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Systematic Review

Factors associated with depression, anxiety and severe mental illness among adults with atopic eczema or psoriasis: a systematic review and meta-analysis

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Abstract

Background Evidence suggests an association between atopic eczema (AE) or psoriasis and mental illness; however, the factors associated with mental illness are unclear.

Objectives To synthesize and evaluate all available evidence on factors associated with depression, anxiety and severe mental illness (SMI) among adults with AE or psoriasis.

Methods We searched electronic databases, grey literature databases and clinical trial registries from inception to February 2022 for studies of adults with AE or psoriasis. Eligible studies included randomized controlled trials (RCTs), cohort, cross-sectional or case–control studies where effect estimates of factors associated with depression, anxiety or SMI were reported. We did not apply language or geographical restrictions. We assessed risk of bias using the Quality in Prognosis Studies tool. We synthesized results narratively, and if at least two studies were sufficiently homogeneous, we pooled effect estimates in a random effects meta-analysis.

Results We included 21 studies (11 observational, 10 RCTs). No observational studies in AE fulfilled our eligibility criteria. Observational studies in people with psoriasis mostly investigated factors associated with depression or anxiety – one cross-sectional study investigated factors associated with schizophrenia. Pooled effect estimates suggest that female sex and psoriatic arthritis were associated with depression [female sex: odds ratio (OR) 1.62, 95% confidence interval (CI) 1.09–2.40, 95% prediction intervals (PIs) 0.62–4.23, $I^2 = 24.90\%$, $\tau^2 = 0.05$; psoriatic arthritis: OR 2.26, 95% CI 1.56–3.25, 95% PI 0.21–24.23, $I^2 = 0.00\%$, $\tau^2 = 0.00$] and anxiety (female sex: OR 2.59, 95% CI 1.32–5.07, 95% PI 0.00–3956.27, $I^2 = 61.90\%$, $\tau^2 = 0.22$; psoriatic arthritis: OR 1.98, 95% CI 1.33–2.94, $I^2 = 0.00\%$, $\tau^2 = 0.00$). Moderate/severe psoriasis was associated with anxiety (OR 1.14, 95% CI 1.05–1.25, I^2 0.00%, $\tau^2 = 0.00$), but not depression. Evidence from RCTs suggested that adults with AE or psoriasis given placebo had higher depression and anxiety scores compared with comparators given targeted treatment (e.g. biologic agents).

Conclusions Our review highlights limited existing research on factors associated with depression, anxiety and SMI in adults with AE or psoriasis. Observational evidence on factors associated with depression or anxiety in people with psoriasis was conflicting or from single studies, but some identified factors were consistent with those in the general population. Evidence on factors associated with SMIs in people with AE or psoriasis was particularly limited. Evidence from RCTs suggested that AE and psoriasis treated with placebo was associated with higher depression and anxiety scores compared with skin disease treated with targeted therapy; however, follow-up was limited. Therefore, long-term effects on mental health are unclear.

What is already known about this topic?

- Previous studies have found evidence of an association between atopic eczema (AE) or psoriasis, and mental health conditions (i.e. depression, anxiety and severe mental illness).
- However, the factors associated with depression, anxiety or severe mental illness among individuals with AE or psoriasis are unclear.

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What does this study add?

- Pooled effect estimates from observational studies suggest that female sex and psoriatic arthritis are associated with increased depression and anxiety, while moderate/severe psoriasis is associated with increased anxiety.
- Trial evidence suggests that AE or psoriasis treated with placebo is associated with increased depression and anxiety compared with skin disease treated with targeted therapy.

Atopic eczema (AE) and psoriasis are inflammatory skin diseases with a lifetime prevalence of 1–3% and up to 10% respectively in adults.[1,2] Mental illness is a leading cause of years lived with disability worldwide.[3]

Evidence from cross-sectional studies and a systematic review suggest that AE and psoriasis are associated with depression, anxiety and severe mental illnesses (SMI), such as schizophrenia, bipolar disorder and other psychoses.[4–8] Longitudinal evidence indicates that AE and psoriasis precede mental illness diagnoses, and are associated with increased newly diagnosed anxiety, depression and bipolar disorder.[9–11]

While associations between AE, psoriasis and mental illness are acknowledged, factors associated with depression, anxiety and SMI in people with AE or psoriasis are unclear. There are plausible mechanisms to explain the association. For example, evidence suggests that individuals with AE or psoriasis engage in unhealthy lifestyle behaviours (e.g. poor diet, smoking or harmful alcohol intake),[12–17] which are associated with increased depression or anxiety risk.[18,19] Disrupted sleep – experienced by individuals with AE as a result of chronic itch – has been recognized as a risk factor for depression.[20] It is possible that inflammation in AE or psoriasis may influence mental illness through elevated proinflammatory cytokines or immune reactivity contributing to depressive symptoms or SMI.[21–24]

Coexisting AE or psoriasis and mental illness may negatively affect skin disease. For example, depression may reduce skin treatment adherence,[25] potentially reducing benefits leading to worsening skin condition, with subsequent potential for mental illness exacerbation. Consequently, it is important to identify factors associated with mental illness among those with AE or psoriasis. This may lead to recognition of groups who would benefit from targeted mental health prevention strategies, or modifiable factors that may modify risk.

