Comorbidity burden in adult atopic dermatitis: A population-based study

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Abstract

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

**Objectives:** The objective was to compare the risk of developing different allergic and nonallergic comorbidities among adult patients with AD to that of a matched reference cohort in Sweden.

**Methods:** This was a nationwide population-based cohort study using longitudinal data from primary and specialist care registers. AD patients were identified by confirmed diagnosis in primary or specialist care. A non-AD reference cohort was randomly drawn from the general population and matched 1:1 with the AD patients on age, gender, and geographical region. The risk of developing the following conditions was evaluated: asthma, food hypersensitivity, allergic rhinitis, neurological disorders, psychiatric disorders, infections, immunological & inflammatory disorders, type 1 diabetes (T1D), type 2 diabetes (T2D), endocrine & metabolic disorders, skeletal disorders, ocular disorders, cardiovascular diseases, and malignancies.

**Results:** This study included 107,774 AD patients [mild-to-moderate (n = 92,413) and severe (n = 15,361)] and an equally-sized reference cohort. AD patients displayed a higher risk of developing comorbid conditions for all investigated categories, except for T1D, compared with the reference cohort. The highest risk compared with the reference cohort was observed for allergic comorbidities followed by immunological & inflammatory disorders (hazard ratio: 2.15) and infections (hazard ratio: 2.01). Patients with AD also had higher risk of developing multiple comorbidities (2 or more). 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: AD patients are at an increased risk of developing many comorbidities that extend beyond allergic conditions. This study highlights the need for interdisciplinary follow-up of comorbidities in the management of AD patients to reduce overall patient burden.

**KEYWORDS**
atopic eczema, epidemiology

**INTRODUCTION**

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease characterized by dry and inflamed skin and pruritus. In Sweden, previous studies have presented 12-months prevalence numbers of 14%. AD causes significant patient burden, impacting quality of life and is associated with significant economic costs. Current disease management aims to improve signs and symptoms and to achieve long-term control. 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). In adulthood, AD patients frequently suffer from hand eczema, as well as irritant and allergic contact dermatitis. Furthermore, a recent guideline by the American Academy of Dermatology evaluated the evidence for the association between AD and infections, autoimmune diseases, mental health disorders, metabolic conditions, and cardiovascular disease and found an association/probable association of several of these conditions with AD.

These comorbidities are associated with considerable disease burden, impacting resource use and treatment costs. Increased levels of disease severity are associated with higher prevalence of comorbidities and increased costs and resource use. Despite the rapid pace of research in AD, observational studies examining the clinical burden of adult AD regarding the assessment of comorbidities are incomplete, which may contribute to suboptimal treatment of patients. Establishing the clinical burden of patients with AD may encourage physicians to proactively screen for clinically relevant and common comorbid conditions and ensure that patients are treated holistically.

This large population-based cohort study examined the clinical burden of AD comorbidities by comparing the time to onset, prevalence, and incidence for a wide range of conditions in adult patients with AD, to that of a matched reference cohort without AD in Sweden. The analyses were controlled for disease severity, including time in remission.

**MATERIALS AND METHODS**

**Data and ethics**

This large population-based cohort study used linkage data from prospectively collected national and regional registers in Sweden. The registers included the National Patient Registry (NPR), which contains medical information for all in- and outpatient specialist visits, including International Classification of Disease version 10 (ICD-10) codes and dates, the Prescribed Drug Registry (PDR), which includes data for all pharmacy-dispensed medications [Anatomical Therapeutic Chemical (ATC)-codes] from both primary and specialist care, including pharmacy dispensation dates, and the Cause of Death Registry (CDR), which contains information on causes of death and corresponding dates. These three databases are managed by the Swedish National Board of Health and Welfare, which requires mandatory reporting and thereby provides complete population coverage.

Data were also extracted from regional primary care databases from two regions in Sweden, that is, Västra Götaland and Skåne. These databases cover approximately one-third of the Swedish population and include healthcare visit information (ICD-10 diagnoses codes and corresponding dates for visits).

Socioeconomic information including household income, education and employment status and migration information, was extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA). Last, the Total Population Registry provides data that includes the entire Swedish population and was used to identify a random sample of individuals without AD (i.e., non-AD cohort). Unique personal identification numbers were used to link the data at the patient level from each registry.

