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ORIGINAL ARTICLE

Comorbidities in childhood atopic dermatitis: A population-based study

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with allergic comorbidities. However, studies examining comorbidities in childhood AD are incomplete, which may contribute to suboptimal care.

Objective: The objective was to compare the risk of developing different allergic and non-allergic comorbidities among children with AD to that of a matched non-AD reference cohort in Sweden.

Methods: This was a nationwide population-based cohort study using longitudinal data from primary and specialist care registers. Patients with AD were identified by confirmed diagnosis in primary or specialist care. The non-AD reference cohort was randomly drawn from the general population and matched 1:1 with the AD patients. The risk of developing the following conditions was evaluated: hypersensitivity and allergic disorders, neurological disorders, psychiatric disorders, infections, immunological and inflammatory disorders, Type 1 diabetes (T1D), endocrine and metabolic disorders, skeletal disorders, ocular disorders and malignancies.

Results: This study included 165,145 patients with AD (mild-to-moderate [$n = 126,681$] and severe [$n = 38,464$]) and an equally sized reference cohort. Patients with AD displayed a higher risk of developing comorbid conditions for all investigated categories, except for T1D and skeletal disorders, compared with the reference cohort. The highest risk compared with the reference cohort was observed for hypersensitivity and allergic disorders (hazard ratio [HR]: 3.87), followed by malignancies (HR: 2.53) and immunological and inflammatory disorders (HR: 2.36). Patients with AD also had higher risk of developing multiple comorbidities (≥2). The risk of comorbidity onset increased alongside AD severity and patients with active AD were associated with increased risk of comorbidity onset compared with patients in remission.

Conclusions: The clinical burden of AD is substantial for children with AD and patients are at an increased risk of developing several comorbid conditions extending beyond the atopic march. Our results also showed a positive association between worsening severity of AD and an increased risk of comorbidity onset.

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INTRODUCTION

Atopic dermatitis (AD) is a common and chronic, inflammatory skin disease characterized by dry skin, pruritus and eczematous lesions.[1] Prevalence of AD among children is high across all continents,[2–5] and in Northern Europe, including Sweden, the prevalence is estimated to be about 15%.[6–9] In roughly 60% of cases, AD manifests during the first year of life, but the disease may begin at any age.[10,11] Parental history of AD is a strong risk factor for AD in children.[12,13]

AD has traditionally been viewed as the first clinical manifestation in the 'allergic march' (also known as 'atopic march' including asthma, allergic rhinitis and food hypersensitivity).[14] Recently, AD has also been associated with non-atopic comorbid conditions including anxiety, depression, infections and skeletal disorders,[15–17] among others. Children with AD seem to have an increased risk of neuropsychiatric conditions[18] including attention deficit hyperactivity disorder (ADHD).[19] A growing body of evidence supports the view of AD as a systemic disease,[20] hypothetically linked to comorbid conditions through inflammation or shared risk factors. Despite the quick pace of research in AD, observational studies examining the clinical burden of childhood AD are incomplete regarding the assessment of comorbidity, which may contribute to suboptimal treatment of patients.[16,21,22] Establishing the clinical burden of AD can encourage physicians to proactively screen for clinically relevant and common conditions and treat patients holistically. Sweden maintains administrative data with complete coverage that provides an excellent source for comprehensive disease identification.

The objective of this study was to assess the clinical burden of AD in children with AD versus a matched non-AD reference cohort (without AD) in Sweden by comparing the time to onset of a wide set of comorbidities. The present study provides valuable population-based evidence relative to the incidence and prevalence rates for comorbid conditions in children with AD compared with that of a matched general non-AD reference cohort, while evaluating them according to disease severity and including data on time in remission.

MATERIALS AND METHODS

Data and ethics

This observational retrospective cohort study used linkage data from prospectively collected national and regional registers from Sweden. Data were extracted from the National Patient Registry (NPR), which contains medical information for all in- and outpatient specialist (specialist care) visits, including International Classification of Disease version 10 (ICD-10) codes and dates, the Prescribed Drug Registry (PDR), which includes data from 1 July 2005 on all pharmacy-dispensed medications from both primary and specialist care, including medications (Anatomical Therapeutic Chemical [ATC]-codes) and pharmacy dispensation dates and the Cause of Death Registry (CDR), which contains information on causes of death and corresponding date. These three databases are managed by the Swedish National Board of Health and Welfare and are mandatory to report to and therefore have complete population coverage.

Data were also extracted from regional primary care databases from Västra Götaland and Skåne (VEGA and RSVD, respectively). These two databases include approximately one-third of the Swedish population and include diagnoses codes (ICD-10) and corresponding dates for visits. Primary care often represents the first point of contact with the healthcare services in Sweden and in some cases, particularly for milder form of AD, patients are managed exclusively in primary care. Socioeconomic information including household income, and migration information used to censor patients that emigrate from Sweden, was extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA).

Lastly, the Total Population Registry provides data that include the entire Swedish population and was used to identify a random sample of non-AD individuals as well as parents to children with and without AD. Unique personal identification numbers were used to link the data at the patient level from each registry.

Ethical approval for this study was received in July 2019 from the Ethical Review Board in Sweden (reference number 2019-03840). Individual patient consent was not required.

Study population and design

A cohort of children (<18 years old) with AD (AD cohort) identified between 2007 and 2017 (inclusive) was included in this study. AD was defined using a registered, observational diagnosis of AD (ICD-10: L20+) in primary (VEGA or RSVD) or specialist care (NPR). The date of the first observable AD diagnosis during the study period was defined as the index date, that is, start of follow up. Inclusion ended on 31 December 2017 with follow up to 31 December 2018, thereby providing a minimum of 1 year of follow up for all individuals. Patients were followed until death, emigration, end of study period (31 December 2018) or adulthood.

The AD cohort was matched 1:1 with replacement to non-AD individuals (non-AD reference cohort) on age, gender and geographic region at index. The non-AD reference cohort was randomly selected from the Swedish population without an AD-diagnosis, without dispensed oral or topical corticosteroids (TCS) and without dispensed topical calcineurin inhibitors (TCI). This minimized the risk of including AD-patients into the non-AD reference cohort which can be considered as a representative sample of the Swedish non-AD population. The study design is presented in Figure 1.

