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Original Research

Allergic sensitization in asthma and COPD in the NOVELTY study

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A R T I C L E I N F O

Keywords:
Asthma
COPD
Allergy
IgE
Severity
Lung function

A B S T R A C T

Background: Allergic sensitization is a hallmark of asthma, linked to increased disease burden. However, its role in chronic obstructive pulmonary disease (COPD) and asthma + COPD remains less understood.
Objective: This cross-sectional study evaluates the prevalence of allergic sensitization and its associations with disease severity, lung function, exacerbations and health status across these conditions in the multinational observational NOVELTY cohort.
Methods: Allergic sensitization was assessed from specific IgE (sIgE) to11 common aeroallergens. Physician-assessed severity, post-bronchodilator FEV1 % predicted, exacerbation history, and health status were evaluated. Mixed-effects multivariable regression models were used to assess associations, adjusted for age, sex, BMI, smoking history, and geographical region.
Results: Baseline sIgE data were available from n = 5389 participants (asthma:2707; asthma + COPD:773; COPD:1909). Allergic sensitization prevalence was 56 % in asthma, 36 % in asthma + COPD, and 19 % in COPD. In asthma, sensitization to any allergen, mites or molds was associated with more severe disease (odds ratios (OR) 1.46 to 2.91) and lower post-BD FEV_1 % predicted (coefficients −1.88 % to −8.94 %). Conversely, in COPD, sensitization was associated with higher FEV_1 and milder severity. Women were less likely than men to be sensitized across all diagnostic groups. Regional differences were evident, with higher sensitization rates in North America and Europe compared to Asia.
Conclusion: Allergic sensitization shows divergent clinical associations across asthma and COPD, being linked to more severe disease in asthma but higher lung function and milder severity in COPD.
Clinical implication: These findings emphasize the phenotypic heterogeneity of allergic sensitization in airway diseases and support its use in guiding personalized diagnostic and therapeutic strategies.

Abbreviations: **ECRHS**, European Community Respiratory Health Survey; GA^{2}LEN, Global Asthma and Allergy European Network; FeNO, fractional exhaled nitric oxide; COPD, chronic obstructive pulmonary disease; NOVELTY he, NOVEL observational longiTudinal study; IgE, Immunoglobulin E; PAU/l, Phadia arbitrary units per liter; FEV_1, forced expiratory volume in 1 s; GLI, Global Lung Initiative; CAAT, Chronic Airways Assessment Test.

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1. Introduction

Being sensitized to airborne allergens is common in the general population. In the European Community Respiratory Health Survey (ECRHS) from the early 1990s, 33 % of adults aged 20–44 were sensitized to at least one common aeroallergen [1]. Among this random sample of subjects, there was a large variation between the centers in the prevalence of sensitization to common individual allergens. Similar results were also reported in the Global Asthma and Allergy European Network (GA^{2}LEN) survey in the mid-2000s [2].

Allergic sensitization is closely correlated with asthma [3], particularly in childhood-onset asthma. Aside from its association with asthma prevalence, the number and type of allergens to which a person with asthma is sensitized is relevant, as multi-sensitization has been associated with greater bronchial responsiveness, higher levels of fractional exhaled nitric oxide (FeNO) [4], and multimorbidities [5]. Furthermore, childhood sensitization to house dust mite is strongly associated with asthma persistence to adulthood [6].

Allergic sensitization is relatively common in chronic obstructive pulmonary disease (COPD). Putcha and coworkers found that the prevalence of atopic sensitization was 35 % and 36 % among COPD patients aged 40–45 years and older in the SPIROMICS and COPDGene cohorts, respectively [7]. No clear association was found between atopic status, lung function, health status, exacerbation frequency, and physical capacity [7]. Tiew et al. reported that sensitization to mold but not to pollen or mites was associated with an increased risk of exacerbations in COPD patients from Southeast Asia [8]. One study found that COPD patients with self-reported allergies against pollen and pets more often had self-assessed severe disease, more exacerbations and worse health status than patients with no reported allergies [9].

Less is known about allergic sensitization in patients with both diagnoses. In the study by Putcha et al., almost 20 % of the COPD patients also had asthma; fewer than half of these had allergic sensitization [7]. Other studies have shown that having both asthma and COPD is associated with a higher risk of exacerbations and poorer health status [10, 11]. In one study, allergic sensitization to mites was higher in patients with asthma + COPD than in patients with only COPD [12].

Based on the studies reported above, we hypothesized that allergic zsensitization is associated with a greater clinical burden in both asthma and COPD. In order to study this, we used data from an international cohort of patients with physician diagnosed asthma and COPD. The current cross-sectional analysis aimed to assess the prevalence of allergic sensitization in patients with asthma, asthma + COPD, and COPD from different geographical areas and to investigate the association with severity and health status in these three diagnostic groups.

