

ORIGINAL ARTICLE

Autoimmune diseases in adults with atopic dermatitis

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Background: An increased susceptibility to autoimmune disease has been shown in patients with atopic dermatitis (AD), but data remain scarce and inconsistent.

Objective: We examined the co-occurrence of selected autoimmune diseases in adult patients with AD.

Methods: Nationwide health registers were used. Adult patients with a hospital diagnosis of AD in Denmark between 1997 and 2012 were included as cases (n = 8112) and matched with controls (n = 40,560). The occurrence of autoimmune diseases was compared in the 2 groups. Logistic regression was used to estimate odds ratios.

Results: AD was significantly associated with 11 of 22 examined autoimmune diseases. In addition, AD was associated with having multiple autoimmune comorbidities. Patients with a history of smoking had a significantly higher occurrence of autoimmune comorbidities compared to nonsmokers.

Limitations: This study was limited to adult patients with AD. No information about AD severity or degree of tobacco consumption was available. Results from a hospital population of AD patients cannot be generalized to the general population.

Conclusions: Our results suggest a susceptibility of autoimmune diseases in adult patients with AD, especially in smokers. While we cannot conclude on causality based on these data, an increased awareness of autoimmune comorbidities in patients with AD may be warranted. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.08.047>.)

Key words: atopic dermatitis; autoimmune disease; comorbidity; epidemiology.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease with an estimated lifetime prevalence of 10% to 20% in Western countries.¹ Symptoms of AD typically present in early childhood and are dominated by pruritus, xerosis, and dermatitis in typical anatomic sites.² It is widely accepted that the etiopathogenesis of AD is multifactorial, where key components include genetic predispositions to skin barrier abnormalities and/or immune dysregulation

in combination with exposure to exogenous stressors.² AD has traditionally been viewed as a helper T cell (T_H2)-skewed condition, but the immune response in AD displays a much more complex interaction between T_H2, T_H1, T_H17, and regulatory T cells, depending on the chronicity of AD and racial influence.³⁻⁵

AD has previously been linked with autoimmune skin conditions, such as vitiligo, alopecia areata, and lupus erythematosus in epidemiologic studies.⁶⁻⁸

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More recent studies have reported an association between AD and inflammatory bowel disease (IBD),^{9,10} while the results have been conflicting in studies of rheumatoid arthritis^{9,11,12} and type 1 diabetes.¹³⁻¹⁵ Although increasing evidence suggests an increased susceptibility for autoimmune diseases in patients with AD, additional data are required to establish a relationship. We therefore examined whether Danish adult patients with AD had a higher co-occurrence of selected autoimmune diseases compared to controls.

MATERIALS AND METHODS

The study was approved by the Danish Data Protection agency (reference 2007-58-0015, internal reference GEH-2014-018, I-suite 02736). Ethical approval is not required for register studies in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.¹⁶

Data sources

Nationwide Danish registries were used to collect data for this study. All Danish residents have equal and universal access to tax-supported health care provided by the Danish National Health Service. We obtained data on morbidity from the Danish National Patient Register, which holds information on all in- and outpatient hospital contacts, based on the *International Classification of Diseases, 10th edition* (ICD-10) codes.¹⁷ Information on tax-reported household income was acquired from records by Statistics Denmark.¹⁸ Encrypted personal identification numbers allowed for linkage between the registers on an individual level.

Study population and covariates

The entire Danish population aged ≥ 18 years between January 1, 1997 until December 31, 2012 served as the source population. All patients with an in- or outpatient diagnosis of AD (ICD-10 code L20) during the study period were included as cases. Each case was matched with 5 controls on age, sex, and calendar time, randomly sampled from all noncases. The index dates for controls were the same for the corresponding case.

The selected autoimmune comorbidities were identified during the same study period based on

ICD-10 codes (Supplemental Table 1; available online at <http://www.jaad.org>). Patients with concurrent diagnoses of Crohn's disease and ulcerative colitis were characterized as having "unspecified IBD," because these conditions may be subject to diagnostic overlap. Information on smoking was collected based on previously described methods.¹⁹

An age-standardized socioeconomic level was calculated based on tax-reported mean household income, up to 5 years before study inclusion. As a measure of health care use, the total number of dermatology clinic visits in the study period was identified by all in- and outpatient contacts in the ICD-10 code group "L."

