

Prevalence, risk factors and comorbidity of rhinitis, asthma and aspirin- intolerance in West Sweden

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Ineko AB

For of him, and through him, and to him, are all things: to whom be glory forever. Amen.

Romans 11:36

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ABSTRACT

The prevalence of rhinitis and asthma has increased considerably over the past century. The cause of this increase remains unknown. Furthermore, rhinitis and asthma are now considered heterogeneous syndromes encompassing several clinical phenotypes. The overall aim of this thesis was to investigate the prevalence, risk factors and comorbidity of rhinitis and asthma phenotypes with a particular focus on aspirin-intolerant asthma.

This thesis is mainly based on a postal questionnaire with 18 087 responders (62%) living in West Sweden. The prevalence of allergic rhinitis (AR) was 20% in those raised on a farm compared to 28% in subjects raised elsewhere. A lower prevalence of AR in subjects raised on a farm was found in all age groups. The prevalence of chronic rhinitis (CR) was 20%. Both AR and CR were more common in urban than in rural areas. Cigarette smoking was associated with a high prevalence of CR and a low prevalence of AR. Both associations were dose-dependent and were found also in two large population surveys conducted in the city of Stockholm. Skin prick testing was performed on a randomly selected subsample of the West Sweden cohort. Prevalence of skin prick test positivity was significantly lower in smokers (34%) than in non-smokers (46%). Considerable overlap was found between asthma and nasal comorbidities and different nasal comorbidities were associated with different symptom expression of asthma. Prevalence of aspirin-intolerant asthma (AIA) was 0.5%. The risk of AIA increased linearly with increasing body mass index. CR was commonly found in AIA.

We conclude that AR and CR are common in the general population of West Sweden. The two rhinitis phenotypes share some, but not all, risk factors. Both conditions are associated with asthma and lower respiratory symptoms, indicating a strong relationship between the upper and lower airways. Aspirin-intolerant asthma was found in the general population as was associated with obesity and chronic rhinitis.

Keywords: epidemiology, rhinitis, asthma, aspirin-intolerance

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SAMMANFATTNING PÅ SVENSKA

Förekomsten av både rinit och astma har ökat påtagligt under det senaste seklet i många delar av världen och så även i Sverige. Orsaken till ökningen är än så länge inte klarlagd. Synen på rinit och astma har förändrats under de senaste decennierna och man ser nu på båda fenomenen som syndrom med flera subtyper med olika klinisk bild och underliggande biologi. Det övergripande syftet med den här avhandlingen var att undersöka förekomst, riskfaktorer och samsjuklighet för olika subtyper av rinit och astma med ett särskilt fokus på den aspirin-intoleranta astman.

Avhandlingen baseras främst på en omfattande postal-enkät om luftvägshälsa som 2008 skickades ut till 30 000 slumpmässigt utvalda individer i Västra Götaland, varav 18 087 svarade. Vi fann att förekomsten av allergisk rinit var betydligt lägre bland dem som växt upp på ett lantbruk (20%) än bland dem som växt upp i en annan miljö (28%). Denna skillnad visade sig finnas i alla åldrar, innefattande de allra äldsta, något som inte tidigare var känt. Förekomsten av kronisk rinit var 20% i befolkningen och 35% bland dem med allergisk rinit. Både allergisk rinit och kronisk rinit var vanligare i större bostadsorter än i små och förekomsten var än lägre på landsbygden.

Kronisk rinit var vanligare bland rökare än bland icke-rökare, medan det motsatta gällde för allergisk rinit. Dessa samband mellan rinit och rökning var dosberoende och påfanns även i två stora befolkningsstudier i Stockholm. Ett slumpmässigt urval av deltagarna i Västra Götaland-studien genomförde en omfattande klinisk undersökning innefattande bland annat pricktester. Ett positivt pricktest för vanliga luftburna allergen påfanns mer sällan bland rökare (34%) än bland icke-rökare (46%). Vi fann även att symtom från näsan är vanligt bland astmatiker och att olika typer av rinit tycks hänga samman med olika symtomuttryck och olika riskfaktormönster av astma. Förekomsten av aspirin-intolerant astma var 0,5%. Risken för aspirin-intolerant astma ökade på ett linjärt sätt med ökande BMI. Kronisk rinit, men inte allergisk rinit var klart vanligare bland dem med aspirin-intolerant astma än bland dem med annan slags astma.

Sammanfattningsvis fann vi att allergisk rinit och kronisk rinit är vanligt förekommande i befolkningen i Västra Götaland. Dessa subtyper av rinit samvarierar ofta och delar vissa riskfaktorer, men inte alla. Båda dessa tillstånd är kopplade till astma och nedre luftvägssymtom, vilket talar för att det finns en stark koppling mellan de övre och de nedre luftvägarna. Aspirin-intolerant astma var kopplat till övervikt och kronisk rinit.

LIST OF PAPERS

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

- I. Jonas Eriksson, Linda Ekerljung, Jan Lötvall, Teet Pullerits, Göran Wennergren, Eva Rönmark, Kjell Torén and Bo Lundbäck.
Growing up on a farm leads to lifelong protection against allergic rhinitis.
Allergy 2010; 65: 1397-1403.
- II. Jonas Eriksson, Linda Ekerljung, Teet Pullerits, Kenneth Holmberg, Eva Rönmark, Jan Lötvall and Bo Lundbäck.
Prevalence of chronic nasal symptoms in West Sweden: risk factors and relation to allergic rhinitis and respiratory symptoms.
International Archives of Allergy and Immunology 2011; 154: 155-63.
- III. Jonas Eriksson, Linda Ekerljung, Britt-Marie Sundblad, Jan Lötvall, Kjell Torén, Eva Rönmark, Kjell Larsson and Bo Lundbäck.
Cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men.
Allergy 2013; 68: 347-354.
- IV. Jonas Eriksson, Anders Bjerg, Jan Lötvall, Göran Wennergren, Eva Rönmark, Kjell Torén and Bo Lundbäck.
Rhinitis phenotypes correlate with different symptom presentation and risk factor patterns of asthma.
Respiratory Medicine 2011; 105: 1611-21.
- V. Jonas Eriksson, Linda Ekerljung, Jan Lötvall, Apostolos Bossios, Göran Wennergren, Eva Rönmark, Kjell Torén and Bo Lundbäck.
Aspirin-intolerant asthma in the population: prevalence and important determinants.
In manuscript

For the papers that had been published at the time of the printing of this thesis, permission was obtained from the publisher.

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ABBREVIATIONS

AIA	Aspirin-intolerant asthma
ATA	Aspirin-tolerant asthma
BMI	Body mass index
CI	Confidence interval
CRS	Chronic rhinosinusitis
EAACI	The European Academy of Allergy and Clinical Immunology
EP ³ OS	The European Position Paper on Rhinosinusitis and Nasal Polyps
FeNO	The fraction of exhaled nitric oxide
FEV ₁	Forced expiratory volume in one second
GA ² LEN	Global Allergy and Asthma European Network
GINA	Global Initiative for Asthma
IgE	Immunoglobulin E
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OLIN	Obstructive Lung Disease in Norrbotten Sweden studies
OR	Odds ratio
SOB	Shortness of breath
SPT	Skin prick test
WSAS	West Sweden Asthma Study

1 INTRODUCTION

“The eyes become extremely inflamed, and discharge very copiously a thick mucus fluid. This state of the eyes comes in paroxysms, at uncertain intervals, from about the second week in June to the middle of July. [...] To this succeeds irritation of the nose, producing sneezing, which occurs in fits of extreme violence, coming on at uncertain intervals. To the sneezings are added a farther sensation of tightness of the chest, and a difficulty of breathing, with a general irritation of the fauces and trachea. [...] The affection of the eyes is recollected to have occurred when the patient was eight years old, and there has been more or less of it every year since; the sneezings came on nearly at the same period, but the first attack of the chest was at the age of sixteen or seventeen.”[1]

This description was made in 1819 by the English physician John Bostock by reporting his own symptoms. It is known as the first clinical description of seasonal hay fever and the author also describes concurrent classic asthma symptoms. In Bostock’s days, allergic rhinitis and asthma were evidently uncommon disorders as he 9 years later had identified only 18 distinct cases despite careful investigation [2]. Today the world faces an epidemic of allergic rhinitis and asthma, but thanks to substantial progress in diagnosis and treatment, symptoms of the intensity described by Bostock are rare.

The increase of allergic diseases and asthma during the past century has led to intensified research efforts in order to elucidate the nature of the diseases and the causes of the increase. Epidemiologic and other research has generated a number of hypotheses indicating explanatory factors such as smaller family size [3], decreased intake of unpasteurized milk [4], decreased exposure to bacteria [5], changed gut flora [6], indoor and environmental air pollution [7], climate change [8], increased obesity [9] and sedentary lifestyle [10]. All these factors are associated with the concept of *westernization* and many of them are consistent with the *hygiene hypothesis*. However, current data on the associations with these factors is inconsistent, especially with respect to asthma.

One of the reasons for this inconsistency may be the heterogeneity of asthma. It is becoming increasingly obvious that asthma is not one disease, but a syndrome encompassing various *phenotypes* with different biologic correlates. Applying epidemiological methods, this investigation aims at describing the prevalence, risk factors and co-existence of rhinitis and asthma phenotypes, respiratory symptoms and aspirin intolerance.

2 BACKGROUND

2.1 Definitions of rhinitis and asthma

Rhinitis is defined as the presence of any of the following symptoms: nasal congestion, rhinorrhea (anterior or posterior), sneezing and itching of the nose [11]. Rhinitis is usually, but not always, associated with inflammation of the nasal mucosa. Rhinitis can be either infectious or non-infectious. There are several forms, or phenotypes, of non-infectious rhinitis, of which allergic rhinitis is the most common. Allergic rhinitis is characterized by IgE-mediated immune response to allergens and is often accompanied by ocular symptoms (i.e. allergic conjunctivitis) [12]. Non-allergic non-infectious rhinitis is a heterogeneous group with several subclasses such as idiopathic rhinitis (non-allergic rhinitis without eosinophilia), gustatory rhinitis, hormonal rhinitis and drug-induced rhinitis. Idiopathic rhinitis can be induced by various different triggers including irritants, cold air, exercise and others [13]. The mucosa of the paranasal sinuses is continuous with that of the nose and swelling of the mucosa surrounding the ostiae may cause sinusitis and thus result in chronic rhinosinusitis (CRS) [12]. There is to date no established consensus on the etiology of CRS. However, the main hypothesis is that the condition is caused by an inappropriate or excessive immune response to foreign agents such as microbes and fungi. Whether allergic rhinitis predisposes for CRS is still a matter of debate [14].

