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Association between atopic dermatitis and autoimmune diseases: a population-based case–control study*

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Summary

Background Atopic dermatitis (AD) is a common chronic skin disorder and is well known to be associated with other atopic conditions. There is increasing evidence for an association also with nonatopic conditions, including autoimmune diseases, but data are limited about several autoimmune diagnoses.
Objectives To investigate the association between AD and autoimmune diseases.
Methods This case–control study used Swedish national healthcare registers. The source population comprised the entire Swedish population aged ≥ 15 years from 1968 to 2016. Cases, including all those with an inpatient diagnosis of AD (from 1968) and/or a specialist outpatient diagnosis of AD (from 2001), were matched by sex and age to healthy controls (104 832 cases of AD, 1 022 435 controls).
Results AD was significantly associated with one or more autoimmune diseases compared with controls – adjusted odds ratio (aOR) 1·97, 95% confidence interval (CI) 1·93–2·01 – and this association was significantly stronger in the presence of multiple autoimmune diseases compared with only one. The association was strongest for autoimmune disorders involving the skin (aOR 3·10, 95% CI 3·02–3·18), the gastrointestinal tract (aOR 1·75, 95% CI 1·69–1·82) or connective tissue (aOR 1·50, 95% CI 1·42–1·58). In the overall analysis, men with AD had a stronger association with rheumatoid arthritis and coeliac disease than did women with AD. In subanalyses, the findings remained stable in multivariable analyses after adjustment for smoking and parental autoimmune disease.
Conclusions This large population-based study indicates significant autoimmune comorbidity of adults with AD, especially between AD and autoimmune dermatological, gastrointestinal and rheumatological diseases. Having multiple autoimmune diseases resulted in a stronger association with AD than having only one autoimmune disease.

What is already known about this topic?

- Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases.
- Some studies have shown that AD is associated with some autoimmune diseases, such as Crohn disease, ulcerative colitis, coeliac disease, alopecia areata and vitiligo, but data are limited for several major autoimmune diagnoses.

What does this study add?

- In this study, AD was associated with several autoimmune diseases, especially those involving the skin, the gastrointestinal tract or connective tissue.
- The association was stronger for individuals with multiple autoimmune comorbidities.

Atopic dermatitis (AD) is one of the most common chronic skin disorders globally.[1] A recent systematic review, with data from all continents, found a 12-month prevalence of AD up to 17·1% among adults and 22·6% among children.[2] Essential features of AD are generalized dry skin, recurrent eczematous lesions and pruritus. Clinical symptoms can have a wide spectrum, with negative impact on health-related quality of life and work life, and having AD is a financial burden for the affected person as well as for society.[3–5]

AD is well known to be associated with other atopic conditions. There is increasing evidence for an association also with several nonatopic conditions, such as certain cancers, cardiovascular diseases, infections and neuropsychiatric disorders, although their relationships with AD are not fully understood.[6–8] Previous studies have also found an association between AD and several autoimmune conditions, including Crohn disease, ulcerative colitis, coeliac disease, alopecia areata and vitiligo.[9,10] A systematic review found that autoimmune diseases involving the skin and gastrointestinal tract were more frequent in individuals with AD, while conflicting results were seen for correlations with type 1 diabetes mellitus (DM1), autoimmune thyroiditis and rheumatoid arthritis (RA).[11] Increased knowledge within this field might lead to better monitoring of comorbidity and a deeper understanding of the disease burden and pathophysiology of AD. The aim of the present study was to explore the association between AD and a wide spectrum of autoimmune diseases in a large-scale, population-based study using Swedish national registers.

Patients and methods

Data sources

Each person registered in Sweden has a civic registration number enabling cross-linkage of information between registers for a specific individual. The Swedish Board of Health and Welfare maintains several national health registers. The National Patient Register (NPR) contains information on inpatient diagnoses since 1964 and specialist outpatient (non-primary care) visits since 2001. Data on smoking are available from the Medical Birth Register for pregnant women registered for antenatal care since 1982. Statistics Sweden runs additional registers covering the entire Swedish population. The highest attained level of education was included as a proxy for socioeconomic status, with data obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA).[12] The Total Population Register (TPR) holds information about deaths, emigration and immigration. The Multi-Generation Register contains information about index persons, with links back to their parents and forward to their children. It includes people registered in Sweden since 1961 and people born in 1932 or later.