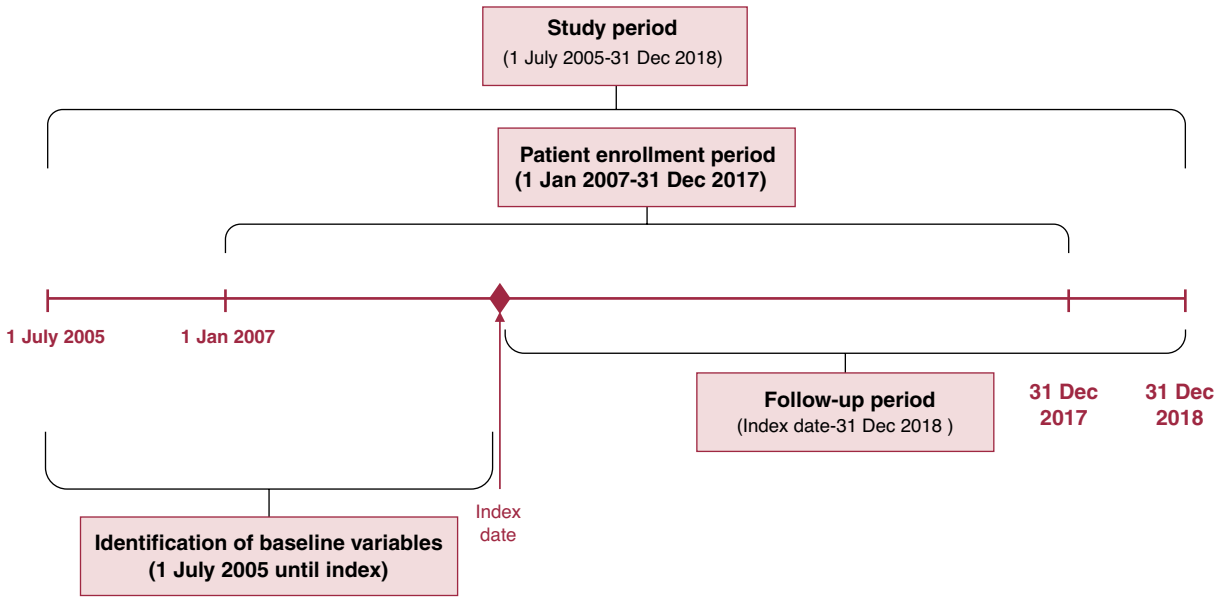

FIGURE 1 Schematic of study design: Patients were identified at the time of their first AD diagnosis in 2007–2017 (inclusive; index date) and followed until death, emigration, end of study period (31 December 2018) or adulthood. Patients with prior history of the evaluated condition were excluded.

Comorbidity onset

This study evaluated time to first diagnosis for a broad set of possible comorbid conditions in AD cohort and in the non-AD reference cohort, aged <18 years at index. The following conditions were analysed individually: hypersensitivity and allergic disorders, neurological disorders, psychiatric disorders, infections, immunological and inflammatory disorders, Type 1 diabetes (T1D), endocrine and metabolic disorders (excluding T1D and Type 2 diabetes [T2D]), skeletal disorders, ocular disorders and malignancies. Endocrine and metabolic disorders did not include Type 1 or Type 2 diabetes. T1D was analysed separately whereas T2D was not included in the analysis. The investigated conditions were chosen based on clinical input and the association of these conditions to AD as reported in the published literature.[15,18] The list of ICD-10 codes for all conditions evaluated is provided in Table S1. In each analysis of comorbidity onset, patients were excluded if they had experienced the specific comorbidity under analysis before the index date in order to minimize the likelihood of bias in assessing an increased risk of comorbidities.

Disease severity

Patients were classified into AD severity subgroups using an algorithm based on AD treatments and received AD diagnosis (See Table S2 for complete classification criteria). AD patients' severity was evaluated on an annual basis from index date until the end of the study period, except for the first year when severity was evaluated from 1 year before index date to—and including—30 days after index. Dispensation of systemic treatment was assumed to indicate severe AD following European treatment guidelines.[23,24] Dupilumab is only reimbursed for patients with severe AD in Sweden further supporting that its use is assumed to indicate severe AD.[25] Dispensation of potent or very potent TCSs was assumed to indicate severe AD since it is only recommended to be used when milder TCSs have failed to provide a therapeutic effect. As some patients in their later adolescent years may be treated as adults, two (or more) dispensations of potent TCSs were required to indicate severe AD in adolescent patients. Patients in remission did not have any healthcare contacts with an AD diagnosis nor were they dispensed any AD treatment (TCSs, TCIs, emollients or systemic treatments). These patients could therefore be considered to have a non-active AD. As an AD diagnosis was part of both the inclusion criteria and the severity criteria, all patients were classified as either mild-to-moderate (M2M) or severe AD at start of follow up.

Statistical analyses

Descriptive statistics were computed for patients at risk, stratified by severity and compared with the non-AD reference cohort as mean and standard deviation (SD) for continuous variables and number and percentage for categorical variables.[26] The association between time to the start of a clinically managed condition and the presence of AD (M2M, severe or AD in remission) was displayed using cumulative incidence curves (calculated as 1 – the Kaplan–Meier [KM] estimates), forest plots and analysed using Cox proportional hazards models.[26] Two types of Cox regression models were used in this study:

(1) adjusted models, estimating the hazard ratio (HR) for the severity variables while controlling for baseline age, sex, pre-existing conditions profile, disposable household income, region of residence and index year; (2) unadjusted models which used the presence of AD as the single covariate when estimating the HR.

