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Title

Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis

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Author Contributions

Drs. Egeberg and Gislason had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Egeberg.

Acquisition, analysis, and interpretation of data: All authors. *Drafting of the manuscript:* Thyssen and Egeberg. *Critical revision of the manuscript for important intellectual content:* All authors.

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Abstract

Background

Atopic dermatitis (AD) is a common chronic skin disorder, which may persist into adulthood, however the prevalence of comorbidities in patients with AD is not well characterized. AD is considered a systemic disorder like psoriasis, which has raised a need for data on the comorbidity profile of patients with AD, to assess the potential risks, benefits, and complications in management of patients with AD. We described the occurrence of medical and psychiatric comorbidities and associated risk factors in adults with AD compared with psoriasis and the general population.

Methods

All Danish individuals aged ≥ 18 years with a hospital (inpatient or ambulatory) diagnosis of AD or psoriasis during the study period (January 1st 1995 – December 31st 2012) were linked in administrative registers.

Results

Overall, prevalence of smoking and alcohol abuse was higher among AD patients than the general population, but lower than psoriasis patients. Similarly, AD patients had more risk factors and higher prevalence of comorbidity than the general population, but lower prevalence and reduced risk compared to psoriasis patients, except for use of anxiolytics, which was higher in severe AD.

Prevalence of diabetes was lower in AD than psoriasis patients as well as general population controls.

Conclusions

Despite an increased risk of various medical and psychiatric comorbidities compared to general population controls, adult AD patients had markedly lower prevalence of cardiovascular disease than psoriasis patients. However, prevalence of psychiatric co-morbidity and tobacco smoking was alarmingly high in severe AD patients, which might be target for intervention in patient management.

Introduction

Atopic dermatitis (AD) is a common chronic and relapsing disease of childhood that persists into adulthood in as many as 50% of patients.¹ Little is known about risk factors for disease persistence, but they include early onset of AD, filaggrin gene (*FLG*) mutations, and atopic comorbidity.^{2,3} While AD has troubled physicians and affected patients for centuries, AD first became epidemic (or endemic) after World War II with continuously increasing incidence rates reported in Western Europe.^{4,5}

These relatively large generations of AD patients have now become adult, and it is therefore relevant to examine whether they have comorbidities, beyond the atopic ones, that should be addressed by treating physicians. Recent studies have shown that adult patients with AD have co-occurrence of inflammatory bowel disease (IBD), rheumatoid arthritis, anxiety, and depression, but also type 2 diabetes, hypertension, stroke, and cardiovascular disease (CVD).^{6–10} We recently showed that Danish adult patients with severe AD indeed had a higher incidence of major adverse cardiovascular events, compared with age- and sex-matched controls from the general population; however, after adjustment for smoking and other modifiable risk factors, the ‘independent’ risk conferred by AD was non-significant.¹¹ The negative CVD finding was recently supported by a US study.¹² One explanation for the somewhat conflicting results could be differences in life style factors, but also in patient management and use of systemic therapy as well as study design and analysis.

AD has been put forward as a systemic disorder similar to psoriasis.¹³ A clinically relevant question is whether AD patients with extra-cutaneous inflammation would benefit from systemic anti-inflammatory agents, e.g. to prevent the occurrence of CVD or other inflammatory comorbidities. A natural first step is an examination of risk factors and comorbidity in AD patients. In this study, we primarily compared patients with AD and psoriasis, respectively, but also included general population controls. We examined health care, socioeconomic and prescription claims data from nationwide registers, to estimate the prevalence of comorbidity and associated risk factors, i.e. a measure of disease burden in patients with AD.

Materials and methods

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark.

Data sources

Each Danish citizen receives a unique identification number at birth or on immigration, which enables unambiguous linkage among all Danish population-based administrative and health registries.¹⁴ The universal Danish National Health Service provides tax-supported health care to all residents with unrestricted access to hospitals and general practitioners. The Danish National Patient Register contains information on all patients admitted to Danish hospitals as well as outpatient (ambulatory) visits according to the Danish version of the International Classification of Diseases (ICD).¹⁵ All pharmacy-dispensed prescriptions in Denmark are recorded in the Register of Medicinal Product Statistics, and drugs are classified according to the Anatomical Therapeutic Chemical classification.¹⁶

