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Asthma in combination with rhinitis and eczema is associated with a higher degree of type-2 inflammation and symptom burden than asthma alone

To the Editor,

Asthma is common and often accompanied by rhinitis and eczema, especially in the presence of allergy. (1) Increased total immunoglobulin E (IgE) is associated with polysensitization and atopic multimorbidity. (1) There is some evidence linking allergic multimorbidity to increased levels of other type-2 inflammatory markers, such as fractional exhaled nitric oxide (F_ENO) (2), blood eosinophils (B-Eos) (1), and eosinophil activation markers (3), but the evidence is scarce and to some extent conflicting.

The aim of this study was to investigate type-2 inflammatory markers, IgE sensitization, and respiratory and food hypersensitivity symptoms in young asthmatics (aged 10–35 years) with allergic multimorbidity. Furthermore, we investigated eventual differences between adolescents and young adults with regard to the relation between type-2 inflammatory markers and allergic multimorbidity. For methodology, please see the Online Supplement and Online Figure S1. Subject demographics are supplied in the Online Table S1.

We found that asthmatics with allergic multimorbidity (either having rhinitis or both rhinitis and eczema) had a higher degree of type-2 inflammation, as assessed by F_ENO, total IgE, B-Eos count, and plasma eosinophil-derived neurotoxin (P-EDN), but not serum eosinophil cationic protein (S-ECP), both before and after adjustments for age, sex, BMI, sensitization to airborne allergens, and use of inhaled and nasal corticosteroids (Table 1). Stratifying for age with 18 years as cut-off, we found that higher levels of F_ENO were only associated with allergic multimorbidity in subjects younger than 18 years (Online supplement Table S2). Furthermore, an interaction with the age groups (< or ≥18 years) was noted with regard to the relation between allergic multimorbidity and elevated levels of F_ENO (asthma vs asthma, rhinitis: p=0.032 and asthma vs asthma, rhinitis, eczema: p=0.048, both p-values for the interaction terms with age groups). No significant interactions with age groups were found for the relation between allergic multimorbidity and the other type-2 inflammation markers.

Asthmatics with allergic multimorbidity were more likely to be IgE-sensitized to both aeroallergens and food allergens (Figure 1).

Subjects with multimorbidity were more likely to report respiratory symptoms when exposed to aeroallergens, allergic reactions to food (Figure 1), as well as wheezing and asthma attacks within the preceding 12 months (Online Table S3), and were more likely to use antihistamines and nasal steroids within the last 12 months (Online Table S4).

Our main finding is that commonly used type-2 inflammation markers, such as F_ENO and B-Eos count, are increased in subjects with allergic multimorbidity. Previous findings in the literature have not been consistent.(4) We could show, for the first time, that the increase in F_ENO was more pronounced for asthmatics with allergic multimorbidity under the age of 18, suggesting that F_ENO, as a marker of airway inflammation, is more closely related to allergic multimorbidity in children than adults. Besides F_ENO, total IgE and B-Eos also differed between the groups in subjects aged under 18 years, but these findings were also found to some extent in adults (Online Table S2), and therefore, no interactions with age groups were found on the relation between these last-named inflammatory markers and allergic multimorbidity.

Among the eosinophil activation markers, we found that P-EDN, but not S-ECP was related to allergic multimorbidity. This might be due to the fact that S-ECP reflects not only the presence of eosinophils, but also the degree of eosinophil activation, while P-EDN mainly reflects the former. (5)

We also found that both total IgE and sensitization to aeroallergens and food allergens related to allergic multimorbidity. These results are in accordance with previous findings (1)

Finally, a higher burden of symptoms was noted among those with allergic multimorbidity, both with regard to allergic reactions to food and aeroallergens, and to asthma attacks and wheezing during the previous year. These results are in line with our previous studies, showing that allergic multimorbidity increases the likelihood of reporting an allergic reaction to food (4) and comorbidities increase disease severity (6).

