Association between hospital-diagnosed atopic dermatitis and psychiatric disorders and medication use in childhood

I Vittrup, y M F Andersen, Catherine Droitcourt, L Skov, A Egeberg, M C Fenton, P Mina-Osorio, S Boklage, J P Thyssen

DR IDA VITTRUP (Orcid ID : 0000-0002-3192-6135)

DR YUKI M F ANDERSEN (Orcid ID : 0000-0001-6131-2815)

DR CATHERINE DROITCOURT (Orcid ID : 0000-0001-6714-6643)

DR LONE SKOV (Orcid ID : 0000-0002-4784-9680)

DR ALEXANDER EGEBERG (Orcid ID : 0000-0001-8257-1816)

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I. Vittrup,[1,2] Y.M.F. Andersen,[1,2] C. Droitcourt,[1,2,3,4] L. Skov,[1,2] A. Egeberg,[1,2] M.C. Fenton,[5*] P. Mina-Osorio,[6†] S. Boklage[6‡] and J.P. Thyssen[7]

[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[2]Copenhagen Research Group for Inflammatory Skin (CORGIS), Herlev and Gentofte Hospital, Hellerup, Denmark

[3]Department of Dermatology, CHU Rennes, F35000 Rennes, France

[4]University of Rennes, EA 7449 REPERES "Pharmacoepidemiology and Health Services Research", F35000 Rennes, France

[5] Formerly Sanofi Genzyme, Cambridge, MA, USA

[6] Formerly Regeneron Pharmaceuticals, Tarrytown, NY, USA

[7] Department of Dermatology and Venereology, Bispebjerg Hospital, University of Copenhagen, Denmark

* Current Affiliation: Syneos Health, Boston, MA, USA

† Current Affiliation: Aurinia Pharmaceuticals, Victoria BC, Canada

‡ Current Affiliation: GlaxoSmithKline, Collegeville, PA, USA

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Corresponding author: Jacob P. Thyssen

Email: jacob.pontoppidan.thyssen@regionh.dk

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What's already known about this topic?

- Children with atopic dermatitis have reduced quality of life, but, besides the well-established association with attention deficit hyperactivity disorder, little is known about psychiatric diagnoses and treatments in association with pediatric atopic dermatitis.

What does this study add?

- Risk of psychotropic medication use, of consulting a psychiatrist or psychologist, and of being diagnosed with ADHD was higher in children with hospital-diagnosed atopic dermatitis.
- Children with hospital-diagnosed atopic dermatitis did however not have higher risk of receiving a hospital-diagnosis of depression, anxiety or self-harming behavior.

Abstract

Background: While adult atopic dermatitis (AD) is associated with anxiety and depression and pediatric AD is linked to attention deficit hyperactivity disorder, the relationship between AD in childhood and other psychiatric disorders is largely unknown. **Objectives:** To determine the relationship between AD and diagnosis and treatment of psychiatric disorders in children. **Methods:** All Danish children born between January 1st, 1995 and December 31st, 2012 with a hospital diagnosis of AD (n=14,283) were matched 1:10 with children without a hospital diagnosis of AD. Endpoints were psychotropic medication use, hospital diagnoses of depression, anxiety, ADHD, or self-harming behavior, accidental/suicidal death, and consultation with a psychiatrist or psychologist. **Results:** Significant associations were observed between hospital-diagnosed AD and antidepressant [adjusted hazard ratio (aHR) 1.19; 95% confidence interval (CI) 1.04-1.36], anxiolytic (aHR 1.72; 95% CI 1.57-1.90), and centrally acting sympathomimetic (aHR 1.29; 95% CI 1.18-1.42) medication use. Consultation with a psychiatrist (aHR 1.33; 95% CI 1.16-1.52) or psychologist (aHR 1.25; 95% CI 1.11-1.41) were also associated with AD. No association with a hospital-diagnosis of depression (aHR 0.58; 95% CI 0.21-1.56), anxiety (aHR 1.47; 95% CI 0.98-2.22) or self-harming behavior (aHR 0.88; 95% CI 0.27-2.88) was observed, but a diagnosis of attention deficit hyperactivity disorder (aHR 1.91; 95% CI 1.56-2.32) was significantly associated with AD. The absolute risks were generally low. **Conclusions:** The increased risk of treatment, but not of hospital-diagnosis of psychiatric disorders in children with hospital-diagnosed AD, suggests that psychiatric issues in children with AD could be of transient, reversible or mild-moderate nature.