Asthma is a chronic disorder characterized by bronchial hyperresponsiveness and inflammation of the airways, leading to recurrent episodes of wheezing, breathlessness, chest tightness and coughing. These episodes are generally associated with variable airflow obstruction that is often reversible, either spontaneously or with treatment [15, 16]. Episodes of airflow obstruction and symptoms may be induced by allergen exposure, physical exercise, viral infections and irritants such as tobacco smoke [17-19]. In susceptible individuals, bronchial obstruction can further be induced upon ingestion of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibiting cyclooxygenase-2 (COX-2) [20]. It is becoming increasingly clear that asthma is not a single disease entity, but rather a syndrome encompassing a number of clinical phenotypes as well as biological endotypes [21-23]. Asthma is commonly divided into allergic and non-allergic asthma [24, 25]. Another frequent division is made by inflammatory subtypes [26, 27]. A well-defined phenotype of asthma is the aspirin-intolerant asthma (AIA), which is characterized by bronchial obstruction upon intake of aspirin and/or other NSAIDs and is often accompanied by CRS with nasal polyps [20, 28].

2.2 The epidemic of rhinitis and asthma

The prevalence of allergic rhinitis/hay fever has increased considerably over the past century in the westernized parts of the world including Sweden [29-35] (figure 1). In 1923, the prevalence of hay fever in the United States was estimated at 1.5% [36], increasing to 6-10% in 1960 [37] and in 1993, the prevalence of allergic rhinitis was found to be 14% in a nationwide US survey [38]. However, methodologies were different in these studies as the first study was register based, the second interview based and the third questionnaire based. This may in part explain the increase since register based studies tend to underestimate disease occurrences [39-41]. Using identical methods at different time points, the prevalence of allergic rhinitis according to medical records from Finnish conscripts was <0.1% until 1970 and then increased steadily reaching 8.9% in 2000 [30]. The very low initial prevalence in this study is probably due to substantial under-diagnosis [42], but the linear time trend indicates a true rise in prevalence. In Swedish conscripts, the prevalence of allergic rhinitis increased from 4.4% in 1971 to 8.4% in 1981 [29]. In Swedish questionnaire based studies, the prevalence of allergic rhinitis was found to be 20-27% in the 1990s [43-47] and 25-31% from 2000 onwards [31, 32, 48, 49]. Two recent Swedish studies investigating time trends of allergic rhinitis among adults indicate that the prevalence is still on the increase [31, 32]. In contrast, recent surveys from the capitals of Sweden and Finland found no or little increase in the prevalence of allergic rhinitis [49, 50]. This is in line with the international pediatric ISAAC study, which found that the prevalence of allergic rhinoconjunctivitis was increasing in some localities but in all [51, 52].

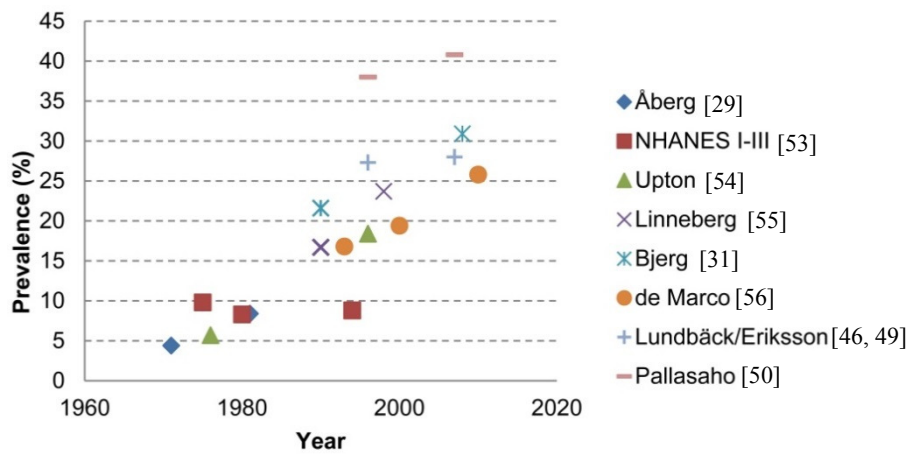


Figure 1. Prevalence trends of allergic rhinitis in adults over the past decades.

Similarly, there are numerous reports of an increase in the prevalence of asthma during the second half of the 20th century [29, 30, 57-60]. Although increased diagnostic activity and disease awareness may have contributed to the increase [40, 61], this cannot fully explain the overall increase. Furthermore, reports of parallel increases in hospital admissions for asthma [62], bronchial hyperresponsiveness [63] and symptoms common in asthma including wheeze [57-59], convincingly suggest a true increase in prevalence of asthma. Previous studies have provided no clear time trend in asthma mortality, and there seems to be large geographical differences [64-67]. In a number of Western countries, deaths from asthma increased from 1970 to 1985 with no further increase thereafter, possibly due to increasing usage of efficient asthma medication [68]. As for allergic rhinitis, recent studies indicate that the increase in asthma may be leveling off, both in children [51, 69] and in adults [31, 32, 70-72].

2.3 The hygiene hypothesis

The hygiene hypothesis was first put forward by Strachan in 1989 as a means of interpreting the finding of a trend of a decreasing prevalence of hay fever and eczema with increasing number of siblings [3]. The author hypothesized that allergic diseases were prevented by infections in early childhood and that the past century's increase in allergic diseases would be explained by declining family size, improved housing and improved personal hygiene. Subsequent investigation could confirm the negative association with family size, not only for hay fever and eczema [73, 74], but also for wheeze and allergic sensitization [74-77]. On an immunological level, it was hypothesized that a lack of early childhood infections would skew the balance between the Th1 and Th2 subsets of T lymphocytes [78] to a persistently Th2 predominant state and thus predispose for Th2-associated diseases including IgE-mediated allergic diseases [79, 80]. However, since Th1 cell-mediated autoimmune diseases are protected by infections leading to a Th1 response and atopy may be protected by parasites inducing a Th2 response, the Th1-Th2 paradigm is currently considered as an oversimplification [81, 82].

Intriguingly, researchers found no correlation between childhood respiratory infections and atopic diseases [73, 74]. Thus, it became evident that some other factor associated with family size was responsible for the trend. In 1997, an Italian study found a lower prevalence of allergic rhinitis, allergic asthma and atopic sensitization among military students seropositive for Hepatitis A, a virus with faecal-oral transmission, than among their

seronegative counterparts [83]. Furthermore, immunological research demonstrated the necessity of the intestinal flora for the induction of oral tolerance to IgE response [84]. Studies such as these indicated that orally transmitted microbes, rather than respiratory viruses, exert protection to allergy, and do so by induction of oral tolerance [85, 86]. In line with this hypothesis, a study on 2-year-old children in Sweden and Estonia found that the composition of the intestinal flora differed between allergic and non-allergic children in both countries [87]. This finding has later been reproduced in several populations [6, 88-90]. An increasing body of evidence indicates that a diverse or “balanced” intestinal microflora is beneficial for maintaining mucosal tolerance and is protective, not only against atopic diseases, but also several other inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis and diabetes type 1 [91-95]. Interestingly, there has been a parallel increase of these diseases in the Western world over the past 50 years [96].

The diversity of the intestinal microflora is lower in Western parts of the world than in more traditional environments [97]. Various factors in the Western society may affect the composition of the gut microflora, including clean water, increased Caesarean sections, increased use of antibiotics, reduced breastfeeding, smaller family sizes, increased bathing and showering and use of antibacterial soaps [98]. Hence, the modified hygiene hypothesis presents a possible explanation for the increase in allergic and autoimmune diseases seen during the past century, at least to a certain extent [10].

2.4 Rhinitis and asthma in farm environments

Although the prevalence of allergic rhinitis and asthma has increased in the Western world, the diseases remain considerably less common in some subpopulations. Particular interest has been given to farming populations [4, 99-117]. In 1999, a Swiss study on a rural population was the first to report a lower prevalence of hay fever and atopic sensitization in farmer’s children than in children to non-farmers, whereas asthma and eczema were not significantly associated [99].

Early in 2000 three studies from Germany, Austria and Finland with consistent findings were published in the same issue of *Clinical and Experimental Allergy* [100-102]. The German and Austrian studies were both performed among children and found a lower prevalence of hay fever as well as asthma in farmer’s children compared with non-farmer’s children. In

addition, in these studies the lower prevalence of atopic diseases in farmer's children appeared to be partly explained by contact with farm animals [100, 101]. The Finnish study was performed in first-year university students and found that individuals having lived on a farm during the first years in life had a lower risk of allergic rhinitis also as young adults. However, physician-diagnosed asthma was not significantly associated with a farm childhood in this study [102]. The same year a Canadian study reported a lower prevalence of asthma, allergic sensitization and airway hyperresponsiveness in adolescents raised on a farm than in those not raised on a farm [103].

While the farm effect on allergic sensitization and hay fever has been reproduced numerous times, data regarding asthma is less consistent. Some studies found no decreased risk of asthma due to farming exposure [104, 114, 118] and there are even studies reporting an increased risk [119-121]. It appears as though the positive farm effect is valid mainly for the atopic phenotype of asthma [5, 116, 117], which may be a reason for the previous inconsistency.

The European Community Respiratory Health Survey (ECRHS) found a reduced risk of allergic sensitization in subjects aged 20-44 years with a farm childhood compared with controls [104]. This indicates that the protective effect of childhood farm exposure is maintained into adulthood. In agreement with this, a study on Finnish women found that the risk of allergic sensitization was lower in subjects with both current farming exposure and childhood farming exposure than in subjects with only one of the exposures and that the highest prevalence was found in those without any farming exposure [105]. The same pattern was found for asthma in a study among farmers and non-farmers in New Zealand [106]. The New Zealand study as well as a German study found a similar pattern for allergic rhinitis, but adult exposure alone did not appear as a protective factor [106, 107]. In summary, it appears that both adult and childhood farm exposures lower the risk of allergy and asthma and that continuous exposure exerts the highest protection.

