Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study

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Background: Little is known about the risk and predictors of autoimmune diseases in children and adults.

Objective: To determine the prevalence, predictors, and excess costs of autoimmune disease in atopic dermatitis (AD) patients.

Methods: Cross-sectional study of the 2002-2012 National Inpatient Sample, which includes a ~20% sample of all US hospitalizations (n = 87,053,155 adults and children).

Results: The prevalence of autoimmune disease was higher in adults with AD (7.9%, 95% confidence interval [95% CI] 7.3-8.5%) than without AD (5.7%, 95% CI 5.7%-5.8%) and higher in children with AD (2.0%, 95% CI 1.7%-2.3%) than without AD (1.0%, 95% CI 0.9%-1.1%). In multivariable logistic regression models controlling for sociodemographics, adult (adjusted odds ratio 1.45, 95% CI 1.32-1.58) and pediatric (adjusted odds ratio 2.08, 95% CI 1.73-2.50) AD were associated with any autoimmune disorder. In particular, AD was associated with 18 of 32 autoimmune disorders examined in adults and 13 of 24 examined in children, including disorders of the skin, endocrine, gastrointestinal, hematologic, and musculoskeletal systems. AD patients hospitalized with any autoimmune disorder had a higher cost of inpatient care, with $2.5-$50 million excess annual costs.

Conclusions: Adults and children with AD had increased cutaneous and extracutaneous autoimmune disorders, which were associated with a considerable cost burden. (J Am Acad Dermatol 2019;80:382-9.)

Key words: atopic dermatitis; autoimmune; hospitalization; inpatient; systemic disorders.

Atopic dermatitis (AD) is a chronic pruritic skin condition affecting ~7%-10% of US adults,[1-3] and 13% of US children.[4] Proposed mechanisms for AD include epidermal disruption, decreased cutaneous antimicrobial peptide expression, aberrant toll-like receptor signaling, and dysfunction of the innate immune system.[5-7] These might contribute to the development of other inflammatory disorders.

Previous studies found associations between AD and autoimmune conditions, eg, alopecia areata (AA) and vitiligo.[8,9] These studies were based on a mix of self-reported and physician-diagnosed AD and autoimmune conditions. Some of these associations might be attributed to detection bias of other skin disorders among AD patients seeking care for dermatitis. Recent studies from Germany and Denmark suggested that AD in adults is also associated with extracutaneous autoimmune disorders, eg, rheumatoid arthritis (RA),[10,11] and other autoimmune disorders.[12] We sought to confirm these associations among US adults. Further, we hypothesized that childhood AD is associated with a higher rate of autoimmune disease. We also hypothesized that autoimmune comorbidities contribute toward substantial excess costs in AD patients. In this cross-

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sectional study, we examined whether AD is associated with increased autoimmune disease in adults and children. Further, we examined the predictors, excess costs of autoimmune disease in AD.

METHODS

Study design

A cross-sectional study of the 2002-2012 Nationwide Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project from the Agency for Healthcare Research and Quality was performed. Each year of NIS contains a ~20% stratified representative cross-sectional sample of US hospitalizations. Sample weights factored the sampling design of US hospitals, enabling representative estimates of hospital discharges across the United States. All data were deidentified. No attempts were made to identify any individuals in the database. All parties with access to the NIS were compliant with the formal data use agreement. The study was approved by the institutional review board at Northwestern University.

CAPSULE SUMMARY

- The present study found increased risk for autoimmune disorders of the skin, endocrine, gastrointestinal, hematologic, and musculoskeletal systems in both adults and children with atopic dermatitis, with a predilection for adult females, young age, Asian race/ethnicity in children, and those without asthma.
- Clinicians should consider increased screening for autoimmune disorders in atopic dermatitis patients.

AD and autoimmune disorders

The database was searched for primary and secondary diagnoses of AD (exposure) by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. A previous study validated use of the discharge diagnosis code 691.8 in the inpatient setting for the study of AD.[13] Autoimmune disorders (outcomes) were identified using ICD-9-CM codes or clinical classification software codes.

Statistical analysis

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC). Analyses were performed by using SURVEY procedures. The unit of analysis was an individual hospitalization. All statistical models included discharge trend weights; sample strata that accounted for a hospital's census region or division, ownership/control, location, teaching status, and number of beds provided by the NIS; and clustering by individual hospital. Weighted frequency and prevalence and the 95% confidence intervals (CIs) of either a primary or secondary diagnosis of an autoimmune disorder was determined among patients with and without a primary or secondary diagnosis of AD. Summary statistics were generated for each disorder, including frequency, prevalence, and 95% CI. The hospital cost for inpatient care was calculated on the basis of the total charge of the hospitalization and the cost-to-charge ration estimated by the Healthcare Cost and Utilization Project. Costs were adjusted for inflation to 2014 according to the Consumer Price Index from the US Bureau of Labor Statistics. Excess length of stay (LOS) and cost of care for an autoimmune disorder indirectly related to AD were estimated with the following formula: ([prevalence of that autoimmune disorder in patients with AD]/[prevalence of that disorder in patients without AD]) × (total hospitalization annual days or costs for that disorder in patients with AD). Sensitivity analyses were performed for excess LOS and costs for AD or eczema.

