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Allergic multimorbidity

Association with inflammatory markers, symptoms, lung function, and background factors

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Abstract
Blöndal, V. 2025. Allergic multimorbidity. Association with inflammatory markers, symptoms, lung function, and background factors. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2212. 75 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2669-6.

Background: Asthma, rhinitis, and eczema are common. Considerable multimorbidity exists involving all three diseases, which cannot be explained by chance. Allergic sensitisation increases the risk of multimorbidity, though not much is known about other factors impacting their co-occurrence.

Aim: The overall aim of this thesis was to investigate factors associated with allergic multimorbidity.

Methods and results: We have investigated allergic multimorbidity in terms of background and demographic factors, symptom burden, lung function, allergic sensitisation, and inflammatory markers: total immunoglobulin E (IgE), C-reactive protein (CRP), periostin, fractional exhaled nitric oxide (FENO), alveolar nitric oxide (CANO), blood eosinophil counts, eosinophil activation markers (eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN)).

The study populations were mainly middle-aged adults, except for paper III, which comprised children and young adults. Paper I included 216 individuals from the European Community Respiratory Health Survey (ECRHS II). Paper II was based on 437 individuals from the Swedish part of the Global Allergy and Asthma European Network (GA2LEN). Paper III involved 411 participants from the Minimally Invasive Diagnostics for Asthma and Allergic Diseases Study (MIDAS). Paper IV was based on 255 individuals who were followed for 10 years from ECRHS II to ECRHS III.

The main findings were that individuals with allergic multimorbidity were more likely to be polysensitised to allergens and had higher levels of total IgE compared with those with only one disease. Both factors, as well as higher FENO and ECP at baseline, were associated with persistent allergic disease over time. Multimorbidity was associated with higher levels of FENO in subjects with asthma aged under 18 years and EDN. Those with multimorbidity reported more asthma and allergy symptoms, had heredity, especially maternal heredity. We found both higher and lower lung function among those with more than one allergic disease, which underscores the heterogeneity of asthma as a disease.

Conclusion: We found allergic multimorbidity to be associated with polysensitisation, higher levels of type 2 inflammation, and higher symptom burden compared with those with only one allergic disease. Highlighting the importance of multimodal management when striving to decrease the symptom burden and socioeconomic cost of allergic multimorbidity.

Keywords: Allergic multimorbidity, asthma, rhinitis, eczema

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Breathing should be effortless — unless your T cells have other plans

Unknown

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Study of atopic multimorbidity in subjects with rhinitis using multiplex allergen component analysis. Blöndal V, Sundbom F, Borres MP, Högman M, Alving K, Malinovschi A, Janson C. *Clinical and Translational Allergy*, 2020;10(1):6.

II. Multimorbidity in asthma, association with allergy, inflammatory markers and symptom burden, results from the Swedish GA²LEN study. Blöndal V, Malinovschi A, Sundbom F, James A, Middelveld R, Franklin KA, Lundbäck B, Janson C. *Clinical and Experimental Allergy*, 2021;51(2):262–272.

III. Asthma in combination with rhinitis and eczema is associated with a higher degree of type-2 inflammation and symptom burden than asthma alone. Blöndal V, Janson C, Sundbom F, Borres MP, Hallgren J, Tsolakis N, Alving K, Malinovschi A. *Allergy. European Journal of Allergy and Clinical Immunology*, 2021;76(12):3827-3829.

IV. Allergic sensitisation and type-2 inflammation is associated with new-onset and persistent allergic disease**.** Blöndal V, Sundbom F, Zhou X, Movérare R, Borres MP, Högman M, Alving K, Malinovschi A, Janson C. *Clinical and Translational Allergy*, 2023;13(4):e12240.

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Contents

Abbreviations

ACT	asthma control test
B-Eos	blood eosinophils
BMI	body mass index
C_ANO	alveolar nitric oxide concentration
ECP	eosinophilic cationic protein
F_ENO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	Forced vital capacity
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
ILC	innate lymphoid cells
IL1R1	Interleukin 1 receptor type 1
LABA	long-acting beta-agonists
LTRA	leukotriene receptor antagonists
P-EDN	plasma eosinophil-derived neurotoxin
Th	T-helper cells
TSLP	thymic stromal lymphopoietin
U-EDN	urine eosinophil-derived neurotoxin

Introduction

Asthma was first defined in the 19th century, though it has existed for much longer. The word asthma comes from the Greek and means ”short of breath”. (1) The earliest documented treatment for asthma, around 1500 years before Christ, was inhaling the smoke of herbs. (2) In the 19^{th} century, black coffee was tried, which contains Theobromine, a substance related to Theophylline. (1) Asthma cigarettes containing nonselective muscarinic acetylcholine receptor antagonists were sold in the mid-20^{th} century. (3) Since then, both the knowledge on asthma as a condition as well as treatment options have increased vastly. In the 1892 edition of ” The Principles and Practice of Medicine,” Sir William Osler noted a resemblance to hay fever, adding even more complexity to the disease. (4) Asthma, rhinitis, and eczema often occur together, especially if there is a history of allergy. (5) It has become more apparent over the years that asthma is really an umbrella term for many different phenotypes. (6) It is likely that individuals who develop asthma, rhinitis, and eczema at the same time also differ from other asthma phenotypes in other ways. Having more than one disease at the same time increases the symptom burden for the individual. (7) What is more, healthcare costs in multimorbid disease are estimated to be five times higher than those attributable to asthma alone. (8)

The prevalence of allergies is estimated to be around 25-30% worldwide and is increasing, as are the conditions associated with it. (9, 10) The World Health Organization considers allergy the fourth most common chronic disease and estimates that more than half of the world’s population will have one by 2050. (10) This highlights the importance of finding out more about allergic disease and how we can treat and prevent it.

Multimorbidity instead of comorbidity

The term comorbidity was first used in 1970 to describe any additional disease that has existed or may occur during a patient’s index disease. (11) The term multimorbidity, as it is used in this thesis, was first used by Boyd and Fortin in 2010. Multimorbidity in this case is defined as the co-existence of two or more chronic conditions, where one is not necessarily more central than the others. (11)

Asthma

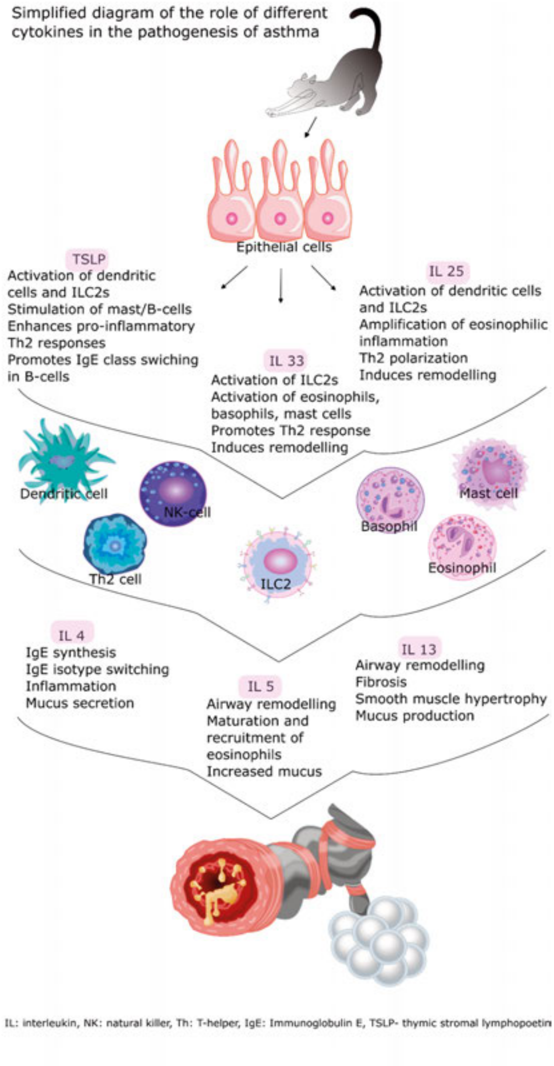

Figure 1

Asthma is a common condition, and the worldwide prevalence is estimated to be around 12% in children (5) and 4.3% in adults globally. (12) Though it varies considerably between populations and is around 11% in Swedish adults,

(13) and as high as 21% in adults in Australia. (14) There is no clear explanation for this large variation between areas, but local differences in healthcare and diagnostic criteria could explain some of it. Especially as wheezing, a potential indicator of asthma, is reported among 8.6% of adults worldwide. (12)

Asthma is a chronic inflammatory disorder of the airways, characterised by reversible airway obstruction. (15) It is, however, clear that asthma encompasses a variety of different phenotypes, and there are several theories on classification systems. (6)

One of the earliest classifications divided asthmatics into allergic and non-allergic. (16) This classification falls short mainly because both allergic and non-allergic asthma share underlying inflammatory processes and clinical presentations. (16)

One of the first attempts to differentiate between asthma phenotypes was by Mosmann in 1986, (17) who described the subpopulations of T helper cells (Th), type 1 (Th-1), and type 2 (Th-2). Th-2 mediated reactions were thought to be the predominant inflammatory pathway in some asthma phenotypes. (18)

It has, however, been demonstrated that cytokines associated with Th2 lymphocytes are secreted by various cell types, and asthma classification has moved beyond the Th2 terminology, being referred to as type 2 inflammatory asthma instead. (16) Type 2 inflammation now encompasses cytokines produced by variant T cells, natural killer cells, mast cells, eosinophils, basophils, Th1 cells under certain conditions, and type 2 innate lymphoid cells (ILC2). (16) ILC2s are critical players in type 2 immunity. (19) ILCs play an important role in tissue homeostasis, especially in the lung and epithelial barrier immunity involved in the pathophysiology of asthma, atopic dermatitis, and food allergy. (16, 20) ILCs encompass a heterogeneous family, including ILC1 that produce interferon-γ, ILC2s that produce interleukin 4 (IL-4), IL-5, IL-9, IL-13, and ILC3s that secrete IL-22 and IL-17. (20) Allergy and asthma are thought to be predominantly driven by the dysregulation of Th2 cells and ILC2s, the major producers of type 2 cytokines. (20, 21)

Alarmins like IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) also participate in the initiation of type-2 inflammation. (16) After a cascade of events Th2 cells migrate to the airway epithelium and secrete IL-4, IL-5 and IL-13. (16, 22) These cytokines contribute to the hallmarks of asthma, mucin production, Immunoglobulin E (IgE) synthesis, subepithelial fibrosis, bronchial remodelling, and airway hyperresponsiveness. (16) IL-25, IL-33 and TSLP also directly activate ILC2s to secrete IL-5, IL-13 and possibly a small amount of IL-4. (16) Type 2 cytokines drive the recruitment of effector cells, mast cells, basophiles, and eosinophiles, and mediate B-cell secretion of IgE when exposed to antigens. (16) Both IL-4 and IL-13 can bind to the IL-4Rα receptor that is broadly expressed on Th cells, eosinophils, mast cells, B-cells, bronchial epithelium, endothelium, and airway smooth muscle cells. (16, 23) IL-4 and IL-13 share many functions, but there are some differences. (24) The main effect of IL-13 lies in remodeling, including mucus hypersecretion, fibrosis, and smooth muscle hypertrophy. (16) IL-4 primarily amplifies inflammatory cascades and drives IgE switching and induces chemokines for the recruitment of eosinophils. (24)

IL-5 is produced by Th2 cells, ILC2s, mast cells, natural killer cells (NK cells), NK T cells, and eosinophils. (16) It controls eosinophil development, maturation, and activation in the bone marrow as well as modulates the development and function of mast cells and basophils. (16)

There are several biomarkers currently available to help distinguish between type 2 low and type 2 high asthma, exhaled nitric oxide (F_ENO), serum IgE, blood and sputum eosinophils, eosinophil activation markers such as ECP and EDN, as well as serum periostin. (16) IL-13 induces nitric oxide synthase, increasing the production of F_ENO, and can thus be used as an indicator for IL-13-driven inflammation. (16)

Another approach is to classify asthma based on the patterns of cellular inflammation in sputum, eosinophils, neutrophils, mixed neutrophilic and eosinophilic, and lastly paucigranulocytic asthma (both neutrophils and eosinophils within normal range). (16)

Elevated levels of eosinophils characterise some of the more severe asthma forms. (25) Also related to worse asthma prognosis and more frequent asthma exacerbations. (26) Eosinophilic asthma can occur in both allergic and non-allergic patients and is often accompanied by sinusitis, nasal polyposis, and acetylsalicylic acid exacerbated respiratory disease. (6, 16) Elevated eosinophils in asthmatics seem to either occur in combination with high total IgE and allergen sensitisation or as isolated blood eosinophilia, likely representing different phenotypes. (27, 28) Complicating matters further, one study showed that up to 75% of asthmatics with eosinophilia and polysensitisation reported no allergic reactions, (6) indicating that sensitisation in this case is probably a sign of high type 2 inflammation and not allergy.

