



## The Twins-Hit Hypothesis of Atopic Dermatitis and Autoimmune Diseases: A Review and Meta-Analysis

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### ABSTRACT

Atopic dermatitis is a common disease that affects all age groups. The disease is on the rise worldwide. There is an increasing concern regarding its association with autoimmune diseases. Literature regarding this important issue lacks. This meta-analysis aimed to assess the association of AD with autoimmune disorders. An electronic literature search was conducted in the PubMed, Cochrane Library, in addition to the first 100 articles in Google Scholar during the period from 2010 up to January 2021. Five hundred forty-three references and abstracts were identified, of them, 8 full texts were screened. While only four studies fulfilled the inclusion and exclusion criteria. The keywords used were atopic dermatitis, atopic eczema dermatitis syndrome, autoimmune disease, skin autoimmunity, gastrointestinal autoimmune diseases to include most of the systematic autoimmune disorders. The current meta-analysis included four studies with 1735789 patients and 14927 events. The studies were published in Asia and Europe. All were retrospective studies with study periods ranging from five years to 48 years. Autoimmune diseases were higher among patients with AD, a significant statistical difference was observed (odds ratio, 1.61, 95 % CI, 1.05-2.45, P-value, 0.03). The random effect was applied due to the substantial heterogeneity observed ( $I^2=98\%$ , P-value<0.001). Autoimmune disease was commoner among patients with AD compared to their counterparts without the disease.

**Keywords:** Atopic dermatitis, Atopic eczema dermatitis syndrome, Autoimmune diseases, SLE, Skin Autoimmunity

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### INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease (10-20% of people are affected during their lifetime); since its first use by Wise and Sulzberger in the years 1933, the disease is on the rise in both rate and severity (Wise & Sulzberger, 1933). Also, atopic eczema dermatitis syndrome or eczema was defined as a non-contagious, severely pruritic, inflammatory disease that runs a chronic and relapsing course (Darsow *et al.*, 2014). AD is the leading cause of healthcare burden worldwide and is characterized by intense skin itching and recurrent eczematous lesion. The pathophysiology is complex and involves multiple immunological pathways including T-cell-driven inflammation (Frazier & Bhardwaj 2020). Genetic predisposition and environmental factors play a major role; the self-perpetuated intense itching might negatively affect the patient's quality of life (Langan *et al.*, 2020). There is an increasing awareness regarding the association of AD with other autoimmune diseases namely connective tissue disorders, type 1 diabetes mellitus, and rheumatic diseases. The evidence is conflicting, the strongest association was observed between autoimmune diseases involving the skin and mucous membranes (Cipriani *et al.*, 2017). Importantly, patients with AD are at increased risk of multiple autoimmune diseases in particular among cigarette

smokers (Andersen *et al.*, 2017). Previous studies assessed the hypothesis that AD might be associated with other autoimmune diseases sharing the same immune reactivity (T-helper 2) and not T-helper 1 reactive autoimmune diseases. However, the study showed no differences between the two categories, besides, the study was limited by the small sample size and assessment bias (Feizy & Ghobadi, 2006). Given the above, the increasing rate and severity of AD observed, and the gap regarding its pathophysiology necessitate further investigation. The matter is complicated further by the emergence of COVID-19 and the great pressure posed on the healthcare system (Magomedova *et al.*, 2020; Siyal *et al.*, 2020). The treatment of both AD and autoimmune disease might increase the susceptibility to COVID-19 (Holmes *et al.*, 2019; Wollenberg *et al.*, 2020). AD was found to be associated with both skin and extra-cutaneous infections, lymphomas, obesity, cardiovascular diseases, psychiatric disease, and in particular autoimmune disorders (Paller *et al.*, 2018). Therefore, this review and meta-analysis aimed to assess the relationship between AD and autoimmune disease.