2. Methods

2.1. Study design and population

The NOVEL observational longiTudinal studY (NOVELTY; clinicaltrials.gov identifier: NCT02760329) is a large global, observational study of people with physician-diagnosed asthma, COPD, and people with both asthma and COPD ('asthma + COPD') [13]. Patients were enrolled in NOVELTY by primary care physicians, allergists, and pulmonologists between September 2015 and March 2017 across 371 sites in community and hospital outpatient settings in 18 countries [13]. The countries and regions included were Australia, Canada, USA, Latin America (Argentine, Brazil, Columbia and Mexico), Japan, Korea, Spain, Italy, France, United Kingdom, Germany and the Nordics (Denmark, Norway, Sweden and the Netherlands). Enrolment was stratified by physician-assigned diagnosis and physician-assessed severity to ensure sufficient numbers for subgroup analysis.

All patients included in NOVELTY met the following inclusion criteria: participants were aged ≥12 years and had a diagnosis or suspected diagnosis of asthma, COPD, or both, according to the treating physician. No diagnostic criteria were specified [13]. All participant gave their informed consent.

Exclusion criteria were to have participated in any respiratory interventional trial within the 12 months prior to enrolment, being unlikely to complete 3 years follow-up and having a primary respiratory diagnosis that was not asthma or COPD.

Blood samples were taken from consenting participants, approximately 50 % of the study's n = 11,243 participants (n = 5477). The present analyses included participants for whom data for specific IgE were available (n = 5389).

2.2. Allergic sensitization

Allergic sensitization was assessed by measuring IgE antibodies in serum using ImmunoCAP Phadiatop™ (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden). The Phadiatop assay includes a mix of common perennial and seasonal aeroallergens, and the Immunoglobulin E (IgE) antibody values are reported as Phadia arbitrary units per liter (PAU/l). Subjects with levels ≥0.35 PAU/l were then further characterized by measuring serum IgE antibodies to house dust mite (*Dermatophagoides pteronyssinus*), birch, timothy, cat, dog, mugwort, ragweed, olive, wall pellitory, *Alternaria alternata*, and *Cladosporium herbarum* using ImmunoCAP™ Specific IgE (Phadia AB/Thermo Fisher Scientific. A value of ≥0.35 kUA/l was defined as positive sensitization to the specific allergen, and allergic sensitization as being sensitized to at least one allergen [14]. The number of allergens that a person was sensitized to was also analyzed. All the IgE analyses were performed at Service Lab, Thermo Fischer Scientific, Copenhagen, Denmark.

2.3. Clinical characteristics

2.3.1. Severity

At baseline, the physician categorized the severity of the patient's asthma or COPD as mild, moderate, or severe based on their assessment; no severity criteria were provided [15].

2.3.2. Lung function

Pre and post bronchodilator forced expiratory volume in 1 s (FEV_1) were measured by trained personnel according to the European Respiratory Society/American Thoracic Society standards [16] and, in the analyses, expressed as % of predicted defined according to Global Lung Initiative (GLI) [17].

2.3.3. Exacerbations

The study physician reported the number of exacerbations during the 12-month period before the baseline visit; exacerbations were grouped into 0, 1, and 2 or more for analysis. Exacerbations were defined as any asthma or COPD exacerbations reported by the physician, irrespective of their severity.

2.3.4. Health status

Health status was assessed using the Chronic Airways Assessment Test (CAAT), an approved modification of the COPD Assessment Test (CAT), which has been validated for use in both asthma and COPD [18, 19].

2.3.5. Sensitivity analyses

In addition to the primary analyses, we also analyzed differences between sensitized and non-sensitized participants regarding GINA treatment steps [20] for asthma and GOLD classification A-E and 1–4 for the groups with asthma + COPD and COPD [21].

2.4. Statistics

Descriptive statistics, unpaired *t*-test, Chi-squared tests and mixed-effects multivariable logistic regression models were produced to

explore the cross-sectional associations of allergic sensitization with physician-assigned disease severity, FEV_1 (%) predicted), health status and exacerbation history, adjusted for age, sex, BMI and smoking status. Logistic regression models were used to evaluate associations, accounting for geographical regions as random effects to control for environmental variability. The results are presented as odds ratios (95 % confidence intervals). The coefficients for the associations with lung function were expressed as numerical changes with 95 % CIs estimated per 1 percentage post-BD FEV_1 % predicted change.

3. Results

Of the n = 5389 participants with data for specific IgE, 2707 had physician-diagnosed asthma, 773 had asthma + COPD, and 1909 had COPD. The participants for whom IgE was available were somewhat older, more likely to be women, less likely to have an asthma diagnosis, and more likely to have had exacerbations than those for whom IgE was not available (Table S1).

3.1. Allergic sensitization across the diagnostic groups

Overall, 40 % of the population was sensitized to at least one allergen. Specifically, the prevalence in those with a diagnostic label of asthma was 56 %, while in subjects with asthma + COPD and those with COPD, the prevalence was 36 % and 19 %, respectively (Fig. 1). House dust mite was the most common allergen to be sensitized against, with a prevalence of 40 %, 24 %, and 12 % in asthma, asthma + COPD and COPD, respectively. In the group with asthma, 39 % were sensitized to at least two allergens and 18 % to more than three. The corresponding figures for the asthma + COPD and COPD groups were 19 % and 9 %, and 9 % and 4 %, respectively.