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

**Study population and study design**

A cohort of adult patients (over 18 years of age) with AD identified between 2007 and 2017 was included in this study. AD was defined using only a registered diagnosis of AD (ICD-10: L20) in primary- (Västra Götaland and Skåne) or specialist care (NPR). The index date i.e., start of follow-up was defined as the date of the first observed AD diagnosis during the study period. The inclusion period ended on 31 December 2017 and the study period ended on 31 December 2018, allowing all included study participants to have a minimum follow-up of 1 year. Individuals were followed from index to comorbidity event or censoring [death, emigration, or end of the study period (31 December 2018)], whichever came first. Individuals with a prior record of the evaluated comorbidity were excluded. The study processes are shown in Figure 1.

The non-AD reference cohort was randomly selected from the Swedish population who did not have an AD-diagnosis nor were dispensed any oral or topical corticosteroid (TCS) or a topical calcineurin inhibitor (TCI) before the index date. This minimized the risk of including AD-patients into the non-AD reference cohort which can be considered a ‘healthy’ representative sample of the Swedish non-AD population. The non-AD reference cohort was matched 1:1 to the AD cohort with replacement, on age at index, gender, and region. Each non-AD reference individual was assigned the same index date as the matched AD patient.

**Comorbidity development**

This study evaluated time to first diagnosis for an extensive set of comorbid conditions in adult patients with AD and a non-AD reference cohort, aged 18 years and above at index. The following comorbidity endpoints were analyzed separately: asthma, allergic rhinitis, food hypersensitivity, neurological disorders, psychiatric disorders, ocular disorders, infections, immunological & inflammatory disorders, type 1 diabetes (T1D), T2D, endocrine & metabolic disorders, skeletal disorders, malignancies (any type of malignant tumors) and cardiovascular diseases (including coronary artery disease and venous thrombotic events). The investigated comorbidities were chosen based on inputs from clinical experts and previously reported associations. The specific diseases and ICD-10 codes for all conditions evaluated are enlisted in Supporting Information: Table S1. In each analysis of comorbidity onset, individuals were excluded if they had the specific comorbidity of interest before the index date.

![Figure 1](https://onlinelibrary.wiley.com/doi/10.1002/jvc2.303)  
**Figure 1** Schematic chart of study design. AD patients were identified at their first AD diagnosis in 2007–2017 and followed until death, emigration, or end of study period (31 December 2018). Patients with a prior record of the evaluated comorbidity were excluded. AD, atopic dermatitis.
Disease severity

Specific assessments to evaluate severity of AD such as the Eczema Area and Severity Index (EASI) or the SCORing Atopic Dermatitis (SCORAD) are recommended for use in clinical trials or clinical practice. However, administrative databases do not include patient-reported outcomes or clinical measures of relevance to define the severity of the disease. To address this challenge, the specific treatments used by patients included in these databases are often used as a surrogate to define AD severity. Severity in this study was defined according to both (a) type of treatment and (b) potential visits to specialist care for AD. This approach is similar to that used in a previous population-based cohort study from the United Kingdom with modifications to better fit the Swedish setting based on inputs from clinical experts. Patients with a dispensation of a very potent TCS (e.g., clobetasol), dupilumab, systemic immunosuppressants or a systemic corticosteroid prescribed by a dermatologist or phototherapy within secondary care were classified as severe AD. Patients with a dispensation of mild, moderate or potent TCS (e.g., hydrocortisone, betamethasone and mometasone), TCI, emollients, phototherapy within primary care, or those who had a healthcare contact with a diagnosis of AD within primary or secondary care, were classified as mild-to-moderate (M2M) AD. Disease severity for AD was evaluated on an annual basis from index date until the end of the study period, except for the first year when severity level was classified as nonactive AD. All patients were classified as having M2M or severe AD in patients who had been previously identified through an AD diagnosis. Since AD is a chronic disease, these patients were considered to have a nonactive AD. All patients were classified as having either M2M or severe AD in the first year since an AD diagnosis was encompassed in both the inclusion criteria and the severity criteria. See Supporting Information: Table S2 for complete classification criteria including corresponding ICD-10-, ATC-, and procedure codes.

Statistical analyses

Descriptive statistics were computed for patients at risk, stratified by severity and compared with the non-AD reference cohort: Mean and standard deviation (SD) were compared for continuous variables and number and percentage for categorical variables. The risk of onset of comorbidities and the presence of AD (M2M, severe, or AD in remission) were analyzed using Cox proportional hazards models and displayed using forest plots and graphs of proportion of patients with onset by follow-up time (i.e., 1- Kaplan-Meier survival function). Cox regression models were used in this study. These included unadjusted models which used the presence of AD as the single covariate when estimating the hazard ratio (HR); and adjusted models estimating the HR for the severity variables while controlling for baseline age, sex, pre-existing conditions profile, disposable household income, education, employment status, region of residence, and index year.