Study design and study population

We used a population-based case–control study design to explore the association between AD and autoimmune diseases. The source population comprised the entire Swedish population aged ≥ 15 years from 1968 to 2016. Cases included all patients with an inpatient diagnosis of AD (from 1968) and/or a specialist outpatient diagnosis of AD (from 2001) identified in the NPR. The AD diagnosis and autoimmune diseases were identified using International Classification of Diseases (ICD) codes (Table S1; see Supporting Information). AD and autoimmune diseases registered in primary care were not included. Ten randomly selected age- and sex-matched controls per case were identified from the TPR. Exclusion criteria applied for the cases and controls included reused civic registration numbers, persons with incomplete records, and lack of matching individuals. Additionally, controls with a diagnosis of AD before 15 years of age, but not later, were excluded. We began with a control-to-case ratio of 10 : 1. In the main analyses, the actual control-to-case ratio was 9·8 : 1, ranging from 1 to 10, and in the subgroup analyses the control-to-case ratio was 6·8 : 1, also ranging from 1 to 10.

Covariates

Education was categorized into ≤ 9 years, 10–12 years and > 12 years of education. The highest educational attainment, according to the LISA register 1990–2015, was used in the multivariable-adjusted analysis. In a subgroup analysis we examined the influence of maternal and/or paternal autoimmune disease. In the first model we defined the covariate as any autoimmune disease. In the second model, the covariate corresponded to the specific autoimmune disease that was investigated among offspring.

Subgroup analyses among women included smoking in a multivariable-adjusted analysis. Nonsmoking was defined as 0 cigarettes per day, light smoking as 1–9 cigarettes per day and heavy smoking as ≥ 10 cigarettes per day. If a mother was registered with more than one birth, and thus more than one value of smoking, the value with most smoking was used in the analysis.

Statistics

Differences in characteristics between cases of AD and controls were evaluated using Pearson's χ^2-test or Student's t-test for

independent samples. Conditional logistic regression was used to calculate crude and adjusted odds ratios (aORs), with 95% confidence intervals (CIs), to estimate the association between AD and autoimmune diseases. There were no statistically significant interactions between autoimmune diseases and the covariates education, hereditary status of autoimmune disease, or smoking. None of the covariates distorted the association between AD and autoimmune diseases by > 10%. Education was included in the main analysis in order to compare our results with those of previous studies within this field. Bonferroni correction was used, given the multiple-hypothesis tests and the increased risk of type I errors. The Bonferroni-adjusted probability $P < 0{\cdot}000427$ was considered statistically significant when exploring the disease association in the overall analysis. For differences between men and women, we applied the Bonferroni-adjusted probability $P < 0{\cdot}00128$, in accordance with the number of comparisons. The latter was also used when comparing age of onset between cases and controls for specific autoimmune diagnoses. All analyses were performed using SPSS, version 20 (IBM, Armonk, NY, USA).

Ethics

The study was approved by the Regional Ethics Review Board, Stockholm (2016/2496-31). All data were anonymized before any analysis.

Results

Patient characteristics

In total, the population used in the analysis consisted of 104 832 cases of AD matched with 1 022 435 controls from the general population (Figure 1). The majority of patients with AD were women (66·1%) and the overall mean age was 34·9 years (Table 1). Comparison of baseline characteristics revealed that patients with AD were younger than controls at first diagnosis of any autoimmune disease (42·9 vs. 45·8 years, $P < 0{\cdot}001$).

Patients with AD had their first diagnosis of RA at a younger age than controls (40·6 vs. 50·8 years, $P < 0{\cdot}001$). In contrast, the first diagnosis of psoriasis was recorded later among patients with AD than controls (44·1 vs. 42·4 years, $P < 0{\cdot}001$), while there were no significant differences in age of onset for other diagnoses.

Association between atopic dermatitis and autoimmune diseases

In the overall crude analysis, association was found between AD and autoimmune diseases as a group (OR 1·96, 95% CI 1·92–2·00). The estimate remained stable when adjusting for education (aOR 1·97, 95% CI 1·93–2·01) (Table 2). AD was associated with autoimmune diseases affecting several organ systems, especially the skin, the gastrointestinal tract and connective tissue. The strongest associations were found between AD and several autoimmune skin diseases, as listed in Table 2, particularly dermatitis herpetiformis (aOR 9·76, 95% CI 8·10–11·8), alopecia areata (aOR 5·11, 95% CI 4·75–5·49) and chronic urticaria (aOR 4·82, 95% CI 4·48–5·19). AD was associated with gastrointestinal diseases, including coeliac disease, Crohn disease and ulcerative colitis. Common connective-tissue diseases among patients with AD included systemic lupus erythematosus (SLE), ankylosing spondylitis and RA. We did not find any statistically significant associations between AD and haematological or hepatic autoimmune diseases.

