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*Additional references 10 – 18 are provided as online supplement.

SUPPORTING INFORMATION

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Association between asthma, rhinitis, and conjunctivitis multimorbidities with molecular IgE sensitization in adults

To the Editor,

Allergic multimorbidity is well established for rhinitis and asthma. However, the role of conjunctivitis in the allergic multimorbidity is not clear. A large number of pollen-allergic patients suffer from both rhinitis and conjunctivitis. Rhinitis is often ascribed to rhinoconjunctivitis and it is thought that ocular symptoms occur during high allergenic exposure. In fact, ocular symptoms are among the most bothering symptoms of allergic rhinoconjunctivitis.^{1,2} However, the links between nasal and ocular symptoms are unclear.

In a novel approach examining daily symptoms with mobile technology (MASK: mobile airways sentinel network), we found previously unrecognized patterns of multimorbidity. Days with eye and nasal symptoms were associated with impaired work productivity by comparison to days with nasal symptoms alone, suggesting the importance of conjunctivitis in allergic multimorbidities.³ In accordance with this hypothesis, a study in a random sample of school aged children showed that rhinoconjunctivitis was associated with multiple allergic sensitization as compared to rhinitis.⁴ However, in the MeDALL study the cluster analysis identified eye symptoms in the multimorbid phenotype but was not considered independently.⁵ There is a need to confirm whether conjunctivitis should be considered separately in allergic multimorbidity.

A cross-sectional study (EGEA, France and BAMSE, Sweden) investigated allergen sensitization using an enhanced micro-array technique and found that patients with multimorbid rhinitis and asthma had significantly more IgE sensitizations to allergen molecules than those with rhinitis alone or asthma alone.⁶ However, the impact of conjunctivitis was not tested as the data of the MASK study were not available when analyses were performed.³

The objective of the current study is to assess whether allergic sensitization profiles differed between allergic multimorbidity patterns including asthma, rhinitis, and conjunctivitis starting from the recently published EGEA study considering only asthma and rhinitis.⁶ We hypothesized that more allergic multimorbidity is associated with increased IgE recognition frequencies and that considering

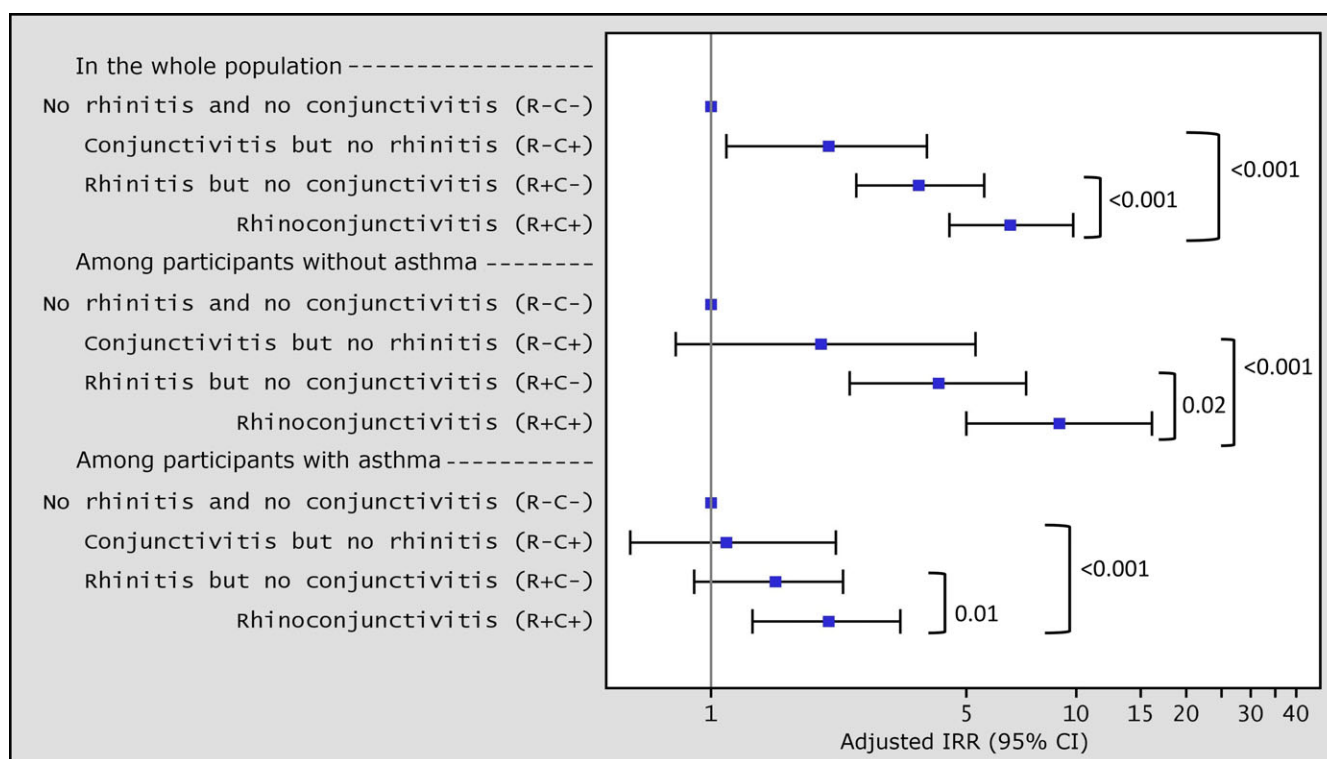
conjunctivitis in addition to rhinitis and asthma in allergic multimorbidities changes the IgE recognition frequencies.

