

Comorbidity of atopic diseases and gastroesophageal reflux- evidence of a shared cause.

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Key Message

- Patients with eczema or hayfever are at risk of also having GERD
- Comorbidity of asthma, atopic diseases with GERD may be due to shared familial or behavioral factors.
- Affective traits such as neuroticism, depression or anxiety may play a role in atopic disease comorbidity with GERD

ABSTRACT

Introduction: Gastroesophageal reflux disease (GERD) is the most common non-allergic comorbidity in adults with asthma, however comorbidity with other atopic diseases such as eczema and hayfever is unclear. The objective was to assess the comorbidity of GERD with asthma and atopic diseases, and to investigate possible mechanisms, including genetic and/or affective factors.

Methods: A co-twin control study harnessing 46 583 adult twins. Questionnaires on health status were linked to national patient and prescribed drug register data. Analyses tested associations of comorbidity between multiple definitions of atopic diseases (self-report and register-based) with GERD. Comparisons were made between unpaired, monozygotic (MZ) and dizygotic (DZ) twins to assess genetic liability. Affective traits (depression, anxiety and neuroticism) were added to models as possible explanatory factors.

Results: The risk of GERD in those with: asthma was OR (odds ratio) 1.52 (95% CI 1.38, 1.68), hayfever OR 1.22 (95%CI 1.12, 1.34), and eczema OR 1.23 (95%CI 1.10, 1.38). Adjusting for affective traits completely attenuated the comorbidity associations for hayfever and eczema with GERD, and partly for asthma with GERD. Co-twin control associations attenuated suggesting a shared cause for both GERD and atopic diseases. For example, all twins adjOR 1.32 (95%CI 1.00, 1.74), 0.97 (95% CI 0.76-1.23), 1.11 (95%CI 0.85-1.45) for self-report asthma, hayfever and eczema with GERD respectively. ∴

Conclusions: GERD is a common comorbidity in adults with asthma, hayfever and/or eczema. We found evidence for shared mechanisms suggesting common underlying causes that may involve affective traits requiring further investigation.

KEY WORDS

Asthma, hayfever, eczema, gastroesophageal reflux, comorbidity

INTRODUCTION

Asthma is a common chronic respiratory inflammatory disease causing acute dyspnoea and wheeze, affecting up to 4-9% of the global population.(1) The most common non-allergic comorbidity of asthma is gastroesophageal reflux disease (GERD), affecting up 30-90% of asthma patients,(2-4) characterized by the reflux of stomach contents causing symptoms such as heartburn and regurgitation often leading to esophagitis and other complications.(2, 5) The risk of developing GERD in patients with asthma is 5.5 (95%CI 1.9, 15.8) times higher compared to the non-asthmatic population,(6, 7) and even higher in patients with difficult to control asthma.(3, 8, 9) Furthermore, there is increasing evidence to suggest comorbidity also exists between GERD and other genetically related atopic diseases(10) such as allergic rhinitis (hayfever),(11-14) although the relationship between GERD and eczema is yet to be reported.

Although there is some observational and animal model evidence to suggest that the comorbidity between asthma and GERD is directional, that is, that one disease causes the other, the mechanisms are still under debate and are not easily translatable to comorbidity of GERD with other atopic diseases.(2, 15, 16) Furthermore, the use of GERD medication as a means to prevent or improve uncontrolled asthma has met with little success in clinical trials suggesting the association between the two diseases may not in fact be causal.(15, 17, 18)

Alternatively, asthma and reflux may share common mechanisms such as a genetic predisposition or or environmental risk factors such as pollution, smoking, diet affecting gut microbiota changes which are known to contribute independently to asthma and atopic disorders as well as GERD.(19) However, these possible mechanisms have not yet been tested in twin or family studies where familial factors can be controlled in order to elucidate common genetic or environmental causality. Furthermore, there may be an intrinsic cause such as an affective trait - depression, anxiety or neuroticism, which are commonly found in both those suffering with atopic diseases or GERD.(20-23)

The objective of this study was to investigate the comorbidity of asthma, hayfever, eczema and gastro-esophageal reflux disease in a large twin cohort and to assess the possible role of genes, common environment and affective traits as an explanation for comorbidity.

Methods

Study participants included three birth cohorts of twins (N= 46 582) from the Swedish Twin Registry (STR) aged 28-102 years: 1) the Study of Twin Adults Genes and Environment (STAGE) cohort with 25,387 twins born 1959-1985 who participated in a web-based questionnaire during 2005-2006; and two cohorts from the Screening Across the Lifespan (SALT) study who participated in a telephone interview during 2004-2010; 2) SALT consisting of 6 605 participants born 1939-1958 and 3) TwinGene consisting of 14 590 participants born 1911-1958. The questionnaire response rates of each cohort were 59.6%, 46%, and 65%, respectively.(24-26) Furthermore, all twins were linked via a unique personal identification number to the Swedish Prescribed Drug Registry (PDR) for dispensed medications since July 2005 to 2015, and to the National Patient Registry (NPR) for doctor-diagnoses from inpatient care since 1987 and outpatient care from 2001 to 2013. Figure S1 shows the sources of twin and health data by year.

Asthma and atopic diseases

We measured asthma and atopic diseases in two ways: 1) self-reported doctor-diagnoses taken from questionnaire/interview data to identify disease at any time up until the interview, referred to as “**self-report asthma/atopic diseases**” (see Methods, Supplemental Digital content for more information); 2) medication and diagnosis data from the PDR and the NPR to identify recent cases, referred to as “**register-based asthma/atopic diseases**”(based on the algorithms developed by Örtqvist AK et al. for asthma,(27) and Henriksen L et al. for hay fever and eczema(28) with some minor modifications to exclude COPD cases, see Methods, Supplemental Digital content 1 for more information).

Additionally, we also stratified **self-report asthma** into asthma phenotypes of interest: 1) **childhood or adult onset asthma** if the reported age of first asthma onset was below or above 18 years of age; 2) **allergic or non-allergic asthma** if the participant also self-reported doctor-diagnosis of hay fever or eczema, or not; 3) asthma comorbid with overweight (BMI 25-29.9) or obesity (BMI $\geq$ 30); 4) **asthma with a history of exacerbation** according to the current GINA guidelines: defined as frequent exacerbations requiring oral corticosteroids (OCS) more than twice in a 12 month period; or serious exacerbation requiring hospitalization more than once per year(29) ; 5) **moderate-to-severe asthma** with step 4-5 therapy according to GINA guidelines,(29) i.e. medium to high dose corticosteroids (ICS) plus long-acting beta agonists/ leukotriene receptor antagonists/ tiotropium, or medium to high dose ICS plus OCS (see Methods, Supplemental Digital content 1 for more information).

Gastroesophageal reflux disease

The questionnaires/interviews collected information on participants' GERD-specific symptoms using questions developed from two institutions in the U.S. and Sweden.(30, 31) In the current study, **GERD** was defined as either of the cardinal symptoms: 1) **Frequent heartburn**: if the participant had reported heartburn more than once per week; OR 2) **Frequent reflux-like chest pain**: if the participant had reported pain behind the sternum (retrosternal) more than once per week AND the pain was relieved by antacid or acid suppressing medicine.

Covariates and Affective Traits

Information on sex, birth year, zygosity of the twins (monozygotic (MZ), same-sex dizygotic (DZ), and different-sex DZ twins), regular smoking, education, and body mass index (BMI) were retrieved from the questionnaires/interviews. In STAGE depression and anxiety were measured using the Structured Clinical Interview for DSM-IV Disorders (SCID).(32) In SALTY and TWINGENE **major depression** and **generalised anxiety disorder** were measured using a computerized version of the Composite International Diagnostic Interview-Short Form (CIDI-SF)(33) and **Neuroticism** was measured using the Eysenck Personality Questionnaire. See the Methods, Supplemental Digital content 1 for more information on how depression and anxiety were defined.

