IMPORTANCE Previous studies found conflicting results as to whether atopic dermatitis (AD) is increased in patients with vitiligo and alopecia areata (AA).

OBJECTIVE To compare the prevalence of AD between patients with either vitiligo or AA and those without these disorders by performing a meta-analysis of observational studies.

DATA SOURCES MEDLINE, EMBASE, Cochrane Library, Google Scholar, and a manual search of 12 additional journals between 1946 and April 5, 2014.

STUDY SELECTION Observational studies published in any language that compared the prevalence of AD among patients with and without either vitiligo or AA.

DATA EXTRACTION AND SYNTHESIS Data were extracted by 2 independent investigators. Quality of evidence was assessed using the Newcastle-Ottawa Scale and Methodological Evaluation of Observational Research checklist. A meta-analysis of studies assessing AD, vitiligo, and/or AA was performed using a fixed-effects model to estimate pooled odds ratios (ORs). Subset analyses were performed for childhood vs adult-onset vitiligo and alopecia totalis or alopecia universalis vs patchy alopecia.

MAIN OUTCOMES AND MEASURES Self-reported and/or physician-diagnosed AD, vitiligo, and AA.

RESULTS In total, 16 studies of vitiligo and 17 studies of AA were included in the review. In the pooled analysis of the studies that included control patients without vitiligo (n = 2) and control patients without AA (n = 3), patients with vitiligo (Cochran-Mantel-Haenszel OR, 7.82; 95% CI, 3.06-20.00, P < .001) or AA (OR, 2.57; 95% CI, 2.25-2.94, P < .001) had significantly higher odds of AD than did control patients without these disorders. Pooled analysis of 3 studies found higher odds of AD in patients with early-onset vitiligo (<12 years) compared with those with late-onset vitiligo (OR, 3.54; 95% CI, 2.24-5.63, P < .001). Pooled analysis of 4 studies found higher odds of AD in patients with alopecia totalis or alopecia universalis compared with those with patchy alopecia (OR, 1.22; 95% CI, 1.01-1.48, P = .04).

CONCLUSIONS AND RELEVANCE Patients with either vitiligo, especially early-onset disease, or AA, especially alopecia totalis or alopecia universalis, have significantly increased risk for AD.
Atopic dermatitis (AD), often called eczema, is a chronic inflammatory skin disease with a complex pathogenesis, including skin barrier disruption, environmental factors, and immune dysregulation. All these mechanisms may contribute to comorbid health disorders. Indeed, AD is associated with multiple comorbid mental and physical health disorders, including asthma, hay fever, and food allergy; increased cutaneous and extra-cutaneous infections; obesity; epilepsy; and injury requiring medical attention.

Vitiligo and alopecia areata (AA) are commonly encountered inflammatory skin disorders. The co-occurrence of AD together with either vitiligo or AA may have important clinical ramifications, with potentially different phenotypes, prognosis, and/or response to therapy. However, previous studies found conflicting results about whether AD is associated with other inflammatory skin disorders, in particular vitiligo or AA. We hypothesized that AD is increased in patients with vitiligo or AA, especially severe disease. We therefore sought to systematically analyze the extant literature of observational studies to determine if AD is indeed associated with having either of these disorders.

Methods

Literature Search

We searched the following databases through April 5, 2014: MEDLINE (1946-present), EMBASE (1947-present), and the Cochrane Library (1992-present). We also hand-searched 12 journals: Acta Dermato-Venereologica (1998-present), Archives of Dermatological Research (1975-present), JAMA Dermatology (formerly Archives of Dermatology; 1960-present), British Journal of Dermatology (1998-present), BMJ (1840-present), Clinical and Experimental Dermatology (1997-present), Dermatology (1894-present), Journal of Investigative Dermatology (1998-present), Journal of the American Academy of Dermatology (1979-present), JAMA (1883-present), Lancet (1991-present), and the New England Journal of Medicine (1928-present). We also searched Google Scholar.

To search for the conditions of interest, we used the terms atopic dermatitis AND vitiligo, eczema AND vitiligo, atopic dermatitis AND alopecia areata, and eczema AND alopecia areata. Studies published online and in print and in press studies from all years were included. All search results with titles and abstracts written in English were eligible for inclusion. Studies were then excluded based on the title and/or abstract if there was no clear indication that they were investigating characteristics of patients with vitiligo, AA, or AD. Relevant studies in foreign languages (1 written in Turkish and 2 written in German) were translated using Google Translate (https://translate.google.com). Three potentially relevant articles written in Korean were unable to be translated by Google Translate. However, data contained in their English abstracts were included.

