The association between eczema, asthma and rhinitis – population studies of prevalence and risk factors among adults

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Gothenburg 2016

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ISBN 978-91-628-9746-8 (Print)
ISBN 978-91-628-9747-5 (PDF)
http://hdl.handle.net/2077/41838
Printed in Gothenburg, Sweden 2016
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ABSTRACT

Background: Allergic diseases such as asthma, rhinitis and eczema have increased significantly since the middle of the past century and are now common conditions among both children and adults. The increase was observed earlier and is more evident in Westernized countries but is now also apparent in urbanized areas in developing countries. The exact cause of this increase is still not fully explored, although several partly contradicting hypotheses exist, including the hygiene hypothesis. Asthma, rhinitis and eczema are common comorbidities and allergic sensitization is commonly seen as a unifying link.

Research questions: The overall aim of this thesis was to investigate the prevalence of eczema; risk factors for eczema; overlapping risk factors for asthma, rhinitis and eczema; the prevalence of allergic sensitization and the impact of allergic sensitization on these diseases in an adult population. Additional objectives included a validation of the representativeness of the recruited population.

Methodology: This thesis is based on a postal survey in Västra Götaland with 18 087 responders (62%) out of a real study sample of 29 218 individuals aged 16 to 75 years. Clinical examinations including structured interviews, lung function tests, anthropometric measures, skin prick tests and assessments of specific serum Immunoglobulin E were performed in 1172 randomly selected responders. A study of non-response was carried out among non-responders to the postal survey and 211 out of the 400 randomly

selected subjects were successfully contacted by phone and agreed to participate.

Results: Non-responders compared to responders to the postal survey tended to be younger, smoke, have male sex and live in the metropolitan area of Gothenburg but they did not differ in prevalence of asthma, airway symptoms, eczema and rhinitis. Ever having had eczema was reported by 40.7% in the postal survey and the prevalence of current eczema was 11.5%. Eczema was more common among women and associated with respiratory symptoms, asthma and rhinitis. Allergic sensitization, obesity, female sex and occupational exposure to gas, dust or fumes were significantly and independently associated with asthma. A risk factors for rhinitis but not for eczema was obesity and allergic sensitization was strongly associated with rhinitis but less so for eczema. Risk factors for eczema but not for rhinitis were female sex and occupational exposure to gas, dust or fumes. Farm childhood was negatively associated with rhinitis and eczema but not asthma. The prevalence of sensitization to at least one common airborne allergen was 29.7%. Sensitization to birch and dog was associated with asthma while rhinitis was associated with sensitization to birch and timothy. No significant association was found between allergic sensitization and current eczema.

Conclusions: We conclude that non-response had minimal effect on the outcome in our study. Eczema was more common than anticipated and associated with asthma and rhinitis. There are different risk factor patterns for asthma, rhinitis and eczema in adults. Allergic sensitization is an important risk factor for asthma and rhinitis but less so for eczema among adults. Rhinitis is mainly associated with sensitization to outdoor allergens while asthma is related to both outdoor and indoor allergens.

Keywords: epidemiology, asthma, eczema, rhinitis, risk factors, allergic sensitization

ISBN: 978-91-628-9746-8 (Print)

SAMMANFATTNING PÅ SVENSKA

Allergiska sjukdomar som astma, rinit och eksem har ökat under senare delen av 1900-talet och är nu vanligt förekommande både bland barn och vuxna. Ökningen är tydligare i samhällen med västerländska levnadsvanor men man ser nu också en ökning i urbaniserade områden i utvecklingsländer. Orsaken till denna ökning är ännu ej helt klarlagd men flera delvis motsägelsefulla teorier inklusive hygienhypotesen existerar. Astma, rinit och eksem uppträder ofta hos samma individ och allergisk sensibilisering anses vara en gemensam faktor. Det övergripande syftet med den här avhandlingen var att undersöka förekomst av eksem och allergisk sensibilisering, samvariationen av riskfaktorer för astma, eksem och rinit och vidare att undersöka relationen mellan allergisk sensibilisering och dessa tillstånd i en slumpvist utvald vuxen befolkning. Ytterligare mål inkluderade att validera representativiteten av studiepopulationen.

Avhandlingen baseras på en tvärsnittsundersökning inom åldersintervallet 16-75 år i Västra Götaland distribuerad med post och efterföljande kliniska undersökningar på en subgrupp av slumpmässigt utvalda deltagare som medverkat i enkäten. Antalet deltagare i enkätstudien var 18 087 personer vilket motsvarar 62% av de 29 218 inbjudna. Kliniska undersökningar inkluderande strukturerad intervju, lungfunktionstester, antropometriska mått, pricktest och analys av specifika antikroppar mot Immunoglobulin E i serum genomfördes på 1172 slumpvist utvalda personer som deltagit i den postala undersökningen av totalt 2000 inbjudna. Bland de personer som inte svarat på den postala enkäten valdes slumptvist 400 individer ut till en bortfallsstudie varav 211 framgångsrikt kontaktades och gick med på att medverka i en strukturerad intervju över telefon innehållande utvalda frågor från den postala enkäten.

Personer som inte svarat på den postala enkäten jämfördes med dem som svarade och tenderade att i högre utsträckning vara yngre, män, rökare och bo i Göteborgs storstadsområde men det var ingen skillnad i förekomst av astma, luftvägssymptom, rinit och eksem. Andelen personer i den postala undersökningen som uppgav sig någon gång ha haft eksem var 40.7% och 11.5% hade nuvarande eksem baserat på symptom under de senaste tolv månaderna. Eksem var vanligare bland kvinnor och associerat med symptom från luftvägarna, astma och rinit.

Allergisk sensibilisering, fetma, kvinnligt kön och exponering för gas, damm eller rök på arbetet var associerat med astma. Fetma var en riskfaktor för rinit

men inte för eksem och allergisk sensibilisering var starkt associerat med rinit men inte tydligt så för eksem. Kvinnligt kön och exponering för gas, damm eller rök på arbetet var riskfaktorer för eksem men inte rinit. Uppväxt med jordbruk inom familjen hade en skyddande effekt på eksem och rinit men inte astma. Förekomsten av allergisk sensibilisering mot minst ett luftburet allergen var 29.7%. Astma var associerat med sensibilisering mot hund och björk medan rinit var associerat med sensibilisering mot björk och timotej. Allergisk sensibilisering var inte signifikant associerat med pågående eksem.

Sammanfattningsvis fann vi att eksem var vanligare än förväntat hos vuxna och associerat med astma och rinit. Riskfaktormönstret bland vuxna skiljer sig åt för astma, rinit och eksem med allergisk sensibilisering som en viktig riskfaktor för astma och rinit men inte tydligt så för eksem. Representativiteten av studien var hög och trots att svarsfrekvensen var måttlig så hade det liten effekt på resultaten.

LIST OF PAPERS

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

I. Erik Rönmark, Linda Ekerljung, Jan Lötvall, Kjell Torén, Eva Rönmark and Bo Lundbäck.
Large scale questionnaire survey on respiratory health in Sweden: Effects of late- and non-response.
Respiratory Medicine 2009; 103; 1807-1815.

II. Erik Rönmark, Linda Ekerljung, Jan Lötvall, Göran Wennergren, Eva Rönmark, Kjell Torén and Bo Lundbäck.
Eczema among adults: prevalence, risk factors and relation to airway diseases. Results from a large-scale population survey in Sweden.
British Journal of Dermatology 2012; 166; 1301-1308.

III. Erik Rönmark, Linda Ekerljung, Roxana Mincheva, Sigrid Sjölander, Stig Hagstad, Göran Wennergren, Eva Rönmark, Jan Lötvall and Bo Lundbäck.
Different risk factor patterns for adult asthma, rhinitis and eczema -results from West Sweden Asthma Study.
In manuscript

IV. Erik Rönmark, Linda Ekerljung, Jan Lötvall, Shintaro Suzuki, Anders Bjerg, Sigrid Sjölander, Magnus P. Borres, Göran Wennergren, Bo Lundbäck and Eva Rönmark.
Different impact of allergic sensitization on asthma, eczema and rhinitis among adults.
In manuscript

CONTENT

ABBREVIATIONS

ATS	American Thoracic Society
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
ECRHS	European Community Respiratory Health Survey
ECSC	European Community for Steel and Coal
EP3OS	European Position Paper on Rhinosinusitis and Nasal Polyps
GDF	Gas, dust or fumes
GINA	Global Initiative for Asthma
ICD	International Classification of Diseases
IgE	Immunoglobulin E
ISAAC	International Study of Asthma and Allergies in Childhood
IUATLD	International Union Against Tuberculosis and Lung Disease
MC	Millennium Criteria
MRC	Medical Research Council
NARES	Nonallergic rhinitis with nasal eosinophilia syndrome
NHLI	National Heart and Lung Institute
OLIN	Obstructive Lung Disease in Northern Sweden
SPT	Skin prick test
UKP	UK Working Party
WAO	World Allergy Organization
WHO	World Health Organization
WSAS	West Sweden Asthma Study

1 INTRODUCTION

There has been a major increase in allergic diseases such as asthma, rhinitis and eczema as well as of allergic sensitization during the second half of the past century. Considerable efforts have been made to better characterize the disorders and elucidate the cause for this increase with progress in numerous areas. The work of scientists across the world has resulted in a number of hypotheses formulated to unravel to the cause for this increase in allergic diseases. Most scientists now agree that no single environmental factor can explain this increase in allergy dubbed "The allergy epidemics" by Thomas Platts-Mills[1].

In the late 1980s, Strachan[2] showed that having older siblings was associated with a lower risk of hay fever and eczema. He theorized that infections in early childhood transmitted by unhygienic contact with older siblings prevented allergic diseases. His theory known as the *hygiene hypothesis* has been expanded to encompass other explanatory factors such as decreased intake of unpasteurized milk[3], decreased exposure to bacteria[4] and changes in the gut flora[5]. Further, allergic diseases and allergic sensitization seem less common among children growing up with pets at home[6,7]. Other explanations are an increase in obesity[8] and sedentary behavior[9] and all these changes are associated with a Westernized lifestyle often called *westernization*.

However, most studies in this field have been conducted among children and due to the heterogeneity of asthma, rhinitis and eczema it is not certain that the explanations and associations found among children are valid in adults. There is a particular gap of knowledge in eczema among adults and Hywel Williams, a leading expert in the field has stated that virtually nothing is known about the epidemiology of eczema in adults except that it affects at least 3% of adults and tends to be persistent[10].

This thesis aims at describing the prevalence and risk factors of eczema in adults, comparison of the risk factor patterns of asthma, rhinitis and eczema, estimating the prevalence of allergic sensitization and the relationship of allergic sensitization with asthma, rhinitis and eczema.

2 BACKGROUND

2.1 Diseases under study

2.1.1 Asthma

Asthma is not a recently discovered disease. The term asthma is a Greek noun derived from the verb *aazein* meaning ”to exhale with open mouth” or “to pant”[11]. The first recorded use of the term is within the poem of Iliad[12]. However, this epic 2700 years old story attributed to Homer is most likely not describing the symptoms of what we today call asthma. The earliest scripture where asthma is found in relation to medicine is in the writings of the school of Hippocrates of Kos[13] (460-360 B.C) but the Hippocratic description of asthma is referring more to a general symptom than a disease entity. The first clinical description of asthma similar to how we view the disease today was recorded by Aretaeus of Cappadocia in the first century A.D[14].

Today, asthma is considered a chronic disease characterized by variable airflow limitation and by symptoms of wheeze, cough, chest tightness and shortness of breath. Characteristically the airflow limitation and symptoms vary in intensity and over time. These variations can be caused or triggered by external factors such as allergen or irritant exposure, viral respiratory infections or change in weather. The variations can also be triggered by internal factors such as exercise[15]. Asthma is usually associated with chronic airway inflammation and airway hyperresponsiveness to direct or indirect stimuli. The inflammation of asthma involves multiple cells, mediators and pathways from both the innate and the adaptive immune system[16]. Airway remodeling involving subepithelial fibrosis[17], goblet cell hyperplasia, submucosal gland enlargement[18,19] and increased smooth muscle mass[18] coexists and is likely caused by the inflammation[20]. The expert committee of The Global Initiative for Asthma (GINA) that was launched in collaboration with the World Health Organization (WHO) has the following definition of asthma[15].

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

It is now clear that asthma does not represent one clearly defined homogeneous disease entity but instead multiple separate clinical

presentations that overlap. Earlier categorizations of asthma in intrinsic and extrinsic types[21] have developed into further subclassifications of the disease which are still in use[7,22]. We now acknowledge that there are multiple endotypes of asthma with different severity, triggers, treatment response and inflammatory components[16,23,24].

The Western world has seen a significant increase in asthma for the past fifty years[25,26]. There are also evidence that the prevalence of asthma is rising in developing countries undergoing changes in terms of industrialization and urbanization such as China[27]. The observed increase in asthma now may have stabilized and reached a plateau for at least some Westernized countries[28-33]. There are methodological difficulties in comparing the prevalence of asthma across the world. Different study designs, age groups, disease definitions and questionnaires make direct comparisons between many studies somewhat unreliable. The majority of studies have also been carried out among children with less data published in adults. The present prevalence of adult asthma in Sweden has been assessed with the same method in 2006 to 2008. The prevalence of ever having had asthma was 13.4% in Norrbotten[34], the most northern region of Sweden. In Stockholm[35], the prevalence was slightly lower with 11.0%. The prevalence of physician diagnosed asthma was 11.6% and 9.3% respectively for Norrbotten and Stockholm while it was 8.3% in West Sweden (Västra Götaland) in the same time period[36]. Finland participated in the same study set-up and the prevalence of physician diagnosed asthma was 10.0%[37] in Helsinki. In Australia, the prevalence of physician diagnosed asthma was 12.2% in 2003[38] but a structured interview was used instead of a self-administered questionnaire. A proportion of the subjects with asthma go into remission and consequently the prevalence of ever having had asthma will be higher than the prevalence of current asthma. Browatzki et al[39] estimated the Danish prevalence of current asthma in 2001 to 5.9% in men and 7.7% in women while Thuesen et al[40] found a prevalence of 11.1% between 2006 and 2008. In Italy[41], the prevalence of current asthma between 2007 and 2010 was 6.6%. Canadian registry-based studies have estimated an asthma prevalence of 13.3%[42].

The exact cause of asthma is not known but several risk factors have been identified. Allergic rhinitis and allergic sensitization have been shown to increase the risk of asthma[43-46]. However, the pattern of allergic sensitization in subjects with asthma varies across the world. Several studies have found animal dander followed by pollen to be the most common sensitizers among asthmatics in the cold and dry climate of Sweden[47,48] with similar results in Finland[49]. Sensitization to house dust mites tends to be more common in areas with warmer climate and in conjunction with animal dander is the most

prevalent sensitization in Germany[50] with similar findings in Australia[51] and New Zealand[52]. House dust mites are also the overall most common sensitizers among asthmatics in the United States[53] but sensitization to cockroach is also common, especially in metropolitan and low-income areas[54,55]. Sensitization to multiple allergens compared to single allergens has also been linked to an even greater risk of asthma[49].

Sex affects the risk of asthma in an age-dependent manner. Asthma is more common in boys until early teenage but after puberty it is more prevalent among girls[56]. Family history of asthma increases the risk of asthma[44] but not in a typical Mendelian pattern. Many loci across several chromosomes have been associated with asthma but the overall effect is weak[57]. This implies that the hereditary component is not only genetic but also due to increased exposure to other risk factors. Obesity increases the risk of asthma[44,58-60] and according to one study in a dose-dependent manner[8]. Exposure to gas, dust or fumes in an occupational setting is associated with asthma[61]. Other identified risk factors that mainly have been studied in children include parental smoking in childhood[62], preterm birth[63] and exposure to visible mould in a domestic setting.[64]

2.1.2 Rhinitis

The term rhinitis stems from the Greek noun for nose, *rhis* and *–itis* denoting inflammation. The Joint Task Force on Practice Parameters has defined rhinitis as a condition characterized by one or more of the following nasal symptoms: congestion, rhinorrhea, sneezing and itching. It is usually but not always associated with inflammation[65]. Rhinitis is classified as either infectious or non-infectious. Non-infectious rhinitis is further classified as either allergic or nonallergic. However, not all types of non-infectious rhinitis can be separated into one of these two categories. Occupational rhinitis may for an example contain components of both allergic and nonallergic rhinitis.

Allergic rhinitis is defined as an immunologic response mediated by IgE and characterized by nasal congestion, sneezing, rhinorrhea and pruritus of the nose. It is frequently accompanied by ocular symptoms such as swelling, redness and a burning sensation of the eyes[66]. Allergic rhinitis can be classified as seasonal (commonly called hay fever), which most frequently is attributed to IgE-mediated sensitivity to pollen allergens. Alternatively, allergic rhinitis can be classified as perennial, which is often caused by allergy to mite or animal dander[67,68]. However, recent guidelines advocate using the terms intermittent and persistent in favor of seasonal and perennial[69]. The prevalence of allergic rhinitis has increased in the last fifty years[70-75]. Recent studies show that the current prevalence of allergic rhinitis

varies considerably and range in Scotland from 15.4-20%[76], 22.5% in Denmark[75], 25.8% in Italy[41], 28% in Sweden[77] and 40.1% in Finland[78].