Statistical analysis

Categorical variables were presented in frequencies and continuous variables in means and standard deviations (SDs). Logistic regression analysis was used to estimate crude and adjusted odds ratios (aORs), respectively. Multivariate models were adjusted for age, sex, socioeconomic status, smoking, and number of dermatology consultations. Because dermatologic comorbidities would be subject to surveillance bias, we conducted sensitivity analyses of such diagnoses, where patients with AD were instead compared with patients with (either generalized or localized) hyperhidrosis (ICD-10 code R61); this condition is considered a chronic noninflammatory condition and is also treated by dermatologists. In addition, we investigated whether patients with AD and a history of smoking had a higher occurrence of autoimmune comorbidities compared to nonsmoking patients with AD using age- and sex-adjusted logistic regression analyses.

Results were presented with 95% confidence intervals (CIs) where applicable. Bonferroni corrected P values $< .002$ were considered statistically significant. Statistical analyses were performed with STATA software (v 13.0; StataCorp, College Station, TX) and SAS software (v 9.4; SAS Institute Inc, Cary, NC).

RESULTS

A total of 5,644,567 individuals ≥ 18 years of age were identified and served as the source population. During the study period, we identified 8112 adults

CAPSULE SUMMARY

- Accumulating evidence suggests an association between atopic dermatitis and autoimmune diseases.
- Adult patients with atopic dermatitis, especially smokers, have a higher occurrence of autoimmune diseases, including dermatologic, gastroenterologic, rheumatologic, and renal autoimmune disease.
- Increased awareness of autoimmune comorbidities in patients with atopic dermatitis may be warranted and smoking should be discouraged.

Abbreviations used:

AD:	atopic dermatitis
CI:	confidence interval
GWAS:	genome-wide association study
IBD:	inflammatory bowel disease
ICD:	International Classification of Diseases
OR:	odds ratio
SD:	standard deviation
RR:	relative risk

who had a diagnosis of AD and 40,560 age- and sex-matched controls. There was a female predominance (61.42%), and the mean age (SD) was 42.4 (15.2) years in both study groups. In the AD and reference groups, 14.3% and 8.6% had a history of smoking, respectively (Table I).

AD was significantly associated with alopecia areata (aOR = 26.31 [95% CI, 14.48-47.80]), vitiligo (aOR = 17.98 [95% CI, 7.70-42.01]), chronic urticaria (aOR = 9.92 [95% CI, 6.43-15.32]), celiac disease (aOR = 5.19 [95% CI, 2.93-9.20]), chronic glomerulonephritis (aOR = 4.17 [95% CI, 2.16-8.07]), Sjögren syndrome (aOR = 3.74 [95% CI, 2.41-5.82]), systemic lupus erythematosus (aOR = 2.65 [95% CI, 1.63-4.31]), ankylosing spondylitis (aOR = 2.33 [95% CI, 1.42-3.83]), Crohn's disease (aOR = 2.09 [95% CI, 1.52-2.85]), unspecified IBD (aOR = 2.07 [95% CI, 1.33-3.24]), ulcerative colitis (aOR = 1.64 [95% CI, 1.31-2.05]), and rheumatoid arthritis (aOR = 1.61 [95% CI, 1.29-2.01]). No significant associations were found between AD and autoimmune thyroid diseases, multiple sclerosis, type 1 diabetes, autoimmune hematologic diseases, or pulmonary fibrosis (Table II). In addition, AD was associated with multiple autoimmune comorbidities, where having ≤ 3 autoimmune diseases showed a stronger association than having 2 or 1 comorbidities—albeit that there were overlapping (yet still significant) confidence intervals (Table III). In the assessment of autoimmune dermatologic comorbidities, analyses comparing AD patients with hyperhidrosis patients yielded no significant changes (Table IV). A history of smoking was significantly associated with ≥ 1 autoimmune comorbidity in patients with AD (age- and sex-adjusted OR = 1.37 [95% CI, 1.13-1.66]; $P = .001$).