Statistical analysis

Firstly, we investigated the association between self-reported and register-based asthma and allergic diseases with GERD using general estimation equations with logit link function. Robust standard errors were used to account for clustering within twin pairs. Estimates included: (1) unadjusted odds ratios (ORs) and 95% confidence intervals (CIs); (2) adjusted ORs and CIs adjusted for measured potential confounders including birth year, sex, cohort, smoking, education, and BMI (based on an informed directed acyclic graph - see Figure S2). Models included asthma and allergic diseases as the independent variables and GERD as the dependent variable. We also tested the associations in the opposite direction and found minimal differences in OR estimates and confidence intervals (not presented for brevity). Secondly, we performed additional analyses to explore whether the association between asthma and allergic diseases with GERD were modified by sex including interaction terms, as well as whether the results remain robust for each of the five asthma phenotypes and for heartburn and reflux-like chest pain analysed separately. Thirdly, we also explored the potential role of the affective traits- depression, anxiety and neuroticism by adding each separately to the adjusted models and then altogether (depression or anxiety or neuroticism) as these traits are often correlated.(34) Finally, we applied the co-twin control analyses to address the

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role of familial confounding and potential causal association using conditional logistic regression analyses, conditioning on twin pair, and additionally controlling for sex, smoking, education, and BMI. In this case, we analysed discordant MZ and same-sex DZ twin pairs (within twin pair comparisons). If the association between asthma and GERD is lower for a co-twin control analysis compared to the whole cohort analysis then this suggests that the association between GERD and asthma can be explained in part by familial factors - common genes or shared environment. To distinguish between common environment or genes we then compare estimates for monozygotic (MZ) twins (sharing all of their segregating genes) and those for dizygotic (DZ) twins (sharing on average 50% of their segregating genes). If the MZ association is lower than DZ association then this implies a role of genetics since we have controlled for all genes among MZ, but only 50% among DZ. If not, then this implies the shared environment may be playing a role.

All analyses were performed using SAS 9.4.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (with approval numbers: 03/224 for STAGE, 2008/1735-31/3 for SALT, and 2011/463-32 for TwinGene) and informed consents were received from all study participants. All data was pseudonymised prior to analyses.

Results

The prevalence of asthma based on self-report was 7.7% and for the register-based definition was 11.6% (Table 1). Similarly, self-report and register-based prevalences for hayfever were 25.3% and 10.7% , and for eczema 12.2% and 6.1%, respectively. The proportion of GERD in the study population was 11.8%, which was made up of 53% reporting frequent heartburn, 30% reporting frequent reflux-like chest pain and 17% reporting both symptoms.

In total, 15-18% of those with asthma, hayfever or eczema also had GERD, and 8-14% of those with GERD also had asthma, hayfever or eczema (Table 2). The odds of having GERD comorbidity was adjOR 1.52 (95% CI 1.38-1.68) in participants with self-report asthma, adjOR 1.22 (95% CI 1.12-1.34) for self-report hayfever, and adjOR 1.23 (95%CI 1.10-1.38) for self-report eczema (Table 3). Similar associations were observed for GERD with register-based definitions for asthma and eczema (Tables S1 and S2, Supplemental Digital content 1), and the odds of having GERD in those with hayfever was even more pronounced for the register-based definition (adjOR 1.55, 95%CI 1.45,1.65).

Comorbidity rates were almost double in women compared with men (Table 2 and Table S1, Supplemental Digital content 1), reflecting the higher prevalence of GERD, asthma and allergic diseases in women. However, the odds ratios for having GERD comorbidity were similar between sexes for asthma and atopic diseases, except for self-report eczema and GERD which was higher in men (Table S3, Supplemental Digital content 1).

Additional analyses found no differences in comorbidity estimates for self-reported asthma diagnosed in childhood or adulthood, nor for allergic versus non-allergic asthma or moderate-to-severe asthma vs. no asthma. Comorbidity for GERD was slightly higher in participants with asthma who were also comorbid for obesity or overweight, but there was still an observed comorbidity for GERD in those with asthma who were not overweight (adjOR 1.43, 95%CI 1.25, 1.64). Comorbidity of GERD in participants who had a history of asthma exacerbations appeared to be slightly more pronounced (adjOR 1.79, 95% CI 1.28-2.51), albeit the confidence intervals being wider (Table 3). No differences were observed for the separate comorbidity associations of frequent heartburn or reflux-like chest pain with asthma and atopic diseases (Table S4, Supplemental Digital content 1). We also adjusted the eczema and hayfever comorbidity estimates for asthma to check that the observed estimates were in fact true associations between GERD and the atopic diseases and not representing an indirect association of GERD with asthma. Results show that comorbidity between eczema, hayfever and GERD is independent of asthma, although the self report

hayfever estimate does attenuate considerably with the lower confidence interval just below the null (Table S5).

Addition of depression, anxiety and neuroticism variables to the adjusted models resulted in slight attenuation of the associations between self-report asthma, hayfever and eczema with GERD (Figure 1, Table S6, Supplemental Digital content 1). When all three affective traits were added to the models together (therefore including any or all combinations of individuals with affective traits) the associations attenuated further, crossing the null for hayfever and eczema (Figure 1). The association remained significant for asthma and GERD comorbidity (adjOR 1.33, 95% CI 1.15-1.53, Table S6, Supplemental Digital content 1). Similar attenuations were seen for register-based definitions such as register-based asthma and GERD adjusted for all three traits (adjOR 1.30, 95%CI 1.15-1.47, Table S5, Supplemental Digital content 1). Adding depression, anxiety and neuroticism independently and collectively to allergic asthma and non-allergic asthma models showed similar results indicating that presence of allergic diseases with asthma does not explain asthma and GERD comorbidity (results not shown).

In co-twin control analyses comorbidity associations for GERD were attenuated for the combined twin (MZ and same-sex DZ twins) compared to the original whole cohort analysis eg adjOR 1.32 (95% CI 1.00-1.74) self-report asthma, adjOR 0.97 (95% CI 0.76-1.23) self-report hay fever and adjOR 1.11 (95%CI 0.85-1.45) self-report eczema (Figure 2, Table S7, Supplemental Digital content 1). When the twins were further separated into MZ and DZ-same sex groups for analyses, all self-report atopic disease comorbidity associations with GERD were lower within MZ twins compared to same-sex DZ twins, for example self-report asthma MZ twins: adjOR 1.24 (95%CI 0.82, 1.87) and same-sex DZ twins: adjOR 1.41 (95%CI 0.96, 2.08). (Figure 2 and Table S7, Supplemental Digital content 1) Similar attenuation patterns for all twins and DZ same-sex compared to MZ twins were also observed for register-based hayfever and eczema definitions supporting the self-report results (Table S7). Although we also observed an attenuation for the analysis of GERD and asthma in all twins, adjOR 0.94 (95%CI 0.77, 1.15) we did not observe a difference between DZ and MZ effect sizes (Table S7).

Discussion

In this large twin cohort we have confirmed that GERD is a common comorbidity of asthma and hayfever, and for the first time demonstrated comorbidity between eczema and GERD. The rates and risk ratios of asthma and GERD comorbidity reported in this Swedish adult twin population are commensurate with other large general population studies.(8, 35-37) In addition, our results support a number of studies which have found that GERD is a risk factor for asthma exacerbations and difficult to control asthma(3, 38-41) . As far as we know our study is the first to report on asthma severity and GERD, and the results do not support an association. These results suggest that GERD is more likely to be associated with an asthma exacerbation rather than severity of asthma as defined by high dose medications GINA guidelines Step 4 and 5.