Survey logistic regression models were used to determine the association of AD (exposure, yes or no) and autoimmune conditions (outcomes, yes or no). Crude odds ratios (ORs) and 95% CIs were estimated. Two different multivariate models were calculated. Age (continuous), sex (male, female), race (white, nonwhite) and insurance status (yes, no) were included as covariables in model 1. Asthma and hay fever (yes, no) were included as covariables in model 2. Clinical classification software codes 128 and ICD-9-CM codes 477.0-477.9 were used to identify asthma and hay fever, respectively. To determine the associations of autoimmune disorders in inpatients with AD, multivariable logistic regression models were constructed with any autoimmune disorder as the outcome and stepwise selection (α = 0.10) from multiple covariables, including age, sex, race/ethnicity, household income, insurance coverage, number of chronic conditions, asthma, and hay fever.

All statistical models included discharge trend weights; sample strata that accounted for the hospital's census region or division, ownership/control, location, teaching status, and number of beds provided by the NIS; and clustering by individual hospital. Comorbidities with a frequency of <5 in each cell were excluded from analyses. A 2-sided P value <.05 was considered statistically significant.

Abbreviations used:

AA:	alopecia areata
AD:	atopic dermatitis
CI:	confidence interval
ICD-9-CM:	International Classification of Disease, Ninth Edition, Clinical Modification
LOS:	length of stay
MS:	multiple sclerosis
NIS:	Nationwide Inpatient Sample
OR:	odds ratio
RA:	rheumatoid arthritis
T_H1:	T cell helper 1
UC:	ulcerative colitis

RESULTS

Population characteristics

There were 87,053,155 adult and pediatric discharges captured in the NIS during 2002-2012, with 9290 adult and 10,196 pediatric admissions with AD (weighted frequency 44,605 and 48,496, respectively). Adults and children hospitalized with AD versus without AD were more likely to be male and nonwhite and have asthma; children hospitalized with AD were also more likely to have hay fever.

Autoimmune disorders in adults

Among hospitalized adults, AD was significantly associated with 18 of 32 autoimmune disorders examined in bivariable survey logistic regression models (Fig 1). In multivariable models controlling for age, race/ethnicity, sex, and insurance status, AD was significantly associated with any autoimmune disorder (adjusted OR [aOR] 1.45, 95% CI 1.32-1.58). Cutaneous disorders with the largest effect sizes included AA (aOR 37.29, 95% CI 13.96-99.59), vitiligo (aOR 11.47, 95% CI 6.64-19.80), and chronic urticaria (aOR 9.15, 95% CI 6.28-13.34). AD was also associated with Hashimoto disease, general thyroiditis, nonalcoholic steatohepatitis, chronic liver disease, eosinophilic esophagitis, pernicious anemia, Crohn's disease, ulcerative colitis (UC), celiac disease, ankylosing spondylitis, RA, and erythema nodosum (Fig 1). The majority of the associations in bivariable models remained significant in multivariable models that controlled for asthma and hay fever, except for RA and autoimmune disease not elsewhere classified.

Thyroid disorders, nonalcoholic steatohepatitis, chronic liver disease, systemic lupus erythematosus, erythema nodosum, AA, chronic urticaria, and vitiligo were associated with AD in bivariable models of adult ages <50 years and ≥50 years (Table I). Multiple sclerosis (MS), pernicious anemia, celiac disease, and Sjogren syndrome were only associated with AD in adults ≥50 years. In contrast, Crohn's disease, UC, eosinophilic esophagitis, ankylosing spondylitis, RA, and autoimmune diseases not elsewhere classified were only associated with AD in adults age <50 years.

Autoimmune disorders in children

Among hospitalized children, AD was significantly associated with 13 of 24 autoimmune disorders examined in bivariable survey logistic regression models (Fig 1). In multivariable models, AD was significantly associated with any autoimmune disorder (aOR 2.08, 95% CI 1.73-2.50). The autoimmune comorbidities with the strongest effects were AA (aOR 23.58, 95% CI 7.34-75.76), vitiligo (aOR 9.40, 95% CI 3.05-28.99), scleroderma (aOR 9.35, 95% CI 2.97-29.44), and chronic urticaria (aOR 7.76, 95% CI 5.23-11.49). AD was also associated with a higher odds of thrombotic thrombocytopenic purpura, pernicious anemia, eosinophilic esophagitis, nonalcoholic steatohepatitis, granulomatosis with polyangiitis, Kawasaki disease, and unspecified autoimmune disease (Fig 1). Most of the significant associations in bivariable models remained significant in multivariable models that controlled for asthma and hay fever, except for UC.

