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ORIGINAL ARTICLE

Asthma and Rhinitis

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Multimorbidity in asthma, association with allergy, inflammatory markers and symptom burden, results from the Swedish GA^{2}LEN study

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Abstract

Background: Asthma is common worldwide and a large part of subjects with asthma have concomitant allergic multimorbidity in the form of rhinitis and/or eczema.

Objective: The aim of this study is to investigate whether the presence of allergic multimorbidity in asthma relates to allergic sensitization, allergic and respiratory symptoms, quality of life, inflammatory markers, lung function, use of medication and background factors.

Methods: A total of 437 asthmatics from the (GA^{2}LEN) cross-sectional survey in Sweden were grouped depending on the presence of rhinitis and/or eczema. The impact of allergic multimorbidity was assessed in terms of allergic sensitization, allergic and respiratory symptoms, quality of life, type-2 inflammatory markers (exhaled nitric oxide, eosinophil activation markers, periostin), lung function, use of medication and background factors.

Results: Subjects with asthma, rhinitis and eczema were more likely to be sensitized to seasonal allergens (67% vs 32%, $P < .001$), food allergens (54% vs 18%, $P < .001$) and to have a higher degree of sensitization than subjects with only asthma (23% vs 10%, $P < .001$). Subjects with allergic multimorbidity more often had allergic reactions to food (28% vs 10%, $P = .002$), more respiratory symptoms and anxiety/depression (40% vs, 14%, $P < .001$) than subjects with only asthma, despite having similar levels of type 2 inflammatory markers. Individuals with allergic multimorbidity were more likely to be diagnosed with asthma before the age of 12 (48% vs 27%, $P = .016$) and to have maternal heredity for allergy (53% vs 33%, $P = .011$) than subjects with only asthma.

Conclusion and clinical relevance: Asthmatics with allergic multimorbidity are more likely to be sensitized to seasonal aeroallergens, food allergens and they have a higher degree of sensitization compared with those with only asthma. Allergic multimorbidity is associated with respiratory and allergy symptoms, anxiety and/or depression.

KEYWORDS
asthma, atopic dermatitis, food allergy, IgE, rhinitis

1 | INTRODUCTION

Many people with asthma also have other comorbidities such as rhinitis and eczema.[1] In previous studies, having more than one allergic disease has been linked to poorer asthma control, a poorer prognosis, breathing-related comorbidities, such as sleep apnoea,[2] and poorer quality of life.[3,4]

It is known that allergic sensitization increases the risk of asthma, rhinitis and eczema,[5] but multimorbidity with asthma, rhinitis and eczema can occur both with and without the presence of atopy.[1,6,7]

Allergic sensitization is a risk factor for developing allergic multimorbidity in both children and adults.[8,9] Some studies suggest that sensitization to seasonal allergens is the largest contributor to developing allergic multimorbidity,[10,11] while others list sensitization to perennial allergens as having a larger impact.[10,12] Allergic multimorbidity is more common among food-sensitized individuals, although this has not been studied as extensively.[12,13] Some inflammatory markers that are part of the type-2 inflammatory pathway are partially linked to allergic multimorbidity.[9] Increased levels of exhaled nitric oxide (F_ENO) have been associated with having more than one allergic disease.[14] Eosinophilia is associated with asthma and allergic disease.[15] However, no difference between eosinophilic activation markers like eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) has been shown when comparing subjects with just asthma with subjects with allergic multimorbidity.[1,15] Periostin has been linked to asthma, rhinitis and eczema separately, although no group difference has been observed when comparing subjects with asthma with those with asthma and rhinitis.[16,17]

2 | OBJECTIVE

The aim of this study is to increase our knowledge of asthmatics with allergic multimorbidity in terms of allergic sensitization, allergic and respiratory symptoms, quality of life, inflammatory markers, lung function, use of medication and background factors.

3 | METHODS

3.1 | Study design

The Global Allergy and Asthma European Network (GA^2LEN) study design has previously been published in detail.[1,18] A clinical study was conducted in 2008-2010 in a randomly selected subgroup of adults with reported symptoms of asthma, chronic rhinosinusitis and controls in 19 European centres.[18] This investigation is based on the Swedish part of the study. In Sweden, four centres participated (Gothenburg, Stockholm, Umeå and Uppsala) and 27 866 persons responded (60% response rate) to the initial postal survey in 2008. From the first survey four groups, we invited to a clinical follow-up. The groups were subjects with asthma, subjects with chronic rhinosinusitis (CRS), subjects with both asthma and CRS and a random sample of subjects that neither had asthma or CRS. In the Swedish part of the study, 1329 participated in the clinical follow-up in 2009 and 2010 (Figure 1).[3,18]

3.2 | Clinical study

Subjects who participated in the clinical follow-up took part in a structured interview and a clinical investigation with a skin prick test (SPT), blood sampling and spirometry. In Sweden, the follow-up also included measurements of F_ENO and assessments of quality of life using the European quality of life health questionnaire (EQ-5D) and the Juniper mini asthma quality of life questionnaire (mAQLQ).

3.3 | Questionnaire

The GA^2LEN follow-up questionnaire included validated questions related to respiratory symptoms, rhinitis, chronic rhinosinusitis and eczema, as well as demographic data. The questions were based on those in the European Community Respiratory Health Survey (ECRHS) and included questions on respiratory symptoms, family history of asthma, diagnosed asthma, use of asthma medications, history of allergy and sinusitis, history of eczema, smoking history and occupation.[19,20]

Asthma was defined as a positive answer to "Have you suffered an asthma attack during the last 12 months?" or a positive answer to having used asthma medications during the last 12 months.[21] Participants with asthma were mainly found in the asthma and asthma plus CRS group, but some were also found in the other groups as there was one to two years between the postal survey and the clinical examination (Figure 1).