The odds of having GERD comorbidity in those with hayfever ranged from 1.22-1.55 confirming the findings of other studies.(13, 42) We did note that the proportion of the population with register-based hayfever was more than double (25%) the self-report proportion (10%). The register-based definition included at least two prescriptions for local corticosteroids for rhinitis (R01AD01-6D) or two antihistamines (R06A) with some exceptions (Methods, Supplemental Digital content 1). It is likely that participants were either undiagnosed at the time of the questionnaire (which was earlier than the registers started collecting information) or did not associate these types of prescriptions with hayfever, and therefore under-reported having a diagnosis for hayfever, pollen allergy or fur allergy. Similar to asthma and hayfever, there was an increased risk of having GERD comorbidity with eczema (OR 1.19-1.23).

When each of the affective traits - depression, anxiety and neuroticism were added to the asthma and allergy models there was a small decrease in the OR for GERD, however when all three affective traits were added together a larger decrease in OR was seen of 10-20%. This was consistent for all atopic conditions and definitions. These results indicate that having at least one of these three related conditions(34) could be an explanatory factor for the comorbidity of GERD and atopic conditions. We hypothesise two possible modes of action: 1) mediation- having an atopic disease may increase the risk of depression, anxiety or neuroticism which in turn triggers and exacerbates GERD. Supporting this theory, a study of 29 000 rescue workers and community members found that participants with asthma who suffered posttraumatic stress disorder from the New York World Trade Centre September 11 attack were more likely to develop new and persistent GERD;(44) 2) a common cause - that having depression, anxiety or neuroticism increases vulnerability towards developing or reporting both atopic diseases and

GERD. Certainly it has been shown separately that depression and anxiety are common comorbidities of patients with atopic diseases(20, 21, 43) and GERD,(22) and there is some evidence for a common genetic cause for depression, neuroticism with asthma.(45) More research is needed to disentangle these phenomenon to sort out the possible shared causes.

Hypothetically, if GERD and atopic diseases have a truly causal relationship then controlling for genes and shared family environment by using a co-twin analysis should result in little change in the estimates.

However, we observed attenuation in all co-twin control comorbidity associations compared to the whole cohort. This implies that the comorbidity associations are not causal but are in fact due to a shared cause- either genetic or shared environment. Observation of further attenuation of the MZ twin pairs compared with the same sex DZ twins suggests the likelihood of a common genetic rather than shared environmental cause for hayfever and eczema with GERD, although the results were non-conclusive for asthma. However, the confidence intervals were wide, hence our interpretation of a possible genetic cause is cautious and requires verification . Further specific genetic analysis may also be informative, for example, investigating the relationships between polygenetic risk scores derived from genome wide association studies for asthma, hayfever and eczema with GERD symptoms.(45, 46),

This study has a number of unique strengths. The first is the very large population of adult twins accessed from three twin cohorts with similar questions and variables for atopic diseases, GERD, affective disorders and covariates for multiple regression increasing the validity and reliability of our findings. The large study population also meant we had sufficient power for co-twin control analyses which requires a sizeable population of discordant twins for exposure and outcome. Thirdly, because the twin data is linked to population register data we were able to define asthma, hayfever and eczema in two different ways, one from self-report questionnaires the other based on hospital diagnoses and medications. The consistency in our findings using two different types of definitions, decreases measurement bias and improves the robustness of our results. Because of the linked twin and register data we were also able to report on a number of different asthma phenotypes which is novel, and as far as we know we are the first to report on eczema and GERD.

This study also has several limitations that need to be considered. The first is in the definition of GERD. The questionnaires only asked about GERD symptoms (heartburn and sternum pain) and did not ask about diagnosis, in addition we could not define this from the registers because GERD is not commonly diagnosed in hospital, but rather in primary care, and medications given for GERD are not specific for GERD. This may have led to some measurement bias pushing the results towards the null particularly in the co-twin control analyses. Secondly, it is possible that registered-based asthma measures might have

the potential non-differential misclassification bias especially among the older twins as some asthma medication dispenses could have been prescribed for other respiratory diseases such as obstructive bronchitis, diluting the association estimates accordingly. Thirdly, since our study is in a twin population it is not necessarily representative of the singleton population, however, we have no reason to think that atopic diseases and GERD would behave differently in twins than singletons.(47)

In conclusion, adults with atopic diseases -asthma, hayfever and eczema- are at higher risk of also having GERD. Our study sheds new light on the high degree of comorbidity suggesting that rather than causal associations, a shared component that involves affective traits may be important. Although we were able to use a large twin cohort with a unique study design further work is needed to explore these possible mechanisms.

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Table 1. Study participants' characteristics

	STAGE (n=25 387)	TwinGene (n=14 590)	SALTY (n=6605)	All (n= 46 582)
Born 1911-1938	0	4855(33.28)	0	4855
Born 1939-1948	0	6450(44.21)	2190(33.16)	8640
Born 1949-1958	0	3285(22.52)	4415(66.84)	7700
Born 1959-1968	10 237(40.32)	0	0	10237
Born 1969-1978	9021(35.53)	0	0	9021
Born 1979-1985	6129(24.14)	0	0	6129
Zygosity				
MZ twins	9208(36.27)	3622(24.83)	1753(26.54)	14583(31.31)
Same-sex DZ twins	7409(29.18)	5605(38.42)	2358(35.70)	15372(33.00)
Unknown zygosity	886(3.49)	59(0.40)	86(1.30)	1031(2.21)
Opposite-sex DZ twins	7884(31.06)	5304(36.35)	2408(36.46)	15596(33.48)
Sex				
Male	11261(44.36)	6753(46.29)	3125(47.31)	21139(45.38)
Female	14126(55.64)	7837(53.71)	3480(52.69)	25443(54.62)
Smoking				
Yes	6766(26.65)	2406(16.49)	1237(18.73)	10409(22.35)
Missing	834(3.29)	69(0.47)	638(9.66)	1541(3.31)
Education				
Compulsory school	1354(5.33)	7688(52.69)	2233(33.81)	11275(24.20)
High school	11105(43.74)	2794(19.15)	1689(25.57)	15588(33.46)
University or higher education	10400(40.97)	4021(27.56)	2044(30.95)	16465(35.35)
Missing	2528(9.96)	87(0.60)	639(9.67)	3254(6.99)
Mean BMI (SD)	23.79 (3.70)	24.98(3.40)	24.77(3.51)	24.31(3.63)
Frequent heartburn				
Yes	2062(8.12)	1284(8.80)	486(7.36)	3832(8.23)
Missing	1857(7.31)	102(0.70)	641(9.70)	2600(5.58)
Frequent reflux-like chest pain				
Yes	1899(7.48)	446(3.06)	172(2.60)	2517(5.40)
Missing	1867(7.35)	135(0.93)	658(9.96)	2660(5.71)
GERD				
Yes	3241(12.77)	1629(11.17)	636(9.63)	5506(11.82)
Missing	1580(6.22)	77(0.53)	637(9.64)	2294(4.92)

Asthma (self-report)

Yes	2333(9.19)	801(5.49)	453(6.86)	3587(7.70)
Missing	3200(12.60)	102(0.70)	650(9.84)	3952(8.48)

Hay fever (self-report)

Yes	3577(14.09)	860(5.89)	546(8.27)	4983(10.70)
Missing	3124(12.31)	267(1.83)	728(11.02)	4119(8.84)

Eczema (self-report)

Yes	1271(5.00)	1096(7.51)	488(7.39)	2855(6.13)
Missing	3095(12.19)	69(0.47)	635(9.61)	3799(8.16)

Asthma (register-based)

Yes	2647(10.43)	1878(12.87)	899(13.61)	5424(11.64)
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Hay fever (register-based)

Yes	6623(26.09)	3456(23.69)	1682(25.47)	11761(25.25)
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Eczema (register-based)

Yes	2474(9.75)	2274(15.59)	931(14.10)	5679(12.19)
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Depression

