UPPSALA
UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 542

A Nationwide Study of Asthma and Allergy in Swedish Preschool Children

– with Special Reference to Environment, Daycare, Prevalence, Co-ocurrence and Incidence

KRISTINA BRÖMS

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2010

ISSN 1651-6206
ISBN 978-91-554-7759-2
urn:nbn:se:uu:diva-121426

Dissertation presented at Uppsala University to be publicly examined in Brömssalen, ingång 11, Länssjukhuset, Gävle, Friday, May 7, 2010 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Bröms, K. 2010. A Nationwide Study of Asthma and Allergy in Swedish Preschool Children – with Special Reference to Environment, Daycare, Prevalence, Co-ocurrence and Incidence. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 542. 69 pp. Uppsala. ISBN 978-91-554-7759-2.

Aim: The aim of this project was to study the age and sex specific occurrence of atopic and non-atopic asthma and other atopic manifestations in a nationwide sample of Swedish pre-school children.

Methods: All 70 allergen avoidance day-care centres (AADC) with 84 sections and 140 matched ordinary day-care centres with 440 sections in 62 municipalities across Sweden were sampled. In 2000 the staff at each section responded to a questionnaire on indoor and outdoor environment at the section. In 2002 parents of 5,886 children attending the AADCs and ODCs responded to a postal questionnaire regarding symptoms indicating prevalent asthma, allergic rhinitis, eczema, and food, furred pet and pollen allergy and other data in their children. In 2007, parents of 4255 children responded to an almost identical follow-up questionnaire.

Results: The AADCs had far more strict rules than ODCs on furred pets and smoking at home and on perfume use, and the indoor environment was better, owing to better cleaning. The age specific asthma prevalence was curvilinear with a peak at age 3 of 11.4% among boys and 9.8% among girls. In addition the prevalence increased by municipality population density, a proxy for degree of urbanisation. There was a highly significant co-occurrence between all asthma-atopic manifestations, but there was no evidence of ordered sequence of manifestation onset. The asthma incidence was highly dependent on presence or absence of co-occurrence variables. Given the variable mix in the present study population, the annual asthma incidence ranged from 0.6% to 1.2%.

Conclusions: AADCs had more strict rules and a better indoor environment than ODCs. The asthma prevalence was affected by age, sex and degree of urbanisation. There was close co-occurrence between all asthma and atopic manifestations but no evidence of ordered sequence of onsets. The annual asthma incidence was strongly dependent of co-occurrence conditions.

Keywords: Asthma, rhinitis, eczema, allergy, indoor environment, daycare centre, prevalence, incidence epidemiology

Kristina Bröms, Family Medicine and Clinical Epidemiology, Uppsala Science Park, Uppsala University, SE-75185 Uppsala, Sweden

ISSN 1651-6206
ISBN 978-91-554-7759-2
urn:nbn:se:uu:diva-121426 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-121426)

Till min familj
Gunnar, Malin, Åsa och Maria

... samt till min mamma Brita

List of Papers

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

I Bröms K, Svärdsudd K, Sundelin C, Norbäck D. A nationwide study of indoor and outdoor environments in allergen avoidance and conventional daycare centers in Sweden. *Indoor Air* 2006;16:277-35.

II Bröms K, Norbäck D, Eriksson M, Sundelin C, Svärdsudd K. Effect of degree of urbanisation on age and sex-specific asthma prevalence in Sweden preschool children. BMC Public Health 2009;9:303.

III Bröms K, Norbäck D, Eriksson M, Sundelin C, Svärdsudd K. Prevalence and co-occurrence of asthma and allergic manifestations in pre-school children. Submitted.

IV Bröms K, Eriksson M, Norbäck D, Sundelin C, Svärdsudd K. A nationwide study of asthma incidence and its determinants in pre-school children during five years of follow up. Manuscript.

Contents

Abbreviations

AADC	Allergen avoidance day-care centre
BAMSE	Children, Allergy Milieu Stockholm Epidemiological
BMHE	Childen's Environmental Health Questionnaire
CI	Confidence interval
DBH	Dampness in Buildings and Health
DC	Day-care centre
EAACI	European Academy of Allergology and Clinical Immunology
GINA	Global Initiative for Asthma
ISAAC	International Study of Asthma and Allergies in Childhood
ODC	Ordinary day-care centre
OLIN	Obstructive Lung Disease in Northern Sweden
OR	Odds ratio
PVC	Polyvinyl Chloride Plastics
SD	Standard deviation
Wald's chi^2	Wald's chi-square
WAO	World Allergy Organization

Prologue

My interest for allergy and asthma began when one of my children was affected by severe allergic problems. Later on when she was supposed to attend a day-care centre no one dared to accept her. Moreover, in my work as a General Practitioner, a GP, I had many child patients with asthma and allergies and gradually my interest for these diseases increased and especially in what way the family was affected by the child's asthma or allergy. Many parents reported problems with day care and schools especially if the child had asthma and allergy to furred pets or severe food allergy. In 1996 I was offered an introduction course in scientific methods given by FoU-forum, a centre for research and development in the county of Gävleborg, in collaboration with Uppsala University. The course was addressed to GPs in Gävleborg and Dalarna and during a year and a half we were supposed to do a minor project and write a scientific report. Together with a colleague and two nurses, patients with asthma in primary health care centres were asked to answer a questionnaire about asthma symptoms and other factors related to asthma, such as smoking and physical exercise.

Kurt Svärdsudd was one of the teachers and on the last day of the course I asked him if it was possible to be accepted as a postgraduate student in Family Medicine at Uppsala University and to start a project about day care for pre-school children. I was invited for further discussions and gradually a research plan was developed, resulting in this thesis.

Introduction

Setting

Sweden is one of the most sparsely populated areas in Europe with a total population of 9 million dispersed over an area of 450,000 square kilometres. The median population density is 26 people per square kilometre, and 80% of municipalities have 82 persons or less per square kilometre. The corresponding numbers for the municipalities included in this study were 57 and 130 persons, respectively.

For administrative purposes Sweden at the time of the data collection was divided into 25 regions and 290 municipalities, the smallest administrative unit. The distribution of mean population density by municipality is shown in Figure 1.

All Swedish pre-school children are entitled by law to day care organised by the local municipality. In 2002, 74% of all pre-school children attended a day-care centre (DC), somewhat fewer among the youngest children and more than 80% among children of 3 or older [1]. The vast majority of DCs are run by the local municipality administration. The few privately operated DCs are all subcontracted to the municipal administration and follow the same set of rules as publicly operated DCs. A DC may have one to four sections. At the time of the study 15-20 children were cared for in each section. Many sections had children of all ages, but some were age stratified (1-3 years or 4-6 years). The day care fees are heavily subsidised by the municipalities; parents usually pay about 10% of the real cost.