Rhinitis was defined as a positive answer to "Have you had problems with sneezing, runny nose or nasal congestion without having a cold during the last 12 months?".[1]

Eczema was defined as a positive response to "Have you had an itchy rash during the last 12 months?".[22]

The subjects for this study were selected on the basis of having asthma and were then divided into three groups: subjects with asthma only (n = 78, 17%), subjects with asthma and rhinitis (n = 247, 54%) and subjects with asthma, rhinitis and eczema (n = 112, 25%) (Figure 1). Only 17 (4%) individuals had asthma and eczema but no rhinitis, and this group was not further included in this investigation.

Reported allergic reactions were categorized according to the anaphylaxis grouping in the Swedish Allergy Society guidelines for

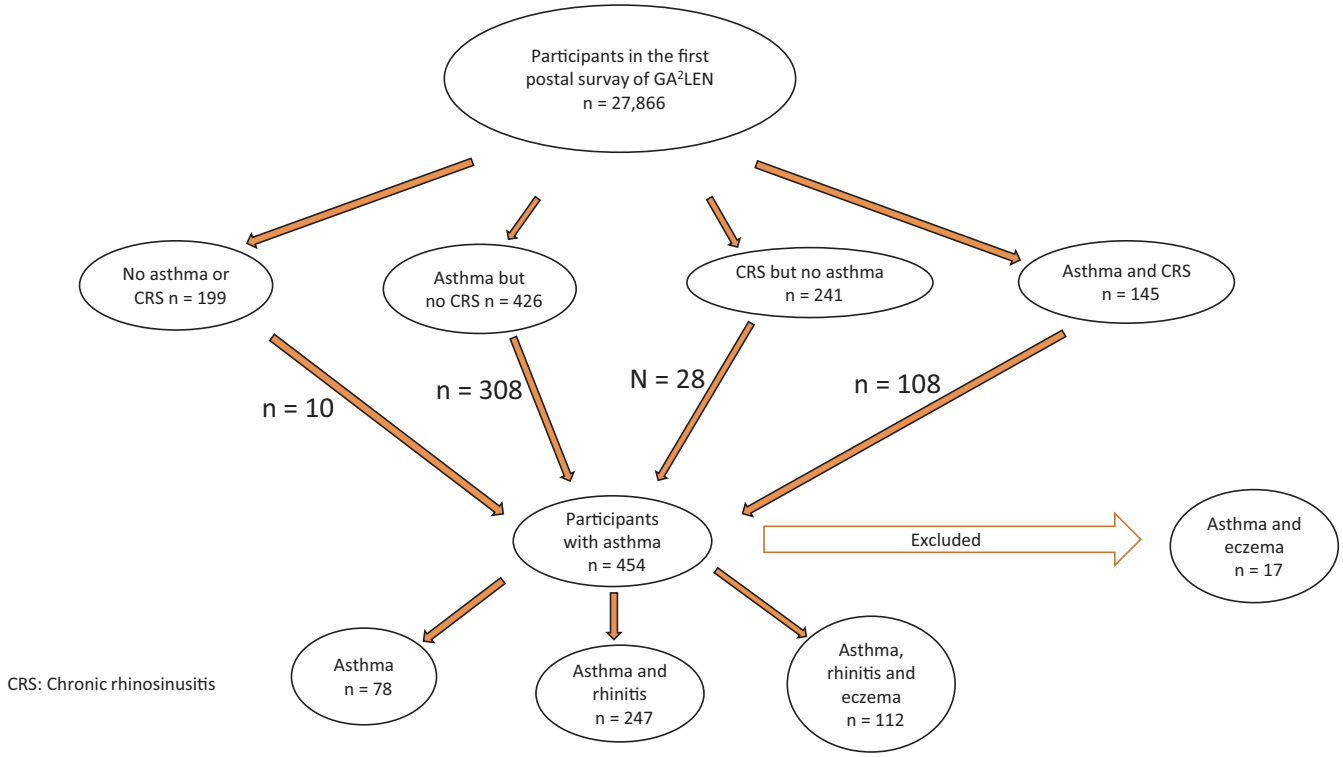

FIGURE 1 Flowchart for the inclusion and grouping of the participants. CRS: Chronic rhinosinusitis

anaphylaxis[23] and further grouped into mild to moderate or serious reactions. A mild to moderate reaction was defined as the presence of at least one the following symptoms: itching of the mouth, lips or throat, rash, diarrhoea, vomiting, rhinoconjunctivitis, difficulties swallowing, joint stiffness and headache. A serious reaction was defined as fainting and/or respiratory distress.

3.4 | Smoking

Smoking was assessed using the questions "Have you ever smoked one or more cigarettes a day for more than one year?" and "Have you smoked at all during the last month?". The subjects were categorized into never-, ex- and current smokers.

3.5 | Skin prick test

A skin prick test was performed on the inside of the forearm using a standard set of aeroallergens for the GA²LEN study[24]: *Dermatophagoides farina*, *Dermatophagoides pteronyssinus*, birch, olive, Parietaria, timothy grass, *Artemisia vulgaris*, mixed grass, cat, dog, *Blattella germanica*, *Alternaria alternata*, histamine (positive control) and diluent (negative control). Standardized extracts from ALK Abelló (Hamburg, Germany), Allergopharma (Reinbek, Germany), Leti Pharma (Witten, Germany) and Stallergènes (Antony, France) were used. The largest and perpendicular diameters of the wheal elicited by the allergens were measured, and the mean value was calculated. A positive wheal was defined as ≥3 mm, if the control solutions showed the expected result, that is histamine ≥3 mm and negative control <3 mm. Skin prick test data were available for 414 participants.

3.6 | Serum IgE measurements

Venous blood samples were drawn from the participants during the clinical visits and frozen at −20°C. In the Swedish GA²LEN study, measurements of serum IgE antibodies against a mix of food allergens, fx 5, shrimp and timothy were performed with the ImmunoCAP system (Immunodiagnostics, Thermo Fisher Scientific, Uppsala, Sweden). The results are presented in kU/L and values of IgE ≥ 0.35 kU/L for an individual allergen defined a subject as being sensitized to that allergen.[25] Subjects with titres of ≥0.35 kU/L against fx5 were further characterized regarding IgE antibody levels against each individual allergen: egg white, milk, cod fish, wheat, peanut and soya bean. Those with titres of <0.35 kU/L were not further examined for each individual allergen in the food panel. Blood sampling for measurements of total IgE was performed using ImmunoCAP® (Phadia Diagnostics AB/ThermoFisher, Uppsala, Sweden).