The analysis is based on IgE reactivity to 64 clinically relevant respiratory allergenic molecules determined with the MeDALL-chip in samples from the French EGEA cohort (n = 840, mean [SD] age = 40.7 ± 17.1 years) (Table S1). For the analysis of the number of allergen-specific IgE reactivities, results are given by medians and 25-75 percentiles. The age- and sex-adjusted associations between the number of IgE reactivities (≥ 0.3 ISU) and the different asthma-rhinitis-conjunctivitis phenotypes were assessed using a negative binomial model, which estimates the incidence rate ratio (IRR), that is the ratio of the mean number of positive allergen-specific IgE (and its 95% confidence interval) between phenotypes. These methods are published elsewhere^{6,7} and presented in the Data S1. Some differences exist between this study and the recently published study⁶: (a) A more sensitive definition of rhinitis was used by considering either the report of allergic rhinitis or hay fever or a positive answer to the question on rhinitis symptoms: "Have you ever had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu?"; (b) we further consider allergic conjunctivitis defined using a positive answer to the question: "Have you ever had allergic conjunctivitis?"

Among the 840 adult participants tested, 463 had asthma, 629 had rhinitis, and 347 had conjunctivitis. There were 143, 187, 278, and 232 participants with 0, 1, 2, and 3 allergic diseases, respectively. The median number of IgE-reactive allergens varied from 0 to 1, 2 to 5, and increased up to 8 in groups with 1, 2, and 3 allergic morbidities, respectively (Table 1). The number and levels of IgE reactivities were statistically significantly increased in each allergic multimorbidity phenotype as compared to the controls (R-C-A-), except for conjunctivitis only (Table 1). The rhinoconjunctivitis multimorbidity was associated with an increased number of IgE reactivities as compared to subjects with rhinitis only ($P < 0.001$) or conjunctivitis only ($P < 0.001$). This pattern was observed whatever the asthma status, and the rhinoconjunctivitis multimorbidity was the only phenotype associated with an increased number of IgE

TABLE 1 Association between the number of IgE-reactive allergens, allergen-specific IgE levels, and allergic diseases

