

The epidemiology of allergic sensitization and the relation to asthma and rhinitis

The Obstructive Lung Diseases in Northern Sweden (OLIN) Studies, Thesis XIV

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To my father Siegfried Warm

"The noblest pleasure is the joy of understanding"
Leonardo da Vinci

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Abstract

Background: Allergic sensitization is the most important risk factor for asthma and rhinitis among children, adolescents and young adults. Less is known about the incidence and remission of allergic sensitization, particularly in older adults. Furthermore, it is not clear if the earlier documented increase in prevalence of allergic sensitization continues. This thesis is focused on prevalence, incidence and remission of allergic sensitization to airborne allergens among adolescents and adults as well as on time trends in prevalence among adults. Furthermore, associated risk factors and the relation of allergic sensitization to asthma and rhinitis were assessed.

Methods: In the study of children and adolescents, incidence, remission and prevalence of allergic sensitization were assessed in a cohort study of schoolchildren, aged 7-8 years (y) at baseline. In the studies of adults, incidence and remission of allergic sensitization were assessed in a randomly selected adult population sample in 1994 (n=664) aged 20-69 y, which was followed up in 2004 (n=555). Trends in prevalence of allergic sensitization were assessed by comparing two cross-sectional studies; the cohort from 1994 and another randomly selected population sample examined in 2009 (n=737). The relation of allergic sensitization to asthma and rhinitis was determined in the adult cohort in 2009. Allergic sensitization was assessed by skin prick test (SPT) with ten common airborne allergens at ages 7-8, 11-12 and 19 y in the cohort of children and in the participants \leq 60 y in the adult cohorts. Specific IgE to nine airborne allergens was analyzed in the adult cohorts in 2004 and 2009. Risk factors for allergic sensitization and variables defining respiratory disease and symptoms were assessed by questionnaires in the cohort of children and by structured interviews in the adult cohorts.

Results: The 10-year cumulative incidence of allergic sensitization among the adults from 1994 to 2004 was 5%, while remission was 32%. In both adult cohorts, the prevalence of allergic sensitization was highest among young adults, aged 20-29 y, 55% and 61% and decreased significantly with increasing age. Among children and adolescents, both incidence and persistence of allergic sensitization were high, and the prevalence of allergic sensitization increased by age from 21% at age 7-8 y to 42% at age 19 y. Multisensitization at age 19 y was strongly associated with early onset of sensitization. The prevalence of sensitization to the major specific allergens birch, timothy, cat and dog as well as multisensitization (from 40% in 1994 to 56% in 2009, $p=0.002$) increased significantly from 1994 to 2009 among

the adults. Sensitization to any allergen increased from 35% to 39%, however not significantly ($p=0.13$). A family history of allergic rhinitis was strongly and consistently associated with allergic sensitization in all ages. Male sex and urban living were significantly positively and birth order and furry animals at home in childhood were negatively associated with onset of sensitization before the age of 7-8 y, but not with onset of sensitization from 11-12y to 19 y. Young adult age and urban living were significant factors associated with allergic sensitization in adult age. Sensitization to any animal was significantly positively associated with current asthma (OR 4.80 (95% CI 2.68-8.60)), whereas both sensitization to any pollen (OR 4.25 (2.55-7.06)) and any animal (OR 3.90 (95% CI 2.31-6.58)) were associated with current allergic rhinitis. The association between allergic sensitization and allergic rhinitis was strongest in young adult age and decreased with increasing age, while asthma was similarly associated with sensitization to any animal across all adult ages. Among asthmatics, the prevalence of allergic sensitization decreased with increasing age of asthma onset.

Conclusion: Both incidence and persistence of allergic sensitization were high among children and adolescents explaining the increase in prevalence by increasing age. An inverse pattern with low incidence and high remission of allergic sensitization was seen among adults. The decrease in prevalence of allergic sensitization by increasing adult age might at least partly be explained by normal ageing and not only by an effect of year of birth (cohort effect). The significant increase in prevalence of sensitization to the specific allergens explained the significant increase in multisensitization over 15 years. A family history of allergy was the strongest and the only consistent risk factor for allergic sensitization in all ages. The prevalence of allergic sensitization decreased with increasing age of asthma onset among adult asthmatics.

Enkel sammanfattning på svenska

Bakgrund: Allergisk sensibilisering är den viktigaste riskfaktorn för astma och rinit bland barn, tonåringar och unga vuxna. Mindre är känt om incidens (uppkomst) och remission (tillbakagång) av allergisk sensibilisering i befolkningen, särskilt bland äldre. Det är vidare oklart om den tidigare dokumenterade ökningen i förekomsten av allergisk sensibilisering fortgår. Denna avhandling fokuserar på förekomst, incidens och remission av allergisk sensibilisering mot luftburna allergen bland barn, ungdomar och vuxna, samt på förändring i förekomst bland vuxna över tid. Riskfaktorer samt sambandet mellan allergisk sensibilisering och astma och rinit studerades också.

Metoder: Studierna bland barn och ungdomar baserades på en longitudinell kohortstudie som inkluderade alla barn i åldern 7-8 år i Kiruna och Luleå vid rekryteringen 1996 (n=2148). Studierna om incidens och remission bland vuxna baserades på ett slumpurval i åldern 20-69 år vid rekryteringen 1994 (n=664) och som följdes upp 2004 (n=555). Förändring av förekomst över tid studerades genom att jämföra två tvärsnittsstudier; kohorten från 1994 och ett annat jämförbart slumpurval som undersöktes 2009 (n=737). Sambandet mellan allergisk sensibilisering och astma och rinit undersöktes i kohorten från 2009. Allergisk sensibilisering undersöktes med pricktest och tio vanligt förekommande luftburna allergen vid åldrarna 7-8, 11-12 och 19 år i barnkohorten och bland individer ≤ 60 år i vuxenkohorterna. Information om potentiella riskfaktorer samt luftvägssymtom, astma och rinit insamlades genom föräldravesvarade enkäter i barnkohorten och genom strukturerade intervjuer bland de vuxna.

Resultat: Den kumulativa incidensen av allergisk sensibilisering bland vuxna under 10-årsperioden 1994 till 2004 var 5% medan remissionen var 32%. I de båda vuxenkohorterna var allergisk sensibilisering vanligast bland vuxna mellan 20-29 år, 55% respektive 61%, och minskade med stigande ålder. Bland barn och ungdomar var både incidens och kvarstående sensibilisering vanligt och andelen med allergisk sensibilisering ökade från 21% vid 7-8 år till 42% vid 19 år. Multisensibilisering vid 19 år var starkt associerat till tidig debut av allergisk sensibilisering. Sensibilisering bland vuxna mot de vanligaste allergenen björk, timotej, katt och hund samt multisensibilisering (från 40% år 1994 till 56% år 2009, $p=0.002$) ökade signifikant mellan åren 2004 till 2009. Ökningen av sensibilisering mot något allergen från 35% till 39% var dock inte signifikant ($p=0.13$). Allergi (rinit) i familjen var starkt och konsistent relaterat till allergisk sensibilisering i alla åldrar. Manligt kön och urbant boende under första

levnadsåret var signifikanta riskfaktorer för sensibilisering före 7-8 års ålder, och ett signifikant negativt samband fanns med födelseordning och att ha pälsdjur i hemmet. Dessa faktorer minskade i betydelse och var inte signifikanta för incidens av allergisk sensibilisering mellan 11-12 och 19 år. Ung ålder och urbant boende var signifikanta riskfaktorer för sensibilisering bland vuxna. Allergisk sensibilisering mot pälsdjur var associerat till astma (OR 4.80 (95% CI 2.68-8.60)), medan sensibilisering mot både pollen (OR 4.25 (2.55-7.06)) och djur (OR 3.90 (95% CI 2.31-6.58)) var associerat till allergisk rinit. Sambandet mellan allergisk sensibilisering och allergisk rinit var starkast bland unga vuxna och minskade med stigande ålder, medan sambandet mellan sensibilisering och astma var lika starkt i alla åldrar. Bland vuxna individer med astma minskade andelen sensibiliserade med åldern för astmadebut.

Sammanfattning: Den höga incidensen och kvarstående allergisk sensibilisering bland barn och tonåringar förklarar den ökade andelen med sensibilisering med stigande ålder. Bland vuxna fanns ett motsatt mönster med låg incidens och hög remission. Minskningen av allergisk sensibilisering med stigande ålder bland vuxna förklaras därför delvis av ett naturligt åldrande och inte enbart av vilket år man är född (kohorteffekt). Den signifikanta ökningen av allergisk sensibilisering mot enskilda allergen förklarar den ökning av multisensibilisering som skett från 1994 till 2009. Allergi i familjen var den starkaste och enda konsistenta riskfaktorn i alla åldrar. Allergisk sensibilisering bland individer med astma var associerat med tidig ålder för astmadebut.

Abbreviations

BAMSE	Barn Astma Miljö Stockholm
CAPS	Childhood Asthma Prevention Study
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECRHS	European Community Respiratory Health Survey
FinEsS	The Finland, Estonia and Sweden studies
GA2LEN	Global Allergy and Asthma European Network
IgE	Immunoglobuline E
ISAAC	International Studies of Asthma and Allergies in Childhood
IUATLD	International Union against Tuberculosis and Lung Disease
MAS	Multicentre Allergy Study
NHANES	National Health and Nutrition Examination Survey
OLIN	Obstructive Lung Disease in Northern Sweden studies
OR	Odds ratio
OSAS	Obstructive sleep apnea syndrome
PAF	Population attributable fraction
PM	Particulate matter
RR	Relative risk
SAPALDIA	Swiss Study on Air Pollution and Lung Disease in Adults
SPT	Skin prick test
UK	United Kingdom
USA	United States of America

Original Papers

- I **Warm K**, Backman H, Lindberg A, Lundbäck B, Rönmark E. Low Incidence and high remission of allergic sensitization among adults. *J Allergy Clin Immunol* 2012;129:136-42.
- II Rönmark E, **Warm K**, Bjerg A, Backman H, Hedman L, Lundbäck B. High incidence and persistence of allergic sensitization to airborne allergens in a population-based cohort followed from age 7 to 19 years – Report from the Obstructive Lung Disease in Northern Sweden (OLIN) Studies. (in manuscript)
- III **Warm K**, Lindberg A, Lundbäck B, Rönmark E. Increase in sensitization to common airborne allergens among adults – two population-based studies 15 years apart. *Allergy Asthma Clin Immunol* 2013;9:20
- IV **Warm K**, Hedman L, Lindberg A, Lötvall J, Lundbäck B, Rönmark E. Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma. *J Allergy Clin Immunol* 2015 (E-pub ahead of print)

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Introduction

In 1906, the Austrian paediatrician Clemens von Pirquet debated the terms “immunity” and “supersensitivity” as followed (1):

“The vaccinated person behaves to vaccine lymph, the syphilitic towards the virus of syphilis, the tuberculous patient towards tuberculin, the person injected with serum towards the serum, in a different manner from him who has not previously been in contact with such an agent. Yet he is not insensitive to it. We can only say of him that his power to react has undergone a change.

For this general concept of a changed reactivity I propose the term “Allergy”. “Allos” implies deviation from the original state, from the behavior of the normal individual, as it is used in the words Allorhythmia, Allotropism.”

This was the first time the term “allergy” was mentioned in a scientific medical journal. Only a few years later in 1921, Prausnitz and Kustner provoked a local skin reaction by injecting subcutaneously a non-allergic individual with serum of an allergic individual (2). This method was further developed and is known as the skin prick test (SPT), commonly used in the diagnosis of atopic diseases.

Finally, in the late 1960s, both Ishizaka et al in the USA and Johansson together with Bennich in Sweden identified Immunoglobuline E (IgE) as the responsible antibody for the allergic type-1-reaction (3). Furthermore, Johansson et al linked IgE to asthma and atopic dermatitis, as raised levels of IgE were found in patients with these conditions (4). Both the SPT and the detection of specific IgE-antibodies have become important tools for the assessment of allergic sensitization not only in the clinical setting, but also in epidemiological research.