3.7 | Inflammatory markers

S-ECP was measured using a fluorescence enzyme immunoassay (ImmunoCAP, Thermo Fisher Scientific, Immunodiagnostics,

Uppsala, Sweden). S-periostin was measured using ELISA with two rat anti-human periostin mAbs (clones SS18 and SS17B).[26] U-EDN (previously called eosinophil protein X) was measured, in accordance with the manufacturer's instructions, with a sandwich ELISA utilizing a polyclonal EDN antibody as the catching antibody and a monoclonal antibody (clone 618) as the detecting antibody (Diagnostics Development, Uppsala, Sweden).

F_ENO was assessed using NIOX MINO, Aerocrine, Stockholm, Sweden, according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations.[27]

3.8 | Spirometry

Lung function measurements were performed using the EasyOne™ Spirometer (Ndd Laboratories, Medizintechnik AG, Zurich, Switzerland) with a daily calibration check. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured, at least three times, each before and at least 15 minutes after bronchodilatation with 200 μg of salbutamol. FEV_1, FVC and FEV_1/FVC were measured according to the ATS/ERS guidelines,[28] with reference values from the European Coal and Steel Community.[29] Height and weight were measured, and body mass index (BMI) was calculated.

Fixed airway obstruction was defined according to the Guidelines from the Global Initiative for Chronic Obstructive Lung Disease as postbronchodilator FEV_1/FVC below 0.7.[26]

3.9 | Questionnaires assessing quality of life and sleep

All subjects fulfilling the criteria for asthma in the postal survey also completed the Mini Asthma Quality of Life Questionnaire (mini-AQLQ).[30] Subjects were asked to assess functional impairment due to their asthma during the last two weeks by responding to 15 questions grouped into four domains on a seven-point scale. The four domains are as follows: symptoms (5 items), activity limitations (4 items), emotional function (3 items) and environmental stimuli (3 items). Each question was scored from severe impairment[1] to no impairment,[7] and the mean overall score was calculated.

The Euro Quality of Life (EQ-5D) health questionnaire was filled out by all participants.[31] It comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The descriptive system is then converted into a single summary index, and we used the United Kingdom time trade-off (TTO) value set.[32] An index of 1.0 corresponds to full health.

The insomnia symptoms that were analysed were as follows: difficulties inducing sleep, difficulties maintaining sleep, early morning awakening and excessive daytime sleepiness at least three to five times/week according to the Basic Nordic Sleep Questionnaire.[33]

3.10 | Statistical analyses

All analyses were performed using STATA 14.2 (STATA Corp, College Station, Texas, USA). Non-normally distributed variables, F_ENO and total IgE were log transformed before analysis. The differences between groups were tested using the chi-square test or the ANOVA test. Multiple logistic regression analysis was used when adjusting for possible confounders. A *P*-value of $<.05$ was considered significant. Missing data were handled with complete cases.

3.11 | Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2008/1100-31/4). Informed consent was obtained from all individual participants included in the study.

4 | RESULTS

4.1 | General characteristics, heredity and home environment

Subjects with more than one allergic disease were more likely to have been diagnosed with asthma before the age of 12 years in comparison with subjects with only asthma (Table 1). Maternal but not paternal allergy was found to a larger extent in subjects with allergic multimorbidity (Table 1).

4.2 | Allergic sensitization and allergy symptoms

Subjects with asthma, rhinitis and eczema were more likely to be sensitized to seasonal aeroallergens, food allergens and were sensitized to a larger number of allergens compared with subjects with only asthma (Figures 2 and 3).

We saw a significant group difference in terms of sensitization to birch, timothy grass, grass mix and *Alternaria alternata* (Figure 2). In terms of food allergens, subjects with allergic multimorbidity were more likely to be sensitized to hazelnut, milk, peanuts and soy compared with those with just asthma (Figure 3).

Individuals with allergic multimorbidity were more likely to report clinical reactions to food compared with subjects with only asthma, 56% and 32%, respectively ($P = .005$). Moreover, having concomitant asthma, rhinitis and eczema increased the likelihood of reporting more serious clinical reactions to food (Figure 4).

4.3 | Inflammatory markers

No group difference was found in the levels of F_ENO, total IgE, EDN, ECP and periostin when comparing those with allergic multimorbidity with those with just asthma (Table 2).

Variable	Asthma, n = 78	Asthma and rhinitis, n = 247	Asthma, rhinitis and eczema, n = 112	*P*-value
Women	47 (60%)	141 (57%)	73 (65%)	.371
Age	48.2 ± 14.5	44.0 ± 15.1	44.1 ± 15.4	.078
BMI	27.0 ± 4.8	26.7 ± 5.2	26.6 ± 5.5	.912
Smoking history				
Never-smoker	50 (64%)	128 (52%)	59 (53%)	.433
Ex-smoker	22 (28%)	91 (37%)	41 (37%)	
Current smoker	6 (8%)	28 (11%)	12 (11%)	
Maternal asthma	12 (15.8%)	58(25.1%)	29(27.9%)	.149
Maternal allergy	22 (33.3%)	79 (36.9%)	53 (53.0%)	.011
Paternal asthma	15(20.0%)	42 (18.7%)	22 (22.2%)	.760
Paternal allergy	21 (32.3%)	62 (30.7%)	40 (42.1%)	.146
Onset of asthma before the age of 12	20 (27.0%)	88 (36.1%)	50 (47.6%)	.016

Abbreviation: BMI, body mass index.