	≥1 positive specific IgE, %	Number of IgE-reactive allergens (≥0.3 ISU) ^a				Levels of allergen-specific IgE (among sera positive to at least 1 allergen) (ISU)			
		n	Median (25-75 percentiles)	P	Age and sex-adjusted relative change ^b (95%CI)	P	n	Median (25-75 percentiles)	P
R-C-A-	18.9	143	0 (0-0)	Ref	1	Ref	27	1.2 (0.7-2.7)	Ref
R-C-A+	61.3	31	1 (0-6)	<0.001	8.2 (4.1-16.6)	<0.001	19	3.1 (1.0-5.7)	0.06
R+C-A-	43.6	133	0 (0-3)	<0.001	4.0 (2.3-7.0)	<0.001	58	4.5 (1.7- 10.3)	<0.001
R-C+A-	26.1	23	0 (0-1)	0.35	2.3 (0.8-6.3)	0.10	6	1.9 (0.6-2.9)	0.51
R+C-A+	76.3	186	5.5 (1-10)	<0.001	11.8 (7.1-19.4)	<0.001	142	5.3 (2.7-9.2)	<0.001
R-C+A+	71.4	14	5 (0-8)	<0.001	9.1 (4.5-18.2)	<0.001	10	2.7 (1.8-3.9)	0.05
R+C+A-	61.5	78	2 (0-6)	<0.001	8.5 (4.9-14.8)	<0.001	48	5.3 (2.8-9.5)	<0.001
R+C+A+	90.5	232	8 (4.5-12)	<0.001	17.3 (10.7-28.1)	<0.001	210	5.8 (2.9-10.0)	<0.001

^aAmong the 64 respiratory allergen components selected (see Table S1).^bRelative change in the mean number of IgE-reactive allergens was calculated with negative binomial model.**FIGURE 1** Age- and sex-adjusted relative change in the mean number of IgE-reactive allergens in rhinitis (R+C-), conjunctivitis (R-C+), and rhinoconjunctivitis (R+C+) as compared to those without rhinitis and conjunctivitis (R-C-, reference group). P values reported are those comparing R+C- and R-C+ to R+C+. Incidence rate ratio (IRR) estimates and 95% confidence interval were estimated using the negative binomial model (an IRR of 2.0 in R-C+ means that mean number of IgE reactivities increased twofold in participants with conjunctivitis as compared to participants R-C-) [Colour figure can be viewed at wileyonlinelibrary.com]

reactivities among subjects with asthma (Figure 1). IgE recognition frequencies and intensities are presented in Figure S1. Among participants without rhinitis, the number of allergen-IgE detected in over 10% of participants was 0 and 11 in participants without and with conjunctivitis. Among participants with rhinitis, this number increased to 14 and 22, respectively.

Overall, our study shows that increase in allergic multimorbidity, irrespective of the disease, is associated with a significant increase in the number of IgE reactivities to respiratory allergens. Among subjects presenting a single allergic disease, the number of IgE-reactive allergens was strongly increased with asthma, moderately increased with rhinitis, and only a mild and nonsignificant association was observed

with conjunctivitis. However, when considering the allergic multimorbidities, the rhinoconjunctivitis phenotype significantly exhibited higher number of IgE reactivities as compared to rhinitis only and conjunctivitis only. This study extends to the adult population previous observations in adolescents indicating that rhinoconjunctivitis increases allergic sensitization as compared to rhinitis only.⁴

The strength of the study is the use of micro-arrays to assess IgE sensitization. One limitation of the study relying on the cross-sectional design of our analyses is the lack of definite information on the timing of the events and of the successive specific allergic sensitization. Although there is increasing knowledge on the evolution of IgE responses toward mite allergens over time and its effect on respiratory allergies,^{8,9} there is little evidence when considering a large spectrum of respiratory allergen sources, and the ocular symptoms have never been considered. A sensitivity analysis not considering mite allergen components hardly inhaled (Der p 10, Der p 11, Der p 14, and Der p 18)¹⁰ led to similar results (not shown).

This study in a well-defined population shows the importance of hypothesis-generating studies using big data³ and their confirmation by classical epidemiologic studies. We confirmed results from the MeDALL study by showing that conjunctivitis provides additional information to rhinitis and asthma when studying the allergic multimorbidities. Interestingly, the multimorbid approach of allergic diseases should consider the three target organs (nose, eye, and lower airways). Further epidemiologic studies are needed to better understand the links between the three organs and the trajectories of allergic diseases across the life cycle.