Study population and covariates

We identified all Danish adults (aged ≥ 18 years) with an inpatient or outpatient (ambulatory) diagnosis of AD (ICD-10 L20) or psoriasis (ICD-10 L40) during the study period (January 1st 1995 – December 31st 2012). Patients were classified with severe disease if they received systemic therapy for AD (methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids, psoralen plus ultraviolet A [PUVA], or cyclosporine) or psoriasis (methotrexate, PUVA, retinoids, cyclosporine, adalimumab, efalizumab, etanercept, infliximab, or ustekinumab) consistent with severe disease. Moreover, each patient with AD was matched (on age and sex) with 10 healthy control subjects from the general population. All comparative analyses were performed between AD and psoriasis patients with, respectively, mild and severe disease.

The examined comorbidities and risk factors were chosen *a priori* and identified within the same study period based on administrative codes (available as online supplementary material). Patients with concurrent diagnoses of both Crohn's disease and ulcerative colitis were characterized as having "unspecified IBD", as these conditions may be subject to diagnostic overlap. Collection of data on

smoking history and alcohol abuse was performed as described previously.^{17,18} We calculated an age-standardized index of socioeconomic status between 0 and 4 based on the average gross annual income during a 5-year period before study inclusion. As a measure of healthcare consumption, the total number of dermatology clinic visits in the study period was identified by all in- and outpatient contacts in the ICD-10 code group “L”.

Statistical analysis

Categorical variables were presented in frequencies and continuous variables in means and standard deviations (SD). Logistic regression analysis was used to estimate crude and adjusted odds ratios (aOR). Multivariate models were adjusted for age, sex, socioeconomic status, and healthcare consumption.

Results were presented with 95% confidence intervals where applicable. All analyses were performed using STATA version 13.0 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

The final study population comprised a total of 7,937 and 24,505 adults with AD and psoriasis, respectively, and 79,370 general population controls matched with the AD cohort on age and sex.

There was a strong female predominance (61.8%) among patients with AD, and 58.2% were categorized with severe disease. Among patients with psoriasis, 51.2% were females, and 44.4% of patients were classified with severe disease. Patients with AD were generally younger compared with patients with psoriasis (34.3 versus 45.5 years), as shown in Table 1. Moreover, patients with AD generally had more risk factors and a higher prevalence of co-morbidity than general population controls, but a reduced risk compared to patients with psoriasis (Table 2). The exception to this observation was the use of anxiolytics which was higher in AD patients with severe disease and the

prevalence of diabetes which was lower in AD patients when compared to patients with psoriasis as well as general population controls. Details are provided below.

Smoking

In the entire cohort, the prevalence of smoking was 14.6% and 21.4% for AD and psoriasis, respectively, with an AD-to-psoriasis aOR of 0.79 (0.73-0.85) (Figure 1). Stratified by disease severity the prevalence of smoking was 9.7% and 21.2% in patients with mild AD and psoriasis, respectively (aOR 0.52; 0.46-0.59), and 18.1% and 21.5% in patients with severe AD and psoriasis, respectively (aOR 0.98; 0.90-1.08) (Table 2).

Alcohol abuse

The prevalence of alcohol abuse was 7.1% among patients with AD, and 12.5% in patients with psoriasis (aOR 0.57; 0.52-0.63) (Figure 1). Among patients with mild disease, the prevalence was 5.9% and 14.0% in patients with AD and psoriasis, respectively (aOR 0.41; 0.35-0.48), and in patients with severe disease the prevalence was 7.9% and 10.6%, respectively (aOR 0.81; 0.71-0.92).

Pharmacotherapy

The prevalence of cholesterol-lowering drug use was significantly lower among patients with AD compared with psoriasis (14.8% and 30.4%), yielding an aOR of 0.55 (0.51-0.59). Antidepressant drug use was less common among patients with AD than those with psoriasis (32.1% and 39.8%, aOR 0.78; 0.74-0.83). Similar results were found when patients were stratified based on disease severity (Table 2) (Figure 3). The prevalence of anxiolytic drug use was lower among patients with AD (34.7%) compared with psoriasis (39.7%), whereas the multivariable model demonstrated a slightly higher risk of anxiolytic drug use among patients with AD (aOR 1.07; 1.01-1.13). Stratified by disease severity, the prevalence of anxiolytic drug use was lower for AD than psoriasis (24.6% and 40.7%) in patients with mild disease (aOR 0.45; 0.40-0.51), whereas the prevalence was higher

among patients with severe AD (41.9%) compared with severe psoriasis (38.5%), yielding an aOR of 1.49 (1.38-1.61) (Figure 3).