Sex-specific association between atopic dermatitis and autoimmune disease

In the overall analysis, men had a stronger association between AD and autoimmune diseases than women (aOR 2·18, 95% CI 2·10–2·25 vs. aOR 1·89, 95% CI 1·85–1·93) (Table 2). However, this sex difference was only statistically significant between AD and RA and between AD and coeliac disease. In addition, AD in men, but not in women, was associated with DM1. Moreover, in sex-stratified analyses, AD only in women was associated with dermatomyositis, systemic scleroderma, SLE, Hashimoto disease, Graves disease, multiple sclerosis (MS) and polymyalgia rheumatica.

Multiple autoimmune comorbidities

There was a significantly stronger association between AD and co-occurrence of two or more autoimmune diseases than between AD and co-occurrence of only one autoimmune disease (Table 3).

Impact of hereditary status and smoking

We identified a subgroup of 92 290 cases with information available on autoimmune diseases among biological parents. In multivariable analyses, adjusting for any parental autoimmune disease, the association between AD and any autoimmune disease remained stable (OR 1·90, 95% CI 1·86–1·94 vs. aOR 1·89, 95% CI 1·86–1·93). Further, the estimates remained stable after adjustment for diagnosis-specific parent–offspring associations when studying 15 of the most common autoimmune diseases (OR changed < 10%).

In a subanalysis of 32 797 pregnant women with AD, registered in antenatal care during 1982–2016, the associations between AD and autoimmune dermatological diseases, gastrointestinal and rheumatological diseases, and MS remained stable in the multivariable analyses after adjustment for smoking (OR changed < 10%) (data not shown).

Discussion

To the best of our knowledge, this is the largest population-based study to assess the association between AD and autoimmune diseases. In our study, patients with AD had a significant association with one or more autoimmune diseases when compared with controls without AD. Furthermore, having multiple

