



ORIGINAL ARTICLE

Exploring the association between parental psychiatric disease and childhood atopic dermatitis: a matched case–control study

C.R. Hamann,^{1,2,3,*} A. Egeberg,^{1,2} J.I. Silverberg,⁴ G. Gislason,⁵ L. Skov,^{1,2} J.P. Thyssen^{1,2}¹Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark²Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark³School of Health and Medical Science, Graduate Programme in Public Health and Epidemiology, University of Copenhagen, Copenhagen, Denmark⁴Departments of Dermatology, Preventive Medicine, and Medical Social Sciences, Feinberg School of Medicine at Northwestern University, Chicago, Illinois, USA⁵Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

*Correspondence: C.R. Hamann. E-mail: hamann511@gmail.com

Abstract

Background Maternal prenatal psychiatric disease has been identified as a possible risk factor for atopic dermatitis development in her children. We quantified the associations between maternal and paternal psychiatric disease and the development of atopic dermatitis in their offspring using nationwide registries.

Methods All children in Denmark born between 1 January 1996 and 31 December 2011 who developed atopic dermatitis prior to their fifth birthday were identified and individually matched 1:10 with controls from the general population and with children receiving care in a similar ambulatory/hospital setting. Conditional logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals.

Results A total of 8602 children with atopic dermatitis were matched with controls. Rates of parental psychiatric care were similar in the atopic dermatitis and control groups. When compared to the general population, weak associations were found between childhood atopic dermatitis and maternal history of depression [OR 1.18 (95% confidence interval: 1.12–1.26)], alcohol abuse [OR 1.37 (1.17–1.60)] and illicit drug use [OR 1.34 (1.14–1.60)]. However, associations became insignificant when the paediatric ambulatory/hospital control group was used [OR 1.05 (0.99–1.13)], [OR 1.14 (0.98–1.34)] and [OR 1.03 (0.88–1.22)], respectively. No paternal psychiatric disease or prenatal maternal psychiatric disease associated with the AD development in the offspring.

Conclusions While we found no consistent associations between maternal or paternal psychiatric disease and the subsequent development of atopic dermatitis in their offspring, children of parents with substance abuse issues may be more likely to receive an atopic dermatitis diagnosis.

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Conflict of interests

Dr. Thyssen has attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma and Sanofi-Genzyme. Dr. Skov has received consultancy and/or speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, and Leo Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma and Janssen Pharmaceuticals. Dr. Silverberg has been attended advisory boards and/or been a consultant for Abbvie, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Medimmune, Menlo, Pfizer, Realm, Regeneron-Sanofi, Roivant. Drs. Hamann and Gislason have no relevant interests to declare.

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Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease that typically debuts in early childhood and is characterized by recurrent or chronic pruritic erythematous eczematous lesions in distinctive anatomical locations.¹ The etiopathogenesis of AD is multifactorial, but the strong association between AD and loss-of-function mutations in the filaggrin gene as well as a family history of atopic disease emphasizes the genetic importance.^{1,2} However, environmental insults on the skin barrier, such as winter/fall birth,^{3,4} exposure to tobacco smoke,⁵ hard water,⁶ low ultraviolet environment⁷ and air pollution, have also been shown to increase AD development risk.⁸

Certain maternal diseases along with pre- and perinatal exposures have been proposed to influence the risk of AD development in the offspring in epidemiological studies. For example, maternal inflammatory bowel disease was protective against AD development risk in Israeli children, while prenatal exposure to chemical haptens and air pollutants has been associated with increased AD in the offspring.^{9–11} Maternal stress during pregnancy and a history of psychiatric disease have been identified as possible risk factors for AD development in the offspring,^{12–18} although these findings are not universal.^{19–23} Notably, method of AD ascertainment and selection of controls differ across these studies, with some studies utilizing standardized symptom-based questionnaires,^{12,13,15–17,20} while others used self-reported physician-diagnosed eczema,^{12,13,20} or AD,¹⁴ and others relied on physical examination and clinical AD criteria.^{15,21} Using different definitions of AD can significantly change risk estimates.²⁴ Additionally, the positive associations between maternal stress/psychiatric disease and factors that can affect the child's AD development risk, such as smoking in the home,²⁵ urban living^{26,27} and lower socio-economic position,^{28,29} can be difficult to precisely account for in these studies. Moreover, the effects of paternal stress and psychiatric disease on the child's AD development risk have not yet been investigated.

