Received: 10 September 2022 | Revised: 6 February 2023 | Accepted: 12 February 2023
DOI: 10.1111/all.15679

REVIEW ARTICLE

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

Rhinitis associated with asthma is distinct from rhinitis alone: The ARIA-MeDALL hypothesis

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

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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 polysensitization and multimorbidity, (iii) advances in mHealth for novel phenotype definitions, (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 sensitization patterns (mono- or pauci-sensitization versus polysensitization), (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 autoimmune diseases.

KEYWORDS
asthma, IL-33, multimorbidity, rhinitis, Toll-like receptors

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 polysensitized 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 approach,[17] 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 polysensitization 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[18]: "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others." 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 coexist, 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]
Polysensitization 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 polysensitized to unrelated allergens. In the present paper, polysensitization will refer to unrelated non-cross-reacting allergens.

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 (GA^2LEN, Global Allergy and Asthma European Network, FP6)[279] to better understand sensitization 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 polysensitization (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, polysensitization) 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.

2 | FROM CLINICAL OBSERVATIONS TO ARIA GUIDELINES (1980–2000)

2.1 | Mono- and polysensitization

IgE sensitization is heterogeneous.[21–23] When comparing polysensitized and monosensitized subjects: (i) Monosensitization is associated with lower total and specific IgE levels[21]; (ii) patients with monosensitization recognize fewer epitopes of individual allergens[22,23]; (iii) there is a lower level of IL-4 release by peripheral blood in monosensitization, suggesting stronger T2 immune response in polysensitization[24]; and (iv) patients sensitized in adulthood for cypress[25,26] or Betulaceae pollen allergy were often monosensitized.[27]

2.2 | From one-airway-one-disease to ARIA and beyond

In the early 1990s, asthma and rhinitis were considered as independent diseases linked by IgE-sensitization.[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-disease,[16] 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 contrary, most patients with asthma have rhinitis.[37] These data suggest common pathways in AR+A, and rhinitis-specific pathways.[38]

1. Mono- and polysensitization 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 sensitization.
4. Bronchial biopsies and allergen challenges show that nasal and bronchial inflammations are similar.
5. Airway remodeling, a characteristic of asthma, does not exist in rhinitis.
6. The concept of one-airway-one-disease is an over-simplification.

3 | POLYSENSITIZATION AND ALLERGIC MULTIMORBIDITIES IN BIRTH COHORTS

3.1 | Polysensitization

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

7. Mono- and polysensitization to different allergens represent expressions of distinct diseases. Compared to monosensitization, polysensitization 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 sensitization—suggesting that these diseases share causal mechanisms. Although IgE sensitization is independently associated with an excess comorbidity of eczema, rhinitis, and asthma, its presence accounted for only 38% of comorbidity. This suggests that IgE sensitization cannot be considered as the dominant causal mechanism of multimorbidity.[39,40]

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

TABLE 2 Differences between mono- and polysensitization.

	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 polysensitized than monosensitized children.	108,282
Current symptoms	BAMSE-MeDALL	Birch pollen: PR-10 polysensitized children had more severe AR than monosensitized. Cat/dog: Children polysensitized to cat/dog molecules had more frequent AR symptoms to cat and dog than those monosensitized.	282 108
	WHEALS	"Highly"-sensitized infants (2 years) 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: Polysensitization to 3 allergen molecules at 4–8 years is a better predictor of cat or dog symptoms at 16 years than monosensitization. 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 years identified children with a high risk of A and/or R at 16 years, in particular for A+R multimorbidity.	110
	Paris	Early polysensitization was associated with later development of allergic multimorbidity in PARIS birth cohort infants.	105,285
	MAAS	The latent class analysis revealed 3 grass-sensitization 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 sensitization. Children in the complete mite sensitization trajectory had the highest A prevalence and were the only group significantly associated with multimorbid A, AD, R. 3 trajectories were found using latent clusters. One was a high-risk atopic cluster with polysensitization, 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
		Polysensitization status at ages 6 mths, 18 mths, 4 years and 6 years 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 sensitization phenotype.	289
	WHEALS	Children sensitized to 4 or more food and inhalant allergens at age 2 had the highest risk of current asthma at 10 years.	290
	MAAS + IoW	Polysensitization early in life is associated with asthma.	291
	Meta-analysis	Polysensitization is a risk factor predicting persistence of early wheezing through school age.	292

Abbreviations: A, asthma; AD, atopic dermatitis; R, rhinitis.

