Association between atopic dermatitis, depression, and suicidal ideation: A systematic review and meta-analysis

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Background: Atopic dermatitis (AD) is associated with psychologic distress. However, previous studies found conflicting results about whether AD is associated with increased depression or suicidality.

Objectives: To determine the complex relationship between AD and depression.

Methods: A systematic review of all published observational studies in the MEDLINE, PubMed, Embase, Global Resource for Eczema Trials (GREAT), Latin American and Caribbean Health Sciences (LILACS), the Cochrane Library, Scopus, and PsychInfo databases that analyzed depression in AD was performed. Two reviewers performed study title and/or abstract review and data abstraction. Pooled meta-analysis was performed by using random-effects weighting.

Results: Overall, 106 studies met the inclusion criteria; 36 had sufficient data for meta-analysis. The prevalence of any depression was higher in persons with versus without AD (20.1% vs 14.8%). Similar results were found in sensitivity analyses of studies assessing clinical depression, depressive symptoms, and adults; studies with healthy controls; and studies of low and high study quality. AD was associated with significantly higher depression scale scores, parental depression, antidepressant use, and suicidality. No publication bias was detected.

Limitations: Individual-level data were not available.

Conclusions: Patients with AD have higher odds of depression and suicidality. (J Am Acad Dermatol 2019;80:402-10.)

Key words: antidepressant; atopic dermatitis; comorbidity; depression; eczema; evidence; mood; suicidal ideation; suicide.

Atopic dermatitis (AD) is a chronic inflammatory disease affecting 20% to 30% of children and 3% to 10% of adults worldwide.[1] AD is associated with multiple comorbidities, including asthma, allergic rhinitis,[2] cardiovascular risks, systemic immune deviation, and malignancy.[3] AD is highly symptomatic, with itch, skin pain,[4] and sleep disturbance.[5,6] These symptoms, combined with unsightly skin lesions, may cause psychologic distress and impair quality of life.[7] However, previous studies found conflicting results about whether AD is associated with increased depression

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Mr Patel and Ms Immaneni contributed equally to this article.

Funding sources: None.

Conflicts of interest: None disclosed.

Dr Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis; he was responsible for the study's concept and design, and he obtained funding for the study. Mr Patel, Ms Immaneni, Mr Singam, and Ms Rastogi were responsible for data acquisition. Mr Patel and Ms Immaneni were responsible for analysis and interpretation of data, drafting of the manuscript, and statistical analysis.

Accepted for publication August 28, 2018.

Reprints not available from the authors.

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Published online October 23, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.08.063

or suicidality.[8-10] We sought to determine whether AD is associated with higher rates of depression. In addition, there are many different aspects of depression that can occur in AD, including depressive symptoms; clinically diagnosed major depression; antidepressant use; suicidality; and impact on children, adults, and family. We hypothesized that all of these are increased in AD. This systematic review and meta-analysis sought to determine the relationship between AD and these different aspects of depression.

CAPSULE SUMMARY

- This meta-analysis found that atopic dermatitis was associated with increased odds of clinical depression, depressive symptoms, antidepressant use, suicidality, and parental depression.
- Presence of depression and suicidality should be incorporated into clinical decision making regarding patients with atopic dermatitis.

METHODS

Literature search

The following databases were searched for articles published up to March 18, 2018: Cochrane Library, MEDLINE, Embase, PubMed, Global Resource for Eczema Trials (GREAT), Latin American and Caribbean Health Sciences (LILACS), Scopus, and PsychInfo. The search strategy was modified from previous reviews of AD,[11] depression,[12] and suicidal ideation[13] (Supplemental Table I; available at https://data.mendeley.com/datasets/ry52gnvxkh/1).

The inclusion criteria were as follows: cross-sectional or cohort study assessing the relationship between AD, depression and/or suicidality; inclusion of at least 20 subjects with AD; published online, in print, or in press; published in any language; and included in the respective databases from their earliest entry up to March 18, 2018. Reviews and editorials were excluded. Title and abstract review was performed by at least 2 reviewers. Studies were excluded on the basis of the title and/or abstract if there was no clear indication of analysis of the relationship of AD with depression, parental depression, antidepressant use, suicidality, or parental suicide. Full-text review was performed by at least 2 reviewers. Foreign language manuscripts were translated. If data were duplicated in multiple studies, the most recent and complete study was included.