This systematic review aims to synthesize and evaluate all available evidence on factors associated with depression, anxiety and SMI among adults with AE or psoriasis.

Materials and methods

We registered this review with PROSPERO (CRD42020163941) and the review was conducted and reported following PRISMA guidelines.[26] A detailed protocol has been published elsewhere.[27]

Eligibility criteria

We included observational studies (cohort, case–control, cross-sectional studies) or randomized controlled trials (RCTs) in adults (age $\geq$ 18 years) with AE or psoriasis where effect estimates of factors associated with depression, anxiety or SMI were reported (Table 1). Language or geographical restrictions were not applied. We included RCTs that investigated AE or psoriasis treatment with biologic therapies to study skin disease treated using placebo – compared with skin disease treated using targeted therapy (i.e. biologic agents) – as a factor potentially associated with depression, anxiety or SMI. Depression and anxiety scores identified using validated questionnaires in included RCTs were considered outcomes, although scores may not correspond to a clinical diagnosis of depression or anxiety,[28] and changes in scores may not be clinically important.[29] As we were not investigating the effectiveness of interventions, we considered RCTs as randomized cohort studies for analyses and when assessing risk of bias.

Search strategy

We searched eight electronic databases (MEDLINE, Embase, Global Health, Scopus, Cochrane Library, Web of Science, Base, PsycInfo), three grey literature databases (PsycExtra, Open Grey, New York Academy of Medicine Grey Literature Report), five large clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register, Japan Primary Registries Network, Australian New Zealand Clinical Trials Registry, International Standard Randomised Controlled Trial Number Registry), and a specialist eczema trial registry [Global Resource of Eczema Trials (GREAT)] from inception to February 2022. Updates to the New York Academy of Medicine Grey Literature Report ceased in January 2017, while updates to GREAT ceased in September 2017. Our search strategy included terms relating to the following three key concepts: (i) 'association' terms; (ii) 'AE or psoriasis'; and (iii) 'mental illness'. We identified additional papers through citation searching large summary papers identified by our search, and manually searching references of included papers (Appendix S1; see Supporting Information).

Data extraction

Two reviewers (E.I.A. and Y.S. or E.I.A. and J.M.) independently screened titles and abstracts of all articles returned by the search. Full-text screening was conducted by two reviewers (E.I.A., J.M.) in accordance with eligibility criteria. Disagreements were discussed by reviewers (E.I.A. and Y.S. or E.I.A. and J.M.), with consultation from a third (K.E.M.) and fourth (S.M.L.) reviewer, if necessary. We developed two data extraction and risk of bias assessment forms (one for observational studies, another for RCTs) to extract information from each article included (Appendix S2; see Supporting Information). Two reviewers (E.I.A. and J.M.) piloted both forms by independently extracting data from a random selection of the larger of 10% or five eligible studies.

Table 1 Systematic review eligibility criteria

Eligibility criteria	Rationale
Studies with adult participants (aged ≥ 18 years) with atopic eczema or psoriasis were eligible for inclusion. Studies including both adults and children where data for adults are reported separately were also eligible	Studies with participants aged < 18 years were excluded as there may be differences in the factors associated with mental illness in children compared with adults
Randomized controlled trials (RCTs), case–control, cohort, or cross-sectional studies	RCTs where the intervention was atopic eczema or psoriasis treatment were considered as randomized cohort studies and were included to investigate skin disease treated using placebo, as these included factors potentially associated with mental illness, compared with skin disease treated with targeted (i.e. biologic) therapy. We investigated this by comparing the change in mental illness from baseline measurements with postintervention measurements (between groups receiving the intervention with groups receiving no intervention) to examine the effect that treating skin disease with placebo had on mental illness in people with atopic eczema or psoriasis Other study types (ecological or case series studies, case reports, systematic reviews) and article types (letters, conference proceedings, editorials, opinion articles) were excluded as they were unlikely to report sufficient information to answer our research question. However, relevant summary reviews were flagged, and reference lists searched for eligible studies
Potential factors were any variable that was analysed for an association with the following outcomes: depression, anxiety or severe mental illness (i.e. schizophrenia, bipolar disorder or other psychoses) in people with atopic eczema or psoriasis, and an effect estimate (i.e. ratio or difference measures) was reported	Studies where effect estimates were not reported (i.e. studies where correlates were instead calculated) were not included, as correlations between variables simply show that there is a pattern in the data, while an effect estimate measures the strength of the association
Studies in any language and from any geographical setting were considered	To capture all eligible studies

This resulted in piloting the forms for six studies (three observational studies, three RCTs). Data from the remaining studies were extracted by a single reviewer (E.I.A.).

Risk of bias

We used the Quality in Prognosis Studies tool to assess risk of bias across the following six domains in the included studies: (i) study participation; (ii) study attrition; (iii) prognostic factor measurement; (iv) outcome measurement; (v) study confounding; and (vi) statistical analysis and reporting.[30] We assessed risk of bias as low, moderate, or high in each domain. We did not produce an overall risk of bias score for each study as summated scores are not recommended (owing to potentially inappropriately assigning equal weights to assessed domains).[30]

Data analysis

We synthesized our results narratively, describing results separately by skin disease (AE, psoriasis) and study type (observational study, RCT). If at least two studies were sufficiently homogeneous (in terms of study design, study population, factor assessed and outcome), we pooled effect estimates in a random effects meta-analysis using the DerSimonian and Laird method,[31] and assessed statistical heterogeneity using the I^2 and τ^2 statistics.[32] Prediction intervals (PIs) were used alongside confidence intervals (CIs) to illustrate the degree of heterogeneity in the forest plots of random effects meta-analysis by providing a 95% range for the possible associations between the factor and outcome.[33] We did not use funnel plots to assess publication bias as the number of studies included was below the recommended minimum of 10.[32] All analyses were conducted using STATA version 16 (StataCorp, College Station, TX, USA).