Parents who want a position for their child in a DC have to file an application. Only children living in the municipality are accepted. If so, the child is put on a municipality administration operated waiting list, common for all DCs in the municipality. As soon as a position becomes vacant the parents of the child next in turn on the waiting list is offered the position. If the parents do not accept the offered position, the child may stay on the waiting list awaiting a position at their favourite DC, but in most instances this is impractical, since the waiting time for a specific DC may be more than a year, and private day care outside the municipality system is not subsidised.

During the 1990s special DCs for children with asthma or allergies, 'allergen avoidance day-care centres' (AADCs) [2] were established at the initiative of municipal school administrations, parents, local politicians, and local DC staffs. The operations, set of rules, and fees for these centres are the

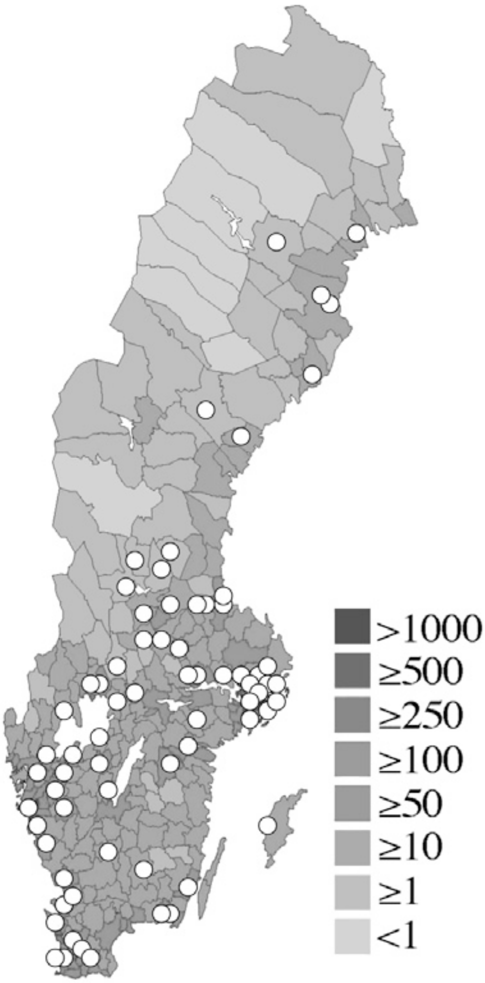

Figure 1. Map showing population density in Sweden by municipality and localisation of the study day-care centres (yellow circles)
(Modified from http://sv.wikipedia.org/wiki/Befolkningst%C3%A4thet)

same as for ordinary day-care centres (ODC) with the exception that AADCs give priority to children with asthma or allergies, but accept other children as well, space permitting.

Indoor environment in day-care centres

Building dampness and mould growth have been shown to be common in DCs in Sweden [3], Norway [4], Taiwan [5], and Finland [6]. Microbial components, such as endotoxins [4], moulds [5] and bacteria [7] have been measured in settled dust or air samples from DCs in these countries. Mesurements of cat and dog allergens in DCs show that DCs in Sweden [8, 9], USA [10], and Norway [4] are contaminated with cat and dog allergens. The cat and dog allergen levels in the DCs correlated to the number of cat and dog owners among the children and staff. The amount of cleaning had no influence on the allergen concentrations [8, 9]. In ODCs the mean concentration of dog allergen (Can f 1) and cat allergen (Fel d 1) in settled dust were six to nine times higher than in AADCs, where none had a cat or a dog at home. Moreover, the mean concentration of airborne cat allergen was ten times higher in the ODCs [9].

No studies on health effects of allergen exposure at DCs were found. However studies from schools indicate that cat allergen exposure at school may increase the number of incident asthma cases [11]. Asthmatic schoolchildren with cat allergy but no cats at home had an increased risk of exacerbated asthma when going back to school after summer holidays. However, the risk was increased only in school classes with a high proportion (>18%) of cat owners [12]. Several studies indicate that children attending DCs were more prone to airway infections than children cared for at home [13-15], others found that children attending DCs had more respiratory symptoms than children cared for at home [14], while still others found no differences [16], or differences only in specific age groups [17].

A number of epidemiological studies have shown that early day care attendance may have preventive effects on allergy development, atopic asthma [18-21], or wheezing at 5 years of age [22], whereas others found no such effect [23].

Studies on indoor and outdoor environment in DCs demonstrated a variety of factors that were suggested to have a negative influence on childrens' health. Additional knowledge on how to improve the indoor environment in DCs is needed. Areas possible to improve may be detected by comparisions of ODCs with AADCs. No large-scale studies on AADCs and ODCs indoor and outdoor environment have been found.

Definitions of atopic diseases, asthma and allergies

A number of definitions have been proposed for atopic or allergic diseases. The European Academy of Allergology and Clinical Immunology (EAACI) [24] and the World Allergy Organization (WAO) [25] have proposed the following definition, or 'nomenclature', of atopy, allergic diseases and asthma. Atopy was defined as 'a personal or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons may develop typical symptoms of asthma, rhiniconjunctivitis, or eczema'.

Allergic rhinitis was defined as nose symptoms including sneezing, itching, blockage or increased secretion due to immunological mechanisms. Allergies to pollen and furred pets are common in children with allergic rhinitis and when the child is allergic to pollen it is also called hay fever. Eczema was defined as a genetically determined skin barrier defect combined with typical clinical skin manifestations, such as dry skin and itchy rash in the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the ears, eyes or neck.

Food allergy was defined as an adverse reaction to food, caused by immunological mechanisms. The most frequent food allergies in pre-school children in Sweden are allergies to milk, egg, fish, wheat-flour, peanuts, nuts, soy and stone fruits.

According to the Global Initiative for Asthma (GINA) [26] asthma was defined as 'a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment'.

According to the GINA report 'Global Strategy for Asthma Management and Prevention in Children 5 Years and Younger' [27] the asthma symptoms in pre-school children are less specific than in older children and adults. In childhood, asthma is the most frequent chronic disease, and before adolescence boys are more affected than girls. The majority of the asthmatic children have an underlying atopic predisposition. Nevertheless, it is difficult to determine, if the child has asthma or episodic wheeze due to common cold, also referred to as viral wheeze, wheezy bronchitis or transitional wheeze.

