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Accepted Article

ARIA-MeDALL hypothesis

Short title: Paradigm shift in rhinitis and asthma

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Abstract

Asthma, rhinitis and atopic dermatitis (AD) are interrelated clinical phenotypes that partly overlap in the human interactome. The concept of “one-airway-one-disease”, coined over 20 years ago, is a simplistic approach of the links between upper- and lower-airway allergic diseases. With new data, it is time to reassess the concept. This article reviews (i) the clinical observations that led to Allergic Rhinitis and its Impact on Asthma (ARIA), (ii) new insights into polysensitisation and multimorbidity, (iii) advances in mHealth for novel phenotype definition, (iv) confirmation in canonical epidemiologic studies, (v) genomic findings, (vi) treatment approaches and (vii) novel concepts on the onset of rhinitis and multimorbidity. One recent concept, bringing together upper- and lower-airway allergic diseases with skin, gut and neuropsychiatric multimorbidities, is the “Epithelial Barrier Hypothesis”. This review determined that the “one-airway-one-disease” concept does not always hold true and that several phenotypes of disease can be defined. These phenotypes include an extreme “allergic” (asthma) phenotype combining asthma, rhinitis and conjunctivitis. Rhinitis alone and rhinitis and asthma multimorbidity represent two distinct diseases with the following differences: (i) genomic and transcriptomic background (Toll-Like Receptors and IL-17 for rhinitis alone as a local disease; IL-33 and IL-5 for allergic and non-allergic multimorbidity as a systemic disease), (ii) allergen sensitisation patterns (mono- or pauci-sensitisation versus polysensitisation), (iii) severity of symptoms and (iv) treatment response. In conclusion, rhinitis alone (local disease) and rhinitis with asthma multimorbidity (systemic disease) should be considered as two distinct diseases, possibly modulated by the microbiome, and may be a model for understanding the epidemics of chronic and auto-immune diseases.

Key words: asthma, rhinitis, multimorbidity, Toll-like receptors, IL-33, IL-17, microbiome

Abbreviations

A: Asthma	HLA: Human leukocyte antigen
A+AR: Asthma and allergic rhinitis multimorbidity	HNEC: Human nasal epithelial cell
A+R: Asthma and rhinitis multimorbidity	IgE: Immunoglobulin E
A+R+AD: Asthma, rhinitis and atopic dermatitis multimorbidity	IL: Interleukin
AD: Atopic dermatitis	ILC2: Innate lymphoid cells type 2
APC: Antigen presenting cell	IoW: Isle of Wight cohort
AR: Allergic rhinitis	Lol p1: <i>Lolium perenne</i> antigen 1
ARIA: Allergic Rhinitis and its Impact on Asthma	MAAS: Manchester Asthma and Allergy Study
BAMSE: Barn/Children, Allergy/Asthma, Milieu, Stockholm	MAS: German Multicentre Allergy study
CAPS: Childhood Asthma Prevention Study	MeDALL: Mechanisms of the Development of Allergy
CD: Cluster Differentiation	MHC: Major Histocompatibility Complex
CpG: Dinucleotide CpG	MyD88: Myeloid differentiation primary response gene 88
CRS: Chronic rhinosinusitis	NF-κB: Nuclear factor-kappa B
CRS w NP: CRS with nasal polyposis	ORMDL3: ORM1 (yeast)-like protein 3
DC: Dendritic cells	QOL: Quality-of-life
DEP: Diesel exhaust particules	R: Rhinitis
Der p: <i>Dermatophagoides pteronyssinus</i>	RSV: respiratory syncytial virus
EGEA: Epidemiological study on the Genetics and Environment of Asthma	RWD: Real-world data
ECRHS: European Community Respiratory Health Survey	S aureus: <i>Staphylococcus aureus</i>
EoE: Eosinophilic esophagitis	SNP: Single nucleotide polymorphism
EVA-PR: Asthma and Epigenetic Variation in Puerto Rican Children	ST2: Interleukin 1 Receptor Like 1
Foxp3: Forkhead box P3	T2: Type 2
GSDMB: Gasdermin B	TLR: Toll-like receptor
GWAS: Genome Wide Association Study	TRIF: Toll/IL-1R domain-containing adaptor-inducing IFN-β
HDM: House dust mite	TSLP: Thymic stromal lymphopoietin
	VAS: Visual analogue scale
	WHEALS: Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

1- Introduction

Allergic diseases [asthma: A, rhinitis: R and atopic dermatitis (AD)] are complex. They are associated with allergen-specific IgE and non-allergic mechanisms that may coexist. In addition, these diseases tend to cluster and patients present concomitant or consecutive diseases (multimorbidity). Important clinical and immunological differences exist between mono- and polysensitised subjects.^{1,2} Complex genetic and epigenetic mechanisms interact with the environment to determine disease expression. They lead to distinct and frequently co-existing phenotypes.² Immunological mechanisms related to these diseases include Type 2 (T2) inflammatory patterns (IgE-mediated and independent),^{3,4} IL-17^{5,6} and CCL17 (CC chemokine ligand 17)⁷. In addition, epithelial barrier defects and microbial dysbiosis are of importance.^{8,9}

Asthma, rhinitis and AD tend to cluster in multimorbidity, partly overlapping in the human interactome.¹⁰ Their relationship should be understood in a multimorbidity framework, rather than through the atopic march.¹¹ Additional multimorbidities due to ocular, cognitive, autism spectrum, thyroid and bowel diseases need to be understood.¹²⁻¹⁴ Asthma, rhinitis and AD are clinical phenotypes that are interrelated. The molecular pathways (as measured by genes, transcripts, metabolites and/or epigenetics) underlying multimorbidity can be measured to determine their common and divergent biology as shown in psychiatric diseases.¹⁵ But such integrated studies looking at the overlapping of genes and pathways between related conditions have not yet been carried out for asthma, rhinitis and AD in samples of sufficient size.

The concept of “one-airway-one-disease”, coined over 20 years ago,¹⁶ may be a simplistic approach¹⁷ and requires reassessment. (Table 1). This article will review (i) the clinical observations that led to Allergic Rhinitis and its Impact on Asthma (ARIA), (ii) new insights into the links between polysensitisation and multimorbidity, (iii) advances in mHealth supporting the definition of novel phenotypes, (iv) confirmation in canonical epidemiologic studies, (v) genomic findings, (vi) treatment approaches, (vii) novel concepts on the onset of rhinitis and multimorbidity and (viii) the putative impact of the microbiome.

Terminology used

Multimorbidity and comorbidity are used in several studies. “In 1970, Feinstein first coined the term ‘comorbidity’ to describe ‘Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study’. In 1996, van den Akker et al. suggested that comorbidity should be defined according to Feinstein’s definition and multimorbidity as “the co-occurrence of multiple chronic or acute diseases and medical conditions within one person”. In 2010, Boyd and Fortin provided a more simple definition of multimorbidity: “the co-existence of two or more chronic conditions, where one is not necessarily more central than the others”.¹⁸ **We therefore selected the term “multimorbidity”.**

In this paper, the term “allergic multimorbidity” will be used primarily for asthma, rhinitis and AD. However, it will also include conjunctivitis, food allergy and the rare manifestation of eosinophilic esophagitis (EoE), although non-allergic mechanisms may co-exist, predominate or even be the only mechanisms in some diseases

of the so-called “allergic multimorbidity”(e.g., non-allergic asthma, non-allergic rhinitis or chronic rhinosinusitis).^{19,20}

Polysensitisation to different pollen species is often based on IgE cross-reactivities to the pan-allergens (e.g., profilins, polcalcins or cyclophilins) present in pollens or plant foods (e.g., birch pollen and apple) or in *Dermatophagoides* and shrimp. Patients are also polysensitised to unrelated allergens. In the present paper, polysensitisation will refer to unrelated non-cross-reacting allergens.

2- From clinical observations to ARIA guidelines (1980-2000)

2-1- Mono- and polysensitisation

IgE sensitisation is heterogeneous.²¹⁻²³ When comparing polysensitised and monosensitised subjects: (i) Monosensitisation is associated with lower total and specific IgE levels;²¹ (ii) Patients with monosensitisation recognise fewer epitopes of individual allergens;^{22,23} (iii) There is a lower level of IL-4 release by peripheral blood in monosensitisation, suggesting stronger T2 immune response in polysensitisation;²⁴ and (iv) Patients sensitised in adulthood for cypress^{25,26} or Betulaceae pollen allergy were often monosensitised.²⁷

2-2- From one-airway-one-disease to ARIA and beyond

In the early 1990s, asthma and rhinitis were considered independent diseases linked by IgE-sensitisation.^{28,29} In the European Community Respiratory Health Survey (ECRHS), rhinitis was found to be an independent risk factor for asthma in allergic or non-allergic subjects.^{30,31}

In nasal and bronchial biopsies, T2-inflammation was similar in the nose and bronchi of asthmatic patients.^{32,33} An interaction between nasal and bronchial T2-inflammation was further confirmed by nasal and bronchial allergen challenges.³⁴⁻³⁶ Nasal allergen challenge induced a T2-inflammation in the lower airways and *vice versa*.

These studies consistent with the concept of one-airway-one-disease¹⁶ led to the development of ARIA (Allergic Rhinitis and its Impact on Asthma) that designed multimorbidity guidelines combining asthma and rhinitis for the first time.¹⁰

However, clinically, two distinct allergic rhinitis (AR) phenotypes are identified: (i) rhinitis alone, affecting around 70-80% of patients with AR and (ii) AR + asthma multimorbidity (AR+A), affecting 20-30%.¹⁷ On the other hand, most patients with asthma have rhinitis.³⁷ These data suggest common pathways in AR+A and rhinitis-specific pathways.³⁸

1- Mono- and polysensitisation appear to be independent.

2- There are additive effects of asthma and rhinitis multimorbidity on quality-of-life (QOL).

- 3- Epidemiological studies have shown that the links between asthma and rhinitis exist independently of IgE sensitisation.
- 4- Bronchial biopsies and allergen challenges show that nasal and bronchial inflammations are similar.
- 5- Airway remodelling, a characteristic of asthma, does not exist in rhinitis.
- 6- The concept of one-airway-one-disease is an over-simplification.

3- Polysensitisation and allergic multimorbidities in birth cohorts

3-1- Polysensitisation

In birth or child cohorts, depending on sensitisation patterns (mono- or polysensitisation), several features and phenotypes have been identified (Table 2).

- 7. Mono- and polysensitisation to different allergens represent expressions of distinct diseases. Compared to monosensitisation, polysensitisation was linked to stronger global IgE response, disease phenotypes (A and/or R), symptoms and trajectories.

3-2- Allergic multimorbidities

MeDALL disentangled multimorbidity.^{1,2} The coexistence of eczema, rhinitis and asthma in the same child is more common than expected by chance alone - both in the presence and absence of IgE sensitisation - suggesting that these diseases share causal mechanisms. Although IgE sensitisation is independently associated with an excess comorbidity of eczema, rhinitis and asthma, its presence accounted for only 38% of comorbidity. This suggests that IgE sensitisation cannot be considered as the dominant causal mechanism of multimorbidity.^{39,40}

- 8. Multimorbidity is partly independent of IgE sensitisation, suggesting distinct causal (genomic) pathways.

3-3- Links between polysensitisation and allergic multimorbidity

MeDALL refined the identification of the polysensitised multimorbid phenotype of allergic diseases.^{19,41} Polysensitised children were at a higher risk than monosensitised ones of developing asthma and rhinitis.⁴² In three US studies of inner-city asthmatic children, rhinitis and polysensitisation were associated with severe asthma.⁴³⁻⁴⁵ “Molecular spreading”, sensitisation to several proteins of one allergen, has been associated with more severe disease (rhinitis or asthma) and/or multimorbidity.⁴⁶

- 9. There is an association between IgE polysensitisation and multimorbidity including age of onset, number of allergic multimorbidities (conjunctivitis and AD), severity of disease, eosinophil levels and total IgE levels.

3-4- Food allergy

Food allergy starting early in life is associated with other allergic diseases. Food allergic patients may be monosensitised to a single molecule ⁴⁷ or polysensitised. Pre-school children sensitised to several peanut proteins develop symptoms more commonly later in life than those sensitised to a single protein. ⁴⁸ This may differ in adults. ⁴⁹ Severity ⁴⁷ and persistence of symptoms may also depend on sensitisation patterns. ^{50,51}

3-5- The atopic march

The atopic march is usually interpreted as the sequential development of symptoms, from AD in infancy to asthma and then AR. ¹¹ However, only a small percentage of children follow the conventional atopic march. ^{52,53} Furthermore, disease co-occurrence does not prove any specific relationship between them, certainly not a progressive or causal one. ⁵⁴

In the trajectories of AD, children with persistent AD have more moderate/severe AD, polysensitisation and current wheeze at 3 years. ⁵⁵ In the CHILD cohort, AD children polysensitised to foods at an early age had the greatest risk of developing other allergic diseases. ⁵⁶ On the other hand, AD without concomitant allergic sensitisation was not associated with an increased risk of asthma.

4- Peri-epithelial inflammation, leaky epithelial barriers and multimorbidities

Allergic multimorbidity is sometimes associated with autoimmune, metabolic and neuropsychiatric multimorbidities, suggesting common molecular mechanisms. Allergic multimorbidities and many chronic non-communicable diseases have increased in prevalence during the past decades ^{12,57-61}. This trend cannot be explained only by genetical factors. In the first group of the multimorbid phenotype, the local epithelial tissue of the affected organ is inflamed (e.g., asthma, chronic rhinosinusitis (CRS), AD, AR, EoE, inflammatory bowel and celiac diseases). A second group consists of metabolic and autoimmune diseases such as obesity, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, fatty liver, autoimmune hepatitis, systemic lupus erythematosus and ankylosing spondylitis. It is associated with gut or lung epithelial barrier defect. ⁵⁷ Intestinal barrier defects and microbiota changes have been associated with many neuropsychiatric disorders (e.g., Parkinson's disease, Alzheimer's disease, autism spectrum disorders and chronic depression). ⁵⁷

The pathogenesis of the diseases of both groups was associated with damage to the epithelial barrier and peri-epithelial inflammation. There are genetic causes such as filaggrin mutations and claudin polymorphisms, epidermal proliferation and differentiation (OVOL1), epithelial-derived alarmins (IL-33), particularly T2 response (IL-4 and IL-13 regulation), and sphingolipid synthesis (ORMDL3). ^{62,63} In addition, epigenetic regulation plays a major role in epithelial barrier integrity and all mucosal

surfaces may be exposed with the same type of environmental factor.^{64,65} These genetic defects influence the barrier integrity of the skin and different mucosal tissues. In our studies within MeDALL, and concomitantly by the exposure of other research groups to particulate matter, diesel exhaust, cigarette smoke, laundry detergents, household cleaners, microplastics, nanoparticles, food emulsifiers and other unidentified hazardous substances can cause epithelial barrier damage (Figure 1).⁶⁶

10. The damage of the epithelial barrier may predispose to allergic and non-allergic multimorbidity.

5- Discovery of novel multimorbid allergic phenotypes using direct patient mHealth data

Very few apps can provide information on rhinitis and asthma multimorbidity and also include medications.⁶⁷ Daily multimorbidity was assessed by MASK-air®, an mHealth app for allergic diseases and asthma.⁶⁸ In a prospective observational cross-over study (4,210 users in 19 countries),⁶⁹ rhinitis and rhinoconjunctivitis appeared to be two distinct diseases. A specific group (“extreme” allergy phenotype) combined rhinitis “High” (VAS>50/100) patterns - asthma “High” - conjunctivitis “High” and was identified in 2.9% of the days. This previously unknown extreme pattern of multimorbidity had the greatest impact on uncontrolled symptoms and work productivity.