Results

Our search identified 17 539 articles. After deduplication and including articles from citation searching and reference lists, we screened 9053 titles and abstracts. We reviewed 40 full-text articles and included 21 (including one article in Mandarin, which was translated by a native speaker) (Figure 1, Appendix S3, Table S1; see Supporting Information). We included 11 observational studies in psoriasis (one cohort, 10 cross-sectional)[34–44] and 10 RCTs (five AE, five psoriasis) (Tables 2 and S2–S4; see Supporting Information).[45–54]

Risk of bias assessments

The percentage agreement for the risk of bias assessments conducted by two reviewers for six of the included studies was 91%. Of 11 observational studies included, one was at moderate risk of bias in one domain and low risk of bias in other domains,[41] and 10 studies[34–40,42–44] were at moderate or high risk of bias in 2 or more domains (Figure 2[55] and Table S5; see Supporting Information). All observational studies were judged to have at least moderate risk of bias owing to confounding. Bias as a result of study participation affected nine observational studies[34–37,39,40,42–44] owing to inadequately describing the sampling frame, source population, recruitment method, or characteristics of nonparticipants.

All five eczema trials and three psoriasis trials were considered to have a low risk of bias in all domains (Figure 2,[55] Table S5).[45–52] Two psoriasis trials had a moderate risk of bias in the statistical analysis and reporting domain,[53,54] and

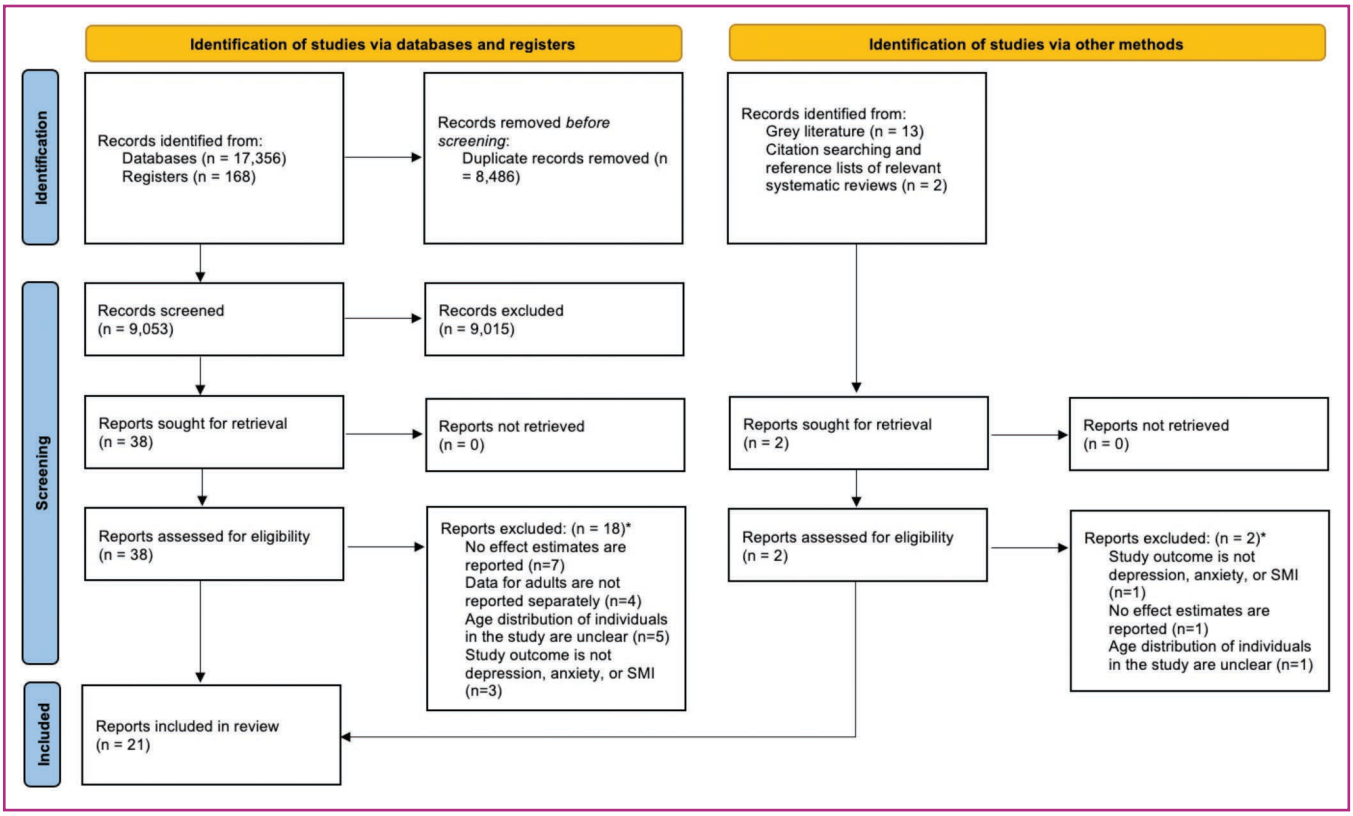

Figure 1 PRISMA flow diagram of the study selection.SMI, severe mental illness. *Some studies were excluded for more than one reason; the total number does not add up to number in brackets.