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CONFLICTS OF INTEREST

Dr. Lupinek reports personal fees from Thermo Fisher Scientific, outside the submitted work. Dr. Bousquet reports personal fees and other from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed INNOV, from null, outside the submitted work. Dr. Valenta reports grants from Biomay Ag, Vienna, Austria, grants from Viravaxx, Vienna, Austria, personal fees from BiomayAG, Vienna, Austria, personal fees from Viravaxx, Vienna, Austria, outside the submitted work. Dr. Siroux reports personal fees from AstraZeneca, Novartis, Teva, outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Distinct Lipid Transfer Proteins display different IgE-binding activities that are affected by fatty acid binding

To the Editor,

Nonspecific lipid transfer proteins (nsLTPs) are relevant food allergens. They have a compact 3D structure, with a hydrophobic lipid-binding cavity.¹ It seems that the complex with a ligand can affect protein allergenicity.² Recently, we have shown that the binding of oleic acid (OLE) to the peach nsLTP, Pru p 3, affects the conformation and IgE-binding activity of the allergen.³ We therefore investigated whether this observation can be extended to other homologous proteins. Thus, we analyzed nsLTPs with different allergenic potential, Mal d 3 from apple (high), Cor a 8 from hazelnut (intermediate), and Hel a 3 from sunflower seed (low),^{4,5} and their interactions with 3 fatty acids: OLE, stearic (STE), and lauric (LAU) acids. We extracted natural nsLTPs and produced recombinant Mal d 3 and Cor a 8 using *Pichia pastoris*. Ligand binding of nsLTPs was assessed by ANS (1-

anilinonaphthalene-8-sulfonic acid) displacement assay, measuring the decrease in ANS fluorescence. IgE reactivity of nsLTPs, alone or bound to fatty acids, was tested by IgE-ELISA using sera from subjects sensitized to peach and/or hazelnut nsLTP. For selected nLTPs/ligand complexes, molecular dynamic (MD) simulations were performed to analyze the impact of ligand binding on the protein conformation with a focus on specific IgE epitopes (details on methods and patients' data are presented in the Supporting Information).

The different natural and recombinant nsLTPs were purified and characterized (Figure S1). rMal d 3, rCor a 8, and nHel a 3 bound the ANS probe to varying extent (Figure 1A). All proteins showed the lowest preference for STE (Figure 1B-D) with a maximum fluorescence reduction of 17% for rMal d 3/STE (50 µmol/L). LAU induced a dose-dependent reduction of ANS binding to all proteins, reaching values at 50 µmol/L of 53%, 7%, and 26% for rMal d 3, rCor a 8, and nHel a 3, respectively. In general, OLE induced a more

Karin Hoffmann-Sommergruber and Tomasz Borowski shared last authorship.

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Online supplement

Change of molecular IgE sensitization associated with conjunctivitis in asthma and rhinitis multimorbidity

Siroux V et al.

Methods

Population and study setting

The EGEA1 cohort is composed of a group of 388 individuals with asthma enrolled in chest clinics, 1,244 first-degree relatives and 415 control individuals.(1) Participants were recruited through self-completed questionnaires and had a complete examination including pulmonary function tests.(2) About 11 years later, 1,601 participants (77.1% of the original cohort + 58 new family members) took part to a complete examination (EGEA2). The analysis of IgE was conducted with serum samples from 840 adults of EGEA2 (463 with and 377 without asthma).(3) Written consent was obtained from all participants. Ethical approval was obtained from the ethics committees (Cochin Royal Hospital, Paris, for EGEA1 and Necker-Enfants Malades Hospital, Paris, for EGEA2).

Definition of asthma, allergic rhinitis and atopic dermatitis

Phenotypes were assessed through validated questionnaires. Ever asthma was defined by a positive answer to either “*Have you ever had attacks of breathlessness at rest with wheezing?*” or “*Have you ever had asthma attacks?*” or being recruited as an asthma case in chest clinics. Allergic rhinitis ever was defined by a positive answer to “*Have you ever had allergic rhinitis?*” or “*Have you ever had hay fever?*” or “*Have you ever had a problem with sneezing or runny or blocked nose when you did not have a cold or the flu?*”. Allergic conjunctivitis was examined using a positive answer to the question: “*Have you ever had allergic conjunctivitis?*”.