The proportional hazards assumption was tested for all adjusted Cox regression models based on the Schoenfeld residuals. Selected variables were used to stratify certain analyses where the proportionality assumption for the Cox model was violated.

The effect of referral bias was tested in a sensitivity analysis in which a subsample of the non-AD reference cohort (who were required to have had at least one in- or outpatient hospital visit or at least two primary care visits within 1 year before the index date) were studied. All p-values were evaluated assuming two-sided tests, with an a priori statistical significance level of α = 0.05. This study followed the extended STROBE guidelines.

Data management, statistical analyses and graphics were performed using Stata version 16.

Missing data

Patients with missing socioeconomic or demographic information were excluded from this study. See the attrition figure for details in Supporting Information: Figure S1.

RESULTS

Patient characteristics

This study included a total of 215,548 adult individuals, with 107,774 patients diagnosed with AD and an identical number of individuals without a diagnosis of AD. At index date, 92,413 AD patients were classified as having M2M AD (65% females) and 15,361 patients were classified as having severe AD (62% females). The prevalence for each comorbidity at baseline was below 20% in all cohorts and the greatest differences in prevalence between the AD- and the non-AD reference cohorts were observed for asthma, allergic rhinitis, cardiovascular disorders, immunological & inflammatory
### TABLE 1  Patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Variable description</th>
<th>AD Cohort (n = 107,774)</th>
<th>Non-AD reference cohort (n = 107,774)</th>
<th>Mild-to-moderate versus non-AD reference cohort Mean difference (95% CI)</th>
<th>Severe versus non-AD reference cohort Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild-to-moderate (n = 92,413)</td>
<td>Severe (n = 15,361)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age at index</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean difference (95% CI)</td>
<td>0.65 (−0.81 to −0.49)</td>
</tr>
<tr>
<td>disposable income (1000€ 2020)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>41.02 (70.67)</td>
<td>40.47 (44.75)</td>
<td>2.31 (1.72–2.90)</td>
<td>1.77 (0.72–2.80)</td>
</tr>
<tr>
<td>Healthcare resource use (365 days before index)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>number of outpatient visits</td>
<td>1.79 (3.66)</td>
<td>2.85 (4.81)</td>
<td>0.95 (0.92–0.98)</td>
<td>2.02 (1.97–2.05)</td>
</tr>
<tr>
<td>number of days in inpatient care</td>
<td>0.84 (7.55)</td>
<td>1.01 (5.72)</td>
<td>0.27 (0.20–0.34)</td>
<td>0.44 (0.30–0.57)</td>
</tr>
<tr>
<td>number of medications dispensed</td>
<td>14.97 (51.13)</td>
<td>24.74 (49.73)</td>
<td>8.44 (8.06–8.82)</td>
<td>18.21 (17.60–18.83)</td>
</tr>
<tr>
<td>female</td>
<td>n (%)</td>
<td>n (%)</td>
<td>Difference in proportions (95% CI)</td>
<td>0.4% (−0.4% to 0.8%)</td>
</tr>
<tr>
<td>treatment history: Share of individuals with (365 days before index)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>azathioprine&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0 (0.0%)</td>
<td>313 (2.0%)</td>
<td>0.0% (0.0%–0.0%)</td>
<td>2.0% (1.8%–2.2%)</td>
</tr>
<tr>
<td>cyclosporine&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0 (0.0%)</td>
<td>201 (1.3%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>methotrexate&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0 (0.0%)</td>
<td>3 (0.0%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>mycophenolate mofetil&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0 (0.0%)</td>
<td>91 (0.6%)</td>
<td>3 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>topical corticosteroid</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>mild</td>
<td>11,650 (12.6%)</td>
<td>2169 (14.1%)</td>
<td>12.6% (12.4%–12.8%)</td>
<td>14.1% (13.6%–14.7%)</td>
</tr>
<tr>
<td>moderate</td>
<td>20,089 (21.7%)</td>
<td>3761 (24.5%)</td>
<td>21.7% (21.5%–22.0%)</td>
<td>24.5% (23.8%–25.2%)</td>
</tr>
<tr>
<td>potent</td>
<td>42,029 (45.5%)</td>
<td>9129 (59.4%)</td>
<td>45.5% (45.1%–45.8%)</td>
<td>59.4% (58.7%–60.2%)</td>
</tr>
<tr>
<td>very potent&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0 (0.0%)</td>
<td>9002 (58.6%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>topical calcineurin inhibitor</td>
<td>6896 (7.5%)</td>
<td>1428 (9.3%)</td>
<td>7.5% (7.3%–7.6%)</td>
<td>9.3% (8.8%–9.8%)</td>
</tr>
<tr>
<td>systemic corticosteroids prescribed by a dermatologist</td>
<td>0 (0.0%)</td>
<td>1917 (12.5%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>AD identification</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>primary care diagnosis (ICD-10 L20)</td>
<td>41,804 (45.2%)</td>
<td>2871 (18.7%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>specialist care diagnosis (ICD-10 L20)</td>
<td>50,609 (54.8%)</td>
<td>12,490 (81.3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>comorbidity profile&lt;sup&gt;3&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>asthma</td>
<td>6937 (7.5%)</td>
<td>1170 (7.6%)</td>
<td>860 (0.8%)</td>
<td>6.7% (6.5%–6.9%)</td>
</tr>
</tbody>
</table>
disorders, infections, and neurological disorders, see Table 1.