There were large differences in allergic sensitization prevalence between the geographical regions (Fig. 2). In the group with asthma, mite was the most common allergen to be sensitized against, except in Germany and the Nordics, where birch and timothy, respectively, were the most common sensitizations (Table 1). Sensitization to ragweed was common in the USA and Korea but less common in other countries. Mite was also the most common allergen in most countries in the group with COPD (Table S2).

3.2. Associations with allergic sensitization

Characteristics of those sensitized and not sensitized in the three diagnostic groups are presented in Table 2. Sensitized participants were more likely to be male than female in all three diagnostic groups. Sensitized participants were younger in the asthma and COPD groups and more likely to be never-smokers in the asthma group. Age of asthma onset was lower and blood eosinophil number higher in the sensitized asthma and asthma + COPD groups. The prevalence of bronchodilator responsiveness was slightly higher in those sensitized in the asthma group. Allergen-sensitized subjects with a diagnosis of asthma had a higher prevalence of physician-assessed severe disease than non-sensitized subjects. In contrast, in subjects with COPD, sensitized participants were less likely to have severe physician-assessed disease than non-sensitized participants. No associations with physician-assigned severity were found in the group with asthma + COPD. The prevalence of allergic sensitization in men and women in the three diagnostic groups is presented in Fig. 3. The prevalence of sensitization was significantly higher in men than in women in all three diagnostic groups ($p < 0.001$).

3.3. Sensitization to individual allergens

When considering individual allergens, participants with severe asthma had a higher prevalence of sensitization to any of the tested allergens, as well as to mite, cat, dog and Cladosporium than those with milder disease (Table 3). Among subjects with COPD, those with severe disease had a lower prevalence of sensitization to most allergens (Table 3). No significant association with disease severity was found in the asthma + COPD group (Table 3).

3.4. Clinical features and individual allergens

In participants with asthma, being sensitized to any allergen, mite, cat, dog, timothy, Alternaria, and Cladosporium was independently associated with having more severe disease after adjustment for age, sex,

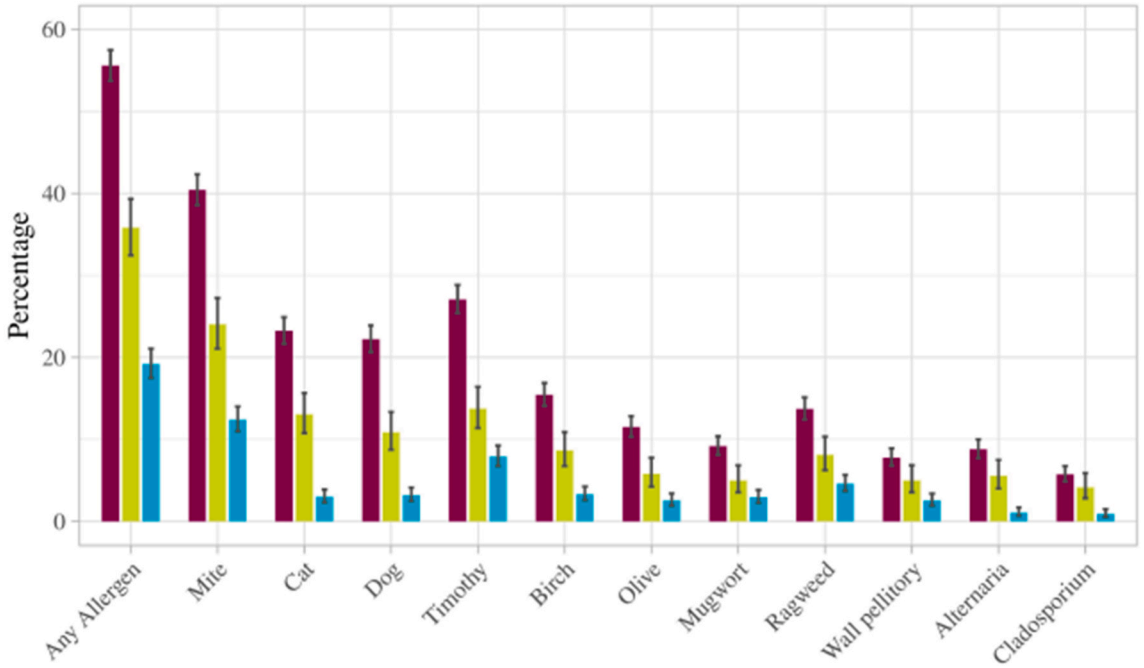

Fig. 1. Prevalence (95 % CI) of allergic sensitization to different allergens in participants with asthma (purple), asthma + COPD (green), and COPD (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