In this nationwide case-control study, using two different sets of control populations, we quantified associations between both maternal and paternal psychiatric disease as well as other markers of family stress such as substance abuse and divorce, and the development of AD in their offspring.

Methods

Data sources and study population

Nationwide health and social registries in Denmark are maintained and routinely updated by the Danish Health Data Authority. These include the Danish National Patient Registry that tracks all diagnostic codes given to patients at hospitals, emergency rooms, and hospital- and university-based ambulatory clinics across the country (according to a modified version of the International Classification of Diseases [ICD] diagnostic codes),³⁰ the Registry of Medicinal Product Statistics that tracks

all prescriptions filled at Danish pharmacies (according to Anatomical Therapeutic Chemical [ATC] codes),³¹ the Income Statistics Register that tracks personal income and tax data,³² the Danish National Health Service Register that tracks healthcare services given by general practitioners and certain medical specialists, including psychiatrists and psychologists (according to governmental health insurance reimbursement codes),³³ and the Civil Person Register that contains data on birth date, sex, parent-child linkage and other vital statistics.³⁴

All children born between 1 January 1996 and 31 December 2011 who developed AD (ICD-10 L20) prior to their 5th birthday were identified using the Danish National Patient Registry. They were individually matched 1:10 with control children from the general population based on birthday and sex. To reduce the risk of surveillance bias, a second control group of children was selected from among children who received care in a similar ambulatory or hospital setting as those with AD, as defined by receipt of the encounter code Z03.8 (medical observation and evaluation for suspected diseases and conditions).³⁵ This code is generally used as a placeholder for a traditional ICD code for billing purposes, predominantly in outpatient clinics. Subsequent ICD diagnoses received include Z01.35C (screening for congenital hearing loss) and Z380 (single liveborn infant, born in hospital). This second control group was also matched at 1:10, on birthday, sex and age at diagnosis or healthcare encounter. Children whose parents were not registered were excluded. The approval for this study was obtained from the Danish Data Protection Agency (ref. 2015-54-0993, int. ref. 706899). The planning and execution of this study was performed according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations.³⁶

Baseline characteristics and exposures

Each child's parents were identified through the Civil Person Register. Parents were categorized as having AD if they had received a diagnosis of AD (ICD-8 691, ICD-10 L20). The ICD-9 coding system was never used in Denmark. Parental asthma was determined if the individual had received a diagnosis of asthma (ICD-8 493, ICD-10 J45) or filled a prescription (e.g. for an inhaled beta-2 agonist) with the indication of 'for asthma'. Socio-economic position was assessed on the basis of average household gross annual income for the 5-year period prior date the child's (or matched child's) diagnosis date. Highest level of educational achievement was determined according to the International Standard Classification of Education.³⁷ Parental tobacco use was determined using an algorithm based on prescription and diagnostic codes, described elsewhere.^{38,39}

Psychiatric exposures included a history of depression/depressive symptoms, determined by diagnostic code (ICD-10 F32, F3), billing code (630214, 630215: individual consultation for depression, 802148: Hamilton depression test) or the filling of medication for the specific indication 'For depression'. Anxiety

was determined by diagnostic code (F40, F41) or medication indication, 'For anxiety'. Obsessive-compulsive disorder was determined by diagnostic code (F42) or medication indication, 'Treatment of obsessive-compulsive disorder'. Schizophrenia was determined by diagnostic code (ICD-10 F20, ICD-8 295) or medication indication 'Treatment of schizophrenia'. Attention-deficit/hyperactivity disorder (ADHD) was determined by diagnostic code (F90) or medication indication 'Treatment of ADHD'.

