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The familial aggregation of atopic diseases and depression or anxiety in children

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Summary

Background: Children with asthma and atopic diseases have an increased risk of depression or anxiety. Each of these diseases has strong genetic and environmental components; therefore, it seems likely that there is a shared liability rather than causative risk.

Objective: To investigate the existence and nature of familial aggregation for the comorbidity of atopic diseases and depression or anxiety.

Methods: Participants came from the Childhood and Adolescent Twin Study in Sweden (CATSS), n = 14 197. Current and ever asthma, eczema, hay fever and food allergy were reported by parents. Internalizing disorders were identified using validated questionnaires. Familial co-aggregation analysis compared monozygotic (MZ) twins and same-sex dizygotic (DZ) twins for atopic disease in 1 twin with internalizing disorder in the other to test for genetic liability. Several familial liability candidates were also tested including parental education, recent maternal psychological stress, childhood family trauma and parental country of birth.

Results: Familial co-aggregation analysis found that if 1 twin had at least 1 current atopic disease the partner twin was at risk of having an internalizing disorder regardless of their own atopic status (adjusted OR 1.22 (95% CI 1.08, 1.37). Similar results were found for each atopic disease ever and current. MZ associations were not higher than DZ associations, suggesting that the liability is not genetic in nature. Including other familial candidates to the models made little difference to effect estimates.

Conclusions and Clinical Relevance: Atopic diseases and depression or anxiety tend to occur together in families; therefore, when treating for 1 disease, the physician should consider comorbidity in both the individual and the individual's siblings. We did not find evidence to support a genetic explanation for comorbidity, and further exploration is needed to disentangle the environmental and epigenetic reasons for familial aggregation.

KEYWORDS
anxiety, asthma, atopic dermatitis, child, depression, eczema, food allergy, rhinitis

1 | INTRODUCTION

It has been recognized for well over a century that children and adults with asthma have a disproportionate burden of depression and anxiety disorders.[1,2] In children, it is estimated that up to one-third of asthmatics meet criteria for anxiety disorders.[1] Similarly, depression or anxiety is more likely in children with other atopic diseases associated with asthma[3] such as eczema, rhinitis and food allergy.[4-6] It is not clear why atopic diseases and depression or anxiety are often comorbid and it has also been difficult to show causality, that is, the chicken-and-egg dilemma, which comes first, allergic disease or depression or anxiety? A review on atopic diseases and psychosocial factors found evidence for causality in both directions.[7] Rather than bidirectional causation, an alternative explanation to the association between atopic diseases and depression or anxiety is a familial liability due to a shared genetic pathway or shared environmental risk factors.[8,9] A common genetic pathway seems to be a plausible explanation as asthma and atopic diseases are highly heritable[10] as are depression and anxiety, although to a lesser extent.[11] In addition, both maternal stress and socio-economic status are associated with both atopic diseases[12-15] and depression or anxiety,[16,17] leading to the hypothesis of a familial aggregation for comorbidity due to social environmental factors.

The aim of this study was to investigate the existence and nature of a familial aggregation for the comorbidity of atopic diseases and depression or anxiety in children.

2 | METHODS

2.1 | Study population

Twins from the Child and Adolescent Twin Study in Sweden (CATSS), born between July 1998 and June 2006, were included in a cross-sectional study (n = 21 398).[18,19] Parents were interviewed about their children when they were 9 years old. After exclusion of those twins who died or emigrated before age 9, whose parents were not fluent in Swedish, or who had a disability, 20 326 eligible twins remained in the cohort. There was a 72% participation rate (n = 14 589) of whom 14 197 had complete information for all covariates used in the current study. The information from CATSS was linked by personal identity number to nation-wide registers held in Sweden by the National Board of Health and Welfare and Statistics Sweden. These include the Medical Birth Register for information on births (MBR), National Patient Register for all inpatient and specialist diagnoses (NPR), the Swedish Prescribed Drug Register for all dispensed medications (SPDR) and the Longitudinal Integration Database for health insurance and labour market studies (LISA).[20] Parents were linked to their children in the CATSS cohort by using the Multi-generation Register (MGR) which matches the personal numbers of individuals in families.