This study was exempt from institutional review board review as the data were gathered from published literature.

Data extraction and analysis

The following data were extracted: first author; year of publication; study design; methods used to diagnose AD and depression; severity of AD and depression where noted; geographic region of the study; distribution by age and sex; frequency of subjects with and without AD and/or depression, antidepressant use, parental depression, and suicide or suicide risk; and funding source. The Newcastle-Ottawa Scale (NOS) was utilized to assess the quality of studies in the meta-analysis, with a scoring system based on 7 aspects and a maximum of 10 points.

Statistical analyses were performed with OpenMeta for Windows (version 10.10, Brown University, Providence, RI). Pooled meta-analyses were performed on all studies with a control group. Rates of depression, depressive symptoms, parental depression, antidepressant use, parental antidepressant use, and suicidality were estimated in subjects with and without AD. Prevalences and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Standardized mean differences (SMDs) of depression scales and 95% CIs were estimated. Random-effects estimates were generated because of significant heterogeneity ($I^2 > 90\%$ for all analyses). Forest plots were generated. Egger regression and Begg rank correlation were used to assess publication bias.

RESULTS

Literature search

Overall, 7740 nonduplicate citations were identified in the database search; 7458 were excluded during title and abstract review, and 177 were excluded during full-text review. In total, 106 observational studies met the inclusion/exclusion criteria and were included in this systematic review as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Fig 1); 67 were used in the quantitative meta-analyses. A complete list of included studies is presented in the Supplemental Results (available at https://data.mendeley.com/datasets/ry52gnvxkh/1).

Study characteristics

A total of 106 studies were included in this review (published from 1963 to 2018). In all, 67 studies examined the association between AD and depression, 10 examined the association between AD and suicide, 9 examined the association between AD and parental depression, 4 examined the

Abbreviations used:

AD:	atopic dermatitis
aOR:	adjusted odds ratio
BDI:	Beck Depression Inventory
CI:	confidence interval
HAM-D:	Hamilton Depression Scale
NOS:	Newcastle-Ottawa Scale
OR:	odds ratio
SMD:	standardized mean difference

association between AD and antidepressant use, and 1 examined the association between AD and parental suicide. In all, 15 articles examined the association of AD and 1 or more of these end points. Additional study characteristics are presented in the Supplemental Results (available at https://data.mendeley.com/datasets/ry52gnvxkh/1).

Prevalence of depression

A total of 36 studies reported on the prevalence of depression in individuals with and without AD and had sufficient data for meta-analysis. The pooled random-effects prevalence of any depression was higher in adults and children with versus without AD (19.2% vs 14.1%), including clinical depression (14.9% vs 12.6%) and depressive symptoms (22.2% vs 14.5%). Patients with AD had higher odds of depression (22 of 36 studies [pooled OR, 1.71; 95% CI, 1.48-1.98; $P < .001$]) (Fig 2). Similar results were observed in sensitivity analyses of studies assessing clinical depression (12 of 24 studies [pooled OR, 1.61; 95% CI, 1.34-1.93]) or depressive symptoms (9 of 11 studies [pooled OR, 1.70; 95% CI, 1.38-2.10]). Likewise, the odds of depression were slightly higher among patients with AD in the 26 studies that included healthy controls (22 of 26 studies [pooled OR, 1.95; 95% CI, 1.67-2.28]). However, there was no significant difference in the odds of depression among those with AD in the 9 studies that compared patients with AD and controls with various other skin conditions in the dermatologic setting, including acne, psoriasis, melasma, alopecia areata, and vitiligo (0 of 9 studies [pooled OR, 0.95; 95% CI, 0.71-1.26]) (Fig 3). In particular, moderate-to-severe AD was associated with significantly higher odds of depression (2 of 4 studies [pooled OR, 1.81; 95% CI, 1.40-2.35]), whereas mild AD was not consistently associated with depression (1 of 3 studies [pooled OR, 1.28; 95% CI, 0.41-4.06]). Moreover, AD was associated with higher odds of depression in adults (16 of 20 studies [pooled OR, 2.08; 95% CI, 1.70-2.55]) than in children (4 of 6 studies [pooled OR, 1.31; 95% CI, 0.99-1.75]). The association between AD and depression was significant among higher-quality studies (NOS score ≥6 in 21 of 33 studies [pooled OR, 1.71; 95% CI, 1.47-1.99]), and in lower-quality studies as well (NOS score <6 in 1 of 2 studies [pooled OR, 2.41; 95% CI, 1.19-4.87]). All of the studies that provided prevalences for AD and depression were cross-sectional studies, so sensitivity analyses accounting for study design could not be performed.