Introduction

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin condition that most often begins in early childhood and affects up to 15% of children in Denmark[1]. Children with AD suffer from pruritus and interrupted sleep, have a higher risk of social isolation, stigmatization and altered self-esteem[2–4], and have significantly reduced quality of life[5,6] with scores being positively correlated with AD severity[7]. While pediatric AD has been shown to be associated with attention deficit hyperactivity disorder (ADHD)[8–11], the relationship between pediatric AD and other psychiatric disorders is largely unknown[12,13].

This study investigated whether Danish children with AD seen within the hospital system had increased occurrence of psychiatric diagnoses, psychotropic medication use, consultations with psychologists or psychiatrists, or death from accident or suicide.

Patients and methods

Data sources

All Danish citizens are registered in the Civil Registration System[14] with a personal identification number, enabling linkage across registries. Data on hospital admissions and diagnoses have been registered in the Danish National Patient Registry[15] since 1978. The diagnostic code for AD has a positive predictive value of 98% for children in this registry[16]. Systematic studies validating the psychiatric diagnoses in this registry do not exist, however, validation of selected diagnoses, e.g. depression and childhood autism, has been carried out with satisfactory results[17–21]. The Danish National Prescription Registry[22] contains accurate data on all medications dispensed from pharmacies, registered according to Anatomical Therapeutic Chemical classification. Data are considered both complete and valid from 1995[22]. The Danish National Health Service Register[23] tracks healthcare services given by all general practitioners and certain medical specialists, including psychiatrists and psychologists. Because the data is connected to reimbursement the coverage is assumed to be very high[23]. Deaths, manner and causes of deaths are registered in the National Causes of Death Registry[24]. Information on tax-reported household income is registered in the Income Statistics Register[25]. All applied administrative codes from registries are presented in Table S3.

Study population

The source population comprised all children born in Denmark between January 1st, 1995 and December 31st, 2012. Children were followed until the first of either December 31st, 2017, their 18th birthday, death, emigration, or occurrence of an endpoint.

Exposure

Among the source population, we identified all children diagnosed with AD (either in- or outpatient) by a hospital physician between January 1st, 1995 and December 31st, 2012. Each child with AD was matched by birth date and sex with ten children from the general population without a hospital diagnostic code of AD in the study period (Figure 1). The date of diagnosis of AD served as index date for both the child with AD, and the ten reference individuals.

AD severity was modeled as a time-dependent variable (Figure S1). Thus, at any given point during follow-up, AD patients belonged to one of four severity categories according to their prescription data: mild, mild-moderate, moderate-severe, or severe, where a higher category overruled a lower one. Atopic comorbidity status was coded as a time-varying covariate and categorized as I) AD only and II) AD plus asthma/hay fever/food allergy. For classification information see Appendix S1.

Outcomes

The outcomes included a first-time hospital diagnosis of depression, anxiety, ADHD, or self-harming behavior, a claimed prescription for antidepressants overall (no specific indication), and specifically for depression or anxiety (antidepressants are first-choice treatment for anxiety in children[26]), for anxiolytics overall and specifically for anxiety/calming and for centrally acting sympathomimetics (CAS), a consultation with a psychiatrist or psychologist, or a recorded suicide or death from accident (to capture suicides possibly contained in this classification[27]).

Other variables

The children's country of origin was defined by parents' country of birth or country of citizenship and categorized into I) Denmark or II) Other. Socioeconomic status was determined based on household income at child's index date, and the study population was divided into quintiles with 1/5 in each category. Somatic comorbidities included a diagnosis of psoriasis, vitiligo, alopecia areata, autism spectrum disorder, type 1 diabetes, inflammatory bowel disease, or juvenile rheumatoid arthritis, coded as time-dependent variables. The variable asthma/hay fever/food allergy was defined as described in Appendix S1 and coded as a time-dependent variable.