These diagnostic exposures were assessed for the 10 years prior to the child's AD diagnosis date, with the exception of schizophrenia and bipolar disorder, which were assessed for any time before child's diagnosis date. All maternal psychiatric exposures were also assessed for a time period of 9 months prior to the birth of the child to capture possible intrauterine effects of maternal psychiatric disease. A history of alcohol abuse within 10 years of the child's AD diagnosis date was assessed using a retrieval algorithm that relies on diagnostic, prescription and medical care visit codes, described elsewhere.³⁹ A similar algorithm based on diagnostic codes (F11-19, R78.1-3, R78.5, T40, T43.6, T43.8, X62, Z71.5, Z50.3) and medication indications ('Treatment of opioid addiction' and 'Methadone substitution treatment') was used to determine a history of substance abuse or illicit drug use.

Statistical analysis

For baseline characteristics, counts and percentages were calculated for categorical variables and means and standard deviations were calculated for continuous variables. Chi-square and *t*-tests were used to compare baseline characteristics between the AD group and control populations. Conditional logistic regression was performed to estimate the associations between each psychiatric exposure and the subsequent development of AD in child. These analyses were performed in tandem for both sets of control populations. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated for both age/sex-adjusted and fully adjusted models. Covariates included in the fully adjusted model were age, sex, parental AD and socio-economic position. Given the high number of exposures analysed and risk for type I errors when using registry data, Bonferroni adjustment was used. For regression analyses, *P*-values <0.00161 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Study population

We identified 8804 children who received a diagnosis of AD prior to their 5th birthday. Two-hundred and two (2.3%) were excluded because of missing parental data. The remaining 8602 were successfully matched with controls from the general

population and from the paediatric ambulatory/hospital population. Of those with AD, 5050 (58.7%) were male; the average age on first registered AD diagnosis was 1.8 years (Table 1). Mothers of the AD children were slightly younger compared to the general population [mean 32.2 years vs. 32.6 (*P* > 0.0001)], but were of similar age to the paediatric ambulatory/hospital controls [32.2 years vs. 32.1 (*P* = 0.5248)]. Fathers of AD children were younger than fathers of the control group [35.0 years vs. 35.5 (*P* = 0.0003)], but older than fathers of the paediatric ambulatory/hospital controls [35.0 years vs. 34.7 (*P* = 0.0003)].

Maternal and paternal asthma as well as maternal and paternal AD were more common in the childhood AD group compared to both sets of controls (chi-squared *P*-values all <0.0001). Maternal tobacco use was also more common in the childhood AD group [8.1% in the childhood AD group vs. 5.8% in general population controls (*P* < 0.0001) and 7.1% in paediatric ambulatory/hospital controls (*P* = 0.0012)]. The socio-economic position distribution of the childhood AD group differed significantly to that of controls; in general, the childhood AD group was skewed towards the lower quintiles compared to the general population controls (*P* < 0.0001) and more centrally skewed compared with the paediatric ambulatory/hospital controls (*P* = 0.0079). Maternal and paternal education achievement in the childhood AD group differed significantly compared to controls (all *P* values < 0.0145).

Maternal and Paternal Exposures

Within the childhood AD group, 27.7% (2381/8602) of mothers and 14.3% (1226/8602) of fathers had at least one contact for psychiatric care within 10 years of their child's first AD diagnosis (Table 2). Among those mothers and fathers, the average number of visits for psychiatric care was 6.4 (SD 8.8) and 5.1 (7.5), respectively. Rates of psychiatric care use were similar in the general population control group [mothers: 23.7% (20 353/86 020), mean number of visits 6.7 (SD 10.2); fathers 12.7% (10 886/86 020), visits 5.7 (9.7)] and in the paediatric ambulatory/hospital control group (mothers: 26.6% [22 864/86 020], visits 6.7 [9.8]; fathers: 13.4% (11 560/86 020), visits 5.6 [9.1]). However, in conditional regression analysis, no significant associations were found between maternal or paternal psychiatric care visits and the development of AD in their children (Table 3).

The only associations between parental psychiatric exposures and the development of AD in their children that were significant after full adjustment and Bonferroni correction were a maternal history of depression/depressive symptoms [OR 1.18 (1.12–1.26), *P* < 0.0001], maternal history of alcohol abuse [OR 1.37 (1.17–1.60), *P* < 0.0001] and maternal history of illicit drug use [OR 1.34 (1.14–1.60), *P* = 0.0005]. However, these associations were not significant when the paediatric ambulatory/hospital group was used as the control group [OR 1.05 (0.99–1.13)], [OR 1.14 (0.98–1.34)] and [OR 1.03 (0.88–1.22)], respectively.