A combination of wheezing, allergic sensitization or symptoms, and asthmatic or atopic parents support an asthma diagnosis. Episodic wheeze during the first years of life, in connection only with viral infections and with no other factors involved, usually disappears before school age [28, 29]. Contrary to episodic wheeze, asthma frequently continues, especially if the child is sensitized to aeroallergens and has eczema or rhinitis [30-32].

During the first two years of life, viral infections are the most important trigger factors for wheezing episodes, whereas after 3 years of age allergies to furred pets and pollen increase in significance [29, 33]. Environmental tobacco smoke at home leads to more frequent wheeze in children with episodic wheeze as well as in children with atopic or allergic asthma [34].

Dampness and mould growth [35], phthalates from polyvinyl chloride (PVC) [36], and exposure to traffic-related air pollution [37, 38] have been associated with symptoms of asthma and allergies. However, more studies are needed on trigger factors and the chaine of causation leading to incident asthma in which the trigger factors are located.

Prevalence and incidence of asthma and allergies in population based cohort studies

In the International Study of Asthma and Allergies in Childhood (ISAAC), a worlwide study of the prevalence of asthma, allergic rhinoconjunctivitis, and eczema symptoms, a questionnaire was distributed to schools in the vicinity of 155 research centres in 56 countries [39]. After 5-10 years, in most instances in 2002-2003, a follow-up questionnaire was distributed. Large differences in prevalence between countries were reported also in the follow-up questionnaire.

The prevalence of asthma symptoms, *i.e.,* wheezing in the past 12 months, in 6 to 7-year-olds varies from 2.8% in Indonesia to 37.6% in Costa Rica, allergic rhinoconjunctivitis from 2.2% in Iran to 24.2% in Taiwan, eczema from 2% in Iran to 22.3% in Sweden. Although Sweden has the highest prevalence of eczema, the prevalence of asthma symptoms (10.2%) and allergic rhinoconjunctivitis (6.9%) are both in the middle of the international range. Moreover, increase of prevalence is more common than decrease of all three disorders in the 6-7 year age group in various countries [40].

Before the present study was initiated there were three large on-going cohort studies in Sweden. The BAMSE birth cohort (Children, Allergy Milieu Stockholm Epidemiological survey) [41], initiated in 1994, covers a cohort of 4089 newborn infants in Stockholm. Follow-up investigations were made at age 1, 2, 4, 8, and 12 years. The OLIN (Obstructive Lung Disease in northern Sweden) [42] first paediatric cohort, initiated in 1996, covers 3431 school children 7-8 years old in Norrbotten, the northernmost region. Yearly follow-up investigations have been made and reported up to13 to 14-years of age [43]. Finally, the DBH cohort (Dampness in Buildings and Health) [44], initiated in 2000, covers 10,851 1 to 6-years old children in Värmland, the westernmost region. A follow-up investigation of the youngest children 1-3 years old at start was made five years after baseline [45]. A ten-year follow-up investigation of the whole cohort, ten years after baseline, is in progress. During the 1980s and 1990s a number of large birth cohort studies were initiated in other European countries [46-53], covering 1,314-3,754 children, and in Tucson USA [54].

All these studies were designed to discover protective factors, risk factors and underlying causes for the development of asthma, atopy and allergy. Generally, the studies reported data on the prevalence of asthma, rhinitis or eczema at age 2, 3, 6, or 8 in various publications, but not how prevalence depended on age in a given publication. In a few reports based on study populations of various ages the asthma, rhinitis and eczema prevalence was given as age specific prevalence [54, 55].

Although there are numerous studies on the prevalence of asthma and allergies, only a few present age and sex-specific prevalence [44, 56, 57] and a minority has taken age in consideration in studies on incidence of childhood asthma [28, 45, 58, 59]. Moreover, the children generally are recruited from a limited area around the study centre or from a region. Furthermore, the definition of asthma varies between studies, for example a cumulative physician asthma diagnosis is used, or only prevalence of wheezing is estimated. Therefore, there is a need of age and sex specific data covering more than one age cohort.

Co-occurrence of asthma, rhinitis, eczema and food allergy - the 'atopic march'

Earlier studies have shown a tendency towards co-occurrence, or co-morbidity, of asthma and allergy manifestations, so that children who have one of the diseases tend to have one or more of the other as well [41, 60]. It has been claimed that the diseases tend to come in a specific, or ranking, order, for instance that eczema tends to be followed by asthma, in turn followed by other allergy manifestations [61, 62]. This phenomenon has been labelled "the atopic march".

In this thesis the issues of co-occurrence and atopic march have been dealt with separately. The information on the extent of co-occurrence is still fragmentary, and co-occurrence may be analysed more efficiently, even in a cross-sectional design. The issue of atopic march, implying the same ranking order of asthma and allergy onset in all affected individuals, imposes a more difficult analysis problem. A preliminary, or provisional, conclusion on whether the atopic march exists or not may be obtained in a cross-sectional design, but a more definite conclusion requires a longitudinal design with a large study population with frequent follow-up examinations.

Rationale and considerations regarding the present study design

The project on which this thesis is based was planned in the late 1990s with the purpose to test the hypothesis that avoidance of allergen exposure in small children, at home and in day care, might lessen the chance of developing asthma and various forms of other allergies. However, the design of the study had to be such that also a number of other hypotheses might be possible to test.

From previous studies it appeared that the prevalence of asthma and other allergies was highly dependent on the geographical and demographic setting of the study area, which probably means that also the determinants of these conditions, *i.e.*, causes and trigger factors, are dependent on geography and demography. For these reasons a study with a nationwide recruitment basis would be preferable to a study performed locally.

Furthermore, the study population should be large enough to allow analyses not only of the total study population but also of subgroups with a reasonable statistical power. To avoid interpretational problems the attrition rate should be small to moderate, and if possible accountable.

Given these considerations we decided to use all available AADCs in the country, and two matching ODCs for each AADC as recruitment base for the study population. The study population proved to be large enough for the project purposes, and the response rate was far better than would expected from a random national sample of children. A first follow-up investigation has been performed. The original hypothesis was not tested in this thesis, mainly because some of the necessary follow-up data were not at hand when the thesis was finalised. However, a number of other, from the project point of view, important hypotheses were successfully tested.

Aims of the thesis

The general aim of this project was to study the age and sex specific occurrence of atopic and non-atopic asthma and other atopic manifestation in a nationwide sample of Swedish pre-school children attending AADCs and matching ODCs.