In two recent cluster analyses (Sousa-Pinto, submitted) - a cross-sectional analysis based on asthma patterns (over 8,000 patients and 267,000 days) and a longitudinal one based on rhinitis patterns (over 2,500 patients and 297,000 days) - the extreme “asthma” and “allergy” phenotypes were confirmed in days (asthma) and patients (rhinitis). These data also suggest that conjunctivitis should be considered as a separate disease in AR or A+AR.

11- There is an extreme allergy phenotype (asthma +AR + Conjunctivitis) with a greater impact on symptoms and work productivity than on the individual diseases.

6- Canonical epidemiology confirming mHealth data

The results of mHealth apps are hypothesis generating and need to be confirmed in classical epidemiologic studies.

6-1- Rhinitis and asthma phenotypes in adolescents and adults

The extreme allergy phenotype was not clearly identified before the availability of MASK-air® results.^{70,71} In EGEA, a French case-control and family study,⁷² AR and A+AR differed in terms of disease

phenotype and polysensitisation (Table 3).^{70,71} Patients with rhinitis alone displayed fewer sensitisations than those with A+AR. These findings were reproduced in BAMSE (Barn/Children, Allergy/Asthma, Milieu, Stockholm). Overall, A+AR is associated with polysensitisation in Europe,⁷³⁻⁸⁰ New Zealand,⁸¹ Brazil⁸² and China.^{83,84}

Patients monosensitised to cat or dog showed IgE patterns dominated by Fel d 1 (>90%) or Can f 5 (67%).⁸⁵⁻⁸⁷ By contrast, cat- or dog-induced A+AR symptoms were associated with polysensitisation.^{85,86}

6-2- Conjunctivitis is an independent contributing disease to multimorbidity

Differences between AR alone or AR associated with conjunctivitis had already been identified before the MASK-air® study.^{70,88} However, new studies following MASK-air® data have shown that ocular symptoms (i) are more common in A+AR than in rhinitis alone,⁸⁹ (ii) are associated with the severity of nasal symptoms^{76,90} and (iii) are important to consider in severe asthma.⁹⁰ In EGEA⁷¹ and a Danish cohort,⁹¹ patients with rhinitis alone had fewer IgE sensitisations than those with rhinitis and conjunctivitis, independently of asthma.

6-3- Number of allergic multimorbidities

The risk of adult-onset asthma increases with the number of allergic multimorbidities and decreases with age.⁷⁹ Severe asthma is associated with multimorbidity.⁹²

12- Rhinitis and rhino-conjunctivitis are separate diseases.

13- The extreme allergy phenotype including asthma, conjunctivitis and rhinitis has been confirmed.

14- For all parameters studied, multimorbidity differs from asthma or rhinitis alone.

6-4- Eosinophilic esophagitis

EoE is a late manifestation of the atopic march.⁹³ An extremely high eosinophil group of EoE patients has been described, which interestingly also displays increased allergic multimorbidities.⁹⁴

6-5- Differences between multimorbid and single disease phenotypes

6-5-1- Nasal physiology and reactivity

The nasal reactivity to allergen and nonspecific stimuli (cold air) of people with A+AR may be greater than in rhinitis alone.^{95,96} The capacity of the nose to humidify air may be reduced in A+AR, compared to AR alone.⁹⁷

6-5-2- Age of onset

In the EGEA study, the age of onset^{70,71} of rhinitis or asthma was around 10 years earlier in A+AR than in single diseases.

6-5-3- Parental allergy

An allergic family history was a stronger predictor of A+AR from childhood to adulthood than single allergic entities.^{98,99} Polysensitised children more often have a parental history of allergy than monosensitised ones.¹⁰⁰

6-5-4- Differential influence of puberty

Allergy prevalence in childhood is higher in boys than in girls, but this imbalance changes after puberty. In McDALL, the gender shift at puberty was seen for A+R (allergic or non-allergic) and not for single diseases.¹⁰¹ These data have been confirmed by a meta-analysis¹⁰² and a canonical epidemiologic study showing that girls have fewer allergic multimorbid phenotypes before puberty.¹⁰³

15- Age of onset and parental allergy suggest that multimorbidity behaves differently to rhinitis or asthma alone.

16- The role of sex hormones at puberty is mostly marked by multimorbidity.

17- These data confirm that multimorbidity behaves differently with respect to R or A alone.

6-6- Trajectories of allergic diseases

6.6.1. Development of asthma in rhinitis patients

Allergic rhinitis is strongly associated with the risk of asthma.¹⁰⁴ However, few studies have assessed the impact of polysensitisation. Early polysensitisation is associated with allergic multimorbidity in PARIS birth cohort infants.¹⁰⁵ Allergic rhinitis is a predictor for the onset of wheezing in school-age children, independently of IgE sensitisation.¹⁰⁶ In ECRHS, in adults, the 8.8-year cumulative incidence of asthma was 2.2%.¹⁰⁷ Only AR with sensitisation to house dust mite was associated with an increased risk of asthma independently of other allergens, and AR patients with polysensitisation more commonly developed asthma.

6.6.2. Trajectories of IgE sensitisation

Trajectories of IgE sensitisation from infancy to childhood show an increase of polysensitisation.^{48,108-110} However, once the disease is fully established (adolescents), IgE sensitisation remains stable, as do the sensitisation clusters.¹¹¹

18- Although rhinitis is strongly associated with the risk of asthma, the role of polysensitisation requires further studies.

19- Sensitisation does not usually change when established in adolescents, suggesting a stable phenotype.

7- OMICs focusing on allergic multimorbidities and polysensitisation

7-1- Computational analysis of allergic multimorbidity

Multimorbidity mechanisms were investigated at a molecular level by identifying proteins and cellular processes using data mining with an *in silico* analysis of the topology of the human interactome.^{112,113} A+R+AD share a larger number of associated proteins than expected by chance, with a significant degree of interconnectedness in the interaction network. In eosinophils, T2-signalling pathways represent a relevant multimorbidity mechanism including IL-4 and TSLP (thymic stromal lymphopoietin) as well as IL1R1- and GATA3-related pathways. In non-eosinophilic cell types,¹¹³ *IL-13*, *LRRC32/C11orf30* and *PLA2G7* were associated with A+AR+AD. However, in eosinophils and non-eosinophilic cell types, *IL-33* was associated with asthma and AD but not with AR alone.

7-2- IL-33, a cornerstone of multimorbid allergic diseases

To our knowledge, before MeDALL, no study had ever assessed the genomics of allergic diseases using the multimorbid approach, although some had combined asthma and rhinitis in their analyses.¹¹⁴⁻¹¹⁷

In MeDALL, an integrated transcriptomic analysis in peripheral blood was conducted in 786 children from three European birth cohorts.¹¹⁸ Fifty-four genes were differentially expressed in allergic diseases, 27 associated to rhinitis alone and none to asthma or AD alone. Eight genes were retrieved in multimorbidity. Eosinophil-associated genes were highly expressed in A+AR+AD. RT-qPCR validated transcriptomic data. A replication phase using data from an independent cohort (EVA-PR, n = 447)^{119,120} and RNA-Sequencing confirmed the MeDALL study. A signature of eight genes (*IL5/JAK/STAT* and *IL33/ST2/IRAK/TRAF*¹²¹) was identified in A+R+AD.

20- Three methods (transcriptomics, RT-PCR and RNA sequencing) yielded the same results in 2 different cohorts (MeDALL and EVA-PR): Multimorbidity is associated with 7 genes of T2 signalling: *IL-5* (eosinophils) and *IL-33* (polysensitisation and eosinophilia).

21- 27 genes were identified for R alone.

22- No specific genes could be identified in A or AD alone in MeDALL (children and adolescents).

7.3. Rhinitis alone is not directly associated with T2 but with IL-17 and several TLR pathways

In the MeDALL gene expression study, participants with rhinitis alone did not express genes associated to multimorbidity, but 27 rhinitis-only genes.¹¹⁸ Functional analysis on these genes (using OmicsNet), considering the presence of miRNAs and other non-protein-coding genes, found that they are mostly

related to Toll-like receptor (TLR)-mediated signalling pathways, IL-17 and MyD88 (myeloid differentiation primary response gene 88) ¹²² pathways (Figure 2).

23- Rhinitis-specific genes have been identified. These genes are mostly associated with TLR signalling pathways and IL-17.

7-4- Genetic polymorphisms

A total of 267 asthma- and/or AR-associated loci were found from 31 GWAS studies and 170 protein coding GWAS-level risk genes. ¹²³

IL33 /*IL1RL1*, *TSLP*, *IL-13-RAD50*, *C11orf30/LRRC32* and genes of allergic sensitisation appear to be important for A+AR. ^{124,125} The *C11orf30-LRRC32* region is involved in the regulation of IgE, ¹²⁶ polysensitisation, ¹²⁷ eosinophilic inflammation ¹²⁸ and A+AR. ^{129,130} *TSLP* is associated with A+AR in children. ¹³¹ However, *IL-33* is not associated with rhinitis alone. ¹³⁰ *TSLP*, *C11orf30/LRRC32*, *IL33* and *IL1RL1* are also genetically linked to EoE. ¹³²⁻¹³⁴

The 17q12-21 locus includes several genes linked to asthma susceptibility ¹³⁵ and wheezing trajectories ^{136,137}, but not to AR alone (e.g., ORM1 (yeast)-like protein 3 ¹³⁸ and gasdermin B (*GSDMB*)). ^{139,140}

Several loci were identified in AR but not in asthma. ¹⁴¹ Among them were the T allele of rs7927894, a common variant on chromosome 11q13.5, ¹⁴² and *IL7R*. ¹⁴³ T- and B-cell receptors for cellular activation by *TSLP* ^{130,143} or *TYRO3* can regulate TLR signalling. ¹⁴⁴

24- Genetic polymorphism studies support the multimorbidity results.

7-5- HLA associations with allergen sensitisation

HLA genes are involved in the control of the IgE response to allergens, ^{145,146} but genetic regulation may differ in mono- and polysensitised patients. Associations between HLA haplotypes or HLA-DQ/DR molecules and allergen sensitivity were confirmed only in low IgE responders (low total serum IgE levels or monosensitised). ¹⁴⁷⁻¹⁵²

In EGEA, ¹⁵³ most significant associations between HLA class-II alleles and IgE sensitisation were observed for pollens. Some HLA class-II alleles were associated with sensitisation to allergens from different families, suggesting that some alleles may favour the development of polysensitisation above cross-reacting allergens.

In food allergy, among the 10 HLA risk alleles associated with peanut allergy, 3 were significantly but weakly associated with asthma, 3 with AR and one with A+AR. ¹⁵⁴

25- The association between HLA class II alleles and allergens is stronger in low IgE responders.

26- A novel pathway of polysensitisation was proposed by EGEA, suggesting that the same HLA class II allele may be associated with different allergen families.

7-6- Epigenetics in multimorbidity

In MeDALL, DNA methylation signatures were studied in blood in childhood asthma.¹⁵⁵ Using a discovery and replication approach in around 5,000 children, 14 CpGs across several chromosomes were strongly associated with asthma. They were linked to eosinophils and cytotoxic T-cell activation. Twenty-one CpGs were differentially methylated and shared between A+AR+AD. None of them were associated with single disease (A, AR or AD).¹⁵⁶ One of the top genes, *ACOT7* (Acyl-CoA Thioesterase 7), has been linked to allergic sensitisation.^{157,158} In nasal brushed cells in childhood, strong DNA-methylation signatures were shared by the A+R phenotype,¹⁵⁹ confirming previous findings in blood. Defective epithelial barriers in the bronchus are epigenetically regulated and are an outcome of the T2 immunity, particularly IL-13.⁶⁵ Increased histone deacetylase activity causes defective epithelial barriers.⁶⁴

A differentially methylated CpG site was found within the melatonin receptor 1A (*MTNR1A*) gene, mediating the effect of a paternally-transmitted genetic variant on A+AR.¹⁶⁰

To our knowledge, multimorbidity has not been addressed in other epigenetic studies. Also, gene-environment interaction effects, including multi-omics analyses, should be considered in allergic multimorbidity.¹⁶¹

27- There are shared epigenetic patterns of allergic multimorbidities.

8- Therapeutic impact on multimorbidity

In the French general population epidemiologic study Constances, participants with A+R had more severe symptoms than those with rhinitis alone.¹⁶² Moreover, they more often reported a treatment with intranasal corticosteroids and oral antihistamines associated with poor control.¹⁶³ In MASK-air, a co-medication pattern was associated with a poorer rhinitis control than in monotherapy.^{164,165} In the combined symptom-medication score, the distinction between rhinitis and A+R was clear with large effect sizes (submitted).

28- Patients with rhinitis and asthma used more co-medication for rhinitis than those with rhinitis alone. Comedication is associated with uncontrolled rhinitis.

29- These findings were observed in a general population cohort.

30- These findings were reproduced in two direct patient mHealth studies, one assessing rhinitis and the other asthma.

9- Phenotypes and trajectories of IgE-mediated diseases across the life cycle: the ARIA-MeDALL hypothesis

As proposed in MeDALL, seven trajectories of allergic disease may be hypothesised (Figure 3).¹⁹ An eighth one has been added to the initial paper.

9-1-The atopic march: persistence of T2 signalling at birth

In the small proportion of infants following the atopic march, a persistence of the foetal T2 signalling may be proposed.¹⁶⁶ IL-33 and IL-9, often associated with early atopic sensitisation, are upregulated in AD infants.¹⁶⁷

9-2- Early sensitisation with very high allergen exposure

High levels of neonatal birch pollen exposure were found to induce birch pollen allergy in some¹⁶⁸⁻¹⁷¹ but not all studies.¹⁷² The effect was also reported with other allergens.¹⁷¹ The window of allergic risk may be around 3 months after birth.