Table 1 Baseline characteristics of control and AD populations

	General population control group (n = 86 020)	Paediatric hospital/clinic control group (n = 86 020)	AD group (n = 8602)	
Child's age, mean (SD)	1.8 (1.3)	1.5 (1.7)	1.8 (1.3)	
Child's sex, males (% male)	50 500 (58.7)	50 500 (58.7)	5050 (58.7)	
Maternal age, mean (SD)	32.6 (5.1)	32.1 (5.3)	32.2 (5.2)	
Paternal age, mean (SD)	35.2 (6.0)	34.7 (6.2)	35.0 (6.2)	
Maternal asthma, n (%)	9670 (11.2)	11 126 (12.9)	1599 (18.6)	
Paternal asthma	8336 (9.7)	8650 (10.1)	1316 (15.3)	
Maternal AD	969 (1.1)	1021 (1.2)	355 (4.1)	
Paternal AD	614 (0.7)	608 (0.7)	237 (2.8)	
Maternal tobacco use	5018 (5.8)	6135 (7.1)	695 (8.1)	
Paternal tobacco use	4859 (5.7)	5131 (6.0)	541 (6.3)	
Maternal education level				
High school only	19 052 (22.2)	20 893 (24.3)	2166 (25.2)	
Technical or vocational school	22 613 (26.3)	23 700 (27.6)	2400 (27.9)	
University degree	27 167 (31.6)	27 456 (31.9)	2747 (31.9)	
Master's degree or higher	12 900 (15.0)	12 256 (14.3)	1107 (12.9)	
Paternal education level				
High school only	19 614 (22.8)	20 870 (24.3)	2085 (24.3)	
Technical or vocational school	31 090 (36.1)	32 518 (37.8)	3283 (38.2)	
University degree	18 321 (21.3)	18 204 (21.2)	1879 (21.8)	
Master's degree or higher	12 990 (15.1)	12 420 (14.4)	1134 (13.2)	
Family socio-economic position				
Lowest quintile	17 084 (19.9)	17 315 (20.1)	1840 (21.4)*	1609 (18.7)**
4th quintile	17 117 (19.9)	17 170 (20.0)	1807 (21.0)	1755 (20.4)
3rd quintile	17 171 (20.0)	17 117 (19.9)	1754 (20.4)	1807 (21.0)
2nd quintile	17 289 (20.1)	17 194 (20.0)	1636 (19.0)	1731 (20.1)
Highest quintile	17 359 (20.2)	17 224 (20.0)	1565 (18.2)	1700 (19.8)

Single asterisk indicates comparison with general population controls. Double asterisk indicates comparison with paediatric hospital/clinic controls.

No paternal psychiatric disease correlated with the development of AD in the offspring. Mothers receiving care for psychiatric disease during their pregnancy was not associated with the child's subsequent development of AD. While combined maternal and paternal disease did tend to correlate, albeit weakly, with AD development in their offspring, no associations met statistical significance. Additionally, in both sets of analysis, having divorced or separated parents did not correlate with AD diagnosis.

Discussion

Main Findings

In this large nationwide case-control study, positive but weak associations were found between, respectively, maternal history of depression, maternal alcohol abuse, maternal illicit drug use and childhood AD. When using a control population of children receiving paediatric care, these associations were lost, suggesting that surveillance bias or residual confounding may have influenced these findings. No associations were found with any paternal psychiatric disease, with maternal psychiatric disease during pregnancy or with combined parental psychiatric disease.