Studies with no primary epidemiologic data reporting either the numbers of AD cases among patients with vitiligo or AA or vice versa were excluded. In addition, studies were excluded if data reported in the abstract and/or body of the results conflicted with a table in the full text. If data were complicated in more than 1 study, the most recent and complete study was included in the meta-analysis.

We also searched MEDLINE for reported AD prevalence in the locations or nearest neighbor to the locations of where the included studies were conducted. We used the search terms atopic dermatitis prevalence AND the country and city name.

Data Extraction

Both reviewers (G.C.M. and J.I.S.) independently performed data extraction from these studies and any differences were resolved by discussion. From these 33 studies (17 studies of AA and 16 studies of vitiligo), data items collected were timeframe of study; study design; how each condition of interest was diagnosed or accounted for; country of study; total number of patients in study; number of patients with AA, vitiligo, and AD; severity of patients with AA, divided into alopecia totalis (AT), alopecia universalis (AU), and non-AT or non-AU; severity of patients with vitiligo, divided into generalized, localized, acrofacial, and segmental; family history of AA or vitiligo; prevalence of AD within subsets of AA or vitiligo; response to any treatment administered; mean age of patients and mean age at onset of disease; number of females in the study; duration of disease; and similar data points in control patients, if present.

The exposures were defined as physician-diagnosed or self-reported AA or vitiligo. Atopic dermatitis was the dependent variable, as defined by self-report by patients, diagnosis by a physician as part of the study, and/or previous recording in medical records. Distribution of AA lesions was categorized into AT or AU vs non-AT or non-AU.

Study Quality Assessment

Measures of study quality were collected for each study, including funding; conflicts of interest; ethical approval of study; journal name; method of sampling of participants; sampling frame; discussion of sampling bias; analysis of sampling bias, including stratifying of participants; response rate if relevant; exclusion rate if reported; exclusion criteria; participant flow; presence of controls; methods or source used to diagnose AD, AA, and vitiligo; validation of AD, AA, and vitiligo diagnoses; severity and frequency of symptoms of AD, AA, and vitiligo; discussion and analysis of confounding factors; precision of estimates; appropriateness of statistical analysis used; assessment of temporality of AD, AA, and vitiligo; dose response with vitiligo or AA severity; and sample size justification. This assessment of study quality was based on the Methodological Evaluation of Observational Research checklist.9

The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analysis was used to assess study quality.10 The scoring system summarized 8 aspects of each study: adequacy of the case definition, representativeness of the cases, selection of controls, definition of controls, comparability of cases and controls on the basis of the design or analysis, ascertainment of exposure, same method of ascertainment for cases and controls, and comparison of non-response rate between cases and controls. The full score was 9 stars, and a high-quality study was defined as a study with 7 or more stars.
Figure 1. PRISMA Flow Diagram

Statistical Analysis

Given the relative dearth of well-constructed studies regarding this topic, we decided a priori to include all studies in the meta-analysis regardless of study quality. Our statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc.). Comparable outcomes of all vitiligo or AA studies were combined, and measures of consistency were obtained. The principal summary measures are pooled prevalence estimates, as well as odds ratios (ORs) of the odds of AD in patients with either AA or vitiligo with 95% CIs estimated by the Cochrane-Mantel-Haenszel method. P < .05 (2-tailed) was considered significant. Additional sensitivity analyses were performed to examine whether AD was associated with early-onset (<12 years) vs late-onset vitiligo (≥12 years), as well as AT or AU vs patchy alopecia. Heterogeneity of results across studies was determined by a Cochran Q statistic P < .05 and/or I^2 statistic greater than 50%. Forest plots were constructed for all studies included in the meta-analysis. Egger regression, Begg rank correlation, and funnel plot regression were used to assess for potential publication bias.

Results

Literature Search

The literature search yielded 1950 articles. After review of the titles and abstracts, 1845 articles did not meet our inclusion criteria and 70 were excluded for lack of data for the prevalence of AD, vitiligo, and/or AA. In addition, 1 AA study was excluded owing to conflicting results between the abstract and text and data tables. 1 vitiligo study was excluded because of data overlap with another study by the same author. In total, 16 studies of vitiligo and 17 studies of AA were included in the review. The PRISMA flow diagram is presented in Figure 1.