2.2 | Variables

Ever asthma was defined as a positive response to 'Has your child ever had asthma?' in the CATSS questionnaire. C*urrent asthma* was defined as a positive response to 'Does your child still have asthma?' Similar questions were used for *eczema, food allergy and hay fever*. A positive response for any of asthma, eczema, food allergy or hay fever was labelled *at least 1 atopic disease*.

Depression or anxiety was identified using the Screen for Child Anxiety Related Emotional Disorders (SCARED) and Shortened Mood and Feelings (SMFQ) questionnaires answered by parents. SCARED is a 41-item questionnaire that is used to screen for: generalized anxiety disorder, panic/somatic disorder, separation anxiety, social phobia and school phobia.[21] SCARED has been validated and tested in a number of countries and is robust against the DSM-IV-T anxiety disorders in children and adolescents.[22] In brief, any child that had a score above the cut-off for any of the 5 disorders was considered to have an anxiety disorder. The SMFQ is a 13-item questionnaire that has been shown to be valid for use in children age 9 years and is comparable to DSM III-R depression.[23,24] Any child who scored above 11 on the SMFQ parent-reported questionnaire was considered to have a depressive disorder.

Covariates: data on gender, birth weight, gestational age, maternal age at delivery and parity were retrieved from the MBR. Zygosity is determined by DNA samples or when DNA is not available, on an algorithm based on 5 questions about twin similarity answered by parents.[19] Socio-economic status was defined as a combination of both parent's level of education at the time of the telephone interview (both parents ≤9 years, 1 or both parents completed 12 years, 1 or both parents completed at least 2 years of graduate education). Parental education and country of birth data were retrieved from LISA.

Recent maternal psychological stress was defined as medication for, or a diagnosis of, an anxiety or depressive disorder in the last 2 years before the telephone interview (that is, when the child was aged 7-9 years) for the child's mother. Dispensation dates of anxiolytic and antidepressant medications were identified using Anatomical Therapeutic codes (ATC) N05B and N06A, respectively, in the SPDR. Diagnoses of depressive or anxiety disorders were identified using International Classification of Disease-10 codes F30-F34, F38-42, F44, F45 and F48 in the NPR.

Childhood family trauma was defined as parents saying yes to a previous traumatic event within the family including: divorce or separation of parents, death or serious illness of a family member, or substance abuse by a family member. These questions were taken from the Life Stressor Checklist.[25]

2.3 | Statistical analysis

2.3.1 | Whole-cohort analysis

We estimated the odds ratios (ORs) of having an *internalizing disorder* for those that had *at least 1 atopic disease* (ever or current) compared to those without *atopic disease*. Estimates were also generated for (ever or current) *asthma*, *eczema*, *hay fever* and *food allergy*. Generalized estimating equations were used including an exchangeable

covariance structure to account for correlation caused by clustering of observations within twin pairs. Estimates were adjusted for sex, gestational age, birth weight, maternal age and parental country of birth. Effect modification by sex was tested by including an interaction term in each model.

2.3.2 | Cross-twin analysis

Cross-twin analysis is a type of familial co-aggregation analysis which compares children with and without atopic disease with regard to the presence of depression or anxiety in their co-twin. Estimates using generalized estimating equations were calculated for the odds of having an *internalizing disorder* in twin 2 (modelled as outcome) if twin 1 had *at least 1 atopic disease* (ever or current, modelled as exposure). Similar estimates were calculated for (ever or current) *asthma*, *eczema*, *hay fever* and *food allergy*. Models included an exchangeable covariance structure and were adjusted for covariates shared by the twin pair—gestational age and maternal age at delivery. Models were also adjusted for the atopic status of twin 2 to remove possible confounding via this pathway.[26] An association between atopy and depression or anxiety in a cross-twin analysis suggests familial liability aggregation.

Monozygotic twins (MZ) are genetically identical, and dizygotic twins (DZ) share on average 50% of their segregating genes. Therefore, if MZ odds ratios are higher than DZ odds ratios, this suggests that the familial aggregation may be due to shared genes. An interaction term for zygosity was added to each familial co-aggregation model to test whether there was a significant difference between MZ and DZ estimates.