Associations of autoimmune disorders in AD

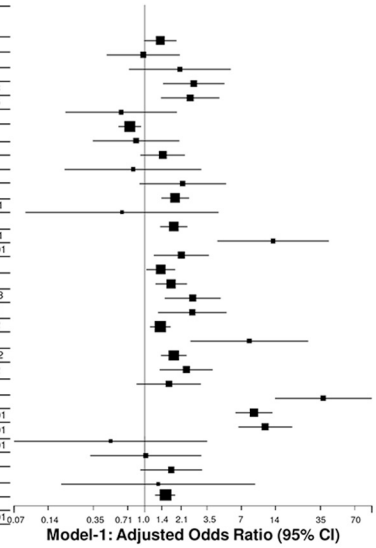
In multivariable models with stepwise selection, any autoimmune disorder in adult inpatients with AD was associated with female sex (aOR 1.57, 95% CI 1.46-1.68) and increasing number of chronic conditions (2-5, aOR 7.23, 95% CI 4.88-10.73; ≥6, aOR 16.01, 95% CI 10.78-23.77) but inversely associated with increasing age (40-59 years, aOR 0.69, 95% CI 0.63-0.76; 60-79 years, aOR 0.58, 95% CI 0.52-0.64; ≥80 years aOR 0.30, 95% CI 0.27-0.35), Asian ethnicity (aOR 0.67, 95% CI 0.55-0.81), lower income quartile (first income quartile, aOR 0.76, 95% CI 0.69-0.84) and asthma (aOR 0.75, 95% CI 0.69-0.81) (Table II).

In multivariable models with stepwise selection, predictors of any autoimmune disorder in pediatric patients with AD included increasing age (2-5 years, aOR 1.43, 95% CI 1.21-1.70; 6-11 years, aOR 2.04, 95% CI 1.70-2.44; 12-17 years, aOR 2.83, 95% CI 2.37-3.38), increasing number of chronic conditions (2-5, aOR 17.73, 95% CI 13.05-24.09; ≥6, aOR 30.16, 95% CI 21.45-42.42), third income quartile (aOR 1.32, 95% CI 1.10-1.58), and Asian ethnicity (aOR 1.61, 95% CI 1.28-2.02); any autoimmune disorders in pediatric patients with AD were inversely associated with not being insured (aOR 0.68, 95% CI 0.51-0.89), being of other (aOR 0.69, 95% CI 0.51-0.94) or black (aOR 0.70, 95% CI 0.60-0.83) race, and asthma (aOR 0.30, 95% CI 0.26-0.34) (Table II).