3.3 | Links between polysensitization and allergic multimorbidity

MeDALL refined the identification of the polysensitized multimorbid phenotype of allergic diseases.[19,41] Polysensitized children were at a higher risk than monosensitized ones of developing asthma and rhinitis.[42] In three US studies of inner-city asthmatic children, rhinitis and polysensitization were associated with severe asthma.[43–45] "Molecular spreading," sensitization 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 polysensitization 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 monosensitized to a single molecule[47] or polysensitized. Pre-school children sensitized to several peanut proteins develop symptoms more commonly later in life than those sensitized to a single protein.[48] This may differ in adults.[49] Severity[47] and persistence of symptoms may also depend on sensitization 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, polysensitization, and current wheeze at 3 years.[55] In the CHILD cohort, AD children polysensitized to foods at an early age had the greatest risk of developing other allergic diseases.[56] On the contrary, AD without concomitant allergic sensitization was not associated with an increased risk of asthma.

4 | PERI-EPITHELIAL INFLAMMATION, LEAKY EPITHELIAL BARRIERS, AND MULTI MORBIDITIES

Allergic multimobidity 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 (4210 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 8000 patients and 267,000 days), and a longitudinal one based on rhinitis patterns (over 2500 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.

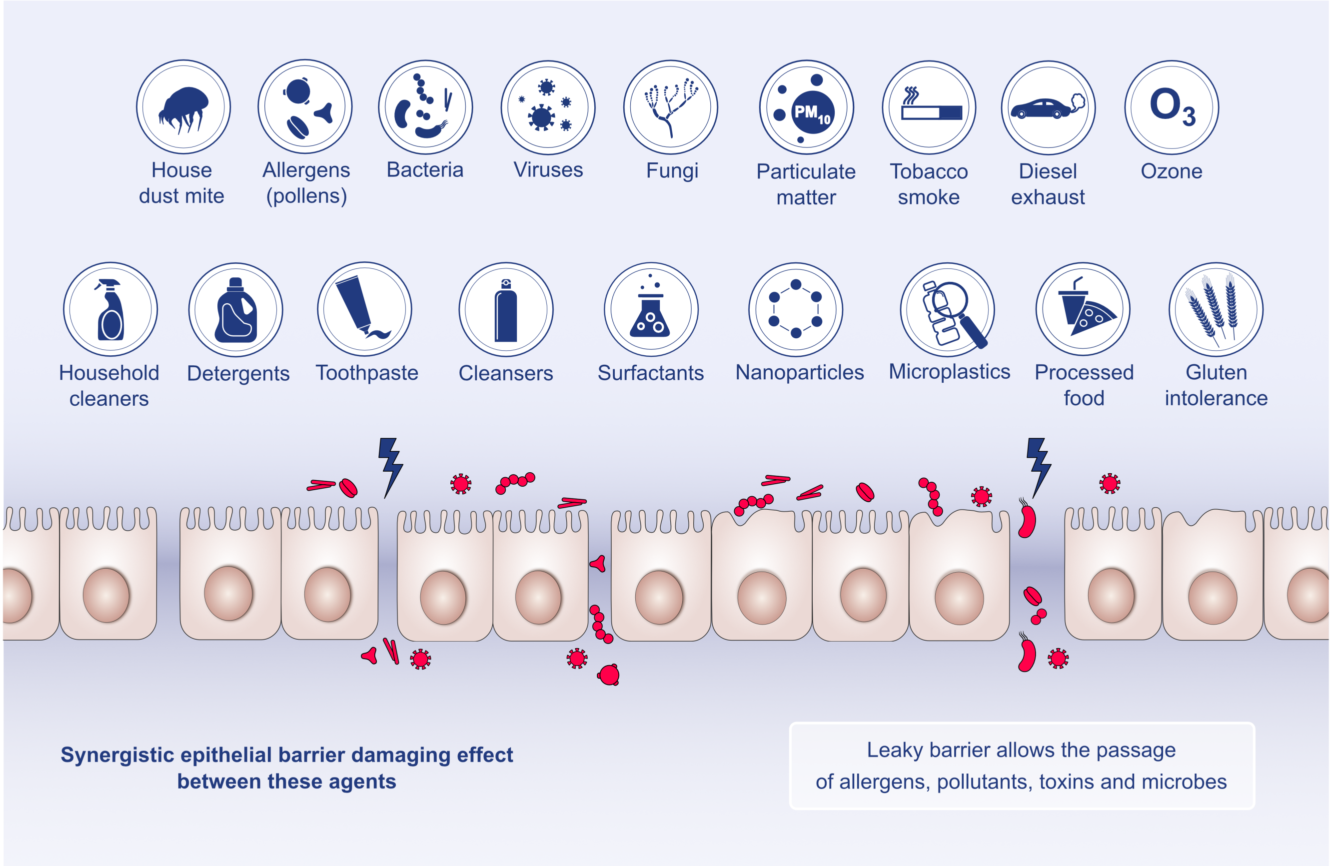

FIGURE 1 Importance of the epithelial barrier in multimorbidity.

TABLE 3 Results of the EGEA study (from Refs 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)[a]		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)

Abbreviations: A, asthma; R, rhinitis.
[a]Score adding symptoms.

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 polysensitization (Table 3).[70,71] Patients with rhinitis alone displayed fewer sensitizations than those with A+AR. These findings were reproduced in BAMSE (Barn/Children, Allergy/Asthma, Milieu, Stockholm). Overall, A+AR is associated with polysensitization in Europe,[73–80] New Zealand,[81] Brazil,[82] and China.[83,84]

Patients monosensitized 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 polysensitization.[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 EGEA[71] and a Danish cohort,[91] patients with rhinitis alone had fewer IgE sensitizations 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] Polysensitized children more often have a parental history of allergy than monosensitized 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 MeDALL, 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-analysis[102] 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 polysensitization. Early polysensitization 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 sensitization.