Two additional studies that were included in the qualitative analysis but had insufficient data for meta-analysis provided adjusted ORs (aORs) for depression in patients with AD. One was a cross-sectional study that was conducted in 5657 Norwegian adults and reported significantly higher rates of depression in patients with AD (aOR, 1.25; 95% CI, 1.04-1.49).[14] Another cross-sectional study of 152 Polish patients reported higher levels of depression in adults with AD (aOR, 2.34; 95% CI, 1.29-4.25).[15]

Mean depression scores

A total of 32 studies examined mean depression scores in patients with and without AD. Overall, there was no significant difference between depression scores in those with versus without AD (11 of 32 studies with significant differences [pooled SMD, 2.00; 95% CI, −0.28 to 4.28]) (Fig 4). However, in sensitivity analyses of specific scales, mean depression scores were significant for the Hamilton Depression Scale (HAM-D) (5 of 5 studies [pooled SMD, 3.66; 95% CI, 2.53-4.79]) and the Beck Depression Inventory (BDI) (4 of 4 studies [pooled SMD, 1.72; 95% CI, 0.51-2.94]).

Effects of AD treatment on depression

Four studies commented on the impact of AD treatment on depression and/or depressive symptoms. A study of Japanese adults with severe AD showed improvement in the Hopkins Symptoms Checklist score for depression in patients who had "tight control" of their AD with use of topical corticosteroids, calcineurin inhibitors, and oral cyclosporine.[16] In a 10-week, single-center, case-control study, patients with AD who received conventional treatments (eg, topical corticosteroids, emollients, and antihistamines) had improved HAM-D scores from baseline.[17] In phase 3, placebo-controlled randomized controlled trials of adults with moderate-to-severe AD, subjects in the dupilumab treatment arm experienced significant improvements in their Hospital Anxiety and Depression Scale scores.[18] Interestingly, 1 study of 20 Japanese adult patients with AD who were treated with the 5-hydroxytryptamine 1A receptor agonist tandospirone citrate found reduced depressive