Yes	4054(15.97)	2819(19.32)	1528(23.13)	8401(18.03)
Missing	3636(14.32)	347(2.38)	738(11.17)	4721(10.13)

Anxiety

Yes	934(3.68)	173(1.19)	109(1.65)	1216(2.61)
Missing	6078(23.94)	2532(17.35)	1810(27.40)	10420(22.37)

Neuroticism, Median (IQR on standardized scale)

-0.27 (-0.74, 0.67)	-0.29 (-0.74, 0.6)	-0.27 (-0.74, 0.6)	-0.27 (-0.74, 0.60)
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Asthma, Mean age of onset (SD)

15.07 (10.18)	29.96(20.20)	23.24(16.84)	18.84(14.76)
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Frequent Reflux-like chest pain, Mean age of onset (SD)

23.46 (6.96)	37.48(14.25)	32.68(11.74)	26.05(10.11)
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Table 2. Comorbidity of self-report asthma, hayfever, eczema and GERD

	All (N=46 582)	Male (n=21 139)	Female (n=25 443)
Asthma & GERD	658 (1.41%)	199 (0.94%)	459 (1.80%)
% of having GERD among those having asthma	18.39	14.41	20.89
% of having asthma among those having GERD	12.51	11.31	13.11
missing asthma or GERD*	4040	2106	1934

Hay fever & GERD	726 (1.71%)	210 (1.11%)	516 (2.20%)
% of having GERD among those having hay fever	14.60	10.01	17.95
% of having hay fever among those having GERD	13.92	12.05	14.87
missing hay fever or GERD*	4208	2189	2019
Eczema & GERD	418 (0.98%)	122 (0.64%)	296 (1.25%)
% of having GERD among those having eczema	14.65	12.87	15.53
% of having eczema among those having GERD	7.93	6.92	8.44
missing eczema or GERD*	3887	2032	1855

* Number of individuals with missing on self-reported doctor-diagnosed asthma/hay fever/eczema or GERD symptoms.

Table 3. Associations for GERD comorbidity in those with self-reported asthma, hayfever or eczema (Odds Ratios and 95% Confidence Intervals, n=46 582)

	OR (95% CI) for GERD	
	Unadjusted	Adjusted ^a
Asthma	1.68 (1.53, 1.83)	1.52 (1.38, 1.68)
No asthma	ref	ref
Hay fever	1.25 (1.14, 1.36)	1.22 (1.12, 1.34)
No hay fever	ref	ref
Eczema	1.24 (1.11, 1.38)	1.23 (1.10, 1.38)
No eczema	ref	ref
Asthma age of onset		
Childhood-onset asthma	1.53 (1.36, 1.71)	1.46 (1.29, 1.65)
Adulthood-onset asthma	1.97 (1.71, 2.26)	1.63 (1.40, 1.90)
Asthma comorbidity with overweight and obesity		
Non-overweight asthma	1.38 (1.22, 1.56)	1.43 (1.25, 1.64)
Overweight asthma	1.92 (1.64, 2.23)	1.66 (1.40, 1.96)
Obese asthma	2.77 (2.22, 3.47)	1.61 (1.24, 2.08)

Asthma comorbidity with other allergic diseases

Allergic asthma	1.64 (1.45, 1.86)	1.50 (1.32, 1.72)
Non allergic asthma	1.69 (1.49, 1.92)	1.53 (1.33, 1.76)

Asthma exacerbation history^b

Yes	1.69 (1.22, 2.33)	1.79 (1.28, 2.51)
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Moderate to Severe Asthma^c

Yes	1.12 (0.96, 1.32)	1.12 (0.94, 1.33)
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^a adjusted for sex, birth year, cohort, education, smoking, and BMI.

^b based on 44,606 individuals (asthma with no exacerbation history excluded), non-asthma is the reference group

^c based on 44,357 individuals (asthma that is not moderate/severe excluded), non-asthma is the reference group.

Figure 1. Associations for GERD comorbidity in those with self-report Asthma, Hayfever, Eczema, additionally adjusted for Depression, Anxiety and Neuroticism (DAN). Odds ratios and 95% Confidence intervals.

Figure 2. Associations for GERD comorbidity in those with self-reported Asthma, Hayfever and Eczema: whole cohort and co-twin control analyses.

REFERENCES

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12:204.
2. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Aliment Pharmacol Ther*. 2018;47:176-91.
3. Hekking PP, Amelink M, Wener RR, et al. Comorbidities in Difficult-to-Control Asthma. *J Allergy Clin Immunol Pract*. 2018;6:108-13.
4. Kiljander TO, Laitinen JO. The prevalence of gastroesophageal reflux disease in adult asthmatics. *Chest*. 2004;126:1490-4.
5. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101:1900-20; quiz 43.
6. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut*. 2007;56:1654-64.
7. Thakkar K, Boatright RO, Gilger MA, et al. Gastroesophageal reflux and asthma in children: a systematic review. *Pediatrics*. 2010;125:e925-30.
8. Nordenstedt H, Nilsson M, Johansson S, et al. The relation between gastroesophageal reflux and respiratory symptoms in a population-based study. *Chest*. 2006;129:1051-56.
9. Tay TR, Radhakrishna N, Hore-Lacy F, et al. Comorbidities in difficult asthma are independent risk factors for frequent exacerbations, poor control and diminished quality of life. *Respirology*. 2016;21:1384-90.
10. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nature Genetics*. 2017;49:1752-7.
11. Hellgren J, Olin AC, Toren K. Increased risk of rhinitis symptoms in subjects with gastroesophageal reflux. *Acta Otolaryngol*. 2014;134:615-9.
12. Schioler L, Ruth M, Jogi R, et al. Nocturnal GERD - a risk factor for rhinitis/rhinosinusitis: the RHINE study. *Allergy*. 2015;70:697-702.
13. Kung YM, Tsai PY, Chang YH, et al. Allergic rhinitis is a risk factor of gastro-esophageal reflux disease regardless of the presence of asthma. *Sci Rep*. 2019;9:15535.
14. Katle EJ, Hatlebakk JG, Steinsvag S. Gastroesophageal reflux and rhinosinusitis. *Curr Allergy Asthma Rep*. 2013;13:218-23.

15. Hait EJ, McDonald DR. Impact of Gastroesophageal Reflux Disease on Mucosal Immunity and Atopic Disorders. *Clin Rev Allergy Immunol*. 2019;57:213-25.
16. Kotzan J, Wade W, Yu HH. Assessing NSAID prescription use as a predisposing factor for gastroesophageal reflux disease in a medicaid population. *Pharmaceutical Res*. 2001;18:1367.
17. Gibson PG, Henry R, Coughlan JLL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database of Systematic Reviews*. 2003.
18. The American Lung Association Asthma Clinical Research Centers. Efficacy of esomeprazole for treatment of poorly controlled asthma. *NEJM*. 2009;360:1487.
19. Walker MM, Powell N, Talley NJ. Atopy and the gastrointestinal tract--a review of a common association in unexplained gastrointestinal disease. *Expert Rev Gastroenterol Hepatol*. 2014;8:289-99.
20. Tedner SG, Lundholm C, Olsson H, et al. Depression or anxiety in adult twins is associated with asthma diagnosis but not with offspring asthma. *Clin Exp Allergy*. 2016;46:803-12.
21. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med*. 2008;70:102-16.
22. Kessing BF, Bredenoord AJ, Saleh CM, et al. Effects of anxiety and depression in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2015;13:1089-95 e1.
23. Wu Y, Murray GK, Byrne EM, et al. GWAS of peptic ulcer disease implicates *Helicobacter pylori* infection, other gastrointestinal disorders and depression. *Nature Communications*. 2021;12.
24. Zagai U, Lichtenstein P, Pedersen NL, et al. The Swedish Twin Registry: Content and Management as a Research Infrastructure. *Twin Res Hum Genet*. 2019;22:672-80.
25. Lichtenstein P, Sullivan PF, Cnattingius S, et al. The Swedish Twin Registry in the third millennium: an update. *Twin Res Hum Genet*. 2006;9:875-82.
26. Pedersen NL, Lichtenstein P, Svedberg P. The Swedish Twin Registry in the third millennium. *Twin Res*. 2002;5:427-32.
27. Ortqvist AK, Lundholm C, Wettermark B, et al. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf*. 2013;22:850-60.
28. Henriksen L, Simonsen J, Haerskjold A, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol*. 2015;136:360-6 e2.
29. Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients- Diagnosis and Management. A GINA Pocket Guide For Health Professionals; 2019.