Study Characteristics

The studies were cross-sectional with respect to prevalence of AD; collected data, either retrospectively or prospectively, included both males and females and encompassed participants of all ages. Published years of studies ranged from 1965 to 2014, which included data gathered from 1946 to 2013. The 16 studies of the association of AD with vitiligo included 10 200 patients from 11 countries, of which 7017 had vitiligo and 3183 were controls. The 17 studies of AD with AA included 798 597 patients from 11 countries, of which 13 810 had AA and 784 787 were controls. Study locations are mapped in eFigure 1 in the Supplement. There was considerable regional variation of AD prevalence (Table 1 and Table 2).

Quality assessment using the Newcastle-Ottawa Scale revealed that only 3 AA studies and none of the vitiligo studies were high quality (eTable 1 in the Supplement). Similarly, quality assessment using the Methodological Evaluation of Observational Research checklist revealed major deficiencies and/or poor reporting in all studies (eTable 2 in the Supplement).

AD in Vitiligo

Overall, 823 (11.7% [range, 0.0%-47.6%]) patients with vitiligo and 192 (6.0% [range, 1.7%-6.1%]) control patients had a previous and/or current history of AD. Among both patients with vitiligo and control patients, AD prevalence was higher in studies with self-report than physician diagnosis of AD (vitiligo, 15.4% vs 2.8%; controls, 6.0% vs not estimated, respectively).

In the pooled analysis of the 2 studies that included control patients without vitiligo, 14,27 patients with vitiligo had significantly higher odds of AD than did control patients without vitiligo (Cochran-Mantel-Haenszel OR, 7.82; 95% CI, 3.06-20.00, P < .001) (Figure 2). No significant heterogeneity was identified between the 2 studies (Cochran Q = 1.71, P = .19; I^2 = 41.5%).

We also performed a sensitivity analysis of pooled data from 3 published studies that compared results between early-onset (<12 years) and late-onset vitiligo (≥12 years). Early-onset vitiligo was associated with significantly higher odds of AD than late-onset vitiligo (OR, 3.54; 95% CI, 2.24-5.63, P < .001) (Figure 2) without significant heterogeneity (Cochran Q = 1.68, P = .43; I^2 = 0.0%). One study stratified AD prevalence by vitiligo body surface area and found that AD prevalence was significantly higher in patients with more extensive vitiligo (body surface area >75%).

AD in AA

Overall, 1296 (9.4% [range, 1.7%-33.4%]) patients with AA and 14701 (1.9% [1.9%-7.7%]) control patients had a previous and/or current history of AD. Among both patients with AA and control patients, AD prevalence was higher in studies with self-report of AD than in studies with physician diagnosis of AD (AA, 13.1% vs 8.2%; controls, 7.5% vs 1.9%, respectively).
Association of Vitiligo and AA With AD