Recent maternal psychological stress, *parental education*, *childhood family trauma and parental birth country* were added separately as covariates to the cross-twin analyses to test these as possible shared familial candidates to explain the familial aggregation of child asthma/atopy and depression or anxiety. These factors have both environmental and genetic components; hence, we have termed them 'familial candidates'. We would expect to see attenuation of the cross-twin estimates if the candidates were the source of familial aggregation.

2.3.3 | Sensitivity analysis

In case of reporting bias by parents in the CATSS questionnaires regarding atopic status and internalizing disorder status, we repeated the analyses for asthma using a validated algorithm for *register-based asthma* definitions.[27]

Register-based Ever Asthma was defined as fulfilling one of the following criteria:

1. Two or more dispenses of preventer medications over the 9 years, that is either; inhaled corticosteroids (ICS), leukotriene receptor agonists (LRTA) or fixed combinations of β2-agonists and corticosteroids (β2-ICS). ATC codes for these medications are R03BA, R03DC03 and R03AK, respectively. If both dispenses were below the age of 4.5 years, the criteria were that there was at least 14 days between each dispense to avoid change of inhaler device.
2. Two dispenses of β2-adrenoceptor agonists (R03AC), and either a third dispense of a β2-adrenoceptor agonist or of a preventer medication (ICS, LRTA, β2-ICS) in any 12-month period.
3. An asthma diagnosis in the NPR after the age of 4.5 years.
4. *Register-based Current Asthma* was defined as having *register-based ever asthma* before age 9 years, AND either a dispensed medication or a diagnosis (based on the NPR which records inpatient and specialist visits) recorded within 18 months of their 9th birthday.

Data management and statistical analyses were conducted using SAS 9.4.

This study was approved by the Regional Ethical Review board in Stockholm, Sweden.

3 | RESULTS

Current prevalence for the traits of interest in 9-year-old children were: asthma 8.7%, eczema 7.6%, hay fever 6.6%, food allergy 9.5% and depression or anxiety 13.3%. Summary characteristics for those with current atopic diseases and depression or anxiety and the whole cohort are listed in Table 1.

Whole-cohort analyses found positive associations between having *at least 1 atopic disease* and *depression or anxiety*, adjusted odds ratios (adjOR) ever 1.33 (95%CI 1.20, 1.47) and current 1.36 (95%CI 1.21, 1.52), as listed in Table 2. For separate atopic diseases, estimates were highest for *asthma* ever (adjOR 1.47, 95%CI 1.29, 1.69) and current (adjOR 1.59, 95%CI 1.36, 1.86) and lowest for *eczema* ever (adjOR 1.23, 95%CI 1.09, 1.38) and current (adjOR 1.11, 95%CI 0.92, 1.35). No effect modification was seen by sex (results not shown).

Cross-twin familial co-aggregation analyses found that having an *atopic disease* of any type in 1 twin (twin 1) was associated with *depression or anxiety* in their partner twin (twin 2), except for current *food allergy* (Table 3). Estimates were similar to those for the within-twin analysis (Table 2) and did not change when further adjusted for the partner twin's (twin 2) atopic status (Table 3). These results suggest that there is a familial aggregation for the comorbidity of atopic diseases and depression or anxiety. A comparison of MZ and DZ twins did not find that the associations in MZ twins were statistically higher than in DZ twins for any of the atopic diseases which suggests that the familial aggregation may not be due to common genes (Table 3).