**TABLE 1** (Continued)

<table>
<thead>
<tr>
<th>Variable description</th>
<th>AD Cohort ((n = 107,774))</th>
<th>Non-AD reference cohort ((n = 107,774))</th>
<th>Mild-to-moderate versus non-AD reference cohort Mean difference (95% CI)</th>
<th>Severe versus non-AD reference cohort Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>7560 (8.2%)</td>
<td>1078 (7.0%)</td>
<td>1262 (1.2%)</td>
<td>7.0% (6.8%–7.2%)</td>
</tr>
<tr>
<td>Food hypersensitivity, IgE sensitization</td>
<td>2342 (2.5%)</td>
<td>455 (3.0%)</td>
<td>393 (0.4%)</td>
<td>2.2% (2.1%–2.3%)</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>8592 (9.3%)</td>
<td>1591 (10.4%)</td>
<td>5822 (5.4%)</td>
<td>3.9% (3.7%–4.1%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>12,359 (13.4%)</td>
<td>2135 (13.9%)</td>
<td>10,224 (9.5%)</td>
<td>3.9% (3.6%–4.2%)</td>
</tr>
<tr>
<td>Immunological &amp; inflammatory disorders</td>
<td>10,111 (10.9%)</td>
<td>3091 (20.1%)</td>
<td>5897 (5.5%)</td>
<td>5.5% (5.2%–5.7%)</td>
</tr>
<tr>
<td>Infections</td>
<td>11,775 (12.7%)</td>
<td>2425 (15.8%)</td>
<td>6342 (5.9%)</td>
<td>6.9% (6.6%–7.1%)</td>
</tr>
<tr>
<td>Skeletal disorders</td>
<td>9250 (10.0%)</td>
<td>1590 (103%)</td>
<td>9312 (8.6%)</td>
<td>1.4% (1.1%–1.6%)</td>
</tr>
<tr>
<td>Endocrine &amp; metabolic disorders</td>
<td>5200 (5.6%)</td>
<td>1130 (7.4%)</td>
<td>3755 (3.5%)</td>
<td>2.2% (2.0%–2.3%)</td>
</tr>
<tr>
<td>Diabetes (type 1)</td>
<td>942 (1.0%)</td>
<td>202 (1.3%)</td>
<td>950 (0.9%)</td>
<td>0.1% (0.1%–0.2%)</td>
</tr>
<tr>
<td>Diabetes (type 2)</td>
<td>2094 (2.3%)</td>
<td>511 (3.3%)</td>
<td>1636 (1.5%)</td>
<td>0.8% (0.6%–0.9%)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>4438 (4.8%)</td>
<td>943 (6.1%)</td>
<td>3319 (3.1%)</td>
<td>1.7% (1.5%–1.9%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9412 (10.2%)</td>
<td>2187 (14.2%)</td>
<td>7912 (7.3%)</td>
<td>2.8% (2.6%–3.1%)</td>
</tr>
<tr>
<td>Ocular disorders</td>
<td>6449 (7.0%)</td>
<td>1318 (8.6%)</td>
<td>4230 (3.9%)</td>
<td>3.0% (2.9%–3.3%)</td>
</tr>
</tbody>
</table>

Note: All variables were reported at index date except when: (1) measured during the year before index date; (2) measured during the calendar year before index date (365 days); (3) measured from 01 July 2005 to—and including—index date; (4) the use was by definition zero in the M2M-cohort since this indicated severe AD. The use was by definition zero in the M2M-cohort since this indicated severe AD. See Table S1 for ICD-10 codes that were used to define the conditions.

Abbreviations: AD, atopic dermatitis; CI, confidence interval; ICD-10, The International Classification of Diseases version 10.