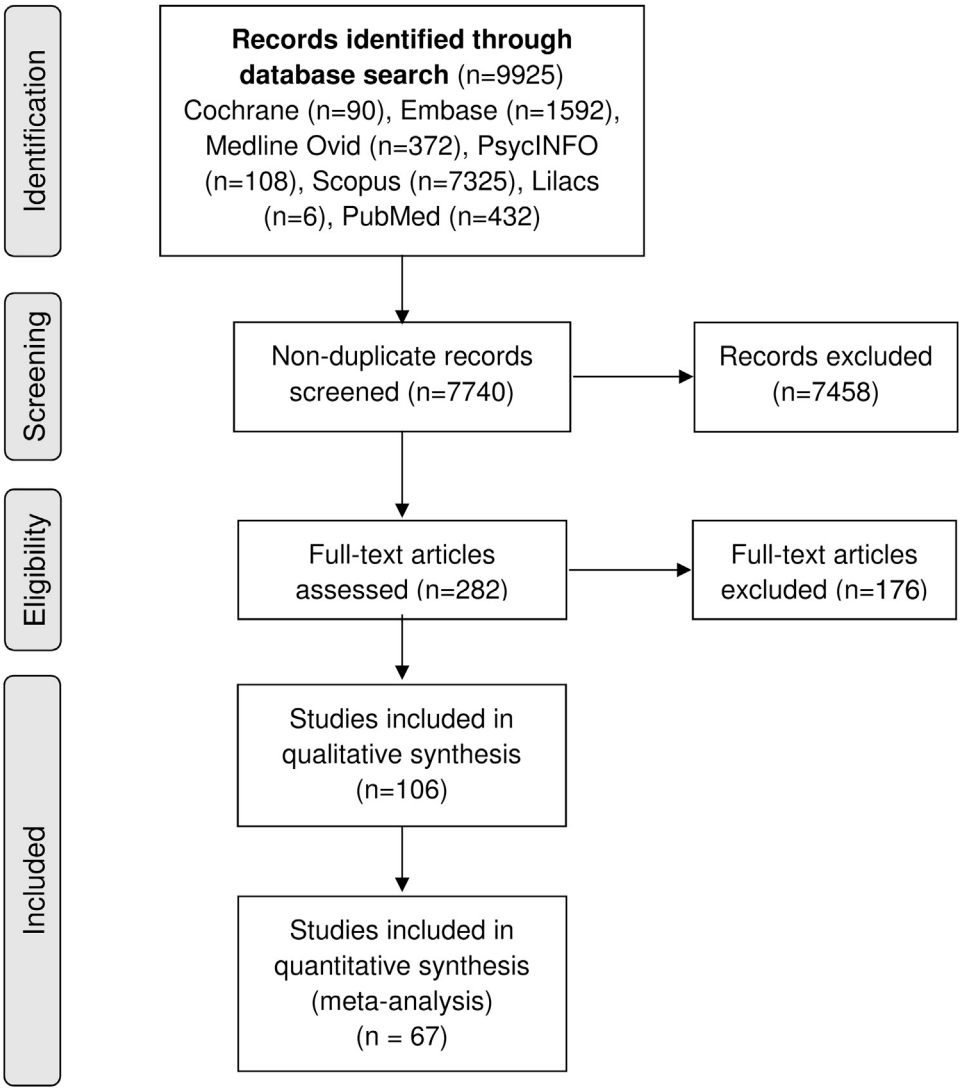

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. *LILACS*, Latin American and Caribbean Health Sciences.

symptoms in the Profile of Mood States questionnaire and in the eczema signs and symptoms in the Scoring Atopic Dermatitis (SCORAD) index.[19]

Prevalence of parental depression

Depression in parents of children with AD was reported in 6 studies and had sufficient data for meta-analysis; 5 of these studies included children younger than 9 years and 1 included children 18 years and younger. The pooled random-effects prevalence of parental depression was higher in children with versus without AD (29.3% vs 20.3%). Overall, parents of children with AD were more likely to have depression (3 of 6 studies [pooled random-effects prevalence, 1.60; 95% CI, 1.01-2.53]). Similar results were found in sensitivity analysis of studies with healthy controls (2 of 3 studies [pooled random-effects prevalence, 1.32; 95% CI, 1.18-1.48]). However, in sensitivity analyses of high-quality studies (NOS score ≥6), parents' depression was no longer associated with AD in their offspring (1 of 3 studies [pooled random-effects prevalence, 1.06; 95% CI, 0.72-1.56]).

One prospective single-center British study found a higher risk of depression among mothers (odds ratio 2.0 [95% CI, 1.1-3.6]) but not among fathers (1.8 [95% CI, 0.9-3.6]).

Antidepressant use

Antidepressant drug use in AD was reported in 4 studies that had sufficient data for meta-analysis. Overall, antidepressant use was numerically greater among adults and children with versus without AD (pooled random-effects prevalences,