Identified risk factors for the development of allergic rhinitis include allergic sensitization[48,79]. Studies from Sweden[48] and Denmark[75] have found outdoor allergens to be the major allergens in allergic rhinitis with pollen as the dominant sensitizer, while sensitization to animal dander was slightly more important in Finland[49]. Having a family history of allergic rhinitis[80,81] increases the risk while growing up in a farm environment[82-84] and having multiple older siblings are associated with a reduced risk for allergic rhinitis[85].

All other types of chronic rhinitis in which there are no specific IgE antibodies to relevant aeroallergens can be broadly classified as nonallergic rhinitis. Nonallergic rhinitis is thus a syndrome with many contained endotypes. Prominent symptoms of nonallergic rhinitis are nasal congestion, rhinorrhea, facial pressure, postnasal drip and throat clearing[86]. The symptoms are usually perennial but intermittent exacerbations may result from environmental changes[87]. Nasopalatal pruritus and ocular symptoms are usually absent in comparison to allergic rhinitis[88,89]. The prevalence of nonallergic rhinitis is difficult to estimate because it can coexist and be reported as allergic rhinitis. The European Community Respiratory Health Survey (ECRHS) found that 25% of subjects with symptoms suggestive of allergic rhinitis in fact had nonallergic rhinitis[90]. The prevalence of rhinitis has been estimated in Belgium where 9.6% of the population had nonallergic rhinitis. The rate of allergic rhinitis was 29.8% in that same study[91].

Nonallergic rhinitis is thus a disorder composed of a heterogeneous group of diseases. It can be further divided in to noninflammatory and inflammatory types. Vasomotor rhinitis is the typical noninflammatory nonallergic rhinitis and is considered a disorder with a functional dysregulation of the nasal mucosa[92]. In vasomotor rhinitis the sensitivity to environmental factors is increased and many patients are hyperresponsive to stimuli such as cold dry air[93]. The inflammatory types of nonallergic rhinitis can further be subdivided based on the histology into eosinophilic, neutrophilic and mixed cellar forms (Figure 1).

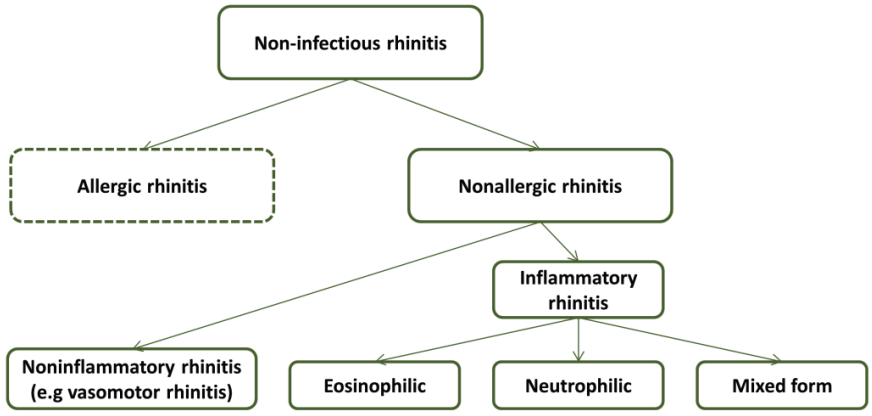

Figure 1. Types of rhinitis by pattern of inflammation.

It is beyond the scope of this thesis to give a detailed description of all these entities, but for more information the author of this thesis recommends reading of the excellent review by Lieberman et al[86]. The most common form of inflammatory nonallergic rhinitis is NARES (nonallergic rhinitis with nasal eosinophilia syndrome). The prevalence of NARES among patients with nonallergic rhinitis has been shown to range from 13% to 33%[94,95]. Biopsies from the nasal mucosa of these patients show increased counts of eosinophils[96] and subjects with NARES tend to respond well to local corticosteroids[97]. Nonallergic rhinitis can also be associated with nasal polyposis with either an eosinophilic or neutrophilic pattern of inflammation[98].

2.1.3 Eczema

In this thesis, eczema is used synonymously with atopic dermatitis. Eczema derives from the Greek word *ekzein* meaning "to boil out" or "to effervesce"[99]. It is an inflammatory skin condition with a predilection for the skin flexures[100]. Major characteristics are pruritus, erythema, edema and vesicles[101]. The skin in eczema is often dry and extremely itchy. Scratching makes eczema worse and causes lichenification with epidermal thickening and increased skin markings[102]. The condition has a clinical appearance and localization that varies by age. Eczema is generally acute in infants with lesions mainly on the face and extensor surfaces of the limbs. After the first 1-2 years the manifestations tend to become polymorphous with different types of skin lesions and an inclination for flexural folds. Older children, adolescents and adults often presents with excoriated and lichenified plaques at flexural sites, ankles, wrists and around the eyes. The upper torso, shoulders and scalp may be involved in a head and neck type and some adults

have only prurigo-like lesions or chronic hand eczema[103]. The skin in eczema is often colonized by *S aureus* and prone to secondary bacterial and viral infections, especially in severely affected patients[104]. The histopathological changes include intercellular edema of the epidermis and a dermal inflammatory infiltrate of predominantly lymphocytes and macrophages. Increased numbers of CD4+ T lymphocytes and Langerhans cells are observed in skin with active lesions[105]. The two main pathophysiological components of eczema are cutaneous inflammation due to an inappropriate immune response and abnormalities in the epidermal structure with an impaired skin barrier function[106]. The primary event which causes these changes is still under debate[107].

The definition of eczema is complicated in that there are many synonyms in use for this disease. The terms most commonly encountered other than eczema are atopic dermatitis and atopic eczema. Other terms encountered in the literature are flexural eczema, childhood eczema and allergic eczema. *Atopic*, as used in both atopic dermatitis and atopic eczema depicts that the disease is purely related to allergy and atopy. The most widely used disease definitions of eczema has atopy incorporated in the definition of the condition and utilizes the term atopic dermatitis[108,109]. Problems with this type of definitions are that they are reflexive. There is no recognized condition called nonatopic dermatitis. This would not pose a problem if all subjects with atopic dermatitis were atopic but that is not the case. Flohr et al[110] reviewed the relationship between eczema and allergic sensitization in a meta-analysis and found that the prevalence of atopy was high in hospital-based studies ranging between 47% and 75%. However, the prevalence in population-based studies were lower, ranging between 7% and 78%[110]. This led The World Allergy Organization (WAO) to revise the nomenclature of eczema in 2004. The recommendations are to use dermatitis as an umbrella term for local inflammation of the skin. The WAO now states that eczema should replace atopic dermatitis and the designation of atopic or nonatopic eczema should only be made after determination of specific IgE antibodies or skin prick testing[111]. Figure 2 shows a graphical presentation of the WAO recommendation with dermatitis as an umbrella term. Based on the recommendations by WAO, the term eczema and not atopic dermatitis is used in this thesis.

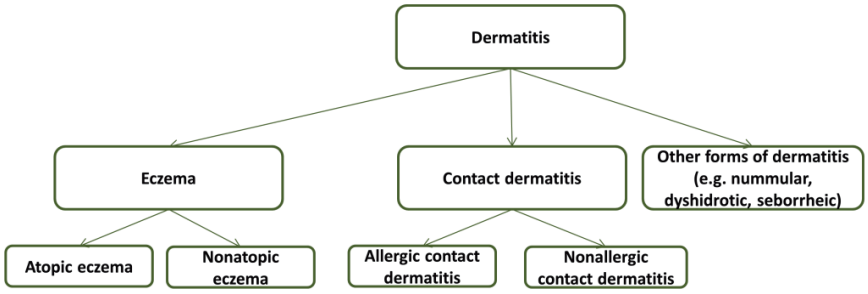

Figure 2. The 2004 revised nomenclature of eczema by the World Allergy Organization.

An increase of eczema has been observed among children in the last 30 years[112-114]. The prevalence among children vary in the Western world with 9.2% in Switzerland[115], 14.3% in France[116], 17.2% in Australia[33] and 25.8% in Sweden[117]. There are considerably less studies on adults than among children. The European Community Respiratory Health Survey II (ECRHS) assessed adult eczema in 11 European countries and the United States in 1998 and found an overall prevalence of 7.1%[118]. The most recent adult study in Sweden was performed in 2004 and found a prevalence of 11.6%[119]. Estimates of adult eczema since the millennium shift from other countries show that prevalence is ranging from 4.7-8.1% in Italy[120,121], 7.9% in France[122], 9% in Turkey[123], 10% in South Korean military conscripts[124], 10.4% in Colombia[125], 10.2%-10.7% in the United States[126,127] to 14.3% in Denmark[128]

Allergic sensitization is a risk factor for eczema in children and is also associated with disease severity. Hospital based studies generally report a stronger association than population-based studies. This phenomenon can at least partly be explained by differences in disease severity with severe cases more likely to be included in hospital based populations[129]. Although allergic sensitization was found to be a risk factor for eczema also among adults in the ECRHS study, the association was relatively weak, OR 1.5 (95% CI 1.2-1.9)[118]. The most common sensitizers among eczematics in ECRHS were cat and grass. Other studies examining the relationship between allergic sensitization and eczema have mainly been carried out among children and have found that the sensitization pattern is similar to asthma. Animals and pollens are the most frequent sensitizers associated with eczema in northern Scandinavia[48,130] while sensitization to mite also is common in Central Europe[131] and the United States[132].

Family history of allergy has been associated with eczema both in children[133] and in mixed populations of both adults and children[131]. Mutations in the

filaggrin gene increase the risk of eczema[134]. The filaggrin gene encodes an epidermal protein abundantly expressed in the epidermis and integral to the skin barrier function[135]. More than 50% of subjects with homozygous mutations in the filaggrin gene have been shown to exhibit eczema[136]. However, less than one fifth of the eczematous subjects in that study had any mutation on the filaggrin gene. There is some evidence for a higher risk of eczema in urban over rural areas[137]. Bråbäck et al examined Swedish military conscripts and found that rural living had a protective effect on eczema[138]. However, other studies have not demonstrated that association[127,139,140]. Other identified risk factors for eczema in adulthood include obesity[141,142], female sex[131,141] and food allergy[143]. Childhood daycare[144] and pet exposure[145] have shown protective effects on eczema among children but no similar studies have been carried out among adults.

2.2 Importance of populations studies

Population based cross-sectional studies are carried out at a particular time point or during a short period of time. They are ideal for estimating the prevalence of an outcome of interest. Prevalence denotes the proportion of subjects in a population at a given time and is most commonly expressed in percentage. Prevalence tells us how common a condition is and is of vital importance to both the individual clinicians and the health authorities of the population in question. It gives the clinician a likelihood of a certain diagnosis and aids in determining what investigations are most prudent. For an example, knowing that a condition is extremely rare in a certain population enables the clinician to pursue other potential diagnoses first. For steering committees, whether it is politicians or trust funds, knowing the prevalence of a condition aids in allocating resources in an efficient way. Cross-sectional studies are also relatively inexpensive and time efficient. Most cross-sectional studies employ self-administered questionnaires but interviews were most commonly used until the 1970s[146]. Advantages of interviews are that they generally tend to give a higher response rate at the cost of more expense and often resulting in a smaller sample size. The relatively simple design of cross-sectional studies lets the investigator collect a lot of information on conditions and possible determinants of disease and multiple outcomes can be studied. The main disadvantage of the cross-sectional study design is that it only gives us a snapshot of the reality. This means that there is no indication of sequencing of the events and we cannot know whether the exposure occurred before or after the onset of the disease outcome. Because of this, it is difficult to infer causality. Nevertheless, associations that are stable over time can be assessed and hypotheses can be formulated for future investigations.

Validity is an expression of the degree to which an examination is capable of measuring what it is intended to measure. A study with high validity corresponds closely to the truth. Validity is divided into internal and external[147]. Internal validity tells us to what degree the results are correct for the particular group of subjects being studied and will be further discussed in the consequence of non-response chapter. External validity or generalizability is the extent to which the results of a study applies to subjects that are not involved in it. Cross-sectional studies that are population based and randomized minimize the risk of selection bias and confer high validity. That means that the estimates to a high degree are representative of the whole population that the sample was taken from. The estimates can also be generalized to other populations if they have similar compositions.

Registers are another commonly used method of estimating prevalence. The healthcare providers often keep registers for administration of cost reimbursement and statistics. The registers in question are predominately connected with digitalized medical records but there are also disease specific registers[148,149]. However, the information that can be extracted from registers is often limited. The data is pre-collected and necessary information may be unavailable. Demographic determinants such as sex, age and area of domicile are usually available but other risk factors such as exposures and confounders are generally lacking. This makes it difficult to assess risk factors of conditions and diseases from register-based data. Further limitations of registers are under-coverage, where a specific subpopulation is missing due to different factors[150]. Another problem with register-based research is that diseases and conditions are classified by codes. The most widely used system for classification is the International Statistical Classification of Diseases (ICD) by WHO. ICD has a wide coverage of most recognized diseases. However, the classification of each case is done by an individual and is often inconsistent in validation studies[151]. This is caused by the fact that definitions of several diseases such as asthma are arbitrary. Generally there is no control over the definitions of diseases in registers and the information is dependent of the perceptions by the individual who entered the case in the register. Population-based studies let the investigator define the conditions. This makes comparisons to other populations more valid. Definitions of some diseases also change over time[108,152,153]. The following sections will cover epidemiologic definitions of asthma, rhinitis and eczema over time.

2.2.1 Asthma in epidemiology

The first widely used questionnaire where symptoms common in asthma was assessed was developed by the British Medical Research Council's (MRC) Committee in 1960. The British MRC questionnaire was primarily designed

for diagnosing chronic bronchitis and did not include any specific item on asthma but included a question on *wheeze* and its relation to common viral colds[154]. The 1968 and 1986 revisions of the MRC questionnaire added an item of *ever having had bronchial asthma* and expanded the questions on wheeze. This included *attacks of shortness of breath* in conjunction with wheeze and nighttime awakenings. Several questionnaires for surveying of asthma were developed simultaneously. The European Community for Steel and Coal (ECSC)[120] with revisions in 1967 and 1987[121] included the item of *doctor diagnosed asthma*. Other, mostly overlapping questionnaires at the time were promoted by the American Thoracic Society (ATS), The US National Heart and Lung Institute (NHLI), The University of Arizona Tucson studies[146] and The International Union Against Tuberculosis and Lung Disease society (IUATLD)[155].

The questions were validated in numerous studies in the 1980s and it became apparent that asthma was an underdiagnosed entity. Validation of *doctor diagnosed asthma* and *ever asthma* against a positive non-specific bronchial challenge with histamine showed rather low sensitivity but a specificity well of 90%[156]. Symptoms of wheeze yielded higher sensitivity but lower specificity. However, using a positive bronchial challenge test as a gold standard for the diagnosis of asthma is problematic because of suboptimal specificity[157] and that the results are not constant over time[158]. Consequently, sensitivity increased but a high specificity was also maintained when the items were validated against a clinical diagnosis of asthma[156,159].

The recent large multinational population-based studies on asthma used selected items from classic questionnaires such as the IUATLD. The European Community Respiratory Health Survey I (ECRHS) in adults emphasized symptoms common in asthma, mainly asthma attacks[160]. Both *ever asthma* and *doctor diagnosed asthma* were assessed in the main questionnaire for interview in the ECRHS[160,161]. The International Study of Asthma and Allergies in Childhood (ISAAC)[162] and the Global Allergy and Asthma European Network (GA^2LEN)[163] included *ever asthma* but not *doctor diagnosed asthma*. All those multinational studies also included questions of symptoms such as wheeze, shortness of breath and asthma medication. Even though the questionnaire items in those surveys are homogeneous, the epidemiologic definitions of asthma vary, even within studies. Some of the Obstructive Lung Disease in Northern Sweden (OLIN) studies have used a composite of symptoms together with physiologically verified airflow variability[44,164]. A common definition of asthma in an epidemiologic setting is a combination of *ever asthma* or *doctor diagnosed asthma* in combination with either medication against asthma or symptoms.

Other studies only use symptom based definitions to facilitate comparisons between countries with less readily access to healthcare. Nevertheless, the individual components of the definitions are often inconsistent between studies[165].

2.2.2 Rhinitis in epidemiology

Epidemiological definitions of rhinitis and its subtypes are challenging and there are no widely agreed criteria for the diagnosis or classification of rhinitis. The British MRC questionnaire[154] and the ECSC questionnaire[166] from the early 1960s were the first attempts at assessing nasal symptoms in a standardized manner. The questions dealt with *runny nose during spring* and *nasal catarrh*. Lifetime prevalence of *hay fever* was later added to the questionnaires[167]. The IUATLD[155] incorporated the question of *do you have any nasal allergies, including hay fever*. The wording enabled estimation of point prevalence instead of lifetime prevalence and is still used by many studies for estimation of the prevalence of allergic rhinitis[41].