In the second half of the 20th century, respiratory allergic diseases gained importance as a major public-health issue, particularly in the industrialized part of the world (5-8). The prevalence of asthma among adults from 18 to 44 years in Europe has been estimated at 5% (9).

Especially among children, adolescents and young adults, allergic sensitization has been identified as a major risk factor for the development of asthma and allergic rhinitis (10-14). This is partly also true for the adult population (15-17). However, less data provide information on the

epidemiology of allergic sensitization in adult age. This thesis focuses therefore on the prevalence, incidence and remission of allergic sensitization to airborne allergens and its association with asthma and rhinitis in a Swedish population.

Background

Prevalence of allergic sensitization

Children and adolescents

A major risk factor for the development of asthma and allergic rhinitis among children and adolescents is the sensitization to airborne allergens (10, 14, 18, 19). The sensitization to certain specific allergens is furthermore assumed to affect the persistence of asthma from childhood into adulthood (20, 21). The assessment of allergic sensitization has therefore become important in epidemiological research to determine prevalence, incidence and also remission of respiratory allergic disease.

In the second half of the past century, a high prevalence of allergic sensitization in childhood and adolescence has been reported not only in Sweden (22, 23), but also in westernized countries worldwide (7, 24-27). In the 1990s, the prevalence of allergic sensitization was observed between 20-27% among Swedish primary schoolchildren (22, 23). A prevalence of similar magnitude was reported from Western Germany (7) while a clearly higher prevalence was observed in the Australian CAPS study with about 40% (26). The British Isle of Wight study found a prevalence of 23% in 4-year-old children (24).

In the beginning of the 21st century, the increase in prevalence of allergic sensitization might at least partly have levelled off (26, 28, 29). However, several studies report an ongoing increase (30-32). In Northern Sweden, the prevalence of sensitization to at least one airborne allergen among 7-8 year old children increased from 21% in 1996 to 30% in 2006 (31). The large international ISAAC II study reported a high prevalence of allergic sensitization with 58% in Italy, 57% in New Zealand and 44% in the UK (33).

Adults

Epidemiological data on the prevalence of allergic sensitization among adults assessed by objective clinical methods is rarer in comparison to children and adolescents. There are few Swedish studies on the prevalence of allergic sensitization among adults (34, 35). During the 1990s, the prevalence ranged between 34 to 37% in a cohort of young adults up to the age of 44.

International studies performed around the same time have found a prevalence of 23% in ages 19-78 years in Denmark and 6-10% in ages 18-59 years in Greenland (36), 21-28% in ages 18 to 69 years in Northern Norway bordering Russia (37), 33% in ages 17 to 66 years in Estonia (38), 44% from 18 to 50 years in Kuwait (39), 55-58% in ages 20 to 70 years in the Netherlands (40) and 33% at age 33 years in Great Britain (41). Studies assessing allergic sensitization in different adult ages found generally the highest prevalence in young adult age up till about 40 years (17, 36, 38, 40). The large ECRHS-I provided an overview about the wide variation in prevalence of allergic sensitization between different European countries among adults aged 20 to 44 years (42).

Studies on time trends in prevalence of allergic sensitization are scarce (43-46). In accordance to studies focusing on children and adolescents, also surveys performed among adults reported increasing trends in prevalence of allergic sensitization during the last decades of the 20th century. A Danish study, comparing the prevalence of elevated specific IgE to at least one allergen in three cross-sectional population-samples over 25 years found an increase in all adult age groups in the range from 30 to 60 years (45). These findings correspond well to the results of a Finnish study (46) and the NHANES from the USA (44).

Geographical variations in patterns of specific sensitization

Due to varying climatic and lifestyle influences, the importance of single specific airborne allergens differs by the geographical area. Also urban and rural environment within one region may cause variations in the sensitization pattern (47). The ISAAC II study also hypothesized that the impact of allergic sensitization on respiratory symptoms differs in different populations (48).

Within the USA, the over-all prevalence of allergic sensitization did not differ significantly by geographical area, although local differing sensitization patterns were found in a recent published study from the NHANES (49). Otherwise, the Tucson-study reported a dominance of sensitization to mould in Arizona (50), two studies from Virginia found the highest prevalence of sensitization to mite (51) and pets, especially cat, in Los Alamos at a higher altitude (12). Cockroach was the dominating allergen in inner-city New York (52). Within Europe, both the GA2LEN-survey and the ECRHS-I detected varying prevalence of SPT-positivity as well as different sensitization patterns between the participating countries (53, 54). Sensitization to mite reached the

highest prevalence of the tested allergens in the Netherlands, Great Britain, Ireland, France, Belgium, New Zealand and Australia whereas sensitization to pet was the dominating allergen in Sweden and Norway in the ECRHS (53). The Gal2EN-survey confirmed these patterns of distribution of the specific allergens (54). Data from Estonian centres which participate in the FinEsS-study reported that sensitization to cockroach was most common (55).

The cold and dry climate of Norrbotten, the area in which the studies included in this thesis were conducted, is the main reason for the absence of mite (56). Highest prevalence was here found for sensitization to furry animals, in particular cat and dog (13). This was confirmed by another Swedish study performed in three geographical areas including both Southern and Northern Sweden (34) and distinguishes the area from other regions where mite is the main prevalent specific allergen (57-61).

Incidence and remission of allergic sensitization

Longitudinal studies assessing the incidence and remission of allergic sensitization are rare due to the costly and time-consuming aspects of these study designs. However, important information is gained from such studies on the natural course of a disease or condition as well as on factors influencing the condition.

Children and adolescents

Studies conducted during early childhood have shown that sensitization to airborne allergens occurs after infancy up to school-age (62-65). A further increase in the development of allergic sensitization during childhood has furthermore been shown (66-68) while remission was low. However, the Tucson-study described a variation of specific sensitization during childhood as sensitization to perennial allergens typical for the area occurred preferably before six years of age in comparison to the incidence of seasonal allergens which peaked between six to eleven years (68). An Australian study reported an incidence of sensitization to any allergen assessed by SPT of about 15% between 8 and 12 years (66), comparable to results from Northern Sweden with a cumulative incidence of about 14% for the same ages (67).

Longitudinal studies assessing incidence and remission of allergic sensitization including adolescence are rare. A recently published Danish

study measured the prevalence of allergic sensitization and allergic conditions continuously in a longitudinal setting and showed an increasing prevalence of any sensitization up to young adulthood, however incidence and remission were not reported (69).

Adults

In contrast to childhood and adolescence, where a high incidence and low remission of allergic sensitization are described up to young adulthood, longitudinal studies performed among adults suggest an inverse pattern. Concerning the Swedish adult population, no previous studies calculating incidence and remission of allergic sensitization have been performed so far.

A study from Denmark assessed incidence and remission of elevated specific IgE in adults in ages 40-60 years and found an incidence of about 7% and a clearly higher remission of about 41% (70). Within the ECRHS, a larger population of younger adults between ages 20 to 44 years over a period of 7 years was examined, but no significant longitudinal changes were detected (71). An Italian study with focus on changes in SPT-reactivity over about 14 years in subjects aged between 14 and 64 years at the first examination did not calculate specific incidence and remission rates but a tendency to more incident cases was seen in the younger age group (72). However, both adolescents and adults were included in this study.

Factors influencing allergic sensitization

A large number of both genetic and environmental factors have been considered to influence the development of allergic sensitization (73, 74). The following section will provide an overview of the so far recognized most important and debated risk factors. As mentioned above, the prevalence of allergic sensitization is world-wide consistently highest in young age up to lower middle-age, why age is not discussed further in this section.

Family history of allergy

The strongest reported risk factor for allergic sensitization is a family history of allergic disease, in particular for allergic rhinitis, hypothesizing a major role of genetic influences on the development of allergic sensitization. The majority of studies among both children and adults determining risk factors

for allergic sensitization have reported high risk estimates for those having a family history of allergy (17, 24, 31, 35, 74).

Sex

Differences by sex in prevalence of allergic sensitization among adults are not as pronounced as for example in asthma where among adults female sex seems to be positively associated with both asthma prevalence (75, 76) and incidence (77-79). A higher prevalence of any sensitization is reported for male sex in several studies among both children (24, 31, 41) and adults (35, 49, 74, 80) whereas others did not detect any significant difference by sex among adults (17) or only for single specific allergens (25, 38). In contrast, a Danish study found the incidence of allergic sensitization among adults to be significantly associated with female sex (81).

Childhood environment

Several factors operating during childhood have been considered as risk factors for allergic sensitization also influencing the prevalence among adults. Sibship size, having grown up in a rural or urban environment, the presence of furry animals at home during childhood and respiratory infections have been discussed as possible determinants for the development of allergic sensitization.

Rural and farming environment in childhood

There is a strong body of evidence that growing up in a rural environment or on a farm has a protective effect against allergic rhinitis and sensitization to airborne allergens. This is also reported by several Scandinavian studies (67, 82, 83). The effect seems furthermore to continue into adulthood (84, 85). Several international studies confirm these findings (86-89). A childhood farming environment might in addition to the protective effect on allergic sensitization promote remission of allergic sensitization (90).

The reason for the negative association between allergy and rural or farm living in childhood is not clear. Exposure to livestock with its different microbial colonization (91) might play a role, though also other factors like e.g. dietary factors or exposure to endotoxin (92) might contribute (82, 93). These aspects support the so-called hygiene-hypothesis, first suggested by Strachan in 1989 (94), hypothesizing that a higher exposure to infections and

a less cleaned environment in childhood may prevent allergies. The thesis has been modified regarding several aspects through the years, however, the idea of a modulation of the immune response by the exposures mentioned above has persisted (93, 95).

Presence of furry animals during early childhood

In the middle of and the late 1990s the first studies were published reporting that exposure to furry animals at home during early childhood was protective for asthma (13, 96), a finding which contradicted the earlier belief that the presence of pets in childhood would promote asthma and allergic diseases. The result was soon supported by others (64, 80, 97) also showing a protective effect of early exposure to animals against the development of allergic rhinitis as well as allergic sensitization. However, there is some evidence supporting the hypothesis that the protective effect on allergic sensitization is restrained to specific pets and specific sensitization and covariates with other factors such as a family history of allergy, and the number of pets in the society correlates with the prevalence of allergic sensitization on a population-level (98). It has been hypothesized that presence of pets in a household induces tolerance for these animals (99, 100). There are also some studies suggesting the opposite, that the presence of pets in the home during early childhood might in fact increase the risk for allergic sensitization (101, 102). A Norwegian study found neither a risk nor a protective effect of pet ownership in early life for allergic rhinitis or asthma among children in ages 6 to 11 years (103).

Number of siblings

Having several siblings has been shown to be negatively associated with allergic sensitization, at first by Strachan et al (94), then also by others (31, 74, 80, 96, 104). Also birth order among siblings plays a role as the presence of older siblings was found to provide a protective effect against SPT-positivity (41, 105). The findings conform to the hygiene hypothesis as several siblings might imply a higher exposure to respiratory infections, which has been suggested to have a preventive effect against allergies (106, 107).

Urbanization and air pollution

Several birth-cohort studies have addressed the possible influence of air pollution on the onset of allergic sensitization in children (108-110). During the first years of life, both the developing immune system and lungs are assumed to be more vulnerable to environmental influences like e.g. traffic-related air pollutants. A German study conducted among 6-year-old children found strong associations between particulate matter from diesel exhaust and sensitization to pollen (108). This was partly confirmed by results of the Swedish BAMSE-study where sensitization to pollen was strongly associated with particulate matter at the age of 4, but no further increase of this risk in the following years of age was observed (109).

Few studies of similar type have so far been conducted among adults. In line with studies performed among children, the Swiss SAPALDIA-study found that sensitization to pollen, but not allergic rhinitis, was positively associated with living nearby main roads (111). Data from the German Health Survey, where traffic at residential address was used as a surrogate for exposure to air pollution, showed no association between traffic-related pollutants and allergic sensitization (112). A study from the ECRHS, however, found only weak and not significant associations between allergic sensitization and single air pollutants (113).