[106] In ECRHS, in adults, the 8.8-year cumulative incidence of asthma was 2.2%.[107] Only AR with sensitization to house dust mite was associated with an increased risk of asthma independently of other allergens, and AR patients with polysensitization more commonly developed asthma.

6.6.2 | Trajectories of IgE sensitization

Trajectories of IgE sensitization from infancy to childhood show an increase of polysensitization.[48,108–110] However, once the disease is fully established (adolescents), IgE sensitization remains stable, as do the sensitization clusters.[111]

18. Although rhinitis is strongly associated with the risk of asthma, the role of polysensitization requires further studies.
19. Sensitization does not usually change when established in adolescents, suggesting a stable phenotype.

7 | OMICS FOCUSING ON ALLERGIC MULTIMORBIDITIES AND POLYSENSITZATION

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-signaling 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 with 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 genes of T2 signaling: *IL-5* (eosinophils) and *IL-33* (polysensitization 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 with 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 signaling 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 signaling 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 sensitization appear to be important for A+AR.[124,125] The C11orf30-LRRC32 region is involved in the regulation of IgE,[126] polysensitization,[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*, *C11ofr30/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 signaling.[144]

24. Genetic polymorphism studies support the multimorbidity results.

7.5 | HLA associations with allergen sensitization

HLA genes are involved in the control of the IgE response to allergens,[145,146] but genetic regulation may differ in mono- and polysensitized 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 monosensitized).[147–152]

In EGEA,[153] the most significant associations between HLA class-II alleles and IgE sensitization were observed for pollens. Some HLA class-II alleles were associated with sensitization to allergens from different families, suggesting that some alleles may favor the development of polysensitization 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 polysensitization was proposed by EGEA, suggesting that the same HLA class-II allele may be associated with different allergen families.