Questions on rhinitis symptoms were added in the ISAAC questionnaire[162]. In addition to assessing lifetime prevalence of hay fever, ISAAC employed questions of lifetime and 12 month prevalence of *have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu* and an additional question in case of an affirmative answer: *in the past 12 months, has this nose problem been accompanied by itchy-watery eyes*. ISAAC studies have defined that current rhinitis is equivalent to the question of nasal symptoms in the absence of a cold in the last 12 months[168] and that current rhinoconjunctivitis is equivalent to current rhinitis accompanied by ocular symptoms[169]. These questions and criteria were also used in the ECRHS II[161].

Separate nasal symptoms such as blockage, itch and rhinorrhea have not seen a uniform definition and were not assessed in the historically important questionnaires. Consequently researchers formulated their own individual questions[170-172]. However, GA^{2}LEN[163] defined nasal symptom in regard to chronic rhinosinusitis in 2005. This syndrome, which is closely related to both allergic and nonallergic rhinitis exhibits inflammation of both the nasal mucosa and the paranasal sinuses. It has been defined for epidemiological studies in the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS)[173]. The EP3OS criteria are presence of two or more of the following symptoms: nasal discharge, nasal blockage, facial pain or pressure and reduction or loss of smell. Also, at least one of the symptoms has to be nasal blockage or nasal discharge.

2.2.3 Eczema in epidemiology

Jon M. Hanifin and Georg Rajka concluded in 1980 that there is no objective laboratory test to diagnose eczema. They proposed that eczema should be defined by a number of diagnostic criteria until a distinctive diagnostic test was made available[108]. Today, 35 years has passed since the statement by Hanifin and Rajka but we are still lacking that specific test. Hanifin and Rajka divided the criteria into basic and minor features. The diagnosis of eczema would require the presence of at least three out of four basic features and at least three out of 23 minor features (Table 1).

Table 1. Basic and minor features of eczema proposed by Hanifin and Rajka.

Basic features (at least three out of four present)	
Pruritus	Typical morphology and distribution
Chronic/chronically-relapsing dermatitis	*Adults: flexural lichenification or linearity*
Personal or family history of atopy	*Infants and children: facial/extensor involvement*

Minor features (at least three out of 23 present)	
Xerosis	Anterior subcapsular cataracts
Food intolerance	Orbital darkening
Type I skin test reactivity	Ichtyosis/palmar hyperlinearity/keratosis pilaris
Elevated serum IgE	*Pityriasis alba*
Early age of onset	Anterior neck folds
Tendency toward cutaneous infections	Itch when sweating
Facial pallor and facial erythema	Intolerance to wool and lipid solvents
Nipple eczema	Perifollicular accentuation
Cheilitis	Tendency for non-specific hand or foot dermatitis
Recurrent conjunctivitis	Influence by environmental/emotional factors
Dennie-Morgan infraorbital fold	White dermographism/delayed blanch
Keratoconus	

The classification with at least three basic and at least three minor features was chosen after discussions on a symposium. The features included were based on empirical clinical experience and without clinical validation. These criteria ensured some degree of uniformity of subjects with eczema in hospital-based studies. However, these criteria were difficult to assess and

not suited for population-based studies. Many of the features had no precise definition, some were very infrequent[174,175] and others were unspecific[176].

The UK Working Party (UKP) addressed these issues in 1994 and developed a definition that was easier to perform in clinical and population-based studies. They revised the classification by Hanifin and Rajka after examining hospital-based cases with eczema and controls. The UKP found that the most useful diagnostic criteria for diagnosing eczema was: a *history of flexural dermatitis, onset under the age of 2 years, presence of an itchy rash, personal history of asthma, history of a dry skin and visible flexural dermatitis*[152]. These criteria were separated into one major criterion and five minor criteria. To qualify as a case of eczema an individual had to have an itchy skin condition (major criterion) and at least three out of the five minor criteria (Table 2). The classification was validated both in hospital[177] and population based settings among pediatric patients and showed a sensitivity of 70% and a specificity of 93%[109].

Table 2. U.K. Working Party diagnostic criteria of eczema.

Major criteria (must have)
An itchy skin condition (or parental report of scratching or rubbing in a child)
Minor features (and at least three out of five)
History of involvement of the skin creases, front of ankles or around the neck
Having a personal history of asthma or hay fever
History of a general dry skin in the last year
Visible flexural eczema
Onset under the age of two

Bos et al. refined the UKP definitions in 1998 and created the Millennium Criteria (MC)[153] with a revision in 2011[178]. This definition separates atopic eczema from nonatopic eczema by specific IgE and personal history of atopy is omitted. It is based on typical morphology as the major criterion and similar minor criteria to UKP with the exception of dry skin and inclusion of the presence of a Dennie-Morgan fold. The Millennium Criteria showed greater specificity but lower sensitivity compared to the UK Working Party classification[178].

The ISAAC used a shortened definition based on the UKP[162]. The ISAAC criteria of eczema required an affirmative answer to the following three questions: '*has your child ever had an itchy rash which was coming and going for at least six months'*, '*has your child has this itchy rash at any time in the last 12 months'* and '*has this itchy rash at any time affected any of the*

following places: fold of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes'. Validated against a point estimate of flexural eczema on examination, the ISAAC criteria showed high sensitivity but lower specificity[179]. Both the UKP and the ISAAC criteria have been validated against a dermatologist diagnosis as the gold standard and showed similar sensitivity and specificity[151].

The ECRHS II applied the ISAAC criteria with appropriate changes to enable estimation of eczema in adult populations[118,161]. In 2005, The GA^{2}LEN was launched[163]. This European Union funded network of excellence used the ISAAC and ECRHS criteria of eczema except that the question regarding localization was excluded. Other researchers have used a more simplified approach and eczema defined by using a one-year history of self-reported healthcare diagnosis has been shown to be valid in the United States[180].

2.3 Consequence of non- response

The degree of error in an epidemiologic estimation is termed accuracy. These errors in estimation are traditionally classified as either random or systematic. Random error is the variation by chance. A common way to reduce random error is by increasing the size of the study. Systematic errors are collectively called biases, which is the opposite of validity. Validity is separated into two components: internal validity and external validity. External validity has already been covered in chapter 2.2. The main threats to internal validity can be classified into three categories: confounding, information bias and selection bias. Confounding can be explained as a confusion of effects. Information bias concerns misclassification of the levels of exposure or the disease outcome. Selection biases are distortions resulting from the procedures used to select subjects in a study and from circumstances that influence participation in a study. This includes self-selection bias where subjects with an outcome of interest may be more inclined to participate in a study[181].

Non-response or non-participation may also cause selection bias. This would not be a problem if non-participants were a random subgroup that was representative of the study population. However, studies on non-responders in respiratory surveys have shown that non-responders differ from responders in some ways. Non-responders tend to work in manual labor and smoke more than responders[182]. Age and sex also influence participation with women and older subjects more likely to cooperate[183]. Respiratory symptoms and diseases have been shown to be more or less equivalent between responders and non-responders[183,184]. The consequence of non-response is a risk of

systematic errors. Maximizing response rates decreases the risk of bias and is of vital importance. Unfortunately, response rates of epidemiological studies on respiratory and allergic conditions have seen a trend of general decline in the last fifty years[34,76,185-196] (Figure 3).

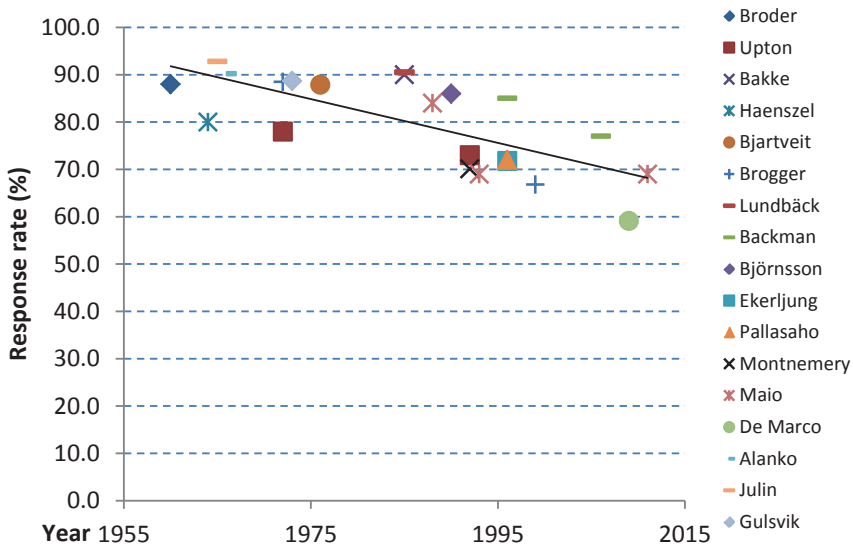

Figure 3. Rates of response to population based respiratory surveys in the last 50 years.

Response rates were high from the 1960s and well into the 1980s with participation rates exceeding 80% in most studies, particularly in the Nordic countries. The 1990s showed a decline that continued after the millennium shift and studies are now struggling with participation lower than 60%[190]. This is a challenge to the epidemiologist and mandates warrant. There are a number of actions that can be taken to increase the response rate but they are often resource intensive. Monetary and other incentives can increase participation but are costly and if too high risk coercion. Follow-up telephone calls to non-responders raise the response rates and the layout and length of the questionnaire affects non-response[197]. If most reasonable precautions against non-response have been made and participation is still low, it is important to at least consider a validation of the results against a subgroup of the non-responders by some other means of contact.

3 AIMS

The overall aim of this thesis was to investigate the prevalence of eczema; risk factors for eczema; overlapping risk factors for asthma, rhinitis and eczema and the impact of allergic sensitization on these diseases in an adult population. Additional objectives included validating the representativeness of the recruited population.

3.1 Specific aims

- ✓ To validate the representativeness of a large epidemiological study with a questionnaire recruited cohort for the study of asthma, respiratory symptoms, rhinitis and eczema (Paper I).
- ✓ To study the prevalence of eczema among adults, identify major demographic and other risk factors for eczema and to investigate the association of eczema with asthma and rhinitis (Paper II).
- ✓ To study the pattern of individual and common risk factors for asthma, rhinitis and eczema (Paper III).
- ✓ To study the prevalence of allergic sensitization and to compare the impact of allergic sensitization for asthma, rhinitis and eczema (Paper IV).

4 MATERIAL AND METHODS

4.1 Study area

All papers in the thesis are based on the West Sweden Asthma Study (WSAS). The study was conducted in the Västra Götaland County of Sweden which is the fifth largest county in Sweden with an area of about 29 000 km^2 and similar in size to Belgium[198]. The region is situated in the southwestern part of Sweden and has a long coastal area facing the Skagerrak connecting it with the Atlantic Ocean by the North Sea. The area is based upon a continental crust of gneiss and granite with a slope towards the west. An archipelago of more than 3000 islands stretches from the coastline. More than half of the interior is covered by forests. Pine trees are dominating but birch is also common. There are vast agricultural areas and the region is the largest farm land in Sweden. One fifth of the area is covered by water and it is neighboring the two largest lakes of Sweden as well as the largest river, Göta älv. The climate is strongly influenced by the sea with relatively warm winters and high humidity. The winter is considerably shorter and warmer than in most areas of Sweden. The interior regions have a hemiboreal and colder climate compared to the coast. The mean annual temperature in Gothenburg was 9.3ºC (lowest -9.4 ºC and highest 30.9 ºC) in 2008.

4.2 Study population

Västra Götaland is the second largest county of Sweden in terms of population and had 1 558 130 inhabitants with a female composition of 50.1% in 2008. The largest city is Gothenburg with a population of 500 197 in 2008 and around 800 000 lived in the city and surrounding areas. The remaining population lived in mostly smaller cities and municipalities. Around 25% lived in sparsely populated areas and 1.5% in remote areas. Figure 4 shows the age composition of the region[199]. The economy is diversified with a strong industry and is highly representative of the overall Swedish economy. The rate of unemployment was 6.3% in 2008 and the mean annual disposable income was €28 121 in 2012[199].

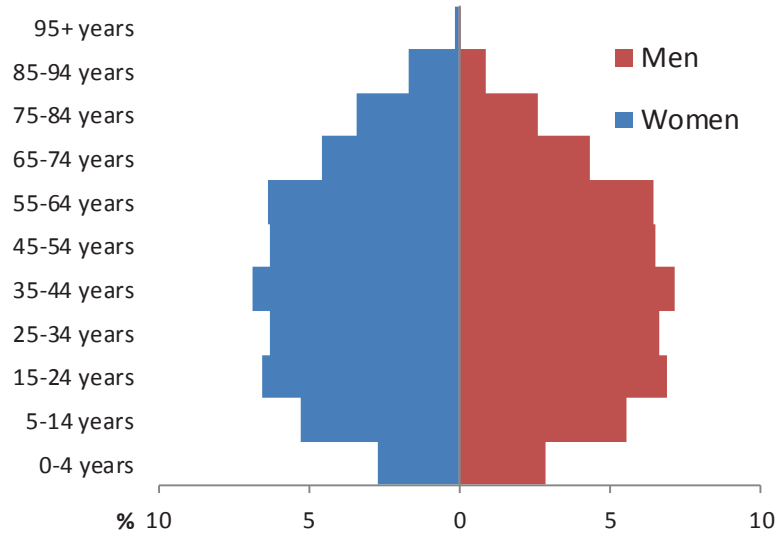

Figure 4. Population composition of Västra Götaland in 2008.

4.3 Questionnaire study

4.3.1 Questionnaire

The West Sweden Asthma Study (WSAS) was launched with the short term objective of measuring prevalence, determinants and covariance of asthma, eczema, rhinitis, chronic rhinosinusitis and respiratory symptoms in adults and older adolescents living in West Sweden. The long term objective of the study is to define clinically relevant phenotypes of asthma for guidance of treatment, prediction of prognoses and to facilitate prevention of the disease.

The first part of the West Sweden Asthma Study was a population-based, cross-sectional study dispatched by mail. All invited subjects were asked to complete a self-administered questionnaire. Subjects could choose to return the questionnaire in a pre-paid business reply envelope or complete the questionnaire on the internet. Individual logins and passwords were enclosed within the letter for this purpose.

The questionnaire consisted of three consecutive sections that was confined by staples to a single layout and is available in the appendix. The first section consisted of the Swedish version of the OLIN questionnaire[182,193,200], which in

1984-85 was developed from a revised version[201] of the 1960 British MRC questionnaire[154]. The OLIN questionnaire was further influenced by the questionnaires developed by the US National Heart, Lung and Blood Institute and the Tucson Studies[146]. From 1992 and 1996, respectively, some questions about chest tightness and wheezing were added from the IUATLD and the ECRHS questionnaires[156,160]. Also, one question on dyspnea from the 1986 revised MRC questionnaire[202] was later added. The OLIN questionnaire has been used in several Nordic countries[193,203] and in Vietnam[204]. Comparative studies have been carried out using the questionnaire in Sweden, Finland and Estonia under the FinEsS label[200,205,206]. The OLIN questionnaire covers questions about asthma, rhinitis, chronic obstructive pulmonary disease (COPD)/chronic bronchitis/emphysema, use of asthma medication, dyspnea, respiratory symptoms and nasal symptoms as well as possible determinants of disease, such as family history of atopic and obstructive respiratory diseases, smoking status and occupation.

The second section of the WSAS questionnaire included questions about working status, profession, work load, fatigue associated with the workplace, appreciated working capacity, sick leave due to respiratory illnesses, water damage and visible mold exposure in the living environment, exposure to gas, dust or fumes at work, physical activity and farm childhood.

The third and last section of the questionnaire consisted of the Swedish version of the GA^{2}LEN questionnaire[163,207]. This questionnaire was mainly built and derived from the questions and definitions used in the ECRHS[160]. Items about asthma, rhinitis and respiratory symptoms were to some extent overlapping with the OLIN questionnaire but it also added questions about eczema and chronic rhinosinusitis. English versions of the OLIN and the GA^{2}LEN questionnaires are available in the appendix.

4.3.2 Participation

A random sample of 30 000 individuals from the general population of Västra Götaland between the ages of 16 and 75 years was selected in January 2008. Proportions of subjects invited were set to reflect the age and sex composition of the area population demographics. The sample was stratified with 15 000 individuals from the metropolitan area of Gothenburg and 15 000 from the whole surrounding area of Västra Götaland. Names and addresses were obtained from the Swedish population registry and provided by an external company.

The questionnaire was dispatched by mail in March 2008. A remainder was mailed after one month to those who had not responded, a second reminder

was sent out after another month and finally, a last reminder was sent out after an additional two months. From the initial 30 000 individuals, 17 had died, 489 were returned because of unknown recipients, 87 had moved, 121 were unable due to handicap or disease and 68 had other reasons which mainly included not understanding the language. This totaled 782 individuals and thus, the potential study sample consisted of 29 218 individuals[36]. The study was closed one month after the third reminder and by that time, 18 087 (62%) individuals had participated. The response rates to each of the four mailings were 33%, 15%, 7% and 7% respectively.