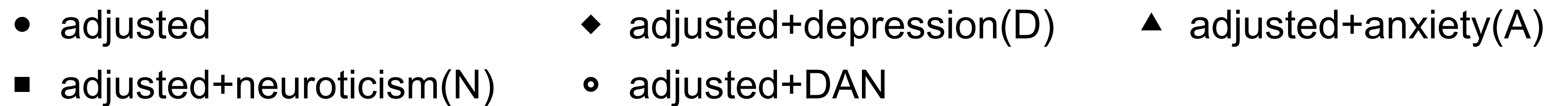
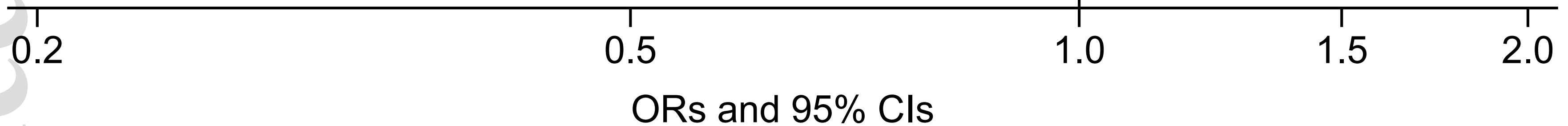
30. Locke GR, 3rd, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112:1448-56.
31. Lagergren J, Bergström R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340:825-31.
32. First M, Spitzer R, Gibbon M, et al. Structured clinical interview for DSM-IV-patients edition (with psychotic screen, version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute.; 1996.
33. Kessler R, Andrews G, Mroczek D, et al. The World Health Organization Composite International Diagnostic Interview Short-Form (CIDI-SF). *Int J Methods Psych Res*. 1998;7:171-85.
34. Kotov R, Gamez W, Schmidt F, et al. Linking "big" personality traits to anxiety, depressive and substance use disorders: a meta-analysis. *Psychol Bulletin*. 2010;136:768-821.
35. Rey E, Eloia-Olaso C, Rodriguez-Artalejo F, et al. Prevalence of atypical symptoms and their association with typical symptoms of gastroesophageal reflux in Spain. *Eur J Gastroenterol Hepatol*. 2006;18:969-75.
36. Kim SY, Min C, Oh DJ, et al. Bidirectional Association Between GERD and Asthma: Two Longitudinal Follow-Up Studies Using a National Sample Cohort. *J Allergy Clin Immunol Pract*. 2020;8:1005-13 e9.
37. Ruigomez A, Garcia Rodriguez LA, Wallander MA, et al. Gastroesophageal reflux disease and asthma. *Chest*. 2005;128:85-93.
38. Engelkes M, Baan EJ, de Ridder MAJ, et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. *Pediatr Allergy Immunol*. 2020;31:496-505.
39. Ciprandi G, Gallo F, Gelardi M. Impact of gastric reflux on asthma in clinical practice. *Respirology*. 2018;23:230-1.
40. Acworth J, Babl F, Borland M, et al. Patterns of presentation to the Australian and New Zealand Paediatric Emergency Research Network. *Emerg Med Australas*. 2009;21:59-66.
41. Tariq K, Schofield JPR, Nicholas BL, et al. Sputum proteomic signature of gastro-oesophageal reflux in patients with severe asthma. *Respir Med*. 2019;150:66-73.
42. Feng MC, Tsai YG, Chang YH, et al. Allergic rhinitis as a key factor for the development of gastroesophageal reflux disease in children. *J Microbiol Immunol Infect*. 2020.
43. Brew BK, Lundholm C, Gong T, et al. The familial aggregation of atopic diseases and depression or anxiety in children. *Clin Exp Allergy*. 2018;48:703-11.

- Accepted Article
44. Li J, Brackbill RM, Jordan HT, et al. Effect of asthma and PTSD on persistence and onset of gastroesophageal reflux symptoms among adults exposed to the September 11, 2001, terrorist attacks. *Am J Ind Med*. 2016;59:805-14.
 45. Lehto K, Pedersen NL, Almqvist C, et al. Asthma and affective traits in adults: a genetically informative study. *Eur Respir J*. 2019;53.
 46. Zhu Z, Hasegawa K, Camargo CA, Jr., et al. Investigating asthma heterogeneity through shared and distinct genetics: Insights from genome-wide cross-trait analysis. *J Allergy Clin Immunol*. 2020.
 47. Ullemar V, Magnusson PKE, Lundholm C, et al. Heritability and confirmation of genetic association studies for childhood asthma in twins. *Allergy*. 2016;71:230-38.

Asthma:adjusted
 Asthma:adjusted+depression
 Asthma:adjusted+anxiety
 Asthma:adjusted+neuroticism
 Asthma:adjusted+DAN

Hay fever:adjusted
 Hay fever:adjusted+depression
 Hay fever:adjusted+anxiety
 Hay fever:adjusted+neuroticism
 Hay fever:adjusted+DAN

Eczema:adjusted
 Eczema:adjusted+depression
 Eczema:adjusted+anxiety
 Eczema:adjusted+neuroticism
 Eczema:adjusted+DAN