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

Total years of follow-up in this study were 648,414 person-years (PYS) for AD patients (mean years of follow-up per patient: 6.02 PYS) and 643,197 PYS for the non-AD reference cohort (mean follow-up per patient: 5.97 PYS). Figure 2 shows the proportion of patients by number of developed comorbidities. In the AD cohort, a total of 23.5% developed one comorbidity during follow-up compared to 20.0% in the non-AD cohort. In addition, 15.9% in the AD cohort developed multiple comorbidities (≥2) compared to 7.2% in the non-AD cohort. This implies that among those patients who developed at least one comorbidity, 39.7% and 26.5%
developed multiple comorbidities (≥2) in the AD cohort and the non-AD cohort, respectively.

Neurological disorders (dizziness and giddiness, headache, etc.) were the most common comorbidities in the AD cohort with 8.73% [95% confidence interval (CI): 8.55%–8.91%] of patients getting these events. The most common events in the non-AD reference cohort were skeletal disorders, which occurred in 6.78% of individuals (6.63%–6.94%). See Table 2 for incidence rates for all evaluated conditions and Supporting Information: Table S3 for details for years of follow-up and number of PYS. The incidence of the investigated conditions is graphically displayed using cumulative incidence curves, see Supporting Information: Figures S2–S15.

Risk of comorbidity onset based on HRs

The risk of developing comorbid conditions was analyzed using unadjusted- and adjusted Cox proportional hazard models. The unadjusted models showed a statistically significant increased risk of onset for all analyzed conditions (except T1D) in the AD cohort compared with the non-AD reference cohort, see Table 2.

Figure 3 shows the adjusted HRs for the Cox proportional hazard models. Adult AD patients had a statistically significant increased risk of onset for all analyzed conditions except for T1D and T2D for patients in remission, compared with the non-AD reference cohort. Atopic comorbidities (asthma, allergic rhinitis, and food hypersensitivity) had the highest risk among the analyzed comorbidities, followed by the immunological- & inflammatory disorders and infections. Patients with AD also had a significantly higher risk of developing cardiovascular disease and malignancies compared to the non-AD reference cohort. The AD cohort had more events of malignancies in all subcategories including melanoma, lymphoma and non-Hodgkin lymphoma. See Supporting Information: Table S5 for statistical testing of differences in HRs by AD severity.

A subsample of the non-AD reference cohort [who were required to have had at least one in- or outpatient hospital visit or at least two primary care visits within 1 year before the index date (data not shown)] were studied in the sensitivity analyses to evaluate any possible effect of referral bias. The results from this subsample were consistent with the overall results.

The comparison of AD patients who had an active disease, with AD patients who were in remission (as per definition) showed a statistically significant increase in risk of onset for all analyzed conditions with the only exception of T2D (remission vs. M2M) and skeletal disorders, see lower panel of Figure 3. Although no significantly increased risk of skeletal disorders and AD was found, osteoporosis (a subcategory within skeletal disorders) had a twofold number of events in the AD population compared to the non-AD reference cohort (286 vs. 140 events, statistically significant at α = 0.05).

All models met the proportional hazards assumption based on Schoenfeld residuals after stratification (p < 0.05). Most models needed to be stratified by calendar year of index and region of residence to satisfy the proportional hazards assumption. Detailed Cox regression results can be found in Supporting Information: Tables S5–S8. The distribution of events for each comorbidity endpoint are presented in Supporting Information: Table S9.

DISCUSSION

Using a large population-based cohort of adult AD patients compared to a non-AD reference cohort from real-world clinical settings in Sweden, the present study showed that the comorbidity burden of AD is substantial. Differences in comorbidity burden between AD patients and non-AD reference individuals were present at baseline and continued to develop over time at a higher rate in AD patients. The development of multiple comorbidities, including either allergic or nonallergic, was also more frequent in patients with AD.

The association between atopic disorders and AD is well documented and can aid the physician in diagnosing AD.9 Our results showed that adults with AD are at an increased risk of many other comorbidities that ultimately have a negative effect on quality of life.32 Extending previous findings, we observed a statistically significant association between AD and nonatopic conditions, including neurological disorders,16 psychiatric disorders,17 infections,18,19 immunological- & inflammatory disorders,20 endocrine- & metabolic disorders (excluding T1D and T2D),21 skeletal disorders,16 ocular disorders,22 and cardiovascular diseases.10

In almost all analyses performed in this study, the point-estimate of the HR showed that patients with severe AD had higher risk of comorbidity onset and some differences in risk for comorbidity onset between severity levels were statistically significant. Similarly, adults in remission tended to have a lower risk of comorbidity onset compared with those who had active AD. Moreover, this is the first study showing that even AD patients in remission are at higher risk of comorbidity onset compared with individuals without AD which indicated that the risk of comorbidities is not associated with the skin manifestations of AD only.
### TABLE 2  
Incidence rates for comorbidities in the AD cohort and the non-AD reference cohort.