The proportional hazards assumption was tested for all adjusted cox regression models based on the Schoenfeld residuals.[26] Selected variables were used as strata to allow the baseline hazard to vary in cases of non-proportionality of variables. The cumulative incidence curves were tested using log rank tests to examine if the groups (M2M AD, severe AD, AD remission and the non-AD reference cohort) were statistically different from each other.[26] Data management, statistical analyses and graphics were produced in Stata version 16. All *p*-values were evaluated as two-sided tests, with an a priori statistical significance level of alpha = 0.05. This study followed the extended STROBE guidelines for observational studies using routinely collected health data.[27]

Missing data

Patients with missing socioeconomic or demographic information were excluded from this study. See the attrition figure for details in the supporting information (Figure S1).

RESULTS

Patient characteristics

A total of 165,145 patients were included in the AD cohort (Table 1). At start of follow up, 120,684 (73%) patients with AD were classified with M2M disease (mean age: 4.64 years; 47.25% females), and 44,461 (27%) patients with severe AD (mean age: 7.52 years; 48.01% females). The greatest differences in prevalence of conditions at baseline between the AD- and the non-AD reference cohorts were observed for hypersensitivity- and allergic disorders and infections which were higher in the AD cohort compared with the non-AD reference cohort. Less than 20% of the AD cohort used systemic treatments during the follow up period and approximately 50% of these patients received their first systemic treatments before the age of 7 years, see Table S3 for more details.

Incidence of comorbidities among AD cohort compared with the non-AD reference cohort

Total years of follow up in the study were 934,356 person-years (PYS) for AD cohort (mean: 5.66 PYS) and 932,403 PYS for the non-AD reference cohort (mean: 5.65 PYS). The total number of events during follow up by comorbidity is presented in Table 2. See Table S4 for details on years of follow up and number of PYS for the different outcomes.

Figure 2 shows the proportion of patients by number of developed comorbidities. In the AD cohort, 36.6% of all patients developed at least one comorbidity during follow up compared to 28.5% in the non-AD reference cohort. Of those patients who developed at least one comorbidity, 27.1% and 19.7% developed multiple comorbidities (≥2) in the AD cohort and the non-AD reference cohort, respectively.

Hypersensitivity- and allergic disorders were the most common comorbidities in the AD cohort and occurred in 18.55% (95% CI [18.31%–18.80%]) of patients in the AD cohort and 10.03% (9.88%–10.18%) of patients in the non-AD reference cohort. Infections and skeletal disorders were the second and third most common comorbidities in the AD cohort and occurred in 18.35% (18.12%–18.59%) and 13.20% (13.02%–13.39%) of the patients in the AD cohort, respectively and in 5.29% (5.18%–5.41%) and 9.65% (9.51%–9.80%) of the patients in the non-AD reference cohort, respectively. The cumulative incidence of the investigated conditions is shown in Figures S2–S11.

Survival analysis of time to comorbidity onset

Figure 3 shows the estimated HRs for the adjusted Cox proportional hazard models. Children with AD had a statistically significant increased risk of onset for all analysed conditions (neurological disorders, psychiatric disorders, infections, immunological- and inflammatory disorders, endocrine- and metabolic disorders and ocular disorders) except for T1D and skeletal disorders compared with the non-AD reference cohort (panel A). The higher risk of onset of comorbid conditions was not limited to patients with active AD (i.e. M2M or severe AD) but time in remission was also associated with a higher risk compared with the non-AD reference cohort. Although the risk of skeletal disorders was not statistically significant, the number of events of osteoporosis, or secondary osteoporosis were more common in the AD cohort compared with the non-AD reference cohort. See Table S8 for distribution of specific diseases across each comorbidity group. The risk of onset of hypersensitivity- and allergic disorders, endocrine and metabolic disorders, immunological- and inflammatory disorders, infections, malignancies and ocular disorders increased with AD severity compared to patients in remission. See Table S5 for statistical testing of differences in HRs for the severity variable. A sensitivity analysis was performed to evaluate any possible effect of referral bias. In this analysis, the risk of comorbidity onset in the AD cohort was compared to that for a sub-sample of the non-AD reference cohort required to have had at least one in- or outpatient hospital visit or at least two primary care visits before index date. The results from this sensitivity analysis were consistent with the overall results.

TABLE 1 Summary of patient characteristics at baseline.