Asthma

Whole cohort

Same-sex DZ twins

MZ twins

Hay fever

Whole cohort

Same-sex DZ twins

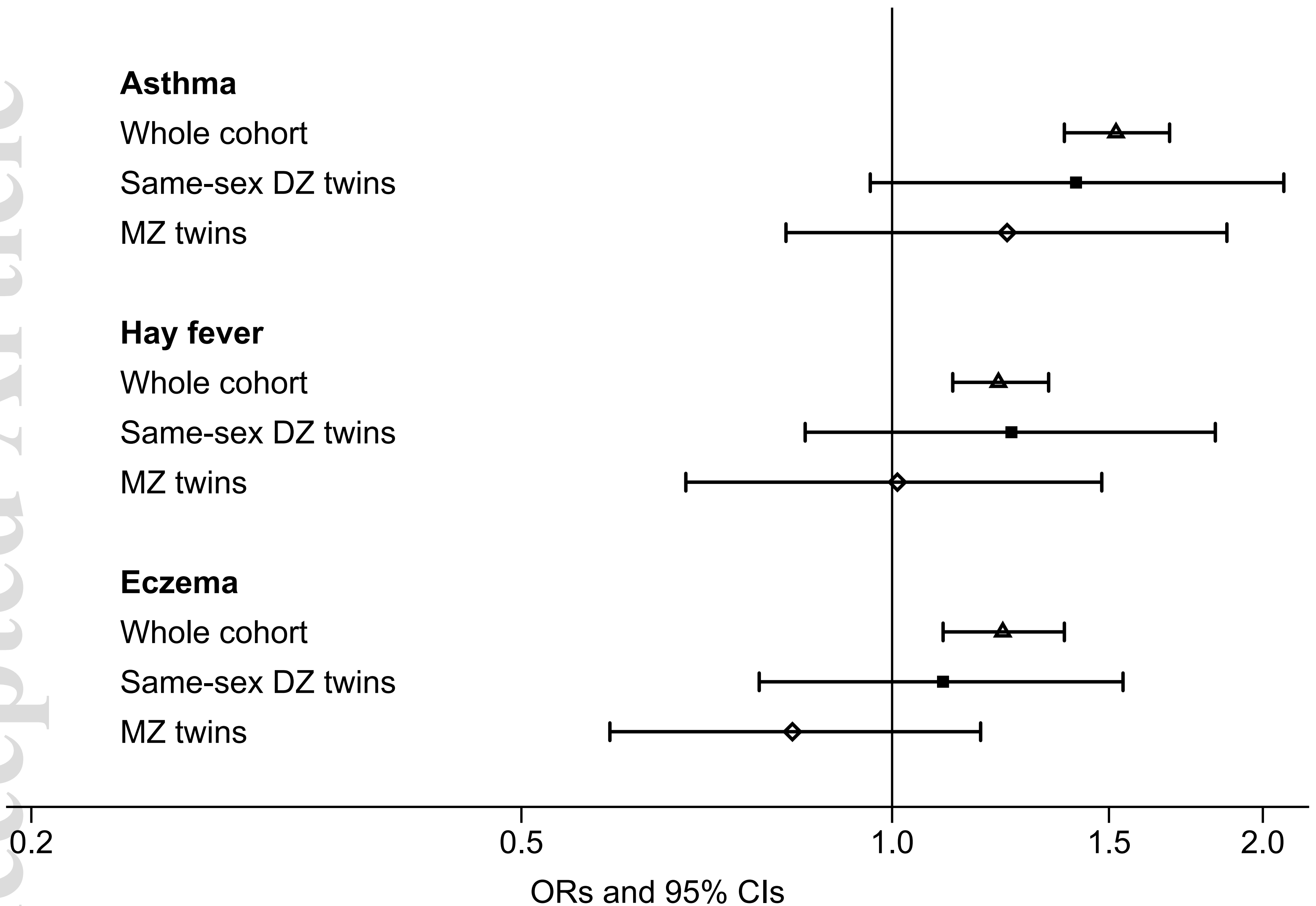
MZ twins

Eczema

Whole cohort

Same-sex DZ twins

MZ twins



$\blacktriangle$ Adjusted ORs among all participants $\blacklozenge$ Adjusted ORs among MZ twins
 $\blacksquare$ Adjusted ORs among same-sex DZ twins

Supplementary materials

Methods

Self-reported doctor-diagnosed asthma and allergic diseases measures from the questionnaires

Self-reported doctor-diagnosed asthma and allergic diseases were measured according to Ferriera et al.¹:

1). if the participant answered yes to “Do you have or have you had asthma?” AND “You said that you have or have had asthma, have you been given that diagnosis by a doctor?”

2) if the participant answered yes to “Do you have or have you had hay fever?” AND yes to any of the following questions: a) if the participant answered yes to “Have you been diagnosed with hay fever by a doctor?” OR b) if the participant answered yes to “Have you been diagnosed with pollen allergy by a doctor?” OR c) if the participant answered yes to “Have you been diagnosed with fur allergies by a doctor?”

3) if the participants answered yes to “Do you have or have you had eczema?” AND “Have you been diagnosed with atopic dermatitis or atopic eczema by a doctor?”

Register-based asthma and allergic diseases measures from the Swedish registers

The measure of register-based asthma was modified from Örtqvist AK et al.². In brief, we define asthma if an individual has fulfilled either criterion below: 1) ever been diagnosed with asthma (ICD-codes: J45-J46) but not been diagnosed with COPD (J44) from the National Patient Register, or 2) dispensed at least two prescriptions of controller medications (ATC-codes: R03AK, R03BA, and R03DC).

The measures of register-based eczema were modified from Henriksen L et al.³. In brief, we define eczema if an individual has fulfilled either criterion below: 1) ever been diagnosed with atopic dermatitis/winter feet (L20, L308C), or 2) dispensed at least one prescription of tacrolimus or pimecrolimus (D11AH) or 3) dispensed at least two prescriptions of topical corticosteroids (D07) without any of the exclusion criteria generated by the researchers. See detailed information in the Appendices of Henriksen L et al.

The measures of register-based hay fever were modified from Henriksen L et al.³. In brief, we define hay fever if an individual has fulfilled either criterion below: 1) ever been diagnosed with hay fever and allergic rhinitis (J30, J31.0), or 2) dispensed at least two prescriptions of inhaled corticosteroids for rhinitis (R01AD01-R01AD60) without any of the exclusion diagnoses generated by the researchers, or 3) dispensed at least two prescriptions of systemic antihistamines (R06A) without diagnoses of pruritus (L29) or allergic urticarial (DL50), or 4) dispensed at least one prescription of allergen subextract therapy (V01A) or medications for allergic conjunctivitis (S01GX). See detailed information in the Appendices of Henriksen L et al.

Moderate-to-severe asthma with step 4-5 therapy according to the current GINA guidelines

The measure of moderate-to-severe asthma with step 4-5 therapy was defined according to the 2019 GINA guideline, by having been prescribed with 1) medium to high dose ICS plus LABA/LTRA/Tiotropium, or 2) Medium to high dose ICS plus systemic OCS, anytime during July 2005 to December 2015 from the PDR. More specifically, we calculated the daily prescribed doses of each ICS-relevant medications by

multiplying the packaged strength of all available products found in the PDR (i.e. Beclometasone dipropionate (CFC) and (HFA), Budesonide (DPI), Fluticasone furoate (DPI), Fluticasone propionate (DPI), Fluticasone propionate (HFA), Mometasone furoate, Triamcinolone acetonide, the combination of fluticasone and LABA, as well as the combination of budesonide and LABA) with the suggested frequency written by doctor in the free text column.

Major Depression and Generalised Anxiety Disorder

Major depression was defined as either: 1) STAGE: having 5 of: depressed mood, loss of interest/pleasure, weight or appetite change, insomnia, psychomotor agitation/retardation, fatigue, feeling worthless, problems concentrating, suicidal ideation with either depressed mood or loss of interest in nearly all activities over a 2 week period and symptoms had to cause significant impairment or distress;^{4,5} 2) SALTY/TWINGENE: a CIDI-SF score >4 with accompanying dysphoria or anhedonia, OR a prescription of anti-depressants.⁶ **Generalised anxiety disorder (GAD)** was defined as: 1) STAGE: excessive anxiety and worry for at least 6 months, associated with three or more symptoms: restlessness or feeling keyed up or on edge; easily fatigued; difficulty concentrating; irritability; muscle tension; sleep disturbance;^{5,7} 2) SALTY/TWINGENE: excessive worry and anxiety for a month or more and at least one in five symptoms for GAD in DSM-IV.