A driving force in the research on asthma phenotypes is the development of new treatment options. (29) It is currently possible to target some specific airborne allergens, total IgE, TSLP, IL-5, as well as IL-4 and IL-13. (30-32)

Rhinitis

Rhinitis is characterized by rhinorrhoea, nasal congestion, sneezing, and/or posterior nasal drainage. (33) Rhinitis is often classified into allergic and non-allergic. (33) Allergic rhinitis is a common problem, and the worldwide prevalence is thought to be up to 15% among children. (34) The prevalence among adults varies considerably between populations, from 12% in Spain to 46% in Australia. (35)

Rhinitis affects all ages and can vary from mild symptoms to more serious ones. (36) Allergic rhinitis can be classified into perennial and seasonal. (37) Documented IgE sensitisation gives an added benefit to the diagnosis as well as treatment options. (36)

Allergic rhinitis does not always get the attention it deserves, often being misdiagnosed and mismanaged. (37) Not to speak of its commonly underestimated economic impact, which in fact is substantial, both in direct and indirect costs. (37, 38) The definition of rhinitis encompasses disease in the nasal passage, which is anatomically connected to the sinuses, nasopharynx, middle ear, lacrimal canals, and lower airways. It is, in fact, rare that rhinitis only involves the nasal passage, often presenting with symptoms from the nose as well as from other anatomically connected areas. (37) It is therefore not surprising that 80% of all asthmatics have rhinitis and 10-25% of those with rhinitis have asthma. (39) Their co-occurrence increases the asthma exacerbation risk by 40%. (40) It is estimated that around 49% of severe asthma patients also have rhinitis. (41) Some think that those with concomitant asthma and rhinitis may represent a separate phenotype. (11, 42) This is supported by findings suggesting that IL-33 and IL-5-driven inflammation is more prevalent in the multimorbid phenotype, whereas IL-17 dominates in rhinitis alone. (11)

Having rhinitis is associated with worse asthma control, (7) and asthmatics have a higher likelihood of having persistent and severe rhinitis even without the presence of allergy. (43) Having rhinitis in combination with allergic sensitisation and allergen exposure increases the risk for hospitalization. (44)

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disease presenting with recurrent eczematous lesions and intense pruritus. (45) The prevalence worldwide is estimated to be around 8% among children, but ranges between 2-33% between countries. The overall prevalence is thought to range between 1-10% in adults, but can vary between 1-23% between countries. (46) There is some evidence that around 50% of those with atopic dermatitis experience some sort of respiratory allergy. (47) Atopic dermatitis is associated with an increased risk for food allergy, asthma, and rhinitis. (48, 49)

It is thought that atopic dermatitis results from a defective skin barrier and type 2 inflammation that further impairs the skin barrier. (45) The pathogenic mechanism of atopic dermatitis is partially mediated by type 2 inflammation, mainly IL-4, IL-5, IL-13, and IL-31 that stimulate B-cells, eosinophils, mast cells, and nerve cells. (45) Blood eosinophilia is associated with atopic dermatitis and disease severity, especially in the presence of concomitant allergy. (50) Skin biopsies often show eosinophils in skin lesions. (51) The relationship seems to be more complex, however, as anti-IL-5 therapy does not seem to be effective in atopic dermatitis, despite lowering blood eosinophil levels. (52) Treatment targeting IL-4 and IL-13, however, is effective in moderate to severe atopic dermatitis, even though an initial transient and asymptomatic blood eosinophilia is common. (53) This is thought to be due to the inhibition of IL-4 and IL-13 that stop the migration of eosinophils into tissue, but not the production in the bone marrow. (53)

It is thought that encountering allergens through the damaged skin barrier under inflammatory conditions promotes the development of specific IgE against environmental allergens. (54) Around 80% of atopic dermatitis patients show IgE sensitisation as well as elevated total IgE levels. (45) Aggressive treatment of eczema in early childhood has been shown to promote tolerance to hen's egg in egg-sensitised children. (54)

Atopic dermatitis also affects mental health and quality of life (55), showing a higher incidence of anxiety, depression, and suicidal thoughts compared with healthy individuals. (55)

Allergic multimorbidity in asthma

Asthma, rhinitis, and eczema often occur together, both with and without the presence of allergy. (56) The likelihood of having all three diseases together is 10 times higher than could be expected by chance, (57) and the worldwide prevalence of having asthma, rhinitis, and eczema at the same time among children is 1%. (5) The prevalence of having all three diseases together in adults is 2% but increases to 6% among sensitized individuals in Sweden. (58) The worldwide prevalence among adults has not been studied. There is clear evidence of a relationship between asthma, rhinitis, and eczema, yet the mechanisms driving this association are not fully understood. (59)

One of the most established theories on allergic multimorbidity is the atopic march, where the damaged skin barrier in infancy leads to polysensitisation and then allergic airway disease. (45) Recent data suggest, however, that symptom progression from skin to airways represents the disease course for only around 7% of those with allergic multimorbidity. (11, 60) Damage to the epithelial barrier in combination with predisposing genetic factors has been of interest in recent years. Genetic causes such as filaggrin mutations and claudin polymorphisms, epidermal proliferation and differentiation of Ovo Like Transcriptional Repressor 1, epithelial-derived alarmins (IL-33), particularly T2 response (IL-4 and IL-13 regulation), and sphingolipid synthesis. (61) These factors, in combination with environmental agents like diesel exhaust, cigarette smoke, laundry detergents, household cleaners, microplastics, nanoparticles, food emulsifiers, and other unidentified hazardous substances, can cause epithelial barrier damage. (62)

Allergic sensitisation increases the risk for multimorbidity between these three diseases (63). Though it accounts for only about 38% of comorbidity. (11) Heredity for allergy increases the likelihood for multimorbidity; those with allergic parents are 2-3 times more likely to have multimorbidity. (64) It is, however, clear that there is a lot to be discovered on multimorbidity involving asthma, rhinitis, and eczema at the same time.

Allergic sensitisation

One of the more established risk factors for having asthma, rhinitis, and eczema at the same time is allergic sensitisation; those with allergic multimorbidity show the highest degree of sensitisation. (63) There is some debate on what type of sensitisation is the most prominent. Some consider seasonal allergens the biggest contributor to developing allergic multimorbidity. (65, 66) Others view perennial allergens as having a larger impact. (65, 67) Allergic multimorbidity is more common among food-sensitised individuals, though this has not been studied as extensively. (67, 68)

Asthma has previously been identified as a risk factor for severe and even lethal allergic reactions, but little data exist on the impact of allergic multimorbidity on allergic reaction severity. (29, 69)

Inflammatory biomarkers in allergic multimorbidity

There is some evidence linking allergic multimorbidity to increased levels of type 2 inflammation: total IgE, (29) F_ENO, and eosinophils. (70, 71) Increased total IgE is associated with polysensitisation and allergic multimorbidity. (29) Clinical guidelines recommend that F_ENO at a flow rate of 50 mL/s be used. (72) Elevated levels of F_ENO have been associated with having concomitant asthma and rhinitis, (73) as well as chronic rhinosinusitis, (41) although it is difficult to separate the association with allergic inflammation from allergic multimorbidity. (74, 75) F_ENO levels can vary considerably in the same individual and are also affected by gender, height, age, as well as modifiable factors like lifestyle, including cigarette smoking and medications. (76-78) All these affecting variables make F_ENO challenging to study, but it is undoubtedly a valuable tool when assessing airway disease.

A complementary biomarker to F_ENO is alveolar nitric oxide (C_ANO), which is supposed to better reflect peripheral airway disease in the lungs. (79) Like F_ENO, higher levels of C_ANO have previously been observed among those with asthma and rhinitis at the same time,(79) though it is considerably less studied. C_ANO is calculated based on NO values at different flow rates and requires at least three exhales as opposed to one exhale for F_ENO. (80) This makes it more time-consuming and thus less practical in clinical practice.

Higher blood eosinophil levels are reported in asthma and allergic disease, (81, 82) and there is some evidence linking eosinophilia to having asthma and rhinitis at the same time. (83) Moreover, asthma, allergic rhinitis, chronic rhinosinusitis, and acetylsalicylic acid intolerance occur more often together in the presence of elevated eosinophils. (84)

The level of eosinophilia in the peripheral blood does not necessarily correlate with the severity of the disease. (85) Several eosinophil activation markers can be measured in the peripheral blood: EDN, MBP1, and ECP. (85) Those markers might, however, not be sensitive enough to correlate with disease activity, as they bind strongly to negatively charged tissue elements with a long half-life, and some believe that they fail to appear in the peripheral blood in sufficient concentrations. (85) EDN could be the exception, as there is some evidence suggesting that it is a useful and reliable biomarker. (27) Another advantage of EDN is that levels are constant throughout the day and not subject to the circadian rhythm like eosinophils, which peak at around 04:00. (27, 86) There is evidence currently that both ECP and EDN are elevated in asthmatics compared with healthy controls, (70) and EDN might even be useful in predicting the severity of diseases. (87) Elevated ECP and EDN levels are associated with rhinitis, asthma, and atopic dermatitis separately (87-89), though not much is known about their role in allergic multimorbidity.

Periostin is a matricellular protein that is part of the IL-4 and IL-13 pathway, and elevated levels could potentially correlate with asthma, atopic dermatitis, (90) as well as eosinophilic inflammation. (16) It is upregulated in allergic conditions, among others, and has been shown to influence tissue remodelling and fibrosis. (90) There is some evidence linking periostin to elevated levels of F_ENO, urine-EDN, and total IgE. (91) Moreover, periostin levels seem to be increased in asthma, rhinitis, and atopic dermatitis separately. (92, 93) One smaller Japanese study showed that levels were higher among asthmatics with concomitant sinusitis. (94) Not much is known about levels of periostin in other allergic multimorbidity.

C-reactive protein (CRP) is a broader and relatively non-specific inflammatory biomarker. Previous studies have shown that CRP is elevated in asthmatics compared with healthy controls, and higher levels may correlate with severity. (95) There is some evidence that elevated CRP is more common in non-allergic asthma and correlates more strongly with neutrophilic inflammation. (95, 96) The likelihood of CRP being elevated increases with the number of concomitant chronic diseases, (97) though it is unclear if this extends to allergic multimorbidity.

Lung function in allergic multimorbidity

Information on lung function among those with allergic multimorbidity is somewhat conflicting. Some studies show that those with asthma, rhinitis, and atopic dermatitis have worse lung function. (98) There is also some evidence that children with asthma, rhinitis, atopic dermatitis, and allergic sensitization have a lower lung function trajectory from birth. (98) Others have, on the contrary, shown that those with rhinitis in combination with asthma have better lung function and are less likely to develop fixed airflow obstruction. (41, 99)

Demographics and heredity

Several studies have shown that those with allergic multimorbidity are, on average, younger when they are diagnosed with asthma. (41) Heredity is a known risk factor for allergic disease and multimorbidity and is estimated to account for about 50-84% of disease. (100, 101)

Aim

The overall aim is to better characterize subjects with multimorbidity involving asthma, rhinitis, and eczema. The specific aims were to:

I. Compare subjects with only rhinitis with those that have rhinitis in combination with asthma and/or eczema in relation to IgE sensitisation, inflammatory markers, family history, lung function, and BMI.
II. Investigate whether the presence of allergic multimorbidity in asthma relates to allergic sensitization, allergic and respiratory symptoms, quality of life, inflammatory markers, lung function, use of medication, and background factors.
III. Investigate subjects with allergic multimorbidity in terms of type-2 markers, allergic sensitization, respiratory, and food hypersensitivity symptoms.
IV. Study the change in asthma and rhinitis over time and to characterize factors contributing to remission and persistence of disease.

Methods

Table 1. Overview of the methods

Paper	I	II	III	IV
Material	ECRHS II	GA_2LEN	MIDAS	ECRHS II, III
Asthma definition	Diagnosed with asthma and having had an asthma attack or one of the following symptoms during the past 12 months: nocturnal chest tightness, attack of shortness of breath, chest wheezing, or whistling	Asthma attack during the last 12 months or having used asthma medications during the last 12 months	Physician-diagnosed and self-reported daily treatment with ICS and/or oral leukotriene-receptor antagonist (LTRA) during at least three months in the year before the study	Diagnosed with asthma and having had an asthma attack and one of the following symptoms during the past 12 months: nocturnal cough, attacks of breathlessness during rest, following activity or at night, chest wheezing, or whistling, taking asthma medication
Rhinitis definition	Sneezing, or a runny or blocked nose, when not having a cold in the last 12 months			
Atopic dermatitis definition	Intermittent itchy rash for 6 months, and within the last 12 months	Itchy rash during the last 12 months	Intermittent itchy rash for 6 months, and within the last 12 months	
Allergy testing	Blood, ImmunoCAP ISAC	Skin prick test and blood tests	Blood tests	Blood, ImmunoCAP ISAC
Total IgE	Blood	Blood	Blood	Blood
F_ENO	Exhaled nitric oxide	Exhaled nitric oxide	Exhaled nitric oxide	Exhaled nitric oxide
C_ANO	Exhaled nitric oxide	-	-	-
ECP	Blood, serum	Blood, serum	Blood, serum	Blood, serum
EDN	-	Urine	Blood, plasma	Blood, serum
Periostin	-	Blood, serum	-	-
CRP	Blood	-	-	-

-: Not available

Study populations

Paper I

The study was based on subjects who participated in the European Community Respiratory Health Survey (ECRHS II), which is the 10-year follow-up of an international multicentre study of asthma and allergy. The design of ECRHS I, which was performed from 1990 to 1994, and ECRHS II conducted 10 years later, has been published in detail. (102) Subjects who had participated in Stage 2 of ECRHS I were invited to participate in ECRHS II. Each participant was sent a brief questionnaire (Stage 1) and, among those who responded, a random sample was invited to undergo a more detailed clinical examination (Stage 2). A ''symptomatic'' sample consisting of additional subjects who reported symptoms of waking with shortness of breath, asthma attacks, or using asthma medication in Stage 1 was also studied. In ECRHS II, 679 subjects from ECRHS I were re-investigated. The subjects answered a standardised questionnaire administered by trained interviewers. A total of 467 subjects were examined with ImmunoCAP ISAC and underwent lung function tests and blood tests for analyses of inflammatory markers. This study involved 216 people with allergic rhinitis who were examined with ImmunoCAP ISAC (Figure 2). Among the subjects with allergic rhinitis, 70 had asthma.