one psoriasis trial had a high risk of bias in the study attrition domain.[54]

Atopic eczema

We did not identify any eligible observational studies in AE. In the five RCTs included (Table S6; see Supporting Information), individuals with AE who were randomized to receive placebo had higher mean depression, anxiety, or combined anxiety and depression scores after 16 weeks than those receiving targeted treatment (dupilumab, abrocitinib).[45–49]

Psoriasis

All observational studies included were conducted in adults with psoriasis. We identified factors associated with depression (Table S7; see Supporting Information), anxiety (Table S8; see Supporting Information) and schizophrenia (Table S9; see Supporting Information). There were five included RCTs of psoriasis treatment (Table S10; see Supporting Information).[50–54]

Observational studies

Depression

Pooled effect estimates (Figure 3a) from two studies of moderate heterogeneity investigating age,[39,44] two studies of moderate heterogeneity investigating psoriasis severity,[39,40] and two studies of low heterogeneity investigating systemic therapy[35,44] found no evidence that age [odds ratio (OR) 1.00, 95% CI 0.97–1.02, $I^2 = 28.00\%$, $\tau^2 = 0.00$], moderate/severe psoriasis (OR 1.15, 95% CI 0.92–1.44, $I^2 = 26.70\%$, $\tau^2 = 0.01$), or systemic therapy (OR 0.62, 95% CI 0.30–1.26, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with depression.

However, pooled effect estimates from five eligible studies of moderate heterogeneity investigating sex[37,39,42–44] and three studies of low heterogeneity investigating psoriatic arthritis[35,36,44] reported that female sex (OR 1.62, 95% CI 1.09–2.40, 95% PI 0.62–4.23, $I^2 = 24.90\%$, $\tau^2 = 0.05$) and psoriatic arthritis (OR 2.26, 95% CI 1.56–3.25, 95% PI 0.21–24.23, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with increased depression, compared with male sex and no psoriatic arthritis, respectively.

Included studies conducted in people with psoriasis found no evidence of associations between depression and urban or rural living,[43] occupation,[43] instrumental social support (e.g. physical assistance),[42] motivational salience (i.e. attention to appearance),[42] facial or genital lesions,[42] psoriasis phenotype,[44] and comorbidities (bipolar disorder, cardiovascular disease, cerebrovascular disease, diabetes, ischaemic heart disease, schizophrenia).[35,38] Multiple studies in people with psoriasis reported conflicting results regarding associations between education,[37,38,43] ethnicity,[38,44] and age at psoriasis onset,[39,42] and depression (meta-analyses not possible owing to differences in definitions between the factors of interest and/or study design).

Evidence from single studies suggested increased associations with depression in people with psoriasis with high