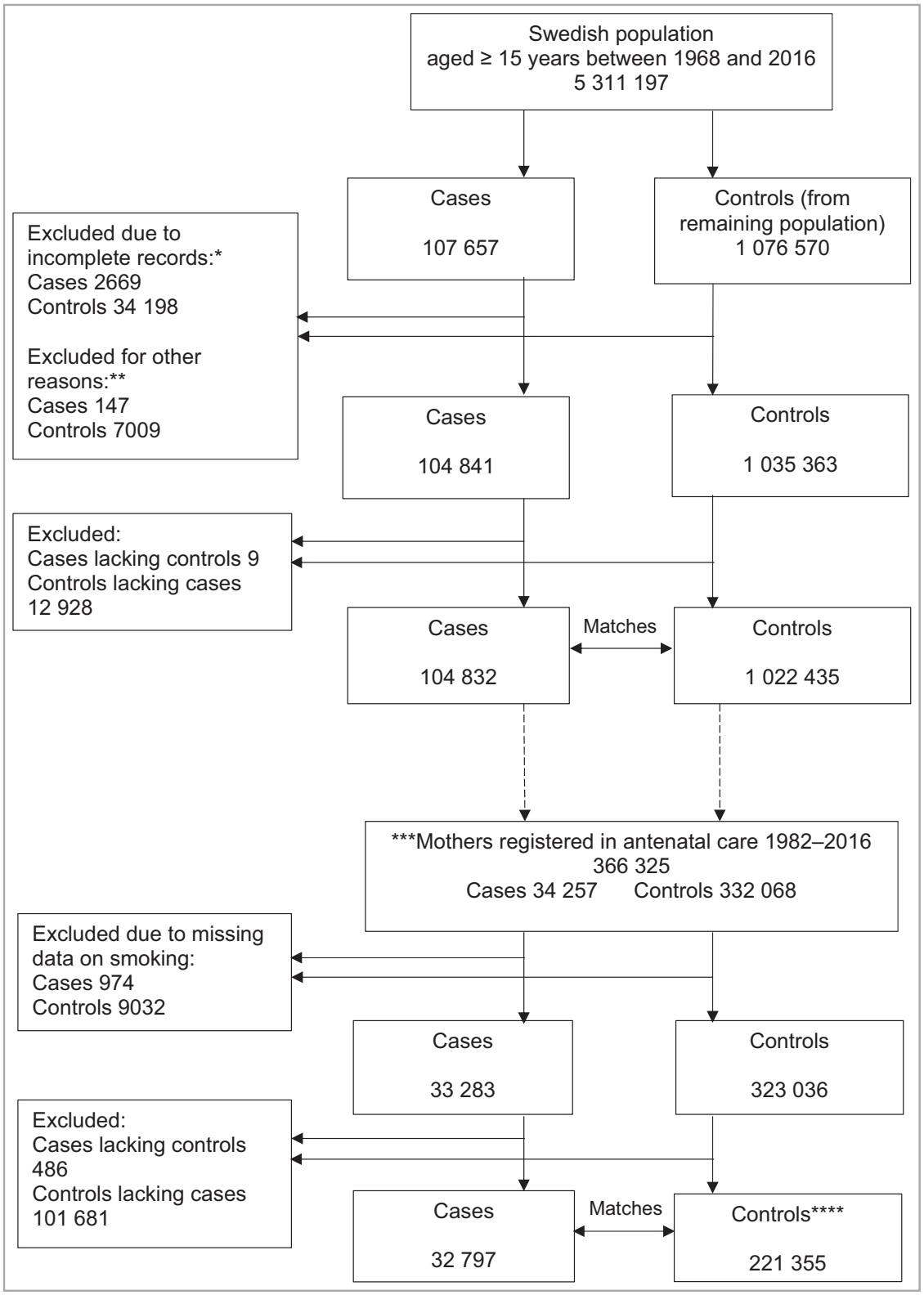

Figure 1 Flowchart of the study including cases and controls. *Mainly lacking data on education level. **Reused civic registration numbers, controls with atopic dermatitis before age 15 years. ***Participants in the subgroup analysis on effects of smoking. ****The pregnancy criterion resulted in a major reduction of participants. Controls had to be pregnant during the period of interest and also had to be matched to a case that had been pregnant during the period of interest.

Table 1 Characteristics of the study population with atopic dermatitis (AD)

Variable	Cases n = 104 832	Controls n = 1 022 435	P-value (t-test, χ^2)
Sex female, n (%)	69 250 (66·1)	676 180 (66·1)	0·62
Age at first AD diagnosis after age 15 years			
Mean (SD)	34·9 (17·8)		
Median (range)	30·0 (15·0–101·0)		
Age at end of study (years)			
Mean (SD)	42·1 (17·0)	42·4 (17·0)	0·079
Median (range)	38·0 (16·0–102)	39·0 (16·0–105)	
Years of education, n (%)			
≤ 9 years	15 619 (14·9)	177 558 (17·4)	< 0·001
9–12 years	46 118 (44·0)	455 777 (44·6)	
> 12 years	43 095 (41·1)	389 100 (38·1)	
Age at first autoimmune diagnosis (years)			
Mean (SD)	42·9 (20·9)	45·8 (20·5)	< 0·001
Median (range)	43·0 (0·0–98·0)	47·0 (0·0–103)	< 0·001

autoimmune diseases resulted in a stronger association with AD than having only one autoimmune disease. The associations were strongest for autoimmune disorders involving the skin, the gastrointestinal tract or connective tissue. The strongest associations between AD and specific skin diagnoses were for dermatitis herpetiformis, alopecia areata and chronic urticaria.

Previous studies have found associations between AD and alopecia areata, vitiligo and chronic urticaria.[10,13–16] A German cohort study found associations between AD and Crohn disease, ulcerative colitis and RA.[14] A cross-sectional study from the USA[13] and a Danish register-based study[10] found associations between AD and autoimmune gastrointestinal diseases and rheumatological diseases, such as RA and SLE.

In general, our findings are in line with previous studies within this field, but there are some differences. In men with AD, but not women with AD, we found a weak significant association between AD and DM1. Previous studies from the USA, Germany and Denmark found no or an inverse association between AD and DM1.[10,13,14] A review from 2017, including both adults and children with AD, concluded that the data on an association between AD and DM1 were conflicting, although most articles seemed to agree on a lower risk of DM1.[11] Furthermore, we found an association between AD and MS; previous studies are conflicting here too.[10,13] Some of the studies that have explored the association with MS have used nonspecific terms such as 'eczema' or 'dermatitis', which may have caused misclassification bias.[17] We found a significant association between AD and autoimmune thyroid diseases, such as Graves disease and Hashimoto disease, which was not found in a previous study.[10] However, previous data were limited, as were data for several other diseases in our analysis. Between-study variations may arise due to differences in study methods and cutoff points for statistical significance rather than true differences.