9-3- Re-occurrence or expansion of T2 signalling in early childhood

The re-occurrence or expansion of T2 signalling may be associated with several mechanisms in which IL-33 appears to play a significant role (Figure 4). Many new chemicals and air pollutants can disrupt the epithelial barriers.⁶⁶

Air pollutants: Diesel Exhaust Particles (DEPs) may increase allergy prevalence,¹⁷³ particularly through IL-33.¹⁷⁴ In nasal biopsies, air pollution-related particulate matter (PM) acts on epithelial barrier function and epithelial barrier tight junction (TJ) and can lead to GM-CSF and IL-33 responses.¹⁷⁵

Viruses. The neonatal lung immune system is functionally immature and the T1/T2 imbalance may predispose rhinovirus-infected neonates to a later asthma development.^{176,177} Rhinovirus C infection induces innate lymphoid cells type 2 (ILC2) expansion and eosinophilic airway inflammation.¹⁷⁸ Influenza A can break tolerance to inhaled allergens and lead to an asthma phenotype in adulthood. IL-33¹⁷⁹⁻¹⁸¹ as well as IL-17¹⁸² can be involved.

Skin barrier dysfunction predisposes to epicutaneous sensitisation to food and aeroallergens.¹⁸³⁻¹⁸⁶ The role of IL-33 is now emerging in skin barrier dysfunction.^{183 187} *S. aureus* is the dominant infective

trigger of AD¹⁸⁸ and its sensitisation may lead to multimorbidity and polysensitisation in adolescence¹⁸⁹ through IL-33.¹⁹⁰

House dust mites. The non IgE-mediated effect of several house dust mite allergens (in addition to the well-known proteases) on the respiratory epithelium induces the production of IL-33.¹⁹¹

9-4- Onset of rhinitis alone

Rhinitis alone is not associated with T2 genes but to rhinitis-specific genes often associated with TLRs and IL-17. Allergens can activate TLRs which in turn activate ILC2 through the myeloid differentiation primary response gene 88 (MyD88) pathways.¹⁹² Few allergens are recognised in these patients, suggesting a specific response to allergens in line with an MHC Class II allergen-specific sensitisation.

9-5- Puberty

In asthmatic patients, blood ILC2 number is increased in women compared to men.¹⁹³ Androgens negatively regulate ILC2 homeostasis, limiting their capacity to expand in response to IL-33.¹⁹⁴ Estrogen signalling increases allergen-induced IL-33 release, ILC2 cytokine production and airway inflammation.¹⁹⁵ Androgen receptor signalling reduces IL-33 release from bronchial epithelial cells, suggesting a negative regulator of allergic airway inflammation. These two mechanisms may explain the post-pubertal female predilection of multimorbidity.¹⁹⁶

9-6- Rhinitis and asthma alone in adults

Allergic diseases can develop in adults. IgE sensitisation may also be associated with co-factors such as DEP.¹⁹⁷ This is the case for tree pollens (cypress,^{26,198} birch¹⁹⁹) or new pollens (ragweed in Northern Italy).¹⁹⁹ There is not usually any family history.^{25,200} In pollen allergy (e.g., cypress), adults were usually monosensitised and often suffered from rhinitis alone.^{25,200} However, newer studies in the same area suggest that adults become polysensitised and suffered from asthma.²⁰¹ In soybean allergy, patients had severe exacerbations of asthma,²⁰² possibly associated with mast cell activation.²⁰³ The association observed for the *DRB1*13* gene was stronger in individuals with low total IgE.¹⁵⁰

9-7- Chronic rhinosinusitis with nasal polyposis (CRSwNP) and late-onset asthma associated with polyclonal IgE response due to *Staphylococcus aureus*

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is well characterised by T2 inflammation and eosinophilia in Western countries. However, neutrophils appear to participate in the inflammation with eosinophils.^{204,205} Many patients with late-onset asthma have co-existing CRS with/without demonstrable allergic sensitisation²⁰⁶ and high total IgE levels. IgE expression is mostly polyclonal, with specific IgE to inhalant allergens low or below detection levels.^{207,208} *S. aureus* enterotoxin-IgE is

associated with severe asthma.²⁰⁹ *S. aureus* manipulates airway mucosal immunology at various levels,²¹⁰ but IL-33 release from the respiratory epithelium and the activation of ILC2 *via* its receptor ST2 represent a major mechanism.²¹¹ IL-17 has also been implicated in CRS.^{205,212} In a recent Chinese cluster analysis in a relatively small sample, (i) IL-33, IL-5 and, to a lesser extent, IL-17 have been implicated in patients with nasal polyposis and uncontrolled asthma and (ii) IL-17 but not IL-33 or IL-5 have been implicated in patients without nasal polyps and partly-controlled asthma.²¹³

9-8- NSAID-exacerbated respiratory disease (N-ERD)

N-ERD usually includes a triad of CRSwNP, asthma and hypersensitivity to aspirin and/or other NSAIDs. N-ERD is a complex inflammatory disorder largely driven by the innate immune system with a cellular dysregulation involving eosinophils, basophils, mast cells and ILC2. N-ERD may be a self-perpetuating vicious circle in which mediators are produced by a differentiated activated epithelial layer, such as IL-25, IL-33 and TSLP.²¹⁴

10- “One-airway-one-disease” disentangled, refined and beyond

Although many pathways may be involved in differentiating rhinitis alone versus A+AR, we focused our hypothesis around the first signals that are involved when people encounter allergens.

10-1- Rhinitis alone and rhinitis + asthma multimorbidity represent two distinct diseases

Clinical data, epidemiologic studies, mHealth-based studies and genomic approaches confirm the existence of two distinct diseases: Rhinitis alone and Rhinitis + Asthma (**disentangling**). However, both diseases need to be **refined** as conjunctivitis and (in children) food allergy and AD may be considered as independent multimorbidities. Thus, the concept “**multimorbid allergic disease**” is more appropriate than “one-airway-one-disease”. In a meta-analysis, AD was strongly associated with allergic and non-allergic rhinitis but not with rhinitis and asthma.²¹⁵ Asthma alone may also be associated with non-T2 mechanisms that are not considered in this paper.

10-2- Multimorbidity: Systemic disease associated with MyD88-dependent IL-33 signalling

Different mechanisms for polysensitisation probably exist including T-cell superantigens of *S aureus* enterotoxin B (SEB).²¹⁶ *S aureus* skin infection in infants and children is associated with a prominent and clinically-relevant IgE response against food and inhalant allergens¹⁸⁹ whereas, in adults, *S aureus* nasal infection induces a weak polyclonal response to inhalant allergens with little or no clinical

relevance.²⁰⁹ *S. aureus* can directly induce IL-33, TSLP, IL-5 and IL-13 in nasal polyp tissue but not in healthy inferior turbinate tissue.²¹⁷ A Staphylococcus-dominant microbiome in the first 6 months of life was associated with increased risk of asthma and early onset of allergic sensitisation.²¹⁸

Atopic dermatitis lesional skin has a defective skin barrier and a T2-dominated local immune response with an increased expression of IL-33, TSLP and IL-25.²¹⁹ Skin inflammatory molecules, such as eosinophil peroxidase, can promote sensitisation to bystander antigens²²⁰ and therefore lead to polysensitisation.

Allergens, viruses and pollutants can directly elaborate TSLP, IL-25 and IL-33 from the lungs.²²¹ On the other hand, rhinoviruses probably act differently, inducing IL-33 release from nasal epithelium,^{222,223} but they are not superantigens. IL-33 activates dendritic cells during antigen presentation²²¹ and drives a T2 response.

10-3- Allergic rhinitis alone: Local disease associated with TLR signalling and IL-17

In MeDALL, several TLR-associated pathways dependent on MyD88 have been found. IL-17 was closely associated with TLRs and MyD88 and is likely to play a role.

The nasal epithelium expresses all known TLRs.²²⁴ Variations in the 10 TLR genes have been associated with AR in several candidate gene studies and three large GWASs. A significant excess of rare variants in rhinitis patients was detected in *TLR1*, *TLR5*, *TLR7*, *TLR9* and *TLR10*²²⁵ but not in *TLR8*.²²⁶ Children carrying a minor rs1927911 (*TLR4*) allele may be at a higher AR risk.²²⁷

The number of neutrophils increases in the nose during the allergy season and there is a large absolute cell number in comparison with eosinophils.²²⁸ In a cluster study in children with rhinitis monosensitised to grass pollen, one of the 3 clusters was associated with IL-17, neutrophilia and intermediate levels of eosinophils.²²⁹

IL-23 is implicated in airway inflammation mediated by T2 and T17 cytokines. Anti-IL-23 monoclonal antibody does not improve severe asthma.²³⁰ Possibly, the T17 pathways are less prominent in the asthma paradigm, but more related to rhinitis.

10-4-The microbiome at the centre of the interplay between IL-17 and IL-33

An Amish environment protects against asthma by shaping the innate immune response in which MyD88 plays a central role.²³¹ Early-life exposures to TLR-enriched environments in farms protect against the development of IgE-mediated diseases,¹⁷¹ including eosinophilic asthma.^{232,233}

In the Karelia study of allergy in school children, sensitisation in Russia is mostly associated with monosensitisation (e.g., *Dermatophagoides*) without clinical symptoms.²³⁴ In Finland, polysensitisation is common with a high occurrence of symptoms.²⁴² Birch pollen allergy is 10 times more common in Finland than in Russia, where food allergy is also rare. The genotype differences between the Finnish and Russian populations did not explain the allergy gap.²³⁵ The network of skin and nasal microbiota and gene expression was richer and more diverse in the Russian subjects.^{235,236} The microbiota disparity paralleled the gene expression differences. High-total IgE was associated with enhanced anti-viral response in the Finnish subjects. In birch-pollen-allergic subjects, the activated innate immune networks seem to be partly similar to those activated during viral infections.²³⁷ In Russian teenagers, Long-Non-Coding RNA is upregulated, obviously mediating the gene-environment and gene-microbiota interactions.²³⁸ Furthermore, high *Acinetobacter* abundance in Russians correlated with suppression of innate immune response.²³⁵ Russians are more capable of differentiating between danger and non-danger, and between self and non-self. Overall, the rich gene-microbe network in Russians seems to support a balanced innate immunity and low allergy prevalence.

These studies suggest that protection against multimorbidity may be related to the influence of the microbiome on the immune system.²³⁵ IL-33 interacts with gut and respiratory microbiome but, depending on the physiological context, it may be host-protective or pathogenic.^{239,240} MyD88 is potentially influenced by the microbiome^{122,241-244} and may be an important mechanism explaining distinct diseases. Multimorbidity may be centred around IL-33 and MyD88 (Figure 5). IL-33 and IL1RL1 are among the most highly-replicated susceptibility loci for asthma.²⁴⁵ Other alarmins acting through MyD88 are also potential candidates.

IL-17 expression is limited to barrier surface tissues (intestine, gingiva, conjunctiva, vaginal mucosa, skin). IL-17 is produced at low amounts in response to the beneficial resident microbiota, and induces production of antimicrobial peptides by the epithelium to maintain a healthy bacterial and fungal population.^{246,247} High proteobacterial diversity was connected to low IL-17A level. There is a delicate balance between IL-17 and microbiota. Dysbiosis drives enhanced Th17 activation and IL-17 production to restore the balance. Dysregulation of healthy microbiota populations contributes to the pathogenesis of several chronic inflammatory or autoimmune diseases in part by disrupting the balance of T17 responses in the gut that then influences systemic Th17 activation.^{246,247}

IL-33 is a negative regulator of T17 cell differentiation and inhibits IL-17 protective immunity in the gut.²⁴⁸

Urbanisation in western countries has been associated with changes in the gut microbiome and intestinal diversity reduction.²⁴⁹⁻²⁵³ Before the turn of the 19th century, allergic diseases existed but were uncommon. One of the first cases of rhinitis (with multimorbidity) described in 1819 was in the UK

where industrialisation had started.²⁵⁴ It is possible that, depending on microbiota changes, IL-17 can be protective or harmful (rhinitis alone) or replaced by IL-33 (multimorbidity) in genetically-predisposed individuals exposed to environmental triggers. In the case of ancestral microbiota, IL-17 has a protective role. When microbiota diversity is reduced, a harmful IL-17 predominates and, with a further reduction, IL-33 becomes the predominant pathway (Figure 6). These findings may explain some of the epidemic trends in allergic diseases.

Two studies performed in Montpellier on cypress pollen-allergic patients may support this hypothesis.

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A double-blinded placebo-controlled study showed that daily exposure to microbial biodiversity is associated with immune modulation in children with an increase in IL-10 and a decrease in IL-17 in peripheral blood.²⁵⁵

The ARIA-MeDALL hypothesis

In allergic and airway diseases

- The hypothesis is centred around IL-17, IL-33 and their interactions with the microbiome and co-factors.
- Depending on the genetic background (TLR, IL-33, others), environmental exposure and other (un)defined factors, the relationship between the cytokines and the microbiome differs.
- In ancestral microbiome, IL-17 plays its normal protective function. As an example, short-chain fatty acids present in ancestral microbiome have multiple activities and are potent regulators of IL-17 and IL-33.^{256,257}
- When the complexity of the microbiome decreases, IL-17 becomes pathogenic and interacts with TLRs (local disease) and other mechanisms. In the case of rhinitis, there is a production of IgE to a relatively small number of allergens. It is likely that co-factors (e.g., viral infections) play a role in the onset of the disease. The disease usually occurs after childhood.
- When the complexity of the microbiome decreases further, the IL-33 pathway is activated and, in genetically-susceptible individuals, there is multimorbidity and polysensitisation. This activation may occur just after birth (atopic march) or later in early childhood (re-occurrence of T2 signalling) associated with viruses, *Staphylococcus aureus*, pollutants or non-allergenic components of allergens.
- IL-33 may decrease the IL-17 pathways.

In other noncommunicable diseases and autoimmunity, the hypothesis is similarly centred around IL-17, IL-33 (or other pivotal cytokines) and their interactions with the microbiome.

10-5- Beyond rhinitis and asthma

10-5-1- Eosinophilic esophagitis

Most but not all EoE patients present multimorbid diseases including mainly rhinitis and asthma and, less often, AD.²⁵⁸ An extreme EoE phenotype combines very high eosinophils with allergic multimorbidities and some of the genes found in asthma, rhinitis and AD multimorbidities.⁹⁴

10-5-2- Chronic diseases, auto-immunity and mental health

The IL-33-IL-17 interplay in rhinitis and asthma may be extended to other diseases. IL-17 is a driver of immunopathology in asthma,²⁵⁹ COPD,²⁶⁰ neurodegenerative diseases,²⁶¹ auto-immune diseases²⁶² or infertility.^{263,264} IL-33 has also been involved in some of these diseases, but often in animal models.^{262,267,268}

It is possible that changes in the microbiome are modifying the protective effects of IL-17 or its interaction with IL-33, and that genetic variations of *IL33* or *IL17* genes associated with environmental influences may confer protective or susceptibility risk in the onset of the disease. It would be of major interest to study whether IL-17-associated COPD or asthma are local diseases by comparison to multimorbid COPD or asthma and rhinitis multimorbidity.