### MATERIALS AND METHODS

*Eligibility criteria according to PICOS (Liberati et al., 2009)*

*Types of the studies*

clinical studies were included (retrospective, prospective cohorts, case-control, and cross-sectional studies) conducted on humans (adults or younger age groups) and published during the period from 2011 to 2021. Experimental studies

and studies published in languages other than English were excluded. Also, studies with no control arms were not included.

#### Outcomes measures

studies comparing AD among patients with autoimmune disease of any type and control subjects without evidence of the same were eligible. Others without comparison or those with a high risk of bias were not.

#### The searching methods

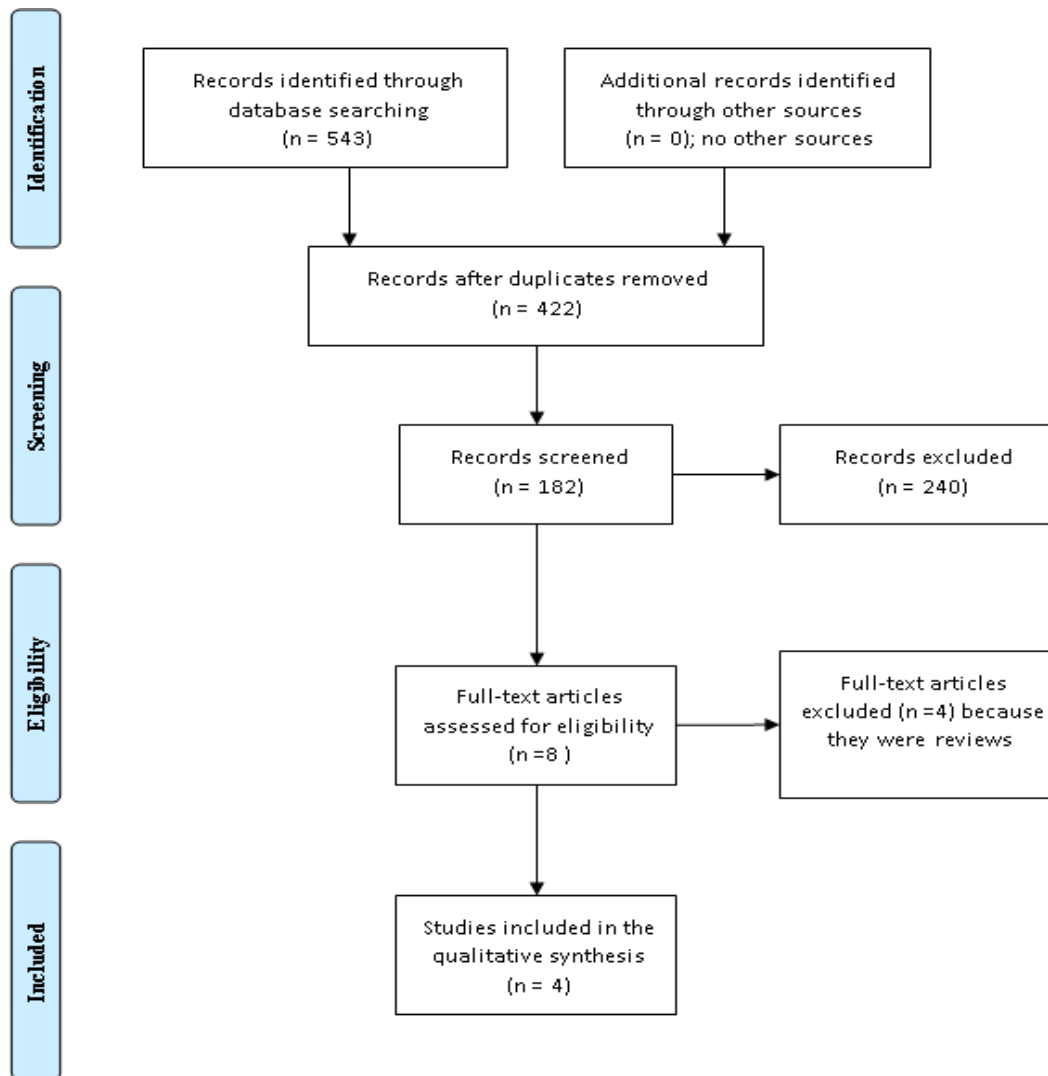
An electronic systematic literature search was used to retrieve articles to fulfill our inclusion and exclusion criteria. The authors searched the literature in PubMed, Cochrane Library, in addition to the first 100 articles in Google Scholar. The searching engine was set for the last ten years (from 2010 up to January 2021). The authors screened five hundred forty-three references and abstracts, and 182 articles were assessed for inclusion and exclusion criteria, of them 8 full texts were investigated. The final meta-analysis included four studies. Discrepancies were solved by a consensus, The greatest