We acknowledge that the main limitation of the study is the use of self-reported symptoms to define rhinitis, eczema, and food hypersensitivity. Some degree of asthma overdiagnosis cannot be excluded despite the requirement of a medical asthma diagnosis in combination with use of anti-inflammatory treatment.

In conclusion, asthmatics with allergic multimorbidity had a higher degree of type-2 inflammation and a higher burden of asthma and allergy symptoms. Asthmatics with allergic multimorbidity and persistent type-2 inflammation despite optimal treatment might benefit from specific type-2 treatment.

TABLE 1 Inflammatory markers and total IgE in relation to co-occurrence of rhinitis or rhinitis and eczema. All results presented as geometric mean 95% confidence interval*

	Asthma (n=50)	Asthma and rhinitis (n=203)	p-value vs asthma	Adjusted** p-value vs asthma	Asthma, rhinitis and eczema (n=141)	p-value vs asthma	Adjusted** p-value vs asthma
F_ENO (ppb)	11.4 (9.4–13.8)	15.8 (14.2–17.7)	0.007	0.065	17.8 (15.7–20.2)	<0.001	0.019
Total IgE (kU/L)	55.6 (33.4–92.7)	131 (105–162)	0.001	0.164	225 (175–289)	<0.001	0.004
B-Eos (10^9/L)	0.12 (0.10–0.15)	0.18 (0.16–0.21)	0.005	0.010	0.21 (0.18–0.24)	0.001	0.001
S-ECP (mg/L)	11.7 (9.1–13.8)	13.0 (11.7–14.3)	0.360	0.773	14.3 (12.7–16.0)	0.088	0.394
P-EDN (µg/L)	14.8 (13.6–16.2)	16.9 (15.9–17.9)	0.068	0.033	17.3 (15.9–18.7)	0.040	0.010

Statistical method: unpaired t tests (unadjusted p-values) and multiple linear regression analyses (adjusted p-values).

Abbreviations: B-Eos: blood eosinophils; F_ENO: fraction of exhaled nitric oxide; IgE: immunoglobulin E; P-EDN: plasma eosinophil-derived neurotoxin; S-ECP: serum eosinophil cationic protein.

A p-value <0.0167 should be considered statistically significant if the Bonferroni correction is applied.

*Data missing for up to 3 individuals per biomarker.

**Adjusted for: age, sex, BMI, sensitization to airborne allergens and use of inhaled and nasal corticosteroids. The comparison between asthma and rhinitis, and asthma, rhinitis and eczema was significant only for total IgE ($p<0.001$).