Medical comorbidity

The prevalence (AD versus psoriasis) and risk of myocardial infarction (2.0% and 4.9%), stroke (3.0% and 6.9%), hypertension (15.0% and 33.9%), renal disease (2.3% and 4.5%), diabetes (4.7% and 15.5%), cancer (9.0% and 17.5%), Crohn's disease (0.6% and 0.8%), and unspecified IBD (0.3% and 0.4%) were all significantly lower among AD compared with psoriasis in adjusted analyses (Table 2) (Figure 2). There was no significant difference in the prevalence (1.4% and 1.6%) and risk (aOR 0.84; 0.67-1.05) of ulcerative colitis. Findings were similar among patients with mild disease, whereas the prevalence and risk of medical comorbidity for the most part were comparable for patients with severe AD or psoriasis (Table 2) (Figure 2).

Psychiatric comorbidity

The prevalence of hospital-diagnosed depression was lower (3.0% and 5.2%) for AD than psoriasis (aOR 0.71; 0.61-0.82). Similar results were found among patients with mild disease (2.2% and 5.7%, aOR 0.49; 0.38-0.62), whereas the prevalence and risk of depression was comparable among patients with severe AD (3.6%) or psoriasis (4.5%), yielding an aOR of 0.95 (0.74-1.14). For hospital-diagnosed anxiety, there were no differences in overall or severity stratified estimates (Table 2) (Figure 3).

Discussion

In this nationwide register-based study, which examined data on life-style factors, pharmacotherapy use, and comorbidity in Danish adults, we showed that patients with AD generally experienced much less medical comorbidity than patients with psoriasis. However, patients with severe AD, who received systemic treatment, had a similar high prevalence of smoking, stroke, inflammatory bowel

disease, depression, and anxiety. The use of anxiolytic drugs even exceeded that of patients with severe psoriasis.

Recently, there has been a growing interest in life-style factors, drug consumption and comorbidity associated with AD. Studies from Taiwan and the US have shown that adult patients with AD are more likely to have hypertension, CVD, stroke, and type 2 diabetes than control subjects without AD.^{7,8,19} This raises the question of whether the prevalence of medical comorbidity is as high as for patients with other skin conditions such as psoriasis, since this should warrant the attention of treating physicians and health care authorities. Based on our nationwide data from Denmark, the prevalence of CVD comorbidity appears to be markedly lower in patients with AD than among patients with psoriasis, even when adjusting for differences such as age and sex. The only exceptions were hypertension and stroke in patients with severe AD, but we emphasize that even though the risk was increased the prevalence was similar. Possible reasons for the generally higher prevalence of CVD in psoriasis patients include high body weight, physical inactivity, alcohol consumption and a higher degree of systemic inflammation, which could result in arteriosclerosis.^{20,21} While the risk of CVD was higher in AD patients than in controls, in a recent study using the same databases as for the present study, we showed that the risk CVD was similar among patients with AD and controls after adjustment for life-style factors, pharmacotherapy, and comorbid conditions.¹¹ A similar finding was afterwards reported from the US.¹² Moreover, we found that the occurrence of diabetes type 2 was lower in AD patients when compared to general population controls, again suggesting that diabetes and CVD risk appears not be increased in Danish adults with AD. The conclusion is that despite the increased relative risk of CVD in AD patients, the numerical risk is comparable to controls.

Both depression and anxiety was prevalent among patients with AD, and in particular among those with severe disease where they reached the estimates for psoriasis. In line with this, smoking and alcohol consumption was increased, and in particular among AD patients with severe disease. Mental