TABLE 1 Characteristics and background information on the participants. Results presented as N (%) with the exception of age and BMI, presented as mean +/− standard deviation

4.4 | Respiratory symptoms

Subjects with allergic multimorbidity reported more wheezing, more breathlessness during activity and more frequent asthma attacks during the last 12 months, compared with those with only asthma (Table 3). These associations remained significant after adjusting for smoking and oral corticosteroid use except for the association with wheeze, which became statically non-significant ($P = .054$) (Online Table S1).

4.5 | Lung function

Subjects with only asthma had a lower FEV_1 and were more likely to have a fixed airway obstruction with post-bronchodilator FEV_1/FVC below 0.7 (Table 3). This association remained after adjusting for smoking and oral corticosteroid use (Online Table S1).

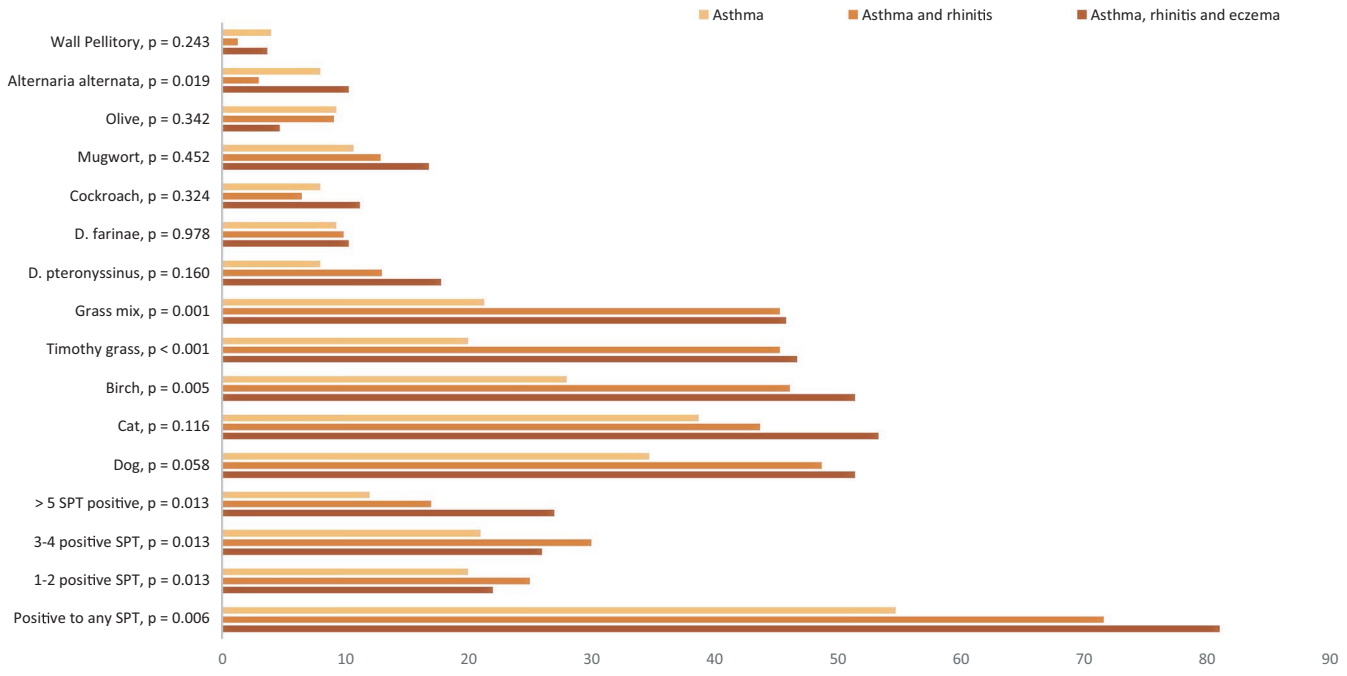

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FIGURE 2 Allergic sensitization according to skin prick test results (%)

