Association of atopic dermatitis with an increased risk of systemic lupus erythematosus: A systematic review and meta-analysis

Ponvilawan B, Charoenngam N¹, Wongtrakul W², Ungprasert P³

ABSTRACT

Context: Previous studies on the association between atopic dermatitis (AD) and systemic lupus erythematosus (SLE) have yielded inconsistent results.

Aims: To investigate the relationship between atopic dermatitis and systemic lupus erythematosus.

Settings and Design: Systematic review and meta-analysis.

Materials and Methods: A systematic review was conducted on EMBASE and MEDLINE databases from inception to March 2020 using a search strategy that consisted of terms related to AD and SLE. Eligible study must be either cohort or case-control study. For cohort studies, they must include patients with AD and comparators without AD, then follow them for incident SLE. For case-control studies, they must include cases with SLE and controls without SLE and examine their prior history of AD.

Statistical Analysis Used: Meta-analysis of the studies was performed using a random-effect, generic inverse variance method to combine effect estimate and standard error. Funnel plot was used to assess publication bias.

Results: A total of 21,486 articles were retrieved. After two rounds of review by three investigators, six case-control studies were qualified for the meta-analysis. The case-control study meta-analysis found a significantly increased odds of SLE among patients with AD with the pooled odds ratio of 1.46 (95% CI, 1.05–2.04).

Conclusions: A significant association between AD and increased odds of SLE was observed by this systematic review and meta-analysis.

KEY WORDS: Atopic dermatitis, eczema, meta-analysis, systemic lupus erythematosus

Introduction

Atopic dermatitis (AD), or atopic eczema, is the most common chronic inflammatory skin disease worldwide which typically develops during childhood. Patients with AD usually present with recurrent eczematous lesions in flexural areas that cause pruritus and can interfere with daily activities. Several epidemiological studies have estimated that around 5–25% of the world population are affected by AD. Family history of atopic diseases and several environmental factors, such as living in urban setting or regions with low ultraviolet light and smoking, are known risk factors for this disease.¹ —³

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with heterogeneous manifestations involving multiple organs such as joints, kidneys, nervous system, bone marrow, and skin.⁴ —¹⁰ The incidence rate varies considerably around

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Multiple studies have demonstrated that AD is associated with an increased risk of several chronic diseases such as cardiovascular, neuropsychiatric, and autoimmune disorders. Known risk factors include family history, tobacco smoking, obesity, and vitamin D deficiency. 

Statistical analysis

Review Manager 5.3 software (The Cochrane Collaboration, London, United Kingdom) was used for analysis of data. Point estimates along with their standard errors were extracted from each study and were combined together to calculate pooled effect estimates using the generic inverse variance method of DerSimonian and Laird which assigns weight for each study based on its variance. Two meta-analyses of cohort studies and case-control studies were performed separately if there are enough number for each type of studies. IRR, HR, and SIR of cohort study was used as an approximation of RR to calculate pooled risk ratio for cohort studies. Random-effect model was used instead of fixed-effect model because of the difference in study design, protocols, and background populations of the included studies. Statistical heterogeneity was evaluated using Cochran’s Q test along with I² statistic which quantifies the proportion of the total variation across studies that is from heterogeneity instead of coincidence. A value of I² of 0–25% implies insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and >75% high heterogeneity. The presence of publication bias was investigated by visualization of funnel plot to look for evidence of asymmetry.

Method

Search strategy

Independent search for all relevant publications indexed in EMBASE and MEDLINE from inception to March 2020 was conducted by three investigators (B.P., N.C., and W.W.) using search terms related to AD and SLE. The detailed search strategy is exhibited in the Supplemental Material 1.

Inclusion criteria

Eligible study must be either cohort or case-control study. For cohort studies, they must include patients with AD and comparators without AD, then follow them for incident SLE. Relative risk (RR), incidence rate ratio (IRR), hazard risk ratio (HR), or standardized incidence ratio (SIR) with associated 95% confidence interval (95% CI) that compare the incidence of SLE between the two groups must be reported. For case-control studies, they must include cases with SLE and controls without SLE and examine their prior history of AD. Odds ratio (OR) with 95% CI of the association between AD and SLE must be reported.

Study eligibility was independently determined by three investigators (B.P., N.C., and W.W.). The senior investigator (P.U.) provided the final determination after discussions with all investigators if different conclusions were made by the three investigators. The Newcastle-Ottawa quality assessment scale for cohort study and case-control study was used for determination of the quality of each study. This quality assessment was performed by two investigators (B.P. and P.U.).