difficulty faced by the authors was which autoimmune spectrum to include due to the vast spectrum. Besides, because AD begins at two years of age we included studies on all age groups (Ivana *et al.*, 2019), the keywords used were atopic dermatitis, atopic eczema dermatitis syndrome, autoimmune disease, skin autoimmunity, gastrointestinal autoimmune diseases to include most of the systematic autoimmune disorders.

Ottawa Newcastle scale was used for the quality and risk of bias assessment (Norris *et al.*, 2020). **Table 1.** The different phases of the literature search were shown in **Figure 1.**

#### Data analysis

The most recent Revman system for reviews (version, 5.4) was used (the Mantel Haenszel test with a 95% confidence interval to estimate the mean difference and heterogeneity. The random effects were used due to the significant heterogeneity observed (> 50 percentage was considered as high). A  $P < 0.05$  was considered significant. Sensitivity was assessed by funnel plot.



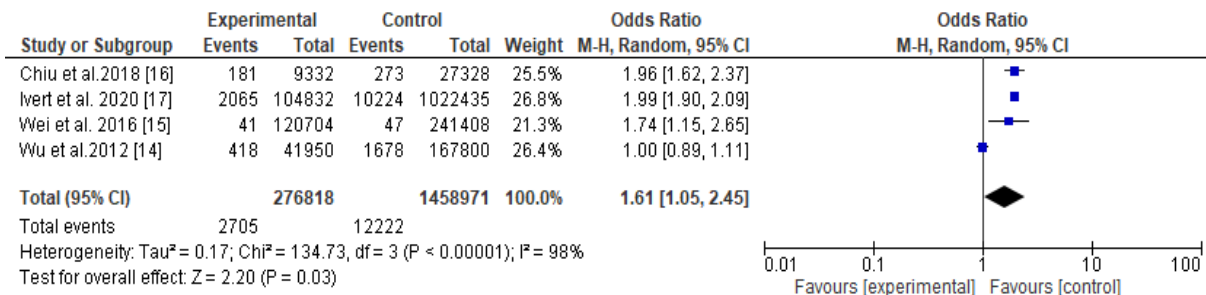
**Figure 1.** Autoimmune diseases associated with atopic dermatitis

**Table 1.** Ottawa Newcastle assessment for the included studies

Author	Selection	Compatibility	Outcome	Score
Wu <i>et al.</i> , 2012	3	2	4	9
Wei <i>et al.</i> , 2016	3	2	4	9
Chiu <i>et al.</i> , 2018	3	2	4	9
Ivert <i>et al.</i> , 2020	3	2	4	9

**Table 2.** Atopic dermatitis and autoimmune diseases

Author	Country	Period	intervention	Control	Significance
Wu <i>et al.</i> , 2012	Taiwan	13	814/ 41950	1678 167800	Equally effective
Wei <i>et al.</i> , 2016	China	7	41/ 120,704	47/ 241,408	significant
Chiu <i>et al.</i> , 2018	Taiwan	5	181/9332	273/27328	significant
Ivert <i>et al.</i> , 2020	Sweden	48	2065/ 104 832	10224/ 1 022 435	significant