Table 1. Study Characteristics for the Prevalence of Vitiligoa

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Cases</th>
<th>Controls</th>
<th>Mean Age of Case at Visit, y</th>
<th>Sex, No. (%)</th>
<th>Assessment of Vitiligo or AA</th>
<th>Assessment of AD</th>
<th>Reported AD Prevalence Near the Study Location, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arican et al,14 2004</td>
<td>Turkey</td>
<td>64</td>
<td>58 F (88.8)</td>
<td>34.9</td>
<td>37 F (88), 27 M in vitiligo; 33 F (51), 27 M in controls</td>
<td>Physician Self-report for cases and controls</td>
<td>8.1 and 4.9, respectively</td>
<td></td>
</tr>
<tr>
<td>Ezzedine et al,11 2012</td>
<td>France</td>
<td>679</td>
<td>NA NA</td>
<td>31.9</td>
<td>440 F (65), 238 M, 1 unknown</td>
<td>Physician Self-report</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Silverberg and Silverberg,24 2013</td>
<td>USA</td>
<td>2645</td>
<td>635 (24.0)</td>
<td>NA NA</td>
<td>40h</td>
<td>1838 F (69), 817 M</td>
<td>Physician Self-report</td>
<td>10.2</td>
</tr>
<tr>
<td>Boisseau-Garsaud et al,15 2000</td>
<td>West Indies, Martinique</td>
<td>32</td>
<td>1 (3.1)</td>
<td>NA NA</td>
<td>29c</td>
<td>23 F (72), 9 M</td>
<td>Physician Self-report</td>
<td>10.8</td>
</tr>
<tr>
<td>Nicolaides et al,20 2012</td>
<td>Greece</td>
<td>233</td>
<td>NA NA</td>
<td>33.7</td>
<td>146 F (63), 84 M, 3 unknown</td>
<td>Physician Self-report</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Henn and Lee,19 1996</td>
<td>Korea</td>
<td>208</td>
<td>NA NA</td>
<td>20</td>
<td>121 F (58), 87 M</td>
<td>Physician Self-report</td>
<td>Range, 0.7-26.5</td>
<td></td>
</tr>
<tr>
<td>Choe et al,16 2003</td>
<td>Korea</td>
<td>134</td>
<td>NA NA</td>
<td>6.7</td>
<td>66 F (49), 68 M</td>
<td>Physician Not reported in abstract</td>
<td>Range, 0.7-26.5</td>
<td></td>
</tr>
<tr>
<td>Iacovelli et al,26 2005</td>
<td>Italy</td>
<td>121</td>
<td>1 (0.8)</td>
<td>9.5</td>
<td>81 F (67), 40 M</td>
<td>Physician Self-report</td>
<td>Range, 11.2-18.1</td>
<td></td>
</tr>
<tr>
<td>Aragwal et al,27 2013</td>
<td>India</td>
<td>762</td>
<td>NA NA</td>
<td>NA</td>
<td>371 F (49), 391 M</td>
<td>Physician Self-report</td>
<td>Range, 0.14 to =9</td>
<td></td>
</tr>
<tr>
<td>Martis et al,21 2002</td>
<td>India</td>
<td>100</td>
<td>2 (2.0)</td>
<td>NA NA</td>
<td>55 F (55), 45 M</td>
<td>Physician Self-report</td>
<td>Range, 0.14 to =9</td>
<td></td>
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<tr>
<td>Handa and Kaur,22 1999</td>
<td>India</td>
<td>1436</td>
<td>20 (1.4)</td>
<td>25</td>
<td>653 F (46), 783 M</td>
<td>Physician Medical records</td>
<td>Range, 0.14 to =9</td>
<td></td>
</tr>
<tr>
<td>Al-Jabri and Al-Raddadi,23 2011</td>
<td>Saudi Arabia</td>
<td>38 2 (5.3)</td>
<td>NA NA</td>
<td>7.9h</td>
<td>24 F (63), 14 M</td>
<td>Physician Medical records</td>
<td>=7</td>
<td></td>
</tr>
<tr>
<td>Fatani et al,27 2013</td>
<td>Saudi Arabia</td>
<td>135</td>
<td>12 (8.9)</td>
<td>24.5</td>
<td>91 F (67), 44 M</td>
<td>Physician Medical records</td>
<td>=7</td>
<td></td>
</tr>
<tr>
<td>Schallreuter et al,28 1994</td>
<td>Germany</td>
<td>321</td>
<td>16 (5.0)</td>
<td>38.1</td>
<td>207 F (65), 114 M</td>
<td>Physician Self-report and clinical findings</td>
<td>Range, 4.5-6.2</td>
<td></td>
</tr>
<tr>
<td>Al-Mutairi et al,29 2005</td>
<td>Kuwait</td>
<td>88</td>
<td>6 (6.8)</td>
<td>NA NA</td>
<td>50 F (57), 38 M</td>
<td>Physician Self-report and clinical findings</td>
<td>8.3 and 31.3, respectively</td>
<td></td>
</tr>
<tr>
<td>Naldi et al,22 2009</td>
<td>Italy</td>
<td>21</td>
<td>10 (47.6)</td>
<td>3125</td>
<td>191 (6.1)</td>
<td>NA 1561 F (49), 1618 M overall Medical records for cases; self-report of no vitiligo history for controls</td>
<td>Physician Self-report for cases and controls</td>
<td>Range, 11.2-18.1</td>
</tr>
</tbody>
</table>

Abbreviations: AA, alopecia areata; AD, atopic dermatitis; NA, not applicable; pts, patients. Some studies have a greater number of total cases than the number of cases evaluated for AD; the number of cases evaluated for AD are indicated in parentheses.

In the pooled analysis of the 3 studies that included control patients without AA,29-35,38 patients with AA had higher odds of AD than did control patients without AA (Cochran-Mantel-Haenszel OR, 2.57; 95% CI, 2.25-2.94, P < .001) (Figure 2). No significant heterogeneity was identified between the 3 studies (Cochran Q = 3.40, P = .18; F² = 41.2%).

