol and certain somatic comorbidities, which, in some patients, had known associations with anxiety, such as obesity. Thus, only 12 studies gave the proportion of obese patients and 12 the BMI. The comorbidity of anxiety and depression is common (8) and there is an increased prevalence of depressive symptoms and clinical depression among patients with psoriasis (12), but only 9 studies, i.e. less than 10%, assessed this co-occurrence. Anxiety in the general population is far more common in women, but the number of sex-related cases of anxiety disorder was very rarely specified in the studies. More social anxiety disorders were observed in studies including more women; however, the link is indirect; we were unable to demonstrate that the prevalence of anxiety disorders is higher in women. Finally, although psoriasis can affect children, very few studies of anxiety disorders have been performed in this category of patients.

Conclusion

This study demonstrates that subjects with psoriasis are significantly more likely to have anxiety disorders or to experience anxiety symptoms than those without psoriasis. More research is now needed to validate the HADS for patients with psoriasis and determine a definitive cut-off point. Future studies should focus on other anxiety disorders than GAD in order to more precisely determine their respective prevalence. For the immediate future, the results of the current study show that all clinicians should be cognizant of the necessity of screening for the presence of anxiety symptoms and anxiety disorders in patients with psoriasis. Indeed, the anxiety disorders, presented by 9–15% of patients with psoriasis, must lead the clinicians to refer such patients for evaluation and appropriate treatment by mental health professionals. However, it must also be emphasized that the anxiety symptoms, presented by more than one-third of patients with psoriasis, should be considered as warning signs, which have to be evaluated regularly to monitor whether they have resulted in anxiety disorders.

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The authors have no conflicts of interest to declare.

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