Statistical analyses

Summary statistics were generated and expressed as median and interquartile range for non-normally distributed continuous variables and frequencies for categorical variables. Chi-square tests (categorical variables), Student's t-test (continuous variables) and Wilcoxon rank-sum test (continuous non-normally

distributed variables) were performed to compare differences between groups. Cochran–Armitage test for trend was applied to assess ordered categorical variables. Number of events, total risk time, incidence rate (IR) per 10,000 person-years and 95% confidence interval (CI) for each outcome were calculated. Cox regression models were conducted to estimate adjusted hazard ratios (aHR). Children with a history (event before index) of a studied outcome were excluded in the analysis of that specific outcome. Adjusting covariates were identified as available variables likely being related to both AD status and the outcomes. Model 1 was adjusted for sex, age, socioeconomic status, country of origin, and somatic comorbidities. Model 2 was further adjusted for the variable asthma/hay fever/food allergy. We added interaction terms for the asthma/hay fever/food allergy variable and AD to the models for each outcome. Results were presented according to exposure status, AD severity and atopic comorbidity status (not applicable for model 2). The proportional hazards assumption was graphically assessed using log-log plots. In a sensitivity analysis, we adjusted the risk of psychiatrist consultations for a diagnosis of ADHD as a time-varying covariate. In another sensitivity analysis, we restricted risk time to only include adolescent risk time (>10 years of age).

A p-value < 0.05 was considered statistically significant. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, U.S.A.) and Stata/MP version 15 (StataCorp, College Station, TX, U.S.A.).

This study was approved by the Danish Data Protection Agency (journal number VD-2018-286). No approval is required from the National Committee on Health Research Ethics for registry-based research.

Results

A total of 14,283 children with AD and 142,830 children without AD were included (Table 1). Most participants were males (57.0%) and the median age at study entry was 1.9 years. More than 80% of children with AD were diagnosed before age 5. The majority of children with AD (57.1%) were classified as having moderate-severe AD at some point during follow-up, whereas 9.8%, 24.1% and 9.1% were classified as having mild, mild-moderate and severe disease, respectively. Increased age at index was positively correlated with maximum AD disease severity (2.9 years for severe AD vs. 1.5 years for mild AD, p<0.0001). More children without AD than children with AD had Denmark as their country of origin (91.3% vs. 87.5%, p<0.0001), and the proportion of ethnic Danes seemed to decrease with increasing maximum AD disease severity (p_{trend} <0.0001). The proportion of children with AD decreased with increasing socioeconomic status group (p_{trend} <0.0001). At index, children with AD had a higher prevalence of asthma/hay fever/food allergy (13.8% vs. 4.3%, p<0.0001).

IRs per 10,000 person-years for all psychiatric outcomes, except a diagnosis of depression and self-harming behavior, were higher for children with AD than children without AD (Table 2). The highest IRs were generally seen for severe AD and for most of the outcomes, IRs increased with increasing AD severity. However, only for a few outcomes the difference between mild AD and severe AD was statistically significant (Table S1). Children with AD with concomitant asthma, hay fever and/or food allergy had higher IRs on all outcomes, except anxiolytic dispensations, than children with AD only (Table S2).

Cox regression models showed no association between AD and a diagnosis of depression (fully adjusted hazard ratio (faHR) 0.50; 95% CI 0.18-1.42), anxiety (faHR 1.29; 95% CI 0.84-2.00) or self-harming behavior (faHR 0.61; 95% CI 0.17-2.12). AD was significantly associated with a diagnosis of ADHD (faHR 1.65; 95% CI 1.33-2.05) (Table 2). As there were very few suicidal events, no inferential analysis was performed. No significant association was detected between AD and accidental deaths. In the crude and adjusted, but not in the fully adjusted model, AD was significantly associated with a filled prescription of antidepressants overall (aHR 1.19; 95% CI 1.04-1.36), and for depression (aHR 1.24; 95% CI 1.03-1.48), but not for anxiety (aHR 1.09; 95% CI 0.83-1.43). Anxiolytics use overall (faHR 1.60; 95% CI 1.44-1.78) and specifically for anxiety/calming (faHR 1.52; 95% CI 1.18-1.96) and filled prescription of CAS (faHR 1.15; 95% CI 1.05-1.27) were all significantly associated with AD. While a significant association was seen between AD and consultation with a psychiatrist (faHR 1.17; 95% CI 1.01-1.34), the association between AD and a psychologist consultation was attenuated in the fully adjusted model and became non-significant (faHR 1.12; 95% CI 0.98-1.26). The addition of interaction terms for the asthma/hay fever/food allergy variable and AD to the models for each outcome, did not show significant interactions except for anxiolytics overall (effect of the asthma/hay fever/food allergy variable was less pronounced in children with AD). In a sensitivity analysis, the risk of psychiatrist consultations was adjusted for a diagnosis of ADHD, and the significant association remained present (data not shown).