10-6- Clinical significance of this novel hypothesis

Combining the data of this hypothesis, rhinitis alone and rhinitis and asthma multimorbidity represent two distinct diseases in terms of genomics, but also with important clinical implications. Overall, patients with rhinitis alone have a better control of nasal symptoms than those with rhinitis and asthma. Moreover, differences in treatment appear to be significant. The impact of conjunctivitis requires further information. These results will need to be embedded in the novel ARIA classification and reflected in the guideline generation.

11- Limitations of the ARIA-MeDALL hypothesis

Several limitations should be considered in the hypothesis. In general, some observations may not fit this hypothesis and more in-depth analysis is required to assess how these observations should be generalised.

Many clinical, epidemiological and mHealth sections are based on the research done by the authors who have been investigating the multimorbidity-polysensitisation concept for decades. Fewer studies on multimorbidity have been carried out by other authors. We have included all of the studies that we came across using an extensive literature search, but a systematic review is required.

Most of the cohort studies have been carried out using questionnaires as this is a standard method. A physician's assessment may be useful in future studies.

Some key studies (e.g., MeDALL) were carried out only on children, and new data need be generated to assess (i) whether the proposed hypothesis can be generalised for adult asthma and rhinitis and (ii) the impact of age as mechanisms may differ between children and adults. Moreover, we focused the

study on T2-asthma, and other endotypes need to be investigated.²⁶⁹ As an example, studies on CRS indicate the presence of T1 or T17 inflammation in a group of patients²⁷⁰⁻²⁷² and studies on asthma propose a role of IL-17 in asthma multimorbidity.²⁷³ However, these multimorbid patterns need to be approached in more detail. We did not investigate non-allergic multimorbidities that increase in prevalence with age²⁷⁴ or the links between chronic obstructive pulmonary disease (COPD) and asthma.²⁷⁵

The hypothesis is based on the microbiome, but other mechanisms are of importance and should be considered. As an example, intestinal mucus layer erosion contributing to barrier disruption by foods, chemicals and other triggers may have a relevant role.^{276,277}

12. Opportunities for research (Table 4)

Conclusions

Based on (i) new insights into polysensitisation and multimorbidity, (ii) advances in mHealth for the definition of novel phenotypes, (iii) confirmation in canonical epidemiologic studies, (iv) genomic findings and (v) therapeutic studies, we propose novel concepts on the onset of rhinitis and multimorbidity. Our main hypothesis is that rhinitis alone and rhinitis and asthma multimorbidity represent two distinct diseases with differences in genetic background, allergen sensitisation patterns, severity of symptoms and treatment response. For mechanistic, biologic, genetic and clinical studies, the two diseases need to be studied separately. The microbiome appears to play a key role in the onset of the two diseases. This study in rhinitis and rhinitis+asthma may be used to understand some of the aspects of the epidemics of chronic and auto-immune diseases. It is clear that other pathways exist. Further research is however required to further explore the solidity of this concept.

References

1. Anto JM, Bousquet J, Akdis M, et al. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol*. 2017;139(2):388-399.
2. Bousquet J, Anto J, Auffray C, et al. MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine. *Allergy*. 2011;66(5):596-604.
3. McHugh T, Levin M, Snidvongs K, Banglawala SM, Sommer DD. Comorbidities associated with eosinophilic chronic rhinosinusitis: A systematic review and meta-analysis. *Clin Otolaryngol*. 2020;45(4):574-583.
4. Niespodziana K, Borochova K, Pazderova P, et al. Towards personalization of asthma treatment according to trigger factors. *J Allergy Clin Immunol*. 2020.
5. Ramakrishnan RK, Al Heialy S, Hamid Q. Role of IL-17 in asthma pathogenesis and its implications for the clinic. *Expert Rev Respir Med*. 2019;13(11):1057-1068.
6. Hofmann MA, Fluhr JW, Ruwwe-Glosenkamp C, Stevanovic K, Bergmann KC, Zuberbier T. Role of IL-17 in atopy-A systematic review. *Clin Transl Allergy*. 2021;11(6):e12047.
7. Renert-Yuval Y, Thyssen JP, Bissonnette R, et al. Biomarkers in atopic dermatitis-a review on behalf of the International Eczema Council. *J Allergy Clin Immunol*. 2021;147(4):1174-1190 e1171.
8. Bousquet J, Chanez P, Campbell AM, et al. Inflammatory processes in asthma. *Int Arch Allergy Appl Immunol*. 1991;94(1-4):227-232.
9. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
10. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147-334.
11. Custovic A, Custovic D, Kljajic Bukvic B, Fontanella S, Haider S. Atopic phenotypes and their implication in the atopic march. *Expert Rev Clin Immunol*. 2020;16(9):873-881.
12. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002;347(12):911-920.
13. Cohen S, Berkman N, Picard E, et al. Co-morbidities and cognitive status in a cohort of teenagers with asthma. *Pediatr Pulmonol*. 2016;51(9):901-907.
14. Tonacci A, Pioggia G, Gangemi S. Autism spectrum disorders and atopic dermatitis: a new perspective from country-based prevalence data. *Clin Mol Allergy*. 2021;19(1):27.
15. Trubetskov V, Pardinas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*. 2022;604(7906):502-508.
16. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol*. 1999;104(3 Pt 1):534-540.
17. 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.
18. Harrison C, Fortin M, van den Akker M, et al. Comorbidity versus multimorbidity: Why it matters. *J Comorb*. 2021;11:2633556521993993.
19. 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.
20. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic Rhinosinusitis with Nasal Polyps and Asthma. *J Allergy Clin Immunol Pract*. 2021;9(3):1133-1141.
21. Bousquet J, Coulomb Y, Arrendal H, Robinet-Levy M, Michel FB. Total serum IgE concentrations in adolescents and adults using the phadebas IgE PRIST technique. *Allergy*. 1982;37(6):397-406.
22. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol*. 1991;88(1):43-53.
23. Bousquet J, Hejjaoui A, Becker WM, et al. Clinical and immunologic reactivity of patients allergic to grass pollens and to multiple pollen species. I. Clinical and immunologic characteristics. *J Allergy Clin Immunol*. 1991;87(3):737-746.
24. Pene J, Rivier A, Lagier B, Becker WM, Michel FB, Bousquet J. Differences in IL-4 release by PBMC are related with heterogeneity of atopy. *Immunology*. 1994;81(1):58-64.

25. Reid MJ, Schwietz LA, Whisman BA, Moss RB. Mountain cedar pollinosis: can it occur in non-atopics? *N Engl Reg Allergy Proc.* 1988;9(3):225-232.
26. Bousquet J, Knani J, Hejjaoui A, et al. Heterogeneity of atopy. I. Clinical and immunologic characteristics of patients allergic to cypress pollen. *Allergy.* 1993;48(3):183-188.
27. Guerra S, Allegra L, Blasi F, Cottini M. Age at symptom onset and distribution by sex and symptoms in patients sensitized to different allergens. *Allergy.* 1998;53(9):863-869.
28. Rosen FL. Hay fever and asthma following maximum exposure to ragweed. *J Am Med Assoc.* 1946;132(14):854.
29. Frankland AW, Gorrill RH. Summer hay-fever and asthma treated with antihistaminic drugs. *Br Med J.* 1953;1(4813):761-764.
30. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: An independent risk factor for asthma in nonatopic subjects: Results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol.* 1999;301-304.
31. Anto JM, Sunyer J, Basagana X, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy.* 2010;65(8):1021-1030.
32. Chanez P, Vignola AM, Vic P, et al. Comparison between nasal and bronchial inflammation in asthmatic and control subjects. *Am J Respir Crit Care Med.* 1999;159(2):588-595.
33. Gaga M, Lambrou P, Papageorgiou N, et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis [In Process Citation]. *Clin Exp Allergy.* 2000;30(5):663-669.
34. Braunstahl GJ, Fokkens WJ, Overbeek SE, Kleinjan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy.* 2003;33(5):579-587.
35. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med.* 2000;161(6):2051-2057.
36. Braunstahl GJ, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med.* 2001;164(5):858-865.
37. Togias A, Gergen PJ, Hu JW, et al. Rhinitis in children and adolescents with asthma: Ubiquitous, difficult to control, and associated with asthma outcomes. *J Allergy Clin Immunol.* 2019;143(3):1003-1011 e1010.
38. Cruz AA, Popov T, Pawankar R, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy.* 2007;62 Suppl 84:1-41.
39. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitized and non-IgE-sensitized children in MeDALL: a population-based cohort study. *Lancet Respir Med.* 2014;2(2):131-140.
40. Garcia-Aymerich J, Benet M, Saeys Y, et al. Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. *Allergy.* 2015;70(8):973-984.
41. Bousquet J, Anto JM, Just J, Keil T, Siroux V, Wickman M. The multimorbid polysensitized phenotype is associated with the severity of allergic diseases. *J Allergy Clin Immunol.* 2017.
42. Fontanella S, Frainay C, Murray CS, Simpson A, Custovic A. Machine learning to identify pairwise interactions between specific IgE antibodies and their association with asthma: A cross-sectional analysis within a population-based birth cohort. *PLoS Med.* 2018;15(11):e1002691.
43. Zoratti EM, Krouse RZ, Babineau DC, et al. Asthma phenotypes in inner-city children. *J Allergy Clin Immunol.* 2016;138(4):1016-1029.
44. Liu AH, Babineau DC, Krouse RZ, et al. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. *J Allergy Clin Immunol.* 2016;138(4):1042-1050.
45. Pongracic JA, Krouse RZ, Babineau DC, et al. Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. *J Allergy Clin Immunol.* 2016;138(4):1030-1041.
46. Barber D, Diaz-Perales A, Escribese MM, et al. Molecular allergology and its impact in specific allergy diagnosis and therapy. *Allergy.* 2021;76(12):3642-3658.
47. Blazowski L, Majak P, Kurzawa R, Kuna P, Jerzynska J. Food allergy endotype with high risk of severe anaphylaxis in children-Monosensitization to cashew 2S albumin Ana o 3. *Allergy.* 2019;74(10):1945-1955.

48. Asarnoj A, Hamsten C, Lupinek C, et al. Prediction of peanut allergy in adolescence by early childhood storage protein-specific IgE signatures: The BAMSE population-based birth cohort. *J Allergy Clin Immunol*. 2017.
49. Gupta RS, Warren CM, Smith BM, et al. Prevalence and Severity of Food Allergies Among US Adults. *JAMA Netw Open*. 2019;2(1):e185630.
50. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. *J Allergy Clin Immunol Pract*. 2020;8(6):1854-1864.
51. Jimenez-Saiz R, Chu DK, Mandur TS, et al. Lifelong memory responses perpetuate humoral TH2 immunity and anaphylaxis in food allergy. *J Allergy Clin Immunol*. 2017;140(6):1604-1615 e1605.
52. Davidson WF, Leung DYM, Beck LA, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "Atopic dermatitis and the atopic march: Mechanisms and interventions". *J Allergy Clin Immunol*. 2019;143(3):894-913.
53. Puneekar YS, Sheikh A. Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database. *Clin Exp Allergy*. 2009;39(12):1889-1895.
54. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. *Front Immunol*. 2020;11:1907.
55. Nakamura T, Haider S, Fontanella S, Murray CS, Simpson A, Custovic A. Modelling trajectories of parentally reported and physician-confirmed atopic dermatitis in a birth cohort study. *Br J Dermatol*. 2022;186(2):274-284.
56. Dharma C, Lefebvre DL, Tran MM, et al. Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: Effects on allergic diseases. *Clin Exp Allergy*. 2018;48(1):48-59.
57. Akdis CA. Does the epithelial barrier hypothesis explain the rise in allergy, autoimmunity and other chronic conditions? *Nature Reviews Immunology* doi: 101038/s41577-021-00538-7. 2021.
58. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time Trends in the Incidence of Parkinson Disease. *JAMA Neurol*. 2016;73(8):981-989.
59. Frye RE. Introduction to Part 1. *Semin Pediatr Neurol*. 2020;34:100802.
60. Chiarotti F, Venerosi A. Epidemiology of Autism Spectrum Disorders: A Review of Worldwide Prevalence Estimates Since 2014. *Brain Sci*. 2020;10(5).
61. Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. *J Affect Disord*. 2012;140(3):205-214.
62. Akdis CA, Arkwright PD, Bruggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy*. 2020;75(7):1582-1605.
63. Yang R, Tan M, Xu J, Zhao X. Investigating the regulatory role of ORMDL3 in airway barrier dysfunction using in vivo and in vitro models. *Int J Mol Med*. 2019;44(2):535-548.
64. Steelant B, Wawrzyniak P, Martens K, et al. Blocking histone deacetylase activity as a novel target for epithelial barrier defects in patients with allergic rhinitis. *J Allergy Clin Immunol*. 2019;144(5):1242-1253 e1247.
65. Wawrzyniak P, Krawczyk K, Acharya S, et al. Inhibition of CpG methylation improves the barrier integrity of bronchial epithelial cells in asthma. *Allergy*. 2021;76(6):1864-1868.
66. Celebi-Sozener Z, Ozdel-Ozturk B, Cerci P, et al. Epithelial barrier hypothesis: Effect of the external exposome on the microbiome and epithelial barriers in allergic disease. *Allergy*. 2021;77:1418-1449.
67. Anto A, Sousa-Pinto B, Czarlewski W, et al. Automatic market research of mobile health apps for the self-management of allergic rhinitis. *Clin Exp Allergy*. 2022;in press.
68. Bousquet J, Anto JM, Bachert C, et al. ARIA digital anamorphosis: Digital transformation of health and care in airway diseases from research to practice. *Allergy*. 2021;76(1):168-190.
69. Bousquet J, Devillier P, Anto JM, et al. Daily allergic multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study. *Allergy*. 2018;73(8):1622-1631.
70. 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.
71. 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.
72. Kauffmann F, Dizier MH, Annesi-Maesano I, et al. EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy)-- descriptive characteristics. *Clin Exp Allergy*. 1999;29 Suppl 4:17-21.