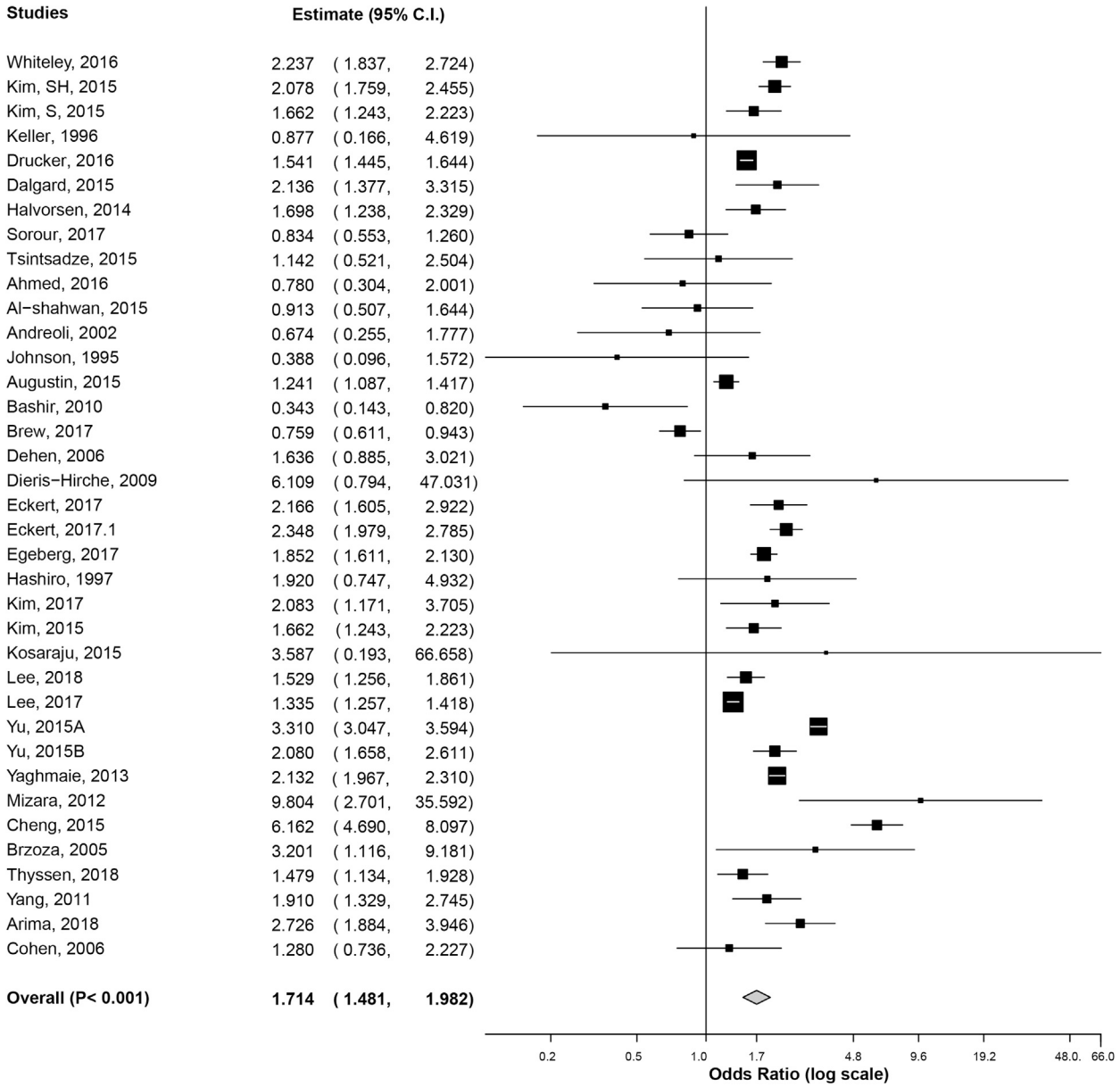

Fig 2. Forest plot of the proportion of depression in persons with versus without atopic dermatitis. Proportion of clinical depression or depressive symptoms, 95% confidence intervals (C.I.s) (*squares*), and pooled proportions (*diamond*) are presented.

29.3% vs 20.3%). The differences in antidepressant use were not significant in pooled analysis of adults and children (significant in 3 of 4 studies [pooled random-effects prevalence, 2.22; 95% CI, 0.93-5.32]), but were significantly greater in adults with AD (3 of 3 studies [pooled random-effects prevalence, 3.05; 95% CI, 1.11-8.41). All studies were of high quality (NOS score ≥6) and used healthy controls.