What may be the reason for the reduced risk of allergy and atopic diseases due to farming environments? Various factors have been suggested including contact with animals [101, 112], drinking of farm milk [108, 113], exposure to environmental microbes [5, 111, 117], exposure to pollens and other allergens [122] and self-selection out of farming (healthy farmer effect) [107, 109].

The healthy farmer effect may play a role for the additive protection from adult farming exposure to that of childhood exposure [107], while historical selective migration by atopic subjects out of farming environments may be one explanatory factor for the effect of childhood farm exposure, as the genetic susceptibility for atopy would gradually decrease over the generations in the farming population [109]. However, considering that farm exposures, such as animal contact and microbe exposure, appears to be protective of allergy also in farmer's children [5, 112], and that the prevalence of allergic rhinitis and asthma was very low only a few generations ago, it is unlikely that selective migration is the main explanation of the farm effect in children.

Since animal contact at an early stage was identified as an explanatory factor for the farm effect on atopy [100, 101], much research has aimed at clarifying the reason for this relationship. In line with the hygiene hypothesis several studies have found an association between exposure to bacterial components such as endotoxin and n-acetylmuramic acid and a decreased risk of asthma and wheeze [5, 111, 123-125]. In contrast, other studies have found an increased risk of asthma and wheeze by endotoxin exposure [126, 127]. Furthermore, studies have reported that the association between endotoxin exposure and wheeze and allergic sensitization, respectively, is modified by genetic variants in CD14 [128, 129], which indicates that the association between endotoxin exposure and allergy may vary between different populations.

2.5 Smoking, rhinitis and asthma

Previous population studies on the association between tobacco smoking and allergic rhinitis have provided diverse results [43, 47, 54, 130-138]. Most studies have found a lower prevalence of allergic rhinitis in smokers than in non-smokers [43, 47, 54, 130-136], but there are also reports of the opposite [137, 138]. Population-based studies on the association between smoking and chronic rhinitis are few, but have consistently found an increased risk in smokers compared to non-smokers [49, 139, 140].

Although it is well known that smoking increases lung function decline [141] and disease morbidity in subjects with asthma [142, 143], the impact of smoking on asthma development is still a matter of debate. Most cross-sectional studies have not found smoking to be associated with asthma [136, 144, 145], while ex-smoking has occasionally been associated [146, 147]. Various studies of case-referent and prospective design have reported significant associations between smoking and development of asthma in adults [39, 148-151].

2.6 The co-existence of asthma and rhinitis

The fact that asthma and rhinitis frequently coexist is not a new notion. Indeed, the first known description of hay fever from 1819 included also symptoms typical for asthma [1] and in the first published series of cases of hay fever (called *catarrhus aestivus* by the author), about half of the patients had a chest involvement of the disease [2].

The ECRHS study reported that 50-77% of European asthmatics had concomitant rhinitis, rising to 74-81% when limited to subjects with allergic asthma [152]. In contrast, a study performed in a predominantly rural area of China found that although 47% of the population were sensitized to at least one aeroallergen, only 6.5% of asthmatics had concomitant rhinitis [153]. These findings indicate that rhinitis is far less common in subjects with asthma in rural China than in populations with a Western lifestyle. A recent study from the Swedish Global Allergy and Asthma European Network (GA²LEN) study group reported that the prevalence of current asthma in rhinitis increased from 70% in 1990 to 75% in 2008 [31]. It is possible that the proportion of asthmatics with concomitant rhinitis increases with increasing westernization. However, more research focusing on time trends and geographic differences is needed to test this hypothesis.

A French study on patients consulting ENT or allergy specialists for allergic rhinitis found that asthma was present in 24% of patients with allergic rhinitis, increasing to 33% in patients with moderate/severe rhinitis [154]. Subjects were classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [155]. Of patients with allergic rhinitis consulting French general practitioners, 20% were found to have asthma [156]. In an Italian study on patients with allergic rhinitis consulting an allergy specialist the coexistence of asthma was as high as 47% [157]. In population-based studies, the prevalence of asthma in allergic rhinitis has been found to be 13% in adults [152] and 32% in children [158].

2.7 The epidemiology of aspirin-intolerant asthma

Several clinical studies based on asthma patients have aimed at measuring the prevalence of aspirin-intolerant asthma (AIA) [159-168]. Some studies have defined AIA as a positive oral aspirin challenge [164-167], while other studies have defined AIA based on medical records [163, 168] or patients' history [161, 162], respectively. A meta-analysis published in 2004 found a

mean prevalence of AIA in asthmatics determined by oral provocation testing of 21%, ranging from 6 to 50% [159]. The large variation in prevalence between studies may be explained by different methods and criteria used for determining aspirin-intolerance and different patient selection according to type of clinical setting (e.g. intensive care unit and asthma clinic).

In contrast to the clinical studies, population-based studies on AIA are very few [160, 169, 170]. A survey conducted in Finland reported a prevalence of aspirin-intolerant breathlessness of 1.2% [170]. A large Polish study found a prevalence of AIA of 0.6% [169]. In addition, an Australian study mainly based on asthma patients, measured the prevalence of AIA also in a smaller population-based sample [160]. In the population-based sample, the prevalence of AIA among asthmatics was found to be 10.9%, which corresponded to 1.1% of the total population.

2.7.1 Risk factors for aspirin-intolerant asthma

Few clinical studies have investigated risk factors for AIA. A US case-control study found a positive association between AIA and smoking and environmental tobacco smoke (ETS), respectively [171]. A Korean study found no association between AIA and obesity [172]. A study conducted in Turkey found that having a family history of aspirin hypersensitivity was a risk factor for AIA [162], which may reflect a genetic component of the disease. Consistent with this, various studies have identified associations between specific genetic polymorphisms and AIA [173-175]. There are, to the author's knowledge, no published population-based studies focusing on risk factors for AIA.

3 AIMS

The overall aim of this thesis was to study the prevalence, risk factors and co-variation of allergic rhinitis, chronic nasal symptoms, chronic rhinosinusitis and asthma, with a specific focus on the aspirin-intolerant phenotype of asthma.

3.1 Specific aims

- To investigate the risk factors of allergic rhinitis with a particular focus on childhood farm living and smoking (I, III).
- To study the prevalence of and risk factors of chronic nasal symptoms (II).
- To study the co-existence of rhinitis with respiratory symptoms and asthma (IV).
- To investigate prevalence, symptom expression and risk factors for aspirin-intolerant asthma (V).

4 METHODS

4.1 Study area and population

The studies in the thesis (I-V) are based mainly on the first part of the West Sweden Asthma Study (WSAS). Paper III also contain data from two population-based cohorts in Stockholm [176] and in paper III and V, data from the clinical part of WSAS are included. The study population of WSAS derived from the Västra Götaland County (Västra Götalandsregionen), which is situated in the southwestern part of Sweden. The county is the second largest of Sweden in terms of population, with 1 590 000 inhabitants (December 2011) and contains Sweden's second largest city, Gothenburg, located at the North Sea. The municipality of Gothenburg has a population of 520 000 inhabitants (December 2011) and a total of more than 700 000 individuals live in city and surrounding urbanized areas. Apart from Gothenburg, the county also comprises a number of small and mid-sized towns, as well as vast agricultural areas and sparsely populated woodlands.

The climate in the western part of the county is oceanic with cool summers and mild cloudy winters while the interior regions of the county experiments a hemiboreal, or cold temperate, climate. The mean annual temperature in Gothenburg in 2008 was 9.3°C (highest 30.9°C, lowest -9.4°C).

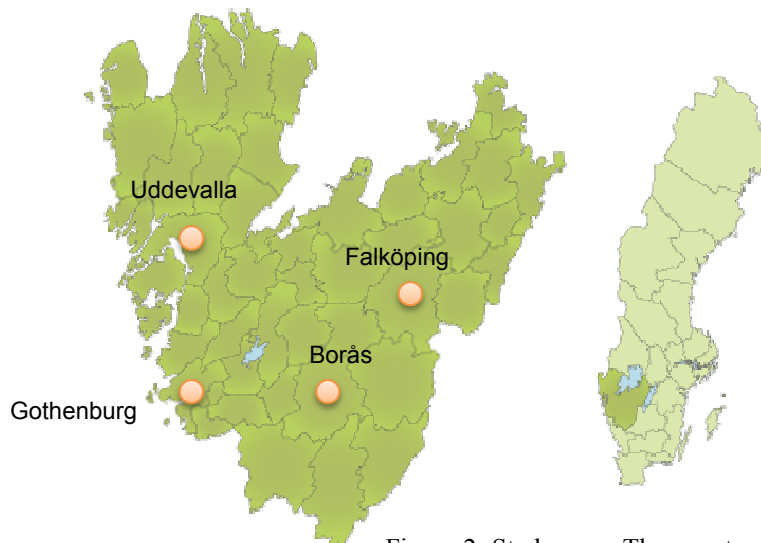


Figure 2. Study area. The county of Västra Götaland. Figure used with permission from Pantzare Information AB ©.

4.2 The West Sweden Asthma Study part I

The West Sweden Asthma Study (WSAS) was initiated as a translational and multi-disciplinary cooperation with the purpose of measuring the prevalence, determinants and co-variance of asthma, allergic rhinitis, eczema, chronic rhinosinusitis and respiratory symptoms in the adult and late adolescent population of West Sweden, and to identify eligible individuals with asthma and controls for further clinical characterization with the overall aim of investigating the heterogeneity of the asthma syndrome.

In February 2008 a postal questionnaire was mailed to 30 000 inhabitants in the Västra Götaland county, aged 16-75 years. The population was randomly selected, 15 000 from the urbanized area of Gothenburg with surroundings and 15 000 from the other parts of the Västra Götaland county. The questionnaire is further discussed below. Complete computerized randomization was applied as method of randomization. The study subjects were identified using the Swedish Population Register, which also provided the addresses. The questionnaires were mailed together with cover letters and prepaid envelopes for returning the completed questionnaires. To non-responders, three reminders were mailed. The invited subjects were also given the possibility to respond over the internet. Of the initial study sample, at least 782 were untraceable. Thus, the real study sample was 29218, of which 18087 (62%) responded. For details, please see figure 3.