health problems seem to develop already in childhood, and should warrant the clinicians' attention.^{22,23} Indeed, several studies have shown that AD has a profound negative impact on patient's quality of life.²⁴ Several factors could be important for the development of mental health disorders in AD patients, including behavioral problems and family disruption as well as concentration problems, potentially increasing the risk of attention deficit/hyperactivity disorder (ADHD).^{25,26} Moreover, AD may disrupt normal sleep patterns, primarily due to pruritus, which could also influence the risk and prognosis of psychiatric comorbidity but also the use of anxiolytics.^{27,28} Hence, the higher use of anxiolytics in AD patients in this study could be explained by sleep problems as well as anxiety. However, hospital (psychiatrist) diagnosed depression and anxiety may represent more severe cases, whereas antidepressant and anxiolytic therapy may also be prescribed by general practitioners whereby patients may not necessarily receive a diagnosis of depression or anxiety. It is currently unclear whether aggressive medical treatment of AD may reduce the risk of psychiatric comorbidity, and future studies are needed to elucidate this important question. We conclude that both the relative and numerical risk of psychiatric comorbidity is increased in adults with AD.

Interestingly, the risk of IBD was similar in AD and psoriasis patients with severe disease. Such data could emphasize the existence of a pathogenic overlap, partly due to shared genetic risk loci,^{29,30} although certain medication may also induce or exacerbate such conditions.

Certain limitations apply to the interpretation of the present results. We examined the prevalence of comorbidity in adults with AD, and extrapolation to children may not be appropriate. Similarly, the Danish population is predominantly white and of Northern European descent and the results may differ among countries and ethnicities. Also, while dichotomous data on smoking history were available, the lack of quantitative data on smoking and alcohol abuse (e.g. number of cigarettes or grams of alcohol consumed per day and number of years) should be emphasized. However, the high frequency of smoking among patients with severe AD should nonetheless warrant focus on smoking cessation. In addition, disease severity was based on use of systemic therapy, and it is likely that some

patients may be undertreated, e.g. managed only with topical therapies even though they have severe AD or psoriasis. Moreover, our study relied on hospital (including dermatology outpatient clinic) diagnoses of AD and psoriasis, and such patients may differ from patients solely treated by their general practitioner or patients not seeking medical treatment at all. Important strengths of the study include the high accuracy of the nationwide registries, the available information on household income, as well as the large number of patients.

In conclusion, we showed in this nationwide study that despite having increased risk of various medical and psychiatric comorbidities when compared to general population controls, adult patients with AD had a much lower prevalence of CVD when compared to psoriasis patients. However, the prevalence of psychiatric co-morbidity and tobacco smoking was alarmingly high in severe AD patients and this should warrant clinicians' attention and might be target for intervention when managing both adolescent and adult patients with AD.

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Figure legends

Figure 1

Title:

Smoking and alcohol abuse

Legend:

Prevalence (%) of smoking and alcohol abuse among patients with atopic dermatitis and psoriasis

Figure 2

Title:

Medical comorbidity

Legend:

Prevalence (%) of medical comorbidity among patients with atopic dermatitis and psoriasis

Figure 3

Title:

Psychiatric burden

Legend:

Prevalence (%) of depression, anxiety, and use of antidepressants and anxiolytics, respectively,
among patients with atopic dermatitis and psoriasis

Table 1 – Demographic characteristics of the study population

	Atopic dermatitis (n=7,937)	Psoriasis (n=24,505)	p-value	General population (n=79,370)	p-value
Overall					
Age, mean (SD)	34.3 (14.1)	45.5 (15.4)	<0.001	34.3 (14.1)	1.000
Sex, n (%)			<0.001		1.000
Women	4,901 (61.8)	12,544 (51.2)		49,010 (61.8)	
Men	3,036 (38.2)	11,961 (48.8)		30,360 (38.2)	
Severe disease, n (%)	4,620 (58.2)	10,891 (44.4)	<0.001	46,200 (58.2)*	1.000
Socioeconomic status, n (%)			<0.001		<0.001
Lowest	2,497 (31.5)	3,992 (16.3)		16,897 (21.2)	
Below average	1,738 (17.4)	5,110 (28.9)		15,486 (19.5)	
Average	1,394 (17.6)	5,094 (20.8)		15,611 (19.7)	
Above average	1,342 (16.9)	5,147 (21.0)		15,734 (19.8)	
Highest	1,326 (16.7)	5,162 (21.1)		15,642 (19.7)	
Age <30 years, n (%)	3,906 (49.2)	4,512 (18.4)	<0.001	39,060 (49.2)	<0.001
Age, mean (SD)	23.5 (3.5)	24.5 (3.5)	<0.001	23.5 (3.5)	1.000
Sex, n (%)			<0.001		<0.001
Women	2,621 (67.1)	2,292 (50.8)		26,210 (67.1)	
Men	1,285 (32.9)	2,220 (49.2)		12,850 (32.9)	
Severe disease, n (%)	2,008 (51.4)	2,079 (46.1)	<0.001	20,080 (51.4)*	1.000
Socioeconomic status, n (%)			<0.001		<0.001
Lowest	2,164 (55.4)	1,964 (43.5)		11,264 (28.8)	
Below average	744 (19.1)	1,013 (22.5)		12,835 (32.9)	
Average	565 (14.5)	849 (18.6)		7,811 (20.0)	
Above average	334 (8.6)	540 (12.0)		5,145 (13.2)	
Highest	99 (2.5)	155 (3.4)		2,005 (5.1)	
Age 30-40 years, n (%)	1,829 (23.0)	4,913 (20.1)	<0.001	18,290 (23.0)	<0.001