A

Associations between AD and autoimmune disorders in US adults

Autoimmune Disorder	Inpatient diagnosis of AD									
	No		Yes							
	Wtd Freq	% Prev [95% CI]	Wtd freq	% Prev [95% CI]	Crude OR [95% CI]	P	Model-1* Adj OR [95% CI]	P	Model-2** Adj OR [95% CI]	P
Multiple Sclerosis	1,377,472	0.4 [0.4-0.4]	238	0.5 [0.4-0.7]	1.33 [1.00-1.78]	.05	1.37 [0.99-1.91]	.059	1.31 [0.98-1.75]	.07
Myasthenia Gravis	338,262	0.1 [0.1-0.1]	38	0.1 [0.0-0.1]	0.88 [0.44-1.74]	.71	0.97 [0.46-2.03]	.93	0.82 [0.41-1.62]	.56
Polymyositis	104,370	0.03 [0.03-0.03]	29	0.1 [0.0-0.1]	2.13 [0.85-5.33]	.11	2.04 [0.72-5.73]	.18	2.05 [0.82-5.13]	.13
Hashimoto's disease	197,975	0.1 [0.1-0.1]	65	0.1 [0.1-0.2]	2.56 [1.49-4.39]	.0006	2.70 [1.45-5.04]	.002	2.29 [1.33-3.95]	.003
Thyroiditis in general	233,015	0.1 [0.1-0.1]	71	0.2 [0.1-0.2]	2.34 [1.39-3.95]	.001	2.51 [1.39-4.54]	.002	2.12 [1.26-3.59]	.005
Giant Cell Arteritis	235,511	0.1 [0.1-0.1]	18	0.04 [0.00-0.08]	0.58 [0.22-1.54]	.27	0.62 [0.20-1.92]	.41	0.58 [0.22-1.55]	.28
Type 1 Diabetes Mellitus	4,882,314	1.4 [1.4-1.5]	519	1.2 [0.9-1.4]	0.83 [0.68-1.01]	.07	0.74 [0.60-0.93]	.008	0.83 [0.68-1.02]	.07
Chronic Glomerulonephritis	255,102	0.1 [0.1-0.1]	25	0.1 [0.0-0.1]	0.74 [0.31-1.80]	.51	0.84 [0.35-2.02]	.69	0.77 [0.32-1.86]	.56
Polyarteritis Nodosa	723,502	0.2 [0.2-0.2]	138	0.3 [0.2-0.4]	1.47 [0.98-2.21]	.06	1.44 [0.92-2.26]	.11	1.09 [0.72-1.64]	.69
Granulomatosis with polyangiitis	119,257	0.03 [0.03-0.04]	19	0.04 [0.00-0.08]	1.26 [0.49-3.27]	.63	0.79 [0.20-3.16]	.74	1.05 [0.39-2.79]	.92
Primary Biliary Cirrhosis	112,520	0.03 [0.03-0.03]	24	0.05 [0.01-0.10]	1.64 [0.69-3.92]	.27	2.16 [0.90-5.21]	.09	1.62 [0.67-3.91]	.28
Non-alcoholic Steatohepatitis	1,320,633	0.4 [0.4-0.4]	319	0.7 [0.5-0.9]	1.86 [1.44-2.41]	<.0001	1.85 [1.40-2.45]	<.0001	1.66 [1.28-2.14]	.0001
Autoimmune hepatitis	69,147	0.02 [0.02-0.02]	≤10	0.02 [0.00-0.05]	1.12 [0.28-4.42]	.87	0.63 [0.09-4.46]	.64	1.07 [0.27-4.28]	.92
Chronic Liver Disease	1,376,078	0.4 [0.4-0.4]	327	0.7 [0.5-0.9]	1.84 [1.43-2.37]	<.0001	1.80 [1.37-2.38]	<.0001	1.64 [1.27-2.11]	.0001
Eosinophilic Esophagitis	9,201	0.003 [0.003-0.003]	20	0.04 [0.00-0.09]	16.71 [6.29-44.42]	<.0001	13.47 [4.35-41.76]	<.0001	12.24 [4.60-32.57]	<.0001
Pernicious Anemia	352,795	0.1 [0.1-0.1]	86	0.2 [0.1-0.3]	1.88 [1.16-3.06]	.01	2.10 [1.20-3.66]	.009	1.88 [1.16-3.05]	.01
Crohn's Disease	1,700,100	0.5 [0.5-0.5]	308	0.7 [0.5-0.9]	1.40 [1.08-1.81]	.01	1.38 [1.03-1.85]	.03	1.36 [1.05-1.76]	.02
Ulcerative Colitis	969,355	0.3 [0.3-0.3]	215	0.5 [0.3-0.6]	1.74 [1.31-2.31]	.0001	1.71 [1.25-2.35]	.0009	1.69 [1.27-2.25]	.0003
Celiac Disease	216,946	0.1 [0.1-0.1]	71	0.2 [0.1-0.2]	2.54 [1.54-4.20]	.0003	2.64 [1.50-4.66]	.0008	2.28 [1.38-3.79]	.001
Ankylosing Spondylitis	134,114	0.04 [0.04-0.04]	47	0.1 [0.0-0.2]	2.70 [1.45-5.05]	.0018	2.63 [1.31-5.27]	.007	2.69 [1.44-5.02]	.002
Rheumatoid Arthritis	4,428,539	1.3 [1.3-1.3]	688	1.5 [1.2-1.8]	1.22 [1.00-1.48]	.046	1.37 [1.11-1.69]	.004	1.10 [0.91-1.35]	.33
Erythema nodosum	21,047	0.01 [0.01-0.01]	22	0.05 [0.00-0.10]	8.18 [2.88-23.19]	<.0001	8.32 [2.51-27.56]	.0005	7.34 [2.58-20.87]	.0002
Systemic Lupus Erythematosus	1,718,768	0.5 [0.5-0.5]	370	0.8 [0.6-1.0]	1.68 [1.31-2.15]	<.0001	1.80 [1.38-2.34]	<.0001	1.48 [1.15-1.89]	.002
Scleroderma	333,637	0.1 [0.1-0.1]	82	0.2 [0.1-0.3]	1.90 [1.13-3.20]	.016	2.32 [1.35-3.98]	.002	1.87 [1.11-3.16]	.02
Sjogren's Syndrome	317,106	0.1 [0.1-0.1]	63	0.1 [0.1-0.2]	1.55 [0.88-2.73]	.13	1.63 [0.85-3.13]	.15	1.33 [0.75-2.36]	.32
Alopecia Areata	4,733	0.001 [0.001-0.002]	34	0.1 [0.0-0.1]	55.73 [26.49-117.24]	<.0001	37.29 [13.96-99.59]	<.0001	44.43 [21.00-94.00]	<.0001
Chronic Urticaria	133,951	0.04 [0.04-0.04]	163	0.4 [0.2-0.5]	9.39 [6.74-13.09]	<.0001	9.15 [6.28-13.34]	<.0001	8.10 [5.81-11.29]	<.0001
Vitiligo	52,847	0.02 [0.01-0.02]	83	0.2 [0.1-0.3]	12.15 [7.27-20.31]	<.0001	11.47 [6.64-19.80]	<.0001	11.16 [6.68-18.64]	<.0001
Unspecified diffuse connective tissue disease	99,646	0.03 [0.03-0.03]	≤10	0.02 [0.00-0.05]	0.77 [0.19-3.10]	.72	0.50 [0.07-3.54]	.49	0.69 [0.17-2.77]	.60
Autoimmune Hemolytic Anemia	136,619	0.04 [0.04-0.04]	14	0.03 [0.00-0.07]	0.83 [0.27-2.52]	.74	1.02 [0.33-3.14]	.98	0.85 [0.27-2.62]	.77
Immune Thrombocytopenic Purpura	340,212	0.1 [0.1-0.1]	69	0.2 [0.1-0.2]	1.57 [0.87-2.83]	.14	1.71 [0.91-3.19]	.09	1.57 [0.86-2.84]	.14
Autoimmune disease, NEC	36,926	0.01 [0.01-0.01]	15	0.03 [0.00-0.07]	3.09 [1.00-9.52]	.0497	1.31 [0.18-9.37]	.79	2.88 [0.94-8.90]	.07
Any autoimmune disease	19,617,655	5.7 [5.7-5.8]	3,506	7.9 [7.3-8.5]	1.41 [1.30-1.53]	<.0001	1.45 [1.32-1.58]	<.0001	1.34 [1.23-1.45]	<.0001