We found several sex differences in comorbidities between women and men with AD when compared with controls. AD only in women was associated with dermatomyositis, systemic scleroderma, SLE, Hashimoto disease, Graves disease, MS and polymyalgia rheumatica. Women are in general more likely to develop autoimmune diseases, and 80% of patients with autoimmune diseases are women.[18] Various mechanisms have been put forward, such as differences in organ vulnerability, genetic predisposition, sex-specific gut microbiota, and heightened immune reactivity in women.[18,19] Oestrogen has been shown to suppress T helper 1-dependent disease, but to potentiate T helper 2-dependent disease. We can only hypothesize, but there might be a link between the heightened immune reactivity in female autoimmune diseases and the course of female AD. A large meta-analysis found that persistent AD was more common among female than male individuals.[20] Surprisingly, we found that the association between AD and RA was stronger among men than among women.

The underlying pathogenic mechanisms of how autoimmunity is related to AD remain unclear. Genetic overlap has been found between AD and immune-mediated diseases, such as psoriasis and inflammatory bowel disease.[7] However, the German cohort study did not find a higher proportion of major genetic risk factors for irritable bowel disease and RA among patients with AD.[14] Environmental factors, such as smoking and socioeconomic status, may be shared. In the present study, adjustment for socioeconomic status did not change the result. Moreover, adjustment for hereditary autoimmune diseases did not change the overall result in a subanalysis; neither did adjustment for smoking in a subanalysis among women. In our study, patients with AD were more likely to present with multiple autoimmune comorbidities in a dose–response-dependent manner, and patients with AD were generally diagnosed with autoimmune diseases, especially RA, earlier than controls. This might support the idea of an autoimmune component of AD and/or shared immune pathways and/or shared environmental factors yet to be discovered. A common mechanism of action between AD and autoimmune disease in general is not established.

Table 2 Autoimmune diseases in patients with atopic dermatitis (AD) compared with individuals without AD