Adjusting for each of the potential familial candidates—*parental education*, *recent maternal anxiety/depression*, *childhood family trauma* or *parental birth place*—only changed estimates slightly (Table 4). Of note, the estimates slightly increased when *parental birth place* was added to the models (Table 4) and slightly decreased when *recent maternal psychological stress* was added to the models (Table 4), the

TABLE 1 Summary characteristics of the full twin cohort and the subgroups with current asthma, eczema, hay fever, food allergy or depression or anxiety

	Full cohort (%)	Current asthma n (%)	Current eczema n (%)	Current Hay fever n (%)	Current food allergy n (%)	Depression or anxiety n(%)
Total number of children	14197	1230 (8.7)[a]	1075 (7.6)[a]	940 (6.6)[a]	1330 (9.5)[a]	1883 (13.3)[a]
Sex						
Male	7161 (50.4)	726 (59.0)	443 (41.2)	558 (59.4)	625 (47.0)	892 (47.4)
Female	7036 (49.6)	504 (41.0)	632 (58.8)	382 (40.6)	705 (53.0)	991 (52.6)
Birth weight (grams)						
≤1999	1936 (13.7)	201 (16.7)	115 (10.8)	110 (11.8)	170 (12.9)	311 (16.7)
2000-2499	3292 (23.4)	326 (26.9)	278 (26.2)	229 (24.6)	319 (24.3)	488 (26.1)
2500-2999	5053 (35.9)	413 (34.1)	396 (37.3)	343 (36.9)	486 (37.0)	620 (33.2)
3000-3499	3085 (21.9)	213 (17.6)	223 (21.0)	195 (21.0)	264 (20.1)	369 (19.8)
≥3500	721 (5.1)	56 (4.6)	51 (4.8)	53 (5.7)	76 (5.8)	80 (4.3)
Gestational age (weeks)						
≤31	916 (6.5)	109 (8.9)	42 (3.9)	49 (5.2)	78 (5.9)	144 (7.7)
32-34	1952 (13.8)	218 (17.7)	162 (15.1)	140 (14.9)	196 (14.7)	312 (16.6)
35-36	3066 (21.6)	283 (23.0)	256 (23.8)	224 (23.8)	268 (20.2)	403 (21.4)
37-38	5531 (39.0)	423 (34.4)	416 (38.7)	351 (37.3)	517 (38.9)	730 (38.8)
39-40	2584 (18.2)	189 (15.4)	185 (17.2)	160 (17.0)	25 1 (18.9)	284 (15.1)
≥41	148 (1.0)	8 (0.7)	14 (1.3)	16 (1.7)	20 (1.5)	10 (0.5)
Number of older siblings						
0	3445 (24.3)	320 (26.0)	263 (24.5)	243 (23.9)	312 (23.4)	469 (24.9)
≥1	10 752 (75.7)	910 (74.0)	812 (75.5)	697 (74.2)	1018 (76.5)	1414 (75.1)
Maternal age at delivery						
≤24	890 (6.3)	83 (6.8)	61 (5.7)	54 (5.7)	79 (5.9)	187 (9.9)
25-29	3862 (27.2)	401 (32.6)	306 (28.5)	290 (30.9)	365 (27.4)	498 (26.5)
30-34	5816 (41.0)	464 (37.2)	436 (40.6)	388 (41.3)	569 (42.8)	732 (38.9)
≥35	3629 (25.6)	282 (22.9)	272 (25.3)	208 (22.1)	317 (23.8)	466 (24.8)
Parent's birth place						
Mother Sweden	12 743 (89.8)	1124 (91.4)	989 (92.0)	859 (91.4)	1202 (90.4)	1617 (85.6)
other	1454 (10.2)	106 (8.6)	86 (8.0)	81 (8.6)	128 (9.6)	266 (14.1)
Father Sweden	12 694 (89.4)	1134 (92.2)	991 (92.2)	860 (91.5)	1207 (90.8)	1601 (85.0)
other	1503 (10.6)	96 (7.8)	84 (7.8)	80 (8.5)	123 (9.3)	282 (15.0)
Highest parental education						
Both ≤9 y	223 (1.6)	13 (1.1)	13 (1.2)	7 (0.8)	21 (1.6)	44 (2.4)
One or both completed 12 y	5654 (40.2)	565 (46.4)	378 (35.4)	353 (37.8)	548 (41.5)	865 (46.7)
One or both ≥2 y Tertiary	8191 (58.2)	640 (52.6)	678 (63.4)	575 (61.5)	753 (57.0)	943 (50.9)
Recent maternal psychological stress	2465 (17.4)	270 (22.0)	214 (19.9)	196 (20.9)	256 (19.3)	541 (28.7)
Childhood family trauma	1415 (10.0)	147 (12.0)	115 (10.7)	112 (11.9)	160 (12.0)	260 (13.8)

[a]% of total number of children.

estimate for current *asthma* attenuated (adjOR 1.18, 95% CI 0.98, 1.42).