Scientific aims

1. To investigate differences in the indoor environment in AADCs and ODCs regarding cleaning frequency and extent, occurrence of indoor and building factors related to dust, allergens and irritants, such as open shelf surface area, use of textiles, and cupboards reaching the ceiling, and restrictions regarding furred pets, smoking and use of perfume.
2. To study the effects on asthma prevalence of various diagnostic criteria, to estimate age and sex-specific asthma prevalence in pre-school children, and to study possible effects on asthma prevalence of geographical location (latitude and longitude) and municipality population size and density as proxies of degree of urbanisation
3. To analyse the age specific prevalence of asthma, rhinitis, eczema, and food allergy, and the co-morbidity, or co-occurrence, of the various atopic manifestations
4. To analyse asthma incidence and its determinants during five years of follow up

Study population and methods

Study population

In the late 1990s all 72 AADCs in Sweden were identified. The two geographically closest ODCs to each AADC were chosen as control centres. One third of the AADCs were located in the same building as a control ODC. A questionnaire was mailed to the local DC directors. After several reminders and phone calls when necessary, 84 out of 91 (92%) AADCs, 185 of the 218 (85%) nearest day-care sections, and 170 of the 222 (77%) of the second nearest sections responded. These DC sections constitute the study population of Paper I. Later, a few AADCs were closed and a few new ones were opened, leaving 70 AADCs with 84 sections and 140 ODCs with 440 sections as basis for Papers II-IV, in 62 municipalities, covering all of Sweden, Figure 1.

The addresses of the 1,412 children attending the AADCs and the 7,345 children attending the ODCs were obtained from the local school authorities. A questionnaire was mailed to the parents of these children. Responses were obtained regarding 1,001 AADC children (70.9%) and 4,958 ODC children (67.5%) after two reminders when necessary. Of the respondents, 1,000 AADC children and 4,886 ODC children were 6 years old or younger. They constitute the study population for Papers II and III.

In 2007 a follow-up questionnaire was sent to the total original sample. Of those who responded to the baseline questionnaire, parents to 742 (74.2%) former AADC children and 3513 (71.9%) former ODC children, aged 1-6 years at baseline and 6-11 years at follow up, altogether 4255 children, responded to the follow up questionnaire. Of these, 227 AADC children and 313 ODC children, altogether 540 children, fulfilled the asthma definition at baseline, leaving 3,715 children exposed to the possibility of suffering from incident asthma during follow up. These children constitute the study population of Paper IV.

Data collection

Day-care centre questionnaire

The questionnaire aimed to gather information related to the particular day-care section. It included questions on numbers of children and staff, age distribution of the children, education on allergy issues among staff, and different aspects of the indoor and outdoor environments. These included building age and design, redecoration, visible mould growth and building dampness, proximity of major roads, and questions on cleaning routines, open shelves, and fixtures. There were also some questions on allergy policies concerning use of perfumes, restrictions concerning serving high risk allergenic food (fish, soy, nuts, peanuts, and eggs), and furry pets and smoking in the dwellings of children and staff.

Parental questionnaire

The baseline questionnaire was based on the validated [63] ISAAC written screening questionnaire with questions about asthma and wheezing, eczema and rhinitis, extensively used all over the world and regarded as the gold standard for postal questionnaires on childhood asthma, was used [64]. Even though intended for children 6 years or older it has been validated down to three years of age with good results [65]. For this study, supplementary questions on medical treatment, physician assessed asthma diagnosis, parental education, smoking habits, breastfeeding, indoor environmental factors, such as moisture, painting, wall-to-wall carpets, etcetera, exposure to furred pets during the first year of life, age of entry to DC, number of older siblings, whether the parents had asthma, rhinitis eczema, and furred pet allergy, and some additional variables not used here, were added.

Regarding asthma the following questions were asked: 1) 'Has your child had wheezing or whistling in the chest in the last 12 months?' (yes/no) indicating current symptoms, 2) 'How many attacks of wheezing has your child had in the last 12 months' (≥4 attacks were used as criterion), 3) 'Has your child received an asthma diagnosis by a physician?' (yes/no), and 4) 'Has your child ever had asthma'(yes/no). Moreover, 5) current use of inhalation steroids was obtained from the requested list of medications during the last year in the questionnaire. We defined prevalent asthma as a positive response to criterion 2, or criteria 3+1, or criteria 4+1, or criterion 5.

The following rhinitis related questions were asked: 1) 'In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when the child did not have a cold or the flu?' (yes/no) indicating current symptoms, 2) 'Has this nose problem been accompanied by itchy-watery eyes?' (yes/no), 3) 'Has your child received a hay fever or allergic rhinitis diagnosis by a physician?' (yes/no), 4) 'Has your child ever had hay fever?' (yes/no), 5) 'Have you noticed allergies to pollen or furred pets'? (yes/no, one question each for cat, dog, horse, and rodent), and 6) current use of antihistamines or nasal steroids was obtained from the list of medications. In accordance with the asthma definition above we defined prevalent rhinitis as a positive response to criterion 2, or criteria 3+1, or criteria 4+1, or criteria 5+1, or criteria 6+1.

In this study the term eczema was used in the sense of atopic dermatitis. The following eczema related questions were asked: 1) 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' (yes/no), 2) 'Has your child had this itchy rash at any time in the last 12 months?' (yes/no) indicating current symptoms, 3) 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?' (yes/no), and 4) 'Has your child received an eczema diagnosis by a physician?' (yes/no), and 5) current use of steroid ointments was obtained from the list of medications. Prevalent eczema was defined as a positive response to criteria 3+2+1, or criteria 4+2+1, or criteria 5+2+1.

The following question related to food allergy: 'Has your child a food allergy' with specification regarding food items. In this study indicated allergy towards milk, egg, fish, peanuts, nuts, soy, or stone fruit, but not lactose or gluten intolerance, were used as definition of food allergy.

The follow-up questionnaire was identical to the baseline one, except that some questions on early life exposure were dropped, and the same definitions as shown above were used.

Register data

Data on the number of boys and girls per one-year age groups in the age range 1-6 years in 2002 for each of the 62 municipalities was downloaded from Statistics Sweden [66], as were data on municipality total population size, population density (population per square kilometre municipality area), and national population distribution in the three traditional parts of Sweden (Götaland, Svealand, and Norrland), and the proportion of children attending DCs by age, sex, and municipality. Information on geographical coordinates (latitude and longitude) of the municipalities was obtained from the National Land Survey of Sweden. The latitude range was 55.6 - 65.7 degrees North and the longitude range was 11.9 - 22.0 degrees East.

The study was approved on several occasions before and during the data collection process, first by the Research Ethics Committee at Uppsala University and later by the National Research Ethics Board.