Age, mean (SD)	34.5 (2.9)	35.1 (2.9)	<0.001	34.5 (2.9)	1.000
Sex, n (%)			<0.001		<0.001
Women	1,081 (59.1)	2,409 (49.0)		10,810 (59.1)	
Men	748 (40.9)	2,504 (51.0)		7,480 (40.9)	
Severe disease, n (%)	1,138 (62.2)	2,367 (48.2)	<0.001	11,380 (62.2)*	1.000
Socioeconomic status, n (%)			0.001		<0.001
Lowest	148 (8.1)	422 (8.6)		3,194 (17.5)	
Below average	215 (11.8)	709 (14.4)		748 (4.1)	
Average	426 (23.3)	1,137 (23.1)		2,846 (15.6)	
Above average	525 (28.7)	1,471 (29.9)		5,268 (28.8)	
Highest	515 (28.2)	1,174 (23.9)		6,234 (34.1)	
Age >40 years, n (%)	2,202 (27.7)	15,080 (61.5)	<0.001	22,020 (27.7)	<0.001
Age, mean (SD)	53.3 (18.8)	55.1 (10.8)	<0.001	53.3 (18.8)	1.000
Sex, n (%)			0.032		<0.001
Women	1,199 (54.5)	7,843 (52.0)		11,990 (54.5)	
Men	1,003 (45.6)	7,237 (48.0)		10,030 (45.6)	
Severe disease, n (%)	1,474 (66.9)	6,445 (42.7)	<0.001	14,740 (66.9)*	1.000
Socioeconomic status, n (%)			<0.001		<0.001
Lowest	185 (8.4)	1,606 (10.7)		2,439 (11.1)	
Below average	419 (19.0)	3,388 (22.5)		1,903 (8.6)	
Average	403 (18.3)	3,117 (20.7)		4,954 (22.5)	
Above average	483 (21.9)	3,136 (20.8)		5,231 (24.2)	
Highest	712 (32.3)	3,833 (25.4)		7,403 (33.6)	

SD, standard deviation

*Matched healthy controls for patients with severe atopic dermatitis

Table 2 – Absolute numbers and adjusted odds ratios for association between comorbidities and associated risk factors in patients with atopic dermatitis compared with patients with psoriasis and the general population, respectively