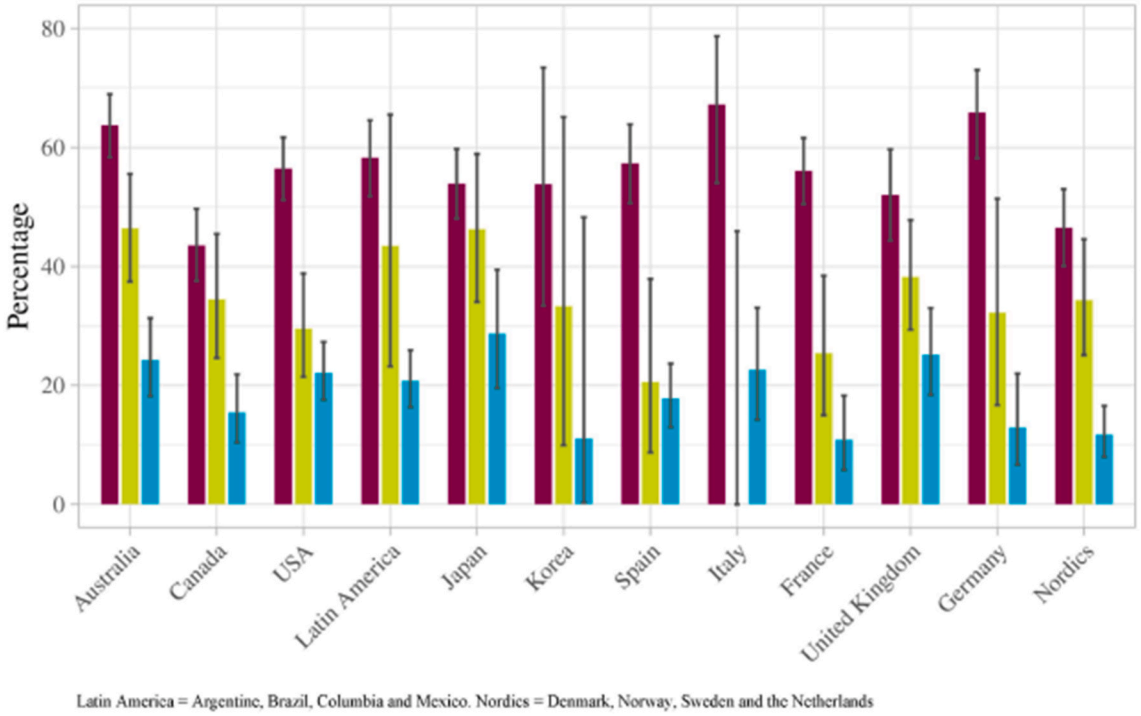

Fig. 2. Prevalence (95 % CI) of allergic sensitization to any of 11 allergens in the different geographical regions in participants with asthma (purple), asthma + COPD (green), and COPD (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Geographical variation in allergic sensitization in participants with asthma (%). The prevalence is indicated by colors with higher prevalence indicated by red tones and lower prevalence with blue tones.

	Australia (n=334)	Canada (n=271)	USA (n=358)	Latin America* (n=242)	Japan (n=293)	Korea (n=26)	Spain (n=229)	Italy (n=61)	France (n=325)	UK (n=193)	Germany (n=169)	Nordics* (n=241)
Mite	58	24	40	55	44	42	44	38	42	42	42	24
Cat	25	21	29	17	14	12	23	23	26	27	36	19
Dog	21	19	33	17	17	12	25	22	21	22	32	16
Timothy	32	18	30	17	21	23	30	27	27	38	38	26
Birch	7.7	17	19	6.4	13	19	10	15	11	16	48	20
Olive	9.2	3.8	14	8.4	8.9	15	21	18	12	12	21	8.4
Mugwort	5.8	4.6	18	7.5	9.6	27	9.3	12	6.6	6.5	11	7.1
Ragweed	8.6	15	27	15	13	27	12	8.5	11	6.6	17	7.1
Wall pellitory	6.1	1.9	13	4.4	8.9	20	13	17	6.3	6	11	3.8
Alternaria	15	9.4	14	8.8	6.5	8.3	7.1	2.1	6.1	6.6	7.7	5.5
Cladosporium	8.7	5.3	7.4	4.5	7.7	13	4.8	2.1	3.6	6.5	5.3	3.6

* Argentine, Brazil, Columbia and Mexico.
** Denmark, Norway, Sweden and the Netherlands.

BMI, smoking history, and geographical region (Fig. 4). Additionally, allergic sensitization to any allergen, mite, or mold was independently associated with lower FEV_1 in the asthma group. In contrast, allergic sensitization to timothy, birch, olive, and mugwort was associated with having mild disease in participants with COPD. Likewise, sensitization to any allergen, olive mugwort, and ragweed was independently associated with higher FEV_1 (Fig. 4). No significant associations existed between allergic sensitization and CAAT in those with asthma or COPD (Fig. S1).

In those with asthma, sensitization to timothy was associated with a higher risk of exacerbations, and sensitization to birch with a lower risk of exacerbations. In those with COPD, sensitization to mugwort and ragweed was associated with a lower risk of exacerbations (Fig. S2).

Patients with asthma + COPD did not demonstrate significant associations between allergic sensitization to individual allergens and disease severity, exacerbations, or CAAT (Table S3). However, an association was found between being sensitized to Alternaria and having lower FEV_1 (Table S3).