From the remaining 10 732 subjects of non-responders, a sample of 400 individuals was randomly selected for a study of non-response (Paper I). Two commercial databases were used to obtain phone numbers to these individuals. Data was collected by structured interviews completed by a single investigator, Erik Rönmark (author) who identified himself as a researcher and physician at the University of Gothenburg. Interviews were conducted between the 6th and the 28th of October 2008 and verbal consent was obtained by all individuals before initiating the interview. Subjects were informed that the information provided would be stored in a confidential database. At least five telephone calls were attempted before considering a subject unreachable. Key questions were chosen from the mailed questionnaire and phrased in an identical way. If not understood, the question was repeated and then, if necessary explained. Questions regarding reason for non-response to the postal questionnaire and what could have been done differently to increase the likelihood of response were also asked.

4.4 Clinical examinations

The second part of WSAS with clinical examinations was conducted by trained nurses between January 2009 and April 2012 at four sites: Gothenburg, Uddevalla, Borås and Falköping. A random sample of 2000 subjects from the 18 087 responders were invited and 1172 attended. All subjects reporting asthma were also invited but only the randomly selected participants formed the study population in this thesis. The clinical examination included a comprehensive structured interview, anthropometric measures of height, weight and waist circumference, skin prick test (SPT) and a drawn venous blood sample. Other examinations that were conducted but not included in this thesis were spirometries with reversibility testing; metacholine challenges; measurements of exhaled nitric oxide fraction, carbon monoxide diffusion capacity, pulse oximetry, blood pressure; blood samples for white blood cell differential counts, genetics and proteomics as well as nasal lavage.

The structured interview contained questions about asthma, allergic rhinitis, COPD, sputum production, cough, wheeze, dyspnea, use of medication for asthma and rhinitis, healthcare utilization, cardiovascular comorbidities, childhood exposures, birth weight, smoking habits, exposure to environmental tobacco smoke and an asthma control grading according to the GINA[15] if applicable.

4.5 Specific Immunoglobulin E

The presence of serum Immunoglobulin E (IgE) was assessed by using a panel of 11 common airborne allergens and included timothy, birch, mugwort, olive, *Parietaria*, cat, dog, horse, *D. pteronyssinus*, *D. farinae* and *Cladosporium herbarum* (ImmunoCAP® Phadiatop, Thermo Scientific). A value of ≥ 0.35 kU_A/l was considered a positive test. All positive Phadiatop tests were then further analyzed for each of the 11 allergens mentioned above with the same cutoff value of 0.35 kU_A/l. Either due to unwillingness or technical difficulties, 69 subjects did not participate in the blood sampling.

4.6 Skin prick tests

Skin prick testing against a panel of airborne allergens (ALK Hørsholm, Denmark) were performed in 802 subjects. The allergens used were *D. pteronyssinus*, *D. farinae*, *Alternaria*, *Cladosporium herbarum*, cockroach, dog, cat, horse, timothy, mugwort and birch. A mean weal size ≥ 3 mm was regarded as a positive response. Histamine was used as the positive control and glycerol as the negative control. Skin prick testing was not performed in subjects using antihistamines, antidepressants or individuals older than 60 years of age.

4.7 Methods used in Paper I

Responders to the postal survey were compared to a sample of 211 non-responders interviewed by telephone. The methods and a detailed description of the populations have been covered in chapter 4.3.

4.8 Methods used in Paper II

The WSAS postal questionnaire survey of 30 000 randomly selected subjects from Västra Götaland was the base for Paper II. The questions used were from all three parts of the questionnaire. Prevalence estimates of asthma, lower respiratory symptoms and most questions on rhinitis were derived from the OLIN section while items on eczema were from the GA^{2}LEN section.

Skin prick testing was performed in 669 randomly selected responders. The base for this population was the clinical examinations with 2000 invited subjects. The clinical examinations were ongoing and not finished at the time of the study and hence the number of subjects assessed for allergic sensitization in this study was lower than in Paper III and Paper IV.

4.9 Methods used in Paper III

The clinical examinations were the base for Paper III. The sample contained 1172 individuals that participated. Either due to unwillingness or technical difficulties, 69 subjects did not participate in the blood sampling for specific IgE (Phadiatop). All 1172 individuals were included in the risk factor analysis and subjects without a valid measurement of Phadiatop were coded as missing. Disease definitions and determinants of disease were derived from both the respective answers in the WSAS postal questionnaire and the structured interview. Anthropometric measures of weight and height for calculation of BMI were obtained by trained nurses in the clinical examinations and not questionnaire derived.

4.10 Methods used in Paper IV

Paper IV studied the same population as Paper III with identical definitions from both the postal survey and the structured interview. Subjects that did not undergo assessment of serum IgE were not included. Serum of participants with a Phadiatop value of ≥ 0.35 kU_A/l were further analyzed for the presence of specific IgE against timothy, birch, mugwort, olive, *Parietaria*, cat, dog, horse, *D. pteronyssinus*, *D. farinae* and *Cladosporium herbarum*.

4.11 Definitions

The more important variables used in the thesis are presented below in the chronologic order they appear in the papers. Definitions derived from the structured interview are commented while all other definitions are derived from the self-administered questionnaire.

4.11.1 Definitions of diseases, conditions and symptoms

Physician-diagnosed asthma: "Have you ever been diagnosed as having asthma by a physician?"

Ever asthma: Yes to "Have you ever had asthma?" or *physician-diagnosed asthma* (Note, *ever asthma* in Paper I and *asthma ever* in Paper II only denotes the first item: "Have you ever had asthma?")

Severe asthma: Yes to "*physician-diagnosed asthma*", "*use of asthma medicines*", "*attacks of shortness of breath*", "*recurrent wheeze*", and at least one symptom out of "*dyspnoea*", "*breathlessness on exertion*", ''*breathlessness in cold*'' or "*breathlessness on exertion in cold*" (Identical to the definition of multi-symptom asthma used by Ekerljung et al[208]).

Current asthma: Yes to either *physician-diagnosed asthma* or *ever asthma* and either *use of asthma medicines*, *recurrent wheeze* or *attacks of shortness of breath* in either the postal survey or the structured interview.

Physician diagnosed COPD, chronic bronchitis or emphysema: "Have you ever been diagnosed as having chronic bronchitis, COPD or emphysema by a physician?"

Use of asthma medicines: "Do you currently use asthma medicines (permanently or as needed?)" (Labeled asthma medicine in Paper II)

Asthma medication 12 months: Yes to "Have you used asthma medicines (permanently or as needed) in the last 12 months?" or any use of corticosteroids, anticholinergics, beta-adrenergic agonists and antileukotrienes (Items derived from the structured interview)

Longstanding cough: "Have you had longstanding cough during the last year?"

Sputum production: "Do you usually have phlegm when coughing or do you have phlegm in the chest which is difficult to bring up?"

Chronic productive cough: *sputum production* for at least three months per year during two subsequent years.

Recurrent wheeze: "Do you usually have wheezing or whistling in your chest when breathing?"

Wheezing last 12 months: "Have you at any time during the last 12 months had wheezing or whistling in your chest?" (Labeled *any wheeze* in Paper II)

Attacks of shortness of breath: Yes to "Have you now or have you had asthma symptoms during the last 10 years (intermittent breathlessness or

attacks of shortness of breath; the symptoms may exist simultaneously with or without cough or wheezing)?" and "Have you had these symptoms during the last year (last 12 months)?"

Dyspnoea (British MRC Dyspnea Scale[209]): "Do you need to walk slower than other people of your age on level ground because of breathlessness?"

Rhinitis (Paper I): "Do you have any nasal allergies including hay fever?"

Allergic rhinitis (Paper II): "Have you ever had allergic eye or nose problems (hay fever)?"

Current rhinitis (Paper III-IV): Yes to either of *nasal congestion* and *runny nose* or both of "Have you ever had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu in the last 12 months?" and "Has this nose problem been accompanied by itchy and watery eyes?" (The last two questions are ECRHS items[160] on allergic rhinitis and were obtained in the structured interview).

Rhinitis ever: Yes to either: *nasal congestion*, *runny nose* or "Have you ever had nasal allergies or hay fever?" (The last item was obtained in the structured interview)

Nasal congestion: "Do you have nasal block more or less constantly?"

Runny nose: "Do you have runny nose more or less constantly?"

Chronic rhinosinusitis: at least two of the following symptoms: nasal blockage, mucus discharge, facial pain or pressure and reduction of smell, with at least one symptom being nasal discharge or blockage[173].

Rhinitis medication 12 months: "Have you used medications for hay fever or other nasal problems such as nasal congestion or a runny nose when you did not have a cold or the flu in the last 12 months?" (item derived from the structured interview)

Ever eczema: "Have you ever had eczema or any kind of skin allergy?" (Labeled *eczema ever* in Paper II)

Itchy rash: "Have you had an itchy rash that was coming and going for at least 6 months?"

Current eczema: Yes to *itchy rash* and "Have you had this itchy rash in the last 12 months?"

Hand eczema only: Yes to *itchy rash* and "Does this affect only your hands?"

4.11.2 Determinants and risk factors of disease

Family history of asthma: "Have any of your parents or siblings ever had asthma?"

Family history of allergy: "Have any of your parents or siblings ever had allergic eye or nose problems (hay fever)?" (Labeled *family history of rhinitis* in Paper III)

Smoking: Smokers reported smoking the year preceding the study and ex-smokers reported having quit smoking at least one year before the study. Non-smokers reported neither smoking nor ex-smoking.

Occupational exposure to gas, dust or fumes (GDF): "Have you been substantially exposed to dust, gases or fumes at work?" (Labeled *exposed to gas, dust or fumes* in Paper I and *exposure to gas, dust or fumes at work* in Paper II)

Degree of urbanization: Localities of residence were classed into four categories based on their number of inhabitants. Localities with more than 10 000 were considered larger towns, 2000 - 10 000 inhabitants considered smaller towns, 500 to 2000 regarded villages and localities with less than 500 inhabitations considered rural areas[210].

Metropolitan domicile: Subjects living within the metropolitan area of Gothenburg

Raised on a farm "Did your family live on a farm during your first 5 years of life?"

Body mass index (BMI): Calculated by $weight_{(kg)}$ / $(height_{(m)})^2$. BMI was defined as normal if 20 kg/m^2 – 25 kg/m^2, underweight < 20 kg/m^2, overweight 25 kg/m^2 - 30 kg/m^2 and more than 30 kg/m^2 considered as obesity.

Childhood smoke exposure: "Did anyone of your parents or relatives smoke in your home or close environment when you were growing up?" (Derived from the structured interview)

Maternal smoking in pregnancy: "Was your mother a smoker when she was pregnant with you?" (Derived from the structured interview)

Furry animals in childhood: "Did you have furred animals in your home or close environment before you were five years old?" (Derived from the structured interview)

Childhood airway infection: "Have you had any severe airway infection or pneumonia before school age, such as whooping cough or croup?" (Derived from the structured interview)

Shared bedroom in childhood: "Did you regularly share bedroom with any children before the age of five years?" (Derived from the structured interview)

Childhood daycare: "Did you attend preschool, day care or an orphanage with other children for at least one year before school age?" (Derived from the structured interview)

Any positive skin prick test: A mean weal size response ≥ 3 mm to any of the tested allergens in the panel covered in section 4.6.

Allergic sensitization: Serum IgE to ImmunoCap® Phadiatop ≥ 0.35 kU_A/l.

Any animal: Serum ImmunoCap® ≥ 0.35 kU_A/l to any of cat, dog or horse.

Any pollen: Serum ImmunoCap® ≥ 0.35 kU_A/l to any of timothy, birch, mugwort, olive or *Parietaria*.

Any mite: Serum ImmunoCap® ≥ 0.35 kU_A/l to either *D. pteronyssinus* or *D. farinae*.

4.12 Analyses

Data from the questionnaire survey was entered manually and the quality was controlled by entering 10% of the material twice. Errors amounted to only 0.1% to 0.2% of the material with few exceptions. Missing answers in both the postal survey and the clinical interview were handled in the same way. Questions on diseases, conditions and symptoms were coded as negative if missing while possible determinants of disease were coded as missing and included as a separate entity in the risk factor analyses.

The statistical analyses were performed with SPSS 16.0-20.0 (IBM, Somers, NY, USA). Fisher's exact test was used to test proportions and the significance level, α was set to 0.05. Tests for trends were calculated with a Mantel-Haenszel test for variables with more than two categories if an ordinal scale could be assumed. Bivariate and multiple logistic regression models were calculated with odds ratios (OR) and 95% confidence intervals (CI). The covariates used as independent variables varied between the papers with factors significantly or borderline significantly associated in the bivariate analyses selected for the multivariate models. Risk ratios (RR) and 95% confidence intervals were calculated for positive versus negative allergic sensitization respectively for current asthma, current rhinitis and current eczema in Paper IV.

Venn diagrams were constructed with eulerAPE[211] (Open source software, Luana Micallef and Peter Rodgers, University of Kent, Canterbury, UK) and are in analogy to all circular Venn diagrams not completely area-proportional.

5 RESULTS

5.1 Study of non- response (Paper I)

5.1.1 Participation and demographics

The real study sample consisted of 29 218 subjects and 18 087 (62%) individuals responded to the postal survey. Non-responders were younger than responders and were more commonly men. Response rate was lower in the metropolitan area of Gothenburg compared to the surrounding areas. The number of responders was greatest in the first mailed questionnaire and fell for each subsequent reminder. However, the third reminder yielded almost as many responders as the second reminder and the proportion of responders was actually higher for reminder three than reminder two (Figure 5).

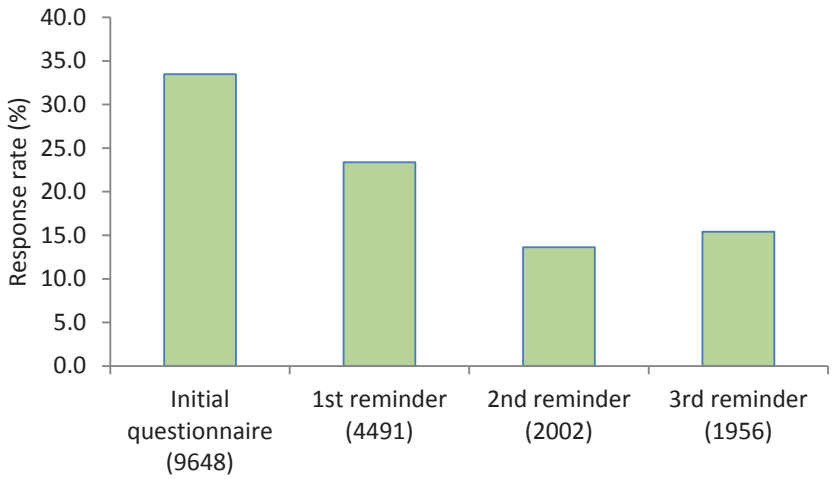

Figure 5. Response rates by dispatch. Numbers of responders within parentheses.

Out of the 400 subjects selected for the study of non-response, 234 were successfully contacted by phone and 211 agreed to participate. Willingness to participate in this part did not differ by gender or area of domicile.

5.1.2 Comparisons of responders and non-responders

Non-responders were more likely to be smokers than responders, 30.3% versus 18.6% ($p<0.001$). No significant differences were found in terms of

asthma, rhinitis, eczema and respiratory symptoms. The prevalence was also similar in absolute numbers. Physician diagnosed asthma was reported by 8.3% of responders and 8.1% of non-responders. The corresponding values for rhinitis were 23.6% and 23.2%. Non-responders reported slightly less eczema than responders, 35.5% versus 40.7% but as mentioned above, the difference was not significant.

5.1.3 Early responders versus late- and non-responders

Eczema, wheeze and use of asthma medicines showed a trend with higher prevalence in early responders and the prevalence decreased with increasing response delay. The opposite was true for smoking where the lowest prevalence was found among the early responders.

5.1.4 Multivariate relationships

The risk of having diseases and symptoms among non-responders compared to responders showed no differences in the multivariate models after adjustments (Paper I, Figure 2). Smoking and occupational exposure to gas, dust or fumes were associated with recurrent wheeze and sputum production among all responders. These associations were significant even when the sample was limited to the participants in the first mailed questionnaire. When the sample was increased by including the respondents to subsequent reminders, the confidence intervals of the associations narrowed, but the magnitude of the odds ratios remained similar (Paper I, Figure 3).

5.2 Prevalence and risk factors of eczema in adults (Paper II)

5.2.1 Prevalence and relation to respiratory diseases and symptoms

The study population in Paper II comprised the 18 087 subjects that responded to the postal survey. Itchy rash was reported by 13.6%. The prevalence of current eczema was 11.5% and 40.7% reported ever having had eczema, while eczema only affecting the hands was present in 2.0%. All measures of eczema were significantly more common among women. There was a trend with lower prevalence of itchy rash, current eczema and eczema ever by increasing age.