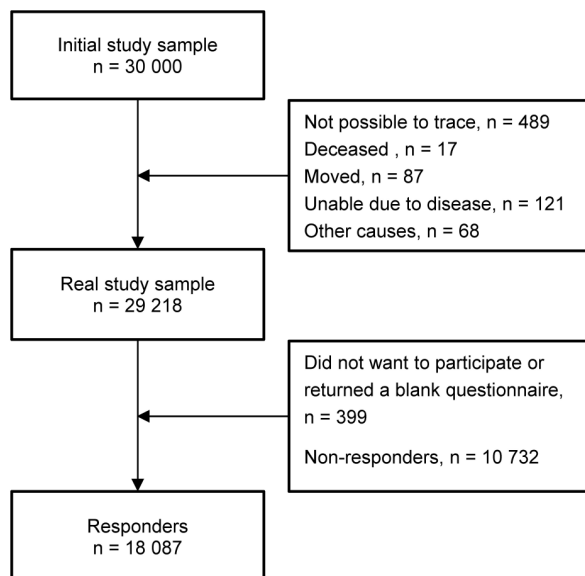


Figure 3.
Study population in
WSAS part I.

4.2.1 Questionnaire

The questionnaire consisted of three parts. The first part was a modified version of the Swedish Obstructive Lung Disease in Norrbotten (OLIN) study questionnaire [177], which is based mainly on the British Medical Research Council (BMRC) questionnaire [178] and the Tucson study questionnaire [179]. The OLIN questionnaire has been used in several studies in the Nordic countries [148, 177], and elsewhere [180]. The questionnaire has been particularly used in comparative studies on obstructive lung diseases and allergies between Finland, Estonia and Sweden [147, 181, 182], entitled the FinEsS studies. Accordingly, that version of the OLIN questionnaire is labeled the FinEsS questionnaire in Finland and Estonia. The OLIN/FinEsS questionnaire contains questions about asthma, rhinitis, chronic bronchitis/COPD/emphysema, respiratory symptoms, use of asthma medication and possible determinants of disease, such as smoking habits and family history of asthma and allergy. The second part included questions about occupation, airborne occupational and environmental exposures, health status and socio-economic status. The third part consisted of the Swedish version of the GA²LEN questionnaire [31, 183], which added detailed questions on chronic rhinosinusitis. The complete study questionnaire is included in Swedish as Appendix I, and an English translation of the current version of the OLIN questionnaire is included as Appendix II.

4.3 The West Sweden Asthma Study part II

Data from part II of the WSAS was used in Papers III and V. A random sample of 2000 participants of the questionnaire study was invited to an extensive clinical examination. In addition, we invited all those in the remaining 16087 who were identified as having asthma (please see 4.4.1 for definition of asthma) in the questionnaire study to the same examinations. The clinical examination included spirometry with reversibility testing, methacholine challenge, measurement of fraction of exhaled nitric oxide, carbon monoxide diffusion capacity and total lung capacity, skin prick testing, blood samples for specific IgE, white blood cell differential, proteomics and genetics, nasal lavage, anthropometric measurements and a structured interview. The collection of data took part between January 2009 and April 2012. Clinical examinations were carried out in four study sites in the Västra Götaland County, namely Gothenburg, Borås, Uddevalla and Falköping (figure 2).

4.3.1 Lung function

Spirometries were performed using the Masterscope equipment (Jaeger, Höchberg, Germany). Spirometers were calibrated in a standardized manner at the beginning of each working day. The test procedure followed the ATS recommendations [184]. The European Community for Coal and Steel (ECCS) reference equation was used for calculating FEV₁% predicted [185].

4.3.2 Methacholine challenge

Methacholine challenges were performed using the Spira equipment (Spira Respiratory Care Center Ltd, Hämeenlinna, Finland). The provocations followed a shortened protocol with a highest administered cumulative dose of 1.96 mg. A 20% fall in FEV₁ from baseline was considered a positive reaction.

4.3.3 Exhaled nitric oxide

The fraction of exhaled nitric oxide (FeNO) was measured using the NIOX monitoring system (Aerocrine AB, Solna, Sweden). FeNO was determined at three different flow rates, namely 50, 100 and 270 mL·s⁻¹. In this thesis, only measurements at a flow rate of 50 mL·s⁻¹ are considered.

4.3.4 Skin prick tests (SPTs)

SPTs were performed on subjects aged 60 years and younger using a standard panel of 11 common airborne allergens. Allergens included were

Dermatophagoides pteronyssinus, *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium herbarum*, dog, cat, horse, timothy, mugwort, birch (ALK, Hørsholm, Denmark) and *Blatella germanica* (Laboratorios LETI, Madrid, Spain). The tests followed the guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) with the only exception being that all skin pricks were applied to only one forearm [186]. Histamine 10 mg/mL was used as a positive control and glycerol was used as a negative control. Allergic sensitization was defined as mean wheal diameter of ≥ 3 mm measured after 15 minutes. Subjects were asked to refrain from anti-histamines for at least 72 hours prior to the visit.

4.3.5 Structured interview and anthropometric measurements

Structured interviews were conducted by trained nurses during the visit at the clinic including questions on nasal, ocular, dermal and respiratory symptoms, childhood and adult environmental exposures, asthma morbidity and asthma medication. Asthma control, as defined by the GINA guidelines [15] was also assessed. In addition, measurements were made of the subjects' height, weight and waist circumference.

4.4 Definitions

The variables of importance to this thesis are presented below. The study variables were based mainly on questionnaire reports. Synonymous definitions employed in individual papers are also given.

4.4.1 Respiratory symptoms and conditions

Allergic rhinitis – “Have you ever had allergic eye or nose problems (hay fever)?” (Labeled “*self-reported allergic rhinitis*” in Paper II.)

Nasal congestion – “Do you have nasal block more or less constantly?”

Runny nose – “Do you have a runny nose more or less constantly?”

Chronic rhinitis – report of *nasal congestion* and/or *runny nose*.

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 blockage or discharge, for more than 12 weeks during the past 12 months [187]. In paper IV, chronic rhinosinusitis was defined as at least 3 of the 4 symptoms in order to improve the specificity of the variable and reduce overlap with chronic rhinitis.

Physician-diagnosed asthma – “Have you been diagnosed as having asthma by a doctor?”

Asthma – report of (i) *physician-diagnosed asthma* or (ii) *ever asthma* with at least one of the following conditions: *current use of asthma medication, attacks of shortness of breath or any wheeze* during the past 12 months.

Aspirin-induced dyspnea - “Have you ever reacted with dyspnea within three hours after taking a pain killer?” followed by a question on which specific drug that caused the reaction. Subjects specifying a drug not containing acetylsalicylic acid or a NSAID were excluded.

Aspirin-intolerant asthma – report of both *asthma* and *aspirin-induced dyspnea* as defined above.

Attacks of shortness of breath: “Do you presently have, or have had in the last 10 years, asthma symptoms (intermittent breathlessness or attacks of shortness of breath; the symptoms may exist simultaneously with or without

cough or wheezing)?” and “Have you had these problems within the last year?”

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

Any wheeze: “Have you had wheezing or whistling in your chest at any time during the last 12 months?”

Longstanding cough: “Have you had a persisting 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 3 months per year during two subsequent years

Waking with tight chest: “Have you woken up with a sensation of chest tightness on any occasion during the last 12 months?”

Dyspnea (MRC 3): “Do you need to walk slower than other people in your age on level ground because of breathlessness?”

4.4.2 Determinants of disease

Farm childhood - “Did your family live on a farm during your first 5 years of life?” (Labeled “*raised on farm*” in Paper I.)

Degree of urbanization. Localities of residence were classed into four categories based on their number of inhabitants. Metropolitan Gothenburg, with approximately 700 000 inhabitants, was used as a separate entity, while other localities with more than 10 000 inhabitants were considered mid-sized towns (all with <100 000 inhabitants). Localities with 500–10 000 inhabitants were considered small towns and those with <500 inhabitants rural areas (<2000 inhabitants in paper I). The classification was performed by matching the subjects’ address information with official population data from Statistics Sweden [188].

Current smokers reported smoking during the year preceding the survey (labeled “*smokers*” in Paper I). *Ex-smokers* reported having stopped smoking at least 12 months prior to the survey. *Non-smokers* reported neither smoking nor ex-smoking. In paper III, current smokers were sub-grouped by mean number of cigarettes smoked per day as *light-moderate smokers* (less than 15

cigarettes per day), *heavy smokers* (15 through 24 cigarettes per day) and *very heavy smokers* (more than 24 cigarettes per day) [189].

Occupational exposure - “Have you been substantially exposed to dust, gases or fumes at work?” (Labeled “*airborne occupational exposure*” in Paper III and V.)

Family history of allergy – “Have any of your parents or siblings ever had allergic eye or nose problems (hay fever)?”

Family history of asthma – “Have any of your parents or siblings ever had asthma?”

Body mass index (BMI) was defined as the weight in kilograms divided by the height in meters squared ($\text{kg}\cdot\text{m}^{-2}$). A BMI over 30 was considered obese [190].

Several other determinants that were not investigated in this thesis were asked for in the questionnaire, including current and previous occupation, fish consumption, physical exercise, exposure to traffic exhaust and snuff usage.

4.5 Analyses and statistical methods

The quality of the data computerization from the postal survey was controlled by entering 10% of the data twice. Errors amounted 0.1-0.2% of the computerized data with only a few exceptions. Data collected in the structured interviews was entered directly into the computers. Control of logical errors have been performed on the clinical data. Regarding missing data from the postal questionnaire, a missing answer was considered a negative answer for calculations of prevalence of diseases and symptoms, while missing answers for possible determinants of disease were coded as missing and not included in the risk factor analyses.

All statistical analyses were performed using SPSS version 16.0-20.0 (IBM, Somers, NY, USA). Comparisons of proportions were tested with two-sided Fisher's exact test. A p-value of less than 0.05 was considered statistically significant. For normally distributed continuous variables, unpaired two-tailed Student's t-test was used for comparing means, while the Mann-Whitney U-test was applied for non-normally distributed variables. Mantel-Haenszel chi-squared test was used for testing for trends. Logistic regression analysis was used for univariate and multivariate risk factor calculations and results were presented as odds ratios (OR) with 95% confidence intervals.