	AD cohort ($n = 165,145$)		Non-AD reference cohort ($n = 165,145$)	Mild-to-moderate vs. non-AD reference cohort	Severe vs. non-AD reference cohort
	Mild-to-moderate ($n = 126,681$)	Severe ($n = 38,464$)			
Variable description	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean difference (95% CI)**	**Mean difference (95% CI)**
Age at index	5.13 (4.99)	6.33 (5.10)	5.42 (5.04)	−0.29 (−0.33 to −0.25)	0.91 (0.85–0.97)
Household's disposable income (1000€ 2020)[1]	45.07 (46.93)	46.13 (92.03)	47.12 (60.74)	−2.05 (−2.45 to −1.65)	−0.99 (−1.74 to −0.24)
Healthcare resource use (365 days prior to index)[2]					
Number of outpatient visits	1.51 (2.54)	1.67 (3.19)	0.80 (1.68)	0.71 (0.69–0.73)	0.87 (0.84–0.89)
Number of days in inpatient care	0.37 (2.93)	0.66 (5.71)	0.35 (3.90)	0.02 (−0.01–0.05)	0.31 (0.26–0.36)
Number of medications dispensed	6.87 (57.72)	9.72 (47.81)	2.30 (41.75)	4.57 (4.21–4.93)	7.42 (6.94–7.90)
	***n* (%)**	***n* (%)**	***n* (%)**	**Difference in proportions (95% CI)**	**Difference in proportions (95% CI)**
Female	60,606 (47.8%)	18,672 (48.5%)	79,278 (48.0%)	−0.2% (−0.6% to 0.2%)	0.5% (−0.5% to 1.1%)
Treatment history: Share of patients with (365 days prior to index)[2]					
Azathioprine[4]	0 (0.0%)	60 (0.2%)	0 (0.0%)		
Cyclosporine[4]	0 (0.0%)	36 (0.1%)	0 (0.0%)		
Methotrexate[4]	0 (0.0%)	4 (0.0%)	0 (0.0%)		
Mycophenolate mofetil[4]	0 (0.0%)	22 (0.1%)	0 (0.0%)		
TCS					
Mild	34,204 (27.0%)	13,019 (33.9%)	0 (0.0%)	27.0% (26.8% to 27.2%)	33.9% (33.4% to 34.4%)
Moderate	31,070 (24.5%)	12,230 (31.8%)	0 (0.0%)	24.5 (24.3% to 24.7%)	31.8% (31.3% to 32.3%)
Potent	4397 (3.5%)	24,881 (64.7%)	0 (0.0%)	3.5% (3.4% to 3.6%)	64.7% (64.2% to 65.2%)
Very potent [4]	0 (0.0%)	1129 (2.9%)	0 (0.0%)	–	2.9% (2.7% to 3.1%)
TCI	1914 (1.5%)	1494 (3.9%)	0 (0.0%)	1.5% (1.4% to 1.6%)	3.9% (3.7% to 4.1%)
Systemic corticosteroids prescribed by a dermatologist	0 (0.0%)	160 (0.4%)	0 (0.0%)	–	0.4% (0.3% to 0.5%)
AD identification					
Primary care diagnosis (ICD-10 L20+)	33,489 (26.4%)	5378 (14.0%)	–		
Specialist care diagnosis (ICD-10 L20+)	93,192 (73.6%)	33,086 (86.0%)	–		
Pre-existing conditions profile[3]					
Neurological disorders	2917 (2.3%)	1076 (2.8%)	2385 (1.4%)	0.9 (0.8% to 1.0%)	1.4% (1.2% to 1.6%)
Psychiatric disorders	2496 (2.0%)	956 (2.5%)	2312 (1.4%)	0.6% (0.5% to 0.7%)	1.1% (0.9% to 1.3%)
Hypersensitivity and allergic disorders	49,963 (39.4%)	14,748 (38.3%)	13,324 (8.1%)	31.3% (31.0% to 31.6%)	30.2% (29.7% to 30.7%)
Immunological and inflammatory disorders	1883 (1.5%)	1000 (2.6%)	1033 (0.6%)	0.9% (0.8% to 1.0%)	2.0% (1.8% to 2.2%)
Infections	45,515 (35.9%)	13,215 (34.4%)	37,094 (22.5%)	13.4% (13.1% to 13.7%)	11.9% (11.4% to 12.4%)
Skeletal disorders	6006 (4.7%)	2150 (5.6%)	7904 (4.8%)	−0.1% (−0.3% to 0.1%)	0.8% (0.5% to 1.1%)
Endocrine and metabolic disorders	3018 (2.4%)	1109 (2.9%)	2054 (1.2%)	1.2% (1.1% to 1.3%)	1.7% (1.5% to 1.9%)
Diabetes (Type 1)	214 (0.2%)	95 (0.3%)	240 (0.2%)	0.0% (0.0% to 0.0%)	0.1% (0.0% to 0.2%)
Cardiovascular disease	171 (0.1%)	84 (0.2%)	139 (0.1%)	0.0% (0.0% to 0.0%)	0.1% (0.1% to 0.1%)

TABLE 1 (Continued)

	n (%)	*n* (%)	*n* (%)	Difference in proportions (95% CI)	Difference in proportions (95% CI)
Malignancies	142 (0.1%)	128 (0.3%)	91 (0.1%)	0.0% (0.0% to 0.0%)	0.2% (0.1% to 0.3%)
Ocular disorders	561 (0.4%)	245 (0.6%)	388 (0.2%)	0.2% (0.2% to 0.2%)	0.4% (0.3% to 0.5%)

Note: All variables were reported at index date except when [1]measured during the calendar year prior to index date, [2]measured during the year prior to index date, or [3]measured from 01 July 2005 to —and including—index date. [4]The use was by definition zero in the mild-to-moderate cohort as this indicated severe.

Abbreviations: AD, atopic dermatitis; CI, confidence interval; ICD-10, The International Classification of Diseases version 10; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid. Analyses with ≤3 observations were reported as NA. See Table S1 for ICD-10 codes that were used to define the conditions.

TABLE 2 Comorbidity incidence rate for the AD cohort and the non-AD reference cohort.

	Number of patients[a]		Number of events[b]		Incidence rate per 1000 PYS (95% CI)[b]		Unadjusted hazard ratios
	AD cohort	Non-AD reference cohort	AD cohort	Non-AD reference cohort	AD cohort	Non-AD reference cohort	AD cohort vs. non-AD reference cohort[c]
Hypersensitivity and allergic disorders (asthma, food hypersensitivity, etc.)	100,434	151,821	18,634	8037	39.11 (38.55–39.68)	9.69 (9.48–9.90)	3.87 (3.77–3.97)
Infections (influenza, acute upper respiratory infections, etc.)	106,415	128,051	19,530	16,903	39.02 (38.47–39.57)	26.09 (25.70–26.48)	1.45 (1.42–1.48)
Skeletal disorders (fractures, osteoporosis, etc.)	156,989	157,241	15,751	15,175	18.76 (18.49–19.08)	18.04 (17.76–18.33)	1.04 (1.02–1.06)
Psychiatric disorders (sleep disorders, anxiety disorders, etc.)	161,693	162,833	9691	7253	10.85 (10.64–11.07)	8.01 (7.83–8.20)	1.36 (1.32–1.40)
Neurological disorders (migraine, epilepsy, etc.)	161,152	162,760	7821	5403	8.78 (8.59–8.98)	5.97 (5.81–6.13)	1.47 (1.42–1.52
Immunological and inflammatory disorders (Celiac disease, psoriasis, etc.)	162,262	164,112	3585	1546	3.95 (3.82–4.08)	1.68 (1.59–1.76)	2.36 (2.22–2.50)
Endocrine and metabolic disorders (overweight, obesity, etc.)	161,018	163,091	3048	1998	3.38 (3.26–3.50)	2.18 (2.09–2.28)	1.55 (1.46–1.64)
Ocular disorders (keratitis, blepharitis, etc.)	164,339	164,757	1646	1012	1.78 (1.70–1.87)	1.09 (1.03–1.16)	1.63 (1.51–1.76)
Type 1 diabetes	164,836	164,905	476	354	0.51 (0.47–0.56)	0.38 (0.34–0.42)	1.34 (1.17–1.54)
Malignancies (solid tumour without metastasis, lymphoma, etc.)	164,875	165,054	210	83	0.23 (0.20–0.26)	0.09 (0.07–0.11)	2.53 (1.96–3.26)

Abbreviations: AD, atopic dermatitis; CI, confidence interval; PYS, patient-years.