Allergen-specific IgE measurement

IgE reactivity to microarrayed allergens was determined in anonymous samples with the MeDALL-chip (an allergen microarray) in both EGEA and BAMSE.(4, 5) The MeDALL-chip comprises 176 allergen components including aero- and food allergen components. In the present study 64 defined clinically relevant respiratory allergenic molecules were studied ([Table S1](#) online supplement). The measurement of allergen-specific IgE was performed as described.(5, 6) Results are given in ISU (ISAC standardized units) and positivity of each allergen-specific IgE was defined by a threshold of 0.3 ISU IgE.(3, 5-7)

Table S1. Frequencies of IgE recognition in the population study for the 64 allergen components studied

Species	Allergen	Molecular Group	Frequency (%)
Pollen	Birch	Bet v 1	PR-10
		Bet v 2	Profilin
		Bet v 4	Polcalcin
	Olive	Ole e 1	Ole e 1-related protein
		Ole e 7	nsLTP, type 1
		Ole e 9	Glucanase1
	Japanese cedar	Cry j 1	Pectate lyase
	Cypress	Cup a 1	Pectate lyase
	Plane tree	Pla a 1	Invertase Inhibitor
		Pla a 2	Polygalacturonases
		Pla a 3	nsLTP, type 1
	Timothy grass	Phl p 1	Grass group 1 (Beta-Expansin)
		Phl p 2	Grass group 2/3
		Phl p 5b	Grass group 5
		Phl p 6	Grass group 5/6
		Phl p 7	Calcium-binding proteins (Polcalcin)
		Phl p 11	Ole e 1-related protein
		Phl p 12	Profilin
	Ragweed	Amb a 1	Pectate lyase
	Mugwort	Art v 1	Defensin-like protein
		Art v 3	nsLTP, type 1
	Goosefoot	Che a 1	Ole e 1-related protein
	Plantain	Pla l 1	Ole e 1-related protein
	Wall pellitory	Par j 2	LTP, type 2
	Saltwort	Sal k 1	Pectin methylesterase
Latex	Latex	Hev b 1	Rubber elongation factor
		Hev b 3	Small rubber particle protein
		Hev b 5	Acidic protein
		Hev b 6.01	Hevein (Prohevein)
Molds	Alternaria	Alt a 1	Acidic glycoprotein
		Alt a 6	Enolase
	Aspergillus	Asp f 1	Mitogillin family (Ribonuclease)
		Asp f 3	Peroxisomal protein
		Asp f 6	Mn superoxide dismutase
	Cladosporium	Cla h 8	Mannitol dehydrogenase

Species	Allergen	Molecular Group	Frequency (%)	
Mites	Der p 1	Group 1 mite allergens (Cysteine protease)	26.4	
	Der p 2	Group 2 mite allergens (NPC2 family)	29.6	
	Der p 4	Group 4 mite allergens (Alpha-amylase)	12.5	
	Der p 5	Group 5/21 mite allergens	17.7	
	Der p 7	Group 7 mite allergens	16.8	
	Der p 10	Group 10 mite allergens (Tropomyosin)	15.1	
	Der p 11	Group 11 mite allergens (Paramyosin)	4.3	
	Der p 14	Vitellogenin (Apolipoporphins)	2.1	
	Der p 15	Chitin-binding domain	3.0	
	Der p 18	Chitin-binding domain	4.5	
	Der p 21	Group 5/21 mite allergens	11.7	
	Der p 23	Chitin-binding domain	26.9	
	clone 16	Chitin-binding domain	7.5	
	Storage mite	Lep d 2	Group 2 mite allergens (NPC2 family)	3.8
	Blomia tropicalis	Blo t 5	Group 5/21 mite allergens	5.4
	Cockroach	Bla g 1	Cockroach group 1	0.4
		Bla g 2	Aspartic protease	0.1
		Bla g 5	Glutathione S-transferase	0.1
	Anisakis	Ani s 1	Serine protease inhibitor	1.0
Animals	Cat	Fel d 1	Uteroglobin	26.2
		Fel d 2	Serum Albumin	3.8
		Fel d 4	Lipocalin	5.6
	Dog	Can f 1	Lipocalin	7.4
		Can f 2	Lipocalin	2.5
		Can f 4	Lipocalin (Odorant-binding protein)	3.3
		Can f 5	Arginine Esterase (Trypsin-like serine protease)	11.9
		Can f 6	Lipocalin	2.9
	Horse	Equ c 1	Lipocalin	4.9
	Mouse	Mus m 1	Lipocalin	4.2