Asthma, allergic rhinitis and chronic rhinosinusitis were associated with all measures of eczema ($p<0.001$). Additionally, both lower and upper respiratory symptoms showed the same pattern ($p<0.001$). The overlap between current asthma, current rhinitis and current eczema was greatest for asthma and rhinitis and 1.1% reported all three conditions. The overlap for eczema was greater with rhinitis than asthma (Paper II, Figure 1).

Allergic sensitization assessed by a positive skin prick test to any allergen was more common in subjects reporting eczema ever, 47.0% versus 34.6% ($p<0.001$). The same was true for sensitization to cat, dog and timothy while no differences were seen for horse, mugwort, birch, dust mites, cockroach, and mould. Prevalence of a positive skin prick test to any allergen was also higher among subjects with itchy rash and current eczema but the differences did not reach statistical significance (48.2% vs. 38.9% and 48.0% vs. 39.2% respectively). Sensitization to *Cladosporium* was rare but associated with itchy rash and current eczema.

5.2.2 Risk factors for eczema

Lower age was predominantly associated with eczema. This was most apparent for itchy rash and in particular, eczema ever. Current eczema showed a similar but less pronounced pattern. Female sex, allergic rhinitis, physician-diagnosed asthma and occupational exposure to gas dust or fumes were independently and consistently associated with all measures of eczema. The strongest associations were observed for allergic rhinitis and family history of asthma and allergy with consistent odds ratios from 1.8 to 2.0 (Paper II, Table 3)

Current smoking was associated with current eczema and itchy rash but not eczema ever, OR 1.06 (95% CI 0.98-1.15). Living in a large town increased the risk of current eczema and itchy rash slightly but had no effect on eczema ever. Raised on a farm was negatively associated with all of current eczema, itchy rash and eczema ever in the crude estimates but was only significant for eczema ever after adjustments.

Having a positive skin prick test was significantly associated with both eczema ever and itchy rash, OR 1.56 and 1.84 respectively. No significant association was seen for current eczema but the lower confidence interval was very close to one, OR 1.56 (95% CI 0.99-2.48). The most important risk factors for current eczema are presented in Figure 6.

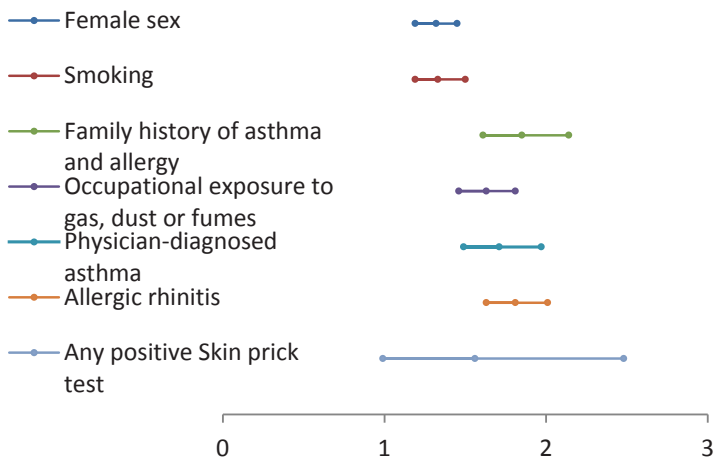

Figure 6. Adjusted risk factors for current eczema expressed in odds ratios with 95% confidence intervals.

5.3 Risk factors for asthma, rhinitis and eczema (Paper III)

5.3.1 Prevalence and relationship with age and sex

The study population consisted of 1172 individuals that participated in the clinical examinations. The prevalence of current asthma was 11.8%, current rhinitis 42.8% and current eczema 13.5%. Asthma ever, eczema ever, rhinitis ever and current rhinitis were all inversely associated with increasing age, as was family history of asthma and rhinitis. Eczema was more common among women but no significant sex differences were found for asthma and rhinitis, however, asthma tended to be more common among women and rhinitis among men (Paper III, Table 1).

The relationship between asthma ever, rhinitis ever and eczema ever is shown in Figure 7. All three conditions were present in 7.1% of the individuals. The overlap was greatest for rhinitis ever and eczema ever. Only 0.8% reported asthma ever and eczema ever without rhinitis ever.

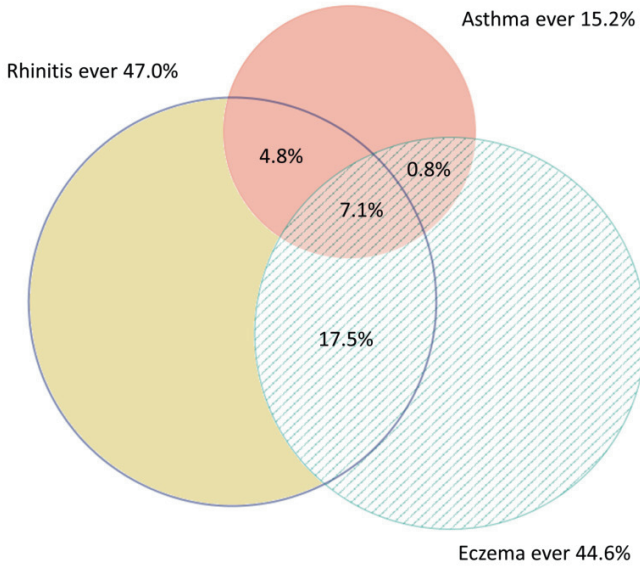

Figure 7. Venn diagram showing prevalence and the relationship between rhinitis ever, asthma ever and eczema ever.

5.3.2 Unadjusted associations

Younger age was associated with current rhinitis but not current asthma. Only the 40-59 years of age category had an increased risk of current eczema compared to the oldest. Female sex was associated with current eczema but not current asthma or current rhinitis. Family history of both asthma and rhinitis had the strongest association with current asthma, OR 5.4 (95% CI 3.4-8.6) but was also significantly associated with current rhinitis and current eczema.

Allergic sensitization was a strong risk factor for current asthma, OR 4.0 (95% CI 2.8-5.8) and current rhinitis, OR 5.8 (95% CI 4.3-7.7) but not significantly so for current eczema, OR 1.4 (95% CI 0.9-1.9). Obesity showed the same pattern as allergic sensitization with an increased risk of current asthma and current rhinitis. Occupational exposure to gas, dust or fumes was a risk factor for current eczema and current asthma. Raised on a farm was associated with a decreased risk of current eczema and current rhinitis, OR 0.5 (95% CI 0.2-0.9) and OR 0.5 (95% CI 0.4-0.8) respectively.

5.3.3 Adjusted associations

No association was found between age and either of current asthma, current rhinitis and current eczema when adjusted odds ratios were calculated by multiple logistic regression analyses. Female sex remained as a risk factor for current eczema, OR 1.7 (95% CI 1.2-2.5) but was also significantly associated with current asthma, OR 1.8 (95% CI 1.2-2.7). Family history of asthma and rhinitis was associated with current rhinitis and even stronger with current asthma, while it was not significantly associated with current eczema in contrast to the unadjusted analysis.

Allergic sensitization showed the same pattern as in the univariate analyses and was the strongest risk factor for current rhinitis, OR 5.1 (95% CI 3.8-6.9) and strongly associated with current asthma, OR 4.1 (95% CI 2.7-6.3) but no significant association was observed for current eczema. Exposure to gas dust or fumes as work remained a stable risk factor for current eczema and current asthma after adjustment. Raised on a farm remained similarly associated with a protective effect on current eczema, OR 0.5 (95% CI 0.3-0.99) and current rhinitis, OR 0.6 (95% CI 0.4-0.96). Obesity was a risk factor for current asthma and current rhinitis but not current eczema.

5.4 Impact of allergic sensitization on asthma, rhinitis and eczema (Paper IV)

5.4.1 Allergic sensitization and relationship with age and sex

The prevalence of sensitization to any airborne allergen assessed by specific IgE was 29.7%. Pollen was the most common sensitization type with a prevalence of 22.1%. Sensitization to animal dander was slightly more frequent than mite, 12.1% versus 10.9%. The most common specific sensitizations were timothy, 16.8% and birch, 15.0%. Cat was the most common animal sensitization with 10.2% followed by dog, 8.1% and horse, 4.4%. Mite sensitization was similar for *D. pteronyssinus* and *D. farinae* with 10.2%. Only three individuals were sensitized to *Cladosporium*, 0.3%.

Sensitization to any airborne allergen was more common in men compared to women, 42.2% versus 36.0% ($p<0.001$) as was pollen and mite sensitization. Specific sensitization to timothy, *D. pteronyssinus* and *D. farinae* were also more frequent among men. Increasing age was strongly associated with decreasing prevalence of sensation to any airborne allergen, any pollen, any mite and the specific sensitizations with some isolated exceptions.

5.4.2 Asthma, eczema and rhinitis in relation to allergic sensitization

The prevalence of current asthma and current rhinitis were uniformly and significantly higher in sensitized subjects (Figure 8). Current eczema showed a tendency for higher prevalence among sensitized subjects but not significantly so. The same pattern was observed for specific sensitizations, where current asthma and current rhinitis but not current eczema were more frequent among sensitized subjects.

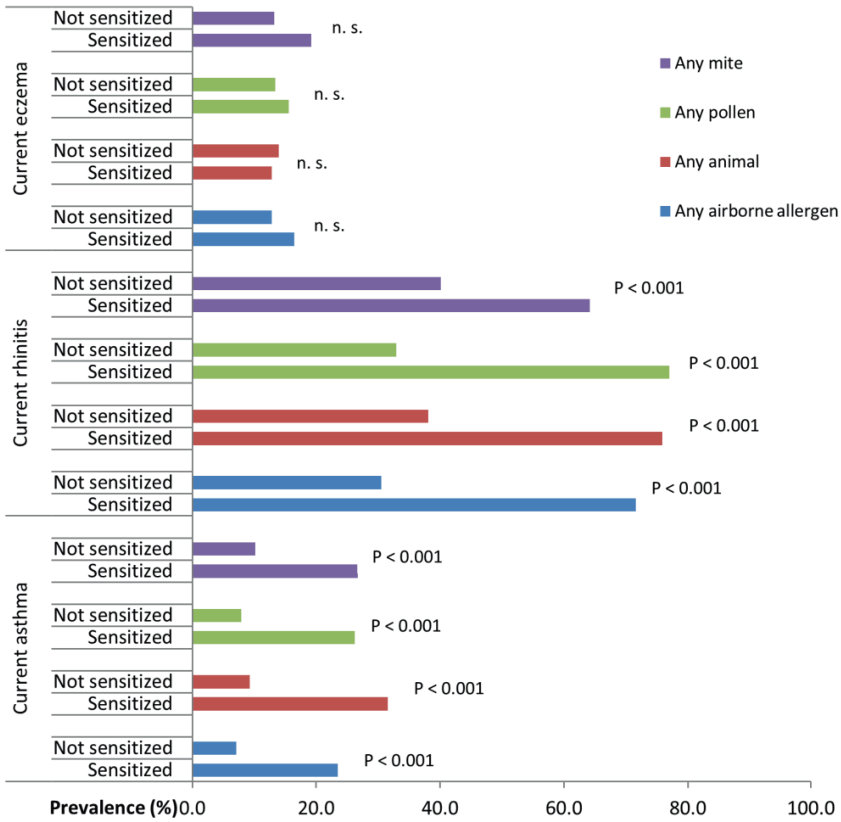

Figure 8. Prevalence of current asthma, current rhinitis and current eczema stratified by sensitization status, difference (p-value) between groups.

5.4.3 Allergic sensitization in asthma, rhinitis and eczema

The prevalence of allergic sensitization among individuals with current asthma was 58.3%, current eczema, 35.3% and 49.9% in subjects with current rhinitis while the prevalence was 61.1% in subjects with allergic rhinitis defined as nasal symptoms in the last year and concomitant symptoms from the eyes. Sensitization to any airborne allergen, any pollen, any animal, any mite and any specific IgE were all more common in subjects with current asthma and current rhinitis compared to subjects without those conditions. No such trend was evident for current eczema (Paper IV, Figure 2).

5.4.4 Multivariate relationship

Adjusted odds ratios calculated in three sets of multivariate models showed that sensitization to any airborne allergen was strongly associated with current rhinitis and current asthma but not current eczema. The analyses on group level showed that current asthma was associated with all of any pollen, any animal and any mite, OR 1.8-2.6. Current rhinitis was only associated with any pollen but strongly so, OR 4.7 (95% CI 3.1-6.9). Adjusted odds ratios for specific sensitizations showed that dog and birch were associated with current asthma while timothy and birch were risk factors for current rhinitis. No significant association was observed for current eczema (Paper IV, Table 3).

6 DISCUSSION OF METHODLOGY

6.1 Study design

6.1.1 Postal survey

The postal questionnaire survey formed the basis for the papers presented in this thesis. For high validity it is important that the study population resembles the original population selected to the study which in this case was the adult population of Västra Götaland in Sweden. All Swedish citizens have a unique personal identity number including date of birth and gender that is linked to an address. Data can be obtained on all individuals residing in a geographic area. This enables selection of subjects for the study population by complete randomness. The population based approach with randomization of the postal survey enables high internal validity. However, as has been mentioned in the introduction, internal validity is also influenced by other factors.

There are methodological concerns with self-administered questionnaires dispatched by mail. Self-reports are highly dependent on the wording of the questions and minor changes in wording, format or context may influence results in a significant way[212,213]. Error rates are higher with the absence of a trained supervisor[214] and prevalence estimates of symptoms and determinants of disease tend to differ somewhat for self-completed questionnaires compared to structured interviews while estimates of disease occurrence are more similar[215,216].

6.1.2 Study of non- response

The non-response study used a mixed study design. Subjects responding to the self-administered postal survey were compared to subjects interviewed by telephone. The different methods used to obtain the estimates merits consideration. Other studies have shown that agreement between the methods is good with high kappa values for important items such as asthma, rhinitis and eczema[216,217]. However, it would have been of interest in this study to validate the telephone interview on a sample of responders.

Participation rate was high among non-responders if successfully contacted by phone and exceeded 90%. More problematic is that no contact was achieved with 41.5% of the selected non-responders. There is thus a gap of knowledge regarding a rather large part of the non-responders. Home visits

have been tried to address this problem in Norway but rate of successful contact was not higher than ours[185].

6.1.3 Clinical examinations

The structured interview in the clinical examination introduced a third method of prevalence estimation. The interviews were conducted in person by trained nurses with infrequent exceptions for trained physicians and Ph.D. students, and were carried out one to four years after the postal survey. This combination may have influenced the results but we believe the overall effect to be small.

The participation rate in the clinical examinations is probably more important with 1172 participants out of 2000 invited equaling approximately 60%. Self-selection bias may result if subjects with the condition under study are more likely to participate. Published reports on self-selection bias are very limited in the field of allergy and respiratory diseases. De Marco et al. demonstrated in Italy that non-participants in a postal survey were healthier than responders[218]. No such difference was found in a study of non-response among adults in northern Sweden[182] and another Swedish study among children found no difference in attendance rate for subjects with and without asthma[219]. Contrary to the findings in the non-response study (Paper I) there are some indications of self-selection bias in the clinical examinations (Table 3).

Table 3. Prevalence (%) and difference (p-value) of atopic conditions in the postal survey compared to the clinical examinations.

	Participants in		
Atopic condition	Postal survey	Clinical examinations	P-value
Current asthma	7.6	9.3	0.04
Current rhinitis	19.8	23.2	0.01
Current eczema	11.5	13.4	0.05

The condition variables in Table 2 are only derived from the postal survey explaining the difference in prevalence compared to Paper III. Participants in the clinical examination were more likely to report asthma, eczema and rhinitis but there were no difference in gender, smoking or use of asthma medication. However, as the primary aim of Paper III was to study risk factors and not prevalence, the overall effect is probably small.

6.2 Allergic sensitization

Allergic sensitization can either be assessed by skin prick testing or measurement of specific IgE with rather high correlation between the two methods[220,221]. Skin prick tests are often preferred in epidemiological studies due to lower cost and that an immediate result is obtained. The clinical examinations were ongoing at the completion of Paper II and specific IgE was yet not analyzed and hence Paper II used skin prick testing while Paper III and Paper IV used specific IgE.

6.2.1 Skin prick testing

The result of skin prick testing is dependent on the potency of the allergen extract, the cut-off limits and the technique used[222]. Interpretation is also influenced by the skill of the person performing the test. Test interpretation is difficult in subjects with aged and wrinkled skin with decreased skin reactivity among older individuals[223] and consequently subjects older than 60 years were excluded. Antihistamines and antidepressants were also withheld as they have been shown to suppress the wheal-and-flare response[224,225].

6.2.2 Specific IgE

Measurement of specific IgE is a quantitative method and dependent of the cut-off values. The cut-off value of ≥ 0.35 kU_A/l is arbitrarily chosen but has been shown to correlate with both skin prick testing and atopic diseases[48,221]. The panel of specific IgE included olive and *Parietaria* which are species not normally found in Sweden. *Parietaria* also known as wall pellitory is a common weed encountered along the western coast of Europe and around the Mediterranean. However, as sensitization to pistachio is common in *Parietaria* allergy[226] it may be of clinical interest. Olive exhibits strong cross-reactivity with European Ash and privet which are common throughout West Sweden[227,228].