<table>
<thead>
<tr>
<th>Comorbidity Category</th>
<th>Number of individuals(^a)</th>
<th>Number of events(^b)</th>
<th>Incidence rate per 1000 PYS (95% CI)(^b)</th>
<th>Unadjusted hazard ratios AD cohort vs. non-AD reference cohort(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological disorders (migraine, epilepsy, etc.)</td>
<td>AD cohort 97,591</td>
<td>AD cohort 8517</td>
<td>Incidence rate 14.95 (14.63–15.27)</td>
<td>1.81 (1.75–1.88)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 101,952</td>
<td>Non-AD reference cohort 4948</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections (influenza, acute upper respiratory infections, etc.)</td>
<td>AD cohort 93,574</td>
<td>AD cohort 7847</td>
<td>Incidence rate 14.39 (14.08–14.71)</td>
<td>2.01 (1.94–2.09)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 101,432</td>
<td>Non-AD reference cohort 4285</td>
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<tr>
<td>Skeletal disorders (fractures, osteoporosis, etc.)</td>
<td>AD cohort 96,934</td>
<td>AD cohort 7843</td>
<td>Incidence rate 13.80 (13.50–14.11)</td>
<td>1.19 (1.15–1.23)</td>
</tr>
<tr>
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<td>Non-AD reference cohort 98,462</td>
<td>Non-AD reference cohort 6677</td>
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<tr>
<td>Immunological &amp; inflammatory disorders (Celiac disease, psoriasis, etc.)</td>
<td>AD cohort 94,572</td>
<td>AD cohort 7350</td>
<td>Incidence rate 13.34 (13.03–13.64)</td>
<td>2.15 (2.07–2.24)</td>
</tr>
<tr>
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<td>Non-AD reference cohort 101,877</td>
<td>Non-AD reference cohort 3723</td>
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<tr>
<td>Psychiatric disorders (sleep disorders, anxiety disorders, etc.)</td>
<td>AD cohort 93,280</td>
<td>AD cohort 7097</td>
<td>Incidence rate 12.73 (13.34)</td>
<td>1.43 (1.38–1.49)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 97,550</td>
<td>Non-AD reference cohort 5186</td>
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<tr>
<td>Ocular disorders (keratitis, blepharitis, etc.)</td>
<td>AD cohort 100,007</td>
<td>AD cohort 6604</td>
<td>Incidence rate 11.27 (11.00–11.54)</td>
<td>1.89 (1.81–1.97)</td>
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<tr>
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<td>Non-AD reference cohort 103,544</td>
<td>Non-AD reference cohort 3645</td>
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<tr>
<td>Cardiovascular disease (hypertension, venous thrombotic events, etc.)</td>
<td>AD cohort 96,175</td>
<td>AD cohort 4762</td>
<td>Incidence rate 7.98 (7.85–8.45)</td>
<td>1.16 (1.11–1.21)</td>
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<td>Non-AD reference cohort 99,862</td>
<td>Non-AD reference cohort 4204</td>
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<tr>
<td>Malignancies (solid tumour without metastasis, lymphoma, etc.)</td>
<td>AD cohort 102,393</td>
<td>AD cohort 4465</td>
<td>Incidence rate 7.11 (7.54)</td>
<td>1.41 (1.35–1.48)</td>
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<tr>
<td></td>
<td>Non-AD reference cohort 104,455</td>
<td>Non-AD reference cohort 3207</td>
<td></td>
<td></td>
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<tr>
<td>Allergic rhinitis</td>
<td>AD cohort 99,136</td>
<td>AD cohort 3623</td>
<td>Incidence rate 6.03 (6.43)</td>
<td>5.13 (4.73–5.55)</td>
</tr>
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<td>Non-AD reference cohort 106,512</td>
<td>Non-AD reference cohort 769</td>
<td></td>
<td></td>
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<tr>
<td>Asthma</td>
<td>AD cohort 99,667</td>
<td>AD cohort 2181</td>
<td>Incidence rate 3.54 (3.85)</td>
<td>12.54 (10.81–14.56)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 106,914</td>
<td>Non-AD reference cohort 188</td>
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<tr>
<td>Endocrine &amp; metabolic disorders (overweight, obesity, etc.)</td>
<td>AD cohort 101,444</td>
<td>AD cohort 1894</td>
<td>Incidence rate 2.95 (3.23)</td>
<td>1.59 (1.48–1.71)</td>
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<td></td>
<td>Non-AD reference cohort 104,019</td>
<td>Non-AD reference cohort 1207</td>
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<tr>
<td>Food hypersensitivity</td>
<td>AD cohort 104,977</td>
<td>AD cohort 1722</td>
<td>Incidence rate 2.62 (2.88)</td>
<td>6.85 (6.01–7.81)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 107,381</td>
<td>Non-AD reference cohort 257</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>AD cohort 105,169</td>
<td>AD cohort 226</td>
<td>Incidence rate 0.31 (0.40)</td>
<td>1.46 (1.19–1.79)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 106,138</td>
<td>Non-AD reference cohort 154</td>
<td></td>
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<tr>
<td>Type 1 diabetes</td>
<td>AD cohort 106,630</td>
<td>AD cohort 174</td>
<td>Incidence rate 0.23 (0.31)</td>
<td>1.07 (0.87–1.33)</td>
</tr>
<tr>
<td></td>
<td>Non-AD reference cohort 106,824</td>
<td>Non-AD reference cohort 161</td>
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</table>