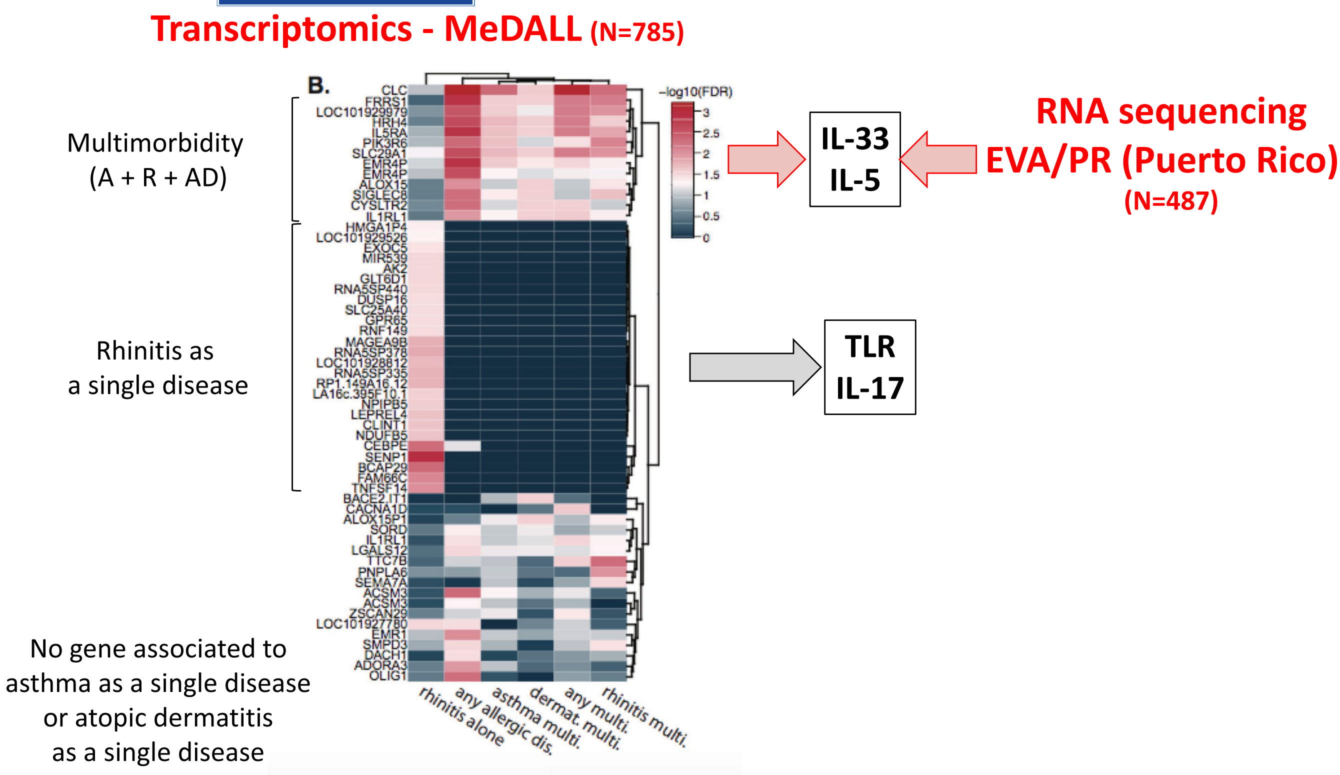

FIGURE 2 Putative differences in mechanisms underlying multimorbidity and single diseases in children and adolescents using blood transcriptomics (from Ref 118).

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 5000 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 sensitization.[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 were 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. Co-medication 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 hypothesized (Figure 3).[19] An eighth one has been added to the initial paper.

9.1 | The atopic march: persistence of T2 signaling at birth

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

9.2 | Early sensitization with very high allergen exposure

High levels of neonatal birch pollen exposure were found to induce birch pollen allergy in some[168–171] 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 signaling in early childhood

The re-occurrence or expansion of T2 signaling 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-33[179–181] and IL-17[182] can be involved.