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Associations between AD and autoimmune disorders in US children

Autoimmune Disorder	Inpatient diagnosis of AD									
	No		Yes							
	Wtd freq	% Prev [95% CI]	Wtd freq	% Prev [95% CI]	Crude OR [95% CI]	P	Model-1* Adj OR [95% CI]	P	Model-2** Adj OR [95% CI]	P
Hashimoto's disease	6,715	0.01 [0.01-0.01]	≤ 10	0.02 [0.00-0.05]	2.17 [0.55-8.64]	.3	1.84 [0.26-13.08]	.5	1.20 [0.30-4.78]	.8
Thyroiditis in general	7,621	0.01 [0.01-0.01]	≤ 10	0.02 [0.00-0.05]	1.91 [0.48-7.63]	.4	1.61 [0.23-11.44]	.6	1.10 [0.28-4.39]	.9
Kawasaki disease	53,730	0.1 [0.1-0.1]	143	0.3 [0.2-0.4]	3.77 [2.53-5.61]	<.0001	3.55 [2.32-5.44]	<.0001	3.69 [2.48-5.48]	<.0001
Type 1 Diabetes Mellitus	362,705	0.5 [0.5-0.6]	217	0.4 [0.3-0.6]	0.85 [0.59-1.21]	.4	0.94 [0.63-1.39]	.7	0.68 [0.48-0.97]	.03
Polyarteritis Nodosa	1,384	0.002 [0.002-0.003]	≤10	0.01 [0.00-0.03]	5.13 [0.71-37.01]	.1	5.15 [0.70-37.61]	.1	2.40 [0.31-18.56]	.4
Granulomatosis with polyangiitis	2,342	0.003 [0.003-0.004]	≤10	0.03 [0.00-0.05]	6.04 [1.59-22.97]	.01	7.93 [2.15-29.26]	.002	4.10 [1.08-15.56]	.04
Primary Biliary Cirrhosis	1,919	0.003 [0.002-0.004]	≤10	0.01 [0.00-0.03]	3.86 [0.55-27.30]	.2	3.88 [0.56-27.09]	.2	3.62 [0.48-27.09]	.2
Non-alcoholic Steatohepatitis	25,174	0.04 [0.03-0.04]	56	0.12 [0.05-0.18]	3.15 [1.88-5.26]	<.0001	2.81 [1.65-4.78]	.0001	2.11 [1.24-3.59]	.01
Chronic Liver Disease	26,465	0.04 [0.03-0.04]	56	0.1 [0.1-0.2]	2.99 [1.79-5.00]	<.0001	2.66 [1.56-4.52]	.0003	2.01 [1.19-3.42]	.01
Eosinophilic Esophagitis	5,580	0.008 [0.006-0.010]	85	0.2 [0.1-0.3]	21.50 [13.87-33.30]	<.0001	23.11 [14.85-35.99]	<.0001	6.55 [4.12-10.41]	<.0001
Pernicious Anemia	193	0.0003 [0.0002-0.0004]	≤10	0.01 [0.00-0.03]	37.44 [5.10-275.31]	.0004	51.21 [7.19-364.80]	<.0001	28.61 [4.19-195.34]	.001
Crohn's Disease	65,941	0.1 [0.1-0.1]	52	0.1 [0.0-0.2]	1.12 [0.61-2.03]	.7	1.32 [0.68-2.56]	.4	0.85 [0.46-1.55]	.6
Ulcerative Colitis	41,617	0.06 [0.05-0.07]	60	0.12 [0.05-0.20]	2.05 [1.13-3.72]	.02	1.95 [0.90-4.20]	.1	1.76 [0.97-3.20]	.06
Celiac Disease	12,931	0.02 [0.02-0.02]	19	0.04 [0.00-0.09]	2.09 [0.63-6.89]	.2	2.90 [0.88-9.54]	.1	1.04 [0.31-3.46]	.9
Rheumatoid Arthritis	24,395	0.04 [0.03-0.04]	24	0.05 [0.01-0.09]	1.37 [0.57-3.30]	.5	1.09 [0.35-3.40]	.9	0.80 [0.33-1.94]	.6
Systemic Lupus Erythematosus	35,522	0.05 [0.04-0.06]	44	0.09 [0.03-0.15]	1.74 [0.87-3.47]	.1	1.27 [0.58-2.80]	.5	1.56 [0.78-3.12]	.001
Scleroderma	2,564	0.004 [0.003-0.005]	19	0.04 [0.00-0.08]	10.57 [3.94-28.35]	<.0001	9.35 [2.97-29.44]	.0001	8.31 [2.93-23.60]	<.0001
Alopecia Areata	819	0.001 [0.001-0.001]	19	0.04 [0.00-0.08]	32.74 [12.05-88.92]	<.0001	23.58 [7.34-75.76]	<.0001	15.45 [5.39-44.28]	<.0001
Chronic Urticaria	24,122	0.04 [0.03-0.04]	146	0.3 [0.2-0.4]	8.61 [5.99-12.37]	<.0001	7.76 [5.23-11.49]	<.0001	4.22 [2.93-6.07]	<.0001
Vitiligo	2,124	0.003 [0.003-0.004]	19	0.04 [0.00-0.08]	12.63 [4.79-33.29]	<.0001	9.40 [3.05-28.99]	<.0001	5.53 [2.02-15.19]	.001
Autoimmune Hemolytic Anemia	8,236	0.01 [0.01-0.01]	14	0.03 [0.00-0.06]	2.47 [0.79-7.69]	.1	1.77 [0.44-7.04]	.4	1.96 [0.62-6.18]	.2
Immune Thrombocytopenic Purpura	30,511	0.04 [0.04-0.05]	32	0.07 [0.02-0.12]	1.51 [0.72-3.17]	.3	1.61 [0.76-3.39]	.2	1.35 [0.64-2.84]	.4
Thrombotic Thrombocytopenic Purpura	1,787	0.003 [0.002-0.003]	≤10	0.02 [0.00-0.05]	8.10 [1.97-33.27]	.004	8.50 [2.05-35.29]	.003	6.80 [1.58-29.26]	.01
Autoimmune disease, NEC	3,135	0.005 [0.004-0.005]	23	0.05 [0.01-0.09]	10.40 [4.32-25.02]	<.0001	7.18 [2.29-22.55]	.001	8.11 [3.31-19.87]	<.0001
Any autoimmune disease	697,171	1.0 [0.9-1.1]	981	2.0 [1.7-2.3]	2.01 [1.70-2.38]	<.0001	2.08 [1.73-2.50]	<.0001	1.55 [1.32-1.82]	<.0001