6.3 Definitions of disease

Objectives of epidemiology include determining the extent and etiology of diseases with the aim of resembling the truth. Asthma, rhinitis and eczema are diseases with arbitrary definitions that change over time without a gold standard. Asthma is in reality merely synonymous to symptomatic variable bronchoconstriction; eczema is a typical itchy rash and rhinitis is a concoction of inflammatory and non-inflammatory changes in the nose. However, the conditions must at least be defined in the particular study to enable epidemiologic research. Whether for research or clinical practice, the definitions of asthma, rhinitis and eczema will never show a sensitivity and

specificity of 100% compared to the truth. The more important definitions used in this thesis will now be discussed further.

Current asthma was in Paper III and Paper IV defined as either a self-report of ever having had asthma or a report of physician-diagnosed asthma in conjunction with either use of asthma medication or symptoms common in asthma. The questions are commonly used in research and reliable in settings with readily access to qualified healthcare[156,164,229]. The definition was based on a positive answer to either the postal survey or the structured interview. Asthma is not a completely stable disease with incidence and also some remission in adulthood[164,191]. The interview was conducted one to four years after the postal survey and thus any incident cases of asthma during that time were added to the prevalence which may result in a slight overestimate. Determinants of disease such as smoking status, history of allergic diseases, occupational exposure and childhood daycare were only assessed in either the postal survey or the interview which mitigates the methodological concern for those entities.

Current rhinitis is wide and more difficult to define but the objective of our definition was to not only include subjects with seasonal/intermittent allergic rhinitis (hay fever) but also of other types of rhinitis including perennial/persistent allergic rhinitis. The ECRHS[160] derived questions of nasal symptoms in conjunction with ophthalmic symptoms were used to include seasonal allergic rhinitis, while the OLIN[200] items on chronic nasal symptoms of congestion and rhinorrhea aimed at including subjects with perennial allergic rhinitis and other types of rhinitis.

The GA^{2}LEN questions used to define current eczema inquired about an itchy rash in the last year. These items originates from the ECRHS[160] questionnaire which also includes a question regarding typical localization. This item was omitted in the GA^{2}LEN version, possible because the localization of eczema is less typical in adults. Adults with eczema tend to less frequently exhibit flexural eczema, facial erythema, neck involvement and xerosis[230]. The ERCHS definition has been validated within the ISAAC among children showing high sensitivity but lower specificity[179]. This is probably the case also among adults where some subjects with skin conditions other than eczema, such as seborrhoeic and nummular dermatitis likely will be categorized as having eczema with the questions used.

6.4 Statistics, associations and causality

Confounders are covariates that are related to both the outcome and the exposure/risk factor. Confounders may either increase or decrease the likelihood of the outcome. This thesis utilized multiple logistic regression models to control for confounding. However, in a cross-sectional study, the models do not differentiate which of the explanatory variables are causes and which are effects of the outcome. The explanatory variable may also be non-causally related with the outcome and only carry association because of mutual relationship with some other causative factor[231]. Does this defer us from making assumptions about causality in cross-sectional studies? The renowned epidemiologist and statistician Sir Austin Bradford Hill would certainly disagree. In 1965 he published nine viewpoints to study association in relation to causation[232]. The viewpoints he proposed are contrary to popular belief not nine mandatory criteria to be fulfilled as a checklist but rather viewpoints that should be evaluated individually. According to Bradford Hill, assumptions of causation can still be made without evaluation of temporality even though it is hampered by its absence. Explanatory variables such as gender and origin which are constant over time and not subject to recall bias are more certain in inferring causality compared to occupational exposures where subjects with an increased risk for a condition may avoid the profession or that subjects with the condition under study may tend to have better recall of past exposures.

7 DISCUSSION OF MAIN RESULTS

7.1 Effects of non- response

Non-responders tended to be younger, have male sex, smoke and live in the metropolitan area of Gothenburg when compared to those who did respond to the postal survey. These demographic characteristics of non-responders unfortunately seem to be universal in respiratory research with similar results in Northern Sweden[182], Northern Finland[183], Southern Finland[233], Western Norway[184,185], Italy[218,234] as well as in a multinational European study[234]. Whether the decreasing response rates in postal surveys are the result of a cohort effect with younger generations being less prone to participation or that it represents an intergenerational trend in society remains to be observed but even lower response rates should be anticipated in the future if the cause is a cohort effect.

The impact of non-response in the survey was relatively small. Prevalence of airway symptoms, obstructive lung diseases, rhinitis and eczema were similar and did not differ among responders and non-responders. Effects of non-response and late-response were further evaluated by analyzing known risk factors for respiratory symptom such as smoking. The associations were significant when the analyses were restricted to the individuals who responded to the first postal questionnaire and the magnitude of the associations remained stable with narrowing confidence intervals when the later responders were added to the analyses. However, smoking was more common among non-responders (30.3% versus 18.6%) and if the prevalence of smoking was adjusted for non-response, it would increase by more than a fifth to 22.9%.

Although the demographics and smoking status of non-responders are similar, they tend to differ in terms of symptoms and diseases in different countries and regions. Non-responders in Northern Sweden[182] reported more asthma and respiratory symptoms; the opposite was true in Finland[183,233] while responders and non-responders were similar in our study. This emphasizes the importance of analyzing response rates, non-participation and if necessary evaluating non-responders by other means of contacts to avoid the uncertainty of bias.

7.2 Prevalence and risk factors for eczema in the postal survey

We found self-reported eczematous conditions to be more common than anticipated among adults in Västra Götaland. The prevalence of ever having had eczema was 40.7% and current eczema was present in 11.5%. Comparisons of eczema prevalence are affected by several obstacles. Most studies presenting data on eczema prevalence have either focused on several allergic diseases[48,123-125,235-237] or the whole spectrum of skin diseases[119,120,122,238,239]. Fewer studies have mainly been focused on eczema, particularly among adults[118,121,126-128,240]. The methods of eczema assessment have varied considerably from self-reports of an itchy rash and ever having had eczema to point prevalence based on skin examinations by dermatologists; the latter results in several-fold lower estimates of prevalence[179]. Lastly, definitions and taxonomy have changed over time[108,111,152].

Lifetime prevalence of eczema among adults varies considerably throughout the world. Only 1.2% reported ever having had symptoms of eczema in Ethiopia[241] while the prevalence in Russian women was 8%. Estimates are higher in Western countries with 24% in New Zealand[235] and 25% in both Finland[236] and Norway[242]. Reports of ever having had eczema are sparse from Sweden but an estimation of the prevalence was 15% in 1992[240]. Our estimate of 40.7% is relatively high and may reflect a real increase but also that the specificity of the definition has decreased.

Prevalence of current eczema seems to be more consistent over the world (Table 4) and ranging from 8% in France[122] and Italy[121], 8-10% in Turkey[123], 10% in South Korea[124], 10-11% in USA[126,127], 12% in Colombia[125] to 14% in Denmark[128]. Overall prevalence in the multinational ECRHS study was 7.1% with high variation between participating countries[118].

Table 4. Prevalence of current eczema in population based studies.

Country	Year	Age	Number	Prevalence	Author
USA	1998	All ages	116 202	10.7%	Hanifin et al[127]
ECRHS	1998	27-56	8202	7.1%	Harrop et al[118]
France	2002	All ages	18 137	7.9%	Wolkenstein[122]
Sweden	2004	18-84	4875	11.6%	Lindberg et al[119]
Turkey	2004	Parents	25843	8.2% men	Kurt et al[123]
				9.6% women	
Italy	2005	20-44	10 083	8.1%	Pesce et al[121]
Sweden	2008	16-75	18 087	11.5%	Rönmark et al[Paper II]
Korea	2009	Military conscripts	3359	9.7%	Lee et al[124]
Colombia	2009	18-59	4026	11.5%	Dennis et al[125]
Denmark	2010	30-89	16 507	14.3%	Vinding et al[128]
USA	2010	18-85	27 157	10.2%	Silverberg et al[126]

Our result for current eczema of 11.5% is somewhere in the middle but direct comparisons are impeded by the plethora of different definitions used. Only the Korean and Colombian study used the same definition and interestingly, the highest prevalence was found in Denmark which utilized the most conservative definition[128,151].

Studies of risk factors for adult eczema are generally lacking[10] and comparisons between existing studies are further complicated by diverging definitions. We found that having a family history of asthma and allergy was significantly associated with all measures of eczema, OR 1.9. This is in agreement with results from studies among children and teenagers[133] while the results in adults so far have been conflicting[118,131,240]. Allergic sensitization in itself was associated with eczema ever but did not reach statistical significance for current eczema OR 1.6 (95% CI 0.99-2.5). Our investigation confirmed eczema to be more common among women, a result in line with most previous studies[118,123,126,131,141,240,242]. Increasing age was associated with lower prevalence of eczema, results also in line with other studies[126,240,242]. Smoking and ex-smoking as risk factors for eczema have been proposed before, but results are conflicting and mostly confined to ex-smokers[118,141,243]. We found ex-smoking to be associated with all measures of eczema while current smoking was associated with current eczema but not eczema ever. The same pattern with higher prevalence of current eczema but not of ever having had eczema among smokers has been observed among adolescents[244] signifying that tobacco smoke may sustain eczema. The proposed mechanism for this possible effect is unclear but it has been shown that smoking increases total IgE[245,246].

7.3 Risk factor patterns for asthma, rhinitis and eczema

The adjusted risk factor patterns for current asthma, current rhinitis and current eczema were compared in Paper III. Allergic sensitization and family history of both asthma and rhinitis were the strongest risk factors for current asthma and current rhinitis but neither was significantly associated with current eczema, where the strongest risk factor was occupational exposure to gas, dust or fumes (GDF). Obesity was similarly associated with current asthma and current rhinitis but not current eczema. Occupational exposure to GDF and female sex were associated with current asthma and current eczema but not current rhinitis. Raised on a farm exerted a protective effect on current rhinitis and current eczema but not for current asthma.

More women than men suffered from current asthma in line with earlier studies[247,248] and we could also replicate the association between female sex and eczema that has been demonstrated in earlier studies on this topic[131,141]. The cause for this gender related difference is largely unknown. Different expression of sex hormones may play a role in asthma[56] but this is yet to be explored for eczema. Occupational exposure to GDF was the strongest risk factor for current eczema and also associated with current asthma. The link between occupational exposure to GDF and asthma has already been established[249,250] and it has been estimated that 14% of adult onset asthma may be attributed to work-related exposure to GDF[61]. The effect of occupational exposure to GDF on eczema is still not known with earlier occupational studies focusing on hand dermatitis. However exposures with similarities have been linked to eczema; using wood for house heating was associated with eczema in Turkey[251], cooking with biofuel has been linked to eczema[123] and an increase in eczema was observed after a large accidental airborne emission of chemicals in Germany[252].

Having lived on a farm during the first five years of life was associated with a protective effect against both current eczema and current rhinitis but no effect was seen for current asthma, OR 1.0 (95% CI 0.5-1.8). The protective effect of farm childhood on rhinitis has been observed among children[253,254], young adults[255] and all adults[83,84]. Farm childhood has also been associated with a protective effect on asthma in childhood[253,254] but results among adolescents and adults are conflicting with some studies supporting a protective effect[256] while others, in line with our results failed to do so[255,257]. Farm living has not been found to be associated with a protective effect on eczema in children[129,253,254]. Bråbäck et al[138] studied more than one million conscripts in the Swedish army and found a protective association. However the effect was

small and may be attributed to the extremely large power of the study, OR 0.93 (95% CI 0.89-0.98). Adult studies on the topic are lacking and this is to our knowledge, the first study observing a protective association between farm childhood and eczema in adults.

Obesity is generally associated with asthma in line with our results[44,58-60,258], while the association with rhinitis is less studied. Obesity was only found to be associated with rhinitis in conjunction with asthma in Japan[259] while no association was found in Poland[260]. However, those studies only included allergic rhinitis which limits comparisons with our study. The relationship between obesity and eczema is conflicting with studies from the United States[141,142] reporting more eczema among obese subjects while the Polish study, in agreement with our results, did not find an association[260]. Having a family history of asthma and allergy was not found to be a risk factor for current eczema in Paper III contrasting the results in Paper II. However, the odds ratios were similar, 1.6 compared to 1.9 and the discrepancy is probably the result of statistical power.

7.4 Sensitization profile in asthma, rhinitis and eczema

The prevalence of allergic sensitization to at least one of the allergens included in the panel was 29.7%. It was more common among men and younger subjects with decreasing prevalence by increasing age. The prevalence of allergic sensitization has increased since the second half of the past century[261-263] but results are supporting that a plateau has been reached with no further increase in at least some Westernized countries[31,32], while an increase probably is ongoing in countries still undergoing urbanization[264]. The Swedish centers participating in the ECRHS I during the 1990s showed the prevalence of allergic sensitization to be 30.4% in Västerbotten, 32.8% in Uppsala and 31.7% in Gothenburg[220]. However, the composition of the populations in that study differed compared to our study with participants aged 20-46 years. Further, fewer allergens were analyzed and included only cat, timothy, birch, *D. pteronyssinus* and *Cladosporium*. Our corresponding prevalence of sensitization to any allergen in that age group was 39.1%, and the prevalence was 36.5% when the same allergens were assessed as in that study. This implies a slight increase of allergic sensitization over the past 20 years. The prevalence of allergic sensitization has not only been shown to vary over time but regional differences are also evident. Higher estimates of allergic sensitization compared to ours have been obtained from studies in northern Sweden, 39.3%[265], Finland, 46.9%[49], United States, 44.6%[266] and Estonia, 34.5%[267] while the prevalence among 30 to 40 year old men in

Denmark ranged from 19,1% to 43.7% depending on the degree of urbanization in the upbringing with the highest prevalence in metropolitan Copenhagen[268].

The gender-related difference with allergic sensitization being more common among men is a general finding in numerous studies[220,261,266,269,270] but the cause is still unknown. It has been shown that levels of IgE are higher in boys compared to girls already at young age suggesting a genetic difference[271]. This may at least partly explain the gender-related differences observed in asthma with higher prevalence in boys compared to girls among children[56] but it cannot explain the shift during adolescence with asthma thereafter being more prevalent among women[248] which also was observed in Paper III. The gender-related difference in asthma prevalence has been attributed to hormonal differences[56] but quality studies in postmenopausal women supporting this theory are lacking

Allergic sensitization was strongly associated with current asthma and current rhinitis but not significantly so for current eczema, OR 1.25 (95% CI 0.85-1.85). The associations between allergic sensitization and asthma and rhinitis have already been clarified in other studies[272] but it may be surprising that allergic sensitization was not a risk factor for current eczema. However, most studies showing an association between eczema and allergic sensitization have been performed among children and considerably less is known about the association among adults. The strongest associations have been observed in hospital based studies among children where subjects often have a more severe disease[273]. Increasing disease-severity is associated with a higher risk for allergic sensitization[274] and consequently the associations will be stronger in those populations. Although the association among children and adolescents is weaker in population-based studies, it is still highly significant[130,274,275]. Allergic sensitization was a risk factor for eczema among adults in the pooled ECRHS sample, OR 1.5 (95% CI 1.2-1.9)[118] but the association was weak compared to studies among children. Thyssen at al[276] observed a stronger association among adults in Denmark, OR 2.5 (95% CI 2.0-3.3) using the UK Working Party epidemiologic definition of eczema[152], which despite its limitations, generally is considered the method of choice for epidemiological studies. However, the UK Working Party definition (see chapter 2.2.3) does not distinguish between past or present disease and is partly based and affected by the presence of asthma and rhinitis. The fact that both asthma and rhinitis are strongly associated with allergic sensitization will therefore convey a stronger relationship between allergic sensitization and eczema with the use of that definition.

One possible explanation for the difference between children and adults may be that allergic sensitization is highly age-dependent and decreases with age[277]. There are no clear evidence that allergic sensitization plays a causal role in the pathogenesis of eczema and it may be a consequence and not a cause of the disease. Interestingly, a similar pattern has been described for symptoms of allergic rhinitis with a strong association to allergic sensitization in younger adults but only borderline significant among older adults[272]. However, allergic rhinitis is clearly the result of an IgE-mediated response to allergens but it has been shown that a relatively large proportion of subjects presenting with symptoms of rhinitis may have a locally mediated IgE response in their nose in the absence of allergic sensitization assessed by serum and skin prick tests[278]. It is therefore possible that some subjects become sensitized and develop allergic rhinitis in early life with persistence of the rhinitis but remission of the systemic sensitization assessed by specific IgE in serum or by skin prick test reactivity as they become older.