Statistical consideration

The statistical analyses were conducted using the SAS software, version 9.1 [67]. Partial non-response (missing data in returned questionnaires) was on average 0.3%-0.6%, depending on variables used. Summary statistics, such as mean values and measures of dispersion, were computed using standard parametric methods. Simple (crude) differences between groups in continuous variables were tested with Student's t-test, and differences in proportions were tested with the chi-square test, based on the total study population.

Paper I

Chi-square statistics and Mann–Whitney U-test was used to compare differences in data with ordinal scales or data which were not normally distributed, *e.g.* cleaning frequency and year of construction. Adjusted odds ratios (OR) with a 95% CI were calculated by logistic regression, adjusting for building age as a continuous variable. AADC sections were coded 1 and ODC sections were coded 0. All tests were two tailed, and a P-value below 0.05 was used to indicate statistical significance.

Paper Π

Two models for the prevalence calculations were used. In the first model, often used in other similar studies, only the ODC study population data was used, on the assumption that it represents a random sample of Swedish preschool children. However, this assumption may be questioned since most of the municipalities were represented in this study by only one AADC and two ODCs, irrespective of population size, causing an under-representation of large municipalities in the calculations of asthma prevalence.

Therefore, a second model was employed in which the number of children with asthma by age and sex and the total number of children by age and sex in each municipality was obtained. The number of children with asthma in each age and sex group was calculated as: (% children with asthma in the local ODCs) x (number of children in the municipality) + number of children with asthma in the local AADCs. The nationwide age and sex specific asthma prevalence was obtained as the ratio of the total number of children with asthma across all municipalities and the total number of children across all municipalities, thereby automatically weighted for municipality size.

The analyses of asthma prevalence determinants were performed with logistic regression using asthma diagnosis (model 1) or asthma prevalence (model 2) as the dependent variable and age, sex and other possible determinants as independent variables, providing odds ratios and their confidence intervals, p-values, and Wald's chi-square. The latter is the test variable on which the p-value is based. Consequently, Wald's chi-square may be used to rank the impact of the independent variables.

As shown in Table 2, the number of one-year-old children was smaller than in the other age groups. However, the results in specific age-sex groups were based on estimates from the full model, which makes small numbers in certain subgroups of less importance. Moreover, age-sex specific confidence intervals are provided for the main results.

The fit between the crude age and sex-specific prevalence and that obtained from the two analysis models was tested with logistic regression technique. In model 2, inclusion of age, age squared and an interaction term between age and sex as independent variables gave the best fit, explaining 50% of the prevalence variation. In model 1, the prevalence across age appeared to be linear for boys, whereas that for girls was similar to the trend line in model 2. On scrutiny, the fits appeared excellent. The curves in Figures 3 and 4 were obtained with logistic regression technique. All tests were two-tailed. The level of significance was set at $p < 0.05$.

Paper III

The analyses of co-occurrence between asthma, rhinitis, eczema, and food allergy were performed with multiple logistic regression analysis with presence of asthma, rhinitis, eczema, and food allergy (yes/no) as dependent variable, one at a time, and the others as independent variables, all analyses adjusted for the influence of age and sex. The analytical technique provides odds ratios (OR) and their, in this case, 95% confidence intervals (95%CI), and Wald's chi-square.

Most of the municipalities represented in this study had only one AADC and two ODCs, irrespective of population size, resulting in under-representation of large municipalities in the prevalence calculations. To adjust for this circumstance, model 2 from Paper II was employed.

The age-specific prevalence functions were then computed with logistic regression. The fit between the crude age-specific prevalence and prevalence data generated from the analysis model was tested with logistic regression technique. A model including a second (asthma and rhinitis) or third (eczema and food allergy) degree age polynomial and an interaction term between age and sex gave the best fit, explaining 50% of the prevalence variation. On scrutiny, the fit appeared excellent. All tests were two-tailed. The level of significance was set at $p<0.05$.

Paper IV

The analyses of asthma incidence and its determinants were based on those in the study population than did not fulfil the asthma definition at baseline. The analyses were performed in two steps. First, a set of bivariate screening logistic regression analyses were performed with incident asthma at follow up as the dependent variable and a wide range of possible candidate determinants as independent variables, one at a time. The analytical technique provides odds ratios (OR), confidence intervals, Wald's chi-square, and degree of explanation. The degree of explanation was receiver operating curve (ROC) based, and provides the so far most unbiased measure of degree of explanation.

Then a final multivariate logistic regression model was set up with incident asthma at follow up as the dependent variable and the significant candidate determinants as the dependent variables. To avoid model overload, backward elimination of non-significant variables was used. To check the results the model was tested with all candidate determinants, whether significant or not in the screening analyses. However, the results of the two approaches were identical. When the final determinants were identified a new model test with only these determinants was done in order to avoid unnecessary exclusions due to missing data.

The analytical model was visualized (Figure 8) by means of logistic regression technique, where the effect of typical values for age and the other determinants was produced. All tests were two-tailed. The level of significance was set at $p<0.10$ in the screening analyses and at $p<0.05$ in the final analytical model. The confidence intervals were computed accordingly.

Results

Characteristics of the study population

The characteristics of the DCs are shown in Table 1. The AADCs had an average of three fewer children per section, and one less child per staff member. Most of the staff at the AADCs had education on allergy issues, but such education was very rare in ODCs. In addition, almost all AADCs had restrictions on keeping furry pets at home, both among the children and among the staff, while such restrictions were very rare in ODCs. The same pattern was found for restrictions on indoor smoking at home, and restrictions on use of perfume.

The characteristics of the children in the study population (N = 5,886) are shown in Table 2. The proportion of children was similar in the age range 2–5 years and lower for those 1 and 6 years old. Boys made up slightly more than half of the study population. The regional distribution was approximately the same as that of the Swedish national population. The age, sex and regional distributions were similar at the AADCs and ODCs.

As expected, the children in the AADCs reported more symptoms and higher rates of asthma than children in the ODCs, Table 3. The most frequently reported symptoms in the total study population were ever wheezing, wheezing any time during the last 12 months, dry cough at night with no cold, and night awakening due to wheezing. Approximately one third of the AADC children reported ever having asthma, a physician assessed asthma diagnosis, or being on inhalation steroid treatment. The corresponding frequencies among the ODC children were 9%, 8% and 6%.

The characteristics of the children free from asthma at baseline (N = 3,715), analysed in Paper IV, are presented in Table 4. The baseline age range was 1-6 years, mean 3.6-3.8, and somewhat less than half were boys. The proportion of children introduced to day-care centres before two years of age was 84%. The most common allergy diseases were in ranking order eczema, food allergy, rhinitis, pollen allergy, and furred pet allergy. The AADC children generally had higher prevalence at baseline of all allergy diagnoses, but not of asthma related symptoms.