**Figure 2.** The association between atopic dermatitis and autoimmune disease

**RESULTS AND DISCUSSION**

There were 543 references, 182 studies were assessed for eligibility, and eight full texts fulfilled the inclusion and exclusion criteria. The current meta-analysis included four studies with 1735789 patients and 14927 events, of which showed a neutral effect (Ivert *et al.*, 2020), while three showed a higher autoimmune disease among AD patients compared to their counterparts without the disease (Wu *et al.*, 2014; Wei *et al.*, 2016; Chiu *et al.* 2018). The studies were published in Asia and Europe. All were retrospective studies with study periods ranging from five years to 48 years. A significant statistical difference was observed (odd ration, 1.61, 95 % CI, 1.05-2.45, P-value, 0.03). The random effect was applied due to the substantial heterogeneity observed (I<sup>2</sup>=98%, P-value<0.001).

**Table 2 and Figure 2.**

The current pooled meta-analysis showed that patients with atopic dermatitis are more likely to develop the autoimmune disease; a previous review observed that the relationship between AD and autoimmune disease is not uniform. The study found an association between AD, skin and gastrointestinal immune disease, and systemic lupus erythematosus, while no association was found with other rheumatic disorders and type 1 diabetes (Cipriani *et al.*, 2017).

We could not find a meta-analysis in the searched databases that pooled autoimmune diseases to investigate their association with AD, because of that; this meta-analysis is unique. However, the common thread of AD and antinuclear antibody had been reported (Grygiel-Górniak *et al.*, 2017)

*The pathophysiology behind the systemic face of AD and the common thread with other autoimmune disorders*

*Immune deviation*

The mechanism linking AD to autoimmune disease is complex and remains elusive. A recent study suggested that autoreactive IgE might shift the adaptive response toward type 2 immunity to create inflammation, blocking the skin barrier and inducing a systemic immune response (Pellegrines, 2020). Evidence is growing that AD is a systemic disease activating many immune pathways (Th-cell subtypes) and not only Th1-Th2 (biphasic). Also, there is increasing evidence that the disease is increasing in the adult population and not only a disease of childhood (Sugaya, 2020). There is more expression of T-helpers that produce interleukin-4, 13, and 22 among patients with AD with a lower expression of interleukin-17 and may be targeted as therapeutic potentials. The low expression of interleukin-17 is thought to predispose AD patients to skin infections (Oliveira & Torres, 2019). The role of interleukins in AD and autoimmune diseases is a hot area of current research (Wang *et al.*, 2014).

*The skin barrier disruption and atopic march*

The well-known atopic march (AM) (a natural progression of AD in a considerable number of patients), AM is the progression of AD to other allergic diseases including but not limited to bronchial asthma and allergic rhinitis. AM might also explain the reported association of AD with other systemic diseases including other autoimmune diseases, cardiovascular

disease, neuropsychiatric diseases, and sleep disorders (Oliveira & Torres, 2019).

#### *Environmental factors and epidermal disruption in AD*

Both experimental and human studies highlighted the importance of environmental factors exposure to the induction of skin inflammation initiating a vicious circle of atopic-inflammation march. The atopic march will develop initiating a positive loop between the environment, skin, and immune system triggering various systemic diseases (Darlenski *et al.*, 2014; Egawa & Kabashima, 2016).

All the above highlighted the deleterious consequences of AD and the burden on the patient quality of life and sleep (Mahmoud *et al.*, 2020), community, and the healthcare system. The prevention and early diagnosis of AD as a systemic disease with meticulous follow-up for early recognition of other comorbidities and introducing the treatment on time are strongly needed.

The study limitations were the small size of the included studies, the limitation of the search engine to the English language, and the significant heterogeneity observed.

#### CONCLUSION

AD was associated with autoimmune diseases. Further studies assessing the possible environmental factors triggering the malignant circle between AD and autoimmune disease are recommended. Assessing the AD relation to individual autoimmune diseases is also needed.