Table 2 Summary of studies included in the review

First author, publication year	Mental health condition: Depression	Anxiety	SMI	Study design	Study setting	Sample size	Factors investigated
Observational studies in psoriasis							
Bakar, 2021[34]	Yes	Yes	No	Cross-sectional study	Dermatology outpatient clinic	174	Lower limb lesions, dyslipidaemia, quality of life
Kwan, 2018[35]	Yes	Yes	No	Cross-sectional study	Dermatology outpatient clinic	102	Psoriasis severity, head involvement, use of systemic therapy, quality of life, diabetes, ischaemic heart disease, cerebrovascular disease, psoriatic arthropathy
Lada, 2022[36]	Yes	No	No	Cross-sectional study	Specialist psoriasis and psoriatic arthritis clinics	219	Comorbid psoriatic arthritis
Petraškienė, 2016[37]	Yes	Yes	No	Cross-sectional study	Inpatient and outpatient units of hospital dermatology department	385	Sex, age group, education
Strober, 2017[38]	Yes	No	No	Longitudinal cohort study	Data from PSOLAR registry	7490	Treatment with biologics or phototherapy, age, sex, ethnicity, years since psoriasis began, baseline PGA score, change in PGA score from baseline to depression, education, insurance, psoriatic arthritis, diabetes, schizophrenia, anxiety, bipolar disease, chronic obstructive pulmonary disease, CAD/MI/ACVD/stroke/TIA
Tian, 2019[39]	Yes	Yes	No	Cross-sectional study	Dermatology department in a hospital	208	Age, sex, stress reaction, psoriasis severity, psoriasis duration, age at psoriasis onset
Tribó, 2019[40]	Yes	Yes	No	Cross-sectional study	Dermatology department in a tertiary referral centre	300	Psoriasis severity
Tu, 2017[41]	No	No	Yes	Cross-sectional study	Electronic health records from the LHID	10 796	Age, gender, psoriasis duration, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatological disease, liver disease, diabetes, hemiplegia or paraplegia and renal disease
Wojtyna, 2017[42]	Yes	No	No	Cross-sectional study	Dermatology outpatient and inpatient clinics, and Polish psoriasis associations	219	Sex, age at onset of psoriasis, psoriasis severity, ASI-SES, ASI-MS, emotional and instrumental social support, facial lesions, genital lesions, and distress
Yu, 2015[43]	Yes	No	No	Cross-sectional study	Dermatology outpatient clinic	246	Sex, education, occupation, and address
Lamb, 2017[44]	Yes	Yes	No	Cross-sectional study	Single centre tertiary psoriasis service	607	Psoriasis severity (using PASI), age, gender, ethnicity, psoriasis phenotype, psoriasis treatment, psoriatic arthritis, previous depression, or anxiety
RCTs in atopic eczema							
de Bruin-Weller, 2018[45]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinics	325	Targeted atopic eczema treatment (dupilumab) plus TCS vs. placebo plus TCS
Simpson, 2016[46]	Yes	Yes	No	Phase IIb, double-blind, parallel dose-ranging trial	Dermatology outpatient clinics	380	Targeted atopic eczema treatment (dupilumab) vs. placebo
Simpson, 2016[47] and Cork, 2019[48a]	Yes	Yes	No	Phase III, double-blind, parallel trials	Dermatology outpatient clinics	1379	Targeted atopic eczema treatment (dupilumab) vs. placebo
Simpson, 2021[49]	Yes	Yes	No	Phase IIb, double-blind parallel trial	Dermatology outpatient clinics	267	Targeted atopic eczema treatment (abrocitinib) vs. placebo
RCTs in psoriasis							
Gordon, 2018[50]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	992	Targeted psoriasis treatment (guselkumab) vs. placebo or adalimumab
Griffiths, 2017[51]	Yes	No	No	Phase III, double-blind, parallel trials	Dermatology outpatient clinic	320	Targeted psoriasis treatment (ixekizumab) vs. placebo
Langley, 2010[52]	Yes	Yes	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	1230	Targeted psoriasis treatment (ustekinumab) vs. placebo
Menter, 2010[53]	Yes	No	No	Phase II, double-blind, parallel trial	Dermatology outpatient clinic	96	Targeted psoriasis treatment (adalimumab) vs. placebo
Tyring, 2006[54]	Yes	No	No	Phase III, double-blind, parallel trial	Dermatology outpatient clinic	620	Targeted psoriasis treatment (etanercept) vs. placebo

ACVD, acute cardiovascular disease; ASI-R, Appearance Schemas Inventory-Revised scale includes ASI-MS (motivational salience) and ASI-SES (self-evaluative salience); CAD, coronary artery disease; LHID, longitudinal health insurance database; MI, myocardial infarction; PSOLAR, Psoriasis Longitudinal Assessment and Registry; RCT, randomized controlled trial; SMI, severe mental illness (including schizophrenia, bipolar disorder and other psychoses); TCS, topical corticosteroid; TIA, transient ischaemic attack. [a]Simpson, 2016 is the original RCT. Cork, 2019 is a pooled analysis of the trials.