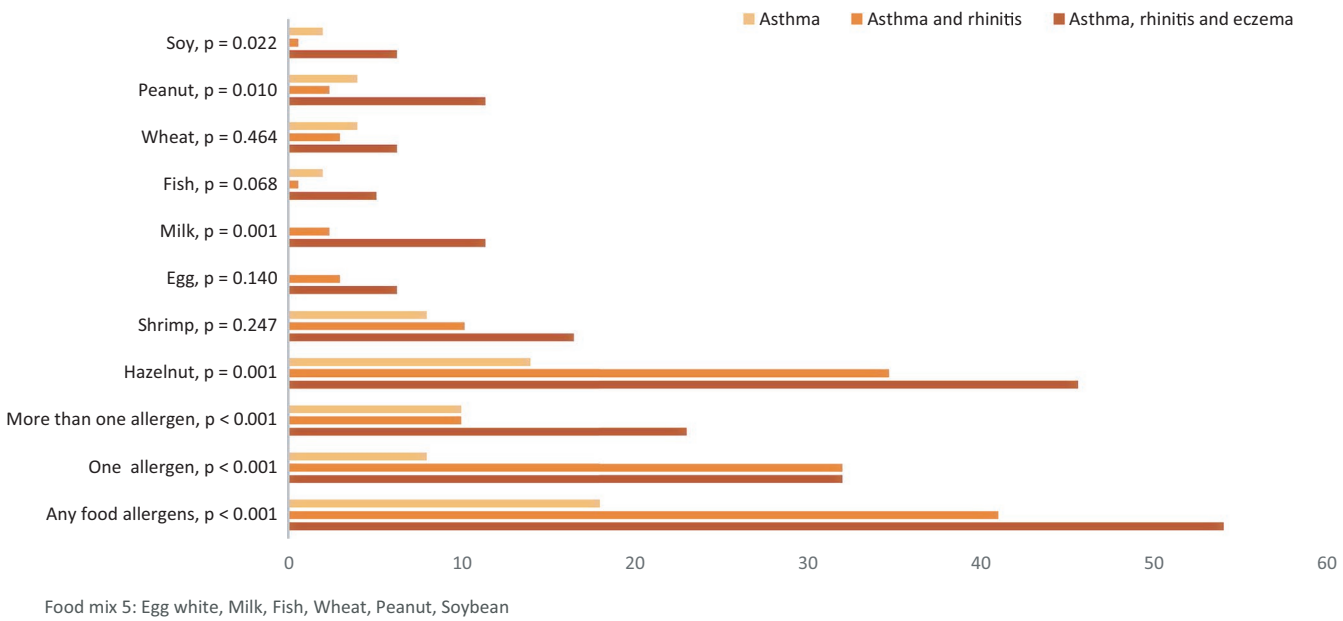
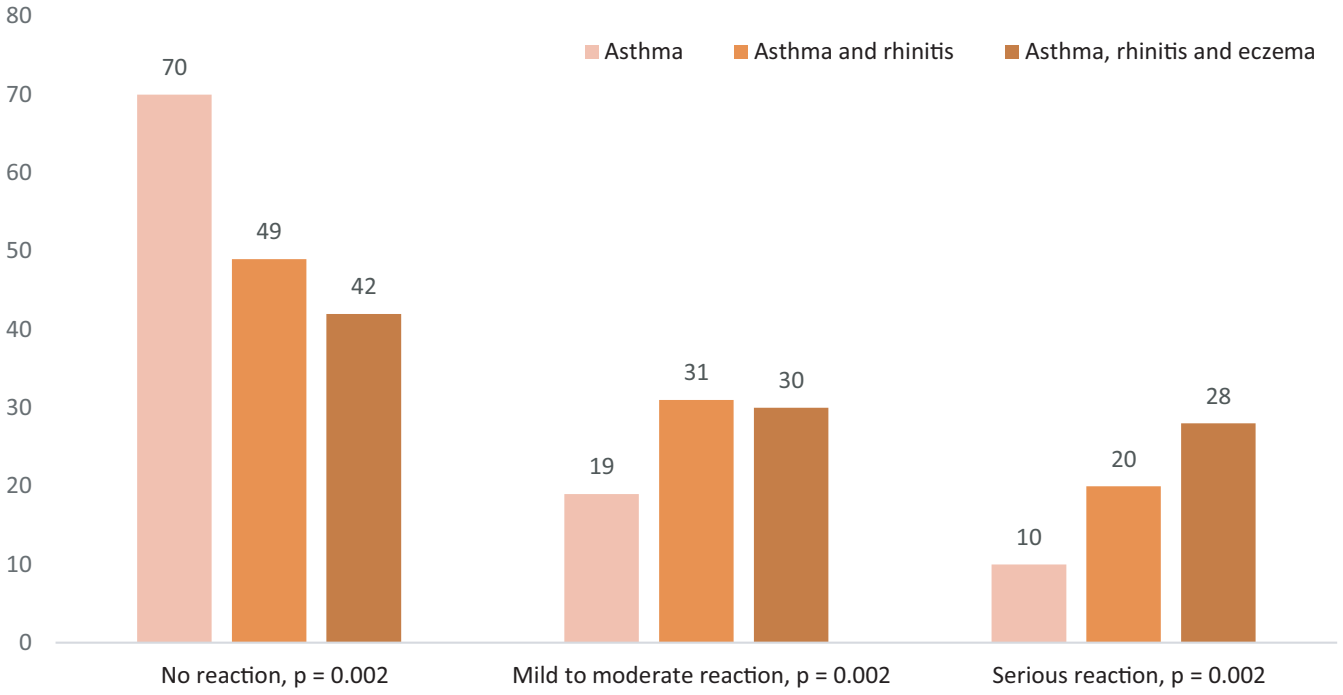


FIGURE 3 IgE sensitization to food allergens (%)



Mild to moderate reaction: Itching of the mouth, lips or throat, rash, diarrhoea, vomiting, rhinoconjunctivitis, difficulties swallowing, joint staleness, headache
Serious reaction: Fainting, respiratory distress

FIGURE 4 Reported allergic reactions to food (%)

4.6 | Medication

Subjects with only asthma were more likely to have been treated with oral corticosteroids during the last 12 months compared with those with allergic multimorbidity. No difference was observed in the use of other oral or inhaled asthma medication (Online Table S2).

4.7 | Insomnia symptoms, anxiety and depression

Having asthma, rhinitis and eczema increased the likelihood of reporting anxiety and/or depression as well as daytime sleepiness when compared with those with only asthma (Table 4). This association remained after adjusting for smoking and oral corticosteroid

TABLE 2 Inflammatory markers and total IgE, presented as geometric mean (95% confidence interval)

Variable	Asthma, n = 78	Asthma and rhinitis, n = 247	Asthma, rhinitis and eczema, n = 112	*P*-value
F_ENO ppb	18.9 (15.8-22.7)	19.0 (17.4-20.8)	19.1 (16.9-21.6)	.997
Periostin ng/mL	63.7 (57.6-70.3)	63.0 (60-66.3)	64.6 (57.3-72.9)	.890
U- EDN mg/mol	52.9 (45.3-61.8)	48.0 (43.6-52.8)	47.6 (41.9-54.1)	.548
S-eosinophilic cationic protein mg/L	12.7 (10.1-15.9)	15.0 (13.3-17.0)	16.3 (13.7-19.4)	.207
Total IgE kU/L	51.8 (36.6-73.2)	61.5 (51.4-73.7)	63.6 (43.4-93.3)	.218

Abbreviations: EDN, eosinophil-derived neurotoxin; F_ENO, exhaled nitric oxide; IgE, Immunoglobulin E.