Sensitization to pollens, animals and mites were all significant risk factors for current asthma when the specific sensitization were divided into groups and entered in a multivariate model with adjustment for confounders and other sensitization groups. Only sensitization to birch and dog were significantly associated with current asthma after adjustment for other specific sensitizations. Plaschke et al[220] found similar results in a Swedish study during the 1990s with sensitization to pollens, animals and mites being risk factors for asthma but with the exception that no association was seen for birch. Another recent study from the northernmost part of Sweden found that sensitization to animals but not pollens and mites were associated with asthma[272]. It thus seems that although sensitization to furred animals is an important risk factor for asthma in our area, sensitization to mites and pollens, most notably birch are also important contrasting results from other regions of Sweden. The difference observed for mites is probably attributed to the absence of mites in the dry and cold climate of the northernmost part of Sweden[279]. The greater importance of sensitization to pollens in our area may reflect a milder climate and consequently a greater exposure to airborne pollens compared to northern Sweden. However, only sensitization to cat was associated with incident asthma in the ECRHS[43] with a majority of subjects from regions warmer than Västra Götaland but direct comparisons are hampered by differences in the pooled populations from multiple countries.

Whereas sensitization to pollens, animals and mites were risk factors for current asthma, the pattern was different for current rhinitis with only pollens playing a significant role. This is different compared to other parts of Sweden were not only pollens but also animals are important sensitizers[272] in allergic rhinitis. Most studies on rhinitis have focused on allergic rhinitis (hay fever)

which by experts in the field is attributed to pollen sensitization while persistent allergic rhinitis is believed to be caused by sensitization to animals and mites[68]. Our results that are highlighting the importance of sensitization to pollens and not animals in current rhinitis are interesting considering that subjects with either symptoms of allergic rhinitis or persistent nasal symptoms were included.

8 CONCLUSIONS

- ✓ The representativeness of the West Sweden Asthma Study was high even though the response rate of 62% was moderate. Non-responders did not differ from responders in terms of asthma, rhinitis, eczema and respiratory symptoms but were more commonly smokers, young and men.

- ✓ Eczema among adults was more common than anticipated in West Sweden and associated with asthma, rhinitis, respiratory symptoms, female sex, smoking and occupational exposure to gas, dust or fumes after adjustments for confounders.

- ✓ The risk factor patterns for asthma, rhinitis and eczema among adults were different. Some risk factors were overlapping between some of the conditions but no uniform pattern was observed. Obesity and family history of allergic diseases were associated with asthma and rhinitis while female sex and occupational exposure to gas, dust or fumes were associated with eczema and asthma.

- ✓ The prevalence of allergic sensitization to at least one common airborne allergen among adults in West Sweden was 30%. Allergic sensitization is an important risk factor for asthma and rhinitis but the entities have different patterns of allergic sensitization. Allergic sensitization was not significantly associated with current eczema suggesting a lesser role in adults compared to children.

9 PERSPECTIVES

Studies with cross-sectional design, such as the first part of WSAS, give important information of diseases and risk factors but large prospective studies carried out over time are necessary in order to further investigate the causal relationship of the determinants of disease for asthma, eczema and rhinitis. Repeated cross-sectional studies with identical inclusion criteria and methods are also necessary for assessments of trends in prevalence of diseases and associated conditions, such as allergic sensitization. There are evidence suggesting a plateau in the rise of allergic sensitization but only repeated studies in the same populations will give us the clear answer. A follow up of the WSAS cohort is planned during 2016 with invitations to all participants in the 2008 study with an additional large random sample which will enable assessments of trends in prevalence and also to study factors associated with incidence and remission of the diseases.

However, it is clear that at least asthma and rhinitis is constituted of multiple separate disease entities, *endotypes*, with different risk factor patterns and underlying pathophysiologic components. Studying these diseases together as one entity is inherited with a risk that an important determinant for a lesser prevalent endotype is concealed. It is therefore of great importance for us to develop novel instruments which can aid in the categorization of asthma and rhinitis. The question to what extent eczema also is comprised of multiple endotypes remains to be answered. Future epidemiological studies among adults are greatly called for. The studies need to not only assess prevalence and risk factors of eczema but also incorporate clinical validations which can aid us in delineating eczema from other skin conditions.

It is likely that studies using information from questionnaires and clinical examinations lacks the necessary tools in addressing all these issues and a translational approach connecting epidemiology with molecular research is doubtlessly needed in the future.

ACKNOWLEDGEMENT

First of all I wish to express my sincere gratitude to all of whom have contributed in different ways to the completion of this thesis. My special thanks go to:

Bo Lundbäck, my main supervisor. You have inspired and motivated me all the way from medical school to the last letter in this thesis. Thank you for inviting me to the field of epidemiology, respirology and allergy and for sharing your great knowledge with me. Also, I would like to thank you for your great patience with your student (author).

Jan Lötvall, my co-supervisor. Thank you for providing an open and affluent environment for research. You have provided me with valuable input and criticism on my work and opened for up new perspectives and point of views.

Linda Ekerljung, my co-supervisor. Thank you for all your work that has helped to complete this thesis. You performed my analyses when we started out and during the way you have given me important tools of medical statistics.

Eva Rönmark, my mother and co-author. Thank you for your unconditional support. This thesis would not be possible without your encouragement.

Stig Hagstad, my dear friend and co-author. Thank you for your meticulous work with the manuscript but above all, your direct feedback telling me to *get a grip* when in dire need.

Göran Wennergren, my co-author for your sincere enthusiasm, positivity and hard work on the manuscripts.

Anders Bjerg, Kjell Torén, Sigrid Sjölander, Magnus Borres, Roxana Mincheva and Shintaro Suzuki, my other co-authors, for the contributions of each one of you. Thank you for your advice and comments on the manuscripts.

Lotte Edvardsson, Maria Falkdal, Helen Friberg, Eva Karlgren, Anna Merlander, Mary-Ann Raneklint and Helén Törnqvist, the research nurses at Krefting Research Centre for conducting the clinical examinations and gathering the data of the study.

Eva-Marie Romell, the department secretary for always having the door open and helping me with the administrative parts of being enrolled in a PhD program.

All other colleagues at Krefting Research Centre for your encouragement, help and support.

All the participants in the West Sweden Asthma Study, with special gratitude to participants in the non-response study and clinical examinations. You enabled the study and this thesis.

My family, Sandra Andersson my love and joy, for endeavoring my frequent visits to Gothenburg. Peder Rönmark, my father for your bolstering and always giving me a laugh.

David Lehtonen Åderman and Susanne Åderman, my wonderful friends. Thank you so much for your friendship and hospitality. It has been a great pleasure being able to spend time with you during this enterprise.

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APPENDIX

Appendix I – The complete WSAS postal questionnaire in Swedish

Appendix II – English translation of the OLIN questionnaire

Appendix III – English translation of the GA^{2}LEN questionnaire

Frågeformulär

Astma, allergi och KOL i Västra Götaland

Vi är tacksamma om Du besvarar alla frågor i bägge frågeformulären, trots att de i vissa fall kan verka lika.

GÖTEBORGS UNIVERSITET

FRÅGEFORMULÄR
Astma, allergi och KOL i Västra Götaland 2008

Besvara frågorna genom att kryssa i lämplig ruta.
Om Du är osäker om svaret, välj ”Nej/vet ej”

		NEJ/ VET EJ	JA
1.	Är det någon av Dina föräldrar eller syskon som har eller har haft		
	a) astma	☐	☐
	b) allergiska ögon- eller näsbesvär (hösnuva)	☐	☐
	c) kronisk luftrörskatarr (bronkit), KOL eller emfysem	☐	☐
2.	Har Du nu eller har Du haft någon av följande sjukdomar:		
	a) astma	☐	☐
	b) allergiska ögon- eller näsbesvär (hösnuva)	☐	☐
	c) kronisk luftrörskatarr (bronkit), KOL eller emfysem	☐	☐
	d) annan lung- eller luftvägssjukdom	☐	☐
	Om “ja”: Vilken eller vilka? ……..……..……		
3.	Har Du av läkare fått diagnosen astma?	☐	☐
	Om ”ja”: Hur gammal var Du när Du fick astma? ……år		
4.	Har Du av läkare fått diagnosen kronisk luftrörskatarr (bronkit), KOL eller emfysem?	☐	☐
5.	Använder Du astmamediciner (ständigt eller vid behov)?	☐	☐
6.	Har Du nu eller har Du under de senaste 10 åren haft astmabesvär? (Dvs. periodvisa eller anfallsvisa andningsbesvär/andfåddhet, besvären kan uppträda med eller utan hosta och med eller utan pip i bröstet)	☐	☐
	Om ”ja”: Har Du haft sådana besvär under det senaste året (de senaste 12 månaderna)?	☐	☐
7.	Har Du haft långvarig hosta under det senaste året?	☐	☐
8.	Brukar Du hosta upp slem eller har Du slem i bröstet som Du har svårt att få upp?	☐	☐
	Om ”ja”: a) Har Du fått upp slem de flesta dagar under perioder som varat minst 3 månader?	☐	☐
	b) Har Du haft sådana perioder minst 2 år i rad?	☐	☐
9.	Brukar Du ha pip, skrål eller väser det i bröstet då Du andas?	☐	☐

	NEJ/ VET EJ	JA
10. Har Du haft pip eller väsningar i bröstet vid **något tillfälle** under de senaste 12 månaderna?	☐	☐
Om ”ja”:	☐	☐
a) Har Du överhuvudtaget varit **det minsta andfådd** när Du haft pip eller väsningar i bröstet?		
b) Har Du haft detta pip eller väsande i bröstet när Du **inte** samtidigt varit förkyld?	☐	☐
11. Har Du vaknat med trånghetskänsla i bröstet vid något tillfälle under de senaste 12 månaderna?	☐	☐
12. Måste Du gå långsammare än jämnåriga på slät mark på grund av andfåddhet?	☐	☐
13. Brukar Du bli andfådd, få pip i bröstet eller hostattacker:		
a) vid ansträngning	☐	☐
b) i kyla	☐	☐
c) vid ansträngning utomhus i kallt väder	☐	☐
d) i dammiga miljöer	☐	☐
e) av cigarett- eller tobaksrök	☐	☐
f) av bilavgaser	☐	☐
g) av starka dofter (parfym, kryddoft, trycksvärta, rengöringsmedel, blommor etc)	☐	☐
h) av pollen från växter som gräs och/eller träd	☐	☐
i) vid kontakt med pälsdjur (katt, hund, häst eller andra pälsdjur)	☐	☐
14. Har Du någon gång reagerat med andningssvårigheter inom 3 timmar efter att ha tagit en värktablett?	☐	☐
Om ”ja”:		
Kommer Du ihåg namnet på medicinen? ……		
15. Har Du nästäppa mer eller mindre ständigt?	☐	☐
Oavsett ”ja” eller ”nej”:		
Har Du snuva mer eller mindre ständigt?	☐	☐
16. Är Du rökare? (Som rökare räknas även de som röker enstaka cigaretter eller pipstopp per vecka och de som slutat röka under det senaste 12 månaderna.)	☐	☐
Om ”ja”:		
Hur många cigaretter röker Du per dag?		
Mindre än 5 ☐ 5 – 14 ☐ 15 – 24 ☐ 25 eller mer ☐		
Om ”nej”:		
Har Du tidigare varit rökare och slutat röka för mer än ett år sedan?	☐	☐
Om Du är eller har varit rökare:		
Hur gammal var Du när Du började röka? ……år		

	NEJ/ VET EJ	JA
17. Är Du yrkesverksam**?**	☐	☐
Om ”ja”:		
Arbetar Du heltid?	☐	☐

18. Vilket har varit Ditt **huvudsakliga** yrke eller sysselsättning?

…….....…….....

Hur många år sammanlagt har Du arbetat i detta yrke? .....…år

19. Har Du **nu** något annat yrke eller sysselsättning (är studerande, arbetssökande, hemmafru, förtidspensionerad, har ålderspension osv.)? ☐ ☐

a) Vilket? …….……

b) Sedan hur många år? ……..år

20. När arbetet blir *kroppsligt besvärande*, har Du då möjlighet att dra ner på takten eller arbeta annorlunda, så att besvären minskar?

☐ Ja, ofta ☐ Ja, ibland ☐ Nej, sällan ☐ Nej, aldrig/nästan aldrig

21. När arbetet *blir psykiskt påfrestande*, har Du då möjlighet att påverka det Du gör, så att påfrestningen minskar?

☐ Ja, ofta ☐ Ja, ibland ☐ Nej, sällan ☐ Nej, aldrig/nästan aldrig

22. Känner Du Dig utvilad och återhämtad när Du börjar arbetet?

☐ Ja, ofta ☐ Ja, ibland ☐ Nej, sällan ☐ Nej, aldrig/nästan aldrig

23. Hur stor är Din arbetsförmåga i Ditt nuvarande arbete (förutsatt heltidsarbete och uttryckt i procent)

……%

Frågan syftar att ta reda på Din totala arbetsförmåga oavsett Din arbetstid.
Om Du arbetar 30 timmar i veckan men skulle orka arbeta 40 timmar, ange då 100% som svar.
Om Du arbetar 40 timmar i veckan, men orkar egentligen bara 30 timmar i veckan, ange då 75% som svar.

24. Har Du varit sjukskriven vid något eller några tillfällen under de senaste 12 månaderna? ☐ ☐

Om Du är sjukskriven just nu, räkna inte med den nuvarande sjukskrivningsperioden.

Om ”ja”:

☐ 1 – 7 dagar ☐ 8 – 30 dagar ☐ 2 – 3 månader ☐ 4 – 12 månader

	NEJ/ VET EJ	JA
25. Har Du varit sjukskriven p g a andningsbesvär under de senaste 12 månaderna?	☐	☐
26. Har Du någon gång ändrat arbetsuppgifter p g a astma eller andra andningsbesvär?	☐	☐

Om "ja":
Vilket år? ……..
Vilket yrke hade Du då?……

27. Har Du någon gång ändrat arbetsuppgifter p g a andra hälsoskäl?	☐	☐

Om "ja":
Vilket år? ……..…
Vilket yrke hade Du då?……

28. Hur störd är Du när Du befinner Dig **hemma** av luftföroreningar utomhus (från trafik, industrier etc) om **Du har Dina fönster öppna**? *(Om Du inte alls känner Dig störd välj 0, om Du känner Dig oerhört störd välj 10 och om Du känner Dig någonstans däremellan välj en siffra mellan 0 och 10)*

0 1 2 3 4 5 6 7 8 9 10

Inte alls störd — Outhärdlig störning

29. Har Du under de senaste 10 åren någon gång haft en vattenskada i Din bostad?	☐	☐

Om "ja":
Vilket år? ……..

30. Har Du under de senaste 10 åren någon gång haft en synlig mögelskada i Din bostad?	☐	☐

Om "ja":
Vilket år? ……..

31. Har Du varit mycket utsatt för damm, gaser eller rök i arbetet?	☐	☐

32. Hur många gånger per vecka (i genomsnitt) äter Du fisk? ……..……

33. Hur många gånger per vecka tränar eller sportar Du så mycket att Du blir svettig eller andfådd, eller går på långpromenad, skidåkning eller motsvarande? ……...

34. Bodde Du på landsbygden (dvs inte stad eller tätort) under Dina fem första levnadsår?	☐	☐
Hade Din familj jordbruk under Dina fem första levnadsår?	☐	☐

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Besvara frågorna genom att kryssa i rätt alternativ.

NEJ	JA
☐	X

Om Du är osäker vid ”nej-ja-frågor”, välj ”nej”-rutan.

1. Har Du haft pip eller har det väst i bröstet vid något tillfälle under **de senaste 12 månaderna*?*** NEJ ☐ JA ☐

OM SVARET ÄR ”NEJ” GÅ TILL FRÅGA 2 *OM ”JA” GÅ TILL FRÅGA 1.1*

1.1 Har Du överhuvudtaget varit det minsta andfådd när Du haft detta pipande ljud? NEJ ☐ JA ☐

1.2 Har Du haft detta pip eller väsande i bröstet när Du **inte** samtidigt varit förkyld? NEJ ☐ JA ☐

2. Har Du vaknat med en trånghetskänsla i bröstet vid något tillfälle under **de senaste 12 månaderna**? NEJ ☐ JA ☐

3. Har Du vaknat av andnödsattack vid något tillfälle **de senaste 12 månaderna**? NEJ ☐ JA ☐

4. Har Du vaknat av hostattack vid något tillfälle **de senaste 12 månaderna?** NEJ ☐ JA ☐

5. Brukar Du under vintern få upp **slem från bröstet** nästan varje dag under **åtminstone tre månader varje år**? NEJ ☐ JA ☐

6. Har Du **någonsin** haft astma? NEJ ☐ JA ☐

OM ”NEJ” GÅ TILL FRÅGA 7 *OM ”JA” GÅ TILL FRÅGA 6.1*

6.1 Hur gammal var Du när Du hade Ditt första astmaanfall? ÅLDER ☐☐
(Om osäker, ange Din bästa gissning!)

6.2 Har Du **någonsin** varit inlagd på sjukhus på grund av astma? NEJ ☐ JA ☐

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NEJ JA

6.3 Har Du haft något astmaanfall under **de senaste 12 månaderna**?

6.4 Tar Du för närvarande någon **astma**medicin, inklusive inhalatorer, sprejer eller tabletter**?**

7. Har Du hösnuva eller någon annan allergisk snuva?

OM "NEJ" GÅ TILL FRÅGA 8 ***OM "JA" GÅ TILL FRÅGA 7.1***

7.1 Har Du haft problem med allergisk snuva **under de senaste 12 månaderna?**

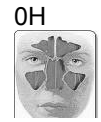
7.2 Har Du någonsin haft problem med allergisk snuva under **mer än 4 dagar under en enskild vecka**?