73. Filiou A, Holmdahl I, Asarnej A, et al. Development of Sensitization to Multiple Allergen Molecules from Preschool to School Age Is Related to Asthma. *Int Arch Allergy Immunol*. 2022;1-12.
74. Blondal V, Malinovschi A, Sundbom F, et al. Multimorbidity in asthma, association with allergy, inflammatory markers and symptom burden, results from the Swedish GA(2) LEN study. *Clin Exp Allergy*. 2021;51(2):262-272.
75. Schoos AM, Jelding-Dannemand E, Stokholm J, Bonnelykke K, Bisgaard H, Chawes BL. Single and multiple time-point allergic sensitization during childhood and risk of asthma by age 13. *Pediatr Allergy Immunol*. 2019;30(7):716-723.
76. Raciborski F, Bousquet J, Bousquet J, et al. Dissociating polysensitization and multimorbidity in children and adults from a Polish general population cohort. *Clin Transl Allergy*. 2019;9:4.
77. Schmidt F, Hose AJ, Mueller-Rompa S, et al. Development of atopic sensitization in Finnish and Estonian children: A latent class analysis in a multicenter cohort. *J Allergy Clin Immunol*. 2019;143(5):1904-1913 e1909.
78. Hose AJ, Depner M, Illi S, et al. Latent class analysis reveals clinically relevant atopy phenotypes in 2 birth cohorts. *J Allergy Clin Immunol*. 2017;139(6):1935-1945 e1912.
79. Toppila-Salmi S, Chanoine S, Karjalainen J, Pekkanen J, Bousquet J, Siroux V. Risk of adult-onset asthma increases with the number of allergic multimorbidities and decreases with age. *Allergy*. 2019;74(12):2406-2416.
80. Bengtsson C, Lindberg E, Jonsson L, et al. Chronic Rhinosinusitis Impairs Sleep Quality: Results of the GA2LEN Study. *Sleep*. 2017;40(1).
81. Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood. I. Gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy*. 1993;23(11):941-948.
82. Aranda CS, Cocco RR, Pierotti FF, et al. Allergic sensitization pattern of patients in Brazil. *J Pediatr (Rio J)*. 2021;97(4):387-395.
83. Zhang W, Xie B, Liu M, Wang Y. Associations between sensitisation to allergens and allergic diseases: a hospital-based case-control study in China. *BMJ Open*. 2022;12(2):e050047.
84. Gao Z, Fu WY, Sun Y, et al. Artemisia pollen allergy in China: Component-resolved diagnosis reveals allergic asthma patients have significant multiple allergen sensitization. *Allergy*. 2019;74(2):284-293.
85. Nwaru BI, Suzuki S, Ekerljung L, et al. Furry Animal Allergen Component Sensitization and Clinical Outcomes in Adult Asthma and Rhinitis. *J Allergy Clin Immunol Pract*. 2019;7(4):1230-1238 e1234.
86. Suzuki S, Nwaru BI, Ekerljung L, et al. Characterization of sensitization to furry animal allergen components in an adult population. *Clin Exp Allergy*. 2019;49(4):495-505.
87. Hemmer W, Sestak-Greinecker G, Braunsteiner T, Wantke F, Wohrl S. Molecular sensitization patterns in animal allergy: Relationship with clinical relevance and pet ownership. *Allergy*. 2021;76(12):3687-3696.
88. Cibella F, Ferrante G, Cuttitta G, et al. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res*. 2015;7(1):44-50.
89. Siroux V, Boudier A, Nadif R, Lupinek C, Valenta R, Bousquet J. Association between asthma, rhinitis, and conjunctivitis multimorbidities with molecular IgE sensitization in adults. *Allergy*. 2019;74(4):824-827.
90. Amaral R, Bousquet J, Pereira AM, et al. Disentangling the heterogeneity of allergic respiratory diseases by latent class analysis reveals novel phenotypes. *Allergy*. 2019;74(4):698-708.
91. Mikkelsen S, Dinh KM, Boldsen JK, et al. Combinations of self-reported rhinitis, conjunctivitis, and asthma predicts IgE sensitization in more than 25,000 Danes. *Clin Transl Allergy*. 2021;11(1):e12013.
92. Toppila-Salmi S, Lemmetyinen R, Chanoine S, et al. Risk factors for severe adult-onset asthma: a multi-factor approach. *BMC Pulm Med*. 2021;21(1):214.
93. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. *J Allergy Clin Immunol Pract*. 2018;6(5):1528-1533.
94. O'Shea KM, Rochman M, Shoda T, Zimmermann N, Caldwell J, Rothenberg ME. Eosinophilic esophagitis with extremely high esophageal eosinophil counts. *J Allergy Clin Immunol*. 2021;147(1):409-412 e405.
95. Corren J. The rhinitis-asthma link revisited. *Ann Allergy Asthma Immunol*. 2005;94(3):311-312.

96. Hanes LS, Issa E, Proud D, Togias A. Stronger nasal responsiveness to cold air in individuals with rhinitis and asthma, compared with rhinitis alone. *Clin Exp Allergy*. 2006;36(1):26-31.
97. Assanasen P, Baroody FM, Naureckas E, Naclerio RM. Hot, humid air increases cellular influx during the late-phase response to nasal challenge with antigen. *Clin Exp Allergy*. 2001;31(12):1913-1922.
98. Lau S, Matricardi PM, Wahn U, Lee YA, Keil T. Allergy and atopy from infancy to adulthood: Messages from the German birth cohort MAS. *Ann Allergy Asthma Immunol*. 2018.
99. 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.
100. Kang H, Yu J, Yoo Y, Kim DK, Koh YY. Coincidence of atopy profile in terms of monosensitization and polysensitization in children and their parents. *Allergy*. 2005;60(8):1029-1033.
101. Keller T, Hohmann C, Standl M, et al. The sex-shift in single disease and multimorbid asthma and rhinitis during puberty - a study by MeDALL. *Allergy*. 2018;73(3):602-614.
102. Frohlich M, Pinart M, Keller T, et al. Is there a sex-shift in prevalence of allergic rhinitis and comorbid asthma from childhood to adulthood? A meta-analysis. *Clin Transl Allergy*. 2017;7:44.
103. Rosario CS, Cardozo CA, Neto HJC, Filho NAR. Do gender and puberty influence allergic diseases? *Allergol Immunopathol (Madr)*. 2021;49(2):122-125.
104. Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. *World Allergy Organ J*. 2019;12(10):100069.
105. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitisation is associated to allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol*. 2016.
106. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126(6):1170-1175 e1172.
107. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008;372(9643):1049-1057.
108. Asarnoj A, Hamsten C, Waden K, et al. Sensitization to cat and dog allergen molecules in childhood and prediction of symptoms of cat and dog allergy in adolescence: A BAMSE/MeDALL study. *J Allergy Clin Immunol*. 2016;137(3):813-821 e817.
109. Ballardini N, Bergstrom A, Wahlgren CF, et al. IgE antibodies in relation to prevalence and multimorbidity of eczema, asthma, and rhinitis from birth to adolescence. *Allergy*. 2016;71(3):342-349.
110. Wickman M, Lupinek C, Andersson N, et al. Detection of IgE Reactivity to a Handful of Allergen Molecules in Early Childhood Predicts Respiratory Allergy in Adolescence. *EBioMedicine*. 2017;26:91-99.
111. Siroux V, Boudier A, Bousquet J, et al. Trajectories of IgE sensitization to allergen molecules from childhood to adulthood and respiratory health in the EGEA cohort. *Allergy*. 2022;77(2):609-618.
112. Aguilar D, Pinart M, Koppelman GH, et al. Computational analysis of multimorbidity between asthma, eczema and rhinitis. *PLoS One*. 2017;12(6):e0179125.
113. Aguilar D, Lemonnier N, Koppelman GH, et al. Understanding allergic multimorbidity within the non-eosinophilic interactome. *PLoS One*. 2019;14(11):e0224448.
114. Dizier MH, Bouzigon E, Guilloud-Bataille M, et al. Genome screen in the French EGEA study: detection of linked regions shared or not shared by allergic rhinitis and asthma. *Genes Immun*. 2005;6(2):95-102.
115. Dizier MH, Bouzigon E, Guilloud-Bataille M, et al. Evidence for a Locus in 1p31 Region Specifically Linked to the Co-Morbidity of Asthma and Allergic Rhinitis in the EGEA Study. *Hum Hered*. 2007;63(3-4):162-167.
116. Ferreira MA, Matheson MC, Tang CS, et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. *J Allergy Clin Immunol*. 2014;133(6):1564-1571.
117. Marenholz I, Esparza-Gordillo J, Ruschendorf F, et al. Meta-analysis identifies seven susceptibility loci involved in the atopic march. *Nat Commun*. 2015;6:8804.
118. Lemonnier N, Melen E, Jiang Y, et al. A novel whole blood gene expression signature for asthma, dermatitis, and rhinitis multimorbidity in children and adolescents. *Allergy*. 2020;75:3248-3260.
119. Forno E, Sordillo J, Brehm J, et al. Genome-wide interaction study of dust mite allergen on lung function in children with asthma. *J Allergy Clin Immunol*. 2017;140(4):996-1003 e1007.

120. Forno E, Wang T, Yan Q, et al. A Multiomics Approach to Identify Genes Associated with Childhood Asthma Risk and Morbidity. *Am J Respir Cell Mol Biol*. 2017;57(4):439-447.
121. Pinto SM, Subbannayya Y, Rex DAB, et al. A network map of IL-33 signaling pathway. *J Cell Commun Signal*. 2018;12(3):615-624.
122. Deguine J, Barton GM. MyD88: a central player in innate immune signaling. *F1000Prime Rep*. 2014;6:97.
123. Laulajainen-Hongisto A, Lyly A, Hanif T, et al. Genomics of asthma, allergy and chronic rhinosinusitis: novel concepts and relevance in airway mucosa. *Clin Transl Allergy*. 2020;10(1):45.
124. Li J, Zhang Y, Zhang L. Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy. *Curr Opin Allergy Clin Immunol*. 2015;15(1):33-40.
125. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8(2):108-352.
126. Li X, Ampleford EJ, Howard TD, et al. The C11orf30-LRRC32 region is associated with total serum IgE levels in asthmatic patients. *J Allergy Clin Immunol*. 2012;129(2):575-578, 578 e571-579.
127. Amaral AF, Minelli C, Guerra S, et al. The locus C11orf30 increases susceptibility to polysensitization. *Allergy*. 2015;70(3):328-333.
128. Sleiman PM, Wang ML, Cianferoni A, et al. GWAS identifies four novel eosinophilic esophagitis loci. *Nat Commun*. 2014;5:5593.
129. Tamari M, Tanaka S, Hirota T. Genome-wide association studies of allergic diseases. *Allergol Int*. 2013;62(1):21-28.
130. Choi BY, Han M, Kwak JW, Kim TH. Genetics and Epigenetics in Allergic Rhinitis. *Genes (Basel)*. 2021;12(12).
131. Bunyavanich S, Melen E, Wilk JB, et al. Thymic stromal lymphopoietin (TSLP) is associated with allergic rhinitis in children with asthma. *Clin Mol Allergy*. 2011;9:1.
132. Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet*. 2014;46(8):895-900.
133. Kottyan LC, Trimarchi MP, Lu X, et al. Replication and meta-analyses nominate numerous eosinophilic esophagitis risk genes. *J Allergy Clin Immunol*. 2021;147(1):255-266.
134. Martin LJ, He H, Collins MH, et al. Eosinophilic esophagitis (EoE) genetic susceptibility is mediated by synergistic interactions between EoE-specific and general atopic disease loci. *J Allergy Clin Immunol*. 2018;141(5):1690-1698.
135. Stein MM, Thompson EE, Schoettler N, et al. A decade of research on the 17q12-21 asthma locus: Piecing together the puzzle. *J Allergy Clin Immunol*. 2018;142(3):749-764 e743.
136. Haider S, Granell R, Curtin J, et al. Modelling Wheezing Spells Identifies Phenotypes with Different Outcomes and Genetic Associates. *Am J Respir Crit Care Med*. 2022.
137. Hallmark B, Wegienka G, Havstad S, et al. Chromosome 17q12-21 Variants Are Associated with Multiple Wheezing Phenotypes in Childhood. *Am J Respir Crit Care Med*. 2021;203(7):864-870.
138. Andiappan AK, Sio YY, Lee B, et al. Functional variants of 17q12-21 are associated with allergic asthma but not allergic rhinitis. *J Allergy Clin Immunol*. 2016;137(3):758-766 e753.
139. Fuertes E, Soderhall C, Acevedo N, et al. Associations between the 17q21 region and allergic rhinitis in 5 birth cohorts. *J Allergy Clin Immunol*. 2015;135(2):573-576.
140. Karunas A, Fedorova Y, GFGimalova, Etkina E, Khusnutdinova E. Association of Gasdermin B Gene GSDMB Polymorphisms with Risk of Allergic Diseases. *Biochem Genet*. 2021;59(6):1527-1543.
141. Waage J, Standl M, Curtin JA, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. *Nat Genet*. 2018;50(8):1072-1080.
142. Poninska JK, Samolinski B, Tomaszewska A, et al. Haplotype dependent association of rs7927894 (11q13.5) with atopic dermatitis and chronic allergic rhinitis: A study in ECAP cohort. *PLoS One*. 2017;12(9):e0183922.
143. El-Husseini ZW, Gosens R, Dekker F, Koppelman GH. The genetics of asthma and the promise of genomics-guided drug target discovery. *Lancet Respir Med*. 2020;8(10):1045-1056.
144. Kanazawa J, Masuko H, Yatagai Y, et al. Association analyses of eQTLs of the TYRO3 gene and allergic diseases in Japanese populations. *Allergol Int*. 2019;68(1):77-81.