Abbreviations: 95% CI, 95% confidence interval; AD, atopic dermatitis; PYS, patient-years.

\(^a\) Individuals with the condition of interest at baseline were excluded.

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

\(^c\) Unadjusted Cox regression models used the presence of AD as the single covariate when estimating the hazard ratio.
FIGURE 3  (See caption on next page).
The mechanisms behind the increased risk of these conditions were not investigated in this study but previous literature points towards multiple causes including skin barrier defects and adverse effects of AD treatments that may underly these comorbidities.33–38

The results from the present study add to the growing body of evidence suggesting that AD should be diagnosed and managed as a systemic condition, or at least it should be recognized that patients with AD can have multiple comorbidities, including nonatopic conditions.6,10 This highlights the need for physicians to take a holistic approach when treating AD and to ensure that patients are monitored for the development of comorbidities on a continuous basis even when symptoms of AD are in remission.

Malignancy

The relationship between AD and malignancy is complex and remains controversial.6 Multiple studies have analyzed the relationship between AD, AD treatments, and malignancy. A previous meta-analysis showed an increased risk for lymphoma in AD cohort studies, but none in case-control studies.39 The literature on the relationship between AD treatments and cancer shows mixed results. Some studies show no association34,35,38,40 while other studies cannot reject an association between the AD treatment and elevated risk for cancer.36,37,40

Cardiovascular disease

Previous studies have reported conflicting results regarding a possible association between AD and cardiovascular diseases. A systematic review and meta-analysis showed that it is unlikely that AD represents an independent and clinically relevant risk factor for cardiovascular diseases.41 The present study could not control some risk factors for cardiovascular disease, such as diet, smoking or low physical activity. These poor health behaviors of patients with AD might have contributed to statistically significantly higher risk of onset of cardiovascular diseases in the AD cohort compared to the non-AD reference cohort.

Immunological & inflammatory disorders

Immunological & inflammatory disorders showed the highest risk of onset in the AD population after the atopic comorbidities. This is perhaps unsurprising as closely related skin conditions are included in this group but the higher risk was also driven by noncutaneous diseases such as ulcerative colitis, rheumatoid arthritis and Crohn’s disease. A previous Danish study showed that adult AD was significantly associated with 11 of 22 examined autoimmune diseases20 and AD has been shown to be a significant risk factor for the development of rheumatoid arthritis and inflammatory bowel disease.42 The full mechanisms linking AD to immunological and inflammatory disorders are not completely understood although known shared susceptibility loci may explain some of the higher risks.

Infections

The results from this study showed that infections had the second highest risk aside from the atopic comorbidities. These results are supported by other studies showing significantly higher odds of infections in AD patients.43,44 Skin barrier defects are potentially contributing factors for the increased risk of skin infections in AD.18 Moreover, Th2/Th1 imbalance which is typically present in patients with AD may contribute to the higher risk of infections as Th2-driven responses are believed to impair the innate immunity defenses against bacterial infections.45,46

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 the AD remission cohort: The Cox regression models used the displayed condition as endpoints and included the covariates: M2M 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. Sociodemographics were defined using age, sex (measured at index), education and household income (measured during the calendar year before the index date). Pre-existing conditions profile was measured from 1 July 2005 to—and including—the index date. The calendar year for index date, and the region of residence were also included as covariates. 95% confidence intervals are presented in the parentheses. Patients were followed from the index date to comorbidity event or censoring [death, emigration, or end of study period (31 December 2018)]. AD, atopic dermatitis; End., endocrine; imm., immunological; inf., inflammatory; M2M, mild-to-moderate; met., metabolic; T1, type 1; T2, type 2.
Diabetes

The significant higher risk of T2D for patients with M2M and severe AD observed in our study differentiates from the results in a Danish study. The Danish study suggests that the association between AD and diabetes could be linked to other factors which the present study could not control for. The imbalance between Th2 and Th1 in patients with AD may have a protective effect on T1D, a Th1-driven disease and our results support this hypothesis.