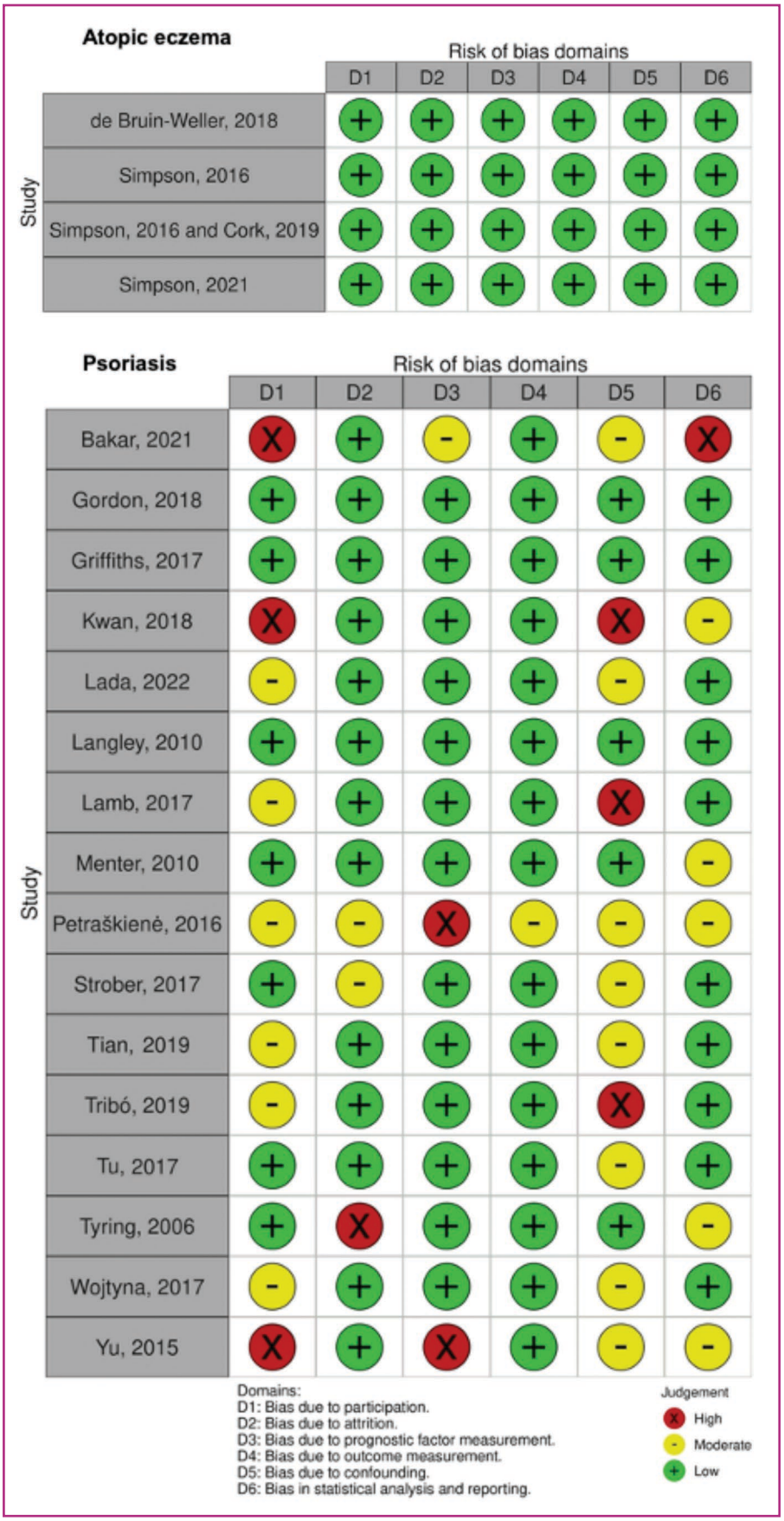

Figure 2 Risk of bias assessments of included studies using the Quality in Prognostic Studies tool.

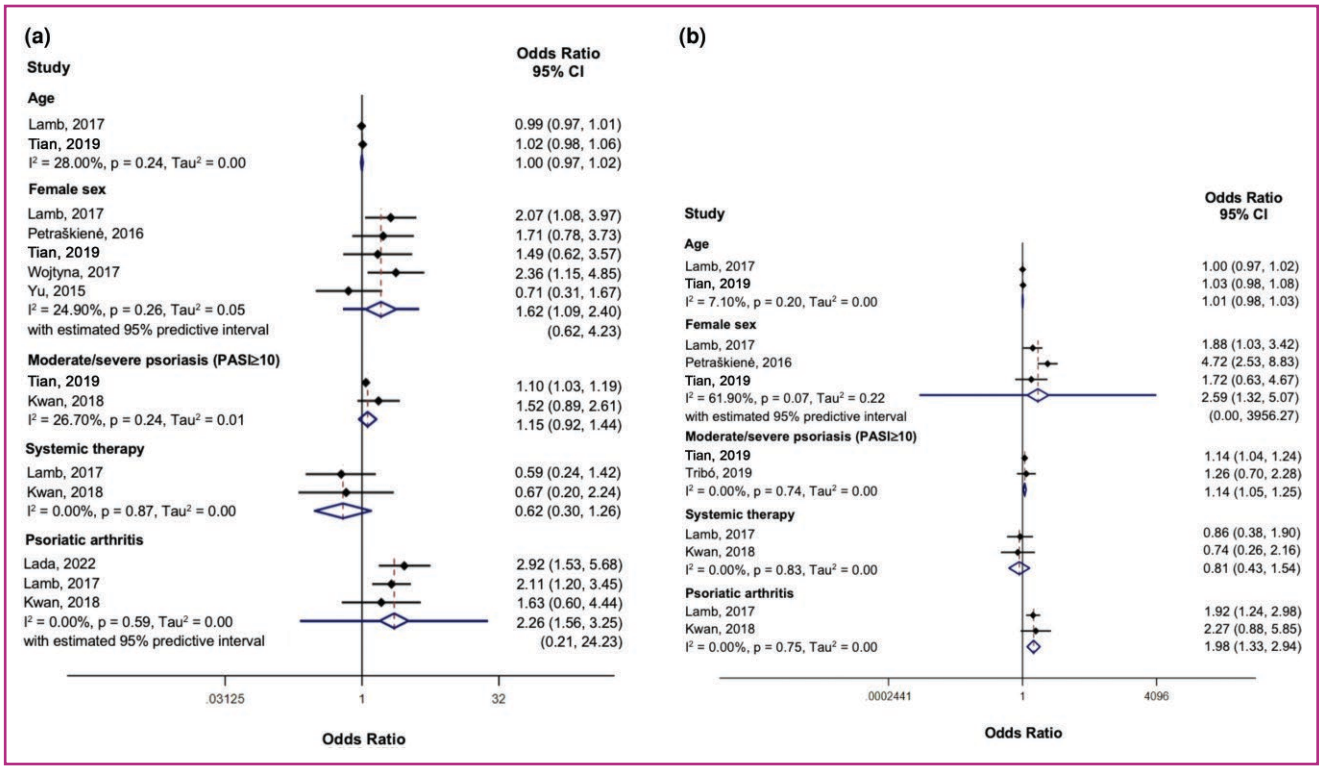

Figure 3 (a) Random effects meta-analyses of factors associated with depression among adults with psoriasis. (b) Random effects meta-analyses of factors associated with anxiety among adults with psoriasis.CI, confidence interval. PASI, Psoriasis Area and Severity Index.