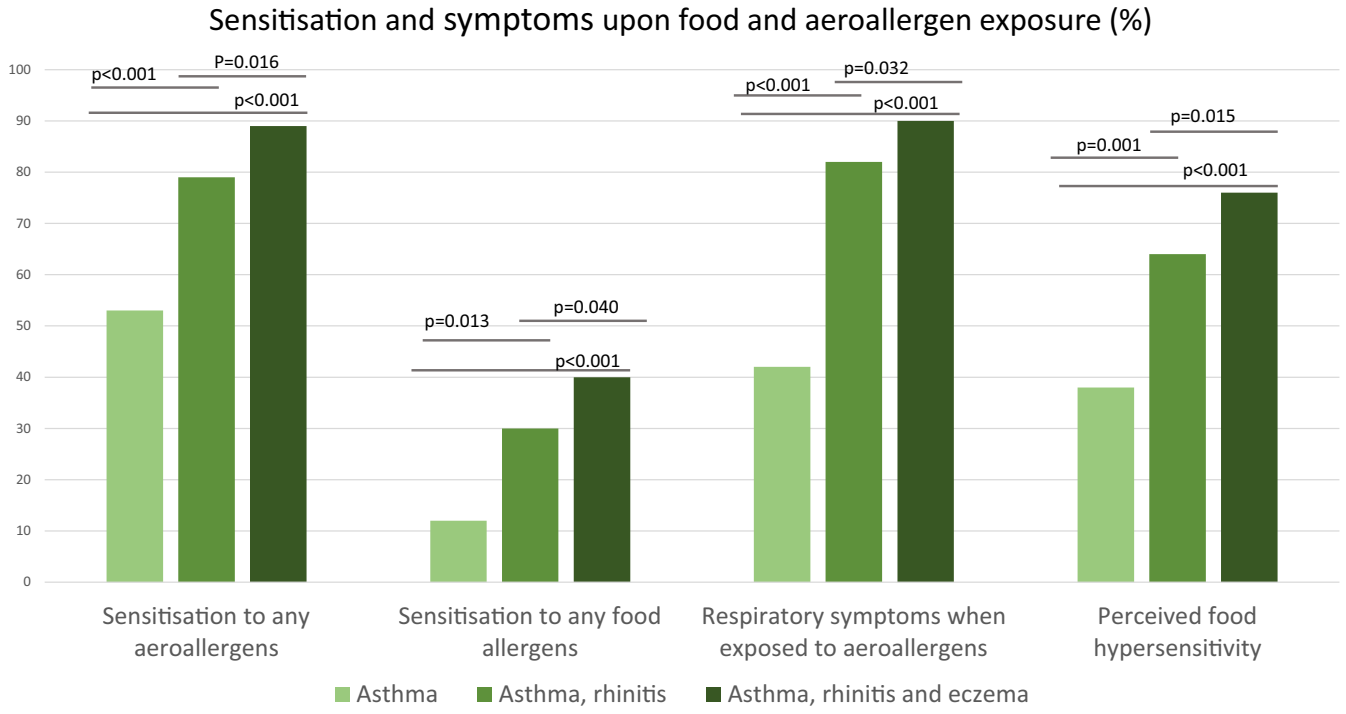

FIGURE 1 Prevalence of sensitization to aeroallergens, food allergens, and symptoms upon exposure to allergens in relation to coexistence of rhinitis or rhinitis and eczema. Statistical analysis: Chi2-test. A p-value <0.0167 should be considered statistically significant if the Bonferroni correction is applied. Respiratory symptoms: chest tightness, wheezing, respiratory distress, cough

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CONFLICT OF INTEREST

Magnus P. Borres is an employee of Thermo Fisher Scientific. Kjell Alving has received research material from Thermo Fisher Scientific and Hemocue.

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SUPPORTING INFORMATION

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

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DAAB-V2: Updated database of allergy and asthma biomarkers

To the Editor,

In the past 25 years, therapy of allergic diseases is mostly restricted to steroids and anti-inflammatory agents, which exert side-effects.[1] With the advent of omics approaches, several biomarkers have been identified which, if exploited, can provide clues about novel therapeutic strategies.[2,3] Keeping this in mind, we have compiled expression biomarkers of allergic diseases in human and other organisms, along with their single nucleotide polymorphisms (SNPs), gene ontology terminologies, structure and drug information in Database of Allergy and Asthma Biomarkers—version2 (DAAB-V2, freely available at http://bicresources.jcbose.ac.in/ssaha4/daab-v2/), an updated version of DAAB—version1 (Figure S1A). DAAB-V2 have been developed as an online, relational database with tables on expression, structure, SNP and drug (Supplementary Material). The master table contains a total of 14,705 entries, with 12,551 newly incorporated entries on genes/proteins that are differentially expressed in allergic diseases (detailed statistics of DAAB-V2 is shown in Figure S1B). Except expression table, all other tables have been newly conceived. SNP, structure and drug tables contain 1201, 10,629 and 320 entries, respectively. Entries in DAAB-V2 have been hyperlinked to BioGRID (for protein-protein interaction data), NCBI, PDB, GEO, DrugBank, PubChem, PubMed, wherever applicable. DAAB-V2 has been compared with DAAB-version1, AllerGAtlas 1.0 and two projects on respiratory diseases and allergy (U-BIOPRED and MeDALL).[1,4-6] DAAB-V2 incorporates entries from relevant publications from MeDALL and U-BIOPRED. DAAB-V2 had better data coverage compared to DAAB-V1 and AllerGAtlas 1.0 databases (Table 1).