Limiting the risk time to adolescent time (>10 years) increased and often doubled the IRs of psychiatric outcomes (except regarding ADHD diagnosis and anxiolytic medication use, where the IRs were unchanged and halved, respectively), but did not change the HRs, except regarding ADHD diagnosis and medication use where the significant association in the fully adjusted models was not present (data not shown).

For filled prescriptions of antidepressants and CAS, an AD severity-dependent tendency was seen (Table S1), while the risk of consulting a psychiatrist or psychologist did not seem to depend on AD disease

severity. For a diagnosis of anxiety, ADHD and use of anxiolytics, the lowest HRs were seen in the mild-moderate group, with the highest risk in the severe group.

Comparing the risk of psychiatric outcomes between children with AD with atopic comorbidities and children with AD only (Table S2) did not show differences in the adjusted model, except regarding psychiatrist consultations, where a higher risk was seen (aHR 1.30; 95% CI 1.00-1.68).

Discussion

MAIN FINDINGS

Higher risks of antidepressant, anxiolytic, and CAS medication use, of consulting a psychiatrist or psychologist, and of being diagnosed with ADHD were observed in children with hospital-diagnosed AD. We found no associations with a hospital-diagnosis of depression, anxiety or self-harming behavior.

INTERPRETATION

While psychiatric diagnoses among Danish children were generally rare (e.g. anxiety IR 0.1 per 1,000 person-years), psychotropic medication use and consulting a mental health professional were slightly more common, for example CAS and psychologist consultation amounted to an IR of almost 3 and 2 per 1,000 person-years, respectively.

Children with AD had higher risk of receiving treatment (pharmacologically and therapeutically) for psychiatric disorders, but generally not of receiving a hospital-diagnosis of psychiatric disease. This indicates that symptoms of psychiatric disorders in children with AD indeed occur at a higher rate, but also that they may be either adequately treated or not severe or persistent enough to lead to hospital referral and generate a hospital diagnosis. The findings are reminiscent of adult AD, where we observed a higher risk of getting diagnosed with psychiatric disease, but this did not lead to hospitalization or suicide[28].

Pediatric contact to the Danish hospital psychiatry is dominated by ADHD, autism spectrum disorders, and other behavioral and emotional disorders, that accounts for more than 60% of contacts. Only around 7% and 4% have affective disorders and anxiety, respectively[29], suggesting that these disorders are generally less severe and can be handled by specialists in the private practice sector, that do not report to the Danish National Patient Registry.

Psychiatric disorders are likely underdiagnosed in children, and maybe to a greater extent in subjects with AD. About 41% of US children presenting to an emergency department with a nonpsychiatric complaint

screened positive for an undiagnosed psychiatric disorder, with depression being one of the most frequent types[30]. Moreover, a substantial proportion of adult AD patients with elevated anxiety and depression scores were not clinically diagnosed with anxiety or depression[31] and despite recommendations for increased screening for depression and suicidality in AD patients[32,33], depression screening is rarely performed[33]. For children with AD, it is plausible that physicians ascribe psychiatric symptoms to the patient's skin disorder and await spontaneous improvement in AD with age or following effective therapy and hope that mental health will improve simultaneously. Clinical trials have shown that a reduction in AD severity correlates well with improvement in quality of life scores and decrease in anxiety and depression scores in turn indicating that these symptoms are reversible[34,35]. Unfortunately, however, the quality of life outcomes typically used tend to be insufficiently sensitive to change[36,37], making it difficult to measure the true effect of AD treatment on the psychiatric symptoms.

Associations seen in previous studies between AD and diagnoses of depression, anxiety and self-harming behavior were not observed in this study, but it did confirm the increased risk of a diagnosis of ADHD[8–11]. Recently, three meta-analyses reported pooled ORs of 1.27 (95% CI 1.12-1.45)[12], 1.40 (95% CI, 1.26–1.57)[38] and 1.31 (95% CI 0.99-1.75)[13] regarding the association between pediatric AD and depression. Importantly, many included studies used self-reported information on depression/depressive symptoms instead of clinical diagnoses as in our study[39–41]. A recent meta-analysis found a significant association between childhood AD and anxiety (OR 1.34; 95% CI 1.06–1.69)[38], but included 7 studies of which only two, that used parental report of mental health problems and behavior, gave significant associations. Higher odds of self-reported suicide attempt (aOR 1.31; 95% CI 1.12-1.52) was found in a study on adolescents[41].