[a]Patients with the condition of interest in baseline were excluded.

[b]Assessed from index to comorbidity event or censoring (death, emigration, end of data [31 December 2018] or adulthood), whichever came first.

[c]Unadjusted Cox regression models used the presence of AD as the single covariate when estimating the hazard ratio.

Panel B in Figure 3 shows the estimated HRs for the adjusted Cox proportional hazard models when risk of onset of the respective comorbidity was estimated in patients with an active disease (M2M AD and severe AD) relative to patients in remission. These models only included patients with AD. The results showed that patient time with an active AD disease was associated with a statistically significant increased risk of onset for all analysed comorbid conditions except for T1D and skeletal disorders.

All of the models met the proportional hazard assumption test based on Schoenfeld residuals (p-value <0.05) after stratification on age and gender, except for the model for hypersensitivity- and allergic disorders which did not meet this assumption (in which case the HR may be interpreted as the average effect over time).[28] For detailed Cox regression model results and distribution of events, see Tables S6–S8. Unadjusted Cox regressions are presented in Table 2.

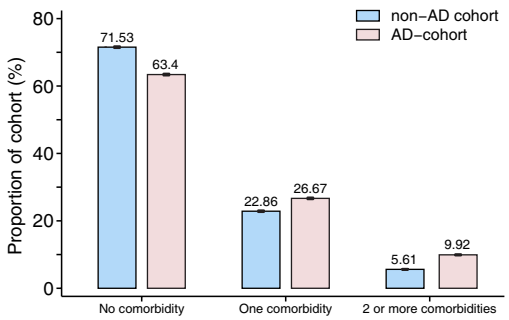

FIGURE 2 Distribution of number of comorbidities developed during follow up: Proportion of individuals in the non-AD reference cohort and the AD cohort by number of comorbid conditions developed until censoring (death, emigration, end of study period [31 December 2018] or adulthood). The error bars represent the 95% confidence intervals.

DISCUSSION

This is one of the largest and most comprehensive studies on the risk of comorbidity in children with AD conducted in a real-world setting evaluating multiple comorbidities in a Swedish population-based longitudinal study. It also considers the effect of AD severity, and AD duration providing further information on the underlying mechanisms behind AD and atopic and non-atopic conditions. We found a statistically significant association between AD and the risk of developing neurological disorders, psychiatric disorders, infections, immunological- and inflammatory disorders, endocrine- and metabolic disorders and ocular disorders.

A review of previously published literature suggests multiple causes for the elevated risk of comorbidities observed in this study, including skin barrier defects, genetics and adverse effect of AD treatment as well as shared risk factors for AD compared with that for other diseases.[20] The association between AD and comorbidities observed in this study showed quite high strength of association, and this association was increasing with increasing severity of AD. Further, this study ensured temporal precedence, and was able to control for important confounders.[29] Results of this study are consistent with those associations previously observed regarding allergic comorbidity. Thus, the results from our study provide additional insight into the complex association between AD and non-atopic conditions. The association between severity of AD and risk of developing comorbidities was particularly evident in hypersensitivity and allergic, immunological and inflammatory disorders as well as in malignancies. The association between AD and hypersensitivity and allergic disorders is well established and is driven by skin barrier dysfunction[30] which may be enhanced by Th2/Th22 skewing.[31] This genetic factor has also been shown to explain the association between AD and immunological and inflammatory disorders.[32,33] In our study, we observed a high frequency of events of alopecia areata, vitiligo, Crohn's disease, ulcerative colitis as well as psoriasis. AD has been shown to share susceptibility loci[32,33] with these diseases and the observed increase in risk by severity is probably explained by a larger unbalance between Th2 and Th1 in patients with more severe AD.

Moreover, we also found a significant association between AD and risk of malignancies. The relationship between AD and malignancy is complex and remains controversial.[20,34] Conventional systemic therapies (azathioprine, methotrexate, cyclosporine and mycophenolate mofetil) have a risk of lymphoma as a potential adverse effect but evidence from studies of patients with AD do not show that the use of systemic therapies is associated with an elevated risk of lymphoma.[35] The role of topical treatment in the link between AD and elevated risk of cancer has been evaluated in numerous studies.[36–38] A meta-analysis with more than 400,000 participants treated with TCIs found no association between TCI use and risk of overall cancer. However, the risk of lymphoma was found to be elevated with TCI users relative to TCS comparators and for treatment-free users.[39] Another meta-analysis on the role of topical treatment and risk of lymphoma found a significant risk between lymphoma and AD in cohort studies but none in case–control studies.[40] The elevated risk of malignancy observed in our study is partly driven by the number of cases of lymphoma (39 and 8 cases in the AD- and non-AD reference cohorts, respectively); however, TCIs are not commonly used by children with AD in Sweden.[41]

The effect of severity of AD was also observed in ocular disorders, partly driven by the higher incidence of blepharitis and uveitis/iritis. Other differences in risk by severity of AD, as observed in psychiatric disorders and infections for example, is probably driven by the symptom burden of AD. Apart from ADHD, which was the most frequent disease observed within psychiatric disorders, sleep, anxiety and stress/mental disorders were more frequent in patients with AD compared to the non-AD reference cohort and are linked to the symptoms of AD.[42] Similarly, increased risk of infections in cutaneous lesions from AD is also well documented.[43,44] Our data also show that viral infections were more common in AD cohort compared to the non-AD reference cohort, further substantiating evidence suggesting that genetic variants in the immune response predispose patients with AD to increased risk of viral skin diseases.[45]

Finally, we found no statistically significant association between AD and risk of T1D or skeletal disorders. While one study has found a positive association between AD and prevalence of diabetes in children aged 0–17 years,[18] another study found AD to have a protective effect on incident T1D.[46] The positive association between AD and skeletal disorders found in the literature[17,18] refers to skeletal retardation or malformation which was not captured in our database. Although the risk of skeletal disorders was not statistically significant, the number of events of osteoporosis (14 and 3 cases in the AD and non-AD reference cohorts, respectively) were more common in the AD cohort compared with the non-AD reference cohort.