DISCUSSION

In this population-based study, adult patients with AD had an overall higher co-occurrence of autoimmune comorbidities compared to controls. Notably, we found positive associations for gastroenterologic, dermatologic, and rheumatologic autoimmune diseases, as well as chronic glomerulonephritis, but

Table I. Characteristics of the study population

	Atopic dermatitis, n = 8112	Controls, n = 40,560
Mean age, y (SD)	42.42 (15.16)	42.42 (15.16)
Women, n (%)	4982 (61.42)	24,910 (61.42)
Men, n (%)	3130 (38.58)	15,650 (38.58)
Any history of smoking, n (%)	1157 (14.26)	3494 (8.61)
Socioeconomic status, n (%)		
Low (0)	1557 (19.19)	8177 (20.16)
Below average (1)	1731 (21.34)	8004 (19.73)
Average (2)	1639 (20.20)	8095 (19.96)
Above average (3)	1368 (16.86)	8366 (20.63)
High (4)	1817 (22.40)	7918 (19.52)

AD, Atopic dermatitis; SD, standard deviation.

not for hematologic, neurologic, and endocrine autoimmune diseases.

In a recent large Dutch epidemiologic study, patients with AD had a significantly increased relative risk (RR) of rheumatoid arthritis (RR = 1.72 [95% CI, 1.25-2.73]), Crohn's disease (RR = 1.34 [95% CI, 1.11-1.61]), and ulcerative colitis (RR = 1.25 [95% CI, 1.03-1.53]). However, no apparent connection with type 1 diabetes apart from a marginal inverse association in sensitivity analyses was observed.⁹ The relationship between AD and type 1 diabetes has been rigorously debated, and several studies have suggested an inverse association based on the T_H1/T_H2 dichotomy theory.^{14,20} However, in line with our findings, a large metaanalysis¹³ based on 18 observational studies failed to find any significant association between AD and type 1 diabetes (OR = 0.82 [95% CI, 0.63-1.06]). Another metaanalysis²¹ found no evidence of an association between AD and multiple sclerosis (OR = 0.93 [95% CI, 0.71-1.23]), also in accordance with our results. The solidity of our findings is further supported by a systematic review article and metaanalysis that found increased odds of AD in patients with vitiligo or alopecia areata.⁶ The existing literature on AD and celiac disease, systemic lupus erythematosus, chronic urticaria, and autoimmune nephropathy is limited, but it reaches similar conclusions.²²⁻²⁹ While previous studies on AD and autoimmune thyroid disease and pulmonary fibrosis have found inconsistent results,³⁰⁻³³ ankylosing spondylitis has not previously been associated with AD.¹¹ Our findings therefore extend the existing literature and broaden the range of possible AD-associated autoimmune comorbidities.

One possible explanation for the observed associations is common immunologic pathways and an increased proinflammatory activation in

Table II. Absolute numbers and odds ratios of association between atopic dermatitis and autoimmune comorbidities

Autoimmune disease	AD, n (%)	Controls, n (%)	OR	95% CI	P value	Adjusted OR*	95% CI	P value
Alopecia areata	77 (0.95)	13 (0.03)	29.89	16.60-53.82	<.001	26.31	14.48-47.80	<.001 [†]
Ankylosing spondylitis	27 (0.33)	53 (0.13)	2.55	1.60-4.06	<.001	2.33	1.42-3.83	<.001 [†]
Celiac disease	28 (0.35)	24 (0.06)	5.85	3.39-10.10	<.001	5.19	2.93-9.20	<.001 [†]
Chronic glomerulonephritis	19 (0.23)	20 (0.05)	4.76	2.54-8.92	<.001	4.17	2.16-8.07	<.001 [†]
Chronic urticaria	72 (0.89)	31 (0.08)	11.71	7.68-17.85	<.001	9.92	6.43-15.32	<.001 [†]
Crohn's disease	66 (0.81)	137 (0.34)	2.42	1.80-3.25	<.001	2.09	1.52-2.85	<.001 [†]
Giant cell arteritis	19 (0.23)	44 (0.11)	2.16	1.26-3.70	<.001	1.84	1.03-3.29	.039
Graves' disease	82 (1.01)	307 (0.76)	1.34	1.05-1.71	.020	1.22	0.94-1.59	.139
Hashimoto thyroiditis	26 (0.32)	60 (0.15)	2.17	1.37-3.44	<.001	2.14	1.29-3.56	.003
Hemolytic anemia	4 (0.05)	14 (0.03)	1.43	0.47-4.34	.529	1.03	0.31-3.37	.965
Immune thrombocytopenia purpura	13 (0.16)	24 (0.06)	2.71	1.38-5.33	.004	2.23	1.09-4.59	.029
Multiple sclerosis	37 (0.46)	159 (0.39)	1.16	0.81-1.67	.406	1.06	0.72-1.56	.775
Primary biliary cirrhosis	6 (0.07)	11 (0.03)	2.73	1.01-7.38	.05	3.82	1.01-14.45	.048
Pulmonary fibrosis	11 (0.14)	22 (0.05)	2.50	1.21-5.16	.013	1.84	0.83-4.07	.134
Rheumatoid arthritis	126 (1.55)	374 (0.86)	1.83	1.49-2.25	<.001	1.61	1.29-2.01	<.001 [†]
Sjögren's syndrome	41 (0.51)	47 (0.12)	4.38	2.88-6.66	<.001	3.74	2.41-5.82	<.001 [†]
Systemic lupus erythematosus	29 (0.36)	46 (0.11)	3.16	1.98-5.03	<.001	2.65	1.63-4.31	<.001 [†]
Systemic sclerosis	16 (0.20)	27 (0.07)	2.97	1.60-5.51	.001	2.42	1.26-4.64	.008
Type 1 diabetes	14 (0.17)	69 (0.17)	1.01	0.57-1.80	.961	0.77	0.42-1.43	.411
Ulcerative colitis	107 (1.32)	279 (0.69)	1.93	1.54-2.41	<.001	1.64	1.31-2.05	<.001 [†]
Unspecified IBD	32 (0.39)	66 (0.16)	2.43	1.59-3.71	<.001	2.07	1.33-3.24	<.001 [†]
Vitiligo	28 (0.35)	7 (0.02)	20.10	8.76-45.95	<.001	17.98	7.70-42.01	<.001 [†]