In papers III and IV, interaction analyses were performed for testing for additive and multiplicative interactions, respectively. Suppose that variables A and B, both have an effect. The relative risk of the variables A and B can be described as OR_A and OR_B , respectively, and the combined effect of the variables as OR_{AB} . If $(OR_{AB} - 1) = (OR_A - 1) + (OR_B - 1)$, it is an additive interaction and if $OR_{AB} = OR_A * OR_B$, it is a multiplicative interaction. When two variables both have an effect, there is always an interaction that may be best described by an additive or multiplicative model.

5 RESULTS

The results of this thesis are not presented paper by paper, but according to the content. These studies focused mainly on prevalence, risk factors and comorbidity of rhinitis, asthma and respiratory symptoms. While asthma and respiratory symptoms have been extensively studied, epidemiological studies on rhinitis, particularly chronic rhinitis, are few. Regarding rhinitis, both allergic rhinitis and chronic nasal symptoms including chronic rhinosinusitis were considered. As for asthma, both the aspirin-intolerant and the aspirin-tolerant phenotypes were studied.

5.1 Prevalence and co-variation of rhinitis phenotypes (Paper I, II and IV)

The prevalence of allergic rhinitis was 26.9%, while the prevalence of chronic nasal congestion and runny nose was 14.9% and 13.1%, respectively, yielding a prevalence of chronic rhinitis of 19.8%. Using the EP³OS criteria with a minor modification (at least 3 out of 4 symptoms), the prevalence of chronic rhinosinusitis was 2.9%.

There was considerable overlap between the different nasal conditions (figure 4). Most subjects with nasal congestion (55%) also had a runny nose. Similarly, most subjects with runny nose (62%) also had nasal congestion. Almost half of subjects with chronic rhinitis (47%) reported also allergic rhinitis, while about a third of subjects with allergic rhinitis (35%) also had chronic rhinitis.

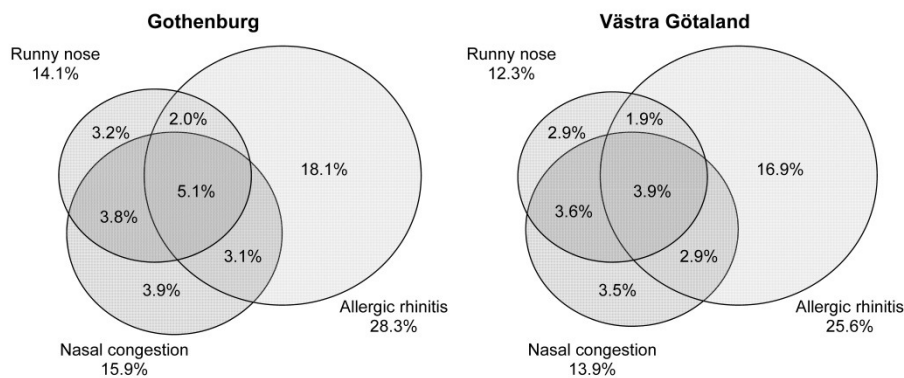


Figure 4. Venn-diagram of prevalence of allergic rhinitis, nasal congestion and runny nose in Gothenburg and the rest of the county of Västra Götaland.

5.2 Risk factors for allergic rhinitis (Paper I-III)

5.2.1 Farm childhood

A significantly lower prevalence of allergic rhinitis was found among subjects who lived on a farm during their first 5 years in life than in those that did not (20.1% *versus* 28.0%, $p < 0.001$). The lower prevalence in those living on a farm during childhood was found in both women and men. Stratifying by age into groups of 20 years each, a significant difference was found in all age groups, even among the oldest (figure 5). In addition, a lower prevalence of allergic rhinitis was found in those with a farm childhood irrespective of the degree of urbanization of their current area of domicile. The inverse association between growing up on a farm and allergic rhinitis remained when adjusting for a number of possible confounders by multiple logistic regression analysis (OR 0.8, 95% CI 0.7-0.9).

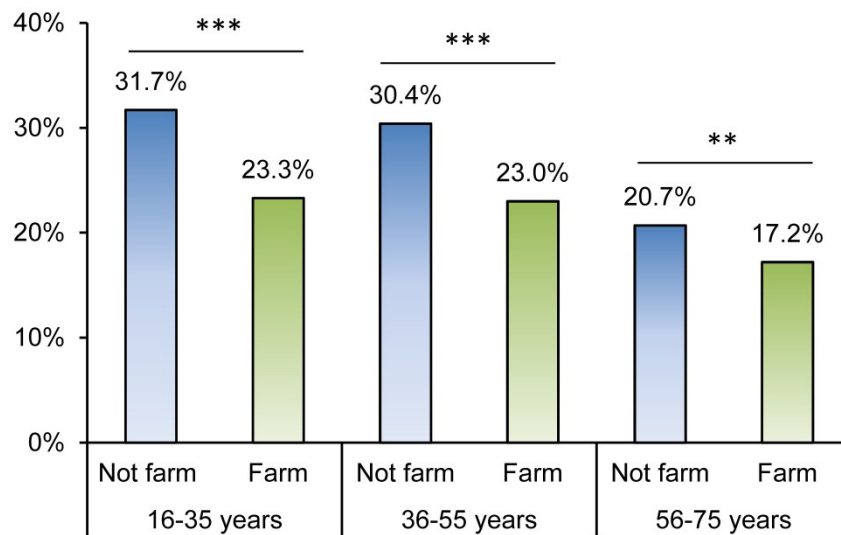


Figure 5. Prevalence of allergic rhinitis by childhood farm living and age. **: P-value < 0.01 ; ***: P-value < 0.001 .

5.2.2 Degree of urbanization

There was a linear trend of an increasing prevalence of allergic rhinitis with increasing degree of urbanization. In rural areas, the prevalence of allergic rhinitis was 22.9%, compared to 28.3% in metropolitan Gothenburg ($p < 0.001$). The trend was found in both men and women and in all ages except among the oldest (61-75 years), where prevalence was similar in all degrees of urbanization. In multiple logistic regression analysis, adjusting for several risk factors including farm childhood, there was an increased risk of allergic rhinitis in highly populated domiciles ($>10\,000$ inhabitants) as compared to rural areas.

5.2.3 Smoking

In paper I, we unexpectedly found a negative association between smoking and allergic rhinitis. The relative risk of allergic rhinitis, adjusted for a various confounders, was lower in smokers compared to non-smokers (OR 0.8). In contrast, we found in paper II that smoking was associated with a higher risk of chronic rhinorrhea and chronic nasal congestion, respectively. These associations were further studied in paper III. In order to test for external validity of the results, we performed the same analyses on data from two population-based studies conducted in Stockholm. In all three cohorts, we found that smoking was associated with a high prevalence of chronic rhinitis in both men and women and a low prevalence of allergic rhinitis in men, while the trend was non-significant in women. These associations were dose dependent and remained when adjusted for a number of possible confounders. In the subgroup that participated in the WSAS II, prevalence of allergic sensitization to pollens was lower in current smokers (25.9%, $P = 0.008$) and ex-smokers (28.2%, $P = 0.022$) than in non-smokers (38.5%), while no significant association was found between smoking and sensitization to house dust mites, furred animals or molds, respectively.

5.2.4 Other risk factors for allergic rhinitis

Family history of allergy was found to be a strong risk factor for allergic rhinitis (OR 5.6). Family history of asthma was associated with allergic rhinitis in univariate analysis, but the association disappeared when adjusting for family history of allergy. Ages 31-45 years and 46-60 years, respectively, were risk factors for allergic rhinitis, using ages 16-30 years as a reference. Visible mold at home (OR 1.2) and occupational exposure to dust, gases, and fumes (OR 1.2) were both weakly associated with allergic rhinitis. Physician-diagnosed asthma was strongly associated with allergic rhinitis (OR 5.6).

5.3 Risk factors for chronic rhinitis (Paper II–III)

Multiple logistic regression analyses were performed for nasal congestion, runny nose and chronic rhinitis (nasal congestion and/or runny nose). The risk factor pattern for nasal congestion was almost identical to that of runny nose. As for allergic rhinitis, living in a highly populated locality was associated with chronic rhinitis. Other risk factors shared with allergic rhinitis were occupational exposure to dust, gases and fumes (OR 1.7) and visible mold at home (OR 1.3).

For chronic rhinitis, an additive interaction was found between family history of allergy and family history of asthma (figure 6). Moreover, smokers and ex-smokers, respectively, were at a higher risk of chronic rhinitis than non-smokers (OR 1.4 and OR 1.2); please see 5.2.3 for further details. Water damage at home was an independent risk factor for chronic rhinitis, even when adjusted for visible mold at home (OR 1.3).

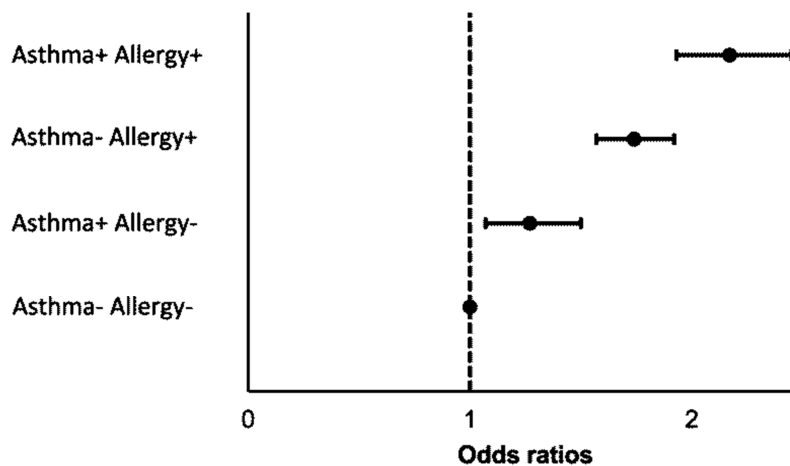


Figure 6. Risk (OR, 95% CI) of chronic rhinitis by combinations of family history of asthma (Asthma) and family history of allergy (Allergy). -: condition not present; +: condition present.