Autoimmune disease by organ or tissue type	All cases (n = 104 832)			Women (n = 69 250)			Men (n = 35 582)			
	n (%)	Adjusted OR (95% CI)[a]	P-value	n (%)	Adjusted OR (95% CI)[a]	P-value	n (%)	Adjusted OR (95% CI)[a]	P-value	Women vs. men P-value (t-test)
Any of the listed autoimmune diseases	14 709 (14·0)	**1·97** (1·93–2·01)	< B	10 137 (14·6)	**1·89** (1·85–1·93)	< B	4572 (12·8)	**2·18** (2·10–2·25)	< B	< 0·0013
Skin	7788 (7·4)	**3·10** (3·02–3·18)	< B	5233 (7·6)	**3·01** (2·91–3·11)	< B	2555 (7·2)	**3·29** (3·14–3·44)	< B	0·002
Dermatitis herpetiformis	222 (0·2)	**9·76** (8·10–11·8)	< B	128 (0·2)	**9·00** (7·08–11·5)	< B	94 (0·3)	**11·0** (8·20–14·8)	< B	0·30
Alopecia areata	1130 (1·1)	**5·11** (4·75–5·49)	< B	845 (1·2)	**4·90** (4·51–5·32)	< B	285 (0·8)	**5·85** (5·04–6·78)	< B	0·040
Chronic urticaria	1077 (1·0)	**4·82** (4·48–5·19)	< B	805 (1·2)	**4·53** (4·16–4·92)	< B	272 (0·8)	**5·98** (5·14–6·96)	< B	0·002
Pemphigoid/pemphigus	525 (0·5)	**3·34** (3·02–3·69)	< B	324 (0·5)	**3·22** (2·84–3·65)	< B	201 (0·6)	**3·55** (3·02–4·18)	< B	0·36
Vitiligo	509 (0·5)	**2·61** (2·37–2·88)	< B	318 (0·5)	**2·43** (2·15–2·75)	< B	191 (0·5)	**2·98** (2·54–3·51)	< B	0·048
Psoriasis	4570 (4·4)	**2·52** (2·44–2·60)	< B	2987 (4·3)	**2·43** (2·33–2·53)	< B	1583 (4·4)	**2·71** (2·56–2·87)	< B	0·002
Gastrointestinal tract	3022 (2·9)	**1·75** (1·69–1·82)	< B	2051 (3·0)	**1·67** (1·60–1·76)	< B	971 (2·7)	**1·94** (1·81–2·08)	< B	< 0·0013
Coeliac disease	1159 (1·1)	**1·96** (1·84–2·09)	< B	849 (1·2)	**1·80** (1·67–1·94)	< B	310 (0·9)	**2·62** (2·31–2·97)	< B	< 0·0013
Crohn disease	957 (0·9)	**1·83** (1·71–1·96)	< B	634 (0·9)	**1·76** (1·62–1·92)	< B	323 (0·9)	**1·97** (1·75–2·22)	< B	0·14
Ulcerative colitis	1247 (1·2)	**1·58** (1·49–1·68)	< B	774 (1·1)	**1·50** (1·39–1·62)	< B	473 (1·3)	**1·72** (1·56–1·90)	< B	0·033
Connective tissue	1445 (1·4)	**1·50** (1·42–1·58)	< B	1089 (1·6)	**1·46** (1·37–1·55)	< B	356 (1·0)	**1·63** (1·46–1·83)	< B	0·083
Dermatomyositis	34 (0·03)	**2·80** (1·91–4·10)	< B	29 (0·04)	**3·09** (2·03–4·70)	< B	5 (0·01)	1·81 (0·70–4·71)	0·22	0·31
Systemic scleroderma	64 (0·1)	**1·87** (1·43–2·44)	< B	56 (0·1)	**1·87** (1·40–2·49)	< B	8 (0·02)	1·86 (0·87–3·95)	0·11	0·99
Systemic lupus erythematosus	214 (0·2)	**1·65** (1·42–1·90)	< B	193 (0·3)	**1·62** (1·39–1·88)	< B	21 (0·1)	**1·97** (1·23–3·14)	0·005	0·44
Ankylosing spondylitis	278 (0·3)	**1·46** (1·29–1·66)	< B	150 (0·2)	**1·51** (1·27–1·79)	< B	128 (0·4)	**1·41** (1·17–1·70)	< B	0·62
Rheumatoid arthritis	896 (0·9)	**1·44** (1·34–1·54)	< B	689 (1·0)	**1·35** (1·25–1·46)	< B	207 (0·6)	**1·83** (1·58–2·13)	< B	< 0·0013
Polymyositis	21 (0·02)	1·35 (0·86–2·14)	0·19	19 (0·03)	**1·73** (1·06–2·82)	0·028	2 (0·01)	0·44 (0·11–1·82)	0·26	0·074
Vascular	384 (0·4)	**1·36** (1·22–1·52)	< B	272 (0·4)	**1·32** (1·16–1·50)	< B	112 (0·3)	**1·48** (1·21–1·81)	< B	0·35
Temporal arteritis	15 (0·01)	**1·78** (1·02–3·09)	0·042	10 (0·01)	1·42 (0·73–2·77)	0·30	5 (0·01)	**3·50** (1·26–9·77)	0·017	0·15
Granulomatosis with polyangiitis[b]	48 (0·04)	**1·59** (1·17–2·16)	0·003	31 (0·04)	**1·52** (1·04–2·22)	0·030	17 (0·05)	**1·75** (1·04–2·93)	0·035	0·67
Polymyalgia rheumatica	331 (0·3)	**1·34** (1·19–1·50)	< B	240 (0·3)	**1·32** (1·15–1·51)	< B	91 (0·3)	**1·39** (1·11–1·73)	0·004	0·70
Neuromuscular	458 (0·4)	**1·26** (1·15–1·39)	< B	362 (0·5)	**1·26** (1·13–1·41)	< B	96 (0·3)	**1·27** (1·03–1·57)	0·027	0·95
Multiple sclerosis	388 (0·4)	**1·28** (1·15–1·42)	< B	316 (0·5)	**1·26** (1·12–1·42)	< B	72 (0·2)	**1·34** (1·05–1·72)	0·019	0·65
Guillain–Barré syndrome	32 (0·03)	1·26 (0·87–1·82)	0·22	18 (0·03)	1·41 (0·86–2·32)	0·17	14 (0·04)	1·11 (0·64–1·93)	0·71	0·53
Myasthenia gravis	38 (0·04)	1·09 (0·78–1·53)	0·61	28 (0·04)	1·11 (0·75–1·64)	0·60	10 (0·03)	1·04 (0·54–2·00)	0·91	0·86
Endocrine	2831 (2·7)	**1·14** (1·10–1·19)	< B	2002 (2·9)	**1·12** (1·07–1·17)	< B	829 (2·3)	**1·21** (1·12–1·30)	< B	0·088
Addison disease	50 (0·05)	**1·43** (1·06–1·93)	0·018	28 (0·04)	1·16 (0·78–1·71)	0·46	22 (0·1)	**2·04** (1·29–3·23)	0·002	0·066
Hashimoto disease	343 (0·3)	**1·36** (1·21–1·52)	< B	323 (0·5)	**1·38** (1·22–1·55)	< B	20 (0·1)	1·16 (0·73–1·84)	0·54	0·48
Graves disease	1027 (1·0)	**1·18** (1·10–1·25)	< B	910 (1·3)	**1·15** (1·07–1·23)	< B	117 (0·3)	**1·39** (1·14–1·68)	0·001	0·079
Diabetes mellitus type 1	1511 (1·4)	**1·08** (1·03–1·14)	0·003	825 (1·2)	1·02 (0·95–1·10)	0·57	686 (1·9)	**1·17** (1·08–1·27)	< B	0·012
Haematological	66 (0·1)	**1·53** (1·18–1·99)	0·001	43 (0·1)	**1·40** (1·02–1·93)	0·038	23 (0·1)	**1·86** (1·19–2·90)	0·007	0·32
Autoimmune haemolytic anaemia	30 (0·03)	**1·88** (1·27–2·78)	0·002	17 (0·02)	**1·72** (1·03–2·88)	0·040	13 (0·04)	**2·14** (1·18–3·91)	0·013	0·58
Antiphospholipid syndrome	12 (0·01)	1·75 (0·95–3·23)	0·074	11 (0·02)	1·89 (0·99–3·61)	0·053	1 (0·003)	0·95 (0·12–7·42)	0·96	0·53
Pernicious anaemia	25 (0·02)	1·23 (0·81–1·87)	0·32	15 (0·02)	1·00 (0·59–1·71)	0·99	10 (0·03)	1·88 (0·95–3·70)	0·068	0·15
Hepatic	68 (0·1)	0·93 (0·73–1·20)	0·58	58 (0·1)	0·91 (0·69–1·19)	0·48	10 (0·03)	1·09 (0·57–2·10)	0·79	0·61
Primary biliary cholangitis[c]	34 (0·03)	1·03 (0·72–1·46)	0·89	29 (0·04)	0·95 (0·65–1·39)	0·79	5 (0·01)	1·90 (0·73–4·96)	0·19	0·12
Autoimmune hepatitis	35 (0·03)	0·84 (0·59–1·18)	0·31	30 (0·04)	0·86 (0·59–1·24)	0·42	5 (0·01)	0·73 (0·30–1·82)	0·51	0·76