AD, Atopic dermatitis; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.

*Adjusted for age, sex, smoking, socioeconomic status, and number of dermatologist visits.

[†]Bonferroni-corrected statistically significant *P* values (<.002).**Table III.** Odds ratios of association between atopic dermatitis and the presence of multiple autoimmune diseases

No. of autoimmune diseases	OR	95% CI	P value
1	2.48	2.26-2.71	<.001
2	3.46	2.58-4.64	<.001
≥3	5.32	1.87-15.18	.002

CI, Confidence interval; OR, odds ratio.

patients with AD. Autoimmune diseases result from a complex dysregulation of innate and adaptive immunity with subsequent tissue damage.³⁴ It has been suggested that AD in reality, is an “umbrella” term that covers several distinct endophenotypes, and that one subtype of AD could be dominated by an autoimmune profile.³⁵ In support of such a hypothesis, a systematic review article found evidence for autoreactivity (ie, immune responses to autologous tissue, cells, or proteins) in patients with AD, especially those with persistent and severe disease.³⁶

Genome-wide association studies (GWASs) have in recent years identified major genetic risk loci shared between autoimmune diseases. For example, a GWAS identified 90 shared genetic regions

associated with celiac disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes.³⁷ A recent comprehensive multi-ancestry GWAS based on 21,000 cases and 95,000 controls identified a total of 31 susceptibility loci for AD, where multiple loci were found to be associated with immune regulation and autoimmunity.³⁸ Human GWASs show that autoimmune diseases may depend on the inheritance of multiple gene loci that encode low-risk susceptibility alleles.³⁹ Notably, many of these genetic risk loci are widely distributed among autoimmune diseases and contribute strongly to their clustering.

We found that patients with more coinciding autoimmune diseases showed a stronger association with AD. While this could be explained by enhanced genetic risk, the onset of autoimmune conditions normally requires environmental triggers that interact with particular genotypes.³⁹ Indeed, the concordance rates of autoimmune diseases among monozygotic twins have been estimated to range from 12% to 67%, indicating that other factors may play important roles, such as environmental factors and epigenetic mechanisms.³⁴ We found that patients with AD who have a history of smoking had a significantly higher occurrence of autoimmune

Table IV. Odds ratios of association between atopic dermatitis and dermatologic disorders when compared with hyperhidrosis

Dermatologic disorder	OR	95% CI	P value	Adjusted OR*	95% CI	P value
Chronic urticaria	6.48	3.43-12.23	<.001	5.04	2.61-9.76	<.001 [†]
Vitiligo	6.90	2.42-19.67	<.001	4.59	1.56-13.41	.002 [†]
Alopecia areata	6.93	3.68-13.05	<.001	6.51	3.34-12.72	<.001 [†]

CI, Confidence interval; OR, odds ratio.