Numbers in bold represent allergens recognized by >3% in the study population

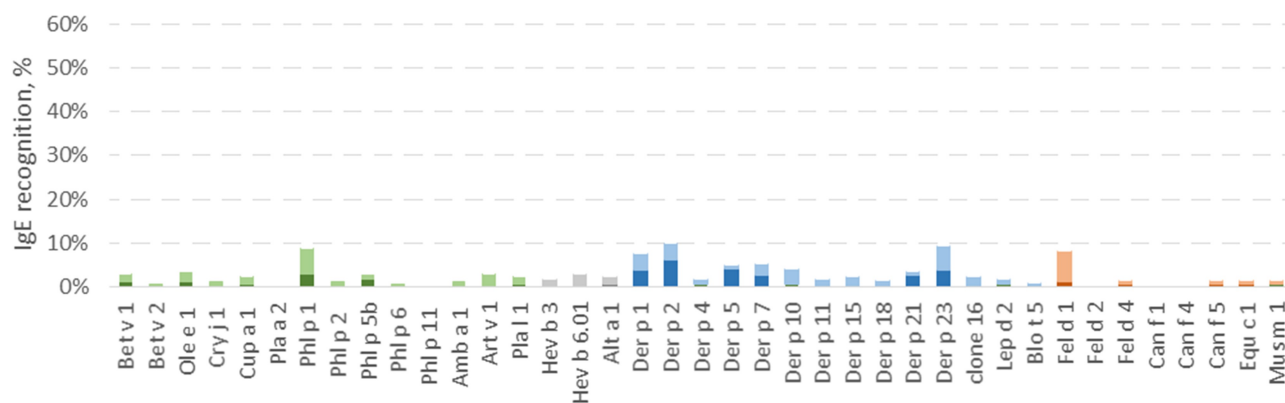
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Figure S1. IgE recognition frequencies and intensities to respiratory allergens recognized by >3% of the EGEA samples, in subjects with: A, no rhinitis and no conjunctivitis (R-C-), B, no rhinitis but conjunctivitis (R-C+), C, rhinitis and no conjunctivitis (R+C-) and D, rhinitis and conjunctivitis (R+C+)