Interpretation

The lack of association between maternal prenatal psychiatric disease markers and childhood AD challenge findings from previous studies. Three large studies from Taiwan and South Korea showed positive associations between maternal depression/depressive symptoms during pregnancy and the subsequent development of AD in her child.^{13,15,40} However, other studies from Europe and Singapore showed no effect.^{19–21} Ascertainment of maternal depression and child AD differed across these studies, as did confounders adjusted for in analysis. It is also possible that differences in societal stigma towards mental health among populations from different cultures may have played a role, altering both self-reporting of psychiatric disease and maternal prenatal immune environment.⁴¹ Proposed mechanistic pathways explaining these observed associations include oxidative stress and cortisol dysregulation,¹⁵ insult to the hypothalamic–pituitary–adrenal axis,^{42,43} and potentiation of a T-helper(Th) 2-skewed immune milieu.⁴⁴ In one large study, decreased placental 11b-hydroxysteroid dehydrogenase type 2 levels and increased immunoglobulin E levels at one year of age were shown to correlate with both prenatal maternal distress and the subsequent development of AD in the offspring.¹⁵ Our study used ICD

Table 2 Parental psychiatric characteristics of control and AD populations

	General population control group (n = 86 020)	Paediatric hospital/clinic control group (n = 86 020)	AD group (n = 8602)
Maternal psychiatric markers			
In person hospital or clinic contact for psychiatric care, n (%)			
During pregnancy	2892 (3.4)	3447 (4.0)	320 (3.7)
Within 10 years of child's AD diagnosis	20 353 (23.7)	22 864 (26.6)	2381 (27.7)
Depression	9854 (11.5)	11 103 (12.9)	1169 (13.6)
During pregnancy	1914 (2.2)	2397 (2.8)	220 (2.6)
Anxiety	3434 (4.0)	3970 (4.6)	391 (4.6)
During pregnancy	696 (0.8)	1009 (1.2)	96 (1.1)
Obsessive-compulsive disorder	155 (0.2)	143 (0.2)	22 (0.3)
During pregnancy	73 (0.1)	59 (0.1)	6 (0.1)
Schizophrenia	99 (0.1)	140 (0.2)	13 (0.2)
During pregnancy	27 (<0.1)	49 (<0.1)	<3 (<0.1)
Bipolar disorder	213 (0.3)	210 (0.2)	16 (0.2)
During pregnancy	33 (<0.1)	39 (0.1)	<3 (<0.1)
ADHD	322 (0.4)	392 (0.5)	44 (0.5)
During pregnancy	90 (0.1)	70 (0.1)	9 (0.1)
Two or more psychiatric diseases	2483 (2.9)	2815 (3.3)	288 (3.4)
Alcohol use disorder	1288 (1.5)	1647 (1.9)	189 (2.2)
Substance abuse or illicit drug use	1155 (1.34)	1572 (1.8)	163 (1.9)
Paternal psychiatric markers			
In person hospital or clinic contact for psychiatric care, n (%)			
During pregnancy	1883 (2.2)	2100 (2.4)	196 (2.3)
Within 10 years of child's AD diagnosis	10 886 (12.7)	11 560 (13.4)	1226 (14.3)
Depression	5887 (6.8)	6146 (7.1)	673 (7.8)
Anxiety	1869 (2.2)	1944 (2.3)	205 (2.4)
Obsessive-compulsive disorder	60 (0.1)	57 (0.1)	7 (0.1)
Schizophrenia	103 (0.1)	89 (0.1)	8 (0.1)
Bipolar disorder	129 (0.2)	106 (0.1)	18 (0.2)
ADHD	570 (0.7)	621 (0.7)	78 (0.9)
Two or more psychiatric diseases	1373 (1.6)	1355 (1.6)	149 (1.7)
Alcohol abuse	2660 (3.1)	3057 (3.6)	328 (3.8)
Substance abuse or illicit drug use	842 (1.0)	969 (1.1)	95 (1.1)
Combined maternal and paternal exposures			
Depression, anxiety, OCD, schizophrenia or bipolar disorder in both parents	1770 (2.1)	1977 (2.3)	227 (2.6)
Alcohol abuse or illicit drug use in both parents	329 (0.4)	411 (0.5)	42 (0.5)
Divorced or separated parents	485 (0.6)	492 (0.6)	56 (0.7)

diagnoses of AD, instead of parental report of AD, and therefore not only have a high specificity, but also reflect disease that has persisted from initial referral to first visit. It is also possible that parental psychiatric disease could have affected the ability to follow primary or secondary care physician treatment recommendations, or the push for referral to a hospital consultation, which in turn would also affect any association.