TABLE 3 Reported respiratory symptoms and lung function. Results presented as N (%) with the exception of FEV1(% predicted) presented as mean ± standard deviation

Variable	Asthma, n = 78	Asthma and rhinitis, n = 247	Asthma, rhinitis and eczema, n = 112	*P*-value*
Wheezing during the last 12 months	59 (75.6%)	198 (80.2%)	100 (89.3%)	.037
Asthma attack during the last 12 months	34 (43.6%)	143 (58.4%)	70 (62.5%)	.026
Breathlessness during rest	12 (15.6%)	53 (21.5%)	32 (28.8%)	.089
Breathlessness during activity	29 (37.7%)	118 (47.7%)	64 (57.6%)	.025
Morning cough during winter months	19 (24.4%)	59 (24.0%)	25 (22.5%)	.944
Daily sputum production during the winter months	41 (52.6%)	109 (44.9%)	64 (58.2%)	.058
Hospitalization before two years of age	7 (9.0%)	19 (7.7%)	11 (9.9%)	.780
Visits to the emergency room because of asthma during the last five years	19 (24.4%)	60 (24.3%)	26 (23.6%)	.990
Stay in hospital during the last 12 months (any reason)	3 (4.3%)	10 (4.4%)	9 (8.6%)	.271
FEV1 (% predicted)	84.7 ± 22.0	91.1 ± 16.8	91.1 ± 16.2	.025
FEV1/FVC under 0.7	30 (44.8%)	61 (28.0%)	19 (20.4%)	.003

Abbreviations: FEV1, forced expiratory volume in the first second; FVC, forced vital capacity.
**P*-value for comparisons between the three groups with chi-squared test or ANOVA (for FEV1% predicted).

use (Online Table S3). No difference was found regarding the other quality of life and sleep-related variables.

5 | DISCUSSION

We found that Swedish subjects with asthma, rhinitis and eczema were more likely to be sensitized to seasonal aeroallergens and food allergens than those with only asthma, whereas no difference was found for type-2 inflammatory markers. Asthmatics with multimorbidity were more likely to report a clinically significant and more serious allergic reaction to food. Moreover, individuals with asthma and multimorbidity had an increased burden of respiratory symptoms and reported more anxiety/depression and daytime sleepiness than those with asthma alone. However, the group with asthma alone had poorer lung function than subjects with asthma and multimorbidity.

5.1 | Allergic sensitization and allergy symptoms

Sensitization to seasonal aeroallergens, food allergens and sensitization to a larger number of allergens was associated with asthma and

TABLE 4 Quality of life assessed by the EQ-5D and sleep-related symptoms, results presented as N (%), mAQLQ, presented as mean ± standard deviation

Variable	Asthma, n = 78	Asthma and rhinitis, n = 247	Asthma, rhinitis and eczema, n = 112	*P*-value
EQ 5D, mobility				
Some problems walking or confined to bed	8 (10%)	28 (11%)	15 (14%)	.749
EQ-5, self-care				
Some problems or unable to wash and dress myself	2 (3%)	5 (2%)	5 (5%)	.419
EQ-5, pain and discomfort				
Moderate to extreme pain or discomfort	35 (45%)	123 (50%)	54 (49%)	.732
EQ-5, anxiety and depression				
Moderate to extreme anxiety or depression	11 (14%)	60 (24%)	44 (40%)	<.001
EQ-5, usual activities				
Some problems or unable to perform usual activities	5 (6%)	19 (8%)	13 (12%)	.350
EQ-index	0.9 ± 1.2	0.8 ± 0.2	0.8 ± 0.2	.235
mAQLQ overall	5.9 ± 1.0	5.7 ± 1.0	5.6 ± 1.1	.290
mAQLQ emotions	5.9 ± 1.0	5.7 ± 1.0	5.6 ± 1.0	.290
mAQLQ symptoms	5.7 ± 1.1	5.5 ± 1.1	5.4 ± 1.1	.436
mAQLQ environment	5.9 ± 1.3	5.7 ± 1.2	5.5 ± 1.4	.179
mAQLQ activities	6.1 ± 1.2	6.0 ± 1.1	5.9 ± 1.3	.510
Difficulties initiating sleep three or more nights per week	11 (14.3%)	52 (21.4%)	22 (19.6%)	.392
Difficulties maintaining sleep three or more nights per week	24 (31.2%)	97 (39.4%)	39 (%)	.373
Daytime sleepiness during three or more nights per week	19 (24.7%)	110 (45.1%)	54 (48.2%)	.002
Early morning awakening three or more nights per week	15 (19.5%)	63 (25.7%)	25 (22.3%)	.491

Abbreviations: EQ-5D, Euro Quality of Life health questionnaire; mAQLQ, Juniper Mini Asthma Quality of Life Questionnaire.

multimorbidity as opposed to just having asthma. Both our study and others have found that polysensitization is a risk factor for developing allergic multimorbidity.[5,8,9,34]

Sensitization to seasonal aeroallergens was more prevalent among asthmatics with multimorbidity than in those with asthma alone. This is in accordance with previous studies.[5,7,34] We did not, however, find that sensitization to perennial allergens was more prevalent in those with asthma, rhinitis and eczema together compared with those with only asthma. This is in contrast to several previous studies which have observed that sensitization to perennial allergens such as *D pteronyssinus* and cat are risk factors for developing allergic multimorbidity.[4,10–12] The prevalence of *D pteronyssinus* is low in most parts of Sweden.[11,35] This variation could partially explain why no association with *D pteronyssinus* was found in our study, even though it appears to be a major contributor to allergic multimorbidity in other geographical areas.[11,12,35]

We found that asthmatics with multimorbidity were more likely to be sensitized to food allergens and to report more serious allergic reactions to food. Sensitization to food allergens has also been associated with allergic multimorbidity in previous studies.[12,13] Asthma has previously been identified as a risk factor for lethal allergic reactions, but few data exist on the impact of allergic multimorbidity on allergic reaction severity.[36]

5.2 | Inflammatory markers

We found no significant group difference in the levels of type-2 inflammatory markers, F_ENO, total IgE, EDN, ECP and periostin. This is in accordance with our previous findings.[34] F_ENO has previously been associated with allergic multimorbidity.[1,14] F_ENO might, however, be a stronger marker of allergic inflammation than allergic multimorbidity.[37] Elevated total IgE levels have been associated with having more than one allergic condition.[10] Markers of eosinophilic degranulation and activation, EDN and ECP, have been associated with an increased risk of asthma, rhinitis and atopic dermatitis separately.[38,39] Limited data are available on the association between ECP and EDN levels and allergic multimorbidity, but ECP levels did not differ between individuals with rhinitis compared with those with both asthma and rhinitis in previous studies.[40,41] Elevated periostin levels have been associated with

eosinophilic inflammation, asthma, rhinitis and atopic dermatitis separately, but no group differences between individuals with asthma and asthma and rhinitis have been observed.[16,17]

5.3 | Respiratory symptoms

Asthmatics with multimorbidity reported more wheezing, more breathlessness during activity and more frequent asthma attacks during the last 12 months compared with subjects with only asthma. Having more than one allergic disease has also been associated with a higher prevalence of symptoms and incomplete asthma control in previous studies.[2,42] It is possible to speculate that part of this could be explained by the addition of nasal symptoms, causing a more significant subjective feeling of breathlessness due to a larger part of the airways being involved.