A positive association between AD and antidepressant use was present in the current analysis, contrasting a Swedish study[42] that reported no association. This may in part be explained by their study population including AD children from both primary and secondary care and use of parental reports of eczema leading to a prevalence of 33% indicating potential misclassification and hence dilution of the association. The increased risk of anxiolytic medication use in adults with AD[28], was confirmed among Danish children with AD, and the association remained present after restricting indications to 'for anxiety'/'calming'/'for unrest'. No association between AD and medications for ADHD at school age was found in Swedish children [42], but we confirmed the association seen in a previous Danish study[9].

A cohort study of 266,182 subjects[43] found that patients (<20 years) with AD had a significantly increased risk of psychiatric consultations (aHR 3.29; 95% CI 3.16–3.42). Our estimate remained significant after

adjusting the risk for a diagnosis of ADHD, suggesting that the increased risk was not explained by the increased occurrence of ADHD.

Stratifying results according to AD disease severity did not reveal any clear tendencies regarding severity dependency. This could simply be due to risk of psychiatric disorders and medication use not being affected by the severity of disease, or that severity categorization was insufficient and led to misclassification. Unfortunately, we did not have access to clinical information about AD severity. Children with AD with atopic comorbidities did not seem to have higher risk of psychiatric outcomes, except a 30% increased risk of a psychiatrist consultation, when compared to children with AD without atopic comorbidities. AD, hay fever, food allergy and allergic asthma may be seen as belonging to the same disease spectrum as they share the same type 2 inflammation and very often co-exist as the atopic triad[44]. A holistic disease understanding would argue against adjustment for atopic comorbidities as the diseases should be studied as one single entity. However, when we adjusted our analyses for the variable asthma/hay fever/food allergy the association with antidepressant use and psychologist consultations disappeared in turn suggesting that these associations cannot be explained by AD alone, but rather the coexistence with atopic comorbidity.

Although the present study found AD to be significantly associated with psychiatric issues, the absolute risk was generally low, and the excess risk seen in AD patients amounted to less than 2 events per 1,000 children with AD per year. Since our outcome definitions were much more stringent than those used in previous publications, it seems possible that psychiatric problems in pediatric AD patients are of a transient or reversible nature and few are of severe, persistent and chronic type that would lead to management by hospital psychiatrists. This, however, could not be clarified from analyses on prescription data, as children with AD had significantly fewer courses of antidepressants and slightly fewer dispensations in each course, but at the same time had more courses and more filled prescriptions in each course of anxiolytics. Another possible explanation for our results, that is difficult to rule out, is findings simply being a marker of increased health care consumption in AD patients.

STRENGTHS AND LIMITATIONS

Strengths of this study include the use and combination of large, nationwide registries with virtually complete data and a long follow-up period. We used a validated definition of AD[16], including only hospital-diagnosed AD, why findings cannot be generalized to children seen in a primary care setting. Despite the use of nationwide registries, absolute event numbers were low in turn reducing the precision of the estimates as well as the absolute risk of these events. While we attempted to stratify on AD severity and

atopic comorbidity status, these variables are proxies based on e.g. medication use, and misclassification is therefore possible. Some error must be expected when using the prescriber's indication for giving a medication, since default indications may be accepted by physicians. Another concern regarding severity categorization based on prescription data is that stronger AD treatment choices are more likely with increasing age, and the probability of psychiatric outcomes in childhood also being higher in older ages. This could cause overestimation of the importance of AD severity. Increased contact with the health care system and thereby earlier diagnosis of psychiatric illnesses in the AD group cannot be completely ruled out.

CONCLUSION

Children with hospital-diagnosed AD had increased risk of receiving a prescription for psychiatric symptoms, but this did not lead to a hospital-diagnosis of a psychiatric disorder. These findings suggest that psychiatric issues in children with AD could be of transient, reversible or mild-moderate nature that for most can be handled in the primary healthcare sector and does not lead to specialist hospital care.