The prevalence of parental asthma and allergies ranged from 62% for rhinitis among AADC children to 18% for asthma among ODC children. The prevalence in parents of AADC children was generally higher than those in parents of ODC children. The most common parental disease in the two

Table 1. *Staffing and rules among allergen avoidance day-care centres and ordinary day-care centres*

	Allergy section (n=84)		Ordinary section (n=355)		
	Mean	95%CI	Mean	95%CI	*P*-value[a]
No. of children	14.9	14.0-15.7	17.6	17.2-18.0	<0.001
No. of staff	3.0	2.8-3.1	3.0	2.9-3.0	0.87
Children per staff	5.2	4.8-5.5	6.1	5.9-6.2	<0.001
Allergy education (%)	86.9	79.7-94.1	24.5	20.0-29.0	0.001
Restrictions on parents (%)					
No furred pets	98.8	96.5-100.0	1.4	0.2-2.6	0.001
No smoking	83.3	75.4-91.3	0.6	0-1.3	0.001
Restrictions on staff (%)					
No furred pets	92.9	87.4-98.4	1.4	0.2-2.6	0.001
No smoking	89.3	82.7-96.0	3.1	1.3-4.9	0.001
Ban on perfume use (%)	100.0	-	24.5	20.0-29.0	0.001

[a] Calculated using 2 x 2 chi-square contingency table

Table 2. *Characteristics of the study population at baseline*

	Asthma and allergy day-care centres		Ordinary day-care centres	
	n	%	n	%
Age	1000	-	4886	-
1	49	4.9	203	4.2
2	219	21.9	916	18.8
3	221	22.1	976	20.0
4	192	19.2	1017	20.8
5	202	20.2	1168	23.9
6	116	11.6	606	12.4
Boys	545	54.5	2476	50.7
Parts of Sweden				
South (Götaland)	416	41.6	2135	43.7
Central (Svealand)	394	39.4	1841	37.7
North (Norrland)	190	19.0	910	18.6

groups were in ranking order rhinitis, furred pet allergy or eczema, and asthma, significantly more in parents of AADC than of ODC children. Half of the parents had college or university education, and 11% or less were smokers. The total breastfeeding time was 10 months, and the time with exclusive breastfeeding was five months in both groups of children.

During the child's life the vast majority had indoor painting performed in their homes, one third had moisture problems, only a few percent had wall-to-wall carpets, and 6% to 18% had dogs or cats in their homes during the first year of life.

Table 3. *Responses to some of the ISAAC asthma and supplementary questions in the baseline questionnaire*

	Asthma and allergy day-care centres		Ordinary day-care centres	
	n	%	n	%
Ever wheezing	454	45.7	1326	27.3
Possibly false croup	5	0.5	58	1.2
Wheezing in last 12 months	385	38.8	908	18.7
1-3 times	170	17.1	656	13.5
4-12 times	139	14.0	193	4.0
>12 times	74	7.5	49	1.0
Wheezing with no cold	207	20.9	299	6.2
Wheezing at exercise	227	22.9	306	6.3
Severe wheezing[a]	105	10.6	134	2.8
Night awakenings[b]	286	28.9	564	11.6
< once a week	203	20.5	435	9.0
Weekly or more often	83	8.4	129	2.7
Dry cough at night[c]	291	29.5	711	14.7
Ever had asthma	328	33.0	446	9.2
Physician diagnosis	304	30.7	364	7.5
On inhalation steroids	276	27.6	274	5.6
Emergency treatment	206	20.8	354	7.3

[a] Wheezing severe enough to interfere with speech
[b] Night awakenings due to wheezing
[c] Dry cough at night with no cold

Paper I

Building characteristics

The median building construction year was 1987 for AADCs (inter quartile range 1975–1990), and 1977 for ODCs (inter quartile range 1972–1986), a significant difference. The oldest DC was built in 1864. The majority of the AADCs were built after 1983, while the majority of the ODCs were built before 1984.

The majority of both types of DCs were in special day care buildings, a minority were situated in the same building as a primary school, or in residential buildings. The distribution of building type differed between AADCs and ODCs, with more AADCs in residential buildings. Vinyl/PVC floor covering was less common, and wooden floors more common in AADCs, otherwise there were no significant differences in type of floor material. None of the AADCs and one (0.3%) of the ODCs had wall-to-wall carpets.

Table 4. *Baseline characteristics of the study population among* allergen avoidance day-care centre *(AADC) and* ordinary day-care centre *(ODC) children free from asthma at baseline (N = 3,715)*

	AADC children		ODC children		
	N	Mean (SD) or %	N	Mean (SD) or %	*P*-value
N	515		3200		
Age, years		3.6 (1.47)		3.8 (1.41)	<0.005
Boys, %	250	48.5	1577	49.3	0.76
Day-care centre introduction before age 2, %	431	84.3	2670	84.0	0.76
Proportion with older siblings, %	294	57.4	1876	59.0	0.79
Diseases and symptoms, %					
Asthma	0	0	0	0	-
Ever wheezing	90	17.5	584	18.3	0.59
Wheezing in last 12 months	51	9.9	348	10.9	0.51
Ever had asthma	17	3.3	65	2.0	0.07
Physician asthma diagnosis	8	1.6	32	1.0	0.26
Rhinitis	56	10.9	193	6.0	<0.0001
Eczema	161	31.3	653	20.4	<0.0001
Food allergy	119	23.2	185	5.8	<0.0001
Pollen allergy	39	7.6	118	3.7	<0.0001
Furred pet allergy	36	7.0	88	2.8	<0.0001
Parental diseases, any parent, %					
Asthma	131	25.5	587	18.4	0.0001
Rhinitis	320	62.3	1600	50.0	<0.0001
Eczema	206	40.1	1014	31.7	<0.0005
Furred pet allergy	220	42.7	947	29.6	<0.0001
Parental information, %					
College or university education	283	55.0	1522	47.6	<0.001
Smoking during pregnancy	22	4.3	302	9.6	0.0001
Smoking at home after pregnancy	26	5.1	353	11.2	<0.0001
Total breast-feeding time, months		10.0 (6.66)		9.8 (6.57)	0.51
Exclusive breast-feeding, months		5.2 (3.34)		5.2 (3.62)	0.98
Home environment during the child's life, %					
Ever indoor painting	454	88.2	2850	89.1	0.54
Ever moisture problems	172	33.4	1024	32.0	0.53
Ever had wall-to-wall carpets	7	1.4	67	2.1	0.27
Cat during first year of life	36	7.0	590	18.4	<0.0001
Dog during first year of life	29	5.6	479	15.0	<0.0001

There were no differences in frequency of re-modeling, such as change of floor material or indoor painting during the last 12 months, Table 5.