baseline physician global assessment score[38] [Physician's Global Assessment (PGA), used to evaluate psoriasis severity and treatment response],[56] psoriatic head involvement,[35] lower limb lesions,[34] self-evaluative salience (e.g. physical appearance importance),[42] high psychological distress,[42] previous depression,[44] positive stress reaction,[39] and comorbid anxiety or chronic obstructive pulmonary disease.[38] Evidence from multiple studies suggested that impaired quality of life was associated with increased depression in people with psoriasis (meta-analysis not possible owing to differences in factor definition).[34,35] Evidence from single studies suggested associations between reduced depression with: emotional social support (e.g., having a confidant),[42] private health insurance,[38] longer psoriasis duration,[38,39] comorbid dyslipidaemia,[34] biologic therapy treatment (specifically adalimumab),[38] and a decrease in PGA score from baseline to depression diagnosis.[38]

Anxiety

Pooled effect estimates (Figure 3b) from two studies of low heterogeneity investigating age,[39,44] and two studies of low heterogeneity investigating systemic therapy[35,44] found no evidence that age (OR 1.01, 95% CI 0.98–1.03; $I^2 = 7.10\%$, $\tau^2 = 0.00$) or systemic therapy (OR 0.81, 95% CI 0.43–1.54, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with anxiety.

However, pooled effect estimates from three eligible studies of substantial heterogeneity investigating sex[37,39,44] two studies of minimal heterogeneity investigating psoriasis severity,[39,40] and two studies of low heterogeneity investigating psoriatic arthritis[35,44] reported that female sex (OR 2.59, 95% CI 1.32–5.07, 95% PI 0.00–3956.27, $I^2 = 61.90\%$, $\tau^2 = 0.22$), moderate/severe psoriasis (OR 1.14, 95% CI 1.05–1.25, $I^2 = 0.00\%$, $\tau^2 = 0.00$) and psoriatic arthritis (OR 1.98, 95% CI 1.33–2.94, $I^2 = 0.00\%$, $\tau^2 = 0.00$) were associated with increased anxiety, compared with male sex, mild psoriasis and no psoriatic arthritis, respectively.

Evidence from single studies found no evidence of associations with anxiety and psoriasis phenotype,[44] or comorbidities (cerebrovascular disease, diabetes, ischaemic heart disease).[35] Evidence from single studies suggested increased anxiety with primary education alone,[37] psoriatic head involvement,[35] positive stress reaction,[39] Asian ethnicity,[44] previous anxiety,[44] and severely impaired quality of life.[35] Evidence from a small cross-sectional study suggested that psoriasis presentation in patients aged $\geq$ 18 years, or longer psoriasis duration, is associated with reduced anxiety.[39]

Schizophrenia

A single cross-sectional study investigated factors associated with schizophrenia in people with psoriasis.[41] Individuals aged 40–59 years were associated with increased schizophrenia compared with those aged 20–39 years. Comorbid cerebrovascular disease or chronic pulmonary disease were also associated with increased schizophrenia. There was no evidence of associations with schizophrenia and sex, psoriasis duration, or comorbidities (congestive heart disease, diabetes, hemiplegia or paraplegia, liver disease, peripheral vascular disease, renal disease, rheumatological disease).

Randomized controlled trials

In all psoriasis trials, individuals with psoriasis randomized to receive placebo had higher depression/anxiety scores

than those receiving targeted treatment (ixekizumab, adalimumab, etanercept, guselkumab, ustekinumab).[49–53] The maximum trial follow-up was 24 weeks.

Discussion

We identified evidence from 11 observational studies and 10 RCTs regarding factors associated with depression, anxiety and SMI in adults with AE or psoriasis. Among adults with psoriasis, pooled effect estimates suggested that female sex and psoriatic arthritis were associated with increased depression and anxiety, while moderate/severe psoriasis was associated with increased anxiety, but not depression. Evidence that related to other factors of interest were often from single studies only. Evidence for factors associated with SMI were limited, with one observational study investigating factors associated with schizophrenia in adults with psoriasis. Evidence from RCTs suggested that AE and psoriasis treated with placebo was associated with higher depression and anxiety scores compared with skin disease treated with targeted therapy; however, follow-up was limited to 24 weeks maximum. Therefore, the prolonged effects on mental health are unclear.

To our knowledge, this is the first study to systematically review literature on factors associated with depression, anxiety and SMI among adults with AE or psoriasis. We followed a prespecified protocol[32] and searched multiple databases, trial registries and grey literature. Language or geographical restrictions were not applied. We assessed risk of bias for individual studies. Despite the comprehensiveness of our search strategy, it may have missed relevant studies. Studies that did not find associations (between factors of interest and depression, anxiety or SMI in people with AE or psoriasis) may not have been published. We were unable to investigate nonpharmacological factors associated with depression, anxiety, and SMI in people with AE, because no eligible studies were found. Our review investigated associations between each factor and mental illness in isolation; however, the reality is likely to consist in a complex relationship between identified factors (e.g. AE or psoriasis severity, stigmatization, lifestyle factors).