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Table 1. Demographic characteristics of children with atopic dermatitis (AD) stratified by AD disease severity and children without AD

	Total	**Children with AD**	**Children without AD**	Maximum AD disease severity n = 14,283			
	n = 157,113	n = 14,283	n = 142,830	**Mild**	**Mild-moderate**	**Moderate-severe**	**Severe**
				1,394 (9.8)	3,438 (24.1)	8,150 (57.1)	1,301 (9.1)
Sex (male), n (%)	89,518 (57.0)	8,138 (57.0)	81,380 (57.0)	794 (57.0)	1,914 (55.7)	4,671 (57.3)	759 (58.3)
Age at index in years, median (p25, p75)	1.92 (0.93, 4.05)	1.92 (0.93, 4.05)	1.92 (0.93. 4.05)	1.47 (0.71, 2.84)	1.57 (0.77, 3.00)	2.13 (1.02, 4.38)	2.86 (1.36, 5.84)
Age at index categories in years, n (%)	157,113 (100.0)	14,283 (100.0)	142,830 (100.0)	1,394 (100.0)	3,438 (100.0)	8,150 (100.0)	1,301 (100.0)
< 1	42,075 (26.8)	3,825 (26.8)	38,250 (26.8)	483 (34.6)	1,112 (32.3)	1,997 (24.5)	233 (17.9)
1 < x < 2	38,940 (24.8)	3,540 (24.8)	35,400 (24.8)	406 (29.1)	986 (28.7)	1,895 (23.3)	253 (19.4)
2 < x < 5	46,244 (29.4)	4,204 (29.4)	42,040 (29.4)	330 (23.7)	908 (26.4)	2,537 (31.1)	429 (33.0)
5 < x < 10	21,736 (13.8)	1,976 (13.8)	19,760 (13.8)	138 (9.9)	350 (10.2)	1,229 (15.1)	259 (19.9)
> 10	8,118 (5.2)	738 (5.2)	7,380 (5.2)	37 (2.7)	82 (2.4)	492 (6.0)	127 (9.8)
Country of origin categories (DK), n (%)	142,862 (90.9)	12,497 (87.5)	130,365 (91.3)	1266 (90.8)	3068 (89.2)	7,056 (86.6)	1107 (85.1)

	156,80		14,27		142,52							
Socioeconomic status, n (%)	0	(99.8)	7	(100.0)	3	(99.8)						
Lowest	31,359	(20.0)	3,058	(21.4)	28,301	(19.9)						
Below average	31,361	(20.0)	2,986	(20.9)	28,375	(19.9)						
Average	31,361	(20.0)	2,757	(19.3)	28,604	(20.1)						
Above average	31,359	(20.0)	2,754	(19.3)	28,605	(20.1)						
Highest	31,360	(20.0)	2,722	(19.1)	28,638	(20.1)						
Missing	313	(0.20)	6	(0.04)	307	(0.21)						
Asthma/hay fever/food allergy at index, n (%)	8,128	(5.2)	1,978	(13.8)	6,150	(4.3)	184	(13.2)	463	(13.5)	1,10 5	(13.6)	226	(17.4)

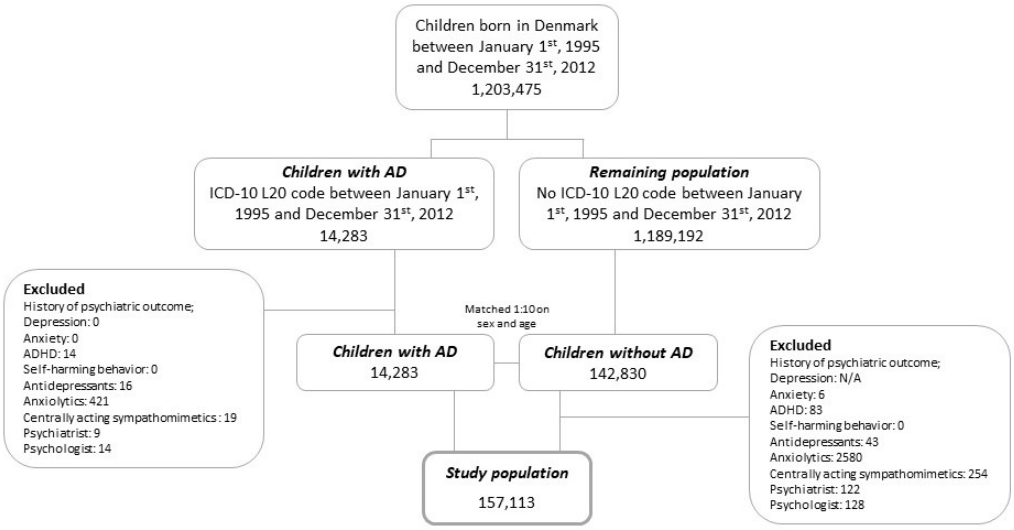
AD = atopic dermatitis; n = number; p25, 25th percentile; p75, 75th percentile; SD, standard deviation, DK = Denmark. AD disease severity was categorized based on prescription data.