It has been suggested that in particular sensitization to pollen seems to be affected by air pollutants (114-117). The allergenicity of pollen might be increased by traffic-related air pollutants promoting the allergen release from the pollen (114, 115), a hypothesis recently supported by a German study focusing especially on the allergenic effect of ozone on birch pollen (118).

Smoking

Data on the effect of smoking on allergic sensitization are inconsistent both concerning environmental tobacco smoke as well as active own smoking. The potential influence of environmental tobacco smoke on allergic sensitization has been addressed by several cohort studies among especially children and adolescents. Maternal smoking and even smoking during pregnancy (41) has been shown to be negatively associated with allergic sensitization among children, both when assessed by SPT (41, 80, 119) and by specific IgE (120). Also the prevalence of atopic disorders such as allergic rhinconjunctivitis and asthma with an allergic component might be reduced among children of

smoking parents as well as among adult smokers themselves (121-123). Within the OLIN-studies, maternal smoking was not associated with allergic sensitization, but was, however, a risk factor for asthma among children (22).

However, other findings contradict these results. A German study reported a higher risk for developing specific sensitization against mite in genetically predisposed children when exposed to environmental tobacco smoke (124), a result partly confirmed by others (125). Results from the Swedish BAMSE study suggest that the risk of having elevated specific IgE levels is increased when being exposed to parental smoking during early childhood (126). Moreover, both smoking during pregnancy and parental smoking during childhood seem to at least partly be responsible for more respiratory symptoms and reduced lung function in young adulthood (127).

The influence of own smoking shows no clear tendency neither as a protective nor promoting factor of allergic sensitization. A lower prevalence of both positive SPT responses as well as of elevated specific IgE-levels among current smokers compared to ex- and never-smokers has been shown in some studies (128-130). An Italian study showed no significant association between allergic sensitization and smoking (129). Data from the ECRHS found a positive association only between sensitization to some specific allergens like grass and cat, but not mite which in contrary showed an inverse association (131). The West Sweden Asthma Study reported a negative association between smoking and allergic rhinitis among men (123), suggesting that gender differences influence the association between smoking and allergic sensitization.

The mechanisms behind the effect of smoking on the development of allergic sensitization are not fully understood. Tobacco smoke has been shown to have an immune-modulating effect, probably by suppressing the activity of T-cell-response and mastcell activation (132, 133), but also a dose-response relationship with allergic airway inflammation might be important to consider (134).

Association with asthma and allergic rhinitis

Asthma prevalence and incidence are influenced by multiple factors (13, 135-137) and allergic sensitization is one of the most important determinants especially in childhood and adolescence (20, 22, 138, 139). Asthma persists to

a high degree also into adulthood if the subjects are sensitized (21, 140, 141), especially multi-sensitization is associated with adult asthma (17). Allergic rhinitis, however, has been described to increase up to young adulthood whereas it decreases again with increasing adult age (142, 143).

Only a few studies have assessed the impact of allergic sensitization among elderly asthmatics (144, 145). House dust mites and furry animals, in particular cat, are the most important allergens that influence asthma prevalence (145, 146). The proportion of elderly in the population, especially in industrialized countries is increasing due to improved health-care and higher living standards.

Single specific allergens might have a stronger impact on the modulation of the lower airways, as certain allergens show a higher capability to penetrate the respiratory epithelium (147, 148). Different sensitization patterns might therefore determine the development of allergic rhinitis and asthma, respectively (149).

The OLIN-studies

The OLIN-studies started in 1985 in the county of Norrbotten. In the beginning, the main purpose was to gain knowledge about the prevalence of obstructive lung diseases and in particular asthma in Northern Sweden among adults (150). The overall aim was to find modifiable risk factors for obstructive airway diseases in order to promote prevention. Through the following years the aims of interest expanded on further epidemiological topics such as the prevalence, incidence and remission of obstructive lung diseases and allergic sensitization and associated risk factors among children, adolescents and adults. Today the OLIN-studies comprise four lines of research: 1. asthma and allergies among adults, 2. as well as among children and adolescents, 3. COPD including also OSAS and 4. health economics. Epidemiological research methods such as cross-sectional and longitudinal study designs as well as case-reference and clinical studies are applied. The overall aim of the OLIN-studies is to increase knowledge on obstructive lung diseases and their determinants and through this contribute to the prevention of these diseases. More than 50,000 individuals in ages 7-96 years have so far participated in postal questionnaires and clinical examinations.

Aims

The overall aims of this thesis were to determine the prevalence, incidence and remission of allergic sensitization as well as factors associated with allergic sensitization. Furthermore the relationship of allergic sensitization with asthma and rhinitis was studied.

The specific aims were

- To assess incidence and remission of allergic sensitization among adults
- To assess incidence and remission of allergic sensitization from school-age to young adulthood and associated risk factors
- To determine trends in prevalence of allergic sensitization and associated risk factors among adults
- To investigate the associations of allergic sensitization with asthma, rhinitis and respiratory symptoms among adults.

Material and methods

Study area

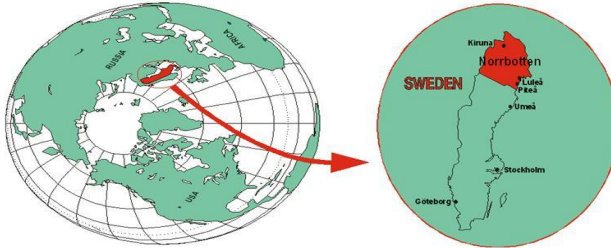


Figure 1. The county of Norrbotten (Sweden)

The county of Norrbotten is located in the Northernmost part of Sweden with an area of about 98,000 km² (Figure 1). The county is sparsely inhabited with a population size of 249,677 inhabitants in 2008. The major part of the population is living in the coastal region with the main cities Luleå and Piteå at the Gulf of Bothnia while the inland with the main communities Gällivare and Kiruna is less populated. The population includes people of mainly Swedish, but also Finnish and Sami origin. The climate is sub-arctic with an average temperature of 11 to 15 degrees in summer and -9 to -17 degrees in winter.

The area is characterized by heavy industries and its accompanying branches. Two large iron ore mines are located in the cities of Kiruna and Malmberget in central Lapland. The iron ore and steel industry as well as the paper-pulp industry have also shaped the coastal region. While these traditional industry branches have been starting to diminish during the last decades, information technology, trade, space research and tourism have gained importance.

Study design

The overall design of the studies of the adult population included in this thesis is presented in Figure 2. Two cohorts of adults have been studied.

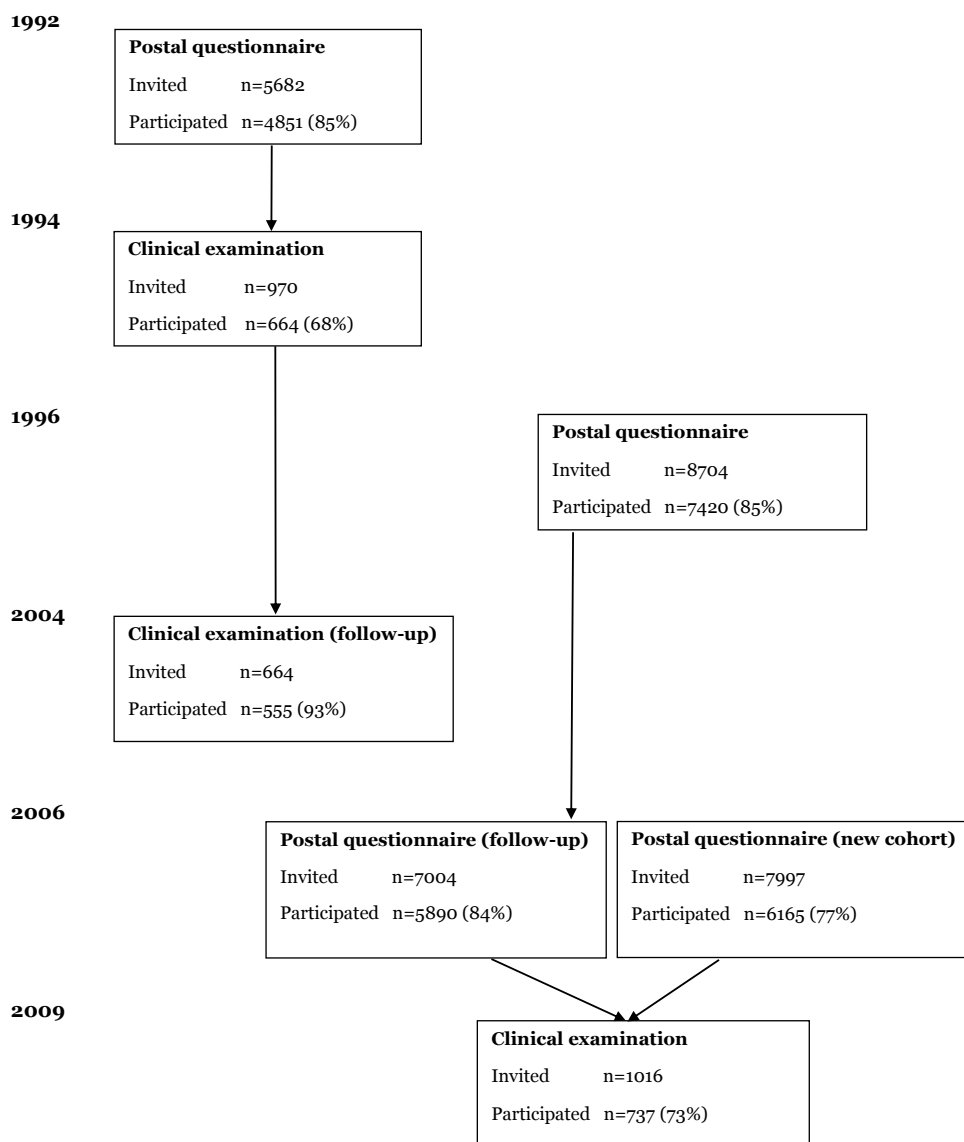


Figure 2. Study design of the adult population (Paper I, III and IV)

Adults

Paper I

The aim of this paper was to determine the incidence, remission, prevalence and associated risk factors in relation to age in an adult population. In 1992, a randomly selected population sample (n= 5682) in ages 20-69 years was invited to participate in a postal questionnaire study. Of the invited subjects, 4,851 (85%) answered the questionnaire. A randomly selected sample (n=970) of these responders was invited to participate in a clinical examination including a structured interview, skin prick test (SPT) and spirometry. The examinations took place in 1994 and 664 subjects participated (151). In general, SPT was performed only in participants in ages <61 y.

Ten years later, in 2004, the participants in these clinical examinations were invited to a re-examination using the same methods as in 1994. Additionally, blood sampling for total and specific IgE was performed this time. Of the 664 participants in 1994, 42 had died, 24 had moved from Norrbotten, 8 could not participate due to illness, 4 could not be traced and 31 subjects refused to participate. In total, 555 subjects (93% of those who were possible to invite) participated.

A more detailed age and sex distribution of the study population of the longitudinal cohort study presented in Paper I is displayed in Table 1.

Table 1. Study population and participants in skin prick test (SPT)* and bloodsampling for specific IgE in 1994 and at follow-up in 2004 (Paper I)

	Age					All
	20-29 y	30-39 y	40-49 y	50-60 y	>=61 y	
1994						
All participants	50	115	168	212	119	664
SPT performed	47 (94%)	109 (95%)	163 (97%)	181 (85%)	-	500
2004						
All participants	-	41	101	167	246	555
SPT performed	-	40 (98%)	100 (99%)	156 (93%)	-	296
Specific IgE sample	-	41 (100%)	98 (97%)	164 (98%)	246 (100%)	550

*17 participants in ages 61 and 62 y underwent SPT in 1994 and were included in the analysis

Paper III and IV

In 2006, a randomly selected population sample in ages 20-69 years (n=7,997) was invited to participate in a postal questionnaire study (152). Additionally, 7,004 subjects now in ages 30-84 years, who already had participated in a postal questionnaire study with identical questions in 1996 (153) were re-invited. In total, 12,055 subjects (5680 subjects of the follow-up, 6165 subjects of the newly recruited cohort) answered the questionnaire.