Suicidal ideation

A total of 14 studies examined prevalence of suicidal ideation in patients with and without AD and provided sufficient data for meta-analysis. The pooled random-effects prevalence of suicidality was higher in adults with versus without AD (12.2% vs 6.4%). Overall, patients with AD were significantly more likely to have suicidal ideation (12 of 14 studies [pooled random-effects prevalence, 1.97; 95% CI, 1.19-3.25]) (Fig 5). These associations remained significant in sensitivity analyses of studies with healthy controls (10 of 11 studies [pooled random-effects prevalence, 2.36; 95% CI, 1.75-3.25]), adults (9 of 10 studies [pooled random-effects prevalence, 2.87; 95% CI, 1.89-4.36]), and high-study quality (10 of 13 studies

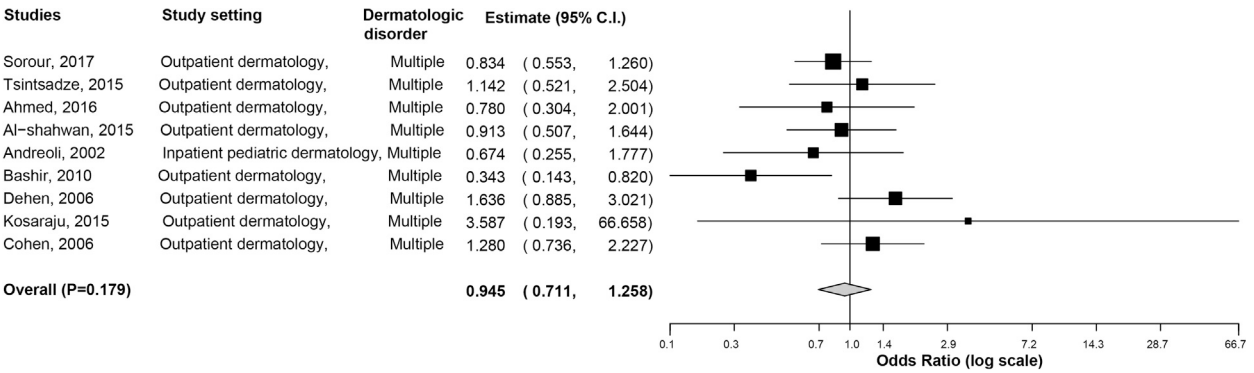

Fig 3. Forest plot of the proportion of depression in persons with atopic dermatitis compared with other dermatologic disorders. Proportion of clinical depression or depressive symptoms, 95% confidence intervals (C.I.s) (*squares*), and pooled proportions (*diamond*) are presented.