In summary, the results from this large population-based study add to the evidence suggesting that childhood AD

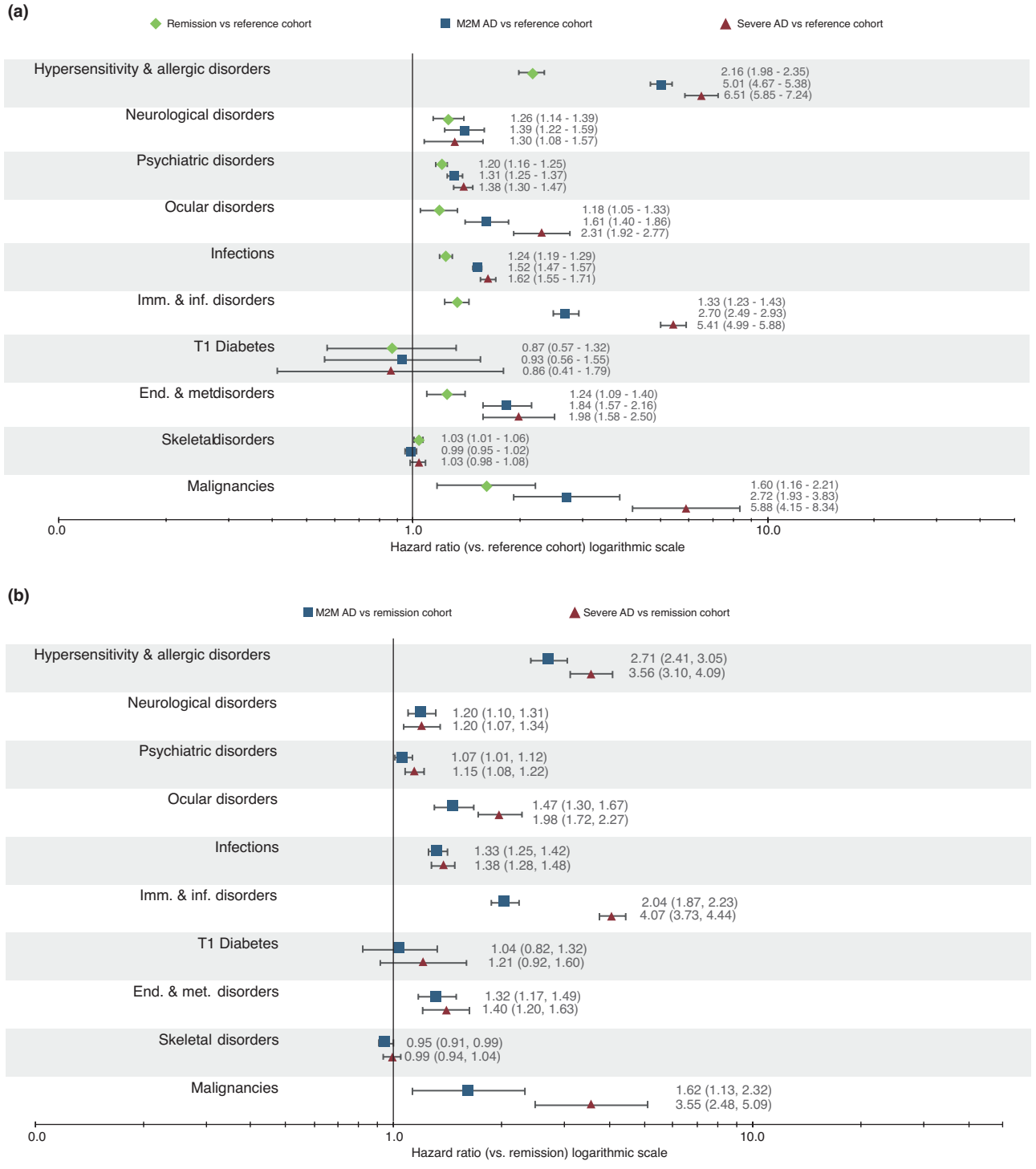

FIGURE 3 Forest plot of the adjusted Cox regression models, showing hazard ratios for (a) AD severity and remission in comparison to the non-AD reference cohort, (b) AD severity in comparison to AD remission cohort: AD, atopic dermatitis; End., endocrine, imm., immunological, inf., inflammatory; M2M, mild-to-moderate; met., metabolic; T1, type 1. Note: The Cox regression models used the displayed condition as endpoints and included the covariates: Mild-to-moderate and severe AD evaluated annually from index date until the end of the study period, except for the first year when the severity was evaluated from one year before index date to—and including—30 days after index. Socio-demographics were defined using age, sex (measured at index), education and household income (measured during the calendar year prior to index date). Pre-existing conditions profiles were measured from 01 July 2005 to—and including—the index date. Calendar year of index and region of residence was also included as covariates. 95% confidence intervals presented in the parentheses. Patients were followed from index to comorbidity event or censoring (death, emigration end of data [31 December 2018] or adulthood).

should be recognized and managed as a systemic condition, or at least it should be recognized that patients often have multiple morbidities that co-occur.[20,21,47–49] Genetics and shared risk factors might be an explanation for the associations between AD and comorbid conditions. Moreover, it cannot be excluded that at least for some comorbid conditions, the increased risk is not associated with AD itself but rather with the treatment of AD. This may be the case for secondary osteoporosis for example.[50] The observed association between AD severity and the risk of developing comorbid conditions is interesting as it may implicate that effective AD treatment lowers the risk of comorbidity onset; however, this was not shown by our study and the study design applied. The possibility of reduced risk of developing comorbid conditions with effective management of AD should be further studied as it would be important not only for the patients but also for healthcare providers and decision makers who manage healthcare resources.