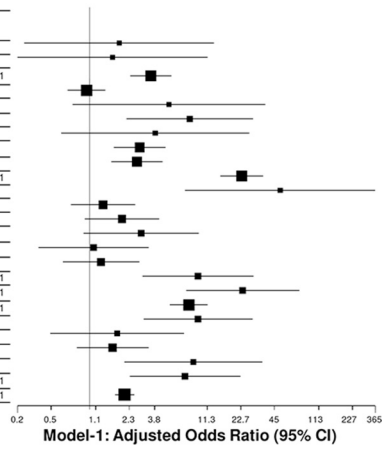

Fig 1. Association between AD and autoimmune disorders among adults (**A**) and children (**B**). Survey logistic regression models were constructed with AD as the exposure and the respective autoimmune disorder as the outcome. Multivariable model 1 included age, sex, race/ethnicity, and insurance status as covariables. Multivariable model 2 include a diagnosis of asthma or hay fever as covariables. Adj ORs and 95% CIs were estimated. Forest plots of the adj ORs and 95% CIs from model 1 are presented. *AD*, Atopic dermatitis; *Adj*, adjusted; *CI*, confidence interval; *Freq*, frequency; *OR*, odds ratio; *Wtd*, weighted.

LOS and cost of care

The geometric mean LOS for AD patients with autoimmune disorders versus those without an autoimmune disorders was significantly higher in children (3.4 days, 95% CI 2.9-3.8 days vs 2.6 days, 95% CI 2.6-2.7 days; P = .0003) but not adults (4.0 days, 95% CI 3.8-4.2 days vs 4.0 days, 95% CI 3.9-4.1 days; P = .9489). LOS of AD patients with an autoimmune comorbidity versus without was higher for 17 of 32 autoimmune disorders in adults and 15 of 24 disorders in children.

The geometric mean cost of inpatient care for AD patients with versus without an autoimmune disorder was significantly higher in adults ($7546 [95% CI $7070-$8054] vs $6943 [95% CI $6731-$7162]; P = .0037) and children ($6022 [95% CI $5080-$7140] vs $3815 [95% CI $3621-$4020]; P < .0001). Cost of inpatient care for AD patients with versus without an autoimmune comorbidity was higher for 26 of 32 autoimmune disorders in adults and 17 of 24 disorders in children. Excess annual costs of hospital care attributed to autoimmune disorders among

Table I. Summary of comorbid autoimmune conditions in adults with atopic dermatitis stratified by age

Autoimmune comorbidity	Adults	Age, y <50	Age, y ≥50	Children
Multiple sclerosis			x	
Hashimoto disease	x	x	x	
Thyroiditis in general	x	x	x	
Kawasaki disease				x
Granulomatosis with polyangiitis				x
Nonalcoholic steatohepatitis	x	x	x	x
Chronic liver disease	x	x	x	x
Eosinophilic esophagitis	x	x		x
Pernicious anemia	x		x	x
Crohn's disease	x	x		
Ulcerative colitis	x	x		x
Celiac disease	x		x	
Ankylosing spondylitis	x	x		
Rheumatoid arthritis	x	x		
Erythema nodosum	x	x	x	
Systemic lupus erythematosus	x	x	x	
Scleroderma	x			x
Sjogren syndrome			x	
Alopecia areata	x	x	x	x
Chronic urticaria	x	x	x	x
Vitiligo	x	x	x	x
Thrombotic thrombocytopenic purpura				x
Autoimmune disease, not elsewhere classified	x	x		x
Any autoimmune disease	x	x	x	x

adults and children with AD were estimated to be $2,162,308-$47,370,869 and $418,436-$2,936,220, respectively.