Table 2. Number of events, total risk time, incidence rate (IR) per 10,000 person-years and hazard ratios (HR) with 95% confidence intervals (CI) of the examined outcomes in patients with atopic dermatitis (AD) compared with children without AD.

					Crude model			Model 1			Model 2		
	Risk	Event	IR	95% CI	HR	95% CI	p	aH	95% CI	p	faH	95% CI	p
Depression													
Children without AD	1,611,60	71	0.44	(0.35-0.56)	ref								
Children with AD	162,117	5	0.31	(0.13-0.74)	0.7	(0.28-	0.45	0.5	(0.21-	0.27	0.50	(0.18-	0.19
Anxiety													
Children without AD	1,611,26	180	1.12	(0.97-1.29)	ref								
Children with	162,050	27	1.67	(1.14-2.43)	1.4	(1.00-	0.05	1.4	(0.98-	0.06	1.29	(0.84-	0.24
ADHD													
Children without AD	1,606,02	650	4.05	(3.75-4.37)	ref								
Children with	161,076	123	7.64	(6.40-9.11)	**1.8**	(1.56-	0.00	**1.9**	(1.56-	0.00	**1.65**	(1.33-	0.00
Self-harming behavior													
Children without AD	1,611,71	35	0.22	(0.16-0.30)	ref								
Children with AD	162,127	3	0.19	(0.06-0.57)	0.8	(0.26-	0.80	0.8	(0.27-	0.82	0.61	(0.17-	0.43
Suicide													
	N/A												
Death from accident													
Children without AD	1,611,79	34	0.21	(0.15-0.30)	ref								
Children with	162,133	4	0.25	(0.09-0.66)	1.1	(0.42-	0.76	1.0	(0.38-	0.87	1.02	(0.33-	0.97
Antidepressants													
Children without AD	1,604,81	2082	12.9	(12.43-	ref								
Children with	161,308	243	15.0	(13.28-	**1.1**	(1.03-	0.01	**1.1**	(1.04-	0.01	1.05	(0.91-	0.48
Antidepressants for depression													
Children without AD	1,608,00	1122	6.98	(6.58-7.40)	ref								
Children with	161,693	134	8.29	(7.00-9.82)	**1.2**	(1.01-	0.04	**1.2**	(1.03-	0.02	1.10	(0.91-	0.31
Antidepressants for anxiety													
Children without AD	1,608,97	545	3.39	(3.11-3.68)	ref								
Children with	161,856	59	3.65	(2.82-4.70)	1.0	(0.83-	0.53	1.0	(0.83-	0.55	0.94	(0.71-	0.68
Anxiolytics													
Children without AD	1,512,70	2871	18.9	(18.30-	ref								
Children with	152,606	501	32.8	(30.08-	**1.7**	(1.57-	0.00	**1.7**	(1.57-	0.00	**1.60**	(1.44-	0.00
Anxiolytics for anxiety/calming													
Children without AD	1,537,97	489	3.18	(2.91-3.47)	ref								
Children with	157,248	81	5.15	(4.14-6.40)	**1.6**	(1.29-	0.00	**1.6**	(1.33-	0.00	**1.52**	(1.18-	0.00
Centrally acting sympathomimetics													
Children without AD	1,587,93	4253	26.7	(25.99-	ref								
Children with	159,147	545	34.2	(31.49-	**1.2**	(1.18-	0.00	**1.2**	(1.18-	0.00	**1.15**	(1.05-	0.00
Psychiatrist consultation													
Children without AD	1,601,89	1882	11.7	(11.23-	ref								
Children with	160,971	246	15.2	(13.49-	**1.3**	(1.14-	0.00	**1.3**	(1.16-	0.00	**1.17**	(1.01-	0.03
Psychologist consultation													
Children without AD	1,601,07	2581	16.1	(15.51-	ref								

Children with AD	160,854	317	19.7	(17.65-	**1.2**	(1.09-	0.00	**1.2**	(1.11-	0.00	1.12	(0.98-	0.08

AD = atopic dermatitis; IR = incidence rate, HR = hazard ratio, CI = confidence interval. Model 1 was adjusted for sex, age, socioeconomic status, country of origin and somatic comorbidities. Model 2 was further adjusted for asthma/hay fever/food allergy. Bold marking indicates statistical significance.



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