In 2009, a sample of 1,016 randomly selected subjects of the participants in the questionnaire study from 2006 were invited to participate in clinical examinations including structured interview, SPT and blood sampling for total and specific IgE.

The study described in Paper III had a cross-sectional design comparing the cohort examined clinically in 1994 to the cohort examined in 2009. The aim was to assess time trends in prevalence of allergic sensitization by comparing the two cohorts. Risk factors for allergic sensitization were assessed as well. Table 2 presents the age distribution of the study populations.

Table 2. Age distribution of the two study populations and participants in skin prick test (SPT) and blood sampling for specific IgE examined in 1994 and 2009, respectively (Paper III)

	Age					All
	20-29 y	30-39 y	40-49 y	50-60 y	>=61 y	
1994						
All participants	50	115	168	191	141	664
SPT performed	47 (94%)	109 (95%)	163(98%)	164 (86%)	-	483
2009						
All participants	57	93	142	195	250	737
SPT performed	56 (98%)	87 (94%)	135 (95%)	185 (95%)	-	463
Specific IgE sample	51 (90%)	83 (89%)	134 (94%)	182 (93%)	242 (97%)	692

In 2009, 426 subjects participated in both SPT and blood sampling for specific IgE.

Paper IV is based on the study population from 2009, however, different age categories were applied in this paper (Table 3). The aim was to study the association of allergic sensitization with asthma and allergic rhinitis in relation to age.

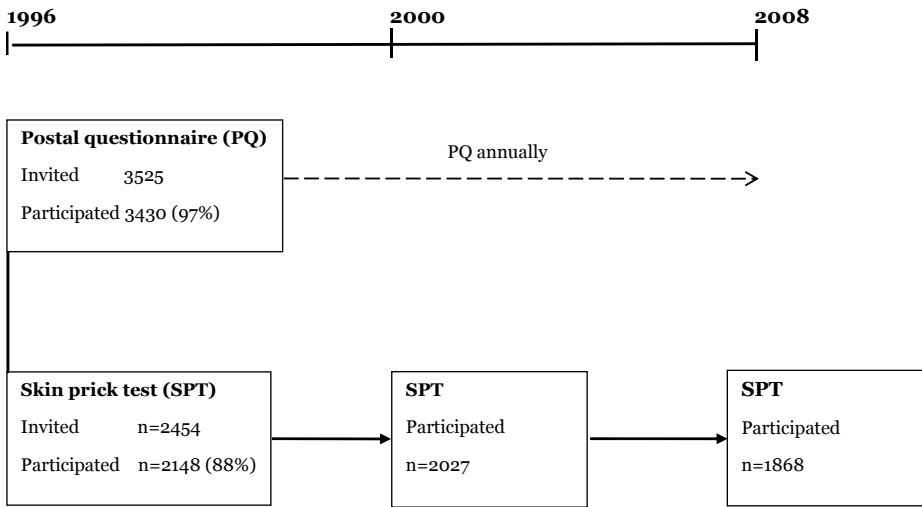
Table 3. Age distribution and participation in bloodsampling for specific IgE in 2009 (Paper IV)

	Age			All
	≤ 40 y	41-60 y	>=61 y	
All participants	171	315	251	737
Specific IgE sample	154 (90%)	259 (82%)	243 (97%)	692 (94%)

Children and adolescents

Paper II

In Paper II, incidence, remission and prevalence of allergic sensitization among children and adolescents were assessed. Additionally, the risk factor patterns for early and late onset sensitization were compared. Participants of the study in Paper II belonged to the first OLIN pediatric cohort, which was recruited in 1996 (22). At baseline the children were 7-8 years old, 3430 children participated (97% of invited). The cohort was followed annually with a questionnaire until 2008. Until the age of 11-12 years the questionnaire was answered by the parents. As the participants became adolescents, the questionnaires were completed by themselves. Furthermore, children at ages 7-8 (22), 11-12 (67) and 19 years in Luleå and Kiruna were invited to SPT. At age 7-8 years 2148 (88% of invited) participated, and 1516 subjects participated in all three SPTs. Study design and participation rates are displayed in Figure 3.



*Participants in SPT 1996, 2000 and 2008 n=1516

Figure 3. Study design of the pediatric cohort (Paper II)*

Methods

Postal questionnaire

The OLIN-questionnaire collected information on respiratory diseases such as asthma, rhinitis, chronic bronchitis and emphysema as well as respiratory symptoms including long-standing cough, wheeze, shortness of breath and sputum production. Furthermore, potentially influencing factors such as heredity for asthma and allergic rhinitis, smoking habits, socio-economic status and profession and use of asthma medication were assessed. The questionnaire was based on versions of questionnaires used by the British Medical Research Council and the American Thoracic Society (154, 155). It has been used in several national (77, 84, 156, 157) and international studies (17, 59, 158). Furthermore, the questionnaire has been externally validated against the GA2LEN-questionnaire (159).

In the study of children and adolescents, the questionnaire was based on core questions from the International Study of Asthma and Allergy in Childhood (ISAAC) (160). It was extended with further questions about respiratory

symptoms, physician-diagnosed conditions and use of medication for asthma, rhinitis and eczema as well as questions screening for possible risk factors for allergy and asthma (31).

Interview questionnaire

The questionnaire used for the structured interview in the clinical examinations of the adult population was an expanded version of the self-administered questionnaire and included also questions from the questionnaires used in the ECRHS and IUATLD (161, 162). It has been widely used in epidemiological research during the last decades (163-165). The interview questionnaire contains detailed questions on both respiratory symptoms and disease as well as on other possibly coexisting morbidities in order to more precisely assess information on debut, duration and intensity of these conditions. Additionally, detailed information on potential risk factors and influences triggering respiratory symptoms was collected.

Assessment of allergic sensitization

Skin prick test (SPT)

Both among adult participants and children skin prick test was performed to detect sensitization to specific airborne allergens. SPTs were performed according to the guidelines of the European Academy of Allergy and Clinical Immunology (166) as single-tests on one forearm with lancets and standardized solutions for the specific allergens (Solo-Prick, ALK, Denmark). A panel consisting of ten common airborne allergens was tested: birch, timothy, mugwort, cat, dog, horse, *D. Pteronyssinus*, *D. farinae*, *Cladosporium* and *Alternaria alternata*. Histamine was used as positive control and Glycerol was used for the negative control. A small number of well-trained and experienced staff performed the tests. The wheal size was calculated as the mean of the two diameters, and a wheal size of at least 3 mm was defined as a positive test. SPT data were applied for the assessment of prevalence, incidence and remission of allergic sensitization in Paper I and II and for the comparison of prevalence of allergic sensitization in Paper III.

IgE

Results of blood sampling for total and specific IgE were available for the two adult study populations, examined in 2004 and 2009, respectively. Specific IgE was analyzed for birch, timothy, mugwort, cat, dog, horse, *D. pteronyssinus*, *D. farinae* and *Alternaria alternata*. The serum samples were frozen and stored before analysis through the Immuno CAP System (ThermoFisher, Uppsala, Sweden). A positive result was defined as a level of at least 0.35 IU/ml to the specific allergen. Specific IgE was applied for the assessment of the prevalence of allergic sensitization in Paper I, III and IV.

Definitions related to allergic sensitization

Allergic sensitization was based on SPT and specific IgE, respectively.

Any SPT: at least one positive SPT reaction

Any elevated IgE: a level of IgE \geq 0.35 IU/ml to any specific allergen

Any allergen: a positive SPT reaction and level of IgE \geq 0.35 IU/ml to at least one specific allergen, respectively

Any animal: a positive SPT reaction (level of IgE \geq 0.35 IU/ml) to cat, dog or horse

Any pollen: a positive SPT reaction (level of IgE \geq 0.35 IU/ml) to birch, timothy or mugwort

Any mite: a positive SPT reaction (level of IgE \geq 0.35 IU/ml) to *D. pteronyssinus* or *D. farinae*

Any mould: a positive SPT reaction (level of IgE \geq 0.35 IU/ml) to *Cladosporium* or *Alternaria alternata*

Multi-sensitization SPT/IgE: \geq two positive SPT reactions (elevated specific IgE)

Assessment and definitions of risk factors for allergic sensitization

Adults

Factors with a potential impact on allergic sensitization were assessed by the structured interview as followed:

Urban/rural living in childhood: “Before school age, where did you live for the most part?” Alternative answers were “rural”, “suburb” or “town/city”.

Siblings: “How many siblings do you have or have had?”

Older siblings: “How many older siblings do you have or have had?”

Day-care attendance: “Did you go to a day nursery or a pre-school or spent time in an orphanage with other children for more than a year before school age?”

Furry animals in childhood: “Did you have furred animals or cage birds at your home or your close environment during the years before your school start?”

Severe airway infection in early childhood: “Did you have any severe respiratory infections before school age, for example whooping cough or croup?”

Smoking habits: “Are you a smoker, previous smoker or non-smoker?” Smokers were defined as those who had smoked at least one cigarette per day during one year. Ex-smokers were defined as those who had smoked for at least one year but not during the last 12 months.

In Paper II and III current and ex-smokers were defined as “*ever smoker*”.

Maternal/paternal smoking: “Did anyone of your parents smoke in your home during the years of your school start or before the age of six?”

Family history of allergy: Have any of your parents or siblings had allergic eye-/nose catarrh (hay fever)? (This question was included in the postal questionnaire.)

Urban living: Living in a town \geq 2000 inhabitants.

Socio-economic status was classified based on occupation defined by Statistics Sweden.

Children

Family history of allergy: Mother, father or sibling reported as having allergic rhinitis in the 1996 questionnaire

Urban living: Living in a town ≥ 2000 inhabitants at age 7-8

Birth order: First-, second-, third-born etc.

Furry animals at home: Ever having had cat or dog at home at age 7

Assessment of respiratory disease and symptoms

Paper IV describes the association between allergic sensitization and respiratory diseases and symptoms. These conditions were assessed by the interview as followed:

Physician-diagnosed asthma: “Have you been diagnosed as having asthma by a physician?”

Current asthma: “Yes” to *Physician-diagnosed asthma* or “Have you ever had asthma?” and at least one of the following questions: “Have you had wheezing or whistling in your chest at any time in the last 12 months?” or “Have you had attacks of shortness of breath at any time in the last 12 months?” or “Have you used asthma medication regularly or as needed in the last 12 months?”

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

Asthmatic wheeze: “Yes” to *Current wheeze* and “Have you been at all breathless when the wheezing noise was present?” and “Have you had this wheezing or whistling when you did not have a cold?”

Ever allergic rhinitis: “Have you or have you had allergic rhinitis or hayfever?”

Current allergic rhinitis: “Yes” to *Ever allergic rhinitis* and one of the following questions: “Have you had sneezing, runny nose or nasal congestion

without having a cold in the last 12 months?” or “Have you used medication for rhinitis in the last 12 months?”

Statistical analysis

Statistical analysis of the data reported in this thesis was carried out with the Statistical Package for the Social Sciences, versions 17.0, 18.0 and 20.0 (SPSS Inc., Chicago, Ill., USA). Chi square test was used for comparison of categorical variables, and Fisher’s exact test was applied when appropriate. The student’s t-test was performed for comparison of continuous variables. Maentel-Haenszel’s test for trend was used to assess the relationship between variables with more than two categories. In all studies included in this thesis, a p-value <0.05 was considered as statistically significant.

The cumulative incidence of allergic sensitization in Paper I was defined as cases with no positive SPT reaction in 1994 but at least one in 2004. Correspondingly, remission of allergic sensitization was defined as cases with at least one positive SPT reaction in 1994 but none in 2004. Correspondingly, incidence and remission of sensitization to the specific allergens was calculated.

In the study of children and adolescents in Paper II, calculations of incidence and remission were based on subjects participating in all three SPTs. The cumulative incidence was calculated from birth to 7-8 years, from 7-8 years to 11-12 years and from 11-12 years to 19 years for both any positive SPT reaction and a positive SPT for each of the specific allergens and allergen groups. We estimated the mean annual incidence rate by dividing the cumulative incidence with the number of observation years between each examination. The population at risk was defined as those with a negative SPT to all allergens at start of the observation period.