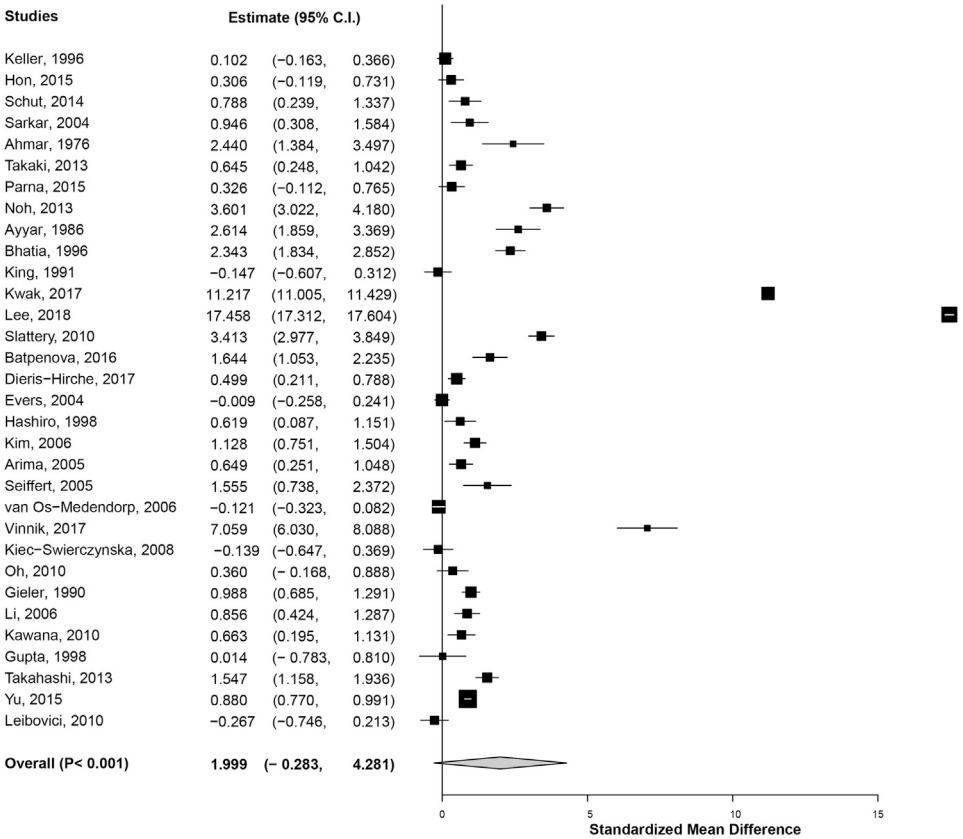

Fig 4. Forest plot of the standardized mean differences of depression scales in persons with versus without atopic dermatitis. Standardized mean differences of depression scales, 95% confidence intervals (C.I.s) (*squares*), and pooled standardized mean differences (*diamond*) are presented.

[pooled random-effects prevalence, 1.84; 95% CI, 1.11-3.06]).

Four studies were included in the qualitative analysis but had insufficient data for meta-analysis. Two studies found increased odds of suicidal ideation in patients with AD (a pooled random-effects prevalence of 2.32 [95% CI, 1.06-5.07] and a pooled random-effects prevalence of 1.07 [95% CI, 1.01-1.14]), whereas 2 studies only found marginally significant associations (a pooled random-effects prevalence of 1.04 [95% CI, 0.96-1.13] and a pooled random-effects prevalence of 1.05 [95% CI, 0.99-1.10]).[15,20-22] One study found an association of AD with suicidal ideation (pooled random-effects prevalence, 1.14; 95% CI, 1.05-1.19), suicide plan (pooled random-effects prevalence,

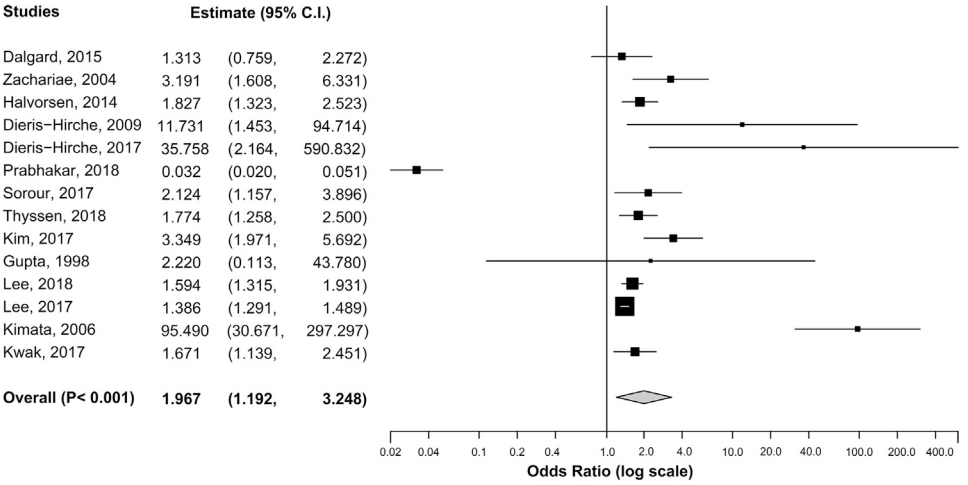

Fig 5. Forest plot of the proportion of suicidality in persons with versus without atopic dermatitis. Proportion of suicidality, 95% confidence intervals (C.I.s) (*squares*), and pooled proportions (*diamond*) are presented.

1.23; 95% CI, 1.12-1.35), and suicide attempt (pooled random-effects prevalence, 1.19; 95% CI, 1.07-1.33), particularly in females.[22]

Publication bias

Publication bias was not detected among studies that provided sufficient data for inclusion in the meta-analysis of AD and depression (P = .97 and .79) or suicidality (P = .62 and .30), as judged by nonsignificant Egger regression and Begg rank correlation values.