5.4 Rhinitis, lower respiratory symptoms and asthma (Paper II)

We found a strong relationship between symptoms from the upper and the lower airways, respectively. In subjects with a number of different lower respiratory symptoms including wheeze, dyspnea, cough and sputum production, the prevalence of allergic rhinitis and chronic rhinitis was markedly higher than in subjects without these symptoms. Among subjects reporting attacks of shortness of breath during the past 12 months, 60% had allergic rhinitis ($p<0.001$) and among subjects with chronic productive cough, 49.9% reported chronic rhinitis ($p<0.001$). Similarly, individuals with allergic and chronic rhinitis, respectively, reported considerably more symptoms from the lower airways.

Among subjects with physician-diagnosed asthma, 63.9% had allergic rhinitis, 39.8% had chronic rhinitis and 8.4% had chronic rhinosinusitis. All rhinitis phenotypes were markedly more common among asthmatics than in the general population. Likewise, the prevalence of physician-diagnosed asthma was 19.8% in allergic rhinitis, 16.5% in chronic rhinitis and 24.4% in chronic rhinosinusitis, which was considerably higher than in the general population. In subjects without either allergic rhinitis or chronic rhinitis, only 3.3% had a physician diagnose of asthma, while the prevalence of physician-diagnosed asthma was 22.9-25.7% among subjects with both allergic rhinitis and at least one chronic nasal symptom (figure 7).

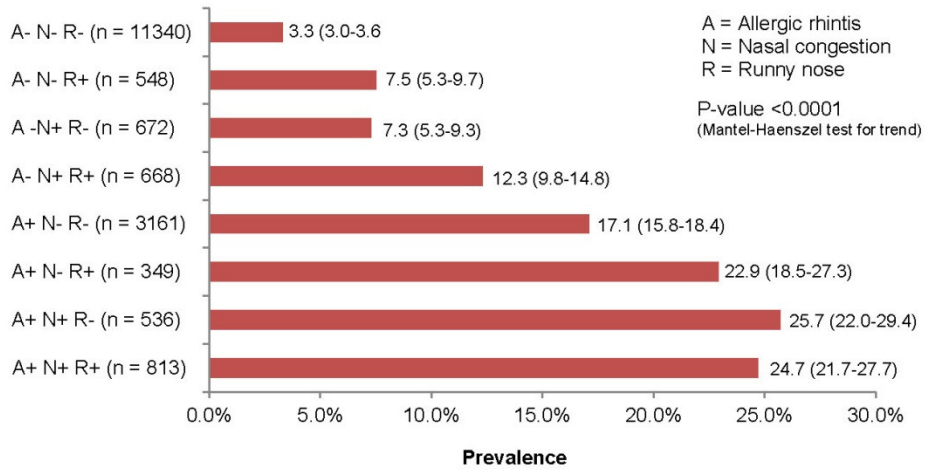


Figure 7. Prevalence of physician-diagnosed asthma in relation to allergic rhinitis, nasal congestion and runny nose with 95% confidence intervals. A indicates allergic rhinitis; N: nasal congestion; R: runny nose; -: condition not present; +: condition present.

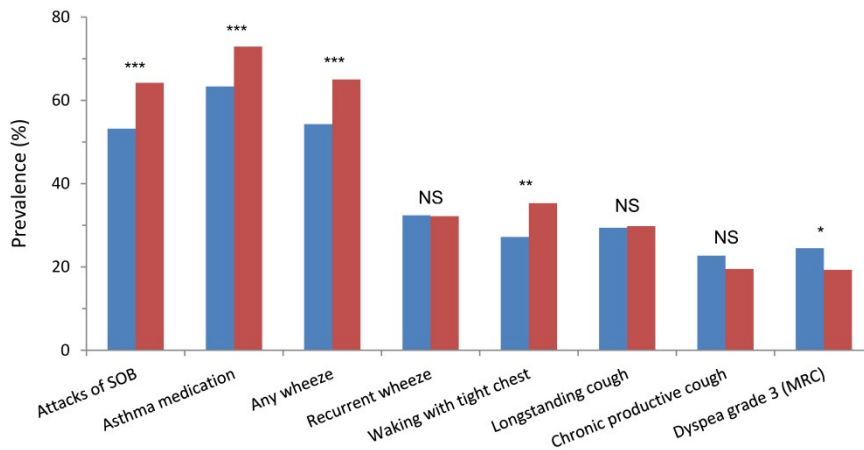


Figure 8. Prevalence of respiratory symptoms and asthma medication among physician diagnosed asthmatics with and without allergic rhinitis. ***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$; NS: not significant.

5.5 Phenotypes of asthma (Paper IV–V)

5.5.1 By nasal comorbidities

The symptom expression and risk factor patterns were investigated for asthma with concomitant allergic rhinitis, chronic rhinitis and chronic rhinosinusitis, respectively. Comparisons were made with physician-diagnosed asthmatics without these nasal conditions.

Symptom expression

Individuals with asthma and allergic rhinitis had significantly more typical asthma symptoms, such as attacks of shortness of breath, any wheeze and waking with tight chest than asthmatics without allergic rhinitis (figure 8). Subjects with asthma and concomitant chronic rhinitis and chronic rhinosinusitis, respectively, reported significantly more of all investigated respiratory symptoms, including both typical asthma symptoms and symptoms of bronchitis, such as longstanding cough, sputum production and recurrent wheeze. Subjects with asthma without any of the examined nasal conditions had significantly less lower respiratory symptoms, with exception for dyspnea grade 3 (MRC), than their counterparts with any nasal condition.

Risk factors

There were differences between the risk factor patterns of asthma with rhinitis and asthma without rhinitis. Moreover, the risk factors pattern of asthma with allergic rhinitis was different from that of asthma with chronic rhinitis and chronic rhinosinusitis, respectively. Ex-smoking was a risk factor for asthma with allergic rhinitis (OR 1.3) and asthma with chronic rhinitis (OR 1.3), while current smoking was not associated. For asthma with chronic rhinosinusitis, however, there was a trend of an increasing risk with increasing smoking exposure. Female sex was a risk factor for asthma with chronic rhinosinusitis (OR 1.7) and asthma with chronic rhinitis (OR 1.3), but not for asthma with allergic rhinitis or asthma without rhinitis.

5.5.2 By aspirin-intolerance

Individuals with current asthma were classified as having either aspirin-tolerant asthma (ATA) or aspirin-intolerant asthma (AIA) based on whether they had a history of an attack of shortness of breath after ingestion of a painkiller or not. Subjects reporting a drug not containing acetylsalicylic acid or another non-steroidal anti-inflammatory drug (NSAID) were not considered aspirin-intolerant.

Prevalence

The prevalence of AIA was found to be 0.5%, which corresponds to 5% of current asthmatics. AIA was more than twice as common in women as in men (0.6% vs. 0.3%, $p=0.014$). ATA was also more common in women than in men (9.8% vs. 8.2, $p<0.001$), but the magnitude of the difference was less. The prevalence of AIA was highest in ages 36-55 years (0.7%), whereas the highest prevalence of ATA was found in ages 16-35 years (10.8%).

Clinical characteristics

Subjects with AIA had a higher body mass index (BMI) than subjects with ATA, both when based on self-report (27.6 vs. 25.9, $p=0.002$) and when based on measurements (29.7 vs. 27.1, $p=0.001$). Compared with individuals with ATA, subjects with AIA had a higher mean neutrophil count in blood (4.55 vs. 3.83, $p=0.009$) and a lower fraction of exhaled NO (FeNO) (17.9 vs. 25.4, $p=0.042$). Chronic nasal congestion, runny nose and chronic rhinosinusitis, as defined in the the EP³OS criteria [14], were all considerably more prevalent in AIA than in ATA, while allergic rhinitis was equally common in AIA and ATA (70.6 vs. 69.6%, $p=1.00$). A considerably higher proportion of subjects with AIA reported multiple symptoms of asthma than of subjects with ATA.

Although the proportion of subjects currently using asthma medication was higher in AIA than in ATA (81.8 vs. 67.6%, $p=0.005$), uncontrolled asthma as defined in the GINA guidelines, was markedly more common in AIA than in ATA (26.7 vs. 11.2%, $p=0.018$). Furthermore, the proportion of subjects reporting emergency visits due to breathing problems was higher in AIA than in ATA (65.9 vs. 45.2%, $p=0.010$). Sick leave and having changed work due to asthma were both more common in AIA than in ATA.

Risk factors

There was a trend of an increasing prevalence of AIA with increasing BMI (p for trend <0.001). The trend remained significant when adjusting for a number of confounders by multiple logistic regression analysis (figure 9). Other significant risk factors for AIA were airborne occupational exposure (OR 2.8), visible mold at home (OR 2.6), current smoking (OR 2.6), ex-smoking (OR 2.1), female sex (OR 2.3) and family history of asthma (OR 2.1). Further, AIA was associated with both allergic rhinitis (OR 7.0) and chronic rhinosinusitis (OR 7.6).

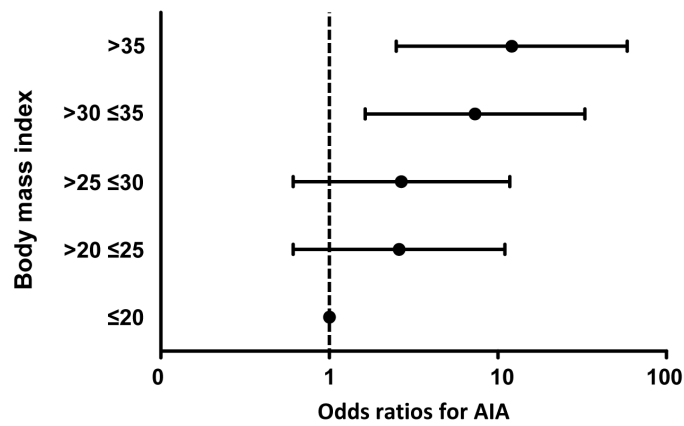


Figure 9. Risk (odds ratios with 95% confidence intervals) of aspirin-intolerant asthma (AIA) by body mass index.