3.5. Sensitivity analyses

There was a statistically significant difference in GINA treatment steps in the asthma group, with fewer patients in treatment steps 1 and 2 and more in step 5 among those who were sensitized than among those who were not ($p = 0.014$) (Table S4). In the non-sensitized COPD groups, there were significantly more patients in groups A and E than in the sensitized group ($p = 0.04$). There was also a difference of borderline significance ($p = 0.054$) with fewer patients in grade 1 and more in grade 3 to 4 in the non-sensitized COPD patients than in those that were sensitized (Table S4). There was no significant difference between non-

Table 2
Characteristics in participants with asthma, asthma + COPD and COPD that were not and were allergic sensitized[a] (N = 5389).

	Asthma			Asthma + COPD			COPD		
	Not sensitized (n = 1202)	Sensitized (n = 1505)	p-value	Not sensitized (n = 496)	Sensitized (n = 277)	p-value	Not sensitized (n = 1542)	Sensitized (n = 367)	p-value
Age (mean ± SD)	59 ± 14	50 ± 16	<0.001	65 ± 10	65 ± 10	0.40	67 ± 9	66 ± 10	0.020
Age, asthma onset (mean ± SD)	42 ± 20	26 ± 20	<0.001	46 ± 21	33 ± 25	<0.001	–	–	–
Age, COPD onset (mean ± SD)	–	–	–	58 ± 11	57 ± 12	0.20	59 ± 11	58 ± 11	0.11
Women %	72	56	<0.001	57	41	<0.001	44	30	<0.001
BMI (mean ± SD)	29 ± 7	28 ± 7	0.061	29 ± 7	29 ± 6	0.900	28 ± 6	28 ± 7	0.700
Smoking history			0.013			0.20			0.40
Never smoker %	59	63		11	16		6.2	8.2	
Ex-smokers%	34	29		64	62		65	63	
Current smokers%	7	8		25	22		29	29	
Physician-assessed severity			0.017			0.40			0.023
Mild %	39	36		18	15		30	35	
Moderate %	34	32		45	44		28	31	
Severe %	27	32		37	41		42	34	
Post-BD FEV1 (% pred) (mean ± SD)	86 ± 21	85 ± 21	0.050	68 ± 22	67 ± 22	0.80	61 ± 24	66 ± 23	0.003
FEV1 % reversibility (mean ± SD)[c]	6 ± 10	7 ± 10	0.042	9 ± 12	8 ± 11	0.70	6 ± 11	7 ± 12	0.40
Blood eosinophils, cells/uL (mean ± SD)	212 ± 173	233 ± 204	<0.001	209 ± 186	224 ± 173	0.026	179 ± 116	199 ± 158	0.50
Exacerbations prev 12 m			0.087			0.70			0.20
0	65	61		51	51		60	65	
1	22	25		29	27		27	23	
≥2	14	14		20	22		13	12	
CAAT (median (IQ range)[b]	14 (8–21)	13 (7–20)	0.039	18 (11–24)	17 (11–24)	0.60	17 (10–23)	16 (9–22)	0.20

P-values calculated with unpaired *t*-test and Chi-squared test.
[a] Allergic sensitization defined as a IgE level ≥0.35 for any of the tested allergens.
[b] A higher CAAT (Chronic Airways Assessment Test) score indicates worse health status.
[c] % FEV1 Reversibility = (Post-BD FEV1 – Pre-BD FEV1) x 100/Pre-BD FEV1.