No significant associations were found between any maternal, paternal or combined psychiatric marker and AD development in their offspring when using the paediatric ambulatory/hospital population as a control group. This second group of controls was selected both to help mitigate any surveillance bias—i.e.

(i) parents with frequent healthcare interaction for their child's AD care could be more likely to have been referred for psychiatric counselling and (ii) children with paediatric hospital consultations are more likely to be referred to a dermatology department for AD. Moreover, while all Danish residents have free and equal access to health care, those referred to a university- or hospital-based clinic for care may differ from those who receive care only in a private clinic setting. These differences are reflected partially in the education and socio-economic distribution differences between the three groups. Other unquantifiable differences due to access/exposure to health care between this AD population and the general public were likely mitigated

Table 3 Age/sex-adjusted and fully adjusted odds ratios with 95% confidence intervals and *P* values for associations between parental psychiatric markers and AD in their offspring, using both general population and paediatric hospital/clinic control groups

	Compared to general population					Compared to pediatric hospital/clinic population				
	Age/sex adjusted OR	95% CI	<i>P</i> value	Fully adjusted OR	95% CI	Age/sex adjusted OR	95% CI	<i>P</i> value	Fully adjusted OR	95% CI
Maternal										
In person hospital or clinic contacts for psychiatric care										
During pregnancy	1.02	0.99	1.05	1.02	0.99	0.99	0.96	1.01	0.2775	0.98
Within 10 years of child's AD diagnosis	1.01	1.00	1.01	1.01	1.00	1.00	1.00	0.9575	1.00	1.00
Depression	1.22	1.14	1.30	<0.0001	1.18	1.12	1.26	<0.0001	1.06	1.00
During pregnancy	1.15	1.00	1.33	0.0474	1.12	0.97	1.29	0.1202	0.91	0.79
Anxiety	1.15	1.03	1.28	0.0127	1.11	0.99	1.24	0.0633	0.98	0.88
During pregnancy	1.38	1.12	1.71	0.0030	1.33	1.07	1.66	0.0091	0.94	0.76
Obsessive-compulsive disorder	1.42	0.91	2.23	0.1234	1.40	0.89	2.20	0.1446	1.50	0.95
During pregnancy	0.82	0.36	1.89	0.6438	0.84	0.37	1.94	0.6894	0.99	0.43
Schizophrenia	1.32	0.74	2.35	0.3549	1.11	0.62	2.00	0.7296	0.92	0.52
During pregnancy	0.74	0.18	3.12	0.6822	0.57	0.13	2.45	0.4494	0.42	0.10
Bipolar disorder	0.69	0.42	1.15	0.1551	0.70	0.42	1.16	0.1619	0.76	0.46
During pregnancy	0.30	0.04	2.22	0.2395	0.29	0.04	2.16	0.2279	0.26	0.04
ADHD	1.37	1.00	1.88	0.0511	1.32	0.96	1.82	0.0865	1.12	0.82
During pregnancy	1.29	0.64	2.57	0.4779	1.26	0.63	2.53	0.5192	1.00	0.50
Two or more psychiatric diseases	1.17	1.03	1.32	0.0153	1.12	0.99	1.27	0.0797	1.02	0.91
Alcohol abuse	1.48	1.27	1.72	<0.0001	1.37	1.17	1.60	<0.0001	1.15	0.99
Substance abuse or illicit drug use	1.42	1.20	1.68	<0.0001	1.34	1.14	1.60	0.0005	1.04	0.88
Paternal										
In person hospital or clinic contacts for psychiatric care										
During pregnancy	0.99	0.95	1.03	0.5715	0.98	0.94	1.02	0.3054	0.98	0.94
Within 10 years of child's AD diagnosis	1.00	0.99	1.01	0.9261	1.00	0.99	1.00	0.4049	1.00	0.99
Depression	1.16	1.06	1.26	0.0006	1.11	1.02	1.21	0.0172	1.10	1.02
Anxiety	1.10	0.95	1.27	0.2036	1.05	0.91	1.22	0.5152	1.06	0.91
Obsessive-compulsive disorder	1.17	0.53	2.56	0.6986	1.13	0.51	2.49	0.7592	1.23	0.56
Schizophrenia	0.78	0.38	1.60	0.4900	0.75	0.37	1.55	0.4422	0.90	0.44
Bipolar disorder	1.40	0.85	2.30	0.1840	1.42	0.86	2.34	0.1661	1.70	1.03
ADHD	1.37	43.313	1.74	0.0090	1.29	1.01	1.64	0.0404	1.26	0.99
Two or more psychiatric diseases	1.09	0.92	1.29	0.3381	1.04	0.87	1.23	0.6994	1.10	0.93
Alcohol abuse	1.24	1.11	1.40	0.0003	1.18	1.05	1.33	0.0062	1.08	0.96
Substance abuse or illicit drug use	1.13	0.91	1.40	0.2618	1.08	0.87	1.34	0.4732	0.98	0.79