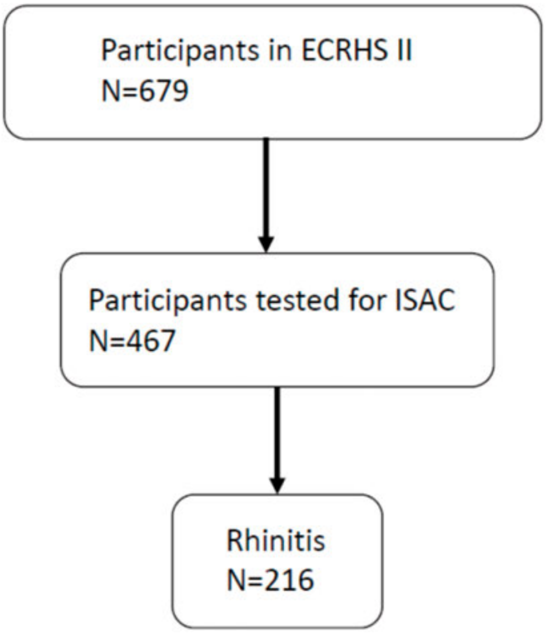

Figure 2

Paper II

The Global Allergy and Asthma European Network (GA^{2}LEN) study design has previously been published in detail. (103, 104) A clinical study was conducted in 2008-2010 in a randomly selected subgroup of adults with reported symptoms of asthma, chronic rhinosinusitis, and controls in 19 European centres. (103) This investigation is based on the Swedish part of the study. In Sweden, four centres participated (Gothenburg, Stockholm, Umeå, and Uppsala) and 27,866 persons responded (60% response rate) to the initial postal survey in 2008. From the first survey, four groups were invited to a clinical follow-up. The groups were individuals with asthma, individuals with chronic rhinosinusitis (CRS), individuals with both asthma and CRS, and a random sample of subjects who neither had asthma nor CRS. In the Swedish part of the study, 1,329 participated in the clinical follow-up in 2009 and 2010 (Figure 3). (103, 105)

Subjects who participated in the clinical follow-up took part in a structured interview and a clinical investigation with skin prick tests (SPT), blood sampling, and spirometry. In Sweden, the follow-up also included measurements of F_ENO and assessments of quality of life using the European Quality of Life Health Questionnaire (EQ-5D) and the Juniper mini asthma quality of life questionnaire (mAQLQ).

The subjects for this study were selected based on having asthma and were then divided into three groups: subjects with asthma only (n=78, 17%), subjects with asthma and rhinitis (n=247, 54%), and subjects with asthma, rhinitis, and eczema (n=112, 25%) (Figure 1b). Only 17 (4%) individuals had asthma and eczema, but no rhinitis, and this group was not further included in this investigation due to the small sample size. A further 10 individuals with asthma were discovered during the structured interview who had initially reported not having asthma in the postal questionnaire.

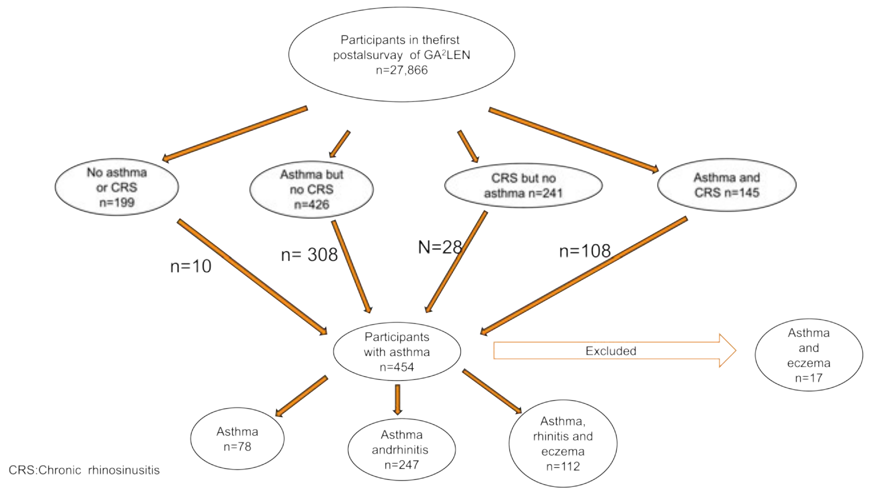

Figure 3. Flow chart for the inclusion and grouping of participants

Paper III

This study was based on participants from the study Minimally-Invasive Diagnostics for Asthma and Allergic Diseases (MIDAS). (106, 107) The study design has been published in detail before. (108) A total of 411 children and young adults (10–34 years) with physician-diagnosed asthma, recruited from both primary and specialist care in Uppsala, Sweden, with data on perceived food hypersensitivity symptoms and food IgE sensitisation, were included in the study. All asthma subjects were on daily treatment with inhaled corticosteroids (ICS) and/or oral leukotriene receptor antagonists (LTRA) during at least three months of the year before study entry. The controls were randomly chosen from the population registry, age- and sex-matched, and reported no asthma or other chronic respiratory diseases.

Grouping of the study population

Of the 411 participants, 17 had asthma and eczema but were excluded due to the small sample size. The remaining 394 participants were included in the current study. Of those, 50 had only asthma, 203 had asthma and rhinitis, and 141 had asthma, rhinitis, and eczema. Blood samples were available for 391 individuals (Figure 4).

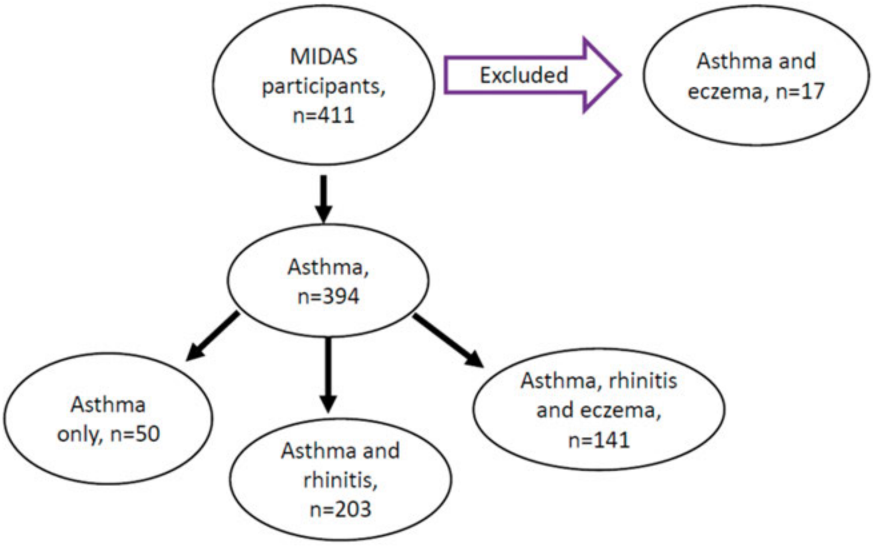

Figure 4. Flow chart for the inclusion and grouping of the participants

Paper IV

The study was based on participants from the European Community Respiratory Health Survey (ECRHS), a multicentre study with three visits, which in Uppsala was conducted 1991–1992, 1999–2000, and 2011–2012. The study design of ECRHS I, II, and III has been published before. (109) Potential participants were sent a brief questionnaire in stage 1, and a random sample of those who responded was invited for a more detailed clinical examination (Stage 2). Additional subjects who reported symptoms of waking with shortness of breath, asthma attacks, or using asthma medication in Stage 1 were also included. Individuals who participated in ECRHS I were invited to participate in ECRHS II and later in ECRHS III. The subjects answered a standardised questionnaire with the help of trained interviewers. The participants underwent lung function and blood tests to analyse inflammatory markers. In Uppsala, 824 individuals participated in ECRHS I, and 679 in ECRHS II. Specific IgE measurements using microarray chip technology were performed on 475 participants from ECRHS II. ECHRS III comprised 422 participants. Paper IV included 255 individuals participating in both ECRHS II and ECRHS III, where specific IgE measurement was done in ECRHS II (Figure 5). The participants were grouped in terms of the presence or absence of rhinitis and asthma in ECRHS II and 10 years later in ECRHS III. In this grouping, 6 individuals, who made up 4. 6% of all participants with only asthma and no rhinitis, were excluded due to the small sample size.

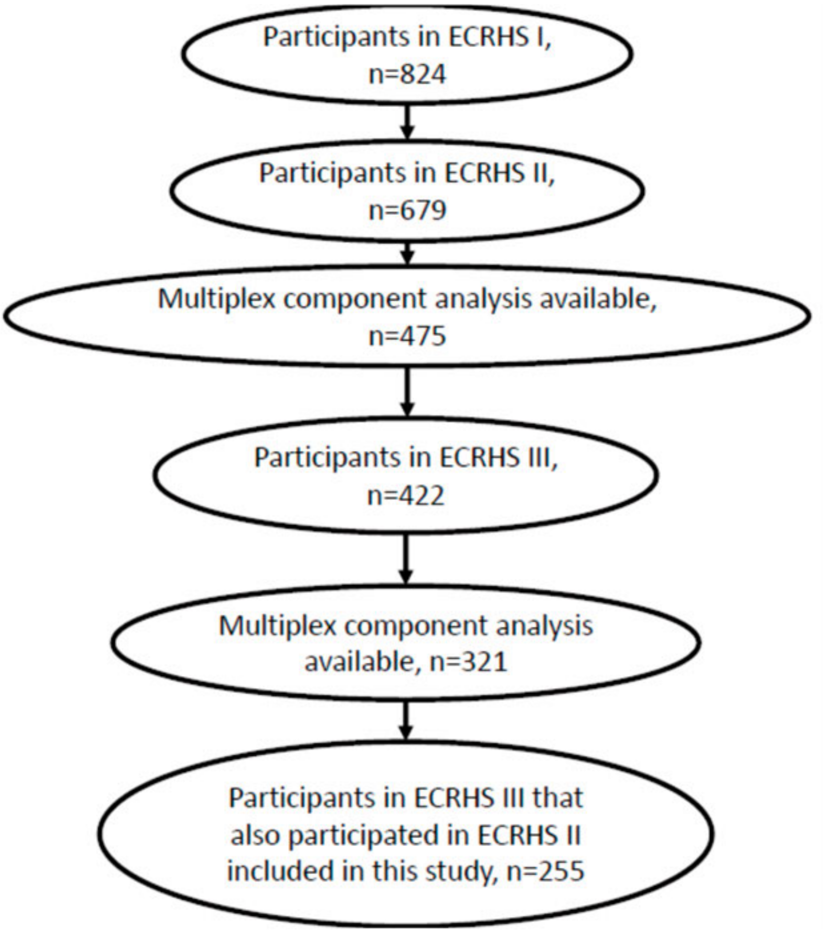

Figure 5. Study participants, European Community Respiratory Health Survey (EC-RHS), parts II and III

Questionnaires and definitions

Paper I

The ECRHS II main questionnaire (https://www. ecrhs. org/questionnaires-and-protocols) (110) was used to obtain information about respiratory symptoms, smoking history, parental allergy, and asthma.

Rhinitis was defined as having had problems sneezing, or a runny or blocked nose, when not having a cold in the last 12 months. (104)

Eczema was defined as having an itchy rash that came and went for at least six months and having had this problem within the past 12 months. (111)

Asthma was defined as ever being diagnosed with asthma and having had an asthma attack or one of the following symptoms during the past 12 months:

nocturnal chest tightness, attack of shortness of breath, chest wheezing, or whistling. (96)

Paper II

The GA^2LEN follow-up questionnaire included validated questions related to respiratory symptoms, rhinitis, chronic rhinosinusitis, and eczema, as well as demographic data. The questions were based on those in the ECRHS and included questions on respiratory symptoms, family history of asthma, diagnosed asthma, use of asthma medications, history of allergy and sinusitis, history of eczema, smoking history, and occupation. (112, 113)

Asthma was defined as a positive answer to "Have you suffered an asthma attack during the last 12 months?" or a positive answer to having used asthma medications during the last 12 months. (114)

Rhinitis was defined as a positive answer to "Have you had problems with sneezing, runny nose, or nasal congestion without having a cold during the last 12 months?". (104)

Eczema was defined as a positive response to "Have you had an itchy rash during the last 12 months?". (111)

Reported allergic reactions were categorised according to the anaphylaxis grouping in the Swedish Allergy Society guidelines for anaphylaxis (115) and further grouped into mild to moderate or serious reactions. A mild to moderate reaction was defined as the presence of at least one of the following symptoms: itching of the mouth, lips, or throat, rash, diarrhoea, vomiting, rhinoconjunctivitis, difficulties swallowing, joint stiffness, and headache. A serious reaction was defined as fainting and/or respiratory distress.