5.4 | Lung function

One of our more surprising findings was that subjects with only asthma had a lower FEV_1 and were more likely to have a fixed airway obstruction compared with those with more than one allergic disease. Allergic rhinitis and atopic dermatitis have previously been considered potentially protective in terms of fixed airway obstruction, although the reason for this is not entirely clear.[43] Poorer lung function and faster FEV_1 decline have been associated with adult onset asthma.[44] In our study, subjects with only asthma were more likely to have onset of asthma after the age of 12 years, compared with asthmatics with multimorbidity. We also found that those with only asthma used oral corticosteroids more frequently. It is known that some asthma phenotypes are less responsive to treatment with corticosteroids.[45] It is possible that those with only asthma in our study may be less responsive to corticosteroids in both inhaled and oral forms, leading to poorer lung function. Lower lung function is on the other side associated with a higher risk for exacerbations.[46] It is therefore also possible that the connection is the other way around, lower lung function being the predictor for more frequent oral corticosteroid use.

5.5 | Quality of life and sleep

We found that asthmatics with allergic multimorbidity reported more anxiety and/or depression and daytime sleepiness than those with asthma alone. Asthma, rhinitis and eczema separately are regarded as risk factors for anxiety and depression.[47,48] Little is known about the impact of asthma with multimorbidity in anxiety and depression, although some studies suggest a common genetic denominator for allergy and depression.[49,50] Daytime sleepiness has been shown to be more common among individuals with asthma and chronic rhinosinusitis compared with those with only asthma.[51]

5.6 | General characteristics, heredity and home environment

Subjects with more than one allergic disease were younger at the time of asthma diagnosis. This is in accordance with previous studies that show that allergic comorbidity often develops during childhood.[9,52,53] Maternal but not paternal allergy was associated with having allergic multimorbidity. Both maternal and paternal allergy have in previous studies been associated with allergic multimorbidity.[7,52,53]

5.7 | Strengths and weaknesses

The strength of these data was that the study was population based and part of the survey questionnaire was filled out with the help of trained research personnel. The subjects answered a variety of different questions that provided us with a relatively multidimensional view of allergic multimorbidity. Another strength was the availability of SPT results, IgE-assessed food sensitization and lung function, in combination with reported clinical symptoms. One limitation was that the group categorization and most of the information were based on self-reported data. Another weakness was that no multiplex component analysis was available to further describe the positive IgE-mediated reactions. Another limitation is that due to the design of the study, only asthmatics were included. The study therefore does not address issues of allergic multimorbidity in other allergic disorder. The sample size was also relatively small which may have been one reason why we did not find any differences in inflammatory makers when comparing the groups.

In conclusion, asthmatics in Sweden with rhinitis and eczema are more likely to be sensitized to seasonal aeroallergens, food allergens and have a higher degree of sensitization than subjects with only asthma. Asthma with multimorbidity is associated with a high prevalence of allergy and respiratory symptoms, daytime sleepiness, anxiety and/or depression. There is no group difference in relation to type-2 inflammatory markers when comparing subjects with asthma with those with more than one allergic disorder. Awareness of asthma and allergic multimorbidity is important, especially considering the increasing availability of allergen-specific immunotherapy and rising evidence on its effectiveness in allergic disease.