We also acknowledge that this study has limitations. Most importantly, data on clinical assessment of severity were not available in this study. Instead, disease severity was assessed through an algorithm that relied on registry-based diagnosis and medication data as a proxy based on treatment guidelines.[24] It is also possible that some patients with AD were assigned to a severity level because of treatment of other conditions (which use the same type of treatments as in our algorithm) and this biased the results towards a positive relationship between severity and some of the studied comorbidities, like alopecia areata, vitiligo, Crohn's disease, ulcerative colitis as well as psoriasis. Another possible limitation is misclassification of AD, as this study relied on administrative data and lacked complete coverage of primary care data. The use of the ICD-10 code L20+ to identify patients with AD has been validated in a Danish study with high accuracy (positive predictive value of 98%) by reviewing medical charts[51] and its results would be relevant in a Swedish setting as well. Moreover, the inclusion criterion of no dispensation of TCSs and TCIs when sampling for the non-AD reference cohort also limited the possible number of misclassified patients. The possible existence of patients with AD in the non-AD reference cohort would have biased the results towards the null, that is, no difference, suggesting that the true difference may be even higher. On the other hand, as the non-AD reference cohort included individuals with no use of oral or topical steroids, results may be biased away from the null. Use of oral steroids were rare in the AD cohort which minimizes the impact of this criterion. Also, the elevated risk of comorbidities remained significant when active AD (for M2M and severe AD) was compared to time in remission. Moreover, a sensitivity analysis where the non-AD reference cohort was required to have at least one secondary care visit, or two primary care visits showed consistent results with the conducted analysis.

CONCLUSIONS

The clinical burden of AD is substantial for children with AD, who are at an increased risk of developing multiple comorbid conditions extending beyond the atopic disorders. Our results also showed a positive association between worsening severity of AD and an increased risk of comorbidity onset. This study highlights the need for holistic management and follow up of comorbid conditions in the care of children with AD. Further research is needed to conclude whether a causal relationship exists between effective treatment of AD and reduced risk of comorbidity onset, and whether certain AD therapies increase the risk of comorbidities.

AUTHOR CONTRIBUTIONS

All authors participated in the conceptualization and design of this study. G Ortsäter, A Rieem Dun, K Geale and I Lindberg were involved in data curation, formal analysis, investigation, provision of resources, software programming and creation of visualizations. D Henrohn, MP Neary, P Neregård, A De Geer, A Cha and JC Cappelleri were involved in supervision and validation of the work. MP Neary acquired financial support for the study leading to this publication. L von Kobyletzki, N Ballardini, G Theodosiou and JP Thyssen provided clinical expertise. G Ortsäter, A Rieem Dun, K Geale and I Lindberg drafted the manuscript. All authors reviewed and approved the final manuscript. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have provided final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

Amy Cha and Joseph C. Cappelleri are employed by Pfizer Inc. and own Pfizer stock and/or stock options. Dan Henrohn was an employee of Pfizer AB and owned Pfizer stocks at the time of analysis. Maureen P. Neary was an employee of Pfizer Inc. and owned Pfizer stock at the time of this work. Anna De Geer was an employee of Pfizer AB and owned Pfizer stock at the time of this work. Petra Neregård was an employee of Pfizer AB and owned Pfizer stocks at the time of this work. Dr. Thyssen has been an advisor, Investigator and Speaker for AbbVie, Pfizer, Almirall, LEO Pharma, Sanofi-Genzyme, Eli Lilly & Co and Regeneron. He has received research grants from Sanofi-Genzyme and

Regeneron. Laura von Kobyletzki has been consultant or speaker for Pfizer, Sanofi-Genzyme, Leo Pharma and Eli Lilly. Dr. Natalia Ballardini has received consultancy fees from Sanofi, Pfizer and Galenica. Grigorios Theodosiou has been Investigator and Speaker for Sanofi, Novartis, Amgen, AbbVie and Eli Lilly & Co. Kirk Geale is an employee and board member of Quantify Research and owns Quantify Research stocks and stock options. Gustaf Ortsäter is an employee of Quantify Research and owns Quantify Research stocks and stock options, Alexander Rieem Dun is an employee of Quantify Research, Ingrid Lindberg was an employee of Quantify Research during the development of this manuscript. Quantify Research AB provides consulting and other research services to pharmaceutical, medical device and related organizations. Quantify Research AB received funding from Pfizer Inc. to conduct this study and for the development of this manuscript.

DATA AVAILABILITY STATEMENT

Data used in this study are protected under Swedish and European law and may only be accessed following relevant ethical approvals, data protection assessments and compliance with GDPR and other legal frameworks.