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#### REFERENCES

- Andersen, Y. M., Egeberg, A., Gislason, G. H., Skov, L., & Thyssen, J. P. (2017). Autoimmune diseases in adults with atopic dermatitis. *Journal of the American Academy of Dermatology*, 76(2), 274-280. doi:10.1016/j.jaad.2016.08.047.
- Chiu, H. Y., Muo, C. H., & Sung, F. C. (2018). Associations of chronic urticaria with atopic and autoimmune comorbidities: a nationwide population-based study. *International Journal of Dermatology*, 57(7), 822-829. doi:10.1111/ijd.14000.
- Cipriani, F., Marzatico, A., & Ricci, G. (2017). Autoimmune diseases involving skin and intestinal mucosa are more frequent in adolescents and young adults suffering from atopic dermatitis. *The Journal of Dermatology*, 44(12), 1341-1348. doi:10.1111/1346-8138.14031.
- Darlenski, R., Kazandjieva, J., Hristakieva, E., & Fluhr, J. W. (2014). Atopic dermatitis as a systemic disease. *Clinics in Dermatology*, 32(3), 409-413. doi:10.1016/j.clindermatol.2013.11.007.
- Darsow, U., Eyerich, K., & Ring, J. (2014). Eczema, Atopic Eczema, and Atopic Dermatitis. World Allergy Organisation. [http://www.worldallergy.org/professional/allergic\\_diseases\\_center/atopiceczema/](http://www.worldallergy.org/professional/allergic_diseases_center/atopiceczema/). Accessed 30/December 2017
- Egawa, G., & Kabashima, K. (2016). Multifactorial skin barrier deficiency and atopic dermatitis: Essential topics to prevent the atopic march. *Journal of Allergy and Clinical Immunology*, 138(2), 350-358. doi:10.1016/j.jaci.2016.06.002. Epub 2016 Jun 22. PMID: 27497277.
- Feizy, V., & Ghobadi, A. (2006). Atopic dermatitis and systemic autoimmune diseases: a descriptive cross sectional study. *Dermatology Online Journal*, 12(3), 3.
- Frazier, W., & Bhardwaj, N. (2020). Atopic Dermatitis: Diagnosis and Treatment. *American Family Physician*, 101(10), 590-598.
- Grygiel-Górniak, B., Rogacka, N., Rogacki, M., & Puszczewicz, M. (2017). Antinuclear antibodies in autoimmune and allergic diseases. *Reumatologia*, 55(6), 298-304. doi:10.5114/reum.2017.72627.
- Holmes, J., Fairclough, L. C., & Todd, I. (2019). Atopic dermatitis and autoimmunity: the occurrence of autoantibodies and their association with disease severity. *Archives of Dermatological Research*, 311(3), 141-162. doi:10.1007/s00403-019-01890-4.
- Ivana, Č., Slavica, D., & Ivan, P. (2019). Filaggrin and Atopic March. *Biochemia Medica*, 29(2), 020501. doi:10.11613/BM.2019.020501.
- Ivert, L. U., Wahlgren, C. F., Lindelöf, B., Dal, H., Bradley, M., & Johansson, E. K. (2020). Association between atopic dermatitis and autoimmune diseases: a population-based case-control study. *British Journal of Dermatology*, 1-8. doi:10.1111/bjd.19624.
- Langan, S. M., Irvine, A. D., & Weidinger, S. (2020). Atopic dermatitis. *Lancet*, 396(10247), 345-360. doi:10.1016/S0140-6736(20)31286-1.
- Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology*, 62(10), e1-e34. doi:10.1016/j.jclinepi.2009.06.006.
- Magomedova, U. G., Khadartseva, Z. A., Grechko, V. V., Polivanova, M. N., Mishvelov, A. E., Povetkin, S. N., Demchenkov, E. L., & Shevchenko, Y. S. (2020). THE ROLE OF COVID-19 in the acute respiratory pathology formation in children. *Pharmacophore*, 11(5), 61-65.
- Mahmoud, M. I., Algarni, M. A., Wedad, H. A., Bawarith, B. M., Bawarith, A. M., & Abrar, T. A. (2020). Atopic dermatitis and sleep quality among preschool children in Jeddah, Saudi Arabia. *Medical Science*, 24(102), 927-934.
- Norris, J. M., Simpson, B. S., Ball, R., Freeman, A., Kirkham, A., Parry, M. A., Moore, C. M., Whitaker, H. C., & Emberton, M. (2020). A Modified Newcastle-Ottawa Scale for Assessment of Study Quality in Genetic Urological Research. *European Urology*, 79(3), 325-326. doi:10.1016/j.eururo.2020.12.017.