Calculating risk factors for aspirin-intolerance in asthma (AIA vs. ATA), BMI >35 (OR 6.4), chronic rhinosinusitis (OR 2.9), current smoking (OR 2.7), ex-smoking (OR 1.8), visible mold at home (OR 2.1) and airborne occupational exposure (OR 2.1) were significantly associated.

6 DISCUSSION

6.1 Discussion of methodology

6.1.1 Rhinitis in epidemiology

Although rhinitis is highly prevalent in the population, its epidemiology is far less studied than that of asthma. Most studies on rhinitis have focused on seasonal allergic rhinitis or hay fever, while little is known about the epidemiology of other phenotypes of rhinitis. One of the most frequently applied methods in epidemiological studies is the use of postal questionnaires. The method is relatively inexpensive, which makes it suitable for studies with large sample sizes.

Of importance for how to better understand the epidemiology of rhinitis is the development of a standardized and well-validated method for identifying the condition. Clinical studies are able to identify only those suffering from symptoms severe enough to warrant medical attention, whereas epidemiological studies may measure the distribution of symptoms in the general population.

Rhinitis in questionnaires

The first standardized questionnaire in the field of respiratory medicine was presented by the BMRC Committee on the Aetiology of Chronic Bronchitis in 1960 [178]. Although primarily designed to measure the prevalence of chronic bronchitis, the questionnaire contained questions on hay fever and nasal catarrh. The European Coal and Steel Community questionnaire from 1967 contained the question: “Have you ever had hay fever?” [191] and so did the American Thoracic Society (ATS) questionnaire published in 1978 [192]. The International Union Against Tuberculosis (IUAT) asthma questionnaire from 1984 [193] included both a diagnostic question, “Do you have any nasal allergies, including hay fever?”, and questions about induction of symptoms of rhinitis and/or conjunctivitis at exposure for animals, feathers or dust and trees, grass, flowers and pollen, respectively. These questions were later included in the European Community Respiratory Health Survey (ECRHS) questionnaire [194]. A question on nasal allergy, similar to the IUAT question, was also included in the OLIN questionnaire from 1985 [177] and has remained in the updated versions of the questionnaire since then [46]. Questions on chronic nasal congestion and runny nose were added to the questionnaire in 2006 [49].

A standardized definition of chronic rhinosinusitis for epidemiological studies was published in the EP³OS paper in 2007 [187]. Definition of chronic rhinosinusitis was: the presence of two or more of the symptoms: nasal blockage, nasal discharge, facial pain/pressure and reduction in sense of smell, for >12 weeks in the past year with at least one symptom being nasal blockage or discharge. Questions on these symptoms were included in the GA²LEN questionnaire together with questions on allergic rhinitis diagnose, symptoms, severity, duration and associated conjunctivitis [183]. A study comparing answers to the OLIN questionnaire and answers to corresponding questions in the GA²LEN questionnaire found a good agreement (kappa coefficient > 0.6) between the questions on allergic rhinitis, asthma, wheeze, aspirin-induced dyspnea and nasal congestion, whereas the questions on rhinorrhea yielded rather different outcomes [195].

6.1.2 Validity

The validity is the degree to which a study is unaffected by systematic errors, i.e. how well it measures what it is supposed to measure. The validity of a study is usually divided into *internal validity* and *external validity*. Internal validity is a measure of the validity of the results for the studied individuals, while external validity refers to the generalizability of the results outside that population. The major factors violating the internal validity of a study are selection bias, information bias and confounding. Each of these factors will be further discussed below.

Selection bias

Selection bias occurs when the association between exposure and disease is different for those who complete a study compared with those who are in the target population. The study population was randomly selected from the general population in West Sweden, which minimize such bias. However, since the response rate was 62% rather than 100%, self-selection bias may have occurred, i.e. that subjects with some given characteristics would be more or less prone to participate in the study. If these characteristics are associated with the outcome of the study results will be biased. A means for controlling for selection bias is by performing a study of non-response, a method commonly applied in the Nordic countries [196-198]. A study on non-responders for the WSAS questionnaire study found that differences were small between responders and non-responders in terms of disease and symptom outcomes. However, non-responders tended to be younger and were more frequently smokers [199]. As a whole, it is unlikely that selection bias has distorted the outcomes in these studies in any major way.

Information bias

Errors in the information obtained from the study subjects lead to information bias. The validity of the information acquired from a question or a measurement depends on its sensitivity and specificity. The *sensitivity* is the probability that someone who is truly exposed or diseased will be classified as such by the method. The *specificity* of the method is the probability that someone who is exposed or diseased will be classified accordingly [200]. The sensitivity and specificity of a test or a question can be measured, but only approximately, since there are no comparative methods available by which patients can be infallibly distinguished from normal subjects.

One possible way of assessing the validity of rhinitis as detected in a questionnaire is to compare the answers with the diagnoses of physicians. Using this method, a Norwegian study found that the sensitivity of the question, “Have you ever had hay fever?” was 67% and the specificity 95% [133]. Similarly to the Norwegian study, the main question on allergic rhinitis used in this thesis asked for presence of the condition regardless of current symptoms. This could imply that some positive responders would not have the condition anymore. In order to verify this we investigated the prevalence of current symptoms of rhinitis in those with allergic rhinitis. We found that 85% of subjects with report of allergic rhinitis also reported current symptoms of rhinitis (table 1, unpublished data).

Table 1. Prevalence of symptoms of rhinitis in allergic rhinitis

Symptoms of allergic rhinitis	81.0%
Nasal secretion	23.0%
Nasal congestion	10.0%
Any of the above symptoms	85.5%

Symptoms data from the GA²LEN questionnaire

Another method to validate rhinitis in questionnaires is to compare the answers with sensitization to common airborne allergens, either by skin prick tests or measurements of serum-specific IgE. In the randomly selected subsample in WSAS II we found that 81% of those with a positive response to the question on allergic rhinitis had a positive skin prick test to at least one common aeroallergen (unpublished data). In ages 16-40 years, 88% of subjects with allergic rhinitis had a positive skin prick test. However, some of those with a negative skin prick test may be sensitized to other aeroallergens than those included in the test panel. Moreover, there are studies showing that some subjects with rhinitis and a negative skin prick test have a local

production of IgE in the nasal mucosa and thus may have an allergic rhinitis [201, 202]. On the other hand, since allergic sensitization is found also in subjects without rhinitis [203], some of those with both a positive skin prick test and a report of allergic rhinitis may in fact have a non-allergic rhinitis (i.e. rhinitis symptoms not being caused by allergy).

A validation study on symptom-based CRS as defined by the EP³OS found that 62% of subjects with symptoms of CRS had a positive nasal endoscopy compared to 38% of subjects without symptoms of CRS [204]. Since we requested at least 3, instead of 2, out of 4 symptoms to define CRS, specificity is probably higher in our studies.

Questions on self-reported asthma and physician-diagnosed asthma in questionnaire studies have been validated on several occasions and in different populations [205].

To our best knowledge, there are no previous studies on the validity of aspirin-intolerant asthma as identified in a questionnaire. The golden standard for diagnosing aspirin-intolerant asthma is provocation testing with either oral or inhaled aspirin [206, 207]. In order to validate the question on aspirin-intolerant asthma, inhaled aspirin challenges were planned on a subsample of aspirin-intolerant asthmatics. However, we did not obtain approval of the study from the regional ethical committee of Gothenburg. Instead, the question was validated by telephone interviews with those having AIA. Of the 41 participants in the clinical examinations with AIA, telephone numbers were available for 39 (one diseased and one had protected identity). Of these, 27 (69%) could be reached by telephone and agreed to participate. Among the interviewed subjects, AIA could be confirmed in 19 (70%). The status of the remaining 30% remains unclear since there may be significant recall bias of past idiosyncrasies.

Confounding

A confounder is a factor that is independently associated with both the exposure and the outcome. The distortion introduced by a confounding factor can lead to either overestimation or underestimation of an effect and can even change the apparent direction of the effect [200]. Controlling for confounders may reduce bias and can be performed either by stratification or adjusted analyses. Since the questionnaire used in this thesis was extensive and included many questions on determinants, confounding could be controlled for. And owing to the large scale of the study, stratified analyses could be performed with maintained power to identify statistically significant

associations. However, bias may still have occurred by other unknown confounders that were not controlled for.

External validity

External validity is the extent to which the outcomes of a study can be generalized to people outside the studied population [200]. A prerequisite for generalizability is good internal validity. One indication that a study lacks external validity is if the sample is not representative. Our large population sample derived from geographical area well-representative for the Swedish demographic composition indicates that our results may be valid for a wider population in Sweden. Another factor important for external validity is if results can be replicated in different populations, places and time periods. The external validity of the associations between smoking and rhinitis described in Paper III is thus strengthened by the fact that the results were uniform in the three different populations.

6.1.3 Precision

The precision describes the extent to which multiple observations of identical phenomena yields identical results, i.e. the degree of non-systematic errors. The precision increases with increasing study population. Thus, the large population samples studied in this thesis grants a good reliability and allows for stratified and sub-sample analyses with maintained stability. The precision of the investigated associations in this thesis was assessed by testing for statistical significance.

6.2 Discussion of main results

In this section the most important findings of the thesis will be discussed, while a more detailed discussion is presented in each paper.

6.2.1 Prevalence and risk factors of rhinitis

In comparison to asthma, the epidemiology of rhinitis, in particular chronic rhinitis, is far less studied. We found a high prevalence of allergic rhinitis (26.9%), nasal congestion (14.9%), runny nose (13.1%) and chronic rhinitis (19.1%). Population-based studies conducted in Sweden have reported a prevalence of allergic rhinitis in adults of 19-31% [31, 43-49, 208], showing a trend of an increasing prevalence of allergic rhinitis over time (table 2). The prevalence of chronic nasal symptoms has rarely been measured and studies have made use of different definitions, which limits inter-study comparisons [47, 49, 209, 210]. However, a study from Stockholm using the same definitions as in this thesis found similar results [49].