145. Acevedo N, Vergara C, Mercado D, Jimenez S, Caraballo L. The A-444C polymorphism of leukotriene C4 synthase gene is associated with IgE antibodies to *Dermatophagoides pteronyssinus* in a Colombian population. *J Allergy Clin Immunol.* 2007;119(2):505-507.
146. Bonnelykke K, Matheson MC, Pers TH, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. *Nat Genet.* 2013;45(8):902-906.
147. Marsh DG, Chase GA, Freidhoff LR, Meyers DA, Bias WB. Association of HLA antigens and total serum immunoglobulin E level with allergic response and failure to respond to ragweed allergen Ra3. *Proc Natl Acad Sci U S A.* 1979;76(6):2903-2907.
148. Fischer GF, Pickl WF, Fae I, et al. Association between IgE response against Bet v I, the major allergen of birch pollen, and HLA-DRB alleles. *Hum Immunol.* 1992;33(4):259-265.
149. Tautz C, Rihs HP, Thiele A, et al. Association of class II sequences encoding DR1 and DQ5 specificities with hypersensitivity to chironomid allergen Chi t I. *J Allergy Clin Immunol.* 1994;93(5):918-925.
150. Soriano JB, Ercilla G, Sunyer J, et al. HLA class II genes in soybean epidemic asthma patients. *Am J Respir Crit Care Med.* 1997;156(5):1394-1398.
151. D'Amato M, Scotto d'Abusco A, Maggi E, et al. Association of responsiveness to the major pollen allergen of *Parietaria officinalis* with HLA-DRB1* alleles: a multicenter study. *Hum Immunol.* 1996;46(2):100-106.
152. Joshi SK, Suresh PR, Chauhan VS. Flexibility in MHC and TCR recognition: degenerate specificity at the T cell level in the recognition of promiscuous Th epitopes exhibiting no primary sequence homology. *J Immunol.* 2001;166(11):6693-6703.
153. Gheerbrant H, Guillien A, Vernet R, et al. Associations between specific IgE sensitization to 26 respiratory allergen molecules and HLA class II alleles in the EGEA cohort. *Allergy.* 2021.
154. Kanchan K, Clay S, Irizar H, Bunyavanich S, Mathias RA. Current insights into the genetics of food allergy. *J Allergy Clin Immunol.* 2021;147(1):15-28.
155. Xu CJ, Soderhall C, Bustamante M, et al. DNA methylation in childhood asthma: an epigenome-wide meta-analysis. *Lancet Respir Med.* 2018;6(5):379-388.
156. Xu CJ, Gruziova O, Qi C, et al. Shared DNA methylation signatures in childhood allergy: The MeDALL study. *J Allergy Clin Immunol.* 2021;147(3):1031-1040.
157. Ek WE, Ahsan M, Rask-Andersen M, et al. Epigenome-wide DNA methylation study of IgE concentration in relation to self-reported allergies. *Epigenomics.* 2017;9(4):407-418.
158. Zhang H, Kaushal A, Merid SK, et al. DNA methylation and allergic sensitizations: A genome-scale longitudinal study during adolescence. *Allergy.* 2019;74(6):1166-1175.
159. Qi C, Jiang Y, Yang IV, et al. Nasal DNA methylation profiling of asthma and rhinitis. *J Allergy Clin Immunol.* 2020;145(6):1655-1663.
160. Sarnowski C, Laprise C, Malerba G, et al. DNA methylation within melatonin receptor 1A (MTNR1A) mediates paternally transmitted genetic variant effect on asthma plus rhinitis. *J Allergy Clin Immunol.* 2016;138(3):748-753.
161. Hernandez-Pacheco N, Kere M, Melén E. Gene-environment interactions in childhood asthma revisited; expanding the interaction concept. *Pediatr Allergy Immunol.* 33(5):e13780.
162. Savoure M, Bousquet J, Leynaert B, et al. Rhinitis phenotypes and multimorbidities in the general population Constances cohort. *Eur Respir J.* 2022.
163. Sousa-Pinto B, Schunemann HJ, Sa-Sousa A, et al. Comparison of rhinitis treatments using MASK-air(R) data and considering the Minimal Important Difference. *Allergy.* 2022;77(10):3002-3014.
164. Bedard A, Basagana X, Anto JM, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. *J Allergy Clin Immunol.* 2019;144(1):135-143 e136.
165. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, et al. Behavioural patterns in allergic rhinitis medication in Europe: A study using MASK-air((R)) real-world data. *Allergy.* 2022.
166. Belgrave DC, Granell R, Simpson A, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. *PLoS Med.* 2014;11(10):e1001748.
167. Renert-Yuval Y, Del Duca E, Pavel AB, et al. The molecular features of normal and atopic dermatitis skin in infants, children, adolescents, and adults. *J Allergy Clin Immunol.* 2021;148(1):148-163.
168. Bjorksten F, Suoniemi I, Koski V. Neonatal birch-pollen contact and subsequent allergy to birch pollen. *Clin Allergy.* 1980;10(5):585-591.
169. Graf N, Johansen P, Schindler C, et al. Analysis of the relationship between pollinosis and date of birth in Switzerland. *Int Arch Allergy Immunol.* 2007;143(4):269-275.

170. Kihlstrom A, Lilja G, Pershagen G, Hedlin G. Exposure to birch pollen in infancy and development of atopic disease in childhood. *J Allergy Clin Immunol.* 2002;110(1):78-84.
171. Aalberse RC, Nieuwenhuys EJ, Hey M, Stapel SO. 'Horoscope effect' not only for seasonal but also for non-seasonal allergens. *Clin Exp Allergy.* 1992;22(11):1003-1006.
172. Schafer T, Przybilla B, Ring J, Kunz B, Greif A, Uberla K. Manifestation of atopy is not related to patient's month of birth. *Allergy.* 1993;48(4):291-294.
173. Peterson B, Saxon A. Global increases in allergic respiratory disease: the possible role of diesel exhaust particles. *Ann Allergy Asthma Immunol.* 1996;77(4):263-268.
174. Ohtani T, Nakagawa S, Kurosawa M, Mizuashi M, Ozawa M, Aiba S. Cellular basis of the role of diesel exhaust particles in inducing Th2-dominant response. *J Immunol.* 2005;174(4):2412-2419.
175. Llop-Guevara A, Chu DK, Walker TD, et al. A GM-CSF/IL-33 pathway facilitates allergic airway responses to sub-threshold house dust mite exposure. *PLoS One.* 2014;9(2):e88714.
176. Han M, Rajput C, Hershenson MB. Rhinovirus Attributes that Contribute to Asthma Development. *Immunol Allergy Clin North Am.* 2019;39(3):345-359.
177. Niespodziana K, Stenberg-Hammar K, Papadopoulos NG, et al. Microarray Technology May Reveal the Contribution of Allergen Exposure and Rhinovirus Infections as Possible Triggers for Acute Wheezing Attacks in Preschool Children. *Viruses.* 2021;13(5).
178. Rajput C, Han M, Ishikawa T, et al. Rhinovirus C Infection Induces Type 2 Innate Lymphoid Cell Expansion and Eosinophilic Airway Inflammation. *Front Immunol.* 2021;12:649520.
179. Jackson DJ, Makrinioti H, Rana BM, et al. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am J Respir Crit Care Med.* 2014;190(12):1373-1382.
180. Werder RB, Ullah MA, Rahman MM, et al. Targeting the P2Y13 Receptor Suppresses IL-33 and HMGB1 Release and Ameliorates Experimental Asthma. *Am J Respir Crit Care Med.* 2022;205(3):300-312.
181. Al-Garawi A, Fattouh R, Botelho F, et al. Influenza A facilitates sensitization to house dust mite in infant mice leading to an asthma phenotype in adulthood. *Mucosal Immunol.* 2011;4(6):682-694.
182. Sahu U, Biswas D, Prajapati VK, Singh AK, Samant M, Khare P. Interleukin-17-A multifaceted cytokine in viral infections. *J Cell Physiol.* 2021;236(12):8000-8019.
183. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev.* 2017;278(1):116-130.
184. De Benedetto A, Kubo A, Beck LA. Skin barrier disruption: a requirement for allergen sensitization? *J Invest Dermatol.* 2012;132(3 Pt 2):949-963.
185. Tham EH, Leung DY. Mechanisms by Which Atopic Dermatitis Predisposes to Food Allergy and the Atopic March. *Allergy Asthma Immunol Res.* 2019;11(1):4-15.
186. Sahiner UM, Layhadi JA, Golebski K, et al. Innate lymphoid cells: The missing part of a puzzle in food allergy. *Allergy.* 2021;76(7):2002-2016.
187. Imai Y. Interleukin-33 in atopic dermatitis. *J Dermatol Sci.* 2019;96(1):2-7.
188. Roesner LM, Werfel T, Heratizadeh A. The adaptive immune system in atopic dermatitis and implications on therapy. *Expert Rev Clin Immunol.* 2016;12(7):787-796.
189. Sorensen M, Klingenberg C, Wickman M, et al. Staphylococcus aureus enterotoxin-sensitization is associated with allergic poly-sensitization and allergic multimorbidity in adolescents. *Allergy.* 2017.
190. Al Kindi A, Williams H, Matsuda K, et al. Staphylococcus aureus second immunoglobulin-binding protein drives atopic dermatitis via IL-33. *J Allergy Clin Immunol.* 2021;147(4):1354-1368 e1353.
191. Smole U, Gour N, Phelan J, et al. Serum amyloid A is a soluble pattern recognition receptor that drives type 2 immunity. *Nat Immunol.* 2020;21(7):756-765.
192. Abdel-Gadir A, Stephen-Victor E, Gerber GK, et al. Microbiota therapy acts via a regulatory T cell MyD88/RORgammat pathway to suppress food allergy. *Nat Med.* 2019;25(7):1164-1174.
193. Cephus JY, Stier MT, Fuseini H, et al. Testosterone Attenuates Group 2 Innate Lymphoid Cell-Mediated Airway Inflammation. *Cell Rep.* 2017;21(9):2487-2499.
194. Laffont S, Blanquart E, Guery JC. Sex Differences in Asthma: A Key Role of Androgen-Signaling in Group 2 Innate Lymphoid Cells. *Front Immunol.* 2017;8:1069.
195. Cephus JY, Gandhi VD, Shah R, et al. Estrogen receptor-alpha signaling increases allergen-induced IL-33 release and airway inflammation. *Allergy.* 2021;76(1):255-268.
196. Gandhi VD, Cephus JY, Norlander AE, et al. Androgen receptor signaling promotes Treg suppressive function during allergic airway inflammation. *J Clin Invest.* 2022;132(4).

197. Munoz X, Barreiro E, Bustamante V, Lopez-Campos JL, Gonzalez-Barcala FJ, Cruz MJ. Diesel exhausts particles: Their role in increasing the incidence of asthma. Reviewing the evidence of a causal link. *Sci Total Environ*. 2019;652:1129-1138.
198. Sposato B, Llicardi G, Russo M, et al. Cypress pollen: an unexpected major sensitizing agent in different regions of Italy. *J Investig Allergol Clin Immunol*. 2014;24(1):23-28.
199. Asero R. Birch and ragweed pollinosis north of Milan: a model to investigate the effects of exposure to "new" airborne allergens. *Allergy*. 2002;57(11):1063-1066.
200. Asero R. Ragweed allergy in northern Italy: are patterns of sensitization changing? *Eur Ann Allergy Clin Immunol*. 2012;44(4):157-159.
201. Caimmi D, Raschetti R, Pons P, et al. Epidemiology of cypress pollen allergy in Montpellier. *J Investig Allergol Clin Immunol*. 2012;22(4):280-285.
202. Anto JM, Sunyer J, Rodriguez-Roisin R, Suarez-Cervera M, Vazquez L. Community outbreaks of asthma associated with inhalation of soybean dust. Toxicoepidemiological Committee. *N Engl J Med*. 1989;320(17):1097-1102.
203. Synek M, Anto JM, Beasley R, et al. Immunopathology of fatal soybean dust-induced asthma. *Eur Respir J*. 1996;9(1):54-57.
204. Poposki JA, Klingler AI, Stevens WW, et al. Elevation of activated neutrophils in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2022;149(5):1666-1674.
205. Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking neutrophils and eosinophils in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2021;148(2):327-335.
206. Lyly A, Laulajainen-Hongisto A, Gevaert P, Kauppi P, Toppila-Salmi S. Monoclonal Antibodies and Airway Diseases. *Int J Mol Sci*. 2020;21(24).
207. Sintobin I, Siroux V, Holtappels G, et al. Sensitisation to staphylococcal enterotoxins and asthma severity: a longitudinal study in the EGEA cohort. *Eur Respir J*. 2019;54(3).
208. Bachert C, van Steen K, Zhang N, et al. Specific IgE against *Staphylococcus aureus* enterotoxins: an independent risk factor for asthma. *J Allergy Clin Immunol*. 2012;130(2):376-381 e378.
209. Bachert C, Humbert M, Hanania NA, et al. *Staphylococcus aureus* and its IgE-inducing enterotoxins in asthma: current knowledge. *Eur Respir J*. 2020;55(4).
210. Krysko O, Teufelberger A, Van Nevel S, Krysko DV, Bachert C. Protease/antiprotease network in allergy: The role of *Staphylococcus aureus* protease-like proteins. *Allergy*. 2019;74(11):2077-2086.
211. Teufelberger AR, Broker BM, Krysko DV, Bachert C, Krysko O. *Staphylococcus aureus* Orchestrates Type 2 Airway Diseases. *Trends Mol Med*. 2019;25(8):696-707.
212. Kato A, Schleimer RP, Bleier BS. Mechanisms and pathogenesis of chronic rhinosinusitis. *J Allergy Clin Immunol*. 2022;149(5):1491-1503.
213. Huang K, Li F, Wang X, et al. Clinical and cytokine patterns of uncontrolled asthma with and without comorbid chronic rhinosinusitis: a cross-sectional study. *Respir Res*. 2022;23(1):119.
214. Eid R, Yan CH, Stevens W, Doherty TA, Borish L. Innate immune cell dysregulation drives inflammation and disease in aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2021;148(2):309-318.
215. Knudgaard MH, Andreassen TH, Ravnborg N, et al. Rhinitis prevalence and association with atopic dermatitis: A systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. 2021;127(1):49-56 e41.
216. Deacy AM, Gan SK, Derrick JP. Superantigen Recognition and Interactions: Functions, Mechanisms and Applications. *Front Immunol*. 2021;12:731845.
217. Lan F, Zhang N, Holtappels G, et al. *Staphylococcus aureus* Induces a Mucosal Type 2 Immune Response via Epithelial Cell-derived Cytokines. *Am J Respir Crit Care Med*. 2018;198(4):452-463.
218. Tang HHF, Lang A, Teo SM, et al. Developmental patterns in the nasopharyngeal microbiome during infancy are associated with asthma risk. *J Allergy Clin Immunol*. 2021;147(5):1683-1691.
219. Leyva-Castillo JM, Geha RS. Cutaneous Type 2 Innate Lymphoid Cells Come in Distinct Flavors. *JID Innov*. 2021;1(3):100059.
220. Chu DK, Jimenez-Saiz R, Verschoor CP, et al. Indigenous enteric eosinophils control DCs to initiate a primary Th2 immune response in vivo. *J Exp Med*. 2014;211(8):1657-1672.
221. Chu DK, Llop-Guevara A, Walker TD, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol*. 2013;131(1):187-200 e181-188.