Skin barrier dysfunction

Skin barrier dysfuntion predisposes to epicutaneous sensitization 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 AD,[188] and its sensitization may lead to multimorbidity and polysensitization in adolescence[189] 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 though the myeloid differentiation primary response gene 88 (MyD88) pathways.[192] Few allergens are recognized in these patients, suggesting a specific response to allergens in line with an MHC Class II allergen-specific sensitization.

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 signaling increases allergen-induced IL-33 release, ILC2 cytokine production, and airway inflammation.[195] Androgen receptor signaling reduces IL-33 release from bronchial epithelial cells, suggesting a negative regulator of allergic airway inflammation. These

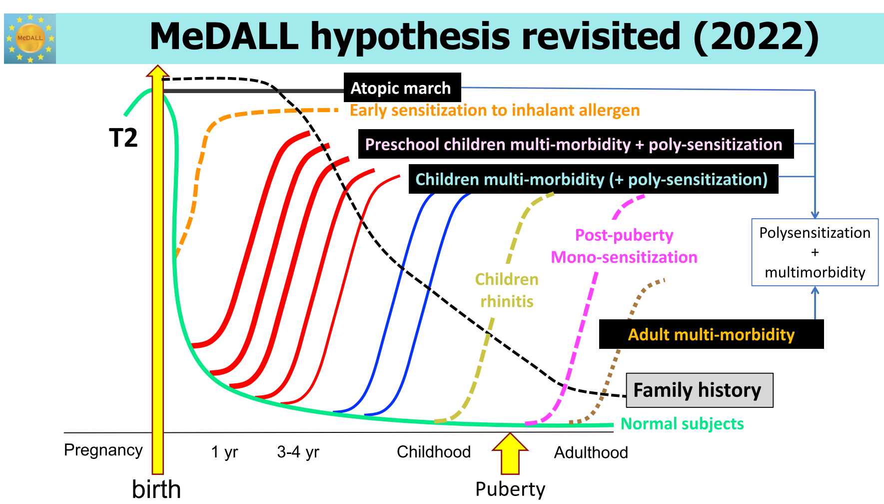

FIGURE 3 Phenotypes of IgE-mediated allergic diseases across the life cycle (adapted from Ref 19).

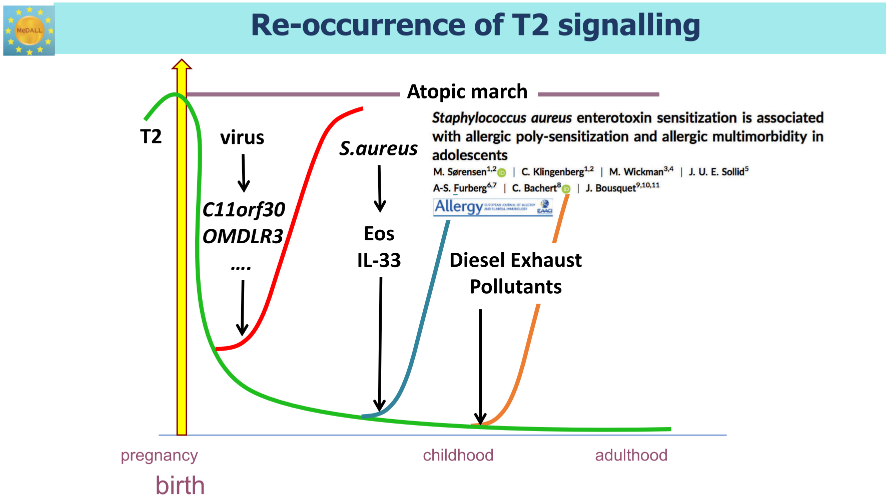

FIGURE 4 Possible mechanisms explaining the re-occurrence of Type 2 signaling.