Building dampness was common both in AADCs and ODCs. A total of 25.3% of the AADCs and 39.1% of the ODCs had either past or present signs of building dampness or indoor mould growth (P = 0.02). Dampness or moulds previous to the last year, was less common in AADCs (20.5%) than

Table 5. *Selected building characteristics of the day-care centre buildings*

	Allergy section (n=84)		Ordinary section (n=355)		
	%	95%CI	%	95%CI	*P*-value
Year of construction					
1870-1974	20.0	11.2-28.8	31.9	27.0-36.8	0.001[a]
1975-1983	20.0	11.2-28.8	39.9	34.8-45.1	
1984-1990	30.0	20.0-40.0	16.5	12.5-20.3	
1990-1998	30.0	20.0-40.0	11.7	8.4-15.2	
Location of the day-care section					
In separate day-care centre building	63.1	52.8-73.4	83.9	80.1-87.8	0.001[b]
In same building as a primary school	3.6	0-7.5	3.1	1.3-4.9	
Situated in a single-family house	11.9	5.0-18.8	2.3	0.9-4.1	
Situated in a multi-family house	15.5	7.7-23.2	4.8	2.6-7.0	
Situated in other type of building	5.6	0.1-11.0	5.9	3.5-8.4	
Building characteristics					
Wooden building	67.5	57.4-77.5	70.2	65.4-75.0	0.63[c]
Basement	16.7	8.7-24.6	17.2	13.3-21.2	0.90[c]
Flat roof	17.9	9.7-26.1	23.5	19.0-27.9	0.27[c]
Type of floor and wall material					
Linoleum floor	56.8	46.0-67.6	51.2	45.9-56.7	0.36[c]
Vinyl (PVC) floor	53.1	42.2-64.0	68.1	63.2-73.0	0.01[c]
Wooden floor	7.4	1.7-13.1	1.7	0.4-3.1	0.005[c]
Wall-to-wall carpet	0	-	0.3	0-0.9	0.63[c]
Textile wall covering	10.7	4.1-17.3	23.1	18.7-27.5	0.01[c]
Recent redecoration					
New floor last year	9.5	3.2-15.8	6.5	3.9-9.1	0.34[c]
Re-painted last year	14.3	6.8-21.8	14.9	11.2-18.6	0.88[c]

Calculated using [a] 2 x 4, [b] 2 x 5, and [c] 2 x 2 chi-square contingency table

in ODCs (31.9%). Moreover, reports of odours, other than a mouldy odour, were less common at AADCs. Condensation on window frames in winter was uncommon both in AADCs (1.2%) and ODCs (4.6%), a non-significant difference, Table 6.

As a next step, predictors of dampness and indoor mould growth were evaluated by comparing building characteristics of buildings with and without dampness/ moulds in the total material of the day care section (N = 439). The main difference was in building age. Sections that had dampness currently or ever were more often located in older buildings built before 1975. For sections located in buildings built during 1975–1983, there was a borderline significance for current dampness problems ($P<0.05$). Sections located in buildings built from 1984 to 1990 had less often current dampness or ever dampness. Finally, the newest buildings had less often ever dampness.

The second predictor of dampness/moulds was a flat roof, which was more common in buildings ever having dampness. In fact, 31.6% of all DCs with a history of dampness problems had a flat roof. Type of external building material (wood/concrete), presence/absence of basement, wet mop-

Table 6. *Reports on dampness, odor and indoor molds in the day-care centre buildings*

	Allergy section (n=84)		Ordinary section (n=355)		
	%	95%CI	%	95%CI	*P*-value [a]
Current dampness					
Water leakage/flooding last year	6.0	0.9-11.0	9.5	6.4-12.6	0.30
Dampness in the floor construction last year	3.6	0-7.5	6.6	4.0-9.2	0.29
Visible indoor mold growth last year	0	0	0.6	0-1.4	0.49
Mouldy odor last year	0	0	3.5	1.5-5.4	0.08
Any type of current dampness[b]	9.5	3.2-15.8	18.3	14.0-22.0	0.06
Previous dampness					
History of dampness/molds before last year	20.5	11.8-29.2	31.9	27.0-36.8	0.04
Current or previous dampness (combinations)					
Neither current nor previous dampness/molds	74.7	65.3-84.1	60.9	55.8-66.1	0.02
Previous but not current dampness/molds	15.7	7.8-23.5	20.4	16.1-24.7	0.33
Current but not previous dampness/molds	4.8	0.2-9.4	7.0	4.3-9.7	0.47
Both current and previous dampness/molds	4.8	0.2-9.4	11.7	8.3-15.1	0.07
Other indoor factors					
Window condensation during winter time	1.2	0-3.5	4.6	2.4-6.8	0.15
Other type of odor (not moldy) last year	8.3	2.4-14.2	20.2	15.9-24.4	0.01

[a] Calculated using 2 x 2 chi-square contingency table

ping, or type of floor material was not related to current or previous building dampness/indoor moulds. Moreover, there were no regional differences in dampness/moulds, Table 7.

Outdoor environment

Most buildings were situated in urban areas: 25% in larger cities (>100,000 inhabitants), 41% in larger towns (50–100,000 inhabitants), 25% in middle-size towns (10–50,000 inhabitants), and 9% in smaller towns/villages (<10,000 inhabitants). A total of 7.2% of the AADCs and 11.6% of the ODCs were situated closer than 500 m from a stable, horse enclosure, or an animal farm. A total of 21.4% of the AADCs and 22.9% of the ODCs were situated closer than 50 m from a heavily trafficked road, and 16.7% of the

Table 7. *Characteristics among all 439 day-care centre sections, in relation to building dampness/molds*