222. Liew KY, Koh SK, Hooi SL, et al. Rhinovirus-Induced Cytokine Alterations With Potential Implications in Asthma Exacerbations: A Systematic Review and Meta-Analysis. *Front Immunol.* 2022;13:782936.
223. Murdaca G, Paladin F, Tonacci A, et al. Involvement of IL-33 in the Pathogenesis and Prognosis of Major Respiratory Viral Infections: Future Perspectives for Personalized Therapy. *Biomedicines.* 2022;10(3).
224. Suzuki M, Cooksley C, Suzuki T, et al. TLR Signals in Epithelial Cells in the Nasal Cavity and Paranasal Sinuses. *Front Allergy.* 2021;2:780425.
225. Henmyr V, Carlberg D, Manderstedt E, et al. Genetic variation of the Toll-like receptors in a Swedish allergic rhinitis case population. *BMC Med Genet.* 2017;18(1):18.
226. Henmyr V, Lind-Hallden C, Carlberg D, et al. Characterization of genetic variation in TLR8 in relation to allergic rhinitis. *Allergy.* 2016;71(3):333-341.
227. Fuertes E, Brauer M, MacIntyre E, et al. Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: results from the TAG Study. *J Allergy Clin Immunol.* 2013;132(2):342-352 e342.
228. Arebro J, Ekstedt S, Hjalmarsson E, Winqvist O, Kumlien Georen S, Cardell LO. A possible role for neutrophils in allergic rhinitis revealed after cellular subclassification. *Sci Rep.* 2017;7:43568.
229. Malizia V, Ferrante G, Cilluffo G, et al. Endotyping Seasonal Allergic Rhinitis in Children: A Cluster Analysis. *Front Med (Lausanne).* 2021;8:806911.
230. Brightling CE, Nair P, Cousins DJ, Louis R, Singh D. Risankizumab in Severe Asthma - A Phase 2a, Placebo-Controlled Trial. *N Engl J Med.* 2021;385(18):1669-1679.
231. Stein MM, Hrusch CL, Gozdz J, et al. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med.* 2016;375(5):411-421.
232. Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med.* 2011;364(8):701-709.
233. House JS, Wyss AB, Hoppin JA, et al. Early-life farm exposures and adult asthma and atopy in the Agricultural Lung Health Study. *J Allergy Clin Immunol.* 2017;140(1):249-256 e214.
234. von Hertzen LC, Laatikainen T, Pennanen S, Makela MJ, Haahtela T, Karelina Allergy Study G. Is house dust mite monosensitization associated with clinical disease? *Allergy.* 2008;63(3):379-381.
235. Ruokolainen L, Fyhrquist N, Laatikainen T, et al. Immune-microbiota interaction in Finnish and Russian Karelia young people with high and low allergy prevalence. *Clin Exp Allergy.* 2020;50(10):1148-1158.
236. Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clin Exp Allergy.* 2017;47(5):665-674.
237. Wisgrill L, Fyhrquist N, Ndika J, et al. Bet v 1 triggers antiviral-type immune signalling in birch-pollen-allergic individuals. *Clin Exp Allergy.* 2022.
238. Ndika J, Karisola P, Lahti V, et al. Epigenetic Differences in Long Non-coding RNA Expression in Finnish and Russian Karelia Teenagers With Contrasting Risk of Allergy and Asthma. *Front Allergy.* 2022;3:878862.
239. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nat Rev Immunol.* 2010;10(2):103-110.
240. Hodzic Z, Schill EM, Bolock AM, Good M. IL-33 and the intestine: The good, the bad, and the inflammatory. *Cytokine.* 2017;100:1-10.
241. Johnson AN, Harkema JR, Nelson AJ, et al. MyD88 regulates a prolonged adaptation response to environmental dust exposure-induced lung disease. *Respir Res.* 2020;21(1):97.
242. Matsushita K, Yoshimoto T. B cell-intrinsic MyD88 signaling is essential for IgE responses in lungs exposed to pollen allergens. *J Immunol.* 2014;193(12):5791-5800.
243. Pawar S, Feehley T, Nagler C. Commensal bacteria-induced MyD88 signaling regulates intestinal permeability to food allergen via anti-microbial peptide and mucin production (MUC9P.741). *J Immunol.* 2015;194:205.
244. Stephen-Victor E, Crestani E, Chatila TA. Dietary and Microbial Determinants in Food Allergy. *Immunity.* 2020;53(2):277-289.
245. Cayrol C, Girard JP. Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family. *Immunol Rev.* 2018;281(1):154-168.
246. Abusleme L, Moutsopoulos NM. IL-17: overview and role in oral immunity and microbiome. *Oral Dis.* 2017;23(7):854-865.

247. Majumder S, McGeachy MJ. IL-17 in the Pathogenesis of Disease: Good Intentions Gone Awry. *Annu Rev Immunol.* 2021;39:537-556.
248. Palmieri V, Ebel JF, Ngo Thi Phuong N, et al. Interleukin-33 signaling exacerbates experimental infectious colitis by enhancing gut permeability and inhibiting protective Th17 immunity. *Mucosal Immunol.* 2021;14(4):923-936.
249. Segata N. Gut Microbiome: Westernization and the Disappearance of Intestinal Diversity. *Curr Biol.* 2015;25(14):R611-613.
250. Bibbo S, Ianaro G, Giorgio V, et al. The role of diet on gut microbiota composition. *Eur Rev Med Pharmacol Sci.* 2016;20(22):4742-4749.
251. Vangay P, Johnson AJ, Ward TL, et al. US Immigration Westernizes the Human Gut Microbiome. *Cell.* 2018;175(4):962-972 e910.
252. Zuo T, Kamm MA, Colombel JF, Ng SC. Urbanization and the gut microbiota in health and inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* 2018;15(7):440-452.
253. Wilson AS, Koller KR, Ramaboli MC, et al. Diet and the Human Gut Microbiome: An International Review. *Dig Dis Sci.* 2020;65(3):723-740.
254. Bostock J. Case of a periodical affection of the eyes and the chest. *Med Surg Trans London.* 1819;xiv:161-166.
255. Roslund MI, Parajuli A, Hui N, et al. A Placebo-controlled double-blinded test of the biodiversity hypothesis of immune-mediated diseases: Environmental microbial diversity elicits changes in cytokines and increase in T regulatory cells in young children. *Ecotoxicol Environ Saf.* 2022;242:113900.
256. Dupraz L, Magniez A, Rolhion N, et al. Gut microbiota-derived short-chain fatty acids regulate IL-17 production by mouse and human intestinal gammadelta T cells. *Cell Rep.* 2021;36(1):109332.
257. Li M, van Esch B, Henricks PAJ, Garssen J, Folkerts G. IL-33 Is Involved in the Anti-Inflammatory Effects of Butyrate and Propionate on TNFalpha-Activated Endothelial Cells. *Int J Mol Sci.* 2021;22(5).
258. Capucilli P, Cianferoni A, Grundmeier RW, Spergel JM. Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population. *Ann Allergy Asthma Immunol.* 2018;121(6):711-716.
259. Mannion JM, McLoughlin RM, Lalor SJ. The Airway Microbiome-IL-17 Axis: a Critical Regulator of Chronic Inflammatory Disease. *Clin Rev Allergy Immunol.* 2022.
260. Ritzmann F, Beisswenger C. Preclinical studies and the function of IL-17 cytokines in COPD. *Ann Anat.* 2021;237:151729.
261. Chen J, Liu X, Zhong Y. Interleukin-17A: The Key Cytokine in Neurodegenerative Diseases. *Front Aging Neurosci.* 2020;12:566922.
262. Yuan C. IL-33 in autoimmunity; possible therapeutic target. *Int Immunopharmacol.* 2022;108:108887.
263. Zhao Q, Xiao X, Wu Y, et al. Interleukin-17-educated monocytes suppress cytotoxic T-cell function through B7-H1 in hepatocellular carcinoma patients. *Eur J Immunol.* 2011;41(8):2314-2322.
264. Hofmann MA, Kiecker F, Zuberbier T. A systematic review of the role of interleukin-17 and the interleukin-20 family in inflammatory allergic skin diseases. *Curr Opin Allergy Clin Immunol.* 2016;16(5):451-457.
265. Paira DA, Silvera-Ruiz S, Tissera A, et al. Interferon gamma, IL-17, and IL-1beta impair sperm motility and viability and induce sperm apoptosis. *Cytokine.* 2022;152:155834.
266. Crosby DA, Glover LE, Brennan EP, et al. Dysregulation of the interleukin-17A pathway in endometrial tissue from women with unexplained infertility affects pregnancy outcome following assisted reproductive treatment. *Hum Reprod.* 2020;35(8):1875-1888.
267. Pandolfo G, Genovese G, Casciaro M, et al. IL-33 in Mental Disorders. *Medicina (Kaunas).* 2021;57(4).
268. Kato T, Yasuda K, Matsushita K, et al. Interleukin-1/-33 Signaling Pathways as Therapeutic Targets for Endometriosis. *Front Immunol.* 2019;10:2021.
269. Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases. *J Clin Invest.* 2019;129(4):1493-1503.
270. Wang X, Zhang N, Bo M, et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol.* 2016;138(5):1344-1353.

271. Wang M, Zhang N, Zheng M, et al. Cross-talk between TH2 and TH17 pathways in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2019;144(5):1254-1264.
272. Stevens WW, Peters AT, Tan BK, et al. Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract*. 2019;7(8):2812-2820 e2813.
273. Wang M, Zhang Y, Han D, Zhang L. Association between polymorphisms in cytokine genes IL-17A and IL-17F and development of allergic rhinitis and comorbid asthma in Chinese subjects. *Hum Immunol*. 2012;73(6):647-653.
274. Chanoine S, Sanchez M, Pin I, et al. Multimorbidity medications and poor asthma prognosis. *Eur Respir J*. 2018;51(4).
275. Roman-Rodriguez M, Kaplan A. GOLD 2021 Strategy Report: Implications for Asthma-COPD Overlap. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1709-1715.
276. Eberl G. Immunity by equilibrium. *Nat Rev Immunol*. 2016;16(8):524-532.
277. Desai MS, Seekatz AM, Koropatkin NM, et al. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell*. 2016;167(5):1339-1353 e1321.
278. Vignola AM, Chanez P, Godard P, Bousquet J. Relationships between rhinitis and asthma. *Allergy*. 1998;53(9):833-839.
279. Bousquet J, Burney PG, Zuberbier T, et al. GA2LEN (Global Allergy and Asthma European Network) addresses the allergy and asthma 'epidemic'. *Allergy*. 2009;64(7):969-977.
280. Bousquet J, Anto JM, Bachert C, et al. Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens. A GALEN project. *Allergy*. 2006;61(6):671-680.
281. Bousquet J, Bedbrook A, Czarlewski W, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy*. 2019;9:16.
282. Westman M, Lupinek C, Bousquet J, et al. Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *J Allergy Clin Immunol*. 2015;135(5):1199-1206 e1191-1111.
283. Havstad S, Johnson CC, Kim H, et al. Atopic phenotypes identified with latent class analyses at age 2 years. *J Allergy Clin Immunol*. 2014;134(3):722-727 e722.
284. Westman M, Aberg K, Apostolovic D, et al. Sensitization to grass pollen allergen molecules in a birth cohort-natural Phl p 4 as an early indicator of grass pollen allergy. *J Allergy Clin Immunol*. 2020;145:1174-1181.
285. Bougas N, Just J, Beydon N, et al. Unsupervised trajectories of respiratory/allergic symptoms throughout childhood in the PARIS cohort. *Pediatr Allergy Immunol*. 2019;30(3):315-324.
286. Custovic A, Sonntag HJ, Buchan IE, Belgrave D, Simpson A, Prosperi MC. Evolution pathways of IgE responses to grass and mite allergens throughout childhood. *J Allergy Clin Immunol*. 2015;136(6):1645-1652 e1641-1648.
287. Tang HH, Teo SM, Belgrave DC, et al. Trajectories of childhood immune development and respiratory health relevant to asthma and allergy. *Elife*. 2018;7.
288. Posa D, Perna S, Resch Y, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol*. 2017;139(2):541-549 e548.
289. Garden FL, Simpson JM, Marks GB, Investigators C. Atopy phenotypes in the Childhood Asthma Prevention Study (CAPS) cohort and the relationship with allergic disease: clinical mechanisms in allergic disease. *Clin Exp Allergy*. 2013;43(6):633-641.
290. Havstad SL, Sitarik A, Kim H, et al. Increased risk of asthma at age 10 years for children sensitized to multiple allergens. *Ann Allergy Asthma Immunol*. 2021;127(4):441-445 e441.
291. Lazic N, Roberts G, Custovic A, et al. Multiple atopy phenotypes and their associations with asthma: similar findings from two birth cohorts. *Allergy*. 2013;68(6):764-770.
292. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Factors predicting persistence of early wheezing through childhood and adolescence: a systematic review of the literature. *J Asthma Allergy*. 2017;10:83-98.
293. Haahtela T, Laatikainen T, Alenius H, et al. Hunt for the origin of allergy - comparing the Finnish and Russian Karelia. *Clin Exp Allergy*. 2015;45(5):891-901.
294. Ke S, Weiss ST, Liu YY. Rejuvenating the human gut microbiome. *Trends Mol Med*. 2022;28(8):619-630.

295. McSorley HJ, Smyth DJ. IL-33: A central cytokine in helminth infections. *Semin Immunol.* 2021;53:101532.
296. Hung LY, Tanaka Y, Herbine K, et al. Cellular context of IL-33 expression dictates impact on anti-helminth immunity. *Sci Immunol.* 2020;5(53).
297. Rajasekaran S, Anuradha R, Bethunaickan R. TLR Specific Immune Responses against Helminth Infections. *J Parasitol Res.* 2017;2017:6865789.
298. Chung SH, Ye XQ, Iwakura Y. Interleukin-17 family members in health and disease. *Int Immunol.* 2021;33(12):723-729.
299. Wen TH, Tsai KW, Wu YJ, Liao MT, Lu KC, Hu WC. The Framework for Human Host Immune Responses to Four Types of Parasitic Infections and Relevant Key JAK/STAT Signaling. *Int J Mol Sci.* 2021;22(24).
300. Bousquet J, Anto JM, Bachert C, et al. Allergic rhinitis. *Nat Rev Dis Primers.* 2020;6(1):95.

Table 1: Stepwise accomplishments and plans for the further understanding of allergy multimorbidities used by ARIA and MeDALL members

Mechanistic ²⁷⁸ and epidemiologic studies (European Community Respiratory Health Survey: ECRHS, Framework Programme , FP2) ³⁰ to better understand the links between asthma and rhinitis that led to ARIA. ¹⁰ EU network of excellence (GA²LEN, Global Allergy and Asthma European Network, FP6) ²⁷⁹ to better understand sensitisation patterns. ²⁸⁰ FP7 EU grant (MeDALL, Mechanisms of the Development of Allergy, FP7) ^{1,2} to understand the mechanisms underlying the complex interactions between multimorbidity and polysensitisation (epidemiologic, genomic and epigenomic studies). ²⁸⁰ Development of mHealth (mobile health) to capture real-world data (direct patients' data) and to obtain further insights into the complex interactions informed by MeDALL. ²⁸¹ Canonical epidemiologic studies to confirm mHealth observational studies which are only hypothesis generating. ⁶⁸ Genomic approaches to test hypotheses on unique and/or shared pathogenesis. ¹¹⁸ Identification of an extreme allergy phenotype (multimorbidity, polysensitisation) confirmed by canonical epidemiologic studies. Testing new hypotheses by assessing therapeutic responses based on multimorbidity vs. single diseases. A new iteration focusing on asthma has been initiated in mHealth observational studies to provide novel insights and to confirm the conclusions raised by the previous data.