Data extraction

Data extraction was performed using a standardized collection form which contains the following information: the first author’s surname, country where the study was conducted, study design (case-control versus cohort study), year of publication, number of participants, recruitment of participants, diagnosis of SLE, diagnosis of AD, follow-up duration (for cohort studies only), average age of participants, percentage of female participants, comorbidities of participants, variables adjusted in multivariate analysis, and adjusted effect estimates along with their 95% CI.
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Discussion

This systematic review and meta-analysis included data from 19,713 participants and found that patients with AD had 1.46-fold increased odds of developing SLE compared with individuals without AD. The results of two cohort studies further supported the result of our meta-analysis as they also reported the significantly increased risk of developing SLE in patients with AD. The exact mechanisms responsible for this association are still not known with certainty. Some possible explanations are discussed below.

First, immunologic pathways involving Th1, Th2, and Th17 cells might be responsible for both AD and SLE. A considerable amount of evidence shows that both patients with AD and SLE have an upregulation of Th2 cytokines, such as IL-5 and IL-13, and Th17 cytokines, such as IL-17 and IL-22. On the other hand, they had a downregulation of IL-2, one of the major cytokines of Th1 cells. Moreover, recent studies have demonstrated an increased level of IgE among patients with SLE, particularly among those with active disease, similar to patients with AD. Thus, it is possible that dysregulation of Th1, Th2, and Th17 activities in AD could give rise to evolution of SLE in the same patients later in life.

Second, genetic factor might also play a role in the association between AD and SLE as family history is a known predisposing factor for both diseases. In fact, individuals with certain human leukocyte antigen (HLA) genotypes, such as HLA-B and HLA-DRB1, are found to have an increased tendency to develop both diseases. Nonetheless, common susceptibility locus and single nucleotide polymorphisms (SNPs) in HLA genes are yet to be found.

Apart from genetic risk factor, AD and SLE also share some environmental risk factors. Tobacco smoking and obesity are reported to be associated with an increased risk of both AD and SLE. Tobacco smoking could promote elevation of serum IgE level and inflammatory response which, in turn, generate dysregulation of T and NK cells, DNA damage, and epigenetic changes. Obesity could create proinflammatory effect via adipokines secreted from dysfunctional adipocytes.

Last, surveillance bias could also partially be responsible for an increased risk of SLE as patients with AD tend to have a more frequent exposure to healthcare providers due to the...
Table 1: Main characteristics of the cohort studies included in the meta-analysis

| Country      | Wei et al. [19] | Krishna et al. [20] |
|--------------|----------------|-------------------|
| Study design | Retrospective cohort | Retrospective cohort |
| Year of publication | 2014 | 2019 |
| Total number of participants | Patients with atopic dermatitis: 192,357 Comparators: 769,428 | Patients with atopic dermatitis: 1,393,570 Comparators: 2,170,618 |
| Recruitment of participants | Patients with atopic dermatitis of age 1 to 18 years were identified from the National Health Insurance Research Database of Taiwan which consisted of half of all insured children in Taiwan from 2000 to 2008. Comparators without atopic dermatitis were randomly identified from the same database. Each patient with atopic dermatitis was matched to four comparators by age, sex, urbanization of residential area, parental occupation, and index year. Participants who were previously diagnosed with SLE before the starting date were excluded. | Patients with atopic dermatitis were identified from the Health Improvement Network database which contained coded data recorded by the patient’s general practitioner from January 1, 1990 to January 17, 2018. This database covered approximately 3 million patients across the United Kingdom. Comparators without atopic dermatitis were randomly identified from the same database. Each patient with atopic dermatitis was matched to up to two comparators by age, sex, and general practitioner. |
| Diagnosis of atopic dermatitis | Presence of at least three consecutive diagnoses of atopic dermatitis from diagnostic code in the database (ICD-9-CM 691) | Presence of diagnostic codes of atopic dermatitis in the Health Improvement Network database |
| Diagnosis of SLE | Presence of diagnostic code of SLE (ICD-9-CM code 710.0) in the database with confirmation by the Registry for Catastrophic Illness Patient Database, which required medical record review by board-certified specialists | Presence of diagnostic codes of SLE in the Health Improvement Network database |
| Follow-up period | Until the development of SLE, death, withdrawal of insurance, or closing date (December 31, 2008) | Until the development of SLE, death, emigration, or closing date (January 17, 2018) |
| Average duration of follow-up (years) | Patients with atopic dermatitis: 5.1 Comparators: 2.1 | Patients with atopic dermatitis: 5.3 (median) Comparators: 3.5 (median) |
| Average age of participants (years) | Patients with atopic dermatitis: 3.2 Comparators: 3.3 | Patients with atopic dermatitis: 29.8 Comparators: 32.7 |
| Percentage of female | Patients with atopic dermatitis: 46.7% Comparators: 46.7% | Patients with atopic dermatitis: 54.1% Comparators: 53.8% |
| Comorbidities | N/A | Patients with atopic dermatitis: Obesity 9.4% Smoking 13.0% Comparators: Obesity 9.3% Smoking 14.0% |
| Variables adjusted in multivariate analysis | Age, sex, urbanization of residential area, parental occupation, and index year | Age, sex, body mass index, race, Townsend deprivation quintile, ethnicity, and smoking status |
| Newcastle-Ottawa score | Selection: 4 Comparability: 2 Outcome: 3 | Selection: 4 Comparability: 2 Outcome: 3 |