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 sensitization may also be associated with co-factors such as DEP.[197] This is the case for tree pollens (cypress,[26,198] birch[199]) or new pollens (ragweed in Northern Italy).[199] There is not usually any family history.[25,200] In pollen allergy (e.g., cypress), adults are usually monosensitized and often suffer from rhinitis alone.[25,200] However, newer studies in the same area suggest that adults become polysensitized and suffer from asthma.[201] In soybean allergy, patients have 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 characterized 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 coexisting CRS with/without demonstrable allergic sensitization.[206] 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 ICL2. 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 signaling

Different mechanisms for polysensitization 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 allergens[189] 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 sensitization.[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 sensitization to bystander antigens,[220] and therefore lead to polysensitization.

Allergens, viruses, and pollutants can directly elaborate TSLP, IL-25, and IL-33 from the lungs.[221] On the contrary, 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 presentation,[221] and drives a T2 response.

10.3 | Allergic rhinitis alone: Local disease associated with TLR signaling 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 monosensitized 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 center 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, sensitization in Russia is mostly associated with monosensitization (e.g., *Dermatophagoides*) without clinical symptoms.[234] In Finland, polysensitization is common with a high occurrence of symptoms.[235] 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.[236] The network of skin and nasal microbiota and gene expression was richer and more diverse in the Russian subjects.[236,237] The microbiota disparity paralleled the gene expression differences. High-total IgE was associated with enhanced antiviral 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.[238] In Russian teenagers, long-non-coding RNA is upregulated, obviously mediating the gene–environment and gene–microbiota interactions.[239] Furthermore, high *Acinetobacter* abundance in the Russians correlated with suppression of innate immune response.[236] The Russians are more capable of differentiating between danger and non-danger, and between self and non-self. Overall, the rich gene–microbe network in the 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.[236] IL-33 interacts with gut and respiratory microbiome but, depending on the physiological context, it may be host-protective or pathogenic.[240,241] MyD88 is potently influenced by the microbiome,[122,235,242–244] and may be an important mechanism explaining distinct diseases. Multimorbidity may be centered 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, partly 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]

Urbanization 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 industrialization 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 (France) on cypress pollen-allergic patients may support this hypothesis.[26,201]
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 centered 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) may 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 polysensitization. This activation may occur just after birth (atopic march) or later in early childhood (re-occurrence of T2 signaling) 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 centered 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, autoimmunity, 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] autoimmune diseases,[262–264] or infertility.[265,266] 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,

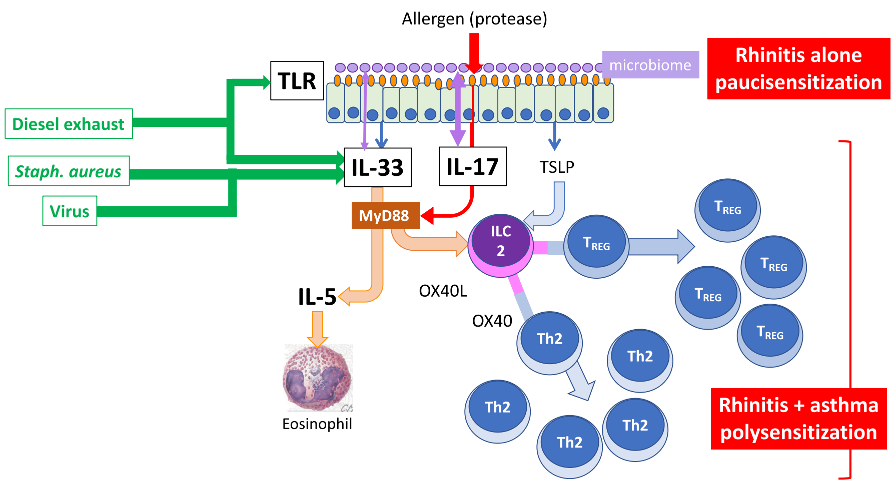

FIGURE 5 Putative mechanisms of rhinitis and rhinitis and asthma multimorbidity.

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 generalized.

Many clinical, epidemiological, and mHealth sections are based on the research done by the authors, who have been investigating the multimorbidity-polysensitization 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 generalized 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 patients,[270–272] 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 age,[274] 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

12.1 | Conclusions

Based on (i) new insights into polysensitization 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 (Table 4). Our main hypothesis is that rhinitis alone and rhinitis and asthma multimorbidity represent two distinct diseases with differences in genetic background, allergen sensitization 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 autoimmune diseases. It is clear that other pathways exist. Further research is, however, required to further explore the solidity of this concept.

ACKNOWLEDGMENTS

None. Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

None for this paper. ECRHS, EGEA, birth cohorts, GA^{2}LEN, MASK-air, MeDALL, and other research studies reported in this paper were funded separately.

CONFLICT OF INTEREST STATEMENT

Dr. Agache reports and Associate editor Allergy and CTA. Dr. C Akdis reports grants from the Swiss National Science Foundation, European Union (EU CURE), European Union, EU Novartis Research Institutes (Basel, Switzerland), Stanford University (Redwood City, Calif), and SciBase (Stockholm, Sweden), other from EAACI, other from Sanofi/Regeneron, Stanford University Sean Parker Asthma Allergy Center, Novartis, GlaxoSmithKline, and SciBase, other from Allergy journal, outside the submitted work. Dr. M. Akdis reports grants from Swiss National science Foundation, Bern and Stanford University, other from Latin American Region, other from Stanford University-Sean Parker Asthma Allergy Center, CA, other from LEO Foundation Skin Immunology Research Center, Kopenhagen, other from World allergy Congress (WAC) Istanbul, 2022, outside the submitted work. Dr. Alobid reports and Isam Alobid has received honoraria for consultancy and conferences from Viatris, Roche, Sanofi, GSK, MSD, Menarini, Salvat and Novartis. Dr. Ansotegui reports personal fees from Roxall, personal fees from UCB, personal fees from Faes Farma, personal fees from Sanofi, personal fees from Bial, personal fees from Abbott, personal fees from Bayer, personal fees from Organon, outside the submitted work. Dr. Bernstein reports grants and personal fees from GSK, grants and personal fees from ALK Abello, grants from AstraZeneca, grants from Adare, grants from Merck, grants from Novartis, grants and personal fees from Regeneron, grants from TEVA, grants from Avillion, grants from Cipla, grants from Knopp, grants from Glenmark, grants from Leo, grants and personal fees from ARS, personal fees from Aquestive, personal fees from Guidepoint global, personal fees from GLG, outside the submitted work. Dr. Bosnic-Anticevich reports grants from TEVA, personal fees from TEVA, personal fees from TEVA, personal fees from AstraZeneca, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Sanofi, personal fees from Mylan, outside the submitted work. Dr. Boulet reports grants from Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Sanofi-Regeneron, personal fees from Astra Zeneca,

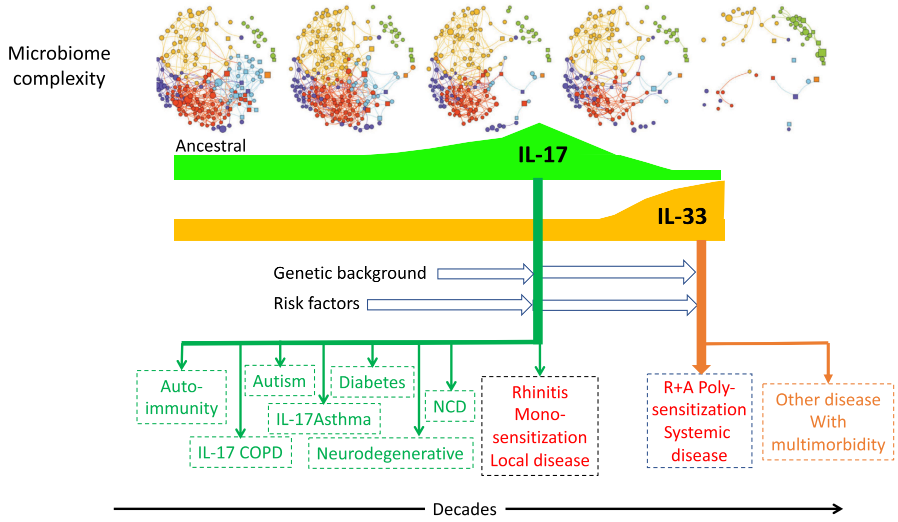

FIGURE 6 Putative interactions with the microbiome.

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 Karelia[293] 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 polysensitization 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 polysensitization: Polysensitization and multimorbidity may be a primary event stemming from (i) differences in innate immunity associated with altered adaptive immunity in some patients or (ii) persisting alterations in innate immunity in others.
Differences between allergy and parasites: IL-33 signaling plays a pathological and protective role in parasitic infections.[295,296] Control of inflammation induced by parasites by IL-17 is also possible for efficient host protection.[297–299]

Novartis, GlaxoSmithKline, Merck, Sanofi-Regeneron, personal fees from AstraZeneca, Covis, GlaxoSmithKline, Novartis, Merck, Sanofi, outside the submitted work. Dr. Bousquet reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from Mask-air-SAS, outside the submitted work. Dr. Brightling reports grants and personal fees from AZ, grants and personal fees from GSK, grants and personal fees from Novartis, grants and personal fees from Chiesi, grants and personal fees from BI, grants and personal fees from Roche, grants and personal fees from Genentech, grants and personal fees from Sanofi, grants and personal fees from Regeneron, grants and personal fees from Mologic, grants and personal fees from 4DPharma, outside the submitted work. 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Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from Streamedup! GmbH, grants from Pohl-Boskamp, grants from Inmunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Regeneron Pharmaceuticals Inc., personal fees from RG Aerztefortbildung, personal fees from Institut für Disease Management, personal fees from Springer GmbH, grants and personal fees from AstraZeneca, personal fees from IQVIA Commercial, personal fees from Ingress Health, personal fees from Wort&Bild Verlag, personal fees from Verlag ME, personal fees from Procter&Gamble, outside the submitted work; and member of EAACI Excom, member of ext. board of directors DGAKI; coordinator, main- or co-author of different position papers and guidelines in rhinology, allergology and allergen-immunotherapy. 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Dr. Valenta reports grants and personal fees from Viravaxx AG, Vienna, Austria, grants and personal fees from Worg Pharmaceuticals, Hangzhou, China, grants from HVD Biotech, Vienna, Austria, outside the submitted work. Dr. Van Ganse reports other from PELyon, during the conduct of the study. Dr. van Hage reports personal fees from Thermo Fisher Scientific, outside the submitted work. Dr. Weiss reports other from NIH, from UpToDate, non-financial support from Histolix, outside the submitted work. Dr. Worm reports other from Regeneron Pharmaceuticals, other from DBV Technologies S.A, other from Stallergenes GmbH, other from HAL Allergie GmbH, other from Bencard Allergie GmbH, other from Allergopharma GmbH & Co. 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Zuberbier reports personal fees from AstraZeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from Meda, personal fees from Menarini, personal fees from Merck, personal fees from MSD, grants and personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, grants and personal fees from Henkel, personal fees from Kryolan, personal fees from L'Oréal, outside the submitted work; and Organizational affiliations: Committee member: WHO-Initiative “Allergic Rhinitis and Its Impact on Asthma” (ARIA), Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI), Head: European Centre for Allergy Research Foundation (ECARF), President: Global Allergy and Asthma European Network (GA2LEN), Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). The other 173 authors have nothing to disclose, outside the submitted work.

DISCLAIMER

Dr. Alkis Togias' co-authorship of this publication does not constitute endorsement by the National Institute of Allergy and Infectious Diseases, the National Institutes of Health or any other agency of the United States Government.

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How to cite this article: Bousquet J, Melén E, Haahtela T, et al. Rhinitis associated with asthma is distinct from rhinitis alone: The ARIA-MeDALL hypothesis. *Allergy*. 2023;78:1169-1203. doi:10.1111/all.15679