Table 2: Differences between mono- and polysensitisation

	Cohort	Findings	
Cross-sectional analyses			
Specific IgE	BAMSE-MeDALL	Birch pollen: Bet-v1 IgE levels increased according to the number of IgE-reactive PR-10 proteins. Cat/dog: IgE levels to cat/dog molecules higher in polysensitised than monosensitised children.	108,282
Current symptoms	BAMSE-MeDALL	Birch pollen: PR-10 polysensitised children had more severe AR than monosensitised. Cat/dog: Children polysensitised to cat/dog molecules had more frequent AR symptoms to cat and dog than monosensitised.	282 108
	WHEALS	“Highly”-sensitised infants (2 yrs) were at risk for a diagnosis of asthma.	283
Rhinitis/asthma phenotypes in longitudinal studies			
A, R and AD Prediction of symptoms over time and trajectories	BAMSE-MeDALL	Birch pollen: Increased risk of R incidence, persistence and severity up to age 16 years with increasing levels of Bet v 1-specific IgE or increasing numbers of IgE-reactive PR-10 proteins at 4 years Cat/dog: Polysensitisation to 3 allergen molecules at 4-8 yrs is a better predictor of cat or dog symptoms at 16 yrs than monosensitisation. Grass pollen and peanut: The likelihood of later symptoms increased with the number of allergen molecules at the age of 4 or 8 years.	48,282,284
	MeDALL (BAMSE-MAS)	IgE reactivity to a few allergen molecules at 4 yrs identified children with a high risk of A and/or R at 16 yrs, in particular for A+R multimorbidity.	110
	Paris	Early polysensitisation was associated to later development of allergic multimorbidity in PARIS birth cohort infants.	105,285
	MAAS	The latent class analysis revealed 3 grass-sensitisation trajectories. The early-onset trajectory was associated with A and diminished lung function. The late-onset trajectory was associated with R. 4 trajectories emerged for mite sensitisation. Children in the complete mite sensitisation trajectory had the highest A prevalence and were the only groups significantly associated with multimorbid A, AD, R. 3 trajectories were found using latent clusters. One was a high-risk atopic cluster with polysensitisation and increased propensity for allergic diseases throughout childhood.	286,287
	MAS	The evolution and predictive value of IgE responses towards a comprehensive panel of house dust mite (HDM) allergens were tested up to 20 years.	288
		Polysensitisation status at ages 6 mths, 18 mths, 4 yrs and 6 yrs was associated with increased risk of asthma at age 13.	75
	CAPS	The strongest association of AD, particularly for A (and AR), was with the mixed food and inhalant sensitisation phenotype.	289
	WHEALS	Children sensitised to 4 or more food and inhalant allergens at age 2 had the highest risk of current asthma at 10 yrs.	290
	MAAS + IoW	Polysensitisation early in life is associated with asthma.	291
	Meta-analysis	Polysensitisation is a risk factor predicting persistence of early wheezing through school age.	292

A: asthma, AD: atopic dermatitis, R: rhinitis

Table 3: Results of the EGEA study (from ⁷⁰ and ⁷¹)

	No A, No R	R	A	A+R
Age	46.8 ± 16.3	45.2 ± 16.3	40.8 ± 17.1	38.4 ± 16.0
Age onset Rhinitis		25.1 ± 15.0		14.2 ± 12.2
Nasal symptoms	0	87.3	0	90.7
Ocular symptoms	0	76.6		80.4
Persistence nasal symptoms (score)*		17,1		32
Atopic dermatitis	22.7	35.3	38.5	52.7
Bronchial hyperreactivity	23.7	29.8	55.8	67.8
Eosinophils	149 ± 106	191 ± 123	196 ± 129	253 ± 192
Total IgE	33.6	79.43	72.77	164.8
Number of IgE reactive molecules ⁷¹	0 (0-0)	2 (0-6)	1 (0-7)	7 (3-12)
Level of sIgE (ISU) ⁷¹	1.3 (0.5-3.5)	5.7 (3.3-10.5)	3.2 (1.5-6.5)	5.5 (2.9-10.0)

*: score adding symptoms

A: asthma, R: rhinitis

Table 4: opportunities for research

Systematic reviews on the different topics of the paper.

Confirmation of the hypotheses in various settings: for example, the IL-33/IL-17-TLR hypothesis should be studied in settings with low allergen/rich microbiome exposures such as Karelia²⁹³ or birth on an animal farm.

Further understanding of the role of the microbiome and biodiversity, and bringing the microbiome back to an ancestral or preindustrial state.²⁹⁴

Food allergy: Relationships to multimorbidity and polysensitisation need to be investigated with regards to the onset, severity and resolution of symptoms.

Cell types involved including epithelium: The epithelial barrier hypothesis may explain the increase in allergy, autoimmunity and other chronic conditions and should be tested.⁹ Other cell types linked to innate immunity should also be considered.

Differences in the efficacy of biologics depending on multimorbid diseases.

Innate versus adaptative immunity in polysensitisation: Polysensitisation and multimorbidity may be a primary event stemming from differences in innate immunity associated with altered adaptive immunity in some patients or from persisting alterations in innate immunity in others.

Differences between allergy and parasites: IL-33 signalling plays pathological and protective roles in parasitic infections.^{295,296} Control of inflammation induced by parasites by IL-17 is also possible for efficient host protection.²⁹⁷⁻²⁹⁹

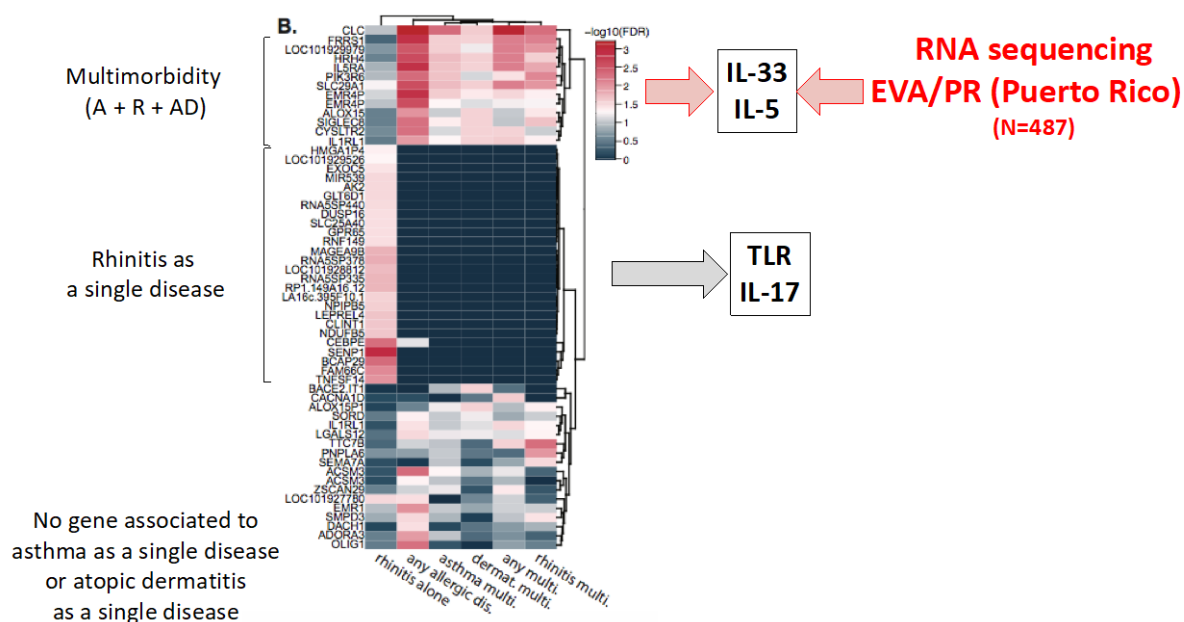


Figure 3: Phenotypes of IgE-mediated allergic diseases across the life cycle (adapted from ¹⁹)

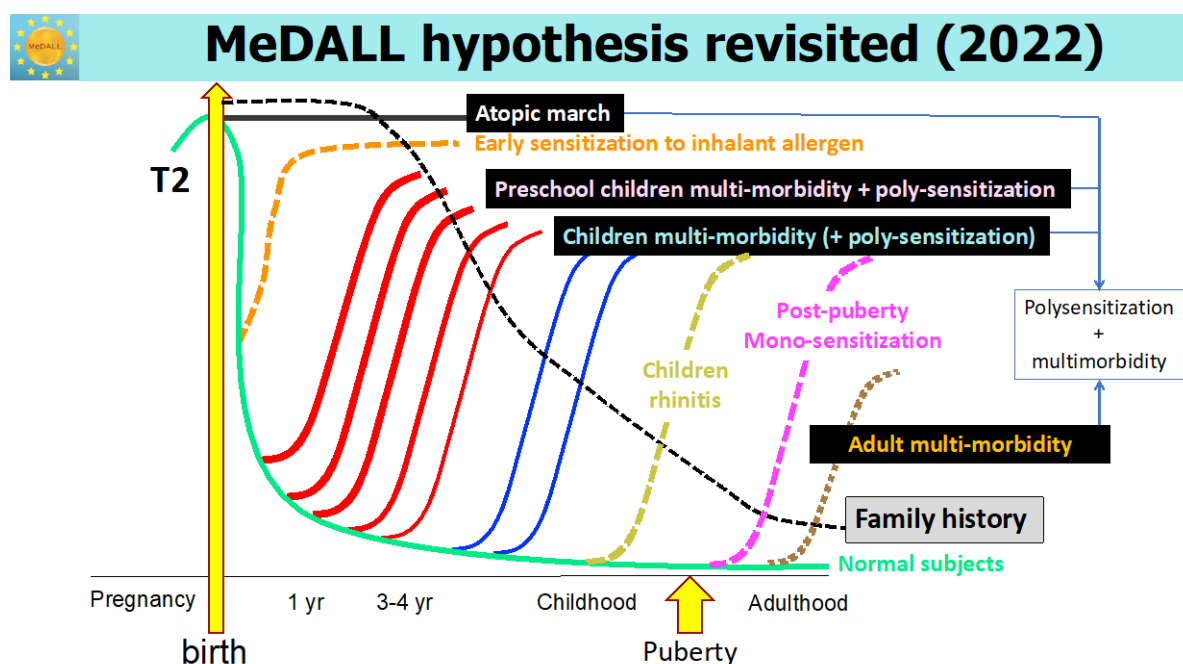


Figure 4: Possible mechanisms explaining the re-occurrence of Type 2 signalling

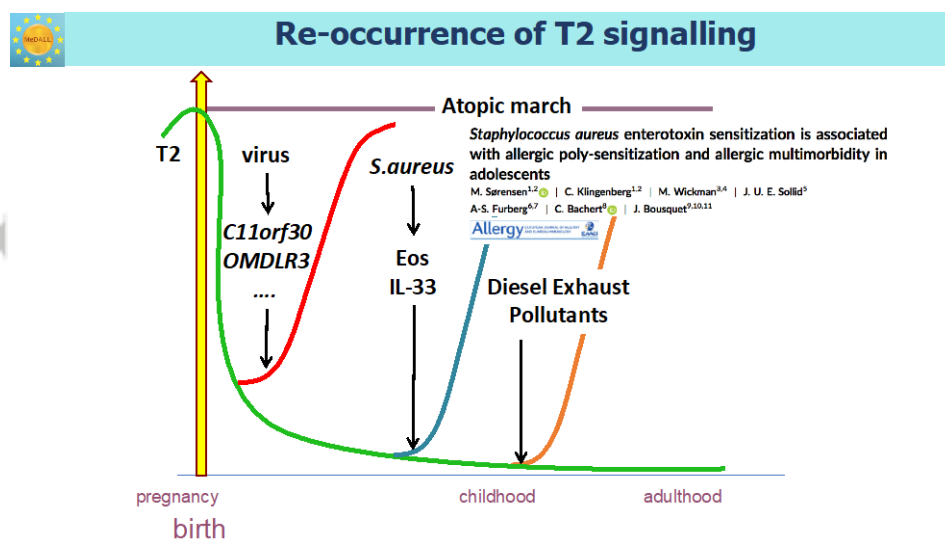


Figure 5: Putative mechanisms of rhinitis and rhinitis and asthma multimorbidity

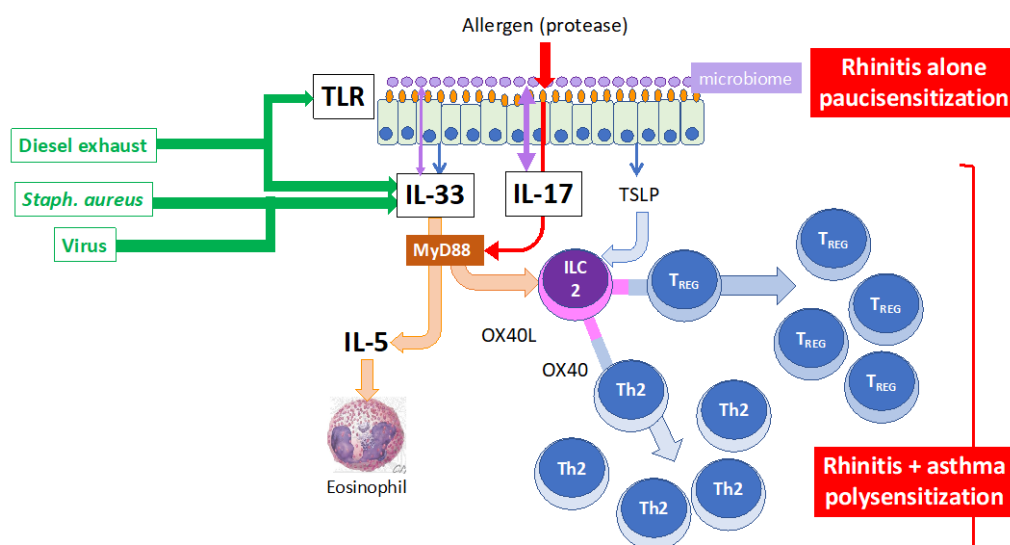
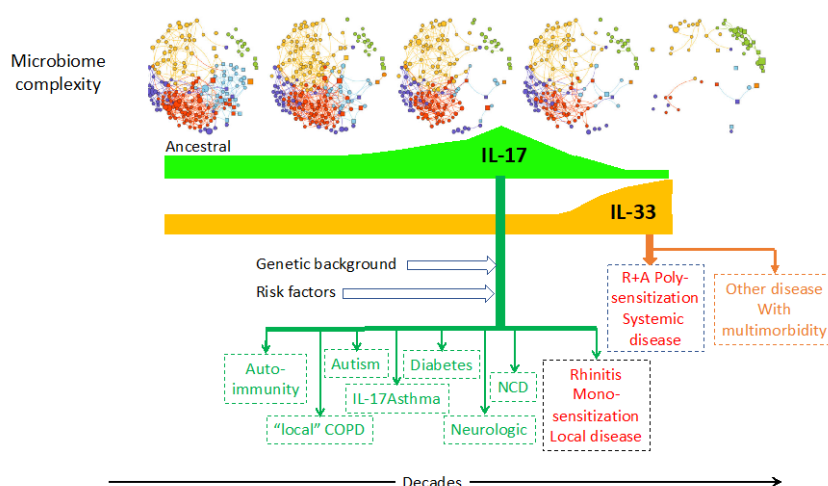


Figure 6: Putative interactions with the microbiome



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