Figure S1. Twin and Health data sources by year

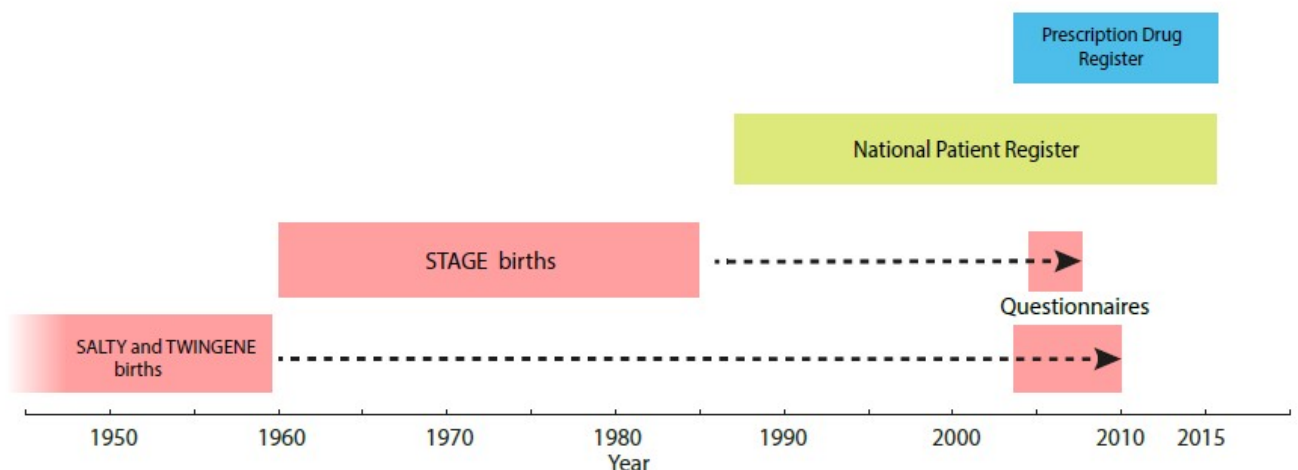


Figure S2. Directed acyclic graph

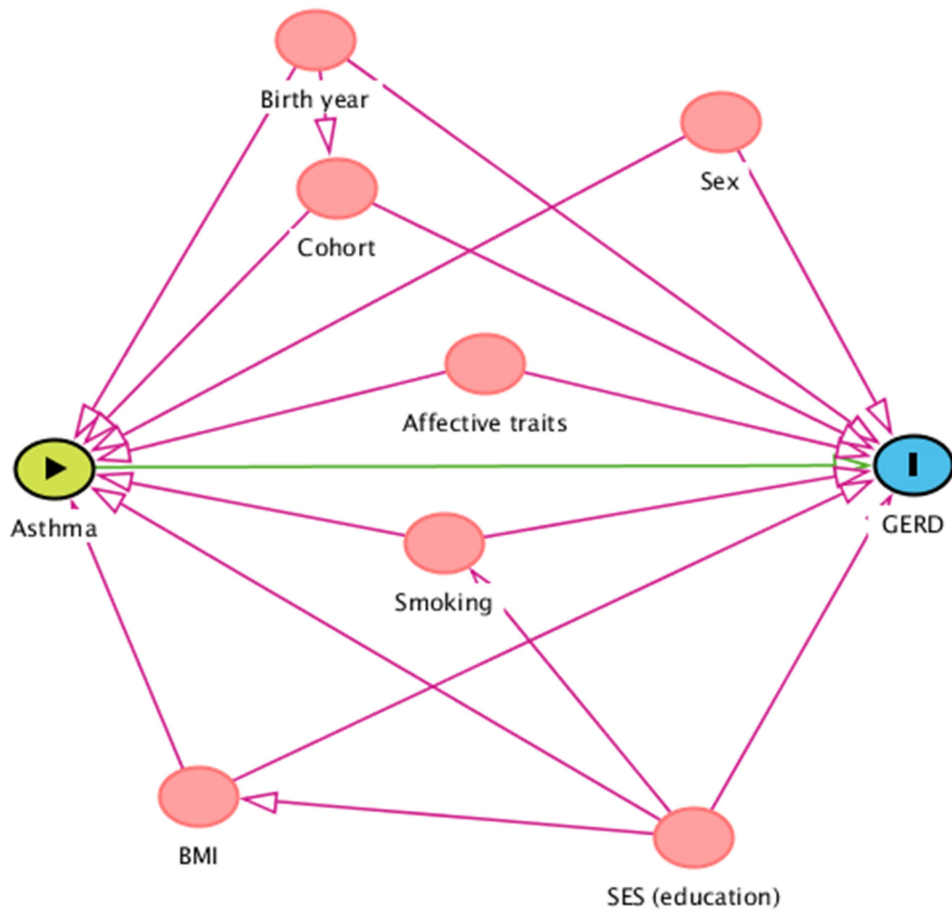


Table S1. Comorbidity of Register-based Asthma, Hayfever and Eczema with GERD, in the whole population and by sex

	All (N=46582)	Male (n=21139)	Female (n=25443)
Asthma	5424 (11.64%)	2042 (4.38%)	3382 (7.26%)
Hay fever	11761 (25.25%)	4251 (9.13%)	7510 (16.12%)
Eczema	5679 (12.19%)	2314 (4.97%)	3365 (7.22%)
GERD	5506 (11.82%)	1845 (3.96%)	3661 (7.86%)
Missing data on GERD*	2294	1054	1240
Comorbid Asthma & GERD	893 (2.02%)	244 (1.23%)	649 (2.66%)
% of having GERD among those having asthma	17.29	12.67	20.04
% of having asthma among those having GERD	16.22	13.22	17.73
Comorbid Hayfever & GERD	1889 (4.27%)	504 (2.53%)	1385 (5.68%)
% of having GERD among those having hay fever	16.87	12.56	19.27
% of having hay fever among those having GERD	34.31	27.32	37.83
Comorbid Eczema & GERD	804 (1.82%)	231 (1.16%)	573 (2.35%)
% of having GERD among those having eczema	14.77	10.45	17.73
% of having eczema among those having GERD	14.60	12.52	15.65

*Number of individuals with missing GERD symptom data = 2294. There is no missing data for register-based allergic diseases, if one person has not been identified with any hospital visit or medication dispense records, he or she will be coded as having no asthma/hay fever/eczema.

Table S2. Odds Ratios of GERD comorbidity in those with Register-based definitions of Asthma, Hayfever and Eczema.

	OR (95% CI) for GERD	
	Unadjusted	Adjusted*
Asthma	1.54 (1.42, 1.67)	1.43 (1.31, 1.56)
No asthma	ref	ref
Hay fever	1.64 (1.54, 1.74)	1.55 (1.45, 1.65)
No hay fever	ref	ref
Eczema	1.25 (1.16, 1.36)	1.19 (1.09, 1.30)
No eczema	ref	ref

*Models adjusted for sex, birth year, cohort, education, smoking, and BMI.

Table S3. Sex-specific odds ratios and interaction terms for GERD comorbidity with Asthma, Hayfever or Eczema. Self-report and Register-based definitions of atopic disease.

	Adjusted OR (95% CI)*		p- interaction
	Male	Female	
<i>OR for GERD by self-reported doctor diagnosed</i>			
asthma	1.68 (1.42, 1.98)	1.45 (1.29, 1.64)	0.17
hay fever	1.10 (0.94, 1.29)	1.29 (1.15, 1.45)	0.10
eczema	1.56 (1.27, 1.92)	1.11 (0.97, 1.28)	0.01
<i>OR for GERD by register-based</i>			
asthma	1.42 (1.22, 1.66)	1.44 (1.30, 1.59)	0.93
hay fever	1.54 (1.37, 1.73)	1.55 (1.43, 1.67)	0.95
eczema	1.14 (0.98, 1.33)	1.22 (1.10, 1.36)	0.45

*Model adjusted for sex, birth year, cohort, education, smoking, and BMI.

Table S4. Sensitivity Analysis for Heartburn and Sternum Pain comorbidity with Asthma, Hayfever and Eczema (self-report and register-based definitions) or Asthma phenotypes (odds ratios and 95% confidence intervals).