Questionnaires assessing quality of life and sleep

All subjects fulfilling the criteria for asthma in the postal survey also completed mAQLQ. (116) Subjects were asked to assess functional impairment due to their asthma during the last two weeks by responding to 15 questions grouped into four domains on a seven-point scale. The four domains are: symptoms (5 items), activity limitations (4 items), emotional function (3 items), and environmental stimuli (3 items). Each question was scored from severe impairment (1) to no impairment (7), and the mean overall score was calculated.

The Euro Quality of Life (EQ-5D) health questionnaire was filled out by all participants. (117) It comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The descriptive system is then converted into a single summary index, and we used the United Kingdom time trade-off value set. (118) An index of 1.0 corresponds to full health.

The insomnia symptoms analysed were: difficulties inducing sleep, difficulties maintaining sleep, early morning awakening, and excessive daytime sleepiness at least three to five times/week according to the Basic Nordic Sleep Questionnaire. (119)

Paper III

Asthma was defined as physician-diagnosed (according to medical records) and self-reported daily treatment with ICS and/or oral leukotriene-receptor antagonist (LTRA) during at least three months in the year before the study.

Rhinitis was defined as a positive answer to “Have you had problems with sneezing, runny nose, or nasal congestion without having a cold during the last 12 months?”. (104)

Eczema was defined as a positive response to “Have you had an itchy rash that has come and gone during 6 months” and a positive answer to the question “ Have you had this rash during the last 12 months?”. (111)

Reported respiratory, allergic, and food hypersensitivity symptoms

Interviews were performed by an allergy nurse, using a questionnaire, and each subject was asked to report respiratory symptoms such as wheezing, cough, respiratory distress, nasal congestion, and itchy/teary eyes.

The history of hypersensitivity reactions to food allergens commonly occurring in Sweden (egg, cow’s milk, fish, wheat, peanut, soy, hazelnut, and shrimp) was also reported. Perceived symptoms were grouped according to the organ systems affected: the lower airways (asthma), the upper airways (rhinitis, conjunctivitis), the oral cavity (oral allergy syndrome), the skin (atopic dermatitis, urticaria, angioedema), the gastrointestinal tract (nausea, vomiting, stomach pain, diarrhoea), and anaphylaxis (self-reported).

Asthma Control Test

Subjects with asthma were asked to fill out the Asthma Control Test (ACT). The ACT consists of five questions, each with a 5-point scale. (120) The score ranges from 5 to 25, with a lower score indicating poorer asthma control. Subjects with an ACT score < 20 were defined as having poorly controlled asthma.

Body mass index

Height and weight were measured, and body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Asthma medication

The use of asthma and allergy medication ICS, combination ICS/long-acting beta-agonist (LABA), and/or use of LTRA during the last three months was recorded in the interview. The prescribed daily dose of ICS was also collected from the subjects' medical records.

Paper IV

The ECRHS II and ECRHS III main questionnaires (http://www.ecrhs.org) (110) were used to obtain information about background factors, smoking history, parental allergy, and asthma.

Rhinitis was defined as having had problems sneezing, or a runny or blocked nose, when not having a cold in the last 12 months. (104)

Asthma was defined as ever being diagnosed with asthma and having had an asthma attack and one of the following symptoms during the past 12 months: nocturnal cough, attacks of breathlessness during rest, following activity or at night, chest wheezing, or whistling, or taking asthma medication. (96)

Eczema was defined as having an itchy rash that came and went for at least 6 months and having had this problem within the past 12 months. (111)

Blood samples and F_ENO

Paper I

Allergy testing

The presence of IgE antibodies was examined using microarray chip technology (ImmunoCAP ISAC; Thermo Fischer Scientific, Uppsala, Sweden). (121, 122) The chip had 103 native or recombinant allergen components from 43 allergen sources. Specific IgE was reported as ISAC Standardised Units (ISU), which is a semi-quantitative estimate of the actual specific IgE titre. Subjects were regarded as being non-IgE sensitised if the signal could not be measured or was very low (<0.3 ISU). The IgE sensitisation pattern was grouped into four allergen source categories: food allergens, seasonal allergens (pollen), perennial allergens (animal, house dust mite, and mould), and other allergen sources (latex, annual mercury, bee venom, and anisakis).

Inflammatory markers

F_ENO measurements were made using an exhalation flow of 50 mL/s. (123) The system used for NO measurements was a computer-based single-breath NO system from Nitrograf (Hässelby, Sweden) that used a chemiluminescence analyser (Sievers NOA 280; Sievers, Boulder, Col, USA). Peripheral or alveolar F_ENO was estimated by calculating the flow-independent alveolar nitric oxide concentration (C_ANO) was estimated by analysing the fractional exhaled NO concentration obtained at three different rates (5-, 100-, and 500-mL s-1). (124)

Blood samples were collected for eosinophil cationic protein (ECP). Samples were kept at 24°C for 60 minutes before centrifuging. The concentration of s-ECP was assayed with a double antibody radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). Blood samples collected for C-reactive protein were analysed on a Hitachi 911 analyser using a commercially available latex-enhanced immunoturbidimetric assay from Roche. The lower detection limit of the assay is 0.1 mg/l.

Paper II

Skin prick test

A skin prick test was performed on the inside of the forearm using a standard set of aeroallergens for the GA^{2}LEN study(125): *Dermatophagoides farina*, *Dermatophagoides pteronyssinus,* birch, olive, Parietaria, timothy grass, *Artemisia vulgaris*, mixed grass, cat, dog, *Blattella germanica*, *Alternaria alternata*, histamine (positive control), and diluent (negative control). Standardised extracts from ALK Abelló (Hamburg, Germany), Allergopharma (Reinbek, Germany), Leti Pharma (Witten, Germany), and Stallergènes (Antony, France) were used. The largest and perpendicular diameters of the wheal elicited by the allergens were measured, and the mean value was calculated. A positive wheal was defined as ≥ 3 mm, if the control solutions showed the expected result, i. e. histamine ≥ 3 mm and negative control < 3 mm. Skin prick test data were available for 414 participants.

Serum IgE measurements

Venous blood samples were drawn from the participants during the clinical visits and frozen at -20°C. In the Swedish GA^{2}LEN study, measurements of serum IgE antibodies against a mix of food allergens, fx 5, shrimp, and timothy were performed with the ImmunoCAP system (Immunodiagnostics, Thermo Fisher Scientific, Uppsala, Sweden). The results are presented in kU/L, and values of IgE ≥ 0.35 kU/L for an individual allergen defined a subject as being sensitised to that allergen. (126) Subjects with titres of ≥ 0.35 kU/L against fx5 were further characterised regarding IgE antibody levels against each individual allergen: egg white, milk, cod fish, wheat, peanut, and soya bean. Those with titres of < 0.35 kU/L were not further examined for each individual allergen in the food panel. Blood sampling for measurements of total IgE was performed using ImmunoCAP® (Phadia Diagnostics AB/ThermoFisher, Uppsala, Sweden).

Inflammatory markers

S-ECP was measured using a fluorescence enzyme immunoassay (ImmunoCAP, Thermo Fisher Scientific, Immunodiagnostics, Uppsala, Sweden). S-periostin was measured using ELISA with two rat anti-human periostin mAbs (clones SS18 and SS17B). (29) Urine-EDN (previously called eosinophil protein X) was measured, in accordance with the manufacturer's instructions, with a sandwich ELISA utilising a polyclonal EDN antibody as the catching antibody and a monoclonal antibody (clone 618) as the detecting antibody (Diagnostics Development, Uppsala, Sweden).

F_ENO was assessed using NIOX MINO, Aerocrine, Stockholm, Sweden, according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations. (123)

Paper III

Serum IgE measurements and inflammatory markers

Aeroallergen sensitisation was defined as IgE levels $\geq$ 0.35 kU_A/L in the multi-allergen test Phadiatop (Thermo Fisher Scientific, Uppsala, Sweden) that contains the following allergens: dog, cat, horse, timothy grass, birch, mugwort, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* and *Cladosporium herbarum.* Participants who tested positive for aeroallergens were further analysed for specific aeroallergens.

Food allergen sensitisation was defined as IgE antibody concentration $\geq$ 0.35 kU_A/L to egg, cow's milk, cod fish, wheat, peanut, soy, hazelnut, or shrimp.

F_ENO was measured with a chemiluminescence analyser (NIOX Flex, Aerocrine AB, Solna, Sweden). Eosinophil blood count (B-Eos) was measured with a routine method (Cell-Dyn Sapphire, Abbott, Illinois, USA). The ImmunoCAP system (Immunodiagnostics, Thermo Fisher Scientific, Uppsala, Sweden) was used for the measurement of total IgE, IgE antibodies, and serum ECP. P-EDN was measured using a sandwich ELISA utilising a polyclonal EDN antibody as the catching antibody and a monoclonal antibody (clone 618) as the detecting antibody, in accordance with the manufacturer's instructions (Diagnostics Development, Uppsala, Sweden).

Paper IV

Allergy testing

The presence of IgE antibodies was examined using microarray chip technology (ImmunoCAP ISAC; Thermo Fischer Scientific, Uppsala, Sweden). (121, 122) The chip had 103 native or recombinant allergen components from 43 allergen sources. Specific IgE was reported as ISAC Standardised Units (ISU), which is a semi-quantitative estimate of the actual specific IgE levels. Subjects were regarded as being non-IgE sensitised if the signal could not be measured or was very low (<0.3 ISU). Allergen component analysis was performed in 475 individuals in ECRHS II. All 255 participants in this study had allergen component analysis available for ECRHS II.

Inflammatory markers

Total serum IgE for both ECRHS II and III was measured using the Pharmacia CAP system (Uppsala, Sweden). Total IgE was available for 470 individuals in ECRHS II and 351 in ECRHS III. Of the participants in our study, 248 had results available in ECRHS II and 217 in ECHRS III.

F_ENO measurements were made using an exhalation flow rate of 50 mL/s. (123) The system used for NO measurements in ECRHS II was a computer-based single-breath NO system from Nitrograf (Hässelby, Sweden) that used a chemiluminescence analyser (Sievers NOA 280; Sievers, Boulder, Col, USA). In ECRHS III, F_ENO was measured using an electrochemical analyser (NIOX MINO; Aerocrine AB. (127) F_ENO was measured in 288 people in ECRHS II and 361 in ECRHS III. In the current study, 156 participants had available results in ECRHS II and 223 in ECRHS III.

Blood samples were collected for ECP. Samples were kept at 24°C for 60 minutes before centrifugation. In ECRHS II, the concentration of serum ECP was assayed with Pharmacia ECP RIA (Pharmacia Diagnostics), and in ECRHS III, with ImmunoCAP ECP (Thermo Fischer Scientific). ECRHS III also included blood samples for serum EDN, which were measured using an ImmunoCAP research assay. (128) ECP was analysed in 409 individuals in ECRHS II, and ECP and EDN in 321 people in ECRHS III. In the current study, 212 participants had ECP available in ECRHS II, and 207 had ECP and EDN available in ECRHS III.

Lung function tests

Paper I

Forced expiratory volume in 1 second (FEV_1) was measured using a dry rolling-seal spirometer (Model 2130; SensorMedics, Anaheim, Cal, USA). Up to five technically acceptable manoeuvres were measured. American Thoracic Society recommendations were followed. (129) The predicted values for FEV_1 were calculated based on European Coal and Steel Union reference values. (130) Weight and height were measured, and BMI was calculated.

Paper II

Lung function measurements were performed using the EasyOne™ Spirometer (Ndd Laboratories, Medizintechnik AG, Zurich, Switzerland) with a daily calibration check. Forced vital capacity (FVC) and FEV_1 were measured, at least three times, each before and at least 15 minutes after bronchodilatation with 200 µg of salbutamol. FEV_1, FVC, and FEV_1/FVC were measured according to the ATS/ERS guidelines (131) with reference values from the European Coal and Steel Community. (132) Height and weight were measured, and BMI was calculated.

Fixed airway obstruction was defined according to the Guidelines from the Global Initiative for Chronic Obstructive Lung Disease as postbronchodilator FEV_1/FVC below 0.7. (133)

Paper III

FEV_1 was recorded with a MasterScope spirometer (Erich Jaeger, Wurzburg, Germany. GLI reference values were used. (134)

Paper IV

FEV_1 was measured in ECRHS II using a dry rolling-seal spirometer (Model 2130; SensorMedics, Anaheim, Cal, USA). Up to five technically acceptable manoeuvres were measured. American Thoracic Society recommendations were followed. (129) The predicted values for FEV_1 were calculated based on European Coal and Steel Union reference values. (130) Weight and height were measured, and body mass index (BMI) was calculated.

Statistical methods

Paper I

Statistical analyses were performed using STATA (14. 2; StataCorp, College Station, Tex). Non-normally distributed variables, F_ENO, total IgE, and ECP, were log-transformed before analysis. The material was divided into four groups according to the prevalence of allergic conditions: rhinitis only; rhinitis and eczema; rhinitis and asthma; rhinitis, asthma, and eczema. The χ^2 test and ANOVA with Bonferroni correction were used when comparing these four groups. Logistic regression was used when analysing an independent association with having rhinitis with asthma and/or eczema as opposed to only having rhinitis. A p-value of < 0.05 was considered statistically significant.