Sensitivity analyses: within analysis using *register-based asthma* found that the associations between *asthma* and *depression or anxiety* were positive (Table 5), although of a lesser magnitude (adjOR ever *asthma* 1.18 [95% CI 1.03, 1.37], adjOR current *asthma* 1.31 [95%CI 1.09, 1.56]) than the analyses using parent-reported asthma (Table 2). Cross-twin analysis found that *register-based ever or current asthma* in 1 twin was associated with *depression or anxiety* in their partner twin (twin 2) with similar magnitude to the analyses using parent-reported asthma in Table 4 (Table 5, adjOR ever *asthma* 1.26 [95% CI 1.09, 1.47], adjOR current *asthma* 1.26 [95%CI 1.04, 1.54]). No significant differences were seen between MZ and DZ twin pair associations for either of the register-based asthma definitions (Table 5). Adjusting for each of the potential familial candidates only changed estimates slightly; again, the addition of *recent maternal*

TABLE 2 Whole-cohort analysis. Asthma, atopic diseases and depression or anxiety in children (N = 14 197)

	Depression or anxiety		Odds Ratios (95% Confidence Intervals) for the association between atopic disease and depression or anxiety	
	n (% of those with atopic disease)	n (% of those without atopic disease)	Crude	Adjusted[a]
Ever				
≥1 atopic disease (n = 5805)	903 (15.6)	980 (11.7)	1.32 (1.19, 1.46)***	1.33 (1.20, 1.47)***
Asthma (n = 2094)	372 (17.8)	1500 (10.6)	1.44 (1.26, 1.64)***	1.47 (1.29, 1.69)***
Eczema (n = 3152)	503 (16.0)	1375 (12.5)	1.23 (1.09, 1.38)**	1.23 (1.09, 1.38)**
Hayfever (n = 1051)	178 (16.9)	1675 (12.9)	1.26 (1.06, 1.51)*	1.28 (1.06, 1.54)**
Food allergy (n = 1980)	322 (16.3)	1561 (12.8)	1.27 (1.11, 1.45)**	1.29 (1.12, 1.48)**
Current				
≥1 atopic disease (n = 3408)	559 (16.4)	1324 (12.3)	1.34 (1.20, 1.50)***	1.36 (1.21, 1.52)***
Asthma (n = 1230)	240 (19.5)	1628 (11.5)	1.59 (1.36, 1.85)***	1.59 (1.36, 1.86)***
Eczema (n = 1075)	167 (15.5)	1712 (13.1)	1.12 (0.92, 1.35)	1.11 (0.92, 1.35)
Hayfever (n = 940)	150 (16.0)	1724 (13.0)	1.17 (0.96, 1.43)	1.19 (0.98, 1.46)
Food allergy (n = 1330)	220 (16.5)	1644 (12.9)	1.31 (1.12, 1.53)**	1.33 (1.14, 1.56)**

[a]adjusted for: sex, gestational age, birth weight, maternal age at delivery, parent's birth country.
*$P \leq .05$, **$P < .01$, ***$P < .0001$.

psychological stress slightly decreased estimates (Table 5, adjOR ever *asthma* 1.23 [95% CI 1.05, 1.43], adjOR current *asthma* 1.23 [95%CI 1.00, 1.53]).

4 | DISCUSSION

This study has found evidence for familial aggregation for the comorbidity of atopic diseases and depression or anxiety in children. The whole-cohort analysis found that overall, parent-reported atopic disease of any type, 'ever' or 'current', was associated with having an internalizing disorder. Of all the atopic diseases we studied, the association between asthma and depression or anxiety was the strongest. Our effect estimates for asthma were comparable with other studies using cohorts of comparable age.[2,28,29] In regard to the other atopic diseases, although less studied than asthma, our study contributes to the growing body of epidemiological evidence finding that eczema,[5,30] food allergy[4,31] and rhinitis[6] are each associated with depression or anxiety in children.