- Oliveira, C., & Torres, T. (2019). More than skin deep: the systemic nature of atopic dermatitis. *European Journal of Dermatology*, 29(3), 250-258. doi:10.1684/ejd.2019.3557.
- Paller, A., Jaworski, J. C., Simpson, E. L., Boguniewicz, M., Russell, J. J., Block, J. K., Tofte, S., Dunn, J. D., Feldman, S. R., Clark, A. R., et al. (2018). Major comorbidities of atopic dermatitis: beyond allergic disorders. *American Journal of Clinical Dermatology*, 19(6), 821-838. doi:10.1007/s40257-018-0383-4.
- Pellefigues, C. (2020). IgE Autoreactivity in Atopic Dermatitis: Paving the Road for Autoimmune Diseases?. *Antibodies*, 9(3), 47. doi:10.3390/antib9030047.
- Siyal, F. J., Shaikh, Z. A., Ahmed, S. Z., Shahid, M. A., Agha, F., Khoso, M., Unar, A. A., Unar, K., Saleem, R., & Shahani, M. P. (2020). Anxiety among COVID-19 Physicians during the Pandemic in the Health Care Center of the Rural Region. *Archives of Pharmacy Practice*, 11(4), 91-93.
- Sugaya, M. (2020). The role of Th17-related cytokines in atopic dermatitis. *International Journal of Molecular Sciences*, 21(4), 1314. doi:10.3390/ijms21041314.
- Wang, R. X., Yu, C. R., Dambuza, I. M., Mahdi, R. M., Dolinska, M. B., Sergeev, Y. V., Wingfield, P. T., Kim, S. H., & Egwuagu, C. E. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nature Medicine*, 20(6), 633-641. doi:10.1038/nm.3554. *Erratum in: Nat Med.* 20(6), 577-80. doi: 10.1038/nm.3554.
- Wei, C. C., Lin, C. L., Shen, T. C., & Tsai, J. D. (2016). Atopic dermatitis and association of risk for primary immune thrombocytopenia and autoimmune diseases among children: a nationwide population-based cohort study. *Medicine*, 95(29), e4226. doi:10.1097/MD.0000000000004226.
- Wise, F., & Sulzberger, M. B. (1933). Year book of dermatology and syphilology. *Year Book of Dermatology and Syphilology*. Chicago: Year Book Publishers, 38-9.
- Wollenberg, A., Flohr, C., Simon, D., Cork, M. J., Thyssen, J. P., Bieber, T., de Bruin-Weller, M. S., Weidinger, S., Deleuran, M., Taieb, A., et al. (2020). European Task Force on Atopic Dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology*, 34(6), e241-e242. doi:10.1111/jdv.16411.
- Wu, L. C., Hwang, C. Y., Chung, P. I., Hua, T. C., Chen, Y. D., Chu, S. Y., Lee, D. D., Chang, Y. T., Wang, W. J., Liu, H. N., et al. (2014). Autoimmune disease comorbidities in patients with atopic dermatitis: a nationwide case-control study in Taiwan. *Pediatric Allergy and Immunology*, 25(6), 586-592. doi:10.1111/pai.12274.