Paper II

All analyses were performed using STATA 14.2 (STATA Corp, College Station, Texas, USA). Non-normally distributed variables, F_ENO and total IgE, were log transformed before analysis. The differences between groups were tested using the χ^2 test or the ANOVA test. Multiple logistic regression analysis was used when adjusting for possible confounders. A p-value of < 0.05 was considered significant. Missing data were handled with complete cases.

Paper III

All analyses were performed using STATA 14.2 (STATA Corp, College Station, Texas, USA). Non-normally distributed variables, total IgE, F_ENO, eosinophils (B-Eos), P-EDN, and ECP were log-transformed before analysis. The differences between groups were tested using the ANOVA test, χ^2 test, or Fisher's exact test when groups were smaller than five persons. Multiple logistic regression analysis was used when adjusting for possible confounders. A p-value of < 0.05 was considered significant. Missing data were handled with complete cases.

Paper IV

Statistical analyses were performed using STATA (14.2; StataCorp, College Station, Tex). Non-normally distributed variables, F_ENO, total IgE, ECP, and EDN were log-transformed before analysis. The χ^2 *test* or Fisher's exact test, in case of low prevalence in groups (<5 individuals), and ANOVA with Bonferroni correction were used when comparing groups. Logistic regression and multinomial logistic regression were used in the multivariable analysis. A p-value of < 0.05 was considered statistically significant.

Ethics

Paper I

All the subjects gave their permission for the utilisation of personal data for this study. The study was approved by the Ethics Committee at the Medical Faculty at Uppsala University (D no 1999/313).

Paper II

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2008/1100-31/4). Informed consent was obtained from all individual participants included in the study.

Paper III

Written informed consent was obtained from each subject and from parents of subjects below 18 years of age, before inclusion in the study. The study was approved by the Regional Ethics Committee in Uppsala, Sweden (2009/349).

Paper IV

The study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr for ECHRS II and III was 1999/313, 2010/068, respectively). Informed consent was obtained from all individual participants included in the study.

Results

An overview of the study cohorts and findings is displayed below.

Table 2. Baseline characteristics of the participants in papers 1-4

	Paper I	Paper II	Paper III	Paper IV
Population, n	216	437	394	255
Age, years	42±7	45±15	20±7	54. 7±7. 4
BMI	25±4	27±5	23±4	26. 6±4. 4
Females	109 (50%)	261 (60%)	201 (51%)	115 (46.4%)

Table 3. Association between allergic multimorbidity and inflammatory markers across papers

	Paper I	Paper II	Paper III	Paper VI
Theme	Allergic multimorbid-ity	Allergic multimorbid-ity	Allergic multimorbid-ity	Persistent allergic disease over time
Total IgE	Yes	No	Yes	Yes
Polysensiti-sation	Yes	Yes	Yes	Yes
Eosinophils	-	-	Yes	-
ECP	No	No	No	Yes
EDN	-	No	Yes	No
Periostin	-	No	-	-
F_ENO	No	No	Yes	Yes
C_ANO	No	-	-	-
CRP	No	-	-	-

-: Not studied or not available

Table 4. Summary of findings: lung function and symptoms

	Paper I	Paper II	Paper III	Paper VI
Theme	Allergic multimorbid-ity	Allergic multimorbid-ity	Allergic multimorbidity	Persistent allergic disease over time
FEV_1	Lower	Higher	Higher in asthma and rhi-nitis	Lower
Asthma symptoms	-	Yes	Yes	-
Allergy symptoms	-	Yes	Yes	-

-: Not studied or not available

Paper I

General characteristics, lung function, and heredity

Those with rhinitis, asthma, and eczema had the lowest FEV_1 ($p < 0.001$) and the lowest BMI ($p = 0.04$). There was no group difference in FEV_1 between subjects with rhinitis and those with both rhinitis and eczema.

Those with allergic multimorbidity were more likely to have maternal heredity for allergy. There was also a difference in relation to medication; those with all three disorders were more likely to use antihistamines and ICS.

Inflammatory markers and IgE

Those with rhinitis, asthma, and eczema had the highest levels of total IgE; there was no difference in the levels of other inflammatory markers. Looking at individual groups, total IgE was significantly higher in the groups with rhinitis and asthma ($P < 0.001$) and the group with rhinitis, asthma, and eczema compared with those with only rhinitis ($P < 0.001$) (Figure 6).

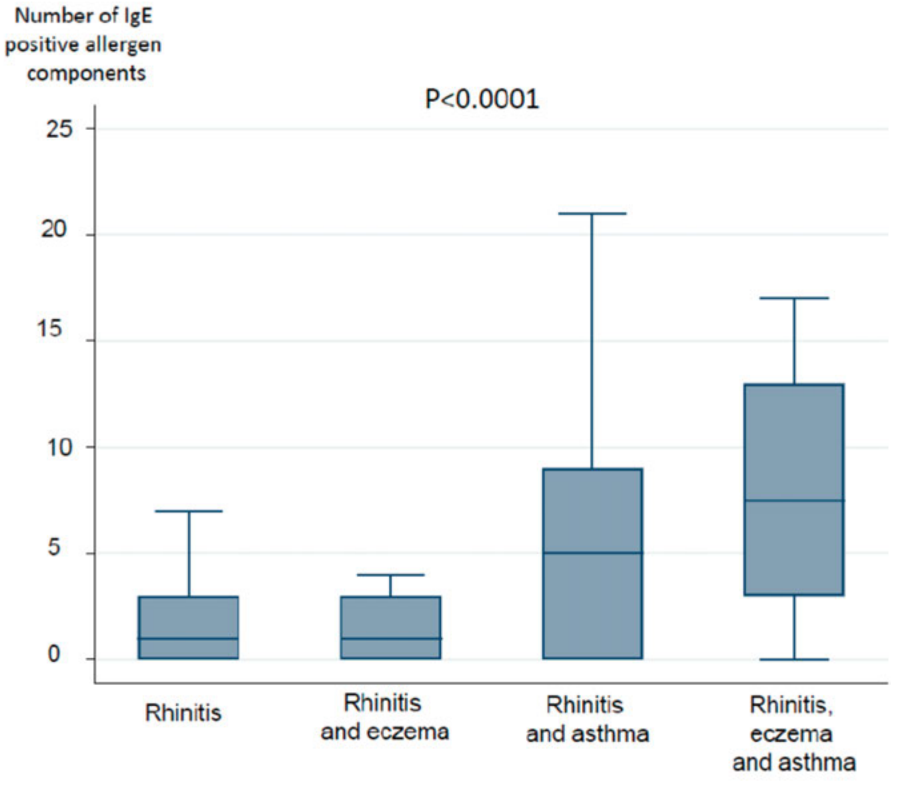

Figure 6. Boxplot (median and interquartile range) of the association between the number of IgE-positive aeroallergen components and having rhinitis with and without eczema and asthma

IgE sensitisation

IgE sensitisation to the different allergen components in the ISAC panel showed differences for many types of IgE sensitisation, with the highest prevalence in the group with rhinitis, eczema, and asthma. The association between total IgE and allergic multimorbidity remained significant after adjusting for IgE sensitisation to specific allergens (adjusted OR (95% CI) 2.38 (1.21–4.69)). There were also significant group differences in the number of IgE-positive allergen components, with the highest number and levels in the group with rhinitis, eczema, and asthma.

When analysing different types of sensitisations, the strongest association was found in participants who were IgE sensitised to both perennial and seasonal allergens. Of the perennial allergens, only sensitisation to furry animals and moulds had a significant association with allergic multimorbidity.

Paper II

General characteristics, heredity, and home environment

Subjects with more than one allergic disease were more likely to have been diagnosed with asthma before the age of 12 years compared with those with asthma alone. Maternal heredity for allergy was more prevalent among those with all three disorders.

Allergic sensitisation and allergy symptoms

Subjects with asthma, rhinitis, and eczema were more likely to be sensitised to seasonal aeroallergens, food allergens, and were sensitised to a larger number of allergens compared with subjects with only asthma (Figures 7 and 8).

We saw a group difference in terms of sensitisation to birch, timothy grass, grass mix, *Alternaria alternata,* as well as hazelnut, milk, peanuts, and soy compared with those with asthma alone (Figures 7 and 8).

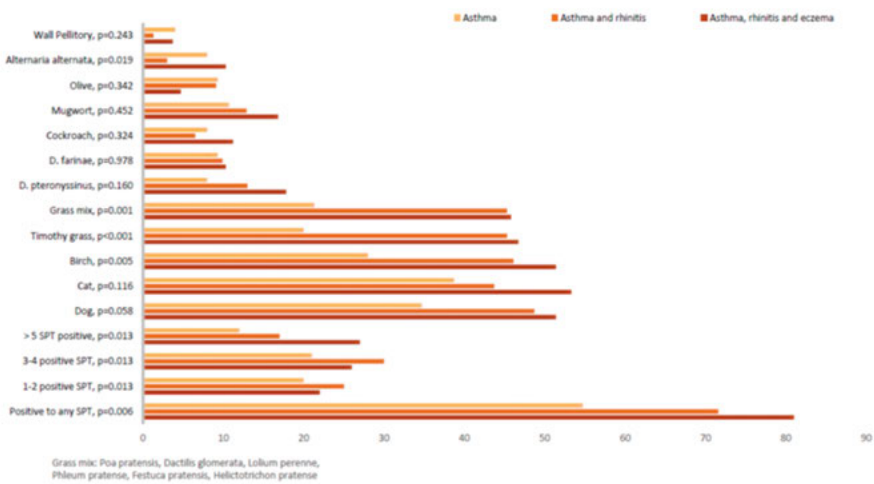

Figure 7. Allergic sensitisation according to prick test results (%)

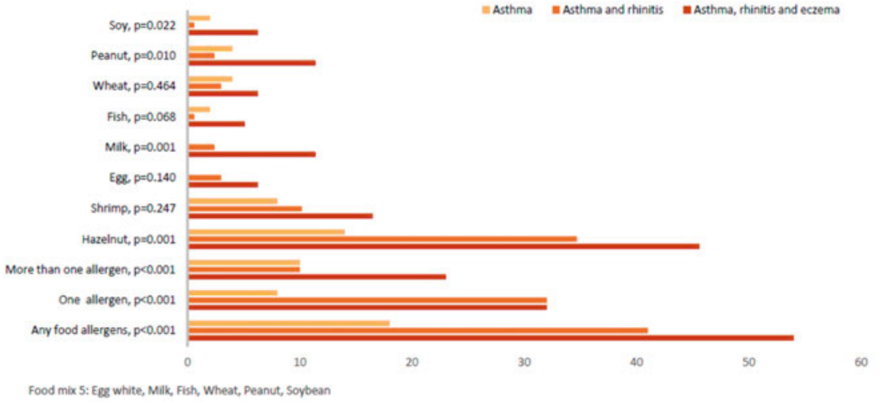

Figure 8. IgE sensitisation to food allergens (%)

Individuals with allergic multimorbidity were more likely to report allergic reactions to food compared with participants with only asthma, 56% and 32% respectively (p=0.005) (Figure 9). Moreover, having concomitant asthma, rhinitis, and eczema increased the likelihood of reporting more serious clinical reactions to food (Figure 9).

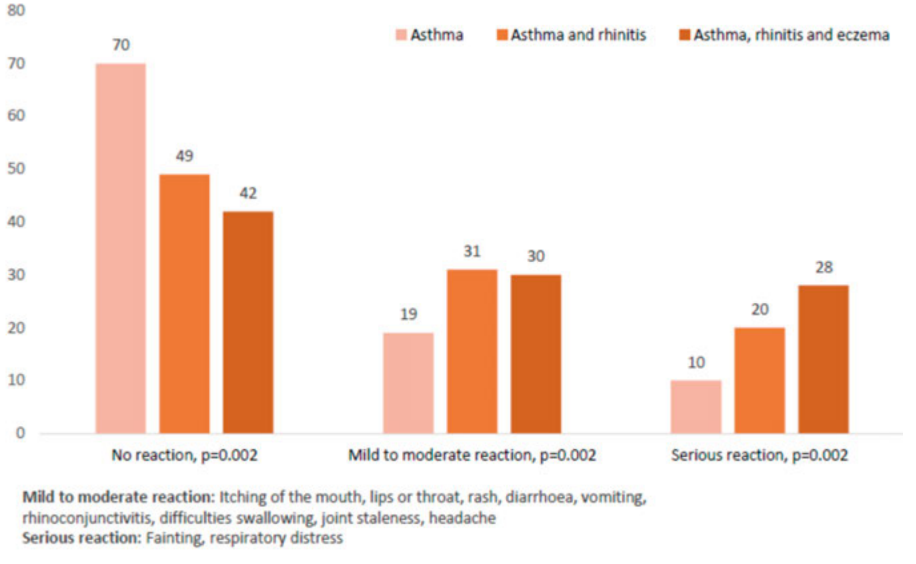

Figure 9. Reported allergic reactions to food (%)

Inflammatory markers

There was no difference in the levels of F_ENO, total IgE, U-EDN, U-ECP, and periostin between those with allergic multimorbidity and asthma alone.

Respiratory symptoms

Subjects with allergic multimorbidity reported more wheezing, breathlessness during activity, and more frequent asthma attacks during the last 12 months, compared with those with only asthma. These associations remained, except for the association with wheeze, which became statistically non-significant ($p=0.054$), after adjusting for smoking and oral corticosteroid use.