	OR (95% CI)	
	Unadjusted	Adjusted*
<i>OR for Heartburn by</i>		
Asthma self-report	1.66 (1.50, 1.84)	1.56 (1.40, 1.75)
Asthma Register-based	1.56 (1.42, 1.71)	1.44 (1.30, 1.58)
Hayfever self-report	1.24 (1.12, 1.37)	1.28 (1.15, 1.43)
Hayfever Register-based	1.61 (1.50, 1.73)	1.56 (1.45, 1.68)
Eczema self-report	1.20 (1.06, 1.36)	1.22 (1.06, 1.39)
Eczema Register-based	1.28 (1.16, 1.41)	1.20 (1.09, 1.33)
Asthma age of onset		
Self-reported childhood-onset asthma	1.56 (1.37, 1.77)	1.56 (1.35, 1.79)
Self-reported adulthood-onset asthma	1.85 (1.57, 2.18)	1.58 (1.32, 1.88)
Asthma comorbidities with other allergic diseases		
Allergic asthma	1.68 (1.46, 1.93)	1.66 (1.42, 1.92)
Non allergic asthma	1.63 (1.40, 1.89)	1.47 (1.25, 1.73)
Asthma with history of exacerbations	1.93 (1.36, 2.75)	2.08 (1.44, 3.00)
Moderate to Severe Asthma	1.21 (1.00, 1.45)	1.22 (1.00, 1.47)
<i>OR for Sternum Pain by</i>		
Asthma self-report	1.84 (1.63, 2.08)	1.48 (1.30, 1.70)
Asthma Register-based	1.65 (1.48, 1.84)	1.54 (1.37, 1.74)

Hayfever self-report	1.42 (1.26, 1.60)	1.21 (1.07, 1.38)
Hayfever Register-based	1.77 (1.63, 1.93)	1.55 (1.42, 1.70)
Eczema self-report	1.24 (1.06, 1.44)	1.21 (1.02, 1.43)
Eczema Register-based	1.15 (1.03, 1.30)	1.15 (1.01, 1.31)
Asthma age of onset		
Self-reported childhood-onset asthma	1.70 (1.46, 1.98)	1.43 (1.21, 1.69)
Self-reported adulthood-onset asthma	2.11 (1.75, 2.54)	1.58 (1.27, 1.95)
Asthma comorbidities with other allergic diseases		
Allergic asthma	1.84 (1.56, 2.17)	1.39 (1.16, 1.67)
Non allergic asthma	1.82 (1.54, 2.16)	1.58 (1.31, 1.92)
Asthma with history of exacerbation	1.33 (0.81, 2.19)	1.38 (0.83, 2.30)
Moderate to Severe Asthma	1.04 (0.82, 1.31)	0.99 (0.77, 1.28)

*Models adjusted for sex, birth year, cohort, education, smoking, and BMI.

Table S5. Comorbidity of hayfever and eczema adjusted for asthma, self report and register based definitions. Odd ratios and 95% confidence intervals

	OR (95% CI) for GERD	
	Unadjusted	Adjusted ^a
Self report		
Hay fever		
Hay fever with mutual adjustment for asthma	1.25 (1.15, 1.36)	1.08 (0.98, 1.20)
Eczema		
Eczema with mutual adjustment for asthma	1.24 (1.11, 1.38)	1.18 (1.05, 1.33)
Register-based		
Hay fever		
Hay fever with mutual adjustment for asthma	1.64 (1.54, 1.74)	1.48 (1.39, 1.58)
Eczema		
Eczema with mutual adjustment for asthma	1.25 (1.16, 1.36)	1.16 (1.07, 1.27)

^a All models adjusted for sex, birth year, cohort, education, smoking, BMI

Table S6. Associations for GERD comorbidity in those with asthma, hayfever, eczema and GERD with additional adjustment for depression, anxiety, and neuroticism (Odds ratios and 95% confidence intervals).

	OR (95% CI) for GERD			
	Adjusted* additionally for depression	Adjusted* additionally for anxiety	Adjusted* additionally for Neuroticism	Adjusted* additionally for depression, anxiety and neuroticism
SELF REPORT				
Asthma	1.46 (1.32, 1.62)	1.42 (1.27, 1.59)	1.44 (1.28, 1.62)	1.33 (1.15, 1.53)
Hay fever	1.18 (1.07, 1.30)	1.14 (1.03, 1.28)	1.17 (1.05, 1.31)	1.10 (0.96, 1.25)
Eczema	1.20 (1.07, 1.35)	1.17 (1.02, 1.33)	1.17 (1.01, 1.35)	1.08 (0.91, 1.27)
REGISTER- BASED				
Asthma	1.38 (1.26, 1.51)	1.40 (1.27, 1.55)	1.32 (1.19, 1.47)	1.30 (1.15, 1.47)
Hay fever	1.49 (1.39, 1.59)	1.52 (1.41, 1.64)	1.48 (1.36, 1.60)	1.45 (1.32, 1.59)
Eczema	1.19 (1.08, 1.30)	1.18 (1.07, 1.31)	1.11 (0.99, 1.24)	1.09 (0.96, 1.24)

* All models adjusted for sex, birth year, cohort, education, smoking, BMI

Table S7. Co-twin control analysis. Associations for GERD comorbidity in participants with asthma, hayfever, eczema (Odds Ratios and 95% Confidence Intervals)

SELF REPORT	OR (95% CI) for GERD								
	Combined (MZ + same-sex DZ twins)			Same-sex DZ twins		MZ twins			
	Unadjusted		Adjusted*	Unadjusted	Adjusted*	Unadjusted		Adjusted*	
Asthma	1.43 (1.83)	(1.11,	1.32 (1.74)	(1.00,	1.54 (1.09, 2.18)	1.41 (0.96, 2.08)	1.31 (0.91, 1.89)	1.24 (1.87)	(0.82,
Hay fever	0.96 (1.19)	(0.77,	0.97 (1.23)	(0.76,	1.23 (0.90, 1.66)	1.10 (0.78, 1.54)	0.72 (0.52, 0.99)	0.83 (1.18)	(0.59,
Eczema	1.06 (1.36)	(0.82,	1.11 (1.45)	(0.85,	1.30 (0.91, 1.85)	1.25 (0.85, 1.83)	0.87 (0.60, 1.25)	1.01 (1.48)	(0.68,
REGISTER- BASED									
Asthma	0.97 (1.17)	(0.80,	0.94 (1.15)	(0.77,	0.99 (0.75, 1.31)	0.96 (0.71, 1.30)	0.97 (0.75, 1.27)	0.92 (1.23)	(0.69,
Hay fever	1.29 (1.50)	(1.10,	1.28 (1.50)	(1.09,	1.46 (1.19, 1.79)	1.50 (1.19, 1.88)	1.12 (0.90, 1.39)	1.06 (1.34)	(0.84,
Eczema	1.14 (1.36)	(0.95,	1.05 (1.27)	(0.86,	1.25 (0.97, 1.60)	1.23 (0.94, 1.62)	1.01 (0.78, 1.31)	0.88 (1.17)	(0.66,

* adjusted for sex, education, smoking, and BMI.

References

1. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nature Genetics* 2017;49(12):1752-57. doi: 10.1038/ng.3985
2. Ortqvist AK, Lundholm C, Wettermark B, et al. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf* 2013;22(8):850-60. doi: 10.1002/pds.3465 [published Online First: 2013/06/12]
3. Henriksen L, Simonsen J, Haerskjold A, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *Journal of Allergy and Clinical Immunology* 2015;136(2):360-66.e2. doi: 10.1016/j.jaci.2015.02.003
4. Cesta CE, Kuja-Halkola R, Lehto K, et al. Polycystic ovary syndrome, personality, and depression: A twin study. *Psychoneuroendocrinology* 2017;85:63-68. doi: 10.1016/j.psyneuen.2017.08.007
5. Tedner SG, Lundholm C, Olsson H, et al. Depression or anxiety in adult twins is associated with asthma diagnosis but not with offspring asthma. *Clin Exp Allergy* 2016;46(6):803-12. doi: <https://doi.org/10.1111/cea.12714>
6. Kendler KS, Gardner CO, Gatz M, et al. The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychological Medicine* 2006;37(03) doi: 10.1017/s0033291706009135
7. Mather L, Blom V, Bergström G, et al. An Underlying Common Factor, Influenced by Genetics and Unique Environment, Explains the Covariation Between Major Depressive Disorder, Generalized Anxiety Disorder, and Burnout: A Swedish Twin Study. *Twin Research and Human Genetics* 2016;19(6):619-27. doi: 10.1017/thg.2016.73