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; N/A: Not Available; SLE: Systemic Lupus Erythematosus

chronic nature of AD. However, SLE is a disease which would generally cause noticeable symptoms that patients usually seek for medical attention. Therefore, surveillance bias is probably not the only reason for the observed relationship.

Nonetheless, this systematic review and meta-analysis carries some limitations and the pooled results should be interpreted with caution. First, statistical heterogeneity of the meta-analysis was not low. We believe that difference in study design, protocols, and characteristics of the participants across the studies was responsible for the inter-study variation. Second, the accuracy of case identification of AD and SLE could be limited as about half of the included studies used diagnostic codes from administrative databases [19,20,25,26] to identify and confirm the diagnosis. Finally, publication bias may have been present as evident by the asymmetrical funnel plot.

**Conclusion**

This systematic review and meta-analysis observed an elevated odds of incident SLE among patients with AD compared with individuals without AD. Limitations included between-study heterogeneity, limited accuracy of case identification in the primary studies, and publication bias. Clinicians who take care of patients with AD should be aware of the higher risk and further evaluation is warranted when they develop new systemic symptoms.
Table 2: Main characteristics of the case-control studies included in the meta-analysis

| Country      | Goldman et al.[21] | Morton et al.[22] | Sekigawa et al.[23] |
|--------------|---------------------|-------------------|---------------------|
| Year of publication | USA 1976 | United Kingdom 1998 | Japan 2002 |
| Total number of participants | Cases: 24, Controls: 27 | Cases: 49, Controls: 98 | Cases: 52, Controls: 52 |
| Recruitment of participants | Cases: Cases were consecutive patients with SLE who were recruited from wards and clinics of Grady Memorial Hospital, Emory University Clinic, and Emory University Hospital. Controls: Controls without SLE were selected from patients who attended the Family Planning Clinic or were hospitalized in the Obstetric, Gynecology, and Orthopedic Services of Grady Memorial Hospital or in the Orthopedic Service of Emory University Hospital. | Cases: Cases were patients with SLE who were randomly selected from the cohort of 180 patients with SLE attending clinical immunology clinics at the Queens Medical Centre, Nottingham. Controls: Controls without SLE were randomly selected from one rural and two urban general practices. They were 1:2 matched to cases by age and sex. | Cases: Cases were patients with SLE who were randomly selected from the cohort of Japanese SLE patients attending Juntendo University Izu-Nagaoka Hospital. Controls: Controls without SLE were randomly selected from the residents near Juntendo University Izu-Nagaoka Hospital. They were matched to cases by age and sex. |
| Diagnosis of SLE | Physician diagnosis using preliminary criteria for the classification of SLE by the American Rheumatism Association or clinical arthritis with positive LE preparation | Physician diagnosis using the 1982 American Rheumatism Association classification criteria of SLE | Physician diagnosis using the 1982 American Rheumatism Association classification criteria of SLE |
| Diagnosis of atopic dermatitis | Self-report from health questionnaire | Self-report from health questionnaire | Self-report from health questionnaire |
| Average age of participants (years) | Total: 36.0 | Cases: 45.6, Controls: 45.4 | Cases: 33.6, Controls: 33.7 |
| Percentage of female participants | Cases: 100.0%, Controls: 100.0% | Cases: 98.0%, Controls: 98.0% | Cases: 90.4%, Controls: 90.4% |
| Variables adjusted in multivariate analysis | None | None | None |
| Newcastle-Ottawa score | Selection: 3, Comparability: 1, Exposure: 2 | Selection: 4, Comparability: 1, Exposure: 2 | Selection: 4, Comparability: 1, Exposure: 2 |
| Country | Parks et al.[24] USA | Hsiao et al.[25] Taiwan | Lin et al.[26] Taiwan |
| Year of publication | 2010 | 2014 | 2018 |
| Total number of participants | Cases: 228, Controls: 293 | Cases: 1673, Controls: 6692 | Cases: 2105, Control: 8420 |
| Recruitment of participants | Cases: Cases were patients with SLE who were identified from the Carolina Lupus Study, comprising of SLE patients referred from 30 of the 40 community-based rheumatologists in eastern and central North Carolina and South Carolina. Controls: Controls without SLE were randomly selected from driver's license registries limited to the geographic region from which cases were identified. They were matched to cases by five-year age group, sex, and state. | Cases: Cases were patients with SLE newly diagnosed between 2002 and 2010 who were identified from the Longitudinal Health Insurance Database 2000. This database collected health information from 1996 to 2010 of one million beneficiaries who were randomly selected from the original registry of beneficiaries in the Taiwan Health Insurance program. Controls: Controls without SLE were randomly selected from the same Longitudinal Health Insurance Database. They were 1:4 matched to cases by age, sex, index-year, and index-month. | Cases: Cases were patients with newly-diagnosed SLE who were identified from the Taiwan’s National Health Insurance Research Database from January 1, 2000 to December 31, 2011. This database contained outpatient and inpatient claims for all beneficiaries enrolled in Taiwan’s mandatory National Health Insurance program. Controls: Controls without SLE were randomly selected from the same database of the National Health Insurance program. They were 1:4 matched to cases by age, sex, and first diagnosis date. |
Table 2: Contd...