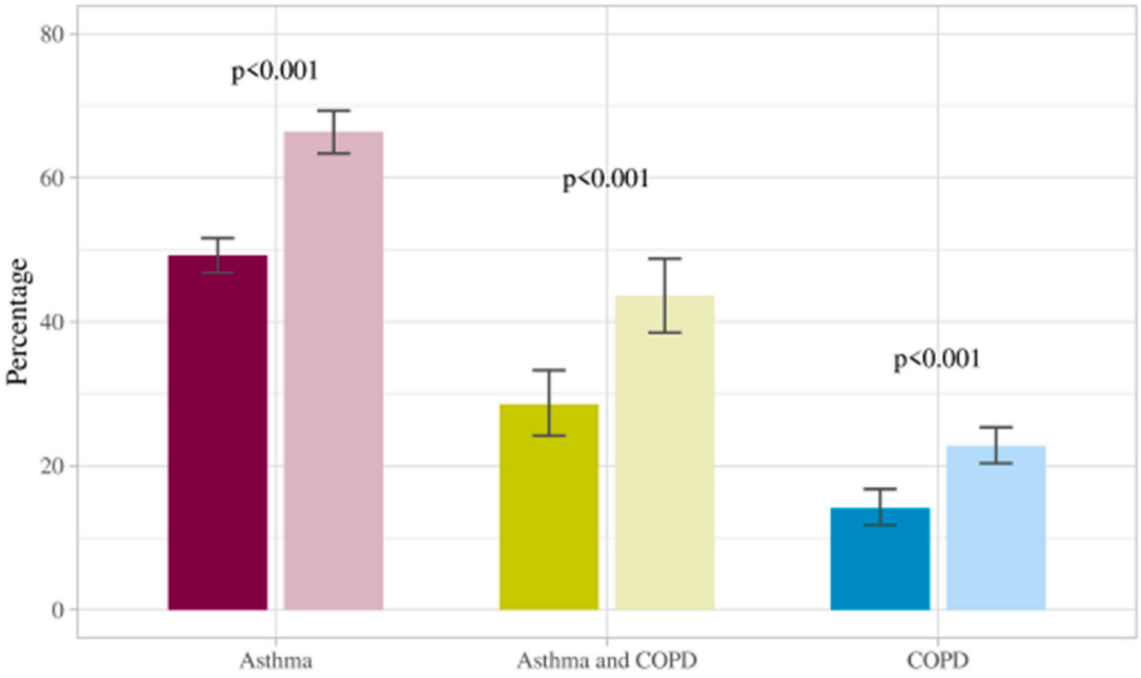

Fig. 3. The prevalence (95 % CI) of allergic sensitization in women (darker color) and men (lighter color) in participants with asthma, asthma + COP and COPD. P-values calculated with Chi-squared test. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sensitized and sensitized patients with asthma + COPD regarding the GOLD classification.

4. Discussion

The main finding of this large international study is that airborne allergen sensitization is frequent in patients with obstructive lung diseases. Different patterns and associations were observed across the

Table 3
The prevalence of IgE sensitization by diagnosis and physician-assessed disease severity (%) (N = 5389).

	Asthma				Asthma + COPD				COPD			
	Mild (n = 1010)	Moderate (n = 901)	Severe (n = 796)	p-value	Mild (n = 132)	Moderate (n = 346)	Severe (n = 295)	p-value	Mild (n = 588)	Moderate (n = 548)	Severe (n = 773)	p-value
Any allergen	53	54	60	0.017	32	35	38	0.040	22	20	16	0.023
Mite	36	40	46	<0.001	20	22	28	0.11	14	12	12	0.400
Cat	22	22	27	0.017	12	12	14	0.70	2.8	3.7	2.7	0.600
Dog	20	22	25	0.025	10	8.4	14	0.080	2.8	4.3	2.8	0.300
Timothy	26	28	28	0.600	9.4	14	15	0.30	11	9.2	5.0	<0.001
Birch	17	15	14	0.200	8.5	9.4	7.9	0.80	4.3	4.0	2.1	0.046
Olive	13	11	11	0.400	3.2	6.1	6.7	0.40	3.7	3.0	1.5	0.034
Mugwort	8.8	8.7	10	0.500	4.8	5.8	4.2	0.70	3.9	3.9	1.6	0.017
Ragweed	14	13	15	0.500	5.6	8.5	8.9	0.80	5.6	5.2	3.5	0.140
Wall pellitory	7.8	7.3	8.4	0.700	3.2	4.8	6.0	0.50	3.2	2.8	2.0	0.400
Alternaria	7.7	9.2	9.7	0.300	4.0	5.0	6.9	0.40	0.5	2.1	0.8	0.031
Cladosporium	4.1	5.3	8.3	0.002	3.2	3.2	5.8	0.20	0.4	1.5	1.0	0.140

P-values calculated with Chi-squared test.