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REFERENCES

1. Deckers IAG, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. PloS One. 2012;7(7):e39803.
2. Von Kobyletzki LB, Bornehag C-G, Breeze E, Larsson M, Lindström CB, Svensson Å. Factors associated with remission of eczema in children: a population-based follow-up study. Acta Derm Venereol. 2014;94(2):179–85.
3. Silverberg J, Wollenberg A, Egeberg A, Slater M, Golden D, Jenkins MP, et al. *Worldwide prevalence and severity of atopic dermatitis*. 2018.
4. Kowalska-Olędzka E, Czarnecka M, Baran A. Epidemiology of atopic dermatitis in Europe. Journal of Drug Assessment. 2019;8(1):126–8.
5. Silverberg JBS, Gadkari A, Simpson E, Weidinger S, Mina-Osorio P, Rossi A, et al. *Epidemiology of atopic dermatitis in the adolescent population: a cross-sectional study in the United States and Europe*. 2019.
6. Eller E, Kjaer HF, Høst A, Andersen KE, Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort. Pediatr Allergy Immunol. 2010;21(2p1):307–14.
7. Johansson EK. Atopiskt eksem vanligt i alla åldrar. Lakartidningen. 2017;114:1–4.
8. Bylund S, von Kobyletzki LB, Svalstedt M, Svensson A. Prevalence and incidence of atopic dermatitis: a systematic review. Acta Derm Venereol. 2020;100(12):adv00160.
9. Ballardini N, Kull I, Söderhäll C, Lilja G, Wickman M, Wahlgren C. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. Br J Dermatol. 2013;168(3):588–94.
10. Illi S, von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol. 2004;113(5):925–31.
11. Garmhausen D, Hagemann T, Bieber T, Dimitriou I, Fimmers R, Diepgen T, et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. Allergy. 2013;68(4):498–506.
12. Ravn NH, Halling A-S, Berkowitz AG, Rinnov MR, Silverberg JI, Egeberg A, et al. How does parental history of atopic disease predict the risk of atopic dermatitis in a child? A systematic review and meta-analysis. J Allergy Clin Immunol. 2020;145(4):1182–93.
13. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. British Journal of Dermatology. 2009;161(5):1166–72.
14. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol. 2014;5(2):1–6.
15. Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major comorbidities of atopic dermatitis: beyond allergic disorders. Am J Clin Dermatol. 2018;19(6):821–38.
16. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;123(2):144–51.
17. Baum WF, Schneyer U, Lantzsch AM, Kloditz E. Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. Exp Clin Endocrinol Diabetes. 2002;110(2):53–9.
18. Gilaberte Y, Pérez-Gilaberte JB, Poblador-Plou B, Bliek-Bueno K, Gimeno-Miguel A, Prados-Torres A. Prevalence and comorbidity of atopic dermatitis in children: a large-scale population study based on real-world data. J Clin Med. 2020;9(6):1632.
19. Ballardini N, Kramer MS, Oken E, Henderson AJ, Bogdanovich N, Dahhou M, et al. Associations of atopic dermatitis and asthma with child behaviour: results from the PROBIT cohort. Clin Exp Allergy. 2019;49(9):1235–44.
20. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. J Invest Dermatol. 2017;137(1):18–25.
21. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol. 2018;121(5):604–612.e3.
22. Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ. 2018;361:k1786.
23. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32(6):850–78.
24. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657–82.
25. TLV. *Dupixent ingår i läkemedelsförmånerna med begränsning 2018*. [cited 2022 May 19]. Available from: https://www.tlv.se/download/18.2ec090df16367c5c52cd5e37/1527144790875/bes180517_dupixent.pdf

26. Van Belle G, Fisher LD, Heagerty PJ, Lumley T. Biostatistics: a methodology for the health sciences. Second ed. Hoboken, NJ: John Wiley & Sons; 2004.
27. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ. 2007;85:867–72.
28. Borucka J. Extensions of Cox model for non-proportional hazards purpose. Ekonometria. 2014;45:85–101.
29. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
30. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365(14):1315–27.
31. Gutowska-Owsiak D, Schaupp AL, Salimi M, Taylor S, Ogg GS. Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes. Br J Dermatol. 2011;165(3):492–8.
32. Weidinger S, Willis-Owen SA, Kamatani Y, Baurecht H, Morar N, Liang L, et al. A genome-wide association study of atopic dermatitis identifies loci with overlapping effects on asthma and psoriasis. Hum Mol Genet. 2013;22(23):4841–56.
33. Ellinghaus D, Baurecht H, Esparza-Gordillo J, Rodriguez E, Matanovic A, Marenholz I, et al. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. Nat Genet. 2013;45(7):808–12.
34. Halling-Overgaard AS, Ravnborg N, Silverberg JI, Egeberg A, Thyssen J. Atopic dermatitis and cancer in solid organs: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2019;33(2):e81–2.
35. Megna M, Napolitano M, Patruno C, Villani A, Balato A, Monfrecola G, et al. Systemic treatment of adult atopic dermatitis: a review. Dermatol Ther. 2017;7(1):1–23.
36. Siegfried EC, Jaworski JC, Hebert AA. Topical calcineurin inhibitors and lymphoma risk: evidence update with implications for daily practice. Am J Clin Dermatol. 2013;14(3):163–78.
37. Arellano FM, Wentworth CE, Arana A, Fernandez C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol. 2007;127(4):808–16.
38. Hagstromer L, Ye W, Nyren O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. Arch Dermatol. 2005;141(9):1123–7.
39. Lam M, Zhu JW, Tadrous M, Drucker AM. Association between topical Calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. JAMA Dermatol. 2021;157(5):549–58.
40. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. J Am Acad Dermatol. 2015;72(6):992–1002.
41. von Kobyletzki L, Ballardini N, Henrohn D, Neary MP, Ortsater G, Geale K, et al. Care pathways in atopic dermatitis: a retrospective population-based cohort study. J Eur Acad Dermatol Venereol. 2022;36:1456–66.
42. Thyssen JP, Hamann CR, Linneberg A, Dantoft TM, Skov L, Gislason GH, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy. 2018;73(1):214–20.
43. Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis DJ. Increased risk of cutaneous and systemic infections in atopic dermatitis-a cohort study. J Invest Dermatol. 2017;137(6):1375–7.
44. Wang V, Boguniewicz J, Boguniewicz M, Ong PY. The infectious complications of atopic dermatitis. Ann Allergy Asthma Immunol. 2021;126(1):3–12.
45. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. Clin Rev Allergy Immunol. 2016;51(3):329–37.
46. Schmitt J, Schwarz K, Baurecht H, Hotze M, Folster-Holst R, Rodriguez E, 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(1):130–6.
47. Cheng BT, Silverberg NB, Silverberg JI. Association of childhood atopic dermatitis with atopic and nonatopic multimorbidity. Dermatitis. 2020;32:214–9.
48. Silverberg J, Garg N, Silverberg NB. New developments in comorbidities of atopic dermatitis. Cutis. 2014;93(5):222–4.
49. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol. 2013;24(5):476–86.
50. Henneicke H, Gasparini SJ, Brennan-Speranza TC, Zhou H, Seibel MJ. Glucocorticoids and bone: local effects and systemic implications. Trends Endocrinol Metab. 2014;25(4):197–211.
51. Andersen Y, Egeberg A, Skov L, Thyssen JP. Demographics, healthcare utilization and drug use in children and adults with atopic dermatitis in Denmark: a population-based cross-sectional study. J Eur Acad Dermatol Venereol. 2019;33(6):1133–42.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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