Table 2. Prevalence of allergic rhinitis in adults in Sweden

Author	Year	Age	Number	Prevalence	Area
Björnsson et al. [43]	1990	20-44	2884	22.2%	Göteborg
		20-44	3146	22.2%	Uppsala
		20-44	3294	21.1%	Västerbotten
Montnémary et al. [44]	1992	20-59	8469	20.5%	Skåne
Larsson et al. [45]	1992	20-69	2349	18.5% (♂)	Norrbotten
		20-69	2299	20.4% (♀)	
Lundbäck [46]	1996	20-69	5698	27.3%	Stockholm
		20-69	7014	22.0%	Norrbotten
Olsson et al. [47]	1997	19-80	10680	24.0%	Stockholm
Nihlén et al. [48]	2000	28-67	4933	25.0%	Skåne
Eriksson et al. [49]	2006-2007	20-80	9792	28.0%	Stockholm
Lötvall et al. [32]	2008	16-75	8657	28.3%	Göteborg Västra Götaland
		16-75	9430	25.6%	
Bjerg et al. [31]	2008	20-44	9156	30.9%	Göteborg

Childhood farm environment

We found that living on a farm during the first 5 years of life was associated with a low prevalence of allergic rhinitis in all adult age groups including ages 60-75 years. Various studies have found a negative association between childhood farm exposure and allergic rhinitis [4, 99, 100, 104, 106, 107, 117], but no previous study has demonstrated such an association in subjects above 44 years of age. Thus, our study suggests that growing up on a farm may give lifelong protective effects against allergic rhinitis. For asthma, however, a negative association by farm childhood was found in adolescents [211], but not in adults [32], in the WSAS studies. Although allergic rhinitis was significantly less common in subjects raised on a farm in all age groups, the difference was of less magnitude in older subjects. This finding is in accordance with a study on Swedish conscripts that found that the ‘farming effect’ on allergic rhinitis was greater in subjects born in the 70s than in those born during the two preceding decades [110], as well as the ECRHS study, that found a negative association between pollen-induced rhinitis and childhood farm living in subjects born after 1961, but not in older individuals [104]. Altogether, these data suggest that the protective effect of childhood farm living on allergic rhinitis has increased over the past decades.

Urbanization

Furthermore, we found a linear association between the degree of urbanization and the prevalence of allergic rhinitis. This association could not be entirely explained by a lower proportion of subjects having been raised on a farm in the more populated localities, and is thus likely to be due also to other environmental factors. Two possibly relevant factors for the urbanization effect are traffic-related air pollution and differences in pollen exposure [122, 212, 213]. Toxicological studies have shown that diesel exhaust particles may act as carriers of antigens and increase their allergenicity in the airways [213]. However, there are few studies on the effect of traffic exposure on allergic rhinitis and their results are not consistent [212].

Smoking

In line with our results, several previous population-based studies have found a negative association between allergic rhinitis and smoking [43, 47, 54, 130-136], whereas two studies found the opposite [137, 138]. An early Norwegian study from 1990 found a trend of a decreasing risk of hay fever with increasing number of cigarettes smoked per day [133]. In line with this finding, the Dutch ECRHS group found a decreased risk of allergic rhinitis in smokers compared to never-smokers [132]. Moreover, a Swiss study from the same year found a lower prevalence of hay fever in smokers than in

nonsmokers [130]. Various subsequent cross-sectional studies have reported similar results [47, 131, 134, 136]. To the author's knowledge, the only longitudinal study on the association between smoking and allergic rhinitis is a Japanese study that demonstrated a decreased risk of developing cedar pollinosis in smokers compared to nonsmokers [135]. In contrast, two studies on adolescents, conducted in France [137] and Great Britain [138], respectively, found an increased prevalence of allergic rhinitis in smokers than in non-smokers. Apart from different study populations and methods, geographical differences in sensitization patterns to airborne allergens may also have contributed to these discrepancies. Our and other studies [214-216] have found that smoking may correlate differently to outdoor vs. indoor allergens, thus arguing that the association between smoking and allergic rhinitis would be different in areas where outdoor allergens predominate compared to areas where indoor allergens predominate.

We found a significantly lower prevalence of allergic sensitization to pollens in smokers than in non-smokers. Sensitization to furred pets was also less common in smokers, than in non-smokers, but statistical significance was not reached. Similar findings have been reported by the ECRHS and the Swedish OLIN studies [214-216]. The ECRHS found an inverse relation between smoking and sensitization to cat and grass pollen, but not to house dust mites [214, 215]. The Swedish study, which was of longitudinal design, found a decreased risk of developing allergic sensitization to pollens in smokers compared to nonsmokers, while sensitization to animals was not significantly associated [216]. Altogether, the body of evidence suggests that smoking is negatively associated with allergic sensitization to pollens. This association may be due to different pollen exposure in smokers compared to nonsmokers (e.g. smokers may spend less time outdoors than indoors and thus be less exposed to pollens) or that smoking interacts differently with pollens than with other common aeroallergens on a mechanistic level. These questions need to be elucidated in future epidemiologic and experimental studies.

Our finding of a linear association between smoking and chronic rhinitis is in line with previous studies [48, 49, 132, 139, 140]. Although studies are few, results are fairly consistent.

6.2.2 Rhinitis and asthma

Although there has been much emphasis on the connection between asthma and rhinitis recently [12], population-based studies on the comorbidity of asthma and rhinitis are few and most of them focus on asthma and allergic rhinitis without considering upper and lower respiratory symptoms [46, 131,

152, 210]. Our finding that the prevalence of allergic rhinitis in asthma was 64% is in line with a European multi-center study reporting a prevalence of 50-77% [152]. Our finding of a considerable concurrence in symptoms from the upper and lower airways further strengthens the view of an extensive interaction between nasal and bronchial disorders.

There is a common clinical observation that nasal comorbidities are associated disease severity of asthma [217, 218]. Although asthma severity is difficult to measure in questionnaire studies, the burden of lower respiratory symptoms could serve as a proxy for severity [219]. We found that asthma subjects with chronic rhinosinusitis reported considerably more respiratory symptoms than other asthmatics, thus confirming previous clinical observations.

Data on risk factors for asthma with different nasal comorbidities has not been published previously. Our finding of different risk factor patterns for asthma with allergic rhinitis, asthma with chronic rhinosinusitis and asthma free from rhinitis suggests that nasal comorbidities may be markers of different disease phenotypes of asthma.

6.2.3 Aspirin-intolerant asthma

Although a number of studies of asthma patients have sought to measure the prevalence of AIA [159-168], population-based studies on AIA are very few [160, 169, 170]. These three studies conducted in Finland, Australia and Poland, found a prevalence of AIA fairly similar that of our study (0.6%).

No previous population-based study has investigated risk factors of AIA. We found a strong and dose-dependent association between AIA and obesity. Obesity has previously been found to be associated with development of asthma [220-222] as well as with a high severity of asthma [223, 224]. We found that obesity was associated with both AIA and other asthma, although the strength of association was considerably higher for AIA. In contrast, a clinical Korean found no significant difference in BMI between patients with AIA and patients with AIA [172]. However, this study defined obesity as a BMI exceeding the 95th percentile of the controls and not according to the World Health Organization (WHO) classification [225]. Since the prevalence of obesity is considerably lower in Korea than in Sweden [226, 227], the group studied in the Korean study probably contains very few subjects with a BMI exceeding 35, which was the group that was found to be significantly associated with aspirin-intolerance in asthma in our study. Our finding of an

association between smoking and AIA is in line with a clinical study from the US [171].

Aspirin hypersensitivity has been associated with severe asthma in two large scale international studies, namely the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) and the North American Severe Asthma Research Program (SARP) studies [228]. We found a higher prevalence of various respiratory symptoms in AIA compared to other asthma, which may indicate a higher disease severity in AIA [219]. Our findings of a higher proportion of uncontrolled asthma, emergency visits and sick-leave in AIA compared to other asthma further confirm a relatively higher morbidity associated with AIA.

7 CONCLUSIONS

- There was a negative association between allergic rhinitis and childhood farm living in all ages, including ages 60-75 years. The prevalence of allergic rhinitis increased with increasing degree of urbanization. These factors were both independently associated with allergic rhinitis.
- Chronic nasal symptoms were prevalent in West Sweden and correlated to a high extent with allergic rhinitis and symptoms from the lower airways.
- Smoking was associated with a high prevalence of chronic and a low prevalence of allergic rhinitis. These associations were dose-dependent and remained significant when adjusting for a number of possible confounders.
- Symptom characteristics and risk factor patterns of asthma differed substantially with different nasal comorbidities, suggesting that nasal comorbidities may reflect different disease phenotypes of asthma.
- Obesity as well as other environmental exposures, including current smoking and visible mold at home, were associated with AIA. The association between obesity and AIA was dose-dependent and markedly stronger than for ATA.

8 FUTURE PERSPECTIVES

The western part of the world has faced a tremendous increase in rhinitis and asthma over the past century, an increase that most likely is due to environmental factors. Although modern therapeutics, in particular inhaled and nasal corticosteroids, has alleviated the burden of the diseases, they still cause significant suffering and costs for the society and the affected individuals.

The great influence of environmental factors for the development of rhinitis and asthma suggests that societal intervention aiming at primary prevention would be feasible and efficacious. In order to develop such intervention strategies, modifiable risk factors for rhinitis and asthma need to be recognized. The value of risk factor analyses in cross-sectional studies is limited, since associations do not necessarily reflect causality, but they may generate hypotheses for future research. Prospective studies render more reliable data on risk factors. While there are some prospective population studies on asthma, longitudinal studies on rhinitis are very scarce and represent an important subject for future studies.

Another factor of importance for the future is the studies of phenotypes of rhinitis and asthma. The results of this thesis and other recent studies argue that different phenotypes of rhinitis and asthma have different risk factor patterns, which in turn indicate different underlying pathophysiologic mechanisms. If rhinitis and asthma is studied as single disease entities in epidemiological studies, factors that affect only one phenotype, or affect different phenotypes in different directions, may remain undisclosed. Thus, an important scope for future research is to identify relevant phenotypes of rhinitis and asthma and develop instruments to measure these in epidemiological studies.

Of great importance for future progress in the field of asthma and allergy will be the application of translational methods, connecting epidemiology and clinical research with studies on cellular mechanisms. The role of epidemiology in such research is primarily to grant a good representativeness of the studied conditions and to provide knowledge of the distribution of important phenotypes in the population.

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APPENDIX

Appendix I – Complete postal questionnaire in Swedish

Appendix II – English translation of the OLIN questionnaire