Table 3 Continued

	Compared to general population					Compared to pediatric hospital/clinic population				
	Age/sex adjusted OR	95% CI	P value	Fully adjusted OR	95% CI	P value	Age/sex adjusted OR	95% CI	Fully adjusted OR	P value
Combined maternal and paternal										
Depression, anxiety, OCD, schizophrenia or bipolar disorder in both parents	1.29	1.12	1.49	0.0003	1.04	1.39	1.15	1.00	1.16	0.0452
Alcohol abuse or illicit drug use in both parents	1.28	0.93	1.77	0.1351	0.85	1.63	1.02	0.74	1.04	0.8934
Divorced or separated parents	1.16	0.88	1.53	0.3055	0.86	1.51	1.14	0.86	1.11	0.3562
										0.4500

Yellow indicates P values <0.05 . Green indicates statistical significance (P values <0.00161).

when using this second population of paediatric ambulatory/hospital controls. However, we acknowledge that this strategy was cautious and could mask a true positive association. Similarly, Bonferroni correction is a conservative tool to account for multiple significance testing, and its use here lowered the level of reported statistical significance.⁴⁵ Use of a less strict tool would have yielded different results.

Maternal history of depression/depressive symptoms correlated better with AD development in her offspring than prenatal depression did. This positive, albeit very weak, association between maternal history of depression and AD development in her offspring, in the absence of any association between prenatal depression and AD development, argues against a depression-mediated Th-2 immune skew or other biologic pathway as an explanation for associations between prenatal depression and AD development risk noted in some studies.¹⁵ Similarly, no significant associations were found between maternal anxiety and AD development in their offspring. While most studies addressing this relationship have found significant associations,^{14,15,20} some have reported mixed results.^{19,21} These associations are even more commonly reported when the definition of anxiety is broadened to include stress/work stress,^{12,16,18,40,46,47} or stressful life events.^{17,18,47,48} Markers of a stressful home life such as having divorced or separated parents or self-reported parenting difficulties have been shown to correlate with the subsequent development of atopic diseases in the offspring,^{18,49–52} although only one study has identified increased AD in particular.⁴⁷ We found no significant relationship between having divorced or separated parents and receiving an AD diagnosis. Interestingly, while parents of AD children had increased AD themselves compared to controls, and AD is associated with anxiety and anxiolytic use, no association between these parents and anxiety was found in age/sex-adjusted analyses.⁵³

While the effects of paternal psychiatric disease on the development of other atopic diseases in the offspring have been studied previously, with mixed results,^{54,55} no studies have investigated the effects of paternal psychiatric disease on the development of AD in the offspring. Fathers of children who developed AD were more likely to have a history of depression, but this association did not meet statistical significance after adjustment. Given that paternal depression likely does not have a strong biologic effect on prenatal Th-1/Th-2 balance in his children, this association between paternal depression and AD in the offspring, although weak, may suggest that reported associations between maternal depression and AD in the offspring are more likely secondary to uncontrolled confounding or behavioural differences than a result of a biologic pathway. While the genetic risk loci for depression and other psychiatric disease are not fully understood, there appears to be no clear genetic overlap between AD and depression.^{56,57}