In order to assess the relationship between potential risk factors and allergic sensitization, multiple logistic regression analysis was performed. Factors with a significant association in bivariate analysis were included in these analysis. In the study of children and adolescents, multinomial logistic regression analysis was applied to assess risk factors for the incidence of allergic sensitization between the examinations.

For the purpose of determining the potential influence of specific allergens on asthma and allergic rhinitis in Paper IV, different models of logistic regression were applied: the allergens were included one by one in the analysis, in

another model all allergens were included. Associations calculated in all logistic regression analyses described above were expressed as Odds ratios (OR) with 95% confidence intervals (95% CIs).

Additionally, the population attributable fraction (PAF) for asthma and allergic rhinitis related to allergic sensitization was calculated in Paper IV.

Calculations were performed according to the formula:

$$PAF = P(RR - 1) / RR$$

P expresses the percentage of cases with sensitization to any allergen, RR expresses the relative risk, which in this case was expressed by the adjusted OR.

Results

The studies included in this thesis focused on the prevalence, incidence and remission of allergic sensitization among adults (Paper I and III) as well as among children and adolescents (Paper II). Risk factors for allergic sensitization were determined both among children and adolescents as well as among adults. Among children and adolescents, risk factors associated with early (before the age of 7-8 years) and late onset (between 11-12 and 19 years) of allergic sensitization were assessed. The association between allergic sensitization and respiratory symptoms, in particular asthma and rhinitis among adults was described as well (Paper IV).

Prevalence of allergic sensitization

Prevalence of allergic sensitization by age

The prevalence of allergic sensitization increased during childhood and adolescence up to young adulthood and decreased by increasing adult age (Figure 4). This age-dependent trends in prevalence were found for both sensitization to *any allergen* as well as for the allergen groups *any pollen*, including birch, timothy and mugwort, and *any animal*, including cat, dog and horse. Sensitization to mite and mould was low in all ages.

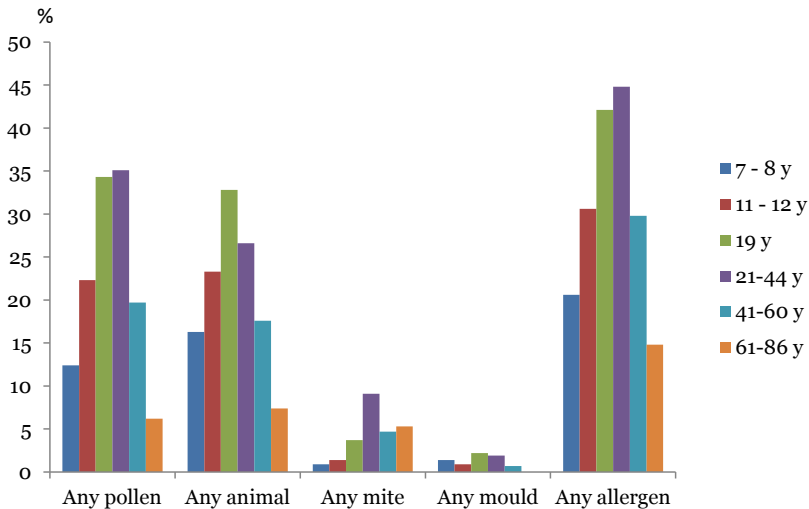


Figure 4. Prevalence of sensitization to allergen groups and any allergen by age (sensitization ≤ 19 y assessed by SPT (Paper II), sensitization > 21 years assessed by specific IgE (Paper IV))

Among children and adolescents, sensitization to *any allergen* was more common among boys. However, this difference by sex was only significant at age 11-12 years (34% among boys vs 27% among girls, $p < 0.001$) and at 19 years (46% vs 39%, $p = 0.003$). Differences by sex for the specific allergens are displayed in Paper II, Table 2. Among adults no significant differences by sex for neither sensitization to *any allergen* nor to the specific allergens were found.

Time trends in prevalence of allergic sensitization among adults

In Paper III, the prevalence of allergic sensitization, assessed by SPT, was compared in two adult cohorts examined in 1994 and 2009, respectively. A significant increase in prevalence of sensitization to the most common allergens was observed between the study years. Sensitization to cat was most common both in 1994 and 2009 and increased from 16.1% to 26.1% ($p < 0.001$), followed by dog (from 13.3% to 25.3%; $p < 0.001$), birch (from 13.3% to 18.4%; $p = 0.031$) and timothy (from 11.8% to 21.2%, $p < 0.001$).

Sensitization to *any allergen* increased from 34.6% to 39.3% between 1994 and 2009, however not significantly ($p = 0.13$). The increase in sensitization to the specific allergens resulted in a significant increase in multisensitization between the surveys. The proportion with sensitization to at least three allergens among all sensitized subjects in each study year, respectively increased from 40% to 56% ($p = 0.002$), (Paper III, Figure 2).

Blood sampling for specific IgE, performed in 2009, confirmed the sensitization pattern observed for SPT, however with a generally somewhat lower prevalence for both sensitization to the specific allergens as well as to *any allergen* (Figure 5). Significant differences between the two methods were seen for sensitization to cat (25.4% when assessed by SPT, 16.9% when assessed by specific IgE, $p = 0.002$) and dog (24.9% vs 17.8%, $p = 0.012$).

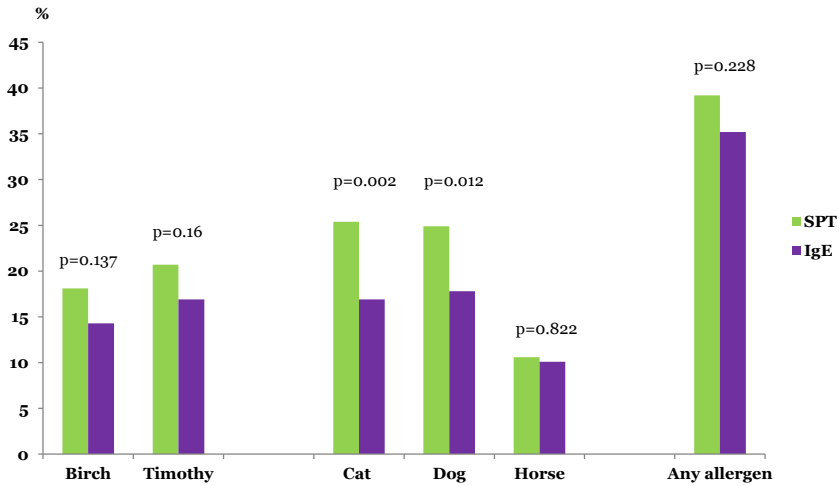


Figure 5. Comparison of prevalence [%] of allergic sensitization assessed by SPT and specific IgE among subjects (n=426) who participated in both methods

Incidence and remission of allergic sensitization

Children and adolescents

The cumulative incidence of sensitization to *any allergen* was 13.5%, yielding a mean annual incidence rate of 3.4/100/year from age 7-8 to 11-12 years. From 11-12 to 19 years, a cumulative incidence of 18% was measured while the mean annual incidence rate during this time period was 2.8/100/year (Paper II, Table 3). The incidence rate of sensitization to *any animal* was highest before the age of 7-8 years (2.2/100/year) and decreased by age (1.9/100/year from 7-8 years to 11-12 years; 1.4/100/year from 11-12 years to 19 years). The incidence rate of sensitization to pollen remained on a similar level with 1.7/100/year before the age of 7-8, 2.1/100/year from 7-8 to 11-12 years and 1.8/100/year from 11-12 to 19 years (Paper II, Table 3). Remission of sensitization was uncommon.

Additionally, multisensitization expressed as numbers of positive SPT at age 19 was associated with onset of sensitization at young age (Paper II, Figure 2).

Adults

The adult sample consisted of a random population sample in ages 20-60 years which was assessed in 1994 and followed up 10 years later in 2004 (Paper I).

The cumulative incidence of sensitization to *any allergen* during the 10-year observation period was 5% (9 of the 173 subjects with a negative SPT-response in 1994 developed sensitization). No significant sex or age differences for the incident cases were found. The cumulative incidence of sensitization to the specific allergens was highest for dog with 8.6% whereas the incidence of sensitization to the other specific allergens varied between 0.4 and 2.8%.

Remission of sensitization to *any allergen* was greater, as 32% (36 of the 112 subjects with a positive SPT response in 1994) were not sensitized when examined in 2004. Remission of specific sensitization to cat was highest with 8.5% while remission of sensitization to the other specific allergens varied from 2.6 to 4.2%.

The relationship between airway disease, respiratory symptoms and sensitization status was determined (Table 4). The group of subjects with persistent sensitization from 1994 to 2004 showed a higher prevalence of asthma, asthmatic wheeze and allergic rhinitis in 1994 compared to those who acquired sensitization during the study period, those who lost their sensitization during the study period, and those who never were sensitized. Furthermore, subjects with persistent sensitization showed a higher prevalence of multisensitization, defined as at least three positive SPT responses. Among remittent cases, monosensitization at base-line was most common, 61.6%.

Table 4. Prevalence [%] of respiratory symptoms and disease in 1994 among subjects with persistent, incident and remittent sensitization and subjects never sensitized between 1994 and 2004

Symptoms/disease 1994	Sensitization			
	Persistent	Incident	Remittent	Never sensitized
Ever asthma	25.0	11.1	5.6	3.7
Asthmatic wheeze	28.7	11.1	11.1	15.2
Ever allergic rhinitis	73.7	22.2	13.9	9.8
Sensitization 1994				
Any pollen	81.6	-	33.3	-
Any animal	61.8	-	41.7	-
Number positive SPT				
1	22.4	-	61.6	-
2	22.4	-	33.3	-
≥3	55.3	-	5.5	-

Risk factors of allergic sensitization

Factors related to the prevalence of allergic sensitization among adults

In the multivariate regression analyses, increasing age was negatively associated with any positive SPT response in both 1994 (OR 0.31 (95% CI 0.15 – 0.65) for age group 50-60 years) and 2009 (OR 0.39 (95% CI 0.20-0.77)), as well as with any elevated level of specific IgE in 2009 (OR 0.20 (95% CI 0.10-0.40) for age ≥61 years). A similar age-dependent association was found for sensitization to *any animal* and *any pollen* (Paper III, Table 3). Having a family history of allergic rhinitis was consistently and positively associated with sensitization both to *any pollen*, *any animal* and *any allergen*, regardless of study year and method of assesment of allergic sensitization (Paper I, Table IV; Paper III, Table 3).

Urban living was positively associated with both sensitization to *any pollen* (OR 1.79 (95% CI 1.06-3.03)) and *any allergen* (OR 1.54 (95% CI 1.00–2.36)) in 2009, when assessed by specific IgE. When allergic sensitization was measured by SPT, the association became only significant for sensitization to *any allergen* (OR 1.66 (95% CI 1.03-2.66)).

Multiple logistic regression analysis was also performed to determine risk factors for multisensitization in 2009 (Table 5). Belonging to the oldest age group was significantly negatively associated with multisensitization. Having a family history of allergic rhinitis was the strongest risk factor for multisensitization both when assessed by SPT and specific IgE (OR 3.89, 95% CI 2.41-6.28 and OR 3.39, 95% CI 2.13-5.41, respectively).