DISCUSSION

This systematic review and meta-analysis found that almost 1 in 6 persons with AD had clinical depression, 1 in 4 had depressive symptoms, and 1 in 8 had suicidal ideation. Persons with AD, particularly adults with moderate-to-severe AD, had significantly higher odds of clinical depression and depressive symptoms than healthy controls did, but their odds were similar to those of persons with other dermatologic disorders in the dermatologic setting. This suggests that the associations with depression are not unique to AD and may occur in individuals with other chronic inflammatory skin disorders (eg, acne and psoriasis). In addition, adults with AD had significantly higher odds of antidepressant drug use than healthy controls did. Almost 1 in 3 parents of children with AD were depressed. Finally, patients with AD had higher rates of suicidal ideation across studies and higher rates of planning and attempting suicide in 1 study. Interestingly, several studies found that various treatments that reduced AD signs and symptoms resulted in concomitant reductions in depressive symptoms, suggesting that many of the depressive symptoms of AD are modifiable. The results indicate substantial comorbidity from depression and suicidality in AD.

The present study found higher odds of suicidal ideation in persons with AD. Chronic disease in general has been shown to be associated with suicidality, though the association is typically thought to be mediated by depression and other psychiatric illness.[23] Thus, increased suicidality in AD may be mediated by increased depression in AD. On the other hand, many who are suicidal do not meet the criteria for depression.[24] It is therefore possible that even nondepressed patients with AD have increased risk of suicidality. Unfortunately, no studies examined the mediating effects of depression on suicidality risk in AD or whether suicidality improves with AD treatment.

These associations are clinically relevant given that depression severely affects patients' quality of life and may result in self-harm and psychiatric emergencies. Depressive symptoms were particularly associated with more severe AD and may be modifiable with improved control of AD signs and symptoms. We recommend that depressive and other mental health symptoms be assessed in patients with AD, particularly those with more severe and/or burdensome disease, and incorporated into therapeutic decision making and monitoring in AD.

Childhood AD was associated with higher rates of parental depression. Psychosocial stressors may contribute to this. A cross-sectional Australian study of 64 parent-child dyads reported that more severe childhood AD led to increased rates of parental stress, worsening behavioral problems in children, and difficulty managing AD.[25] Another

cross-sectional study conducted in twins with parent-reported current and/or past eczema found that atopic diseases and depression tend to occur together in families.[26] The burden of AD treatment may contribute to familial stress. This possibility is supported by a cross-sectional study of 579 parents of children with AD that found significant problems associated with topical corticosteroid use and major difficulties managing AD in their children.[27]

Despite the aforementioned significant associations of AD with clinical depression and self-reported depressive symptoms, there were inconsistent associations of AD with different depression scales. One reason for this is that only a subset of patients with AD have depression. Consequently, depression scores of 0 in patients with AD without depression dilute the overall mean depression scores in patients with AD. Nevertheless, AD was associated with consistently and significantly higher HAM-D and BDI scores. HAM-D, which is one of the most frequently used observer-rated depression scales and exhibits validity and reliability, can be used to assess depression severity and dose-response to antidepressants, despite the fact that its initial purpose was to be a screening tool.[28,29] However, some self-rating scales may take less time to complete, do not require trained personnel, and tend to be more standardized.[30] BDI is the criterion standard self-reported depression scale for clinical practice, as it measures symptoms "at that moment" and has adequate reliability and validity.[31] However, the measurement properties, validity, and reliability of various depression scales have not been examined in patients with AD. Future research is needed to determine the optimal ways to assess depression in AD.

Strengths of this study include use of a comprehensive search strategy; inclusion of international and foreign language studies; and distinction between clinical depression, depressive symptoms, and multiple sensitivity analyses. Limitations include lack of longitudinal studies, individual-level data, or ability to adjust for AD phenotypes or confounders across studies.

In conclusion, patients with AD are at a higher risk of depression and suicidality. We hope that these data will increase awareness of comorbidity between AD, depression, and suicidal ideation among health care providers and payers. Further longitudinal studies are needed to determine the complex relationship between AD and depression, mechanisms of depression and suicidality, and optimal strategies for their prevention and treatment.

We would like to acknowledge Victor Quan, Lukasz Jaros, Dr Nicholas Konowitz, and Dr Pedram Golnari for assistance in translating foreign language articles.

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