Strength and limitations

A major strength of this study is the comprehensive assessment of comorbidities in adult AD patients in this population-based registry study. This study included over 200,000 individuals (AD patients and non-AD reference individuals combined), more than 1.2-million-person years of follow-up and almost 100 individual conditions grouped into 14 comorbidity-categories. The main results were based on comparisons between the AD cohort and a matched non-AD reference cohort. In addition to these results, we also compared patients with an active AD disease to patients in remission to demonstrate the robustness of the findings and we observed similar results. Moreover, all models included age, sex, income, education-level, employment status, region residence as well as the presence of other comorbidities which address some of the risk of confounding that generally exists in observational studies like this.

The longitudinal Swedish register data used in this analysis allowed for the evaluation of a wide range of comorbidities in a single cohort with a high level of coverage. Both primary and specialist care registers were utilized in the present study to identify AD patients, allowing the inclusion of the mildest to the most severe AD patients.

Despite the comprehensive databases used in the present study, certain limitations still exist. Most importantly, data on clinical assessments of severity of AD were not available. Instead, disease severity was assessed through a case-finding algorithm that relied on registry-based diagnosis and medication data based on treatment guidelines as a proxy.

Misclassification of AD was possible since this study lacked complete coverage of primary care data in Sweden. Patients with an AD diagnosis from a primary care region which was not included in this study may have been included in the non-AD reference cohort. However, while sampling of the non-AD reference cohort, an inclusion criterion of no dispensation of TCSs and TCIs was used, therefore the number of misclassified AD patients in the non-AD reference cohort should be low but cannot be completely ruled out. The ICD-10 code used for AD (L20+) identification in this study has a positive predictive value of 92% as validated in a Danish study which can be generalized to a Swedish setting. Misclassified AD patients in the non-AD reference cohort would likely bias the results towards smaller differences being observed between cohorts, when the true difference may be higher. Finally, given the observational design of the present study, the observed association between AD and various comorbidities might have also been confounded by factors that were not observable in this study like smoking and alcohol consumption or body weight. Nonetheless, the study did control for various sociodemographic factors like income, education and employment status.

Future research

The associations between AD severity and remission with the onset of a large number of comorbidities may be attributable directly to disease severity or mediated indirectly by treatment decisions. Due to the current fast-paced development of pharmaceuticals in AD, the interplay between comorbidity, disease severity and treatments should be further investigated. Both adult and pediatric patients with AD have been shown to have a high comorbidity burden with large differences between the incidence of many comorbidities. Additional investigations of these differences may yield data that could be used to further improve the long-term management of AD.

CONCLUSIONS

The clinical burden of AD is substantial, and adult patients are at an increased risk of developing a large number of comorbid conditions that extend well beyond the atopic disorders. This study highlights the need for interdisciplinary approaches in the management and care of adult AD patients.

AUTHOR CONTRIBUTIONS

All authors participated in the conceptualization and methodology of this study. Gustaf Ortsäter, Alexander R. Dun, Kirk Geale and Ingrid Lindberg were involved in data curation, formal analysis, investigation, resources, software programming, creation of visualizations, and writing original draft. Dan Henrohn, Maureen P. Neary, Petra Neregård, Anna De Geer, Amy Cha, William
Romero and Joseph C. Cappelleri were involved in supervision and validation of the work. Maureen P. Neary acquired financial support and administered this project. 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, and have provided final approval of the version to be published.

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CONFLICTS OF INTEREST STATEMENT
Amy Cha and Joseph C. Cappelleri are employed by Pfizer Inc. and own Pfizer stock and/or stock options. William Romero is employed by Pfizer Ltd and owns Pfizer stock and/or stock options. Dan Henrohn was an employee of Pfizer AB and owned Pfizer stocks at the time of this work. Maureen P. Neary was an employee of Pfizer Inc. and owned 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. Maureen P. Neary was an employee of Pfizer AB and owned Pfizer stocks at the time of this work. William Romero is employed by Pfizer Ltd and owns Pfizer Inc. and own Pfizer stock and/or stock options. Amy Cha and Joseph C. Cappelleri are employed by Pfizer Inc. and own Pfizer stock and/or stock options.

DATA AVAILABILITY STATEMENT
Data used in this study is 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.

ETHICS STATEMENT
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.

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REFERENCES


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