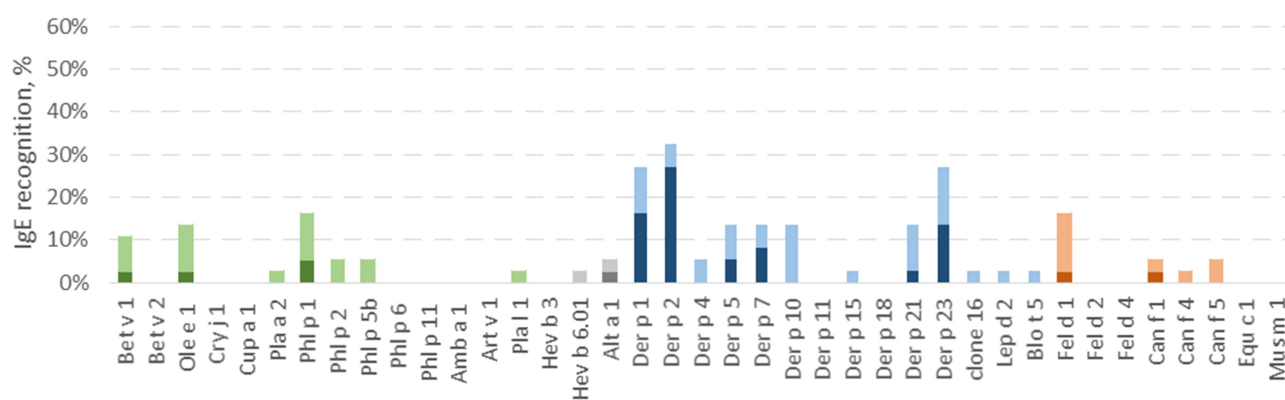
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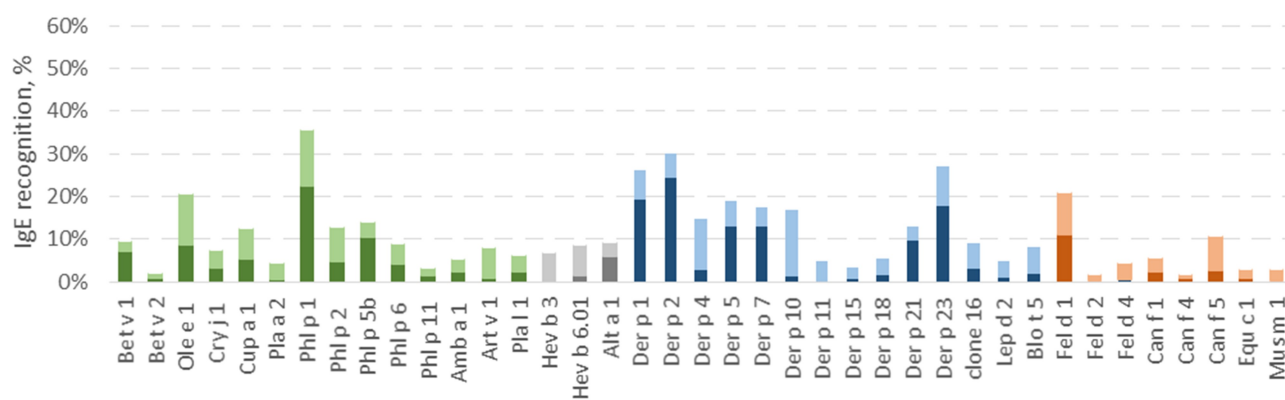
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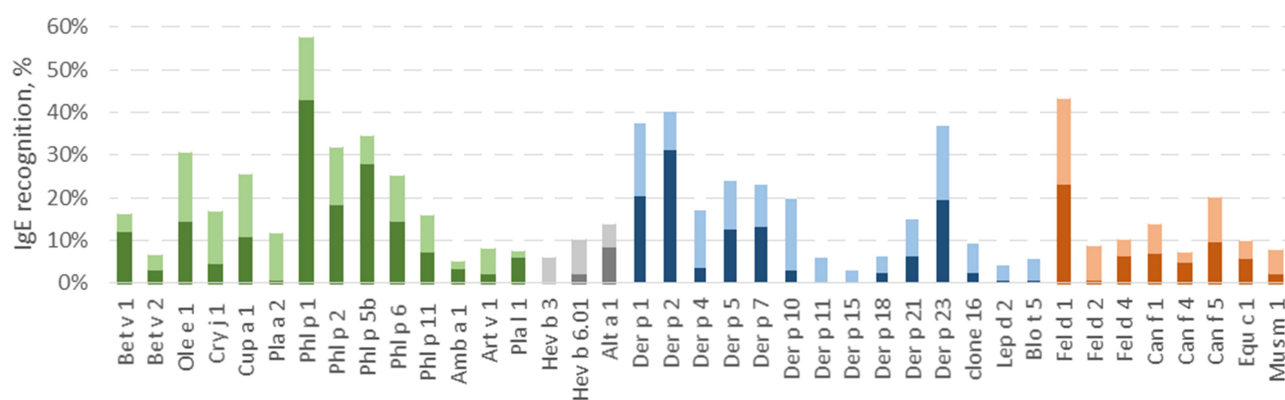
B)



C)



D)



Pollen
House dust mite

IgE ≥ 3.0 ISU
IgE [0.3-3.0] ISU

Animal
Latex/alternaria

IgE ≥ 3.0 ISU
IgE [0.3-3.0] ISU