CI, confidence interval; OR, odds ratio. Bold indicates P-values < 0·05. B (green shading) indicates statistical significance (P < 0·000427) after Bonferroni correction. Yellow shading indicates statistical difference in ORs between men and women (P < 0·00128) after Bonferroni correction. [a]Adjusted for sex, age and education. [b]Previously known as Wegener's granulomatosis. [c]Previously known as primary biliary cirrhosis.

Table 3 The number of autoimmune diseases in patients with atopic dermatitis (AD) and the overall association with AD (n = 104 832)

No. of autoimmune diseases	Cases n (%)	AD (all) OR (95% CI)	AD (women) OR (95% CI)	AD (men) OR (95% CI)
0	90 123 (86·0)	1·00 (reference)	1·00 (reference)	1·00 (reference)
1	12 840 (12·2)	1·89 (1·85–1·93)	1·82 (1·77–1·86)	2·07 (2·00–2·14)
2	1650 (1·6)	2·57 (2·43–2·71)	2·37 (2·22–2·53)	3·17 (2·87–3·51)
3–5	219 (0·2)	3·33 (2·86–3·87)	3·14 (2·63–3·74)	3·96 (2·92–5·37)

A strength of our study is the use of Swedish civic registration numbers and linkage of high-quality registers covering the entire Swedish population. The large number of people allows for robust estimates. Among patients with AD, 80% had received their diagnosis at a dermatology department, which reduces the risk of misclassification. The population-based design allows for generalization to other populations with similar genetic and environmental backgrounds and prevalence of autoimmune diseases.

The study also has several limitations. Unfortunately, the dataset did not allow us to explore the temporal relationship between AD and autoimmune diseases. Moreover, we did not include diagnoses from primary-care visits. Patients with AD diagnosed by general practitioners or not seeking healthcare at all may have been misclassified as controls. The majority of autoimmune diagnoses in the study were assessed by specialists within specific medical disciplines, but we recognize that the NPR may have low sensitivity for certain autoimmune diseases, such as Hashimoto disease, pernicious anaemia and some common skin disorders managed in primary care (e.g. chronic urticaria).