Many observational studies included in our systematic review had small sample sizes, which limited their power to detect associations between factors of interest and mental illness. Additionally, most observational studies tested associations between multiple factors and mental illness, suggesting some observed associations occurred by chance owing to multiple testing. Most observational studies included were cross-sectional, so we cannot exclude bidirectional relationships between factors and mental illness. Variability in factor definitions and differences in study design prevented us calculating pooled effect estimates for some factor and outcome pairs. Owing to the limited number of studies, we were unable to conduct explorations of study heterogeneity. We were unable to have data from all included studies extracted by two independent reviewers, even though this is considered best practice. We deviated from our original protocol as we were unable to use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool to evaluate the quality of evidence for each mental illness outcome (depression, anxiety and SMI) and factor pair. This deviation was due to the paucity of specific guidelines for the application of GRADE to systematic reviews identifying variables associated with an outcome (rather than reviews identifying prognostic factors).[57]

Included RCTs investigated only short-term effects of treating skin disease with placebo on depression or anxiety in people with AE or psoriasis; maximum follow-up was 16 weeks for AE and 24 weeks for psoriasis. Consequently, it is difficult to draw conclusions about long-term effects of skin disease treatment on depression/anxiety in people with skin disease. Some included RCTs had strict eligibility criteria where individuals with multimorbidity[52,54] were excluded from participating, suggesting that trial study populations may be healthier and not represent broader patient populations.

Studies that use surveys to capture information on the factors of interest may be susceptible to recall bias and subsequent misclassification. They also have limited generalizability as survey responders are often systematically different to nonresponders.[58] All included observational studies were assessed to have at least moderate risk of bias in the confounding domain, suggesting that results of associations between factors of interest and depression, anxiety and SMI may be subject to residual confounding, and should be interpreted with caution.

Our review identified factors associated with mental illness consistent with those seen in the general population (e.g. female sex and lack of social support with depression and anxiety).[59,60] However, some factors associated with mental illness in the general population were not identified (e.g. female sex with schizophrenia, diabetes with depression),[59,61,62] potentially owing to bias and small sample sizes in the included studies. Our finding that individuals with AE or psoriasis treated with biologics have reduced depression or anxiety symptoms is consistent with two systematic reviews of the effect of biologic therapies in people with skin disease.[63,64] A review of psychiatric comorbidities associated with psoriasis identified correlations between facial or genital psoriatic lesions and depression;[65] however, our review found no evidence of these associations.

The variety of factors associated with anxiety and depression identified in people with psoriasis in this review reflects potential mechanisms described in the literature to explain the link between AE or psoriasis and mental illness, including (i) a bidirectional relationship owing to shared immunological changes in AE, psoriasis and mental illness leading to high proinflammatory cytokine levels[21,65,66] and (ii) stigmatization owing to visible skin conditions leading to low self-esteem and psychological burden.[63,65]

Our review included studies demonstrating associations between high baseline PGA (used to evaluate psoriasis severity and treatment response)[56] and depression, and moderate/severe psoriasis and anxiety, both of which support the theory that inflammation is associated with mental illness. Evidence from included RCTs showing that treatment of AE or psoriasis is associated with reduced symptoms of depression or anxiety also supports an inflammatory mechanism, as biologics treat skin disease by limiting overreaction of the immune system and reducing inflammation.[67,68] However, other explanations for the association between psoriasis severity and anxiety could include severe disease

exacerbating problems with stigmatization and increasing mental illness risk.[65,69] The observed association between self-evaluative salience (i.e. importance of physical appearance) and increased depression in psoriasis is consistent with visible skin disease resulting in stigmatization and affecting mental health.[65,69]

We found limited evidence relating to factors associated with SMIs in people with AE or psoriasis. From observational studies, we identified that female sex, and psoriatic arthritis were associated with depression and anxiety, while moderate/severe psoriasis was associated with anxiety, suggesting that individuals with psoriasis and these characteristics may benefit from targeted prevention strategies such as mental health screening. However, this interpretation should be taken with caution owing to the limitations of the included studies. The large number of factors assessed in the included studies suggest that an accurate account of the relationships between AE or psoriasis and mental illness is complex and multifactorial. Including mental health screening in primary care as part of overall psoriasis and AE care may overcome limitations associated with identifying higher-risk individuals. In RCTs, we noted short-term benefits of biological therapies on depression and anxiety in people with both AE and psoriasis. Trials with longer follow-up and inclusive eligibility criteria are required to establish whether biological therapies have longer-term effects on depression or anxiety symptoms and improve the generalizability of findings.

Our review reveals a gap regarding known factors associated with depression, anxiety and SMI in people with AE or psoriasis. Evidence on factors associated with mental illness in psoriasis was often conflicting or from single studies; however, pooled effect estimates suggest that female sex and psoriatic arthritis are associated with increased depression and anxiety, while moderate/severe psoriasis is associated with increased anxiety. There was no corresponding observational evidence in AE. Critically, we found little evidence for factors associated with SMIs. Future research should focus on better understanding factors associated with mental illness – particularly SMIs – in people with AE or psoriasis and identifying high-risk groups to reduce mental illness burden on people with skin diseases.

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Conflicts of interest

J.F.H. has received consultancy fees from Wellcome Trust and juli Health. R.M. has received consultancy fees from AMGEN.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Ethics statement

Ethics approval was not required for this systematic review.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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References: 1. BIMZELX (bimekizumab) Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/12834/smpc. Accessed April 2023. **2.** Strober B et al. Poster P1491 presented at the European Academy of Dermatology and Venereology (EADV) meeting, September 7–10 2022; Milan, Italy.

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