Inpatient mortality

Inpatient mortality was generally low among adult inpatients with AD. However, type 1 diabetes mellitus, Crohn's disease, systemic lupus erythematosus, Sjogren syndrome, and autoimmune hemolytic anemia were associated with numerically higher inpatient mortality rates among AD patients. Inpatient mortality was nil among pediatric AD inpatients with versus without any autoimmune comorbidity.

DISCUSSION

In this cross-sectional study, hospitalized adults and children with AD, whether or not they had asthma or hay fever, were found to have a higher odds of multiple autoimmune disorders, including those affecting the skin, endocrine, gastrointestinal, hematologic, and musculoskeletal systems. Most of these disorders were increased in children and adults with AD of all ages, although some disorders were only associated with AD in either older or younger adults. Autoimmune disorders were particularly increased in women and during late adolescence and young adulthood, consistent with the well-established patterns for numerous autoimmune disorders.[14] AA and vitiligo were among the associated autoimmune disorders with the strongest effect sizes. There were considerable excess costs secondary to hospitalization for autoimmune disorders among AD patients. This is consistent with previous studies that demonstrated substantial excess costs in AD patients indirectly related to its comorbidities.[15,16] Together, there appear to be higher rates of autoimmune disorders in both children and adults with AD.

Our results are consistent with the results of a previous systematic review and meta-analysis that showed higher rates of vitiligo, particularly early-onset disease, and AA, particularly alopecia totalis and universalis, among persons with AD.[9] Moreover, in a German cohort study of 655,815 adults aged ≤40 years, AD patients had increased risk for incident RA, Crohn's disease, and UC but a lower risk for type 1 diabetes.[11] In a recent study of 5,644,567 adults from the nationwide Danish registries, AD was associated with significantly higher odds of AA, vitiligo, and chronic urticaria, ankylosing spondylitis, celiac disease, chronic glomerulonephritis, Crohn's disease

Table II. Associations of autoimmune disorders in US adults and children with atopic dermatitis

	Autoimmune disorder					
	Adults			Children		
Variable	Prevalence (95% CI)	aOR (95% CI)	*P* value	Prevalence (95% CI)	aOR (95% CI)	*P* value
Age, y						
0-1				22.9 (16.8-29.1)	1.00 (reference)	-
2-5				24.3 (17.8-30.8)	1.43 (1.21-1.70)	.0006
6-11				24.7 (19.3-30.1)	2.04 (1.70-2.44)	<.0001
12-17				28.0 (21.9-34.1)	2.83 (2.37-3.38)	<.0001
18-39	27.1 (23.5-30.6)	1.00 (reference)	-			
40-59	34.9 (31.3-38.5)	0.69 (0.63-0.76)	<.0001			
60-79	29.2 (25.7-32.7)	0.58 (0.52-0.64)	<.0001			
≥80	8.8 (5.9-11.7)	0.30 (0.27-0.35)	<.0001			
Sex						
Female	63.9 (60.3-67.6)	1.57 (1.46-1.68)	<.0001			
Male	36.1 (32.4-39.7)	1.00 (reference)	-			
Race/ethnicity						
White	63.0 (58.3-67.7)	1.00 (reference)	-	38.4 (29.6-47.2)	1.00 (reference)	-
Black	22.4 (18.3-26.4)	1.10 (1.00-1.20)	.0960	25.9 (19.0-32.8)	0.70 (0.60-0.83)	.0003
Hispanic	7.2 (4.9-9.4)	1.06 (0.93-1.28)	.4349	21.0 (14.0-28.1)	1.11 (0.94-1.31)	.3127
Asian	3.1 (1.6-4.5)	0.67 (0.55-0.81)	.0005	10.0 (5.6-14.4)	1.61 (1.28-2.02)	.0006
Other	4.4 (2.6-6.2)	1.08 (0.92-1.12)	.4929	4.7 (1.6-7.8)	0.69 (0.51-0.94)	.0445
Insurance						
Insured				94.0 (90.7-97.3)	1.00 (reference)	-
Not Insured				6.0 (2.7-9.3)	0.68 (0.51-0.89)	.0184
Income quartile						
1	26.3 (22.5-30.0)	0.76 (0.69-0.84)	<.0001	27.6 (20.9-34.2)	0.92 (0.76-1.11)	.4694
2	28.3 (24.7-32.0)	1.02 (0.92-1.12)	.7982	20.3 (14.4-26.2)	0.98 (0.81-1.20)	.8929
3	23.2 (19.8-26.6)	0.92 (0.83-1.01)	.1427	31.3 (24.5-38.0)	1.32 (1.10-1.58)	.0112
4	22.2 (18.5-25.9)	1.00 (reference)	-	20.8 (14.3-27.4)	1.00 (reference)	-
No. chronic conditions*						
0-1	0.5 (0-1.0)	1.00 (reference)	-	6.3 (3.0-9.6)	1.00 (reference)	-
2-5	36.9 (33.0-40.9)	7.23 (4.88-10.73)	<.0001	80.9 (75.8-85.9)	17.73 (13.05-24.09)	<.0001
≥6	62.5 (58.6-66.5)	16.01 (10.78-23.77)	<.0001	12.9 (8.5-17.2)	30.16 (21.45-42.42)	<.0001
Comorbidity						
Asthma	23.0 (19.6-26.3)	0.75 (0.69-0.81)	<.0001	37.0 (30.8-43.2)	0.31 (0.26-0.37)	<.0001