Table 5. Risk factors for multi-sensitization assessed by SPT and specific IgE expressed as odds ratios (OR) with 95% confidence intervals (95% CI)

Risk factor	≥2 positive SPT		≥2 elevated specific IgE	
	OR	95% CI	OR	95% CI
Male sex	1.55	0.97-2.47	1.50	0.96-2.36
Age group				
20-29 y (reference)	1	-	1	-
30-39 y	0.38	0.17-0.84	0.49	0.21-1.13
40-49 y	0.55	0.27-1.13	0.57	0.26-1.24
50-60 y	0.31	0.15-0.64	0.37	0.17-0.80
≥ 61 y	-	-	0.12	0.05-0.29
Family history of allergic rhinitis	3.89	2.41-6.28	3.39	2.13-5.41
Ever smoked	0.95	0.59-1.51	0.79	0.50-1.24
Furry animals in childhood	0.73	0.45-1.17	0.74	0.46-1.19
Urban living in childhood	1.10	0.68-1.78	0.85	0.52-1.38
Urban living	1.53	0.90-2.59	1.31	0.79-2.17

Factors related to incidence and remission of allergic sensitization

Risk factor patterns for early onset (from birth to age 7-8 years) and late onset (from age 11-12 years to 19 years) of allergic sensitization were compared in Paper II and are displayed in Figure 6. In the multinomial analysis, having a family history of allergy was significantly and consistently associated with the onset of allergic sensitization with OR 2.2 (95% CI 1.7-2.9) for early onset and with OR 1.6 (95% CI 1.1-2.2) for late onset. Male sex (OR 1.3 (95% CI 1.0-1.7)) was positively associated with early onset of allergic sensitization as well as urban living (OR 1.9 (95% CI 1.2-3.0)), but these variables lost their significance in the analysis for late onset. The birth order among siblings (OR 0.8 (95% CI 0.7-1.0)) as well as the presence of furry animals at home (OR 0.7 (95% CI 0.5-0.9)) showed a protective effect against early onset of allergic sensitization while these associations lost significance in the analysis of late onset of sensitization (OR 0.9 (95% CI 0.8-1.1) and OR 0.8 (95% CI 0.5-1.1), respectively).

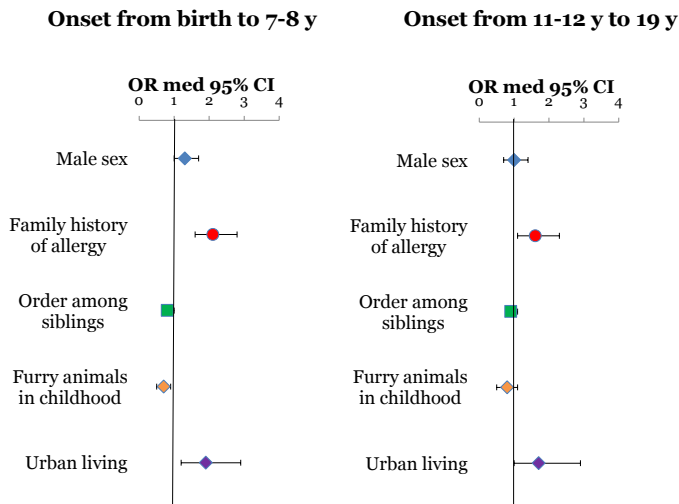


Figure 6. Risk factor patterns for early (birth to 7-8 y) and late (11-12 y to 19 y) onset of allergic sensitization, expressed as odds ratios (OR) with 95% confidence intervals (95% CI)

Among adults, a higher remission than incidence of allergic sensitization was found. Belonging to the age group 40-60 years and absence of allergic rhinitis were significantly positively related to remission of allergic sensitization (Paper I, Table V).

Due to the low number of incident cases, no multiple logistic regression analysis of possible risk factors was performed. However, no significant differences by sex and age group were found for the incidence of allergic sensitization among adults.

Association of allergic sensitization with asthma and allergic rhinitis among adults

In the study population examined in 2009, the association of allergic sensitization with asthma and allergic rhinitis was assessed (Paper IV). The prevalence of asthma, asthmatic wheeze and allergic rhinitis by age is displayed in Figure 7. A significant decrease in prevalence of allergic rhinitis by age was found, but not of asthmatic wheeze and asthma. The prevalence of asthma, asthmatic wheeze and allergic rhinitis was similar among men and women.

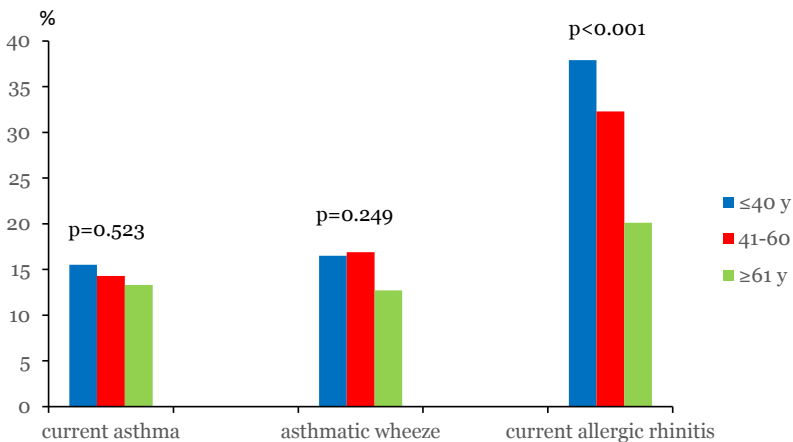


Figure 7. The prevalence [%] of current asthma, asthmatic wheeze and current allergic rhinitis by age

The sensitization pattern in asthma and allergic rhinitis

The prevalence of current asthma, 24.5%, and current allergic rhinitis, 56.3%, was significantly higher among subjects sensitized to any allergen compared to non-sensitized subjects (10.7% and 17.6%, respectively). Corresponding significant differences were observed for sensitization to the most common specific allergens birch, timothy, cat and dog (Paper IV, Table III).

The positive association between both any and specific sensitization remained also when these variables were included one by one in a multivariate model adjusted for confounders (sex, age, ever smoked, family history of asthma/allergic rhinitis).

When adjusting the specific allergens and allergen groups, respectively, for each other, specific sensitization to both birch (OR 2.59 (95% CI 1.33-5.07)) and timothy (OR 4.31 (95% CI 2.22-8.36)) as well as to cat (OR 2.49 (95% CI 1.07-5.80)) was significantly and positively associated with current allergic rhinitis. Corresponding to this finding, sensitization to *any pollen*, OR 4.25 (95% CI 2.55-7.06) as well as to *any animal*, OR 3.90 (95% CI 2.31-6.58) was significantly associated with allergic rhinitis.

In contrast, current asthma was significantly associated with sensitization to dog, OR 2.58 (95%CI 1.01-6.57), and horse OR 2.64 (95% CI 1.02-6.84). Correspondingly, sensitization to *any animal* was significantly associated with current asthma, OR 4.80 (95% CI 2.68-8.60).

In order to assess the impact of allergic sensitization on asthma and allergic rhinitis in relation to age, separate multiple logistic regression analysis were performed in the three age groups. Regarding allergic rhinitis, sensitization to *any allergen*, *any pollen* and *any animal* were most strongly associated in the youngest age group. This difference between age groups was not found for asthma, and sensitization to *any animal* was strongly associated with asthma in all age groups (Paper IV, Table IV).

Allergic sensitization among subjects with asthma and rhinitis

Both the prevalence of sensitization to *any allergen* and to the specific allergens decreased significantly by age among current asthmatics. Sixty-eight % of the asthmatics in ages 21-40 years were sensitized to *any allergen* while

this was the case for only 22% of the subjects between 61 and 86 years (Figure 8, Paper IV, Table V). All of these 22% were also sensitized to *any animal*.

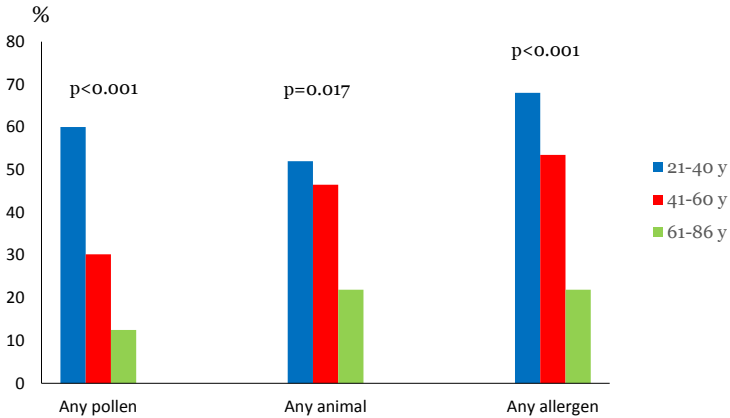


Figure 8. Prevalence [%] of allergic sensitization by age among current asthmatics

A similar trend of a decreasing prevalence of allergic sensitization by age was also found among subjects with current allergic rhinitis. This age-dependent trend was apparent for both any and for specific sensitization (Figure 9, Paper IV, Table V).

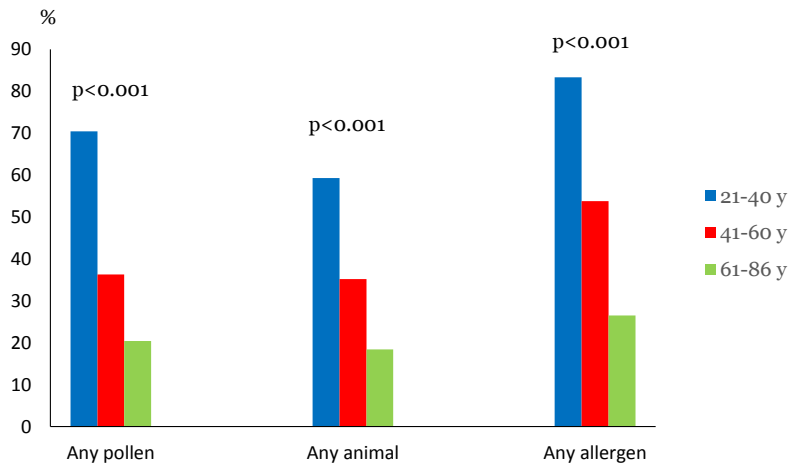


Figure 9. Prevalence [%] of allergic sensitization by age among subjects with current allergic rhinitis

The fraction of both asthma and rhinitis cases attributable to allergic sensitization (PAF) was calculated for each age group. The PAF for asthma was highest among subjects aged 21-40 years with 49% and decreased with increasing age to 37% in age group 41-60 years and 11% in age group 61-86 years. A higher PAF was found for subjects with current allergic rhinitis with 79% in the youngest age group, followed by 44% and 16% for the corresponding older age groups (Paper IV, Figure I).

Age of onset of asthma in relation to allergic sensitization

Among current asthmatics, the relationship between allergic sensitization and age of asthma onset was assessed. In adult age, the prevalence of allergic sensitization was highest among subjects with an asthma onset ≤ 6 years, 86%, and decreased with higher ages of onset; 56% among asthmatics with an asthma onset between 7 and 19 years and 27% among those who acquired asthma ≥ 20 years (Paper IV, Figure II). Both increasing age of asthma onset and age at examination were negatively associated with allergic sensitization. Therefore, these variables were included in a multivariate model adjusted for sex which showed a remaining negative significant association between age of asthma onset and sensitization to any allergen, but not with age at examination.

Discussion

Discussion of methodology

The following section addresses methodological aspects with focus on study design, the use of postal and interview questionnaires for the definition of disease outcomes and the methods for the assessment of allergic sensitization. In the respective subtopics, aspects of internal and external validity, reliability and bias will be discussed.

Study design

Cross-sectional study designs are commonly used for the assessment of prevalence, a measure of occurrence of a disease or condition on a specific point of time or during a defined time period in a population. Furthermore, the relationship between a condition and other variables of interest can be examined (167). We used a cross-sectional design to determine the prevalence of both allergic sensitization and associated risk factors. Furthermore, the comparison of two cross-sectional randomly selected population samples recruited and examined 15 years apart allows analysis of time trends in prevalence of allergic sensitization (Paper III). Furthermore, associations between allergic sensitization and potential risk factors (Paper I and III) as well as the associations between allergic sensitization and asthma and rhinitis were described (Paper IV).

An important limitation of a cross-sectional study design is the impossibility to detect the temporal sequences of causes and effects of the assessed variables (167). This issue is of special importance concerning the assessment of the population-attributable fraction, a term expressing the proportion of an outcome attributable to a certain exposure. In Paper IV, this calculation was performed to determine the proportion of asthma and rhinitis cases attributable to allergic sensitization. It gives, however, no information if allergic sensitization forewent the onset of asthma or rhinitis or vice versa and thus, cause and effect cannot be evaluated.