	Overall								
	AD, n (%) (n=7,937)	Psoriasis, n (%) (n=24,505)	General population, n (%) (n=79,370)	AD versus psoriasis			AD versus general population		
				Adjusted OR*	95% CI	p-value	Adjusted OR*	95% CI	p-value
Smoking	1,157 (14.6)	5,235 (21.4)	7,196 (9.1)	0.79	0.73-0.85	<0.0001	1.32	1.22-1.42	<0.0001
Alcohol abuse	563 (7.1)	3,068 (12.5)	3,520 (4.4)	0.57	0.52-0.63	<0.0001	1.38	1.24-1.53	<0.0001
Hypertension	1,192 (15.0)	8,294 (33.9)	9,571 (12.1)	0.58	0.54-0.63	<0.0001	1.09	1.01-1.19	0.0332
Myocardial infarction	159 (2.0)	1,205 (4.9)	1,290 (1.6)	0.71	0.59-0.84	0.0001	1.10	0.92-1.33	0.2982
Stroke	234 (3.0)	1,685 (6.9)	1,559 (2.0)	0.78	0.68-0.91	0.0010	1.52	1.32-1.74	<0.0001
Cancer	711 (9.0)	4,282 (17.5)	5,376 (6.8)	0.80	0.73-0.87	0.0001	1.20	1.09-1.32	0.0002
Renal disease	181 (2.3)	1,104 (4.5)	884 (1.1)	0.84	0.71-0.99	0.0361	1.67	1.40-2.00	<0.0001
Diabetes	453 (5.7)	3,792 (15.5)	4,135 (5.2)	0.47	0.42-0.52	<0.0001	0.81	0.72-0.91	0.0005
Crohn's disease	49 (0.6)	198 (0.8)	263 (0.3)	0.59	0.43-0.83	0.0019	1.65	1.20-2.26	0.0020
Ulcerative colitis	112 (1.4)	385 (1.6)	557 (0.7)	0.84	0.67-1.05	0.1258	1.85	1.49-2.29	<0.0001
Unspecified IBD	27 (0.3)	100 (0.4)	113 (0.1)	0.58	0.37-0.91	0.0176	2.10	1.37-3.23	0.0007
Depression	240 (3.0)	1,263 (5.2)	1,314 (1.7)	0.71	0.61-0.82	<0.0001	1.57	1.35-1.83	<0.0001
Antidepressant use	2,546 (32.1)	9,748 (39.8)	18,472 (23.3)	0.78	0.74-0.83	<0.0001	1.20	1.13-1.27	<0.0001
Anxiety	95 (1.2)	316 (1.3)	592 (0.8)	0.81	0.63-1.03	0.0828	1.43	1.14-1.79	0.0021
Anxiolytic use	2,750 (34.7)	9,727 (39.7)	15,583 (19.6)	1.07	1.01-1.13	0.0187	1.48	1.39-1.57	<0.0001

Cholesterol-lowering drugs	1,176 (14.8)	7,437 (30.4)	9,677 (12.2)	0.55	0.51-0.59	<0.0001	1.11	1.03-1.20	0.0072
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	Mild disease								
	Mild AD, n (%) (n=3,317)	Mild psoriasis, n (%) (n=13,614)	General population, n (%) (n=33,170)	Mild AD versus mild psoriasis			Mild AD versus general population		
				Adjusted OR*	95% CI	p-value	Adjusted OR*	95% CI	p-value
Smoking	323 (9.7)	2,891 (21.2)	2,818 (8.5)	0.52	0.46-0.59	<0.0001	0.86	0.75-0.99	0.0323
Alcohol abuse	197 (5.9)	1,912 (14.0)	1,358 (4.1)	0.41	0.35-0.48	<0.0001	1.26	1.06-1.49	0.0073
Hypertension	350 (10.6)	4,573 (33.6)	3,437 (10.4)	0.44	0.39-0.50	<0.0001	0.83	0.72-0.95	0.0083
Myocardial infarction	43 (1.3)	691 (5.1)	452 (1.4)	0.52	0.38-0.71	0.0001	0.88	0.63-1.23	0.4704
Stroke	71 (2.1)	1,061 (7.8)	541 (1.6)	0.57	0.45-0.74	<0.0001	1.23	0.94-1.60	0.1343
Cancer	216 (6.5)	2,518 (18.5)	1,906 (5.8)	0.59	0.50-0.68	<0.0001	0.97	0.82-1.14	0.6742
Renal disease	59 (1.8)	659 (4.8)	308 (0.9)	0.75	0.57-0.99	0.0427	1.68	1.25-2.26	0.0005
<i>(Table 2 continued)</i>									
	Mild AD, n (%) (n=3,317)	Mild psoriasis, n (%) (n=13,614)	General population, n (%) (n=33,170)	Mild AD versus mild psoriasis			Mild AD versus general population		
				Adjusted OR*	95% CI	p-value	Adjusted OR*	95% CI	p-value
Diabetes	161 (4.9)	2,109 (15.5)	1,512 (4.6)	0.44	0.37-0.53	<0.0001	0.82	0.68-0.98	0.0334
Crohn's disease	8 (0.2)	99 (0.7)	105 (0.3)	0.27	0.13-0.57	0.0006	0.71	0.35-1.46	0.3532
Ulcerative colitis	36 (1.1)	204 (1.5)	237 (0.7)	0.66	0.45-0.97	0.0325	1.45	1.01-2.06	0.0428
Unspecified IBD	4 (0.1)	44 (0.3)	55 (0.2)	0.28	0.10-0.80	0.0173	0.69	0.25-1.91	0.4757