aOR, Adjusted odds ratio; *CI*, confidence Interval.
*Chronic conditions were defined by Healthcare Cost and Utilization Project as conditions lasting 12 months or longer and meeting 1 or both of the following: (1) places limitations on self-care, independent living, and social interactions and (2) results in the need for ongoing intervention with medical products, services, and special equipment. Chronic condition count was calculated and provided by the Healthcare Cost and Utilization Project. Multivariable logistic regression models were constructed with any autoimmune disorder as the outcome. Stepwise selection (alpha 0.1) was used from the following covariables: age (0-1, 2-5, 6-11, 12-17, 18-39, 40-59, 60-79, and ≥80 years), sex (female, male), race/ethnicity (white, black, Asian, Hispanic, other, multiracial), median annual income of the hospital ZIP code (quartiles), insurance coverage (Medicaid, Medicare, private, self-pay, no charge, other), number of chronic conditions (0-1, 2-5, ≥6), asthma (yes, no), and hay fever (yes, no).

and UC, giant cell arteritis, Hashimoto thyroiditis, immune thrombocytopenic purpura, primary biliary cirrhosis, RA, Sjogren syndrome, SLE, and systemic sclerosis, but no associations were found with Grave disease, hemolytic anemia, MS, pulmonary fibrosis, or type 1 diabetes.[12] Overall, these results are consistent with our results. Though, there were several differences. For example, we found significant associations with MS and no significant associations with immune thrombocytopenic purpura or Sjogren disease. However, these differences might be due to inadequate statistical power in both studies for some rarer autoimmune comorbidities. Of note, we also found an inverse association between AD and type 1 diabetes, which is consistent with multiple previous studies.[17-19] Taken together, the results of these studies suggest that AD is associated with multiple cutaneous and extracutaneous autoimmune disorders in adults and children, further supporting that AD is a systemic disease.[20]

Despite a well-established association between AD and atopic disorders, eg, asthma and food

allergy, the relationship between AD and autoimmune disorders is not as well recognized. This might be due to the fact that autoimmune disease occurs far less commonly than asthma and atopic disease, which are among the most prevalent chronic disorders in children and adults.[21] Though, it might be that not all AD patients have increased risk for autoimmune disease. Rather, there might be specific subsets of AD patients that are particularly at risk. It is unknown if AD patients with autoimmune comorbidities have different skin manifestations, clinical course, severity, or treatment response than those without autoimmune comorbidities. The present study and other studies to-date were not able to answer these questions.

Interestingly, the odds of autoimmune disease in persons with and without AD increased throughout childhood into middle-age, but then decreased with older age. Some autoimmune disorders were more prevalent in children and young adults, eg, eosinophilic esophagitis and UC, and others particularly in older adults, eg, MS and celiac disease. These differences might be related to differential changes of T cell helper 1 (T_H1) and T_H2 cytokines with age among those with versus without AD.[22] Different immunologic profiles might also explain observed differences of autoimmune odds in Asian children versus adults and lower odds of autoimmune disease in black children. However, future studies are needed to confirm these studies and determine potential mechanisms underlying these associations.

The mechanisms of association between AD and autoimmune disorders are unknown. AD patients have aberrant innate immune responses, including alterations in toll-like receptor signaling.[7] AD patients have higher differentiation of central and effector memory T-cell subsets and more persistent T-cell activation than even seen in psoriasis.[23] T_H1 and T_H17 responses that have been implicated in a subset of AD patients are also present in some autoimmune disorders, eg, inflammatory bowel disease and RA.[24] Interestingly, the present study found that autoimmune disorders were particularly increased among children of Asian race/ethnicity. A previous study of the AD transcriptome suggested that Asian patients with AD had more psoriasiform lesions and increased T_H17 responses.[25] Interestingly, autoimmune disorders were inversely associated with a diagnosis of asthma in both children and adults. This finding suggests that AD patients with autoimmune disease might have less systemic atopy, potentially related to greater activation of T_H1 pathways and less activation of T_H2 pathways. Thus, it might be that distinct immune pathways are activated and contribute to autoimmune disorders in a subset of AD patients. Future research is needed to determine the mechanism and clinical characteristics of the association between AD and autoimmune disorders.

The strengths of this study include analysis of a large-scale nationally representative cohort. We previously found the code 691.8 to be sufficiently valid to identify AD in the inpatient setting.[13] However, there are some limitations. The cross-sectional nature of the study precluded analysis of the temporal relationship between AD and autoimmune disorders. Data on AD severity, phenotype, and age-of-onset and treatments used in the inpatient or outpatient setting were unavailable. Last, there is potential for selection bias, as we analyzed an inpatient database; consequently, autoimmune disorders might not be associated with all AD patients, but rather ones with more severe disease. Future studies are needed to determine the impact of AD severity on these associations.

In conclusion, adults and children with AD had significantly higher odds of autoimmune disorders affecting the skin, endocrine, gastrointestinal, hematologic, and musculoskeletal systems. Further studies are needed to confirm these associations, determine the mechanisms and specific risk factors for comorbid autoimmune disease in AD, and develop interventions to screen and monitor for them.

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