Lung function

Participants with only asthma had lower FEV_1 and were more likely to have fixed airway obstruction with post-bronchodilator FEV_1/FVC below 0.7. This association remained after adjusting for smoking and oral corticosteroid use.

Medication

Subjects with only asthma were more likely to have used oral corticosteroids during the last year compared with those with allergic multimorbidity. No difference was observed in the use of other oral or inhaled asthma medications.

Insomnia symptoms, anxiety, and depression

Those with allergic multimorbidity were more likely to report anxiety and/or depression and daytime sleepiness when compared with those with only asthma. This association remained after adjusting for smoking and oral corticosteroids. There was no difference in the other quality of life and sleep-related variables.

Paper III

General characteristics and lung function

Subjects with allergic multimorbidity were more likely to report maternal allergic rhinitis and both maternal and paternal eczema. There were no group differences in age, gender, BMI, or smoking status. Subjects with asthma and rhinitis had a higher FEV_1 and FEV_1/forced vital capacity (FVC) than those with only asthma and those with asthma, rhinitis, and eczema.

Inflammatory markers

We found that asthmatics with allergic multimorbidity (either having rhinitis or both rhinitis and eczema) had a higher degree of type-2 inflammation, as assessed by F_ENO, total IgE, blood eosinophil count, and plasma eosinophil-derived neurotoxin (P-EDN), but not serum eosinophil cationic protein (S-ECP), both before and after adjustments for age, sex, BMI, sensitization to airborne allergens, and use of inhaled and nasal corticosteroids (Table 5).

Stratifying for age with 18 years as a cut-off, we found that higher levels of F_ENO were only associated with allergic multimorbidity in subjects younger than 18 years. Furthermore, an interaction with the age groups (< or ≥18 years) was noted with regard to the relation between allergic multimorbidity and elevated levels of F_ENO (asthma vs asthma, rhinitis: p=0.032 and asthma vs asthma, rhinitis, eczema: p=0.048, both p-values for the interaction terms with age groups). No significant interactions with age groups were found for the relation between allergic multimorbidity and the other type-2 inflammation markers.

Table 5. Inflammatory markers and total IgE in relation to co-occurrence of rhinitis or rhinitis and eczema. All results presented as geometric mean 95% confidence interval †

	Asthma (n=50)	Asthma and rhinitis (n=203)	p-value vs asthma	Adjusted* p-value vs asthma	Asthma, rhinitis and eczema (n=141)	p-value vs asthma	Adjusted* p-value vs asthma
F_ENO (ppb)	11.4 (9.4–13.8)	15.8 (14.2–17.7)	0. 007	0. 065	17.8 (15.7–20.2)	<0.001	0.019
Total IgE (kU/L)	55.6 (33.4–92.7)	131 (105–162)	0. 001	0. 164	225 (175–289)	<0.001	0.004
B-Eos (10^9/L)	0.12 (0.10–0.15)	0.18 (0.16–0.21)	0. 005	0. 010	0.21 (0.18–0.24)	0.001	0.001
S-ECP (mg/L)	11.7 (9.1–13.8)	13.0 (11.7–14.3)	0. 360	0. 773	14.3 (12.7–16.0)	0.088	0.394
P-EDN (µg/L)	14.8 (13.6–16.2)	16.9 (15.9–17.9)	0. 068	0. 033	17.3 (15.9–18.7)	0.040	0.010

†Data missing for up to 3 individuals per biomarker

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

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

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

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

Allergen sensitisation and symptoms

Subjects with multimorbidity were more likely to report respiratory symptoms when exposed to aeroallergens, allergic reactions to food (Figure 10), as well as wheezing and asthma attacks within the preceding 12 months, and were more likely to use antihistamines and nasal steroids within the last 12 months. Asthmatics with allergic multimorbidity were more likely to be IgE-sensitized to both aeroallergens and food allergens (Figure 10).

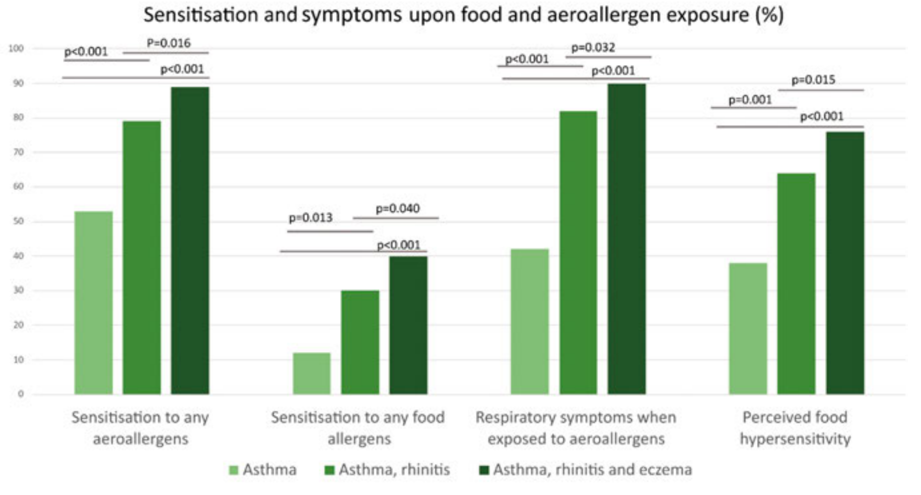

Figure 10. Prevalence of sensitization to aeroallergens, food allergens, and symptoms upon exposure to allergens in relation to the coexistence of rhinitis or rhinitis and eczema.

Paper IV

Over 10 years, comparing ECRHS II and ECRHS III, we found that of the 132 healthy individuals at baseline, 112 remained healthy, 16 developed rhinitis, and 4 developed asthma and rhinitis (Figure 11). Out of 82 subjects with rhinitis, 26 went into remission, 53 remained unchanged, and 3 developed asthma in addition to rhinitis (Figure 11). None of the 41 participants with asthma and rhinitis went into remission.

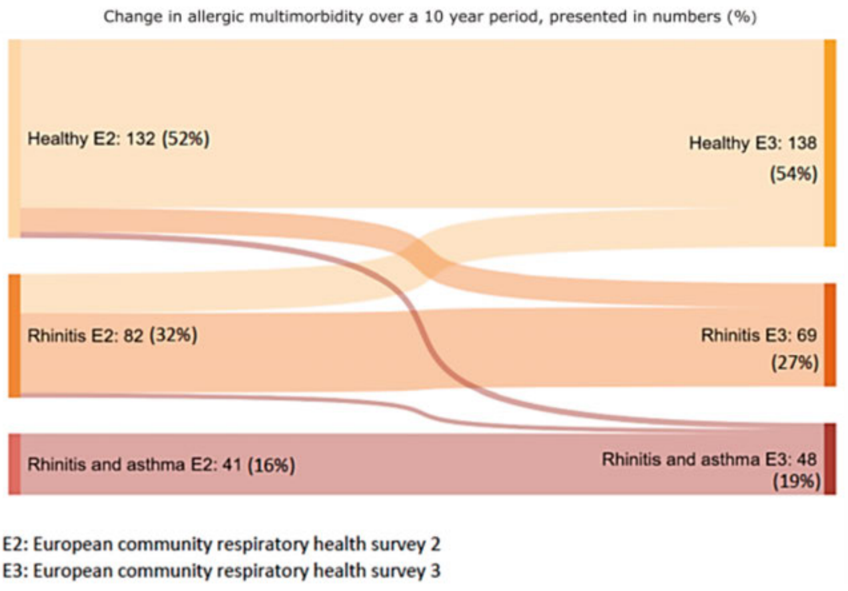

Figure 11. Change in allergic multimorbidity over 10 years, presented in numbers (%)

Participants with persistent rhinitis and asthma were younger compared with healthy individuals. Subjects with persistent disease were more likely to have a hereditary for allergic disease and asthma. Individuals with persistent disease, but mainly concomitant asthma and rhinitis, had lower lung function at inclusion in ECRHS II. No difference was seen in gender, BMI, or smoking status.

Sensitisation

Participants with persistent rhinitis were more likely to be sensitised to any allergen, food of plant origin, grass, and tree pollen at baseline (Table 6) than individuals who were healthy both at baseline and at follow-up. Subjects with persistent rhinitis were more likely to be sensitised to grass and tree pollen than those who went into remission (Table 6). Individuals with persistent asthma were more likely to be sensitised to tree pollen and furry animals than those with only persistent rhinitis.

Table 6. Multivariable analysis comparing healthy participants with those with persistent rhinitis and those with remission of rhinitis presented as risk ratio, 95% confidence interval

	Remission of rhinitis, n=26	Persistent rhinitis, n=53	p-value*
Age[A]	0.97 (0.91–1.03)	1 (0. 96–1. 06)	0.25
FEV_1%[AC]	0.99 (0.68–1.44)	1.05 (0.78-1.41)	0.78
Eczema [A]	3.29 (1.17-9.22)	1.53 (0.59-4.01)	0.18
No heredity for allergy [A]	1	1	
Heredity from 1 parent [A]	0.93 (0.36-2.39)	1.35 (0.64–2.84)	0.47
Heredity from both parents [A]	0.88 (0.09-8.72)	1.94 (0.43-8.75)	0.51
Sensitisation to foods of plant origin, E2[B]	1.79 (0.59-5.42)	2.98 (1.32-6.74)	0.37
Sensitisation to grass pollen, E2[B]	1.22 (0.12-12.7)	11.9 (3.16-45.1)	0.04
Sensitisation to tree pollen, E2[B]	2.62 (6.42-10.7)	7.96 (2.85–22.3)	0.09
Sensitisation to weed pollen, E2[B]	3.15 (0.38-26.3)	5.36 (0.98–29.2)	0.57
Sensitisation to furry animals, E2[B]	3.11 (0.17-55.1)	13.8 (1.58-120.3)	0.20
Sensitised to any allergen, E2[B]	2.61 (1.02-6.64)	5.22 (2.53-10.8)	0.17
Total IgE E2[B] (per one log unit increase)	1.41 (0.62–3.2)	4.07 (1.99-8.32)	0.02
Total IgE E3[B] (per one log unit increase)	1.3 (0.61–2.77)	3.45 (1.74–6.84)	0.03
F_ENO E2[B] (per one log unit increase)	2.51 (0.32-19.9)	2.13 (0.41-11.1)	0.89
F_ENO E3[B] (per one log unit increase)	0.69 (0.09-5.42)	1.88 (0.34-10.4)	0.40
ECP E2[B] (per one log unit increase)	1.90 (0.29-12.6)	6.80 (1.35-34.2)	0.02
ECP E3[B] (per one log unit increase)	1.09 (0.23-5.16)	0.99 (0.28-3.56)	0.92
EDN E3[B] (per one log unit increase)	1.33 (0.24-7.36)	1.36 (0.34-5.50)	0.98

*p-value when comparing those with remission with those with persistent rhinitis

[A] Adjusted for age, FEV_1, current eczema, heredity for allergy and being sensitised to any allergen

[B] Adjusted for age, FEV_1, current eczema, heredity for allergy

[C] Change calculated in 10% decrease intervals in FEV_1

E2: European community respiratory health survey II

E3: European community respiratory health survey III

Inflammatory markers were log-transformed

IgE: Immunoglobulin E

F_ENO: Exhaled nitric oxide

ECP: Eosinophil cationic protein

EDN: Eosinophil-derived neurotoxin

Inflammatory markers

Participants with persistent rhinitis had higher levels of total IgE in ECRHS II and 10 years later in ECRHS III, compared with both healthy individuals and those with remission of rhinitis (Table 6). Levels of ECP were elevated at baseline when comparing healthy individuals with those with persistent rhinitis (Table 6). Subjects with persistent rhinitis and asthma had higher levels of F_ENO at baseline than those with only persistent rhinitis. Subjects with persistent rhinitis and asthma had higher levels of total IgE at baseline and after 10 years, as well as F_ENO and ECP at baseline, compared with those who remained healthy. No difference was seen in F_ENO, ECP, and EDN in ECRHS III between those with persistent rhinitis and those who went into remission or remained healthy (Table 6). The above-mentioned findings persisted after adjusting for age, FEV_1, eczema, and allergic heredity (Table 6).