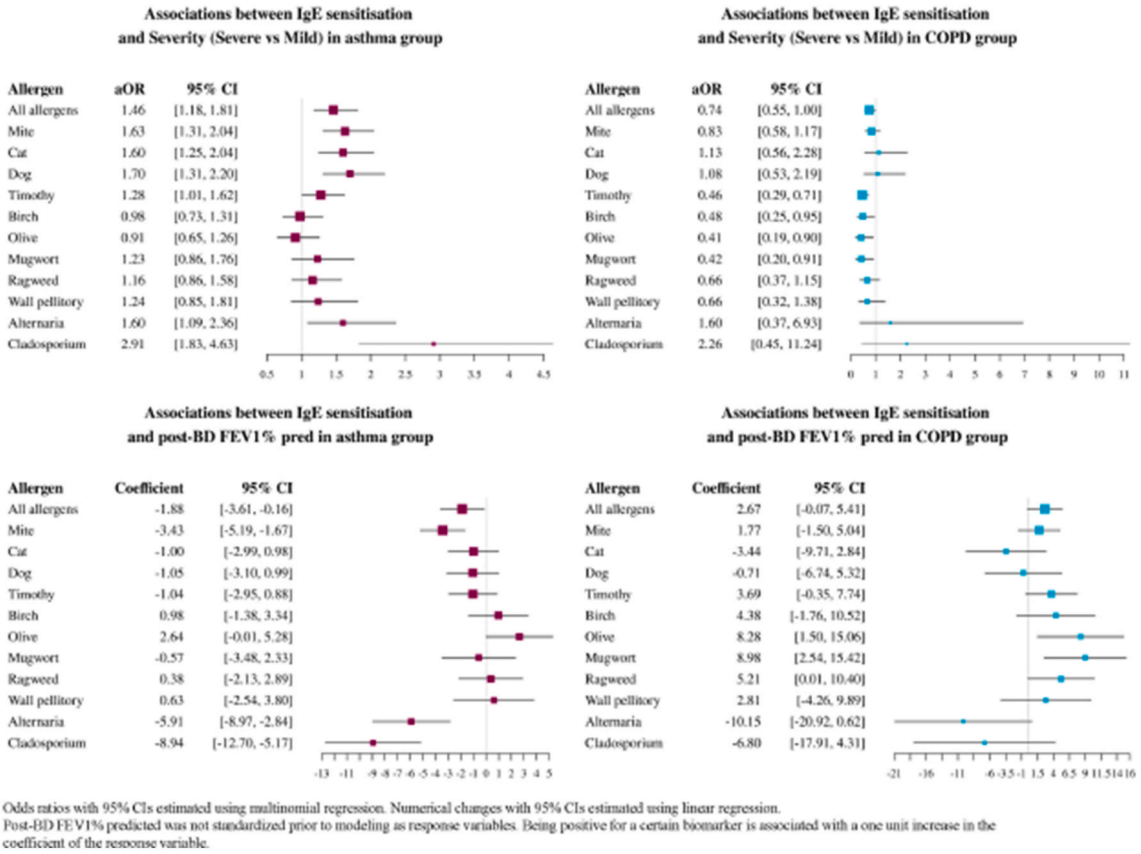

Fig. 4. Associations between allergic sensitization and physician-assessed disease severity, and post-BD FEV_1 % predicted, after adjustment for age, sex, BMI; smoking status and geographical region. The results for severity are expressed as odds ratios with 95 % CI estimated using multinominal regression, while the results for FEV_1 % predicted is expressed as numerical change with a 95 % CI using linear regression.

diagnostic label groups. In the NOVELTY cohort, allergic sensitization was more prevalent in asthma (56 %) and asthma + COPD (36 %) than in COPD (19 %). The main novel results were that sensitization was associated with lower lung function and worse health status, having more severe disease in asthma but not in COPD, while the opposite was found in COPD. We also found large geographical variations in allergic sensitization in all three diagnostic groups. No major associations were found in the group with both diagnostic labels.

In the present study, 56 % of the participants with asthma were sensitized to at least one allergen. Being sensitized was independently associated with more severe disease and lower FEV_1. The association was strongest with sensitization to molds and mites. This result aligns with Backman and coworkers, who, in a study from northern Sweden, found that sensitization to mite and mold was more common in those with severe asthma than in other patients [22]. Likewise, Neukirch et al. found that participants sensitized to Alternaria had more severe asthma than those not sensitized, in an analysis from the French centers of ECRHS [23]. Our finding that sensitization to mite was associated with lower FEV_1 in patients with asthma aligns with what previously was shown in the ECRHS, where those with asthma and mite sensitization had lower FEV_1 than non-sensitized asthmatics [24].

In the participants with COPD, the prevalence of allergic sensitization was, not surprisingly, much lower than in those with asthma. Allergic sensitization was associated with higher FEV_1, and sensitization

to pollen allergens with milder severity. Thus, the direction of the association with allergic sensitization was opposite to that seen in asthma. The prevalence of allergic sensitization in COPD was lower than reported in data from SPIROMICS and COPDGene patient cohorts [7]. However, our results are in line with what was found in the Swedish part of the Burden of Obstructive Lung Disease (BOLD) study, where the prevalence of allergic sensitization among those who fulfilled the spirometric criteria for COPD and did not have asthma was 24 % [25]. Similar results were found in a Swedish COPD patient cohort where allergic sensitization was 20 % [26]. The more extensive IgE test profile used in SPIROMICS and COPDGene might explain the higher prevalence of sensitization in these US-based COPD patients. Putcha et al. [7] tested their subjects against a grass and mold mix, whereas we used only one grass and two molds in our 11-test algorithm. In addition, they also tested for cockroach and mouse urine proteins, which we did not do. The association between allergic sensitization and milder severity and higher lung function in COPD is surprising, as a previous study showed associations in the opposite direction [9]. However, that study, at variance with the current one, was based on self-reported allergies.

The prevalence of allergic sensitization in the group with asthma + COPD (sometimes called in the past 'asthma-COPD overlap') was between those with only asthma or COPD, in line with previous data [25]. No significant associations were found in this group, perhaps related to the smaller number of participants. The only exception was that sensitization to Alternaria was associated with lower lung function. The fact that allergy plays a role in patients with asthma + COPD is suggested by a study showing that anti-IgE is equally effective in patients with asthma + COPD as in patients with only asthma [27].

Our study showed large geographical differences in the prevalence of allergic sensitization. As an example, over 60 % of those with asthma were sensitized to at least one allergen in Australia, Italy, and Germany. The corresponding prevalence was less than 50 % in Canada, the United Kingdom, and the Nordics. There were also large differences in sensitization to individual allergens. These differences are at least partly related to different geographic prevalence of the allergens themselves [28]. For example, birch trees are uncommon in Australia and ragweed does not grow in Sweden. Notably, the prevalence of mite sensitization in those with asthma was two times higher in Australia than in Canada and the Nordics, perhaps related to the lower humidity in the latter countries. However, mites were the most prevalent sensitization for asthmatic patients in all the geographical areas. The geographical pattern found in NOVELTY has many similarities to what has been found in previous international population studies such as ECRHS and the GA^{2}LEN survey [1,2,29].