The incidence of a condition describes the occurrence of new cases of the disease during a defined period in a population. Remission of a disease or condition is defined as the loss of the disease during a defined period in the population. To gain this information, longitudinal study designs are applied, where a cohort is followed and re-examined over certain time periods. A clear

advantage of this study design is the possibility to analyse cause and consequence relationships between outcome and exposure. In longitudinal studies, large numbers of subjects followed over time are needed to achieve enough power of analysis when studying diseases or conditions with a low incidence or remission.

In Paper I, we calculated the cumulative incidence and remission of allergic sensitization based on a 10 year follow-up of an adult cohort. The cumulative incidence expresses the proportion of the disease-free population, i.e. the population at risk, which acquired the disease during the follow-up period. Remission was calculated correspondingly. In Paper II, a cohort of children was followed from 1996 as the children entered school until 2008, when the subjects had reached young adulthood. As the length of the follow-up time differed, the mean annual incidence of allergic sensitization was calculated, which is defined by the number of new cases of sensitization occurring during a defined time period divided by the population at risk of suffering from becoming sensitized, expressed as person time (167).

The *internal validity* of a study expresses the degree to which a study is unaffected from bias or systematic error or, in other words, how truly the study population reflects the situation in the general population. The term *selection bias* describes that the way in which the study subjects are selected affects the chance that a relationship between an exposure and the condition of interest is detected (168). The studies among adults described in this thesis were performed based on randomly selected population samples stratified for the age and gender distribution of the county of Norrbotten. This increases the probability that the measured variables in the study population truly reflect the situation in the general population. A sufficiently high participation rate is of importance, as subjects who participate in a study might differ regarding health conditions and variables of interest compared to non-responders. However, studies addressing potential bias caused by non-responding have found somewhat conflicting results. In a large Swedish postal questionnaire study no significant differences were found between responders and non-responders regarding airway symptoms and disease, however non-responders were slightly more likely to be young men and smokers (169). Other Scandinavian studies have reported a similar or higher prevalence of respiratory symptoms, use of asthma-medication and smoking among non-responders (170, 171). Participation rates in our adult studies varied between 68 to 73% in the clinical examinations and were remarkably high with 93% of those possible to invite in the longitudinal follow-up study in 2004. The

participation rates in the studies of children and adolescents were exceptionally high. We therefore consider our results as highly reliable with no substantial effect due to *non-responder bias*.

The *external validity* of a study expresses to which degree the results of a study are applicable to other populations (168). Due to a lack of similar longitudinal studies addressing the epidemiology of allergic sensitization, the external validity is somewhat difficult to assess for the study population in Paper I. However, studies from Scandinavia reporting the prevalence of allergic sensitization conducted among comparable populations correspond well to our results (34, 172).

The cohort examined clinically in 2009 consisted of two subsamples from a postal questionnaire study performed in 2006 as shown in Figure I in the Material and methods section. Both subsamples were compared with regards to the prevalence of respiratory symptoms, use of asthma medication and smoking as well as SPT results, and the results were similar. Possible bias caused by the study design should therefore play a minor role.

Paper III compared the results of two different cross-sectional studies examined 15 years apart. The two study samples examined in 1994 respectively 2009 showed a similar age and sex distribution, but differed significantly in prevalence of having grown up in a rural environment and smoking habits (Paper III, Table 1). These differences reflect true lifestyle changes in the society, which may have influenced the result of an increasing prevalence of allergic sensitization from 1994 to 2009 as described in Paper III.

Questionnaires

The use of both postal and interview questionnaires is a well-established tool in epidemiological research for the assessment of disease and symptom variables and factors potentially influencing these. Both postal and interview questionnaires used in our studies have been widely used nationally (77, 84, 156, 173, 174) and internationally (17, 158, 175, 176). Furthermore, the postal questionnaire used in the adult studies has been externally validated against the GA2LEN- questionnaire with regards to respiratory symptoms and exposures (159).

The postal questionnaire used in the study of children and adolescents was developed based on the ISAAC-protocol (160). Up to the age of 12 years the parents completed the questionnaire. Thereafter the questionnaire was completed by the adolescents themselves. As this aspect might provide a source of *methodological and recall bias*, parental and self-completed questionnaires have been compared previously considering allergic diseases and influencing environmental factors and there was a good agreement between the parents' and their childrens answers (177, 178).

The interview questionnaires used in the longitudinal setting in 1994 and 2004 of the adult studies were nearly identical. Also here, good agreement was found between questions about constant factors when comparing the answers of the same subjects participating both in 1994 and 2004, which minimizes the risk of *recall bias*. However, *recall bias* might be an issue concerning questions about childhood environment and age of onset of asthma in particular in studies performed among adults.

The definitions of asthma and allergic rhinitis were based on the structured interview performed in 2009. Asthma was assessed both by the question "Have you ever had asthma?" and "Have you been diagnosed as having asthma by a physician?". A similar prevalence was found when comparing the variables *self-reported asthma*, *physician-diagnosed asthma* and *current asthma*. Earlier versions of the questionnaire have been validated against respiratory physiological variables (173) and bronchial hyperresponsiveness (179) and strengthened a high validity of the interview questions on asthma. The absence of a question about physician-diagnosed allergic rhinitis is a limitation. However the classification of rhinitis has been and is currently still under debate (180-183).

Assessment of allergic sensitization

We were able to provide data on allergic sensitization based on both SPT and specific IgE in 2004 and in 2009. The prevalence of sensitization to any allergen and most of the specific allergens assessed by specific IgE was generally somewhat lower than for the SPT-results, but both methods confirmed the described decrease in prevalence by increasing age as well as the sensitization pattern for the most common allergens. This finding corresponds well to these of earlier performed studies using both methods (31, 34, 184) and is explained by the different mechanisms behind each of the

methods. The SPT is an indirect method of detecting IgE-mediated allergy in the skin whereas the level of IgE-antibody is measured directly in the serum. However, there were significant differences in the prevalence of specific IgE and SPT for sensitization to cat and dog in 2009. The reasons for this are not clear. An explanation might be provided by the very complex pattern of allergenic components of especially cat and dog allergen. Several major allergen components for both cat and dog have been identified, and their proportions are assumed to vary by geographic area (99). Component-resolved diagnostics might therefore in the future provide a more precise assessment of sensitization.

Using SPT for the measurement of allergic sensitization demands a standardized test protocol and a trained, experienced staff in order to minimize *methodological bias*. This is especially of importance when analysing time trends in sensitization as was done in Paper III and in the longitudinal study of children and adolescents in Paper II. SPT was performed in accordance to the same protocol at all occasions and by a limited number of experienced, well-trained research nurses. Furthermore, allergen extracts and lancets from the same manufacturer were used both in the adult and the childhood studies. However, minor differences between the batches of the allergen extracts cannot be excluded. According to a recently published Danish study there were inter batch differences of allergen extracts of the same manufacturer. The same study, however, found no further advantage concerning validity in performing double SPT (185). SPT results in the study of children have been validated against specific IgE earlier with good correlation between the two methods (14), and similar mean wheal sizes were found in 1996 and 2006 (31). The mean wheal sizes differed partly for a few allergens between 1994 and 2009 in our adult study (Paper III). In 1994 the mean wheal sizes were somewhat larger compared to those in 2009. Thus the mean wheal sizes may have been overestimated in 1994 or underestimated in 2009, which in fact would strengthen our results of an increase in prevalence of sensitization by time.

Discussion of main results

The following section discusses the most important findings of this thesis. The incidence of allergic sensitization was high throughout childhood and persisted during adolescence up to young adulthood with very low remission whereas an inverse pattern was found among adults. This finding suggests furthermore that the decreasing prevalence of allergic sensitization with age among adults is at least partly an effect of normal aging and not strictly related to the year of birth. Multisensitization at age 19 was associated with early onset of allergic sensitization. A family history of allergy was significantly positively associated with allergic sensitization across all ages. Furthermore, early onset of sensitization among children and adolescents was positively associated with male sex and urban living and significantly negatively associated with order among siblings and the presence of furry animals at home. These negative associations lost significance as the children grew older and were not found among subjects with onset of allergic sensitization during adolescence.

During the last two decades an increase in prevalence of sensitization to the major single allergens as well as multisensitization was observed, whereas sensitization to any allergen increased slightly, but not significantly. The strongest risk factors for allergic sensitization among adults were young age, a family history of allergy and urban living. A detailed discussion on other risk factors assessed in context with this thesis is provided in the respective paper.

Among adult asthmatics, the prevalence of allergic sensitization decreased with increasing age of asthma onset. Asthma was positively associated with sensitization to any animal across all adult ages. Allergic rhinitis was positively associated with both sensitization to any pollen and any animal, and this association was strongest among younger compared to older adults.

Incidence and remission of allergic sensitization during childhood and adulthood

The incidence of allergic sensitization was high up to the age of 19 years as the subjects entered young adulthood and hence continued the already earlier reported finding of a high incidence before adolescence in this cohort (67). The incidence of sensitization to any animal was highest before the age of 7 and decreased in the older age groups. The incidence of sensitization to pollen remained similar throughout childhood and adolescence. Interestingly, the

incidence during early school-age reported in this thesis in an area lacking mite (56) was of similar magnitude compared to Australia (66) where mite is a common allergen. However, to the best of our knowledge, studies in which incidence and remission of allergic sensitization during adolescence have been calculated are rare (32, 119, 186). Both the large Isle of Wight study (32) and a Finnish study (186) found high incidence and persistence of allergic sensitization also during adolescence, consistent with our results. A study from New Zealand followed adolescents up into adulthood at 32 years of age and reported that about 6% of subjects with at least one positive SPT during adolescence were SPT-negative at the age of 32 years, but incidence was not calculated in this paper (119).

Hardly any remission of sensitization was observed up to young adulthood for the tested allergens in our study. The few cases with positive SPT results that turned negative during the observation time might at least partly depend on misclassification when reading the SPT at the earlier examination. Thus, a high incidence and persistence of allergic sensitization is seen during childhood and adolescence. This explains furthermore the increase in prevalence of allergic sensitization from 21% at the age of 7-8 years to 42% at the age of 19 years.

There are to date only a few longitudinal studies evaluating incidence and remission of allergic sensitization during adulthood (70, 187). In our longitudinal study among adults a cumulative incidence of 5 % and a high remission of 32% over 10 years were found. Similar results were reported from Denmark where adults aged 40 years at baseline had been followed over 20 years by analysing specific IgE; an incidence of 7% and remission of 41% was found (70). However, a slightly higher incidence and lower remission with a similar study design as described in this thesis was reported from Great Britain (187). A longitudinal study within the ECRHS evaluated changes in the prevalence of sensitization expressed by elevated specific IgE in a cohort of adults from 20 to 44 years (71). In this younger cohort a slight decrease in prevalence of allergic sensitization was found as the subjects grew older. Thus, as opposed to the pattern among children and adolescents, a low incidence and high remission of allergic sensitization is seen among adults.

Prevalence of allergic sensitization among adults

The analysis of time-trends of prevalence of allergic sensitization delivers important information if the earlier reported increase in prevalence in the general population is still ongoing. Furthermore, changes in the local sensitization pattern and shifting strength of factors affecting sensitization can be detected. This thesis is the first to report such time trends in a Swedish adult population. The prevalence of sensitization to the most common specific allergens increased significantly from 1994 to 2009 which resulted in a significant increase in multisensitization between the surveys. However, there was only a slight, but not significant increase in prevalence from 35 to 39% in sensitization to any allergen.

Figure 10 shows an overview of international studies including our results which have reported time trends in prevalence of sensitization to any allergen from population-based samples.