|                        | Goldman et al.[21] | Morton et al.[22] | Sekigawa et al.[23] |
|------------------------|--------------------|-------------------|---------------------|
| Diagnosis of SLE       | Physician diagnosis using the 1982 and 1997 American College of Rheumatology classification criteria of SLE. | Presence of diagnostic codes of SLE in the database (ICD-9-CM code: 733.34, 695.4, 710.0). | Presence of diagnostic codes of SLE in the database (ICD-9-CM code: 710.0). |
| Diagnosis of atopic dermatitis | Self-report through direct interview | Presence of diagnostic codes of atopic dermatitis in the database (ICD-9-CM code: 691.8) from at least one inpatient visit or two outpatient visits | Presence of diagnostic codes of atopic dermatitis in the database (ICD-9-CM code: 691.8) from at least two outpatient claims six months before and after the index date |
| Average age of participants (years) | Cases: N/A | Cases: 40.1 | Cases: N/A |
| Percentage of female | Cases: 89.5% | Cases: 82.5% | Cases: 82.5% |
| Variables adjusted in multivariate analysis | None | None | Number of hospital visits, infection/no infection and atopic diseases |
| Newcastle-Ottawa score | Selection: 4 | Selection: 4 | Selection: 4 |
|                        | Comparability: 1 | Comparability: 1 | Comparability: 2 |
|                        | Exposure: 3       | Exposure: 3       | Exposure: 3       |

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; LE: Lupus Erythematosus; N/A: Not Available; SLE: Systemic Lupus Erythematosus; USA: United States of America

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Conflicts of interest
There are no conflicts of interest.
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Supplemental Material 1 – Searching Strategy

EMBASE Database
1. ‘asthma’/exp OR ‘asthma’
2. ‘reactive airway disease’/exp OR ‘reactive airway disease’
3. ‘bronchus hyperreactivity’/exp OR ‘bronchus hyperreactivity’
4. ‘bronchial hyperreactiveness’/exp OR ‘bronchial hyperreactiveness’
5. ‘atopic dermatitis’/exp OR ‘atopic dermatitis’
6. ‘eczema’/exp OR ‘eczema’
7. ‘allergic rhinitis’/exp OR ‘allergic rhinitis’
8. ‘atopy’/exp OR ‘atopy’
9. atopic
10. ‘autoimmune disease’/exp OR ‘autoimmune disease’
11. ‘rheumatic disease’/exp OR ‘rheumatic disease’
12. ‘lupus’/exp OR ‘lupus’
13. ‘systemic lupus erythematosus’/exp OR ‘systemic lupus erythematosus’
14. ‘lupus erythematosus’/exp OR ‘lupus erythematosus’
15. ‘sle’/exp OR ‘sle’
16. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
17. #10 OR #11 OR #12 OR #13 OR #14 OR #15
18. #16 AND #17

Ovid MEDLINE Database
1. asthma.mp. or exp asthma/
2. exp bronchial hyperreactivity/or reactive airway disease.mp.
3. reactive airway disease.mp
4. atopic dermatitis.mp. or exp dermatitis, atopic/
5. eczema.mp. or exp eczema/
6. allergic rhinitis.mp. or exp rhinitis, allergic/
7. atopic.mp.
8. atopy.mp.
9. rheumatic disease.mp. or exp rheumatic diseases/
10. autoimmune disease.mp. or exp autoimmune diseases/
11. systemic lupus erythematosus.mp or exp lupus erythematosus, systemic/
12. sle.mp
13. 1 or 2 or 3 or 4 or 5 or 6 or 7
14. 8 or 9 or 10 or 11 or 12
15. 13 and 14