Allergic sensitization was significantly associated with younger age, particularly in asthma and asthma + COPD, reflecting a combination of a decline in sensitization with age and an age cohort effect [30]. An age difference with a higher prevalence of allergy in younger subjects has been found in several previous studies [2,31]. Women were less likely to be sensitized across all diagnostic groups, with the lowest prevalence observed in older female COPD patients. In the ECRHS, men were more likely than women to be sensitized to mite and grass than women [32]. Allergic sensitization in asthma was associated with earlier age of disease onset and slightly higher blood eosinophil counts and bronchodilator reversibility [33,34]. Although these differences were statistically significant, their clinical relevance appears modest and warrants cautious interpretation.

The study's strengths are its robust sample size, global representation, and meticulous statistical analyses. However, the cross-sectional nature of the data limits causal inference, and the lack of detailed mechanistic exploration leaves open questions about the biological basis of the observed differences between asthma and COPD. The severity criteria used in NOVELTY were based on the physician assessment. This is partly because conventional severity criteria for asthma and COPD differ and the study aims to cover both.We did, however, find differences in the same direction when we replaced our severity classification with the GINA classification for asthma [20] and the GOLD classification for COPD [21]. There was also a risk of selection bias, as only half of the NOVELTY participants volunteered to provide blood samples. When comparing the group that showed IgE data with those that did not, there were several statistically significant differences regarding age, sex and lung function, but as they were numerically small, we do not think this has influenced our results.

Our findings represent another step forward in understanding the role of allergic sensitization across obstructive airway diseases. By highlighting distinct sensitization patterns and their clinical relevance, it paves the way for more precise phenotyping and personalized care. However, it also raises important questions. What mechanisms underlie the apparent protective association between sensitization and lung function in COPD? It is possible that allergic COPD patients respond better to treatment in the same way that COPD patients with higher blood eosinophil numbers are more sensitive to inhaled corticosteroids [35]. Other questions that arise are whether allergen-specific interventions improve outcomes in sensitized COPD and patients with asthma + COPD? And how can we better integrate regional and environmental factors into global management strategies?

This study has several important clinical implications. In asthma, allergic sensitization should improve targeted interventions, particularly the use of biologics that inhibit IgE (omalizumab), IL-4/IL-13 pathways (dupilumab) or anti-alarmins such as tezepelumab in severe asthma. Patients' allergic status was often not reported in past asthma clinical trials, and this pattern continues today. Testing for sensitization to perennial allergens, such as house dust mites, should become a routine part of disease management to stratify patients better and personalize treatment strategies. For COPD, the findings that 20 % were sensitized to airborne allergens challenges the traditional non-allergic paradigm of the disease and highlights a potential new treatable trait. The promising treatment results with dupilimab indicated that targeting IL-4 may be important in a subgroup of COPD patients [36].

In the NOVELTY cohort, allergic sensitization was more prevalent in asthma and asthma + COPD than in COPD. Sensitization was associated with lower lung function and worse health status in asthma. In contrast, associations in the opposite direction were found in patients with COPD, and there was no significant association in participants with both diagnoses. More mechanistic and clinical studies are warranted to understand the contrasting effects of allergic sensitization in asthma and COPD.

CRediT authorship contribution statement

Christer Janson: Writing – original draft, Methodology, Conceptualization. **Andrei Malinovschi:** Writing – review & editing. **Magnus Borres:** Writing – review & editing. **Rosa Faner:** Writing – review & editing, Methodology. **Rod Hughes:** Writing – review & editing, Resources, Methodology. **Anastasios Mangelis:** Writing – review & editing, Formal analysis. **Xiaomeng Ma:** Writing – review & editing, Formal analysis. **Hana Mullerova:** Writing – review & editing, Project administration, Methodology, Funding acquisition. **Alberto Papi:** Writing – review & editing, Supervision, Methodology. **Helen Reddel:** Writing – review & editing, Supervision, Methodology, Investigation. **Jose Maria Olaguibel:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The NOVELTY study is funded by AstraZeneca. The sponsor participated in the design of the study, data analysis, and preparation of the manuscript.

Disclosure of potential conflicts of interest: C.J. has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Teva outside of the submitted work. AM has received lecture and/or

advisory board fees from Boehringer Ingelheim and Chiesi outside the submitted study as well as in-kind support in form of nitric oxide sensors from NIOX (a producer of FeNO devices) and reagents for allergy testing and inflammation biomarkers from Thermo Fisher Scientific, both within a frame of investigator-initiated studies, MB is an employee of Thermo Fisher, RN, RH, AM, XMand HM are employees of AstraZeneca. A.P. has received personal fees for consultation or board membership or lecturing for AstraZeneca, Boehringer Ingelheim, ChiesiFarmaceutici, Edmond Pharma, GSK, Mundipharma, Novartis, Sanofi/Regeneron, Teva, and Zambon. His Institution has received industry-sponsored grants from AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, and GSK. HKR has participated in advisory boards for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis and Sanofi Genzyme; and has received honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Sanofi and Teva Pharmaceuticals for independent medical educational presentations; consulting for Novartis and AstraZeneca; and independent research funding from Astra-Zeneca, GlaxoSmithKline, and Sanofi. She is Chair of the Global Initiative for Asthma Science Committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108605.

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