There is physiological evidence supporting a causal association between stress and asthma involving immunologic and epigenetic mechanisms.[32,33] However, there is also epidemiological evidence indicating bi-directionality for atopic diseases and depression or anxiety.[7] Mechanisms for how atopic diseases may 'cause' depression or anxiety seem most likely to do with the stress of managing a chronic disease and lowered quality of life; for example, itching at night from eczema affecting sleep;[34] constantly assessing food choices;[35] absenteeism from school due to atopic illness.[2] We do not refute that causal pathways can occur in either direction. However, the results from the cross-twin analysis found that if 1 twin had an atopic disease the other twin was at risk of having an internalizing disorder, regardless of their own atopic status. This means if the link from atopic disease to stress was purely causal (in either direction), then we should have found that when we adjusted for twin 2's atopic status the effect estimates attenuated, which they did not. Therefore, from the adjusted cross-twin results Model 2 we can conclude that there is a familial liability, that is, a common genetic or environmental component explaining atopic disease and internalizing disorder comorbidity that is separate from direct causation between the 2 diseases. A further comparison of MZ and DZ twins in our study did not find evidence to prove that the familial liability is genetic in nature. However, an earlier Finnish adult twin study did find evidence for a small shared additive genetic effect for atopic diseases and depression or anxiety in adults.[9] It is possible that the different findings between studies are due to aetiologic differences for atopic diseases and depression or anxiety in adults and children, reflected in notable differences in disease prevalence between studies. However, more research is required, such as polygenic risk score analysis using published genome-wide association study (GWAS) summary statistics for asthma and anxiety. Early genetic studies have suggested a possible gene candidate—ADCYAP1R1, a susceptibility gene for post-traumatic stress disorder and anxiety that has also been shown to be associated with reduced bronchodilator response in children with asthma.[33]

Familial aggregation for disease comorbidity could also suggest other familial factors may be playing a role in the aetiology of the 2 diseases such as those with an environmental component. This includes physical, socio-psychological and cultural factors in the shared environment of the twin pairs. We tested several shared familial candidates that have been shown previously to be associated with atopic diseases and/or depression or anxiety. These included parental education (a marker for socio-economic status),[15,17] recent maternal psychological stress[16,36] and childhood family trauma.[37] However, we found that including these covariates

TABLE 3 Cross-twin familial co-aggregation analysis. Initial analyses and MZ and DZ same-sex analyses

	Depression or anxiety in Twin 2		Odds Ratios (95% Confidence Intervals) for the association of atopic disease in twin 1 and depression or anxiety in twin 2			
Atopic Diseases in Twin 1	n (% of twin 1 with atopic disease)	n (% of twin 1 without atopic disease)	All twin pairs[a]	All twin pairs[a]adjusted for twin 2 atopic status	MZ twins[a]	DZ same-sex twins[a]
Ever						
≥1 atopic disease	780 (15.2)	918 (11.7)	1.25 (1.12, 1.40)***	1.24 (1.12, 1.39)***	1.17 (0.94, 1.46)	1.25 (1.05, 1.50)*
Asthma	314 (17.2)	1384 (12.4)	1.33 (1.14, 1.54)**	1.29 (1.12, 1.49)**	1.18 (0.88, 1.59)	1.35 (1.06, 1.72)*
Eczema	455 (16.2)	1243 (12.2)	1.30 (1.14, 1.48)***	1.32 (1.16, 1.50)***	1.36 (1.05, 1.78)*	1.28 (1.04, 1.58)*
Hay fever	166 (17.8)	1532 (12.7)	1.39 (1.14, 1.68)**	1.40 (1.16, 1.68)**	1.20 (0.81, 1.77)	1.25 (0.91, 1.73)
Food allergy	269 (16.0)	1429 (12.6)	1.24 (1.07, 1.45)**	1.23 (1.05, 1.42)**	1.34 (1.01, 1.79)*	1.05 (0.80, 1.37)
Current						
≥1 atopic disease	474 (15.5)	1224 (9.4)	1.23 (1.08, 1.39)**	1.22 (1.08, 1.37)**	1.36 (1.06, 1.75)*	1.08 (0.88, 1.33)
Asthma	187 (17.1)	1511 (12.7)	1.22 (1.02, 1.46)*	1.23 (1.03, 1.46)*	1.14 (0.78, 1.66)	1.40 (1.05, 1.87)*
Eczema	172 (17.7)	1524 (12.7)	1.45 (1.20, 1.76)***	1.45 (1.20, 1.76)***	2.07 (1.46, 2.94)***	1.08 (0.76, 1.55)
Hay fever	146 (17.5)	1548 (12.8)	1.38 (1.12, 1.69)**	1.39 (1.14, 1.70)**	1.12 (0.73, 1.71)	1.27 (0.91, 1.78)
Food allergy	182 (15.3)	1516 (12.9)	1.15 (0.96, 1.37)	1.15 (0.96, 1.36)	1.33 (0.96, 1.82)	0.94 (0.68, 1.29)