7.3 Om "ja", hände detta under **mer än 4 veckor i sträck?**

7.4 Har Du **klåda eller irritation i ögonen** samtidigt med Dina näsbesvär?

8. Har Du varit täppt i näsan i **mer än 12 veckor under de senaste 12 månaderna?**

9. Har Du haft värk eller tryck runt pannan, näsan eller ögonen i **mer än 12 veckor under de senaste 12 månaderna?**



10. Har Du haft missfärgat nässekret (snor) eller missfärgat slem i halsen **i mer än 12 veckor under de senaste 12 månaderna?**

11. Har Ditt luktsinne varit nedsatt eller borta i **mer än 12 veckor under de senaste 12 månaderna?**

12. Har en läkare **någon gång** sagt att Du har **kronisk** bihåleinflammation?

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NEJ JA

13. Har Du någonsin under **minst 6 månader** haft besvär av återkommande kliande utslag? ☐ ☐

OM "NEJ" GÅ TILL FRÅGA 14 *OM "JA" GÅ TILL FRÅGA 13.1*

NEJ JA

13.1 Har Du haft det kliande utslaget **under de senaste 12 månaderna**? ☐ ☐

NEJ JA

13.2 Drabbar detta **endast** Dina händer? ☐ ☐

NEJ JA

14. Har Du någonsin haft eksem eller någon form av hudallergi? ☐ ☐

NEJ JA

15. Har Du någon gång haft svårt att andas inom 3 timmar efter att Du intagit smärtstillande läkemedel? ☐ ☐

OM "NEJ" GÅ TILL FRÅGA 16 *OM "JA" GÅ TILL FRÅGA 15.1*

15.1 Var vänlig skriv ner läkemedlets namn……

NEJ JA

16. Har Du någonsin rökt under minst ett års tid? ☐ ☐

["JA" betyder ***minst en cigarett om dagen eller en cigarr i veckan under minst ett år*****]**

OM "NEJ" GÅ TILL FRÅGA 17 *OM "JA" GÅ TILL FRÅGA 16.1*

ÅLDER

16.1 Hur gammal var Du när Du började röka? ☐☐

NEJ JA

16.2 Har Du rökt alls under **sista månaden**? ☐ ☐

OM "JA" GÅ TILL FRÅGA 16.3 *OM "NEJ" GÅ TILL 16.2.1*

ÅLDER

16.2.1 Hur gammal var Du när Du slutade röka? ☐☐

Cigaretter per dygn

16.3 I genomsnitt, hur mycket röker (rökte) Du? ☐☐

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17. Är Du **för närvarande**: ***Kryssa bara i en ruta!***

anställd	1.	☐
egen-företagare	2.	☐
arbetslös	3.	☐
sjukskriven, sjukbidrag	4.	☐
hemarbetande full tid	5.	☐
studerande, full tid	6.	☐
pensionerad	7.	☐
övrigt	8.	☐

18. Arbetar Du **för närvarande**:

a. inom sjukvården (t.ex. som sjuksköterska, undersköterska, medicintekniker, läkare, ambulanssjukvårdare eller liknande)? NEJ ☐ JA ☐

b. i ett jobb som huvudsakligen innefattar någon typ av arbete med rengörning eller städning NEJ ☐ JA ☐

19. Hur **lång** är Du? cm ☐☐☐

20. Hur mycket **väger** Du?

kg ☐☐☐

21. Ange Ditt **födelsedatum** DAG ☐☐ MÅNAD ☐☐ **19** ÅR ☐☐

22. Ange **dagens datum** DAG ☐☐ MÅNAD ☐☐ **20** ÅR ☐☐

23. Är Du **man** eller **kvinna**? MAN ☐ KVINNA ☐

24. Vad har Du för **postnummer**? ☐☐☐☐☐

25. Hur många år har du bott på **nuvarande adress**? ÅR ☐☐

26. Hur **lång tid per dygn** vistas Du vanligtvis i bostaden? TIMMAR ☐☐

27. Hur ofta brukar Du uppleva luften i **Ditt bostadsområde** som **irriterande**?

Kryssa bara i en ruta!

Dagligen/nästan dagligen	1.	☐
Ibland/periodvis	2.	☐
Sällan/aldrig	3.	☐

28. Hur **besvärande** är avgaserna från trafiken i **Ditt bostadsområde**?

Kryssa bara i en ruta!

Inget/lite	1.	☐
Något	2.	☐
Mycket	3.	☐

29. Hur lång tid reser/går Du **omgiven av stadstrafik** en vanlig vardag? MINUTER ☐☐

30. Har något av följande konstaterats i Din bostad **de senaste 12 månaderna**?

	NEJ	JA
a Vattenskador/fuktskador inomhus på väggar, golv, eller tak?	☐	☐
b ”Buckliga” plastmattor, gulnade plastmattor eller svartnad parkett?	☐	☐
c Synlig mögelväxt på väggar, golv eller i taket?	☐	☐

31. Vilken är den **högsta utbildning** Du har? ***Kryssa bara i en ruta!***

Gått i skola mindre än 5 år	1.	☐
Folkskola eller grundskola	2.	☐
Realskola eller flickskola	3.	☐
2-årigt gymnasium eller yrkesskola	4.	☐
3-4-årigt gymnasium	5.	☐
Universitet eller högskola, 2,5 år eller kortare (mindre än 120 p)	6.	☐
Universitet eller högskola, 3 år eller längre (mer än 120 p)	7.	☐

32. Har Du någon gång haft ett arbete där Du utsatts för **gas, rök eller damm**? NEJ ☐ JA ☐

33. Har en läkare någon gång sagt att Du har **kroniskt obstruktiv lungsjukdom (KOL)**? NEJ ☐ JA ☐

34. Frågor om sömn och sömnkvalité:

Siffrorna betyder
1: *aldrig eller sällan*
2: *mindre än en gång i veckan*
3: *1 till 2 ggr i veckan*
4: *3 till 5 ggr i veckan*
5: *nästan varje dag eller natt*

Hur ofta har det hänt under de senaste månaderna:

Ringa in rätt svar

a. att Du snarkar högt och störande?	1	2	3	4	5
b. att Du har svårt att somna på kvällen?	1	2	3	4	5
c. att Du vaknar flera gånger under natten?	1	2	3	4	5
d. att Du känner Dig sömnig under dagen	1	2	3	4	5
e. att Du vaknar för tidigt och kan inte somna om?	1	2	3	4	5

GA²LEN
Global Allergy and Asthma European Network
Network of Excellence

35. Tar Du för närvarande **medicin** för

		NEJ	JA
högt blodtryck	1	☐	☐
KOL	2	☐	☐
sockersjuka/diabetes	3	☐	☐
sömnbesvär	4	☐	☐

36. Har Du någonsin snusat dagligen **under minst 6 månader**? NEJ ☐ JA ☐

36.1 Om ”ja” snusar Du **fortfarande**? NEJ ☐ JA ☐

37. Använder Du **tuggtobak**, **nikotinplåster** eller **nikotintuggummi**? NEJ ☐ JA ☐

38. **Hur ofta** brukar Du **motionera** så mycket att Du blir andfådd eller börjar svettas?

Kryssa bara i en ruta!

varje dag	1.	☐
4-6 gånger per vecka	2.	☐
2-3 gånger per vecka	3.	☐
en gång i veckan	4.	☐
en gång i månaden	5.	☐
mindre än en gång i månaden	6.	☐
aldrig	7.	☐

39. Hur **många timmar per vecka** brukar Du **motionera** så mycket att Du blir andfådd eller börjar svettas?

Kryssa bara i en ruta!

aldrig	1.	☐
ungefär ½ timma	2.	☐
ungefär 1 timma	3.	☐
ungefär 2-3 timmar	4.	☐
ungefär 4-6 timmar	5.	☐
7 timmar eller mer	6.	☐

40. Får vi ta kontakt med Dig igen för ytterligare hjälp med projektet eller för att be om ytterligare information? NEJ ☐ JA ☐

40.1 Om ”ja”, på vilket **telefonnummer** kan vi lättast nå Dig?

☐☐☐☐☐☐☐☐☐☐☐☐

Tack för hjälpen!

The English version of the 2006 FinEsS questionnaire
used in the OLIN Study area (Norrbotten) and Stockholm /PLACE FOR NAME/

Answer be ticking a cross (x) in the bracelets or writing on appropriate line

	Yes	No/ Don´t know
1. Have or have any of your parents, brothers or sisters had:		
a) Asthma	( )	( )
b) Allergic rhinitis (hay-fever) or allergic eye catarrh	( )	( )
c) Chronic bronchitis, COPD or emphysema	( )	( )
2. Have you now or have you ever had any of the following diseases :		
a) Asthma	( )	( )
b) Allergic rhinitis (hay-fever) or allergic eye catarrh	( )	( )
c) Chronic bronchitis, COPD or emphysema	( )	( )
d) Any other lung- or airways disease	( )	( )
If "yes", which?.....		
3. Have you been diagnosed as having asthma by a doctor?	( )	( )
If "yes":		
a) How old were you when you got asthma?.....years	( )	( )
4. Have you been diagnosed as having chronic bronchitis, COPD or emphysema by a doctor?	( )	( )
5. Do you currently use asthma medicines (permanently or as needed)?	( )	( )
6. Have you now or have you had asthma symptoms during the last 10 years (intermittent breathlessness or attacks of shortness of breath, the symptoms may exist simultaneously with or without cough or wheezing)?	( )	( )
If "yes":		
a) Have you had these symptoms during the last year (last 12 months)?	( )	( )
7. Have you had longstanding cough during the last year?	( )	( )
8. Do you usually have phlegm when coughing, or do you have phlegm in your chest, which is difficult to bring up?	( )	( )
If "yes":		
a) Do you bring up phlegm on most days during periods of at least three months?	( )	( )
b) Have you had such periods during at least two successive years?	( )	( )
9. Do you usually have wheezing, whistling or a noisy sound in your chest when breathing?	( )	( )
10. Have you **at any time** during the last 12 months had wheezing or whistling in your chest?	( )	( )
If "yes":		
a) Have you been **at all breathless** when the wheezing or whistling was present?	( )	( )
b) Have you at any time had this wheezing or whistling when you **did not** have a cold?	( )	( )
11. Have you woken up with tightness in your chest at any time during the last 12 months?	( )	( )
12. Do you get short of breath when you walk with other people of your own age on level ground at normal pace?	( )	( )

Please, continue to next page!

13. Do you usually have breathlessness, wheeze or severe cough:
    a) on effort ( ) ( )
    b) in cold weather ( ) ( )
    c) on effort in cold weather during winter ( ) ( )
    d) in dusty places ( ) ( )
    e) by cigarette or tobacco smoke ( ) ( )
    f) by car exhaust fumes ( ) ( )
    g) by strong smelling scents (parfumes, spices, printing ink, cleaner, smelling flowers)? ( ) ( )
    h) by pollen from grass and/or trees ( ) ( )
    i) at contact with furred animals (cat, dog, horse, pets and other furred animals) ( ) ( )

14. Have you ever reacted with breathing difficulties within 3 hours after taking a pain killer? ( ) ( )
    If "yes":
    a) Do you remember the name of the tablet?.....

15. Do you have blocking of your nose more or less constantly? ( ) ( )
    Irrespectively of "yes" or "no":
    a) Do you have a runny nose more or less constantly? ( ) ( )

16. Do you smoke? (Smokers also include those who smoke a few cigarettes or pipe fills a week and those who have stopped smoking during the last 12 months.) ( ) ( )
    If "yes":
    a) How many cigarettes do you smoke per day?
    Less than 5 ( ) 5 – 14 ( ) 15 or more ( ) 25 or more ( )
    If "no":
    b) Have you been a smoker but have stopped smoking more than one year ago? ( ) ( )
    If you are or have been a smoker:
    c) How old were you when you started to smoke? .....years

17. What is or has been your **main** work or occupation?

.....
    a) How many years have you had this main work or occupation? .....years

18. Have you now another work or occupation (other work / profession, or are you studying, unemployed, house-wife, retired, have sickness pension etc.)? ( ) ( )
    If "yes":
    a) What work or occupation? .....
    b) Since how many years? .....years

19. Have you been heavily exposed to dust, gases or fumes at your work? ( ) ( )

20. How many times a week (on average) do you eat fish? .....

21. How many times a week do you exercise or do sports so much that you sweat or get breathless, or go for long-walks, skiing or similar activities? .....

22. Did you live at country-side (not town or suburb) during your first five years of life? ( ) ( )
    a) Did your family live on a farm during your first five years of life? ( ) ( )

Thank you for your participation!

Area number
Personal number

TO ANSWER THE QUESTIONS PLEASE TICK THE APPROPRIATE BOX **NO** **YES** X

IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE 'NO'

1. Have you had wheezing or whistling in your chest at any time **in the last 12 months**? NO YES

IF 'NO' GO TO QUESTION 2 IF 'YES' GO TO QUESTION 1.1

1.1 Have you been at all breathless when the wheezing noise was present? NO YES

1.2 Have you had this wheezing or whistling when you did not have a cold? NO YES

2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months**? NO YES

3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months**?

NO YES

4. Have you been woken by an attack of coughing at any time **in the last 12 months?** NO YES

5. Do you bring up phlegm from your chest on most days for as much as three months each year? NO YES

6. Have you **ever** had asthma? NO YES

IF 'NO' GO TO QUESTION 7 ***IF 'YES' GO TO QUESTION 6.1***

6.1 How old were you when you had your first attack of asthma? (If unsure, give your best guess!) YEARS

6.2 Have you **ever** been hospitalised with asthma?

NO YES

6.3 Have you had an attack of asthma **in the last 12 months?** NO ☐ YES ☐

6.4 Are you **currently** taking any medicine (including inhalers, aerosols or tablets) for **asthma?** NO ☐ YES ☐

7. Do you have any nasal allergies including hay fever? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 8 ***IF 'YES' GO TO QUESTION 7.1***

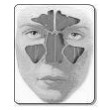
7.1 Have you been troubled by nasal allergies **in the last 12 months?** NO ☐ YES ☐

7.2 Have you ever been troubled by nasal allergies for **more than 4 days in any one week**? NO ☐ YES ☐

7.3 If yes did this happen for **more than 4 weeks continuously?** NO ☐ YES ☐

8. Has your nose been blocked **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

9. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐



10. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

11. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

12. Has a doctor **ever** told you that you have **chronic** sinusitis? NO ☐ YES ☐

NO YES

13. Have you ever had an itchy rash that was coming and going **for at least 6 months?**

IF NO, GO TO QUESTION 14 *IF 'YES' GO TO QUESTION 13.1*

NO YES

13.1 Have you had this itchy rash **in the last 12 months**?

NO YES

13.2 Does this affect **only** your hands?

NO YES

14. Have you ever had eczema or any kind of skin allergy?

NO YES

15. Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer?

IF 'NO' GO TO QUESTION 16 *IF 'YES' GO TO QUESTION 15.1*

15.1 Please write the name of the tablet? …….....

NO YES

16. Have you ever smoked for as long as a year?

['YES' means at least one cigarette per day or one cigar per week for one year]

IF 'NO' GO TO QUESTION 17 *IF 'YES' GO TO QUESTION 16.1*

YEARS

16.1 How old were you when you started smoking?

NO YES

16.2 Have you smoked at all in the **last month**?

IF 'YES' GO TO QUESTION 16.3 *IF 'NO' GO TO 16.2.1*

YEARS

16.2.1 How old were you when you stopped smoking?

Cigarettes per day

16.3 On average how much do you (or did you) smoke?

Tick one box only!

17. Are you currently:
- **a.** employed ☐ 1.
- **b.** self-employed ☐ 2.
- **c.** unemployed ☐ 3.
- **d.** not working because of poor health ☐ 4.
- **e.** full-time house person ☐ 5.
- **f.** full-time student ☐ 6.
- **g.** retired ☐ 7.
- **h.** other ☐ 8.

18. Are you currently working:

a. As a health care worker (e.g. as a nurse, medical technician, doctor, paramedic or similar)? NO ☐ YES ☐

b. In a job that is mainly involved with any sort of cleaning? NO ☐ YES ☐

19. ADDITIONAL QUESTION 1 ☐☐☐☐☐☐☐☐

20. ADDITIONAL QUESTION 2 ☐☐☐☐☐☐☐☐

21. What is your <u>date of birth</u>? DAY ☐☐ MONTH ☐☐ YEAR **19**☐☐

22. What is <u>today's</u> date? DAY ☐☐ MONTH ☐☐ YEAR **20**☐☐

23. Are you male or female? MALE ☐ FEMALE ☐

23. What is your postcode/zip code? ☐☐☐☐☐☐☐☐

May we contact you again to help us further with this research and to provide further information? **NO** ☐ **YES** ☐

Thank you for your help!