*Adjusted for age, sex, smoking, socioeconomic status, and number of dermatologist visits.

[†]Bonferroni-corrected statistically significant *P* values (<.002).

comorbidities compared to nonsmokers. Smoking has previously been identified as a risk factor for both AD and autoimmune diseases, although smoking may exert protective properties against certain diseases (eg, ulcerative colitis).⁴⁰⁻⁴² Biologic effects of cigarette smoking that may influence the development of autoimmune disease are complex, and include increased tissue damage and elevation or reduction of proinflammatory cells and cytokines.⁴¹ It has also been suggested that high living standards and an urban lifestyle are associated with the occurrence of both atopic and autoimmune diseases.^{43,44} Previous studies have observed that when individuals migrate from low- to high-prevalence countries, the first generation offspring may acquire atopic and autoimmune diseases with a higher incidence than individuals who stayed in their country of origin.^{45,46} These data collectively suggest that AD and autoimmune diseases may have shared genetic risk loci but also common environmental triggers.

Strengths and limitations

Several strengths and limitations apply to this study. The Danish administrative registries contain prospectively collected data with high accuracy and virtually no loss to follow-up, enabling large-scale epidemiologic studies with minimal risk of selection and recall bias. As part of an ongoing validation study, we investigated a random sample of patients with ICD-10 code L20 and found that only 2 patients out of 50 did not meet the diagnostic criteria for AD based on clinical information from patient charts. Therefore, the positive predictive value of the diagnostic code is expected to be high. Moreover, the nationwide coverage allows for investigation of rare diseases because of the large sample size. Because the investigated outcomes were numerous, we addressed the “multiple comparisons” issue using Bonferroni correction, which is considered to be a highly conservative way of controlling for statistical significance, but increases the risk of type II errors (ie, missing a true positive association). Our results may be most applicable to AD patients treated in hospitals

(in- or outpatient), because this patient category served as cases in this study. A substantial proportion of patients with AD in Denmark are treated by general practitioners and private dermatologists, and these patients would be attributed to the reference population, resulting in risk of diluting the estimated associations. Several of our estimates had broad CIs because of the low number of events, and we investigated a range of rare diseases.

In addition, some of the observed associations could be subject to surveillance bias (eg, regular consultations with a dermatologist could result in detection of other skin conditions). We therefore compared the AD population to patients with hyperhidrosis, in sensitivity analysis for autoimmune dermatologic disease, and the estimates remained significant, suggesting that the associations are indeed valid. Although we attempted to adjust for possible confounding factors, we cannot eliminate the possibility of residual confounding. While we adjusted for socioeconomic status, we were unable to adjust for family history of autoimmune diseases and certain environmental and lifestyle factors. We only included adults in our study, and children with AD may have a different comorbidity profile. We had no information about AD severity and the smoking variable gave no information about smoking duration or quantity of consumption. Lastly, the Danish population is predominantly of Caucasian descent, which may limit extrapolation of the results to other ethnicities.

In conclusion, our findings show a susceptibility of autoimmune diseases in patients with AD, in particular in smokers, although the exact mechanisms of association are unknown. These are observational data, and we therefore cannot make conclusions about causality. Nevertheless, clinicians who care for patients with AD should be aware of the link with autoimmune disease and discourage smoking in their patients.

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Supplemental Table I. *International Classification of Diseases, 10th revision codes for identification of selected autoimmune diseases*

Disease	ICD-10 code
Alopecia areata	L63
Ankylosing spondylitis	M45 and M081
Celiac disease	K900
Chronic glomerulonephritis	N03
Chronic urticaria	L508A
Crohn's disease	K50
Giant cell arteritis	M315 and M316
Graves' disease	E050
Hashimoto thyroiditis	E060
Hemolytic anemia	D55 and D59
Immune thrombocytopenia purpura	D693
Multiple sclerosis	G35
Primary biliary cirrhosis	K743
Pulmonary fibrosis	J841
Rheumatoid arthritis	M05 and M06
Sjögren syndrome	M350
Systemic lupus erythematosus	M32
Systemic sclerosis	M34
Type 1 diabetes	E10
Ulcerative colitis	K51
Vitiligo	L80

ICD-10, International Classification of Diseases, 10th revision.