There were significant associations between maternal history of alcohol abuse or illicit drug use and AD development in her

offspring that remained significant in adjusted analyses, but only when using general population controls. Alcohol use during pregnancy has been weakly associated with AD development in her offspring—thought to be secondary to propagation of Th2 skew into the peri- and postnatal period.⁵⁸ While the marker used for alcohol abuse in this study was not limited to alcohol use during pregnancy, it has been shown that chronic alcohol use also drives Th2-skewed immune responses and may in part explain the association found here.^{59,60} The marker for illicit drug use in this study captured both psychoactive drug use, such as cocaine or marijuana use, but also opioid addiction and methadone replacement therapy. Like chronic alcohol use, chronic opioid use has been shown to disrupt the Th1/Th2 balance, driving an increase in Th2 predominant cytokines such as interleukin (IL)-4 and IL-10, potentially contributing to this association.^{61–63} Additionally, alcohol and drug use likely influence a parent's ability to adhere to AD treatment recommendations/guidelines, which often requires daily discipline and awareness of AD flares. The AD in their children could therefore worsen to an extent where referral to larger treatment centres such as hospital- and university-based clinics that care for moderate-to-severe AD (and at the same time contribute to the Danish health registries) is necessary.⁶⁴ It is also worth noting that a child's AD may adversely influence the emotional health and social functioning of his or her parents potentially driving or worsening substance abuse issues.^{65,66}

In this study, no attempt was made to differentiate the possible effects of psychotropic medication use compared with the psychiatric disease itself. In general, use of psychotropic medications is a marker of both 'use of psychotropics' but also more severe psychiatric disease. Separating the effects of psychotropic drug use and severe psychiatric disease is difficult, and any associations found would be difficult to interpret. Additionally, we theorize that the potential immune alterations caused by psychotropic medications are outweighed by the immune milieu of the psychiatric disease itself. Theoretically, the most commonly used psychiatric medications, selective serotonin reuptake inhibitors as well as atypical antidepressants, generally push towards a Th1 shift, newer classes of antidepressants such as the norepinephrine reuptake inhibitor reboxetine, and bupropion, a norepinephrine–dopamine reuptake inhibitor, generally push towards a Th2 shift, and the effects of serotonin–norepinephrine reuptake inhibitors seem to be mixed.⁶⁷ Theoretically, pregnant mothers taking these medications could alter both their and their growing fetus's Th1/Th2 balance. However, again, this would likely be on a scale below the existing alterations to her Th1/Th2 balance from her pregnancy and psychiatric comorbidities. Additionally, women with severely uncontrolled psychiatric disease likely have even more impactful alterations of their and their fetus's immune system, and the treatment of their disease with psychiatric medications may simply restore a more normal immune milieu. More research is needed on the

potential direct effects of psychotropic medications on AD development.

Strengths and Limitations

The use of two control populations in this study is a clear strength and adds nuance to the current understanding of relationships between parental psychiatric disease and AD in the offspring. Use of nationwide registries allowed for complete capture of medication use and psychiatric care contacts and extensive capture of specific psychiatric diagnoses. This study assessed healthcare utilization markers and not parental stress/symptoms themselves and it is unclear how well these correlate. Additionally, medication use was included in many composite markers, and the possible effects of medications themselves were not isolated. ICD codes were used to identify children with AD which, while specific, may not be a sensitive marker for clinical AD. This study was limited to children who developed AD before the age of five and those who sought care at university- and hospital-based clinics. Given the study design, causality cannot be determined. AD severity was not ascertained. A conservative statistical approach was used, as it was decided in a protocol prior to data analysis.

Conclusions

In this large nationwide case–control study, maternal depression, alcohol use and illicit drug use were associated with childhood diagnosis of AD in the offspring. However, when compared to a control population drawing from those receiving care in similar hospital/clinic settings, no associations were found, suggesting possible surveillance bias in our initial analysis. Similarly, no prenatal maternal, paternal or combined parental psychiatric diseases markers and the subsequent development of AD in their offspring were found. Parental psychiatric disease is unlikely to represent a significant risk factor for AD in their children.

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Author Contributions

Dr. Hamann had full access to all of data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hamann, Egeberg, Skov and Thyssen conceived and designed the study. Hamann, Egeberg and Thyssen drafted the manuscript. Hamann involved in statistical analysis. None obtained funding. All authors acquired, analysed and interpreted the data; made critical review of the manuscript for important intellectual content; provided with administrative, technical and material support; and supervised the study.

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