We are also aware that a diagnosis of alopecia areata in ICD 9th Revision may have included other types of alopecia. Furthermore, we cannot exclude selection bias, where one diagnosis may lead to another, which could be a problem in patients seen more frequently in the healthcare system. Another limitation is that the material did not allow for stratification of AD by disease severity. Misclassification bias for some skin diseases may also be a problem among dermatologists. We propose that difficulties in detecting comorbidity of psoriasis in AD may have delayed first diagnosis of psoriasis among patients with AD compared with those without AD. Psoriasis and AD share some clinical characteristics, especially in chronic AD stages,[21] and some exhibit intermediate morphology.[22] We adjusted for hereditary status in the majority of patients, but adjustment for smoking was possible only in a subpopulation of women. We are also aware that the Bonferroni-corrected estimates may have led to type II errors. Therefore, P-values are given in Table 2, with the common critical value of 5% for significance.

In conclusion, AD was significantly associated with several autoimmune diseases, especially disorders involving the skin, the gastrointestinal tract and/or connective tissue, and the association grew stronger with multiple autoimmune diseases in a dose–response-dependent manner. Greater awareness of screening, and monitoring of comorbidities may relieve the disease burden in patients with AD and may give deeper insight into its pathogenesis. Further studies are needed, especially to identify subsets of patients with AD at higher risk for autoimmune disease, and to explore temporal aspects and whether AD severity and treatment may affect these associations.

References

1 Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**:1109–22.
2 Bylund S, von Kobyletzki LB, Svalstedt M, Svensson Å. Prevalence and incidence of atopic dermatitis: a systematic review. *Acta Derm Venereol* 2020; **100**:adv00160.
3 Bieber T. Atopic dermatitis. N *Engl J Med* 2008; **358**:1483–94.
4 Slagor RM, Nørreslet LB, Ebbehøj NE *et al.* Atopic dermatitis is associated with increased use of social benefits: a register-based cohort study. *J Eur Acad Dermatol Venereol* 2020; **34**:549–57.
5 Drucker AM, Wang AR, Li WQ *et al.* The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol* 2017; **137**:26–30.
6 Silverberg JI. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol* 2019; **123**:144–51.
7 Brunner PM, Silverberg JI, Guttman-Yassky E *et al.* Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol* 2017; **137**:18–25.
8 Ivert LU, Johansson EK, Dal H *et al.* Association between atopic dermatitis and cardiovascular disease: a nationwide register-based case–control study from Sweden. *Acta Derm Venereol* 2019; **99**:865–70.
9 Paller A, Jaworski JC, Simpson EL *et al.* Major comorbidities of atopic dermatitis: beyond allergic disorders. *Am J Clin Dermatol* 2018; **19**:821–38.
10 Andersen YM, Egeberg A, Gislason GH *et al.* Autoimmune diseases in adults with atopic dermatitis. *J Am Acad Dermatol* 2017; **76**:274–80.
11 Cipriani F, Marzatico A, Ricci G. Autoimmune diseases involving skin and intestinal mucosa are more frequent in adolescents and young adults suffering from atopic dermatitis. *J Dermatol* 2017; **44**:1341–8.
12 Statistics Sweden. Longitudinal Integration Database for Health Insurance and Labour Market Studies. Available at: http://www.scb.se/LISA (last accessed 21 October 2020).
13 Narla S, Silverberg JI. Association between atopic dermatitis and autoimmune disorders in US adults and children: a cross-sectional study. *J Am Acad Dermatol* 2019; **80**:382–9.

14 Schmitt J, Schwarz K, Baurecht H *et al.* Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. *J Allergy Clin Immunol* 2016; **137**:130–6.
15 Mohan GC, Silverberg JI. Association of vitiligo and alopecia areata with atopic dermatitis: systematic review and meta-analysis. *JAMA Dermatol* 2015; **151**:522–8.
16 Ghazanfar MN, Kibsgaard L, Thomsen SF, Vestergaard C. Risk of comorbidities in patients diagnosed with chronic urticaria: a nationwide registry-study. *World Allergy Organ J* 2020; **13**:100097.
17 Monteiro L, Souza-Machado A, Menezes C, Melo A. Association between allergies and multiple sclerosis: a systematic review and meta-analysis. *Acta Neurol Scand* 2011; **123**:1–7.
18 Rubtsova K, Marrack P, Rubtsov AV. Sexual dimorphism in autoimmunity. *J Clin Invest* 2015; **125**:2187–93.
19 Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. *Front Neuroendocrinol* 2014; **35**:347–69.
20 Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol* 2016; **75**:681–7.
21 Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? *Curr Opin Immunol* 2017; **48**:68–73.
22 Barrett M, Luu M. Differential diagnosis of atopic dermatitis. *Immunol Allergy Clin North Am* 2017; **37**:11–34.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 International Classification of Diseases codes used to identify atopic dermatitis and autoimmune diseases.

Powerpoint S1 Journal Club Slide Set.

Video S1 Author video.