Depression	72 (2.2)	776 (5.7)	532 (1.6)	0.49	0.38-0.63	<0.0001	1.26	0.98-1.62	0.0755
Antidepressant use	893 (26.9)	5,401 (39.7)	7,685 (23.2)	0.64	0.59-0.70	<0.0001	0.89	0.81-0.98	0.0136
Anxiety	36 (1.1)	178 (1.3)	240 (0.7)	0.72	0.49-1.06	0.0978	1.39	0.97-1.98	0.0711
Anxiolytic use	816 (24.6)	5,538 (40.7)	6,215 (18.7)	0.66	0.60-0.72	<0.0001	1.05	0.95-1.16	0.3392
Cholesterol-lowering drugs	367 (11.1)	3,880 (28.5)	3,416 (10.3)	0.45	0.40-0.51	<0.0001	0.96	0.84-1.09	0.5303

	Severe disease								
	Severe AD, n (%) (n=6,620)	Severe psoriasis, n (%) (n=10,891)	General population, n (%) (n=46,200)	Severe AD versus severe psoriasis			Severe AD versus general population		
				Adjusted OR*	95% CI	p-value	Adjusted OR*	95% CI	p-value
Smoking	834 (18.1)	2,344 (21.5)	4,378 (9.5)	0.98	0.90-1.08	0.6941	1.69	1.53-1.86	<0.0001
Alcohol abuse	366 (7.9)	1,156 (10.6)	2,162 (4.7)	0.81	0.71-0.92	0.0012	1.46	1.28-1.66	<0.0001
Hypertension	842 (18.2)	3,721 (34.2)	6,134 (13.3)	0.65	0.59-0.71	<0.0001	1.28	1.16-1.42	<0.0001
Myocardial infarction	116 (2.5)	514 (4.7)	838 (1.8)	0.79	0.64-0.98	0.0296	1.23	0.98-1.54	0.0745
Stroke	163 (3.5)	624 (5.7)	1,018 (2.2)	0.99	0.82-1.19	0.8814	1.45	1.19-1.77	0.0002
Cancer	495 (10.7)	1,764 (16.2)	3,470 (7.5)	0.96	0.86-1.08	0.5313	1.37	1.22-1.55	<0.0001
Renal disease	122 (2.6)	45 (4.1)	576 (1.3)	0.92	0.75-1.14	0.4744	1.68	1.34-2.11	<0.0001
Diabetes	292 (6.3)	1,683 (15.5)	2,623 (5.7)	0.48	0.42-0.55	<0.0001	0.80	0.69-0.93	0.0037
Crohn's disease	41 (0.9)	99 (0.9)	158 (0.3)	0.73	0.50-1.08	0.1129	2.23	1.57-3.01	<0.0001
Ulcerative colitis	76 (1.7)	181 (1.7)	320 (0.7)	0.95	0.71-1.26	0.7097	2.16	1.64-2.85	<0.0001
Unspecified IBD	23 (0.5)	56 (0.5)	58 (0.1)	0.67	0.40-1.12	0.1246	3.33	1.99-5.58	<0.0001
Depression	168 (3.6)	487 (4.5)	782 (1.7)	0.95	0.79-1.14	0.5663	1.79	1.48-2.16	<0.0001

Antidepressant use	1,653 (35.8)	4,347 (39.9)	10,787 (23.4)	0.89	0.82-0.95	0.0014	1.47	1.36-1.59	<0.0001
Anxiety	59 (1.3)	138 (1.3)	352 (0.8)	0.88	0.64-1.22	0.4414	1.48	1.09-1.99	0.0109
Anxiolytic use	1,934 (41.9)	4,189 (38.5)	9,368 (20.3)	1.49	1.38-1.61	<0.0001	1.91	1.76-2.08	<0.0001
Cholesterol-lowering drugs	809 (17.5)	3,557 (32.6)	6,261 (13.6)	0.58	0.53-0.63	<0.0001	1.22	1.11-1.34	0.0001

Adjusted for age, sex, socioeconomic status, and number of dermatology visits

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