	Current dampness %			Never-dampness	Ever dampness	
	No	Yes	*P*-value[a]	%	%	*P*-value[a]
Building characteristics						
Wooden building	69.6	69.6	0.99	67.2	75.2	0.09
Basement	17.6	16.7	0.86	18.5	15.4	0.42
Flat roof	21.0	29.2	0.13	16.6	31.6	0.001
Wet mopping	64.0	70.8	0.27	61.6	70.5	0.06
Linoleum floor	52.7	52.2	0.94	53.6	51.0	0.61
PVC floor	64.6	68.1	0.57	63.0	69.3	0.20
Wooden floor	2.8	2.9	0.98	3.4	2.0	0.40
Year of construction						
1870-1974	29.1	33.3	0.048	21.9	42.4	0.001
1975-1983	34.2	46.4	0.054	33.6	41.4	0.13
1984-1990	21.1	8.7	0.02	25.7	8.0	0.001
1990-1998	15.7	11.6	0.39	18.9	8.6	0.005
Parts of Sweden						
South (Götaland)	41.0	44.4	0.58	43.9	37.4	0.19
Central (Svealand)	48.2	47.2	0.88	45.0	52.9	0.12
North (Norrland)	10.9	8.3	0.52	11.1	9.7	0.65

[a] Calculated using 2 x 2 chi-square contingency table

AADCs and 17.5% of the ODCs were situated closer than 1000 m from an industry or other occupational activity emitting air pollution. As wood heating is common in Sweden, there was a question on perception of smoke from wood combustion outdoors during wintertime. A total of 11.9% of the AADCs and 12.6% of the ODCs reported weekly smell from wood heating in winter. None of these differences in outdoor factors were significant, except being situated near an industry with air pollution, a risk factor less common for the AADCs, Table 8.

Furnishing, fixtures and cleaning routines

The AADCs had cupboards reaching up to the ceiling (no interspaces) significantly more often, fewer open shelves with books, fewer long curtains, and fewer flowers and pot plants. The vast majority of the sections, regardless of type, had written cleaning instructions, but such instructions were more common at the AADCs. Most had daytime cleaning and daily floor cleaning, regardless of type. Daytime cleaning was, however, less common in the AADCs, and frequent (daily) floor cleaning was more common. The most common methods of floor cleaning were dry electrostatic mopping and wet mopping. Wet mopping was less common and use of central vacuum cleaner was more common at the AADCs. In addition, wiping of furniture,

Table 8. *Selected outdoor exposure factors for the day-care centre buildings*

	Allergy section (n=84)		Ordinary section (n=355)		
	%	95%CI	%	95%CI	*P*-value [a]
Distance to stable, horses, or animal farm (m)					0.24
<50	0	-	0.9	0-1.8	
50-200	2.4	0-5.6	3.4	1.5-5.3	
200-500	4.8	0.2-9.3	7.3	4.6-10.0	
>500	92.9	87.4-98.4	88.5	85.1-91.8	
Distance to heavy trafficked road (m)					0.98
<25	10.7	4.1-17.3	14.7	11.0-18.3	
25-50	10.7	4.1-17.3	8.2	5.3-11.0	
50-200	29.8	20.0-39.5	26.8	22.2-31.4	
>200	48.8	38.1-59.5	50.4	45.2-55.6	
Distance to industry with air pollution (m)					0.048
<1000	16.7	8.7-24.6	17.5	13.6-21.5	
1000-5000	10.7	4.1-17.3	24.0	19.6-28.5	
>5000	72.6	63.1-82.2	58.5	53.3-63.6	
Smell from wood heating in winter					0.55
Never	61.9	51.5-72.3	66.4	61.4-71.3	
<1/week	26.2	16.8-35.6	21.1	16.8-25.3	
1-4 times/week	9.5	3.2-15.8	8.6	5.6-11.5	
Every day	2.4	0-5.6	4.0	1.9-6.0	

[a] Calculated using Mann-Whitney *U*-test

and washing of pillows/mattresses and curtains was more common at the AADCs, Table 9.

Finally, multiple logistic regression was used to calculate OR with 95% CI for significant indoor environmental characteristics, adjusting for building age as a continuous variable, Table 10. Adjusting for age did not change the results. In the bivariate analysis (Tables 5 and 6) there were no significant differences between the AADCs and the ODCs regarding water damage, floor dampness, having a basement, a flat roof, or being situated in a wooden house. Multiple regression analysis, adjusting for building age, did not change these findings.

Characteristics of the allergy avoidance day-care centres

There was a set of questions specifically aimed to characterize different aspects of the AADCs. The AADCs had different names, the most common being ’allergy adapted day-care centre’ (48%), other names were ’allergy day-care centre’ (26%) or ’allergy sanitized day-care centre’ (19%). The initiative to establishing the AADCs come from many different sources, including municipal school administrations, parents, local politicians, and

Table 9. *Furnishing, fixtures and cleaning procedures in the day-care centre sections*

	Allergy section (n=84)		Ordinary section (n=355)		
	%	95%CI	%	95%CI	*P*-value
Furnishing and fixtures					
Cupboard reaching up to the ceiling	66.3	56.1-76.4	19.2	15.1-23.2	0.001[a]
Total shelves length <1 m	56.1	45.4-66.8	32.7	27.8-37.6	0.001[a]
Short or no window curtains	44.1	33.4-54.7	29.3	24.6-34.0	0.009[a]
Presence of any flowers or pot plants	20.2	11.6-28.8	90.4	87.4-93.5	0.001[a]
No. of flowers or pot plant per section (mean)	1.5	0.8-2.3	11.9	10.9-12.9	<0.001[a]
General cleaning procedures					
Written cleaning instructions available	84.0	76.0-91.9	70.5	65.6-75.4	0.014[a]
Daytime cleaning (6.30 AM to 6 PM)	73.4	63.7-83.2	86.1	82.5-89.8	0.006[a]
Daily floor cleaning	97.6	94.4-100	80.3	76.1-84.4	0.001[a]
Floor cleaning methods					
Ordinary vacuum cleaning	32.9	22.8-43.1	35.9	30.9-40.9	0.62[a]
Central vacuum cleaning	34.2	23.9-44.4	3.4	1.5-5.3	0.001[a]
Dry electrostatic mopping	61.0	50.4-71.5	63.0	58.0-68.0	0.73[a]
Wet mopping	52.4	41.6-63.2	67.5	62.6-72.4	0.01[a]
Wiping of furniture[b]					<0.001[c]
Less than once/month	0	-	26.9	22.3-31.5	
A few times/month	10.0	3.4-16.6	28.9	24.2-33.6	
1-3 times/week	47.5	36.6-58.4	38.8	33.7-43.9	
4-7 times/week	42.5	31.7-53.3	5.4	3.0-7.7	
Textile cleaning					
Pillows/mattress washing >2/year	87.7	80.5-94.8	71.1	66.3-75.8	0.002
Curtain washing >2/year	43.6	32.6-54.6	8.0	5.1-10.8	0.001

[a] Calculated using 2 x 2 chi-square contingency table
[b] Chairs, shelves, window ledges
[c] Calculated using Mann-Whitney *U*-test

local day care staