Title	Rhinitis associated with asthma is distinct from rhinitis alone: The ARIA-MeDALL hypothesis
Type	Article
URL	https://clok.uclan.ac.uk/id/eprint/45841/
DOI	https://doi.org/10.1111/all.15679
Date	2023
Citation	Bousquet, J, Melén, E, Haahtela, T, Koppelman, G H, Togias, A, Valenta, R, Akdis, C A, Czarlewski, W, Rothenberg, M et al (2023) Rhinitis associated with asthma is distinct from rhinitis alone: The ARIA-MeDALL hypothesis. Allergy. ISSN 0105-4538
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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.15679

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
A+AR: Asthma and allergic rhinitis multimorbidity
A+R: Asthma and rhinitis multimorbidity
A+R+AD: Asthma, rhinitis and atopic dermatitis multimorbidity
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: Chronic rhinosinusitis
CRS w NP: CRS with nasal polyposis
DC: Dendritic cells
DEP: Diesel exhaust particules
Der p: *Dermatophagoides pteronyssinus*
EGEA: Epidemiological study on the Genetics and Environment of Asthma
ECRHS: European Community Respiratory Health Survey
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

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 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 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-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 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 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 (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] Brazil [82] 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 EGEA [71] 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 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 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, 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 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 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 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-33 [179-181] as well as IL-17 [182] 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 AD [188] and its sensitisation may lead to multimorbidity and polysensitisation 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 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] 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 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 sensitisation [206] 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 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 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 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 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 antigens [220] 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 presentation [221] 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 monosensitsation (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 parallelled 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 potently 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. [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 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 diseases [262] [263,264] 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, 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 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 (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.

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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^{2}LEN, 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 group 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 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 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 1: Importance of the epithelial barrier in multimorbidity

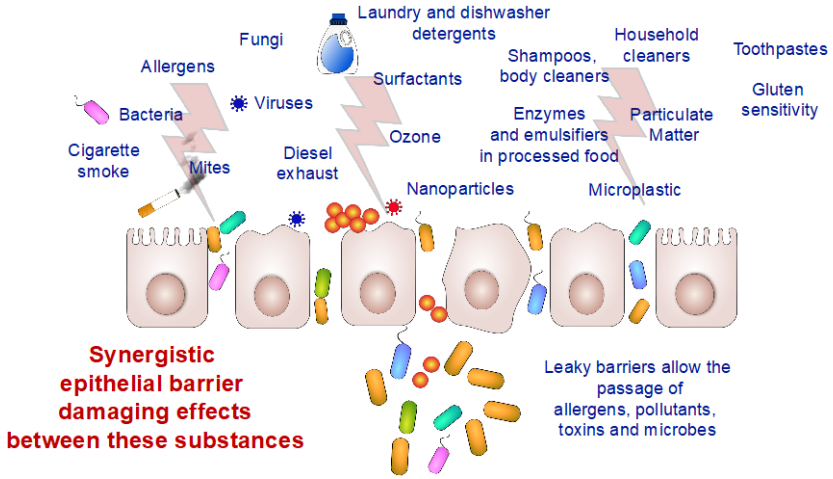


Figure 2: Putative differences in mechanisms underlying multimorbidity and single diseases in children and adolescents using blood transcriptomics (from [118])

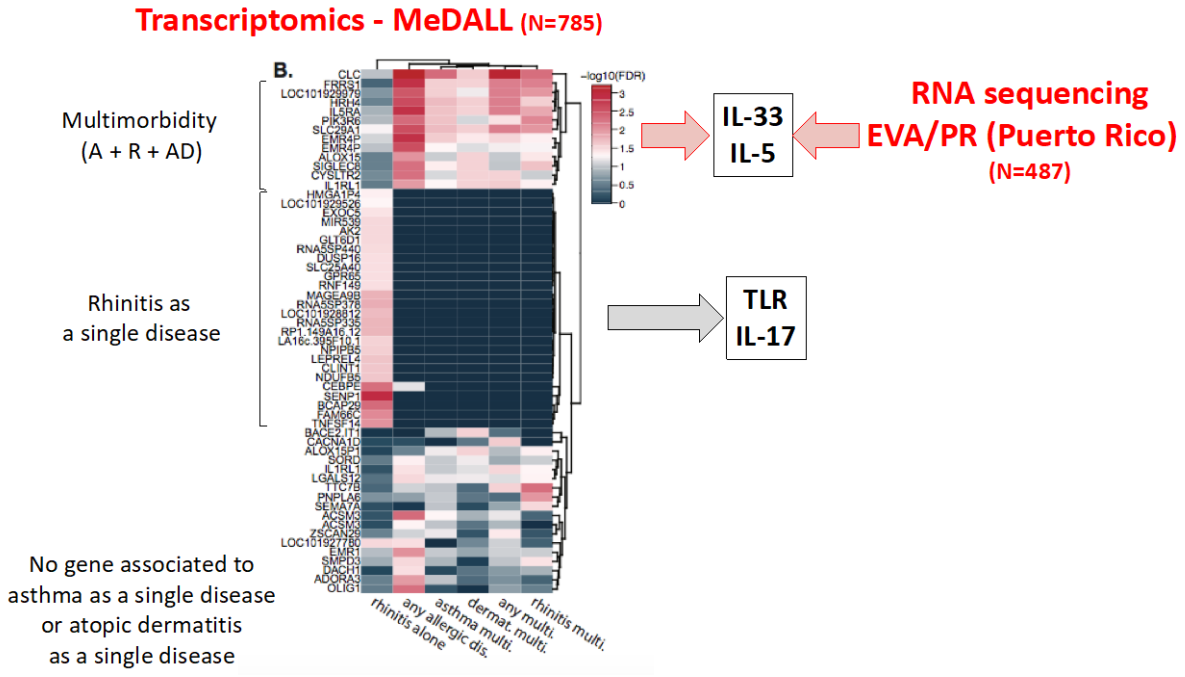


Figure 3: Phenotypes of IgE-mediated allergic diseases across the life cycle (adapted from [19])

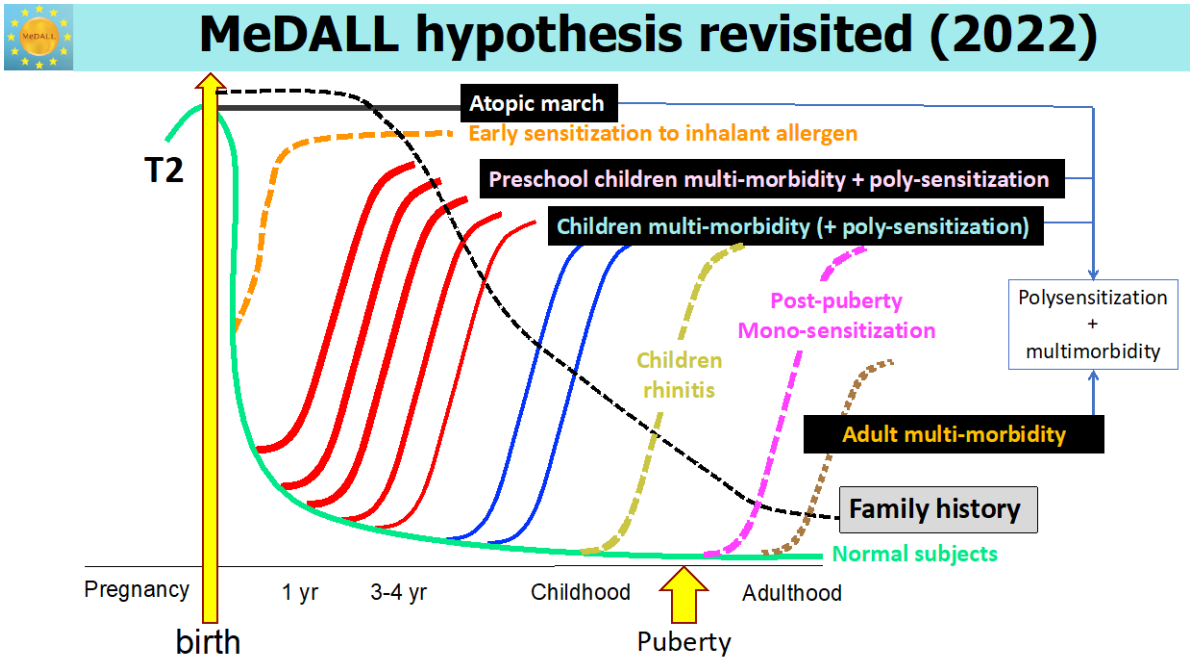


Figure 4: Possible mechanisms explaining the re-occurrence of Type 2 signalling

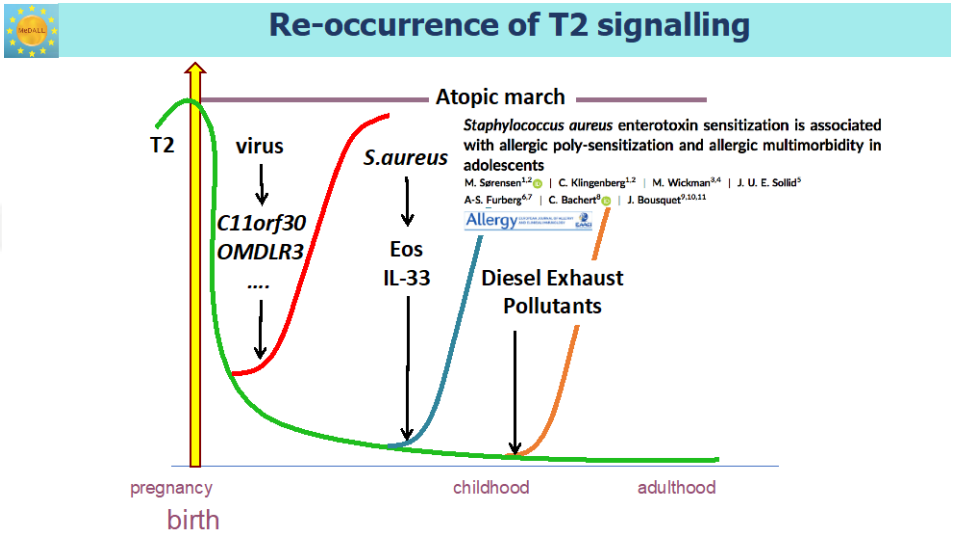


Figure 5: Putative mechanisms of rhinitis and rhinitis and asthma multimorbidity

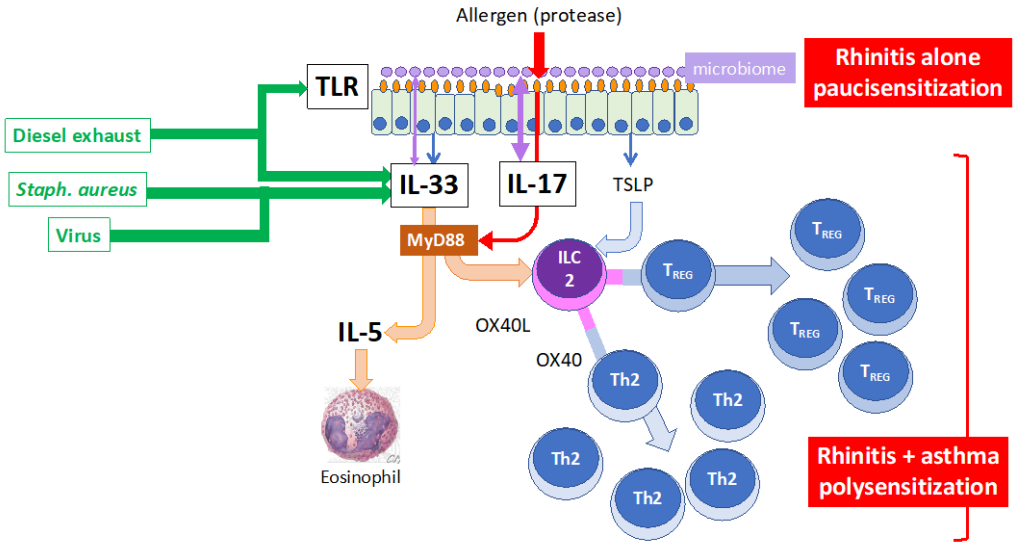
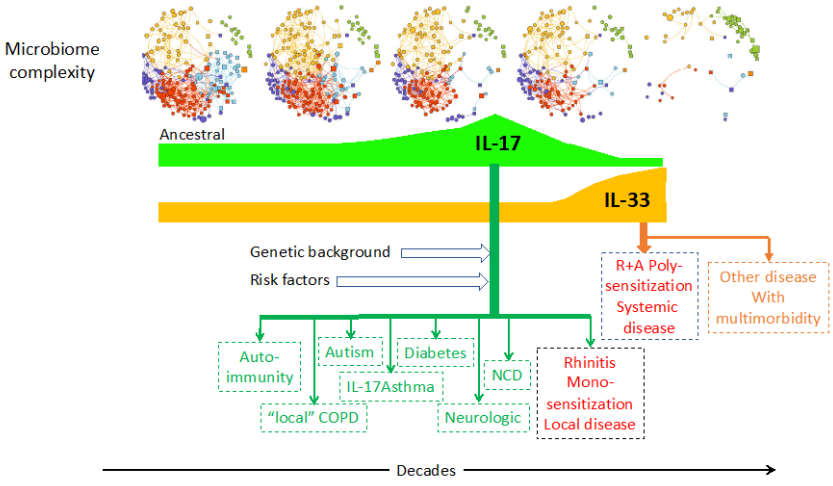


Figure 6: Putative interactions with the microbiome



Funding: 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.

Acknowledgments: None

Data sharing: **Not applicable for this paper**

Ethics: Not applicable for this paper.

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AH Abdul Latiff, W Aberer, I Agache, M Al-Ahmad, I Alobid, HS Arshad, E Asayag, A Baharudin, KS Bennoor, EC Bergea, D Bernstein, M Bewick, H Blain, M Bonini , F Braido, R Bumbacea, A Bush, M Calderon, G Calvo, P Camargos, L Caraballo, V Cardona, WW Carr, P Carreiro-Martins, T Casale, AM Cepeda Sarabia, R Chandrasekharan, I Cherez-Ojeda, T Chivato, E Chkhartishvili, G Christoff, D Chu, C Cingi, J Correia da Sousa, C Corrigan, A Custovic, G D'Amato, S Del Giacco, F De Blay, P Devillier, A Didier, M do Ceu Teixeira, D Dokic, H Douagui, C Durham M Dykewicz, T Eiwegger, ZA El Sayed, R Emuzyte, A Fiocchi, N Fyhrquist, RM Gomez, M Gotua, MA Guzman, J Hagemann, S Halken, DMG Halpin, M Hoffman, E Hossny, M Hrubiško, C Irani, Z Ispayeva, E Jares, T JarttI, E Jassem, K Julge, J Just, M Jutel, I Kaidashev, O Kalayci, O Kalyoncu, P Kardas, B Kirenga, H Kraxner, I Kull, S La Gruta, Lau, L Le Tuyet Thi, M Levin, B Lipworth, O Lourenço, B Mahboub, MJ Mäkelä, E Martinez Infante, P Matricardi, N Miculinic, N Migueres, F Muhaltan, Y Mohamad, M Moniuszko, S Montefort, H Neffen, K Nekam, E Nunes, D Nyembue Tshipukane, R O'Hehir, I Ogulur, K Ohta, Okubo, S Ouedraogo, H Ozle, I Pali-Schöll, O Palomares, K Palosuo, C Panaitescu, Y Panayotis, P Panzner, HS Park, V Patella,

Pitsios, D Plavec, TA Popov, F Puggioni, S Quirce, M Recto, R Repka-Ramirez, C Roballo-Cordeiro, N Roche, J Romantowski, N Rosario Filho, M Rottem, H Sagara, F Sarquis-Serpa, Z Sayah, S Scheire, P Schmid, JC Sisul, D Sole, M Soto-Martinez, M Sova, A Sperl, O Spanger, R Stelmach, C Suppli-Ulrik, M Thomas, T To, A Todo-Bom, PV Tomazic, M Urruta-Pereira, M Valentin-Rostan, E van Ganse, M Van Hage, T Vasankari, P Vichyanond , G Viegi, D Wallace, DY Wang, S Williams, M Worm, O Yussuf, F Zaitoun, M Zerrnotti, M Zidarn, J Zuberbier are ARIA members for the dissemination of the hypothesis.

All authors read the paper, most gave some comments and all agreed on its publication.

Conflict Of Interest:

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, 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.
Dr. Buhl reports grants to Mainz University Hospital from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche, and personal fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Novartis, Roche, Sanofi, and Teva, all outside the submitted work.

Dr. Cardona reports personal fees from ALK, personal fees from Allergopharma, personal fees from GSK, grants from Thermofisher, outside the submitted work.
Dr. Carr reports personal fees from Astra Zeneca, personal fees from Teva, non-financial support from Aluna, outside the submitted work.
Dr. Carreiro-Martins reports and personal fees from Abbvie, AstraZeneca, Bial, GSK, Mylan Medinfar, Novartis and Sanofi all outside the submitted work.
Dr. Casale reports personal fees from SANOFI REGENERON, personal fees from GENENTECH, non-financial support from GSK, outside the submitted work.
Dr. Cecchi reports personal fees from Thermofisher, personal fees from Astra Zeneca, personal fees from Sanofi, personal fees from Novartis, outside the submitted work.
Dr. Celedón reports other from GSK, other from Merck, other from Pharmavite, outside the submitted work.
Dr. Chaves Loureiro reports grants from GSK, from AstraZeneca, from GSK, from Novartis, from Sanofi, from Teva, outside the submitted work.
Dr. Cruz reports personal fees from AstraZeneca, personal fees from Boehringer-Ingelheim, personal fees from Chiesi, personal fees from Abdi-Ibrahim, personal fees from GSK, personal fees from Novartis, personal fees from Sanofi, personal fees from Eurofarma, outside the submitted work.
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Dr. Devillier reports personal fees and non-financial support from Astra Zeneca, personal fees from Chiesi, personal fees and non-financial support from Boehringer Ingelheim, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees and non-financial support from Stallergenes, personal fees and non-financial support from ALK Abello, outside the submitted work.
Dr. Durham reports other from Revelo, other from ANGANY Inc., personal fees from PneumoUpdate, personal fees from Abbott Lab., personal fees from ALK A/S, personal fees from Stallergenes, outside the submitted work.
Dr. Eiwegger reports personal fees from Danone/Nutricia/Milupa, grants from DBV, non-financial support from Novartis, personal fees from ThermoFisher, personal fees from Aimmune, grants and personal fees from ALK, non-financial support from MADX, personal fees from EFSA, outside the submitted work; and is a Co-I or scientific lead in three investigator initiated oral immunotherapy trials supported by the Allergy and Anaphylaxis Program Sickkids and serves as an associate editor for Allergy.
Dr. Fiocchi reports grants from Sanofi, grants from Novartis, personal fees from ABC Farmaceutici, outside the submitted work.
Dr. Fokkens reports the Amsterdam University Medical Centre to receive grants from GSK, Novartis, Sanofi, grants from AK, Mylan, Allergy Therapeutics, from null, outside the submitted work; and Prof. Fokkens was in advisory boards of GSK, Sanofi, and Dianosic.
Dr. Gemicioglu reports grants from AstraZeneca, grants from Sanofi, grants from Deva, grants from Abdi Ibrahim, grants from Sandoz, grants from GSK, outside the submitted work.
Dr. Haahtela reports other from Orion Pharma, outside the submitted work.
Dr. Haggeman reports personal fees from Sanofi Genzyme, personal fees from Novartis, personal fees from GlaxoSmithKline, during the conduct of the study.
Dr. Halpin reports personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, personal fees from Inogen, personal fees from Pfizer, personal fees from Novartis, personal fees from Sanofi, personal fees from Menarini, outside the submitted work.
Dr. Ivancevich reports personal fees from Laboratorios Casasco, personal fees from Faes Farma, personal fees from Abbott Ecuador, personal fees from Bago Bolivia, outside the submitted work.

Dr. Jutel reports personal fees from ALK-Abello, personal fees from Allergopharma, personal fees from Stallergenes, personal fees from Anergis, personal fees from Allergy Therapeutics, personal fees from Leti, personal fees from HAL, during the conduct of the study; personal fees from GSK, personal fees from Novartis, personal fees from Teva, personal fees from Takeda, personal fees from Chiesi, outside the submitted work.

Dr. Klimek reports grants and personal fees from Allergopharma, grants and personal fees from MEDA/Mylan, personal fees from HAL Allergie, grants from ALK Abelló, grants and personal fees from LETI Pharma, grants from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeut., grants from AstraZeneca, grants from GSK, grants from Inmunotk, personal fees from Cassella med, outside the submitted work; and Membership: ÚeDA ÝGHNOÝeutsche Akademie für Allergologie und klinische ImmunologieÐNO-BV ÐPAÞAACI.

Dr. Koppelman reports grants from Lung Foundation of the Netherlands, TEVA the Netherlands, ZON-MW (VICI grants), Ubbo Emmius Foundation, GSK, Vertex, outside the submitted work; and Advisory board meetings to GSK, Astra Zeneca and Pure IMS.

Dr. Kuna reports personal fees from Adamed, personal fees from Berlin Chemie Menarini, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Glenmark, personal fees from Krka, personal fees from Novartis, personal fees from Polpharma, personal fees from GSK, personal fees from Sanofi, outside the submitted work.

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Dr. Larenas Linnemann reports personal fees from ALK, Allakos, Amstrong, Astrazeneca national and global, Chiesi, DBV Technologies, Grunenthal, GSK national and global, Mylan/Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot, grants from Abbvie, Lilly, Sanofi, Astrazeneca, Lilly, Pfizer, Novartis, Circassia, UCB, GSK, Purina institute., outside the submitted work.

Dr. Lau reports grants and personal fees from DBV, personal fees from Sanofi-Aventis, personal fees from Allergopharma, personal fees from Leti, personal fees from Nutricia, outside the submitted work.

Dr. Le Thi Tuyet reports personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from Glaxo-Smith Kline, personal fees from MSD, personal fees from DKSH, personal fees from Gigamed, personal fees from Abbott, personal fees from Pfizer, personal fees from Cheisi, personal fees from Materia Medica, personal fees from Hyphens, personal fees from Tedis, outside the submitted work.

Dr. Lipworth reports personal fees from Glenmark, grants and personal fees from AstraZeneca, grants and personal fees from Chiesi, personal fees from Cipla, grants, personal fees and other from Sanofi, outside the submitted work; and Son of BJL is employee of AstraZeneca.

Dr. Louis reports and Grants from GSK, Chiesi and AZ and adboard and lecture fees from AZ, GSK, Chiesi.

Dr. Makris reports personal fees from NOVARTIS, personal fees from MENARINI, other from GSK, personal fees from ASTRA ZENECA, personal fees and other from SANOFI, personal fees and other from PFIZER, outside the submitted work.

Dr. Maurer reports other from Astria, Allakos, Alnylam, Amgen, Aralez, ArgenX, AstraZeneca, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GIInnovation, GSK, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pfizer, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third Harmonic Bio, UCB, and Uriach., outside the submitted work.

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Dr. Mullol reports personal fees and other from SANOFI-GENZYME & REGENERON, personal fees and other from NOVARTIS & GENETECH, grants and personal fees from VIATRIS (MEDA / MYLAN Pharma), grants and personal fees from NOUCOR / URIACH Group, personal fees from Mitsubishi-Tanabe, personal fees from Menarini, personal fees from UCB, personal fees and other from AstraZeneca, personal fees and other from GSK, personal fees from MSD, outside the submitted work.
Dr. Naclerio reports other from Sanofi, other from Lyra, other from Regeneron, outside the submitted work.
Dr. Nadeau reports grants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS), and Food Allergy Research & Education (FARE); Director of World Allergy Organization (WAO) , Advisor at Cour Pharma, co-founder of Before Brands, Alladapt, Latitude, and IgGenix; and Nartional Scientific Committee member at Immune Tolerance Network (ITN), and National Institutes of Health (NIH) clinical research centers, outside the submitted work; In addition, Dr. Nadeau has the following patents: "Special Oral Formula for Decreasing Food Allergy Risk and Treatment for Food Allergy," (with royalties paid to Before Brands and Alladapt), "Granulocyte-based methods for detecting and monitoring immune system disorders," (issued), "Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders," (issued), "Microfluidic Device and Diagnostic Methods for Allergy Testing Based on Detection of Basophil Activation," (pending).
Dr. Okamoto reports personal fees from Torii Co., LtD., personal fees from ALK, personal fees from Novartis, personal fees from Kirin pharmaceutical Co., personal fees from Tanabe-Mitsubishi Pharmaceutical Co., outside the submitted work.
Dr. Olze reports grants and personal fees from F. Hoffmann-La Roche Ltd, grants and personal fees from Sanofi-Aventis Deutschland GmbH, grants and personal fees from AstraZeneca GmbH, grants and personal fees from GlaxoSmithkline GmbH & Co., grants and personal fees from KGĐ grants and personal fees from Novartis, outside the submitted work.
Dr. Palomares reports and Oscar Palomares received research grants from Inmunotek S.L., Novartis, MINECO, MICINN and CAM Đ'dOscar Palomares has received fees for giving scientific lectures from:Úllergy Therapeutics, Amgen, AstraZeneca, GSK, Inmunotek S.L, Novartis, Sanofi-Genzyme and StallergenesĐ'dOscar Palomares has participated in advisory boards from Novartis, AstraZeneca, Pfyzer, and Sanofi-Genezyme.
Dr. Papadopoulos reports personal fees from Novartis, personal fees from Nutricia, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI, personal fees from MYLAN/MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT BIOTECH, personal fees from Boehringer Ingelheim, grants from Gerolymatos International SA, grants from Capricare, outside the submitted work.
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.

Dr. Plavec reports grants and personal fees from GlaxoSmithKline, personal fees from Berlin Chemie Menarini, personal fees from Pliva, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Belupo, personal fees from Novartis, personal fees from MSD, personal fees from Chiesi, personal fees from Revenio, non-financial support from Philips, outside the submitted work.

Dr. Quirce reports personal fees and non-financial support from GSK, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Novartis, personal fees and non-financial support from Mundipharma, personal fees and non-financial support from Teva, personal fees and non-financial support from Allergy Therapeutics, outside the submitted work.

Dr. Regateiro reports personal fees from Novartis, personal fees from Sanofi, personal fees from AstraZeneca, personal fees from GSK, personal fees from Medinfar, personal fees from Azentis, outside the submitted work.

Dr. Ring reports and Honoraria for lectures: AbbVie, Sanofi, Viatris and Allergika.

Dr. Roche reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, grants and personal fees from GSK, personal fees from AstraZeneca, personal fees from Chiesi, grants and personal fees from Pfizer, personal fees from Sanofi, personal fees from Zambon, personal fees from MSD, outside the submitted work.

Dr. Rosario Filho reports and I receive honoraria as speaker, consultant fand research grants for Sanofi, Abbvie, AstraZeneca, Boehringer, Chiesi, Novartis,Mantecorp, Janssen, Vertex, Abbott.

Dr. Rothenberg reports personal fees from Pulm One, personal fees from Spoon Guru, personal fees from ClostraBio, personal fees from Serpin Pharm, personal fees from Allakos, personal fees from Celldex, grants and personal fees from Glaxo Smith Kline, grants and personal fees from Regeneron/Sanofi, personal fees from Nextstone, personal fees from Bristol Myers Squib, personal fees from Ellodi Pharm, personal fees from Revolo Biotherapeutics, other from Ception Therapeutics/Teva Pharm, outside the submitted work.

Dr. Samoliński reports personal fees from Polpharma, personal fees from Viatris, grants and personal fees from AstraZeneca, personal fees from TEVA, personal fees from patient ombudsman, personal fees from Polish Allergology Society, grants from GSK, outside the submitted work.

Dr. Sarquis-Serpa reports personal fees and other from Novartis, personal fees from Takeda/Shire, personal fees from Sanofi, personal fees from GSK, other from AstraZeneca, outside the submitted work.

Dr. Sastre reports grants and personal fees from SANOFI, personal fees from GSK, personal fees from NOVARTIS, personal fees from ASTRA ZENECA, personal fees from MUNDIPHARMA, personal fees from FAES FARMA, outside the submitted work.

Dr. Schmid reports other from AbbVIe, ALK Abello, Astra Zeneca, Glaxo Smith Kline, LEO, Lilly, Novartis, Pfizer, Roche Pharma, SanofiGenzyme, Stallergenes, Thermo Fisher, during the conduct of the study.

Dr. Suppli-Ulrik reports grants and personal fees from AZ, grants and personal fees from GSK, personal fees from Chiesi, personal fees from Orion Pharma, grants and personal fees from Sanofi, personal fees from TEVA, personal fees from Pfizer, grants and personal fees from BI, personal fees from Novartis, outside the submitted work.

Dr. Thomas reports personal fees from GSK, outside the submitted work.

Dr. Todo-Bom reports grants and personal fees from Novartis, personal fees from Astra Zeneca, grants and personal fees from GSK, grants and personal fees from Sanofi, grants and personal fees

from AbbVie, personal fees from Mylan, grants and personal fees from Leti, personal fees from Bial, outside the submitted work.

Dr. Toppila-Salmi reports grants from GSK, personal fees from AstraZeneca, personal fees from ALK Abello, personal fees from Roche, personal fees from Novartis, personal fees from Sanofi Pharma, outside the submitted work.

Dr. Torres reports grants from European Comission, grants from SEAIC, grants from ISCIII, personal fees from Diater Laboratories, personal fees from Leti Laboratories, other from Aimmune Therapeutics, outside the submitted work.

Dr. Tsiligianni reports grants from GSK Hellas, Astra Zeneca Hellas,Boehringer Ingelheim, , personal fees from Astra Zeneca Hellas,Boehringen Ingelheim Novartis, Chiesi, outside the submitted work.

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. KG , other from ALK-Abelló Arzneimittel GmbH, other from Mylan Germany GmbH, other from Leo Pharma GmbH, other from Sanofi-Aventis Deutschland GmbH, other from Aimmune Therapeutics UK Limited, other from Actelion Pharmaceuticals Deutschland GmbH, other from Novartis AG, other from Biotest AG, other from AbbVie Deutschland GmbH & Co. KG, other from Lilly Deutschland GmbH, other from Phadia GmbH, other from Amgen GmbH , other from Boehringer Ingelheim Pharma GmbH , other from Swixx Biopharma, other from AstraZenceca GmbH, other from Pharm Research Associates (UK) Ltd, other from Worg Pharmaceutics (Hangzhou) Co. Ltd, other from med update GmbH, outside the submitted work.

Dr. T. 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.