N = 12 474 (those with all information who have a twin with all information).
[a]Adjusted for gestational age and maternal age at delivery.
*$P \leq .05$, **$P < .01$, ***$P < .001$.

TABLE 4 Cross-twin familial co-aggregation analysis. Testing potential familial candidates

	Odds ratios (95% Confidence intervals) for the association of atopic disease in Twin 1 and depression or anxiety in Twin 2			
Atopic diseases in Twin 1	All twin pairs[a]adjusted for parental education	All twin pairs[a]adjusted for recent maternal psychological stress	All twin pairs[a]adjusted for family trauma	All twin pairs[a]adjusted for parental birth place
Ever				
≥1 atopic disease	1.26 (1.12, 1.40)***	1.23 (1.10, 1.37)**	1.25 (1.12, 1.39)***	1.27 (1.14, 1.42)***
Asthma	1.31 (1.13, 1.53)**	1.30 (1.12, 1.50)**	1.32 (1.14, 1.53)**	1.36 (1.17, 1.58)**
Eczema	1.30 (1.14, 1.48)***	1.29 (1.13, 1.47)**	1.30 (1.14, 1.47)***	1.31 (1.15, 1.49)***
Hayfever	1.42 (1.17, 1.72)**	1.37 (1.12, 1.66)**	1.37 (1.13, 1.67)**	1.41 (1.16, 1.71)**
Food allergy	1.22 (1.04, 1.42)*	1.22 (1.05, 1.43)**	1.23 (1.05, 1.43)**	1.26 (1.08, 1.46)**
Current				
≥1 atopic disease	1.22 (1.08, 1.39)**	1.20 (1.06, 1.36)**	1.22 (1.08, 1.38)**	1.25 (1.10, 1.442)**
Asthma	1.21 (1.02, 1.44)*	1.18 (0.98, 1.42)	1.22 (1.03, 1.45)*	1.25 (1.04, 1.50)*
Eczema	1.45 (1.19, 1.76)**	1.44 (1.18, 1.75)**	1.46 (1.20, 1.77)**	1.48 (1.22, 1.80)***
Hayfever	1.41 (1.15, 1.73)**	1.35 (1.10, 1.66)**	1.36 (1.11, 1.67)**	1.41 (1.15, 1.73)**
Food allergy	1.15 (0.96, 1.38)	1.12 (0.94, 1.35)	1.14 (0.95, 1.36)	1.16 (0.97, 1.39)

N = 12 474 (those with all information who have a twin with all information).
[a]Adjusted for gestational age and maternal age at delivery.
*$P \leq .05$, **$P < .01$, ***$P < .001$.

in the models (Model 3) made little difference to effect estimates, although recent maternal psychological stress decreased estimates slightly and did attenuate for current asthma. We found in another study based on Swedish and Puerto Rican data that asthma risk increased in children whose mothers had both depression and asthma compared to children of mothers who only had one of these comorbidities.[38] In addition, a number of studies have found that early exposure to maternal and caregiver stress is associated with offspring asthma and atopy.[12,14,39,40] Unfortunately for the current study, we were unable to test the effect of exposure to maternal stress early in life due to the recency of the prescribed drug register (SPDR). Other possible social environmental factors that have been shown to particularly influence asthma morbidity in children and could be investigated as potential familial candidates include family