Sensitivity analysis of pooled data from 4 published studies29,30,32,36 was performed, comparing results between AT or AU and patchy alopecia. Alopecia totalis or AU was associated with a small but higher odds of AD than patchy alopecia (OR, 1.22; 95% CI, 1.01-1.48, P = .04) (Figure 2), without significant heterogeneity (Cochran Q = 1.69, P = .64; F² = 0.0%). One study found that AA patients with filaggrin gene mutations had more severe AA, although such mutations were not associated with AA overall.30 None of the vitiligo or AA studies included any details about AD severity, onset, distribution, phenotype, or duration.

AD Prevalence
Atopic dermatitis prevalences are presented for the locations where the included studies were conducted or the nearest neighbor with reported prevalence estimates (Tables 1 and 2). Of note, most of these prevalence studies were conducted in children, while the mean or median age of patients in many of the studies included for meta-analysis was older than 18 years. Further information regarding these prevalence studies is presented in eTable 3 in the Supplement.
The results of this meta-analysis suggest that patients with either vitiligo or AA have higher rates of AD compared with patients who do not have these disorders. While major issues related to heterogeneity and publication bias were not detected, many of the studies were not of high quality and had major deficiencies and poor reporting. Most studies only reported AD prevalence without accounting for potentially confounding factors, such as age, sex, severity of AA or vitiligo, duration of disease, or age of disease onset. However, pooling the data of these individual studies provides a greater sample size and inherently provides stronger evidence for this association. The broad time spanned by the data (1946-2013) and the fact that all studies originated from different countries inherently provides strong evidence for the association. The broad time spanned by the data (1946-2013) and the fact that all studies originated from different countries inherently provides strong evidence for this association. The broad time spanned by the data (1946-2013) and the fact that all studies originated from different countries inherently provides strong evidence for this association.
is another potential limitation, since AD rates have increased during the past few decades.46 Unfortunately, there are no other systematic reviews or meta-analyses that have been performed on these associations with which we can compare our results. Studies included in this review and meta-analysis were performed in geographically diverse locations. The prevalences of AD observed in these studies were largely within the range of prevalences previously reported for those locations, although some reported AD prevalences differed. This suggests that some of the studies may have had selection bias with cohorts not entirely generalizable to their respective locations. This emphasizes the importance of such observational studies to include control groups for statistical comparison.

It is intriguing that the odds of AD were higher in those with early-onset vitiligo compared with adult-onset vitiligo or in those with AT or AU compared with patients with patchy alopecia. These results suggest that AD may be associated with specific subsets of vitiligo or AA and perhaps indicates poor prognostic value for these disorders. Conversely, it is possible that history of vitiligo or AA is associated with specific subsets of AD. However, none of the studies included data about the AD severity and/or phenotype. Furthermore, the cross-sectional nature of all the included studies precludes determination of which disorders appeared first. Future high-quality studies are needed to determine the effects of vitiligo or AA on AD severity and identify whether specific patient subsets are at risk for the combination of these disorders.

The co-occurrence of AD with vitiligo or AA raises the question whether these patients have the same mechanisms of disease response to therapy. However, the mechanisms of association between AD, vitiligo, and AA are yet unknown. There may be common pathways that are activated in these disorders, such as thymic stromal lymphopoietin47,48 and T-helper 17,49,50 which may explain the associations. However, none of the studies incorporated any assessment of inflammatory pathways or disease biomarkers. There may also be shared genetics that underlie the associations. For example, filaggrin gene mutations in patients with AA were found to be associated with more severe AA.39 Future translational and therapeutic studies are needed to determine the interaction between these complex disorders.

Figure 2. Association Between Atopic Dermatitis, Vitiligo, and Alopecia Areata (AA)

Forest plots are presented for the log odds ratios (ORs) and 95% CIs of atopic dermatitis in vitiligo compared with control patients and subset analysis for early-onset compared with late-onset vitiligo (upper panel) and atopic dermatitis in AA compared with control patients and subset analysis of alopecia totalis or alopecia universalis (AT/AU) compared with patchy alopecia (lower panel).

Conclusions

Patients with vitiligo, especially early onset, or AA, especially AT or AU, appear to have increased risk of AD. However, further high-quality studies are needed, given the small number and low quality of studies to date. Future investigation into common risk factors and the mechanism of association between these disorders is also warranted.

References

ARTICLE INFORMATION

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Author Contributions: Drs Mohan and Silverberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Silverberg. Study supervision: Silverberg.

Conflict of Interest Disclosures: None reported.

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