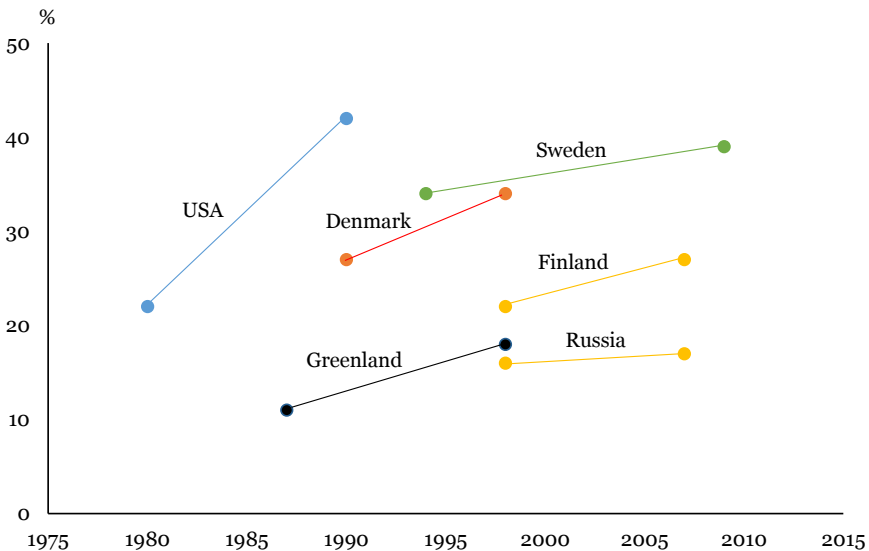


Figure 10. International prevalence trends of allergic sensitization among adults

Corresponding to our results, several studies have found an increase in prevalence of allergic sensitization (30, 43, 44, 188-190) during the last decades. The large NHANES found an increase in prevalence from 22 to 41%, however also children were enclosed in the study population (44). A Finnish study compared prevalence trends in Finland and neighboring Russian

Karelia (190) and found a diverging trend in prevalence between the two regions. The prevalence in Finland increased slightly whereas the prevalence in Russia remained on a similar level between the surveys. A study from Denmark evaluated sensitization by specific IgE nine years apart and found a prevalence of similar magnitude as well as a similar increasing trend between the surveys comparable to our study. This study also reports a significant increase in multisensitization corresponding to our results (188).

As the study area described in this thesis is free from mite (56) which is a dominating allergen in other parts of Europe (53, 191), the prevalence of allergic sensitization reported in this thesis can be regarded as high. However, studies comparing prevalence trends in allergic sensitization among adults have in common that the sensitization in the study subjects may have occurred earlier in life during childhood and adolescence. Therefore these dynamic changes in prevalence might in fact have occurred several years or decades before the respective study was performed.

The significant increase in prevalence of multisensitization in our study could be regarded as remarkable and raises the question in what way respiratory disease can be affected by this finding. An Italian study reported a higher prevalence of multiple sensitized subjects in a cohort of men with allergic rhinitis and these subjects suffered also from more severe rhinitis symptoms (192). A study from Australia among mild to moderate asthmatics found an association between multisensitization and increased bronchial hyperreactivity (193). The association between multisensitization and asthma has furthermore been confirmed by others (17, 188, 191, 194, 195). It will be of further interest if the increase in prevalence of multisensitization in our study area will influence the prevalence of allergic respiratory diseases in the future.

Factors associated with allergic sensitization

Having a family history of allergy was the only consistent risk factor for both early and late onset allergic sensitization during childhood and adolescence as well as for prevalent allergic sensitization among adults which is in line with earlier published reports (17, 24, 31, 74, 196). The role of genetics in allergy is still a subject for intensive research. Interactions between the genetic profile and environmental factors are of importance when predicting if a subject will develop allergic sensitization (197, 198). Furthermore, different genetic profiles in combination with environmental factors seem to result in different

phenotypes of allergy, as suggested by data from Finland and Russian Karelia (199).

Male sex at age 7-8 years was significantly positively associated with the onset of sensitization from birth to the age of 7-8 years, but the association lost its significance with increasing age. Several studies report a strong association between male sex and allergic sensitization in childhood (24, 41). The finding corresponds well to a study from Belgium (200). It is assumed that complex interactions between the immune system and hormonal mechanisms, especially during adolescence, might influence the development of allergic sensitization (201). The higher proportion of boys with allergic sensitization might partly explain the higher prevalence of asthma among boys compared to girls.

The positive association between allergic sensitization and young adult age is well documented in numerous studies both in Scandinavia (17, 34, 74) and internationally (49, 55, 176, 202). The prevalence of allergic sensitization decreased with increasing age in our study, which also is consistent with the studies mentioned above. As we also report a low incidence and higher remission of allergic sensitization in this thesis, we conclude that the decreasing prevalence of allergic sensitization with age is related to normal aging and not only to the year of birth.

In line with the results described in this thesis, also others report an association between urban living and allergic sensitization. A German study found an increased risk for sensitization to pollen in 6-year-old children with exposition to ambient particulate matter (108), a result partly confirmed by the Swedish BAMSE-study which, however, assessed younger children at the age of 4 years (109). Among adults, urban living was significantly positively associated in particular with sensitization to *any pollen*. The variable “urban living” was considered as a surrogate for a higher exposure to air pollutants such as e.g. traffic exhaust. There are to date few population-based studies among adults describing possible associations between air pollutants and allergic sensitization (111, 113). Within the ECRHS-II, a weak but not significant association between air pollutants, such as fine particulate matter and sulphuroxides, and allergic sensitization was found (113). The results presented in this thesis correspond to earlier findings of the Swiss SAPALDIA-study which reported a significant association between sensitization to pollen and living nearby trafficated roads (111). The mechanisms behind this association are still debated. Several data point to a pro-inflammatory effect of

air pollutants on pollen (114), especially nearby heavy trafficated roads (115, 117). Recently published data from the NHANES showed a positive association between nitrogendioxide, particulate matter (PM_{2.5}) and allergic sensitization (203). Interestingly, the association was here particularly strong between PM_{2.5} and sensitization to indoor allergens.

Order among siblings was significantly negatively associated with early onset of allergic sensitization which is in line with aspects of the hygiene hypothesis (94) and other results from studies of allergic sensitization performed among young children (104, 204, 205). This protective effect has also been shown among adults in the ECRHS (98), however, in this thesis the association did not reach significance neither among adolescents nor among adults. Furthermore, the presense of furry animals in childhood was a protective factor for early onset of sensitization, however, the association was weaker and only borderline-significant in association with late onset of sensitization. Numerous studies have reported this negative association (64, 96, 206). However, others report conflicting results (65, 101, 102) where especially exposure to cat seems to promote the development of sensitization. In our study of adults, the presence of furry animals at home during childhood was significantly negatively associated with elevated specific IgE for *any animal*. Previous data from a young adult population suggest a protective effect of earlier cat or dog ownership on both allergic sensitization and asthma (85). It has been hypothesized that immunomodulatory mechanisms may influence the development of tolerance against pet allergens (99) while also a dose-response relationship may be important (207). In what exact way these mechanisms operate in childhood as well as in adulthood is still not clear.

The small number of incident cases of allergic sensitization among adults did not allow a detailed analysis of potential risk factors for the incidence of allergic sensitization. Remittent subjects tended to be sensitized to only one allergen, older than 40 years and had significantly more often had furry animals at home during early childhood. This finding is consistent with Danish data reporting a significant association between incidence and persistence of sensitization defined by elevated specific IgE and atopic disease at 60 years of age (172).

Associations of allergic sensitization with rhinitis and asthma

Due to the cross-sectional design of the study presented in Paper IV, we had no information about the age when the study subjects became sensitized.

However, the prevalence of allergic sensitization among asthmatics was highest among those with an onset of asthma before the age of six years. Another study based on the cohort of children described in this thesis, showed that the majority of subjects with persistent asthma at 19 years was already sensitized to cat or dog at the age of seven years (21). This is partly in line with results published by Sears et al who described a significant relationship between persistent and relapsing wheeze from childhood into young adulthood and sensitization to mite acquired during childhood (20). A study from the United States reported a significant association between SPT-positivity among adults and an early age of asthma onset as well as a more severe asthma phenotype (208). An Australian study found a lower prevalence of sensitization among asthmatics with an onset of asthma after the age of 30 (193). Thus, allergic sensitization may have an impact on the persistence of asthma which starts early in life into adulthood and seems also to affect disease severity.

Rhinitis was significantly associated with both sensitization to *any pollen* and *any animal*, and this association weakened with increasing adult age. Among asthmatics, the association with allergic sensitization was of similar magnitude irrespective of age group, and sensitization to any animal was significantly positively associated with asthma across all adult age groups. Data from the Finnish part of the FinEsS-study showed a strong association between rhinitis and allergic sensitization among young adults (17), in line with our results. Data on age-dependent patterns of sensitization among asthmatics comparable to our results have so far not been reported. However, our finding of a stronger association between allergic sensitization and rhinitis compared to asthma is confirmed by several previous studies (140, 176, 209). In contrast to rhinitis, asthma is associated with several other environmental factors such as obesity (16, 210), traffic exhausts (211), socioeconomic status (136, 212) and smoking (16, 137, 209).

The different patterns of sensitization for rhinitis and asthma with a dominance of sensitization to animals among adult asthmatics have also been described in studies performed among children (14, 210). In the late 1990s, a French study reported a stronger association between sensitization to outdoor allergens like pollen among atopic patients, whereas sensitization to indoor allergens such as mite and pets was most common among asthmatic patients (213), a finding confirmed by others (146). The more continuous exposure to perennial allergens including mite and pets in comparison to the seasonal pollen allergens might partly explain the stronger relationship between

asthma and sensitization to indoor allergens. It has further been hypothesized that pollen due to their particle size more likely affect the upper airways and are dependent on the presence of other environmental factors (148). Pet allergens are smaller and have a higher ability to penetrate the smaller airways and remain in the air for a long time (147, 214).

The strong association between rhinitis and sensitization to pollen has been intensely described, both among children (14, 215, 216) and adults (180, 181, 217). A recent study using the ISAAC-dataset focusing on children reported high risk estimates of both sensitization to pollen and animals in relation to the onset of rhinitis whereas persistent rhinitis was mainly associated with sensitization to pollen (215). Rhinitis among adults was in this thesis equally associated with both sensitization to pollen and animal, consistent with results from other studies performed among adults (209), however, also sensitization to mite has been associated with rhinitis (180).

Conclusions

The main contributions of this thesis are summarized as follows:

- The low incidence and high remission of allergic sensitization among adults explain at least partly the decreasing prevalence of allergic sensitization by age. The low prevalence among older adults is thus not exclusively related to year of birth, but also to normal ageing.
- Incidence and persistence of allergic sensitization were high during childhood and adolescence, while in these ages hardly any remission was found.
- A family history of allergy was the strongest and the only consistent risk factor for both early and late onset of allergic sensitization among children and adolescents.
- The prevalence of sensitization to the most common airborne allergens as well as multisensitization increased significantly from 1994 to 2009 among adults.
- A family history of allergy, young age and urban living are important risk factors for allergic sensitization among adults.
- Early onset of asthma was associated with allergic sensitization among adult asthmatics.
- Sensitization to both pollen and animal was strongly and age-dependently associated with rhinitis, whereas sensitization to animal was associated with asthma with a similar magnitude regardless of age.

Perspective

Allergic sensitization is an important pre-clinical condition foregoing the development of rhinitis and asthma. Especially among children and adolescents a high prevalence and incidence of allergic sensitization are still seen, a finding important to consider for the clinical assessment of patients with allergic respiratory diseases as well as for the future planning of respective health-care resources.

As the general population is characterized by a further growing proportion of elderly adults, also the proportion of allergic elderly patients is assumed to increase. Therefore, also old patients with respiratory disease should be assessed with regards to allergic sensitization in order to provide health-care which as good as possible addresses the needs of these patients. Continuing epidemiological research assessing prevalence trends as well as incidence and remission of allergic sensitization, rhinitis and asthma will thus also be needed in the future.

Prevention is an important tool in order to control a disease, and in the best case decrease the further development of a disease. The assessment of risk factors of a condition is therefore of great importance. It is currently hard to take influence on a genetical predisposition for allergies. There are however several environmental risk factors such as air pollution that could decrease the risk of developing allergic disease when their exposition is reduced, if not eliminated. This thesis underlines furthermore that the etiology of allergic sensitization is multifactorial why focus should also be put on gene-environment interactions influencing the onset and persistence of allergic sensitization.

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