TABLE 5 Sensitivity analysis. Register-based asthma and depression or anxiety in children aged 9 years

	Odds ratios (95% Confidence Intervals)	
	Ever register-based asthma	Current register-based asthma
Whole cohort (N = 14 197)		
Depression or anxiety[a]	1.18 (1.03, 1.37)*	1.31 (1.09, 1.56)**
Cross-twin familial co-aggregation (N = 12 474)		
Depression or anxiety		
All twin pairs[b]	1.26 (1.09, 1.47)**	1.26 (1.04, 1.54)*
All twin pairs adjusted for twin 2 atopic status[b]	1.26 (1.09, 1.47)**	1.27 (1.05, 1.54)*
MZ twins[b]	1.23 (0.91, 1.65)	1.20 (0.80, 1.79)
DZ same-sex twins[b]	1.26 (0.99, 1.62)	1.33 (0.96, 1.85)
All twin pairs adjusted for parental education[b]	1.26 (1.08, 1.47)**	1.26 (1.03, 1.54)*
All twin pairs adjusted for recent maternal psychological stress[b]	1.23 (1.05, 1.43)**	1.23 (1.00, 1.50)*
All twin pairs adjusted for family trauma[b]	1.26 (1.08, 1.46)**	1.26 (1.03, 1.53)*
All twin pairs adjusted for parental birth place[b]	1.29 (1.11, 1.50)**	1.30 (1.06, 1.58)*

aadjusted for: sex, gestational age, birth weight, maternal age at delivery, parents' birth country. badjusted for gestational age and maternal age at delivery. *$P \leq .05$, **$P < .01$, ***$P < .0001$.

support,[41,42] negative parenting[43] and socio-economic disadvantage.[2,44]

We considered the possibility of over-reporting by parents for their child's atopic status and depression or anxiety which could cause inflated associations. To test this hypothesis, we were able to use an objective definition for asthma based on a previously validated algorithm for register-based asthma.[27] The whole-cohort effect estimates using register-based asthma were lower but still significant than the estimates for parent report, suggesting that some parental over-reporting may be occurring. However, the cross-twin effect estimates were similar between register-based asthma and parent-reported asthma which means that the parents were just as likely to report an internalizing disorder in the co-twin regardless of whether the first twin's asthma was recorded by parental report or healthcare register. Therefore, we feel that the sensitivity analysis using register-based asthma definition supports the main findings of the cross-twin analysis and that over-reporting by parents is not an explanatory reason for the associations.

The strengths of this study were that we had access to a large twin study and were therefore able to use cross-twin familial co-aggregation analysis. Secondly, our data were linked with administrative and healthcare registers so that we were able to test several environmental factors as candidates for a common environmental liability. The main limitation was that we could not assess severity of the atopic illnesses and therefore are unable to comment on disease severity and depression or anxiety. Secondly, although we were able to use a more objective definition in the sensitivity analysis for asthma based on register data, we were unable to do this for the other atopic diseases as parents do not always seek medical help for eczema, rhinitis and food allergy in their children.[27] Finally, there may be an issue with generalizability from twins to singletons. However, it has been shown that twins have a lower prevalence of asthma than singletons once gestational age and birth weight are adjusted for;[45] therefore, our results may be slightly tending more towards the null than expected in a group of singletons.

In conclusion, this study found evidence for familial aggregation for the comorbidity of atopic diseases and depression or anxiety in children. We found no evidence to suggest the familial aggregation is genetic in nature; however, more investigation is needed to discover the nature of the familial aggregation. The clinical implication may be that physicians treating patients with asthma or allergy need to consider comorbidity with depression or anxiety in the individual and relatives when taking a family history.

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CONFLICT OF INTEREST

Henrik Larsson has served as a speaker for Eli-Lilly and Shire and has received research grants from Shire, all outside the scope of the submitted work. The other authors have no conflict of interest to declare.

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