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AUTHOR CONTRIBUTION

VB drafted the manuscript, performed the data analysis and interpretation with the help of CJ. CJ, FS, AM, AJ, RM, KF and BL reviewed the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Kampe M, Vosough M, Malinovschi A, et al. Upper airway and skin symptoms in allergic and non-allergic asthma: Results from the Swedish GA(2)LEN study. *J Asthma*. 2018;55(3):275-283.
2. Jantunen J, Haahtela T, Salimaki J, et al. Multimorbidity in Asthma, Allergic Conditions and COPD Increase Disease Severity, Drug Use and Costs: The Finnish Pharmacy Survey. *Int Arch Allergy Immunol*. 2019;179(4):273-280.
3. Ek A, Middelveld RJ, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. *Allergy*. 2013;68(10):1314-1321.
4. Ana B, de la Torre F. Characteristics, quality of life and control of respiratory allergic diseases caused by house dust mites (HDMs) in Spain: a cross-sectional study. *Clin Transl Allergy*. 2019;9:39.
5. Bousquet J, Anto JM, Wickman M, et al. Are allergic multimorbidities and IgE polysensitization associated with the persistence or re-occurrence of foetal type 2 signalling? The MeDALL hypothesis. *Allergy*. 2015;70(9):1062-1078.
6. Greisner WA 3rd, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc*. 1998;19(4):185-188.
7. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*. 2004;113(1):86-93.
8. Siroux V, Ballardini N, Soler M, et al. The asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults. *Allergy*. 2018;73(7):1447-1458.
9. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol*. 2019;143(1):46-55.
10. Burte E, Bousquet J, Siroux V, Just J, Jacquemin B, Nadif R. The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study. *Clin Exp Allergy*. 2017;47(4):520-529.
11. Plaschke P, Janson C, Norrman E, Björnsson E, Ellbjär S, Järvholm B. Association between atopic sensitization and asthma and bronchial hyperresponsiveness in Swedish adults: Pets, and not mites, are the most important allergens. *Journal of Allergy and Clinical Immunology*. 1999;104(1):58-65.
12. Raciborski F, Bousquet J, Bousqet J, et al. Dissociating polysensitization and multimorbidity in children and adults from a Polish general population cohort. *Clin Transl Allergy*. 2019;9:4.
13. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol*. 2016;27(8):831-837.
14. Gemicioglu B, Musellim B, Dogan I, Guven K. Fractional exhaled nitric oxide (FeNo) in different asthma phenotypes. *Allergy Rhinol*. 2014;5(3):157-161.
15. Buhl R, Humbert M, Bjermer L, et al. Severe eosinophilic asthma: a roadmap to consensus. *Eur Respir J*. 2017;49(5):1700634.
16. Mogensen I, James A, Malinovschi A. Systemic and breath biomarkers for asthma: an update. *Curr Opin Allergy Clin Immunol*. 2019;20(1):71-79.
17. James A, Janson C, Malinovschi A, et al. Serum periostin relates to type-2 inflammation and lung function in asthma: Data from the large population-based cohort Swedish GA(2)LEN. *Allergy*. 2017;72(11):1753-1760.
18. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. 2012;67(1):91-98.
19. Bjerg A, Ekerljung L, Middelveld R, et al. Increased prevalence of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish adults: comparisons of the ECRHS and GA(2)LEN surveys. *PLoS One*. 2011;6(2):e16082.
20. Burney PG, Laitinen LA, Perdrizet S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J*. 1989;2(10):940-945.
21. Sundbom F, Lindberg E, Bjerg A, et al. Asthma symptoms and nasal congestion as independent risk factors for insomnia in a general population: results from the GA(2)LEN survey. *Allergy*. 2013;68(2):213-219.
22. Ronmark E, Perzanowski M, Platts-Mills T, Lundback B. Different sensitization profile for asthma, rhinitis, and eczema among 7-8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol*. 2003;14(2):91-99.
23. Allergologi SFF. Anafylaxi. 2015:1.
24. Heinzerling LM, Burbach GJ, Edenharter G, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64(10):1498-1506.
25. Bousquet J, Chanez P, Chanal I, Michel FB. Comparison between RAST and Pharmacia CAP system: a new automated specific IgE assay. *J Allergy Clin Immunol*. 1990;85(6):1039-1043.
26. Disease GIfCOL. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2020.
27. ATS/ERS. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912-930.
28. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
29. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:5-40.
30. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.
31. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy* (Amsterdam, Netherlands). 1990;16(3):199-208.
32. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-1108.
33. Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J Sleep Res*. 1995;4(S1):150-155.
34. Blöndal V, Sundbom F, Borres MP, et al. Study of atopic multimorbidity in subjects with rhinitis using multiplex allergen component analysis. *Clin Transl Allergy*. 2020;10(1):6.
35. Zock JP, Heinrich J, Jarvis D, et al. Distribution and determinants of house dust mite allergens in Europe: the European Community Respiratory Health Survey II. *J Allergy Clin Immunol*. 2006;118(3):682-690.
36. Humbert M, Bousquet J, Bachert C, et al. IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy. *J Allergy Clin Immunol Pract*. 2019;7(5):1418-1429.
37. Malinovschi A, Ludviksdottir D, Tufvesson E, et al. Application of nitric oxide measurements in clinical conditions beyond asthma. *Eur Clin Respir J*. 2015;2:28517.
38. Venge P. Monitoring the allergic inflammation. *Allergy*. 2004;59(1):26-32.

39. Jung YG, Kim KH, Kim HY, Dhong HJ, Chung SK. Predictive capabilities of serum eosinophil cationic protein, percentage of eosinophils and total immunoglobulin E in allergic rhinitis without bronchial asthma. *J Int Med Res*. 2011;39(6):2209-2216.
40. Kampe M, Stalenheim G, Janson C, Stolt I, Carlson M. Systemic and local eosinophil inflammation during the birch pollen season in allergic patients with predominant rhinitis or asthma. *Clin Mol Allergy*. 2007;5:4.
41. Sin A, Terzioglu E, Kokuludag A, Sebik F, Kabakci T. Serum eosinophil cationic protein (ECP) levels in patients with seasonal allergic rhinitis and allergic asthma. *Allergy Asthma Proc*. 1998;19(2):69-73.
42. Oka A, Hirano T, Yamaji Y, et al. Determinants of Incomplete Asthma Control in Patients with Allergic Rhinitis and Asthma. *J Allergy Clin Immunol Pract*. 2017;5(1):160-164.
43. Zhang L, He L, Gong J, Liu C. Risk Factors Associated with Irreversible Airway Obstruction in Asthma: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2016;2016:9868704.
44. Coumou H, Westerhof GA, de Nijs SB, Zwinderman AH, Bel EH. Predictors of accelerated decline in lung function in adult-onset asthma. *Eur Respir J*. 2018;51(2):1701785.
45. Dunican EM, Fahy JV. Asthma and corticosteroids: time for a more precise approach to treatment. *Eur Respir J*. 2017;49(6):1701167.
46. committee G. Global Initiative for Asthma (GINA). (2020):33.
47. Rogliani P, Sforza M, Calzetta L. The impact of comorbidities on severe asthma. *Curr Opin Pulm Med*. 2020;26(1):47-55.
48. Brew BK, Lundholm C, Gong T, Larsson H, Almqvist C. The familial aggregation of atopic diseases and depression or anxiety in children. *Clin Exp Allergy*. 2018;48(6):703-711.
49. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. 2017;49(12):1752-1757.
50. Thomsen SF, Kyvik KO, Backer V. Etiological relationships in atopy: a review of twin studies. *Twin Res Hum Genet*. 2008;11(2):112-120.
51. Kallin SA, Lindberg E, Sommar JN, et al. Excessive daytime sleepiness in asthma: What are the risk factors? *J Asthma*. 2018;55(8):844-850.
52. Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy*. 2012;67(4):537-544.
53. Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol*. 2015;26(5):431-437.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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