Discussion

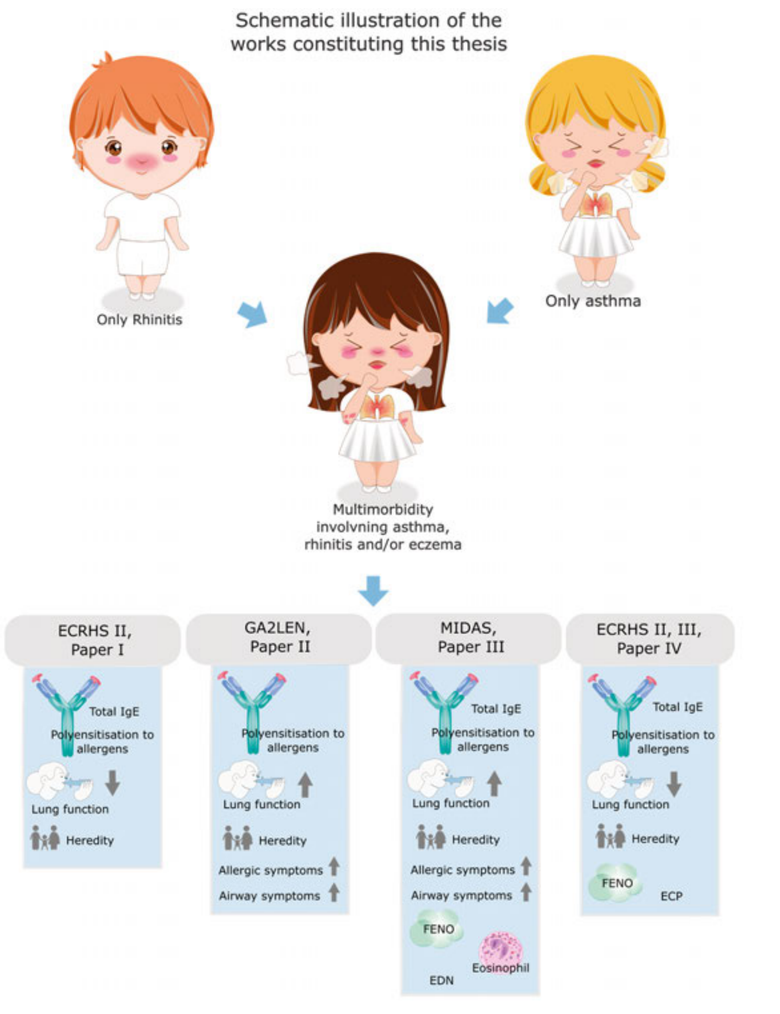

Figure 12

We investigated allergic multimorbidity in three different cohorts. Material from ECRHS was used for papers I and IV. The ECRHS cohort was enriched with individuals reporting airway symptoms or using medication indicative of asthma. Here, we found that 41% of participants had asthma or eczema in addition to rhinitis, and 9% had all three. We analysed self-reported asthmatics in the GA_2LEN cohort, and 58% had rhinitis or eczema in addition to asthma, 25% had all three. The MIDAS cohort consisted of young participants with physician-verified asthma, and 54% had rhinitis or eczema in addition to asthma, with 34% having all three. The factors impacting allergic multimorbidity discussed here are allergen sensitisation and type, airway and allergic symptoms, type-2 inflammatory markers, allergic disease over time, lung function, demographics, and heredity.

The main findings were that those with allergic multimorbidity had higher levels of total IgE and were more likely to be polysensitised with higher levels of antibodies to allergens. Elevated levels of F_ENO and EDN were associated with allergic multimorbidity in young asthmatics. Polysensitisation and elevated total IgE, F_ENO, and ECP were associated with persistent allergic disease over time.

Allergen sensitisation

In papers I and III, we found that those with allergic multimorbidity had the highest levels of both total and specific IgE, as well as antibodies against a higher number of allergens, compared with those with rhinitis or asthma alone. Total IgE was not elevated in allergic multimorbidity in paper II. However, we did see an association between allergic multimorbidity and sensitisation to food and aeroallergens in paper II. Elevated total IgE and polysensitisation at baseline and after 10 years were predictors for persistent allergic disease and allergic multimorbidity in paper IV.

Elevated total IgE and allergic polysensitisation are the most well-known biomarkers in allergic multimorbidity, and this finding has been consistent in several cohorts across the world. (135) Not as much is known when it comes to allergic disease over time. There is some evidence that total IgE might be a predictor of allergic disease throughout life. Starting at birth, elevated levels of total IgE in newborns have been described as a risk factor for developing asthma and rhinitis later in life (136, 137) and have been linked to persistent asthma in adults. (138) Persistent allergen sensitisation with age is associated with continued allergic disease. (139) Sensitisation to food and house dust mites in early childhood increases the risk of developing asthma and rhinitis later. (140) These observations, together with our findings, suggest that allergic sensitisation shapes the long-term course of allergic multimorbidity.

Type of allergen sensitisation

We found the seasonal allergens birch and grass to be associated with allergic multimorbidity in papers I, II, and IV. Allergens were grouped in paper III and not analysed individually. Furry animals were most relevant among perennial allergens. Allergen components were available in papers I and IV and showed that sensitisation to food (hazelnut, peanut, soya, peach) mostly involved proteins in the pathogenesis-related protein type 10 family (PR-10) and can likely be interpreted as cross-reactivity due to tree and grass pollen. We found allergic multimorbidity to be associated with sensitisation to milk, hazelnut, and peanut in paper II. No components are available in paper II, but one can speculate that cross-reactivity might be involved in peanut and hazelnut sensitisation even here. It is still unclear if some allergens have a greater impact on allergic multimorbidity. A Chinese study showed sensitisation to dust mites, cat dander, dog dander, soybean, milk, and shrimp to be most relevant to allergic multimorbidity. (141) A Polish study showed cat allergens to have the greatest impact besides polysensitisation. (67) One multicentre study from Sweden and France showed a marked difference in allergen sensitisation to dust mites, with around 1% of the Swedish and 26% of the French participants being sensitised. (142) Dust mite sensitisation has a large impact globally, but might not be a large problem in Sweden, as the climate in most parts is relatively inhospitable for them. (143) The most common sensitisers vary geographically, birch and timothy grass being most prevalent in Scandinavia, and house dust mites and timothy grass being more common in central Europe. (144) It is likely that there really is no universal allergen that has the largest impact, as geography and the local prevalence of allergens have a big impact on the development of allergen sensitisation.

Airway and allergic symptoms

We were able to show that those with allergic multimorbidity were more likely to report allergic reactions to food, compared with those with asthma alone in papers II and III. Symptoms were not analysed in papers I and IV.

Although allergic sensitisation is associated with increased risk, it is not synonymous with clinical allergy, and sensitisation magnitude does not consistently correlate with reaction severity. (145, 146) Others have shown that being polysensitised as opposed to monosensitised increases the likelihood of allergic multimorbidity as well as developing symptoms when exposed to the relevant allergen. (63, 147, 148) A potential contributor to allergic reaction severity in our study may be atopic dermatitis, as it is associated with the development of both elevated total IgE and specific IgE. (54) Asthma is a known risk factor for both more severe anaphylactic reactions and even fatal outcomes. (149, 150) There is some evidence that having more than one allergic disease simultaneously increases the likelihood of experiencing an allergic reaction to food, (69, 151, 152) though more research is needed for allergic multimorbidity to be considered a definite risk factor.

Allergic multimorbidity was associated with increased asthma, nasal symptoms, anxiety, and daytime sleepiness in papers II and III. The asthma symptoms that differed were wheezing, asthma attacks, and breathlessness during activity. Previous studies have mainly focused on asthma with concomitant rhinitis, showing that the co-occurrence of nasal disease also increases the symptom burden for asthma. (7, 153) We were able to show that there is an increase in reported asthma and psychological symptoms when asthma, rhinitis, and atopic dermatitis occur together. Not much is known about the impact of atopic dermatitis in terms of asthma symptoms. Atopic dermatitis is very common among those with severe asthma, 38% according to one study. (154) Another study showed that having any comorbidities increases the symptom burden for asthmatics, (41) all in all supporting our findings that atopic dermatitis adds to the symptom burden in asthma.

Type-2 inflammatory markers

We were able to show that individuals with asthma, rhinitis, and eczema had higher levels of F_ENO, P-EDN, and blood eosinophils, though not levels of ECP, compared with those with only asthma in paper III. Individuals with allergic multimorbidity are not only polysensitised with elevated total IgE, as discussed above, but also have higher levels of type-2 inflammation. The difference in F_ENO levels seemed to correlate more strongly with allergic multimorbidity among persons under the age of 18. Elevated levels of F_ENO and ECP at baseline were associated with persistent disease and allergic multimorbidity after 10 years in paper IV.

The production of F_ENO is in part governed by IL-13, and the production of eosinophils by IL-5. (16) There is some evidence that those with more than one allergic disease have elevated levels of type-2 inflammation, though not much information is available in the context of allergic multimorbidity. Higher levels of F_ENO and eosinophils have been observed among asthmatics with chronic rhinosinusitis. (155) Elevated F_ENO has previously been seen among children with persistent wheezing over time, (156) as well as persistent and new-onset rhinitis and the development of asthma in adults. (157, 158) Elevated eosinophils in infants increase the likelihood of developing atopy in early childhood (27) as well as being linked to having both asthma and rhinitis in adults. (65) Eosinophil activation markers are not well studied in this context.

Part of the explanation for our findings in paper III could be that we found increased eosinophilic inflammation in those with allergic multimorbidity. Higher F_ENO levels also correlate with eosinophilic inflammation and are, in some studies, associated with having both asthma and rhinitis at the same time. (73, 104, 159) Blood eosinophil counts were only available in paper III. ECP was measured in papers I, II, and IV, showing potential as a possible predictor for allergic multimorbidity over time only in paper IV. In paper II, we measured plasma EDN, not urine EDN, as in the third paper, which could have impacted the results. Both urine and plasma EDN correlate with elevated levels of eosinophils in the blood, though it is not clear if one measuring method is more sensitive than the other. (160)

Another factor in our findings in paper III could be that the cohort comprised children and young adults, whereas the rest of the papers studied middle-aged adults. In pediatrics, we are taught that "children are not small adults," and the immune system in children and young adults may react differently, even in terms of type-2 inflammation. Comparative studies between paediatric and adult immune systems are mainly available in the context of SARS-CoV-2 infection and immunisation responses. One such study showed that children produced twice the number of antibodies after vaccination compared with adults. (161) Another study showed that newborn myeloid-type dendritic cells stimulated via Toll-like receptor 4 secrete adult-like concentrations of pro-inflammatory cytokines that promote Th17 immune responses, (162) which would then lead to a proportionally high immune response compared to adults. IL-17 is most known for its association with neutrophilic asthma, but also participates in the recruitment of eosinophils and type-2 inflammation. (163) It is possible that the immune system is more reactive in early life and could contribute to the higher levels of type-2 inflammation in allergic multimorbidity we saw in paper III.

Periostin, induced by IL-4 and IL-13, (16) was only measured in paper II, and we found no association with allergic multimorbidity, though there is some indication in the literature that asthmatics with nasal involvement may have higher levels. (94)

C_ANO was only available in paper I; no connection was seen to allergic multimorbidity. There is some evidence that C_ANO levels may be elevated in allergic multimorbidity, although limited information is available on this topic. (79) C_ANO overlaps with F_ENO to some extent, but other studies have shown elevated levels in chronic obstructive lung disease without a simultaneous increase in F_ENO, indicating that it might reflect the distal airways better. (80) Lung function, as measured by FEV_1, was lowest among those with allergic multimorbidity in paper I, though the majority still had normal values, and it is possible that the peripheral airways simply were not affected enough for it to make a difference in terms of C_ANO.

CRP

CRP was only analysed in paper I, and we found no association between allergic multimorbidity and CRP. Previous studies indicate that CRP is not usually elevated in allergic disease and multimorbidity, though the latter is not well studied. (95)

Allergic disease over time

The main finding in the fourth study was that allergic disease remains relatively consistent over time. Some movement between groups was seen in those with allergic rhinitis. Elevated levels of total IgE, F_ENO, and ECP at baseline and elevated total IgE after 10 years, as well as polysensitisation, predicted persistent allergic disease over time and having more than one allergic disease.

Information on changes in allergic multimorbidity over time is scarce, but single diseases are relatively well studied. Remission of asthma seems to be more likely in children than in adults. (164, 165) Factors negatively associated with remission of rhinitis and asthma in the literature are heredity for allergy, allergen sensitisation, total IgE, as well as allergic multimorbidity, (138, 166) as discussed in the section on total IgE and allergen sensitisation above.

Previous studies on allergen immunotherapy in children have shown that it is possible to prevent about half of future asthma cases if allergic rhinitis is treated early. (167) The lion's share of current research on allergic disease modification is focused on food allergy. Treatment for peanut hypersensitivity in children has shown promising results, with approved treatment available both in Europe as well as the United States of America. (168) Current results in adults are, however, not as impressive, the main struggle being the induction of persistent food allergen tolerance. (169, 170) Allergen immunotherapy to airborne allergens shows the best results thus far, though long-term data is only available up to 9 years. (171) One can speculate that there might be a therapeutic window even in adults if identified in time. Or the key may lie in aggressive treatment from the start, to limit organ damage. As shown by a Japanese research group, early and aggressive treatment of atopic dermatitis in children reduced hen's egg allergy by about 10%. (172) More aggressive treatment of those with allergic multimorbidity and higher type-2 inflammation might limit the burden of disease over time, even in adults.

Lung function in allergic multimorbidity

Lung function (FEV_1) was lowest in those with allergic multimorbidity in papers I and IV, both using material from the ECRHS study. Papers II and III, both with different cohorts, showed the highest lung function among those with allergic multimorbidity.

Information on lung function is conflicting, even in the literature. Some studies have found that those with increased use of asthma medication and more than one allergic condition also have lower lung function. (98, 173, 174) Another study, however, found that those with rhinitis in combination with asthma are less likely to develop pulmonary function impairment in the form of fixed airflow obstruction. (99) It is known that some asthma phenotypes are less sensitive to steroids. (175) Those with only asthma in paper I were also more likely to have used oral corticosteroids during the last year, though lung function was the lowest in that group, and they may be simply less sensitive to treatment. It has also been proposed that the well-established link between asthma and allergic multimorbidity might speed up the time to diagnosis, leading to earlier intervention and thus better lung function. (41)

Demographics and heredity

We found that those with persistent allergic disease were younger in paper IV; no difference was seen in the rest of the papers. Asthma was more likely to be diagnosed before the age of 12 among those with allergic multimorbidity in paper II; this was not analysed in the rest of the papers. Studies on atopic dermatitis have also found early onset of disease to be associated with allergic multimorbidity, and it is hypothesised that it stems in part from a damaged skin barrier and earlier allergen sensitisation. (176) A pre-existing predisposition from birth, gearing the immune system towards an elevated type-2 inflammatory response and allergen sensitisation, could be part of the explanation. (177) Shorter time to diagnosis due to the well-established link between the diseases might be another contributing factor. (41)

Those with allergic multimorbidity had lower BMI in paper I; no difference was seen in the rest of the papers. Information on BMI in allergic multimorbidity is scarce, though information is available on different diseases, pointing rather towards a connection with higher BMI. High BMI is a known risk factor for type-2 low asthma; one study also found a connection to atopy. (178) Higher BMI has also been observed among those with rhinitis and bronchial hyperreactivity. (179) Higher BMI is linked to atopic dermatitis separately. (180)

Participants with allergic multimorbidity were more likely to use medication for asthma or allergies in papers I and III; those with only asthma were more likely to use oral corticosteroids in paper III; medication use was not analysed in paper IV. Those with allergic multimorbidity often report more severe disease and a higher need for medication, even in other studies. (7, 41, 43, 181)

We found allergic multimorbidity to have a stronger association with maternal allergy in papers I, II, and maternal asthma in paper I. Only maternal heredity for rhinitis and heredity from both parents for eczema increased the risk for allergic multimorbidity in paper III. We also found that heredity for both allergy and asthma was important in persistent allergic disease in paper IV, though maternal and paternal allergy were pooled here.

Heredity is an established risk factor for allergic disease, but it is still not entirely clear how it impacts allergic multimorbidity. Literature supports that heredity increases the risk of having allergic multimorbidity and, in some cohorts, increases the risk by as much as three times and up to eight times if present from both sides. (11, 64, 68, 182) Another study was able to identify eight genes involved in allergic multimorbidity as compared with a single disease, some of them also involved in eosinophils and type-2 inflammation. (183) We found maternal allergy to have a larger impact. Previous studies have shown that subjects with a maternal history of allergies run a four times higher risk, whereas paternal allergy was associated with a two times higher risk of having two or more allergic diseases. (182) (184)

Limitations

The main limitations of these four papers are that the data were self-reported, though some parts of the questionnaires were filled out with the assistance of a trained nurse, increasing their accuracy. The definition of eczema is rather broad and may have led to some misclassification. Further, the relatively small sample size could have impacted the results. Despite random recruitment, the possibility of selection bias remains due to differences between responders and non-responders. Sampling and lung function were cross-sectional; there may be temporal fluctuations that aren't captured.

Conclusions

We concluded that:

I. Having rhinitis, asthma, and eczema together is associated with a higher degree of sensitisation as well as higher levels of total IgE, compared with having rhinitis alone.

II. Asthmatics with rhinitis and eczema were more likely to be sensitised to food and aeroallergens and report allergic reactions to food compared with those with asthma alone.

III. Asthmatics with rhinitis and eczema showed a higher degree of Th-2 inflammation compared with those with asthma alone. Those with allergic multimorbidity were more likely to be sensitised to food and aeroallergens as well as report symptoms when in contact with those allergens.

IV. IgE sensitisation and total IgE levels are associated with the persistence of rhinitis and asthma. Participants with persistent allergic disease had higher levels of allergen sensitisation and type 2 inflammation markers at baseline than those who remained healthy.

Future perspective

Multimorbidity involving asthma, rhinitis, and eczema is well-recognized but remains insufficiently studied. While type 2 inflammation is implicated in each of these diseases individually, its role in driving multimorbidity is poorly understood. (11, 16, 45)

Evidence suggests the existence of distinct multimorbid phenotypes. The best characterized to date are patients with allergic sensitization, often accompanied by additional related conditions such as food allergy, eosinophilic esophagitis, urticaria, and angioedema. (41) How these diseases interact with each other is still not clear. Multimorbidity also occurs in individuals without allergic sensitization, a population that has received little or no attention to date.

Eosinophilic inflammation represents another potential mechanistic driver. Given the availability of effective eosinophil-targeted therapies, future studies should explore whether such treatments can benefit patients with allergic multimorbidity who do not meet current eligibility criteria for biologics targeting single diseases.

At the clinical level, there is a lack of research evaluating integrated, multidisciplinary care tailored to multimorbid patients. Importantly, future research should also assess whether biologics provide therapeutic benefits across multimorbid phenotypes rather than within isolated allergic conditions. In parallel, studies addressing the psychosocial burden and health-economic impact of allergic multimorbidity will be of interest for developing more patient-centered and sustainable management strategies.

Sammanfattning på Svenska- Summary in Swedish

Bakgrund

Astma är en kronisk sjukdom i lungorna där luftvägarna är irriterade och inflammerade. Det gör att det ibland blir svårt att andas, eftersom luftvägarna drar ihop sig och blir trängre. Hur svårt det är att andas kan variera från dag till dag. Allergiframkallande ämnen, så kallade ”allergener”, ökar risken för att insjukna i astma. Det är en vanlig sjukdom som drabbar människor i olika delar av världen, i Sverige ligger förekomsten på cirka 11% bland vuxna. Besvären är vanligtvis milda, men astma kan bli livshotande – även med dagens behandlingar. Idag vet man att astma inte är en enda sjukdom, utan att det finns olika typer som kan ha olika orsaker.

Ett viktigt område för forskning är något som kallas typ 2-inflammation, som kan mätas med olika blod- och andningstester, och som påverkar hur sjukdomen utvecklas. För att ta reda på vilken typ av inflammation en patient har kan vi mäta vissa ämnen i kroppen, så kallade biomarkörer. De tre vanligaste som används i kliniken idag är:

- **IgE** – en antikropp som mäts i blodprov
- **F_ENO** – kväveoxid som mäts i utandningsluften
- **Eosinofiler** – en typ av vita blodkroppar som räknas i blodprov

Det finns även andra markörer som kan mätas, även om de ännu inte är lika etablerade i den kliniska vardagen. Dessa inkluderar periostin (ett protein), C_ANO (kväveoxid från lungblåsorna), samt markörer som visar att eosinofiler är aktiverade, såsom ECP och EDN.

Anledningen till att intresset för biomarkörer har ökat är att det nu finns nya läkemedel som kan rikta in sig mot specifika delar av inflammationen. Det betyder att patienter som inte blir bra av vanlig astmamedicin kan få en mer skräddarsydd behandling som fungerar bättre för just dem.

Rinit, eller hösnuva, är ännu vanligare än astma och påverkar runt 30% av vuxna i Sverige. Trots att sjukdomen är vanlig är den ofta underskattad och den har stora kostnader för både individer och samhället i form av läkemedel, sjukfrånvaro och besök till sjukvården.

Eksem, som orsakar torr och kliande hud, drabbar mellan 2–10% av vuxna i Sverige.

Astma, rinit och eksem förekommer ofta tillsammans, och att hitta en förklaring till detta har länge varit ett intresseområde. Ett begrepp som beskriver detta är ”den atopiska marschen”, en utveckling där eksem ofta visar sig i barndomen, följt av rinit och slutligen astma i tonåren eller som ung vuxen. Vi vet idag att detta endast förklarar cirka 7 % av alla fall med samsjuklighet mellan astma, rinit och eksem. Ungefär 1–2 % av befolkningen har alla tre sjukdomarna, och siffran stiger till 6 % bland dem som också har allergi.

Allergier i sig har blivit allt vanligare och berör idag ungefär 30 % av människor världen över. Världshälsoorganisationen förutspår att detta kommer öka till 50 % år 2050. Det är oklart vad som orsakat denna ökning. En populär teori var ”hygienteorin”, där överdriven renlighet minskade kontakten med bakterier och virus och ledde till en obalans i immunsystemet. Denna teori har sedan dess motbevisats. Man spekulerar däremot att en tänkbar orsak till utveckling av allergi kan vara att man bor i städer och utsätts för skadliga ämnen i rengöringsmedel, giftiga ämnen och mikroplaster som kan skada huden och påverka kroppens immunsystem.

Syfte

Syftet med denna avhandling var att bättre förstå varför vissa personer drabbas av flera allergiska sjukdomar samtidigt – så kallad allergisk samsjuklighet – medan andra bara utvecklar en sjukdom.

Metod

För att undersöka detta använde vi information om deltagarnas bakgrund (som ålder, kön och livsstil), deras symtom och lungfunktion. Vi mätte även antikroppar mot allergen samt olika inflammationsmarkörer i blod och utandningsluft: totalt IgE, CRP, periostin, FENO, CANO, eosinofiler och markörer som visar att eosinofiler är aktiverade (ECP och EDN).

Avhandlingen bygger på fyra studier med totalt över 1 300 deltagare, främst medelålders vuxna, men även barn och unga vuxna:

- **Arbete I:** 216 personer från den europeiska lungstudien European Community Respiratory Health Survey II (ECRHS II)
- **Arbete II:** 437 personer med astma från den svenska delen av Global Allergy and Asthma European Network-studien (GA²LEN)
- **Arbete III:** 411 barn och unga vuxna från studien Minimally Invasive Diagnostics for Asthma and Allergic Diseases Study (MIDAS)

- **Arbete IV:** 255 personer som följdes i 10 år, från ECRHS II till ECRHS III

Resultat

I dessa studier fann vi att de med allergisk samsjuklighet hade antikroppar mot fler olika allergener och hade högre nivåer av dessa antikroppar jämfört med dem som bara hade en allergisk sjukdom. Dessutom var risken att få besvär när man kom i kontakt med allergener större hos personer med samsjuklighet. Vi såg också ett samband mellan ökade nivåer av typ-2 biomarkörer och därmed typ 2 inflammation och allergisk samsjuklighet. I artiklarna I, III och IV visade vi att personer med allergisk samsjuklighet hade högre nivåer av totalt IgE. Artikel III visade också att personer med samsjuklighet hade högre nivåer av eosinofiler, EDN och F_ENO. Skillnaden i F_ENO var mest uttalad hos barn och ungdomar under 18 år.

Artikel IV undersökte om det var möjligt att förutse vilka som skulle behålla sina allergiska sjukdomar jämfört med de som blev friska under en tioårsperiod. Resultaten visade att personer med kvarvarande symtom hade högre nivåer av totalt IgE vid studiens start och 10 år senare, samt förhöjda utgångsnivåer av ECP och F_ENO. Däremot hittades inget samband med andra inflammatoriska markörer: C_ANO, CRP (artikel I) eller periostin (artikel II). Vi undersökte även ärftlighet och fann, att ärftlighet för astma och allergi, särskilt från moderns sida, spelade en roll för allergisk samsjuklighet i samtliga fyra arbeten.

Resultaten för lungfunktion var motstridiga. Vi fann både högre och lägre lungfunktion hos personer med mer än en allergisk sjukdom. Vi undersökte även astmasymtom (artikel II och III) och såg ett tydligt mönster att personer med alla tre sjukdomarna också upplevde mer besvär.

Diskussion

I artiklarna I–IV såg vi att både mängden IgE-antikroppar och känslighet mot många olika allergener hänger ihop med att ha flera allergiska sjukdomar samtidigt. Våra resultat bekräftar vad andra forskare tidigare har observerat. Vi kunde också visa att personer med astma, rinit och eksem var mer benägna att få allergiska symtom när de kom i kontakt med allergener. Eftersom mekanismen bakom allergiska reaktioner fortfarande till stor del är okänd kan våra fynd bidra till att bättre identifiera vilka som löper störst risk att få en reaktion.

Vi fann också att F_ENO var förhöjt hos personer med allergisk samsjuklighet, särskilt tydligt bland barn och ungdomar under 18 år. Även nivåerna av eosinofiler och EDN var förhöjda (artikel III). Dessutom kunde förhöjda nivåer av F_ENO och ECP förutsäga kvarstående allergisk sjukdom över tid.

Däremot fann vi inget samband mellan allergisk samsjuklighet och andra typ 2-biomarkörer som studerades i artiklarna I och II (C_ANO, CRP och periostin).

Vi har därmed till viss del kunnat visa en koppling mellan allergisk samsjuklighet och högre nivåer av typ 2-inflammation.

Slutsatser

Sammanfattningsvis fann vi att både mängden IgE-antikroppar och känslighet mot många olika allergiframkallande ämnen hänger ihop med allergisk samsjuklighet. Dessa personer har högre nivåer av typ 2-inflammation och fler symtom jämfört med dem som bara har en allergisk sjukdom. Det understryker behovet av att kombinera olika behandlingsmetoder för att både lindra patienternas besvär och för att minska samhällets kostnader för allergiska sjukdomar.

Author’s declarations

All content in this thesis has been drafted by the author. Artificial intelligence (AI) from chatgpt.com and Grammarly has been used to refine language and improve grammar. All AI suggestions have been reviewed, edited, and approved by the author. This aligns with Uppsala University’s policy on the use of generative AI tools. All illustrations have been created by the author using Inkscape. The cover was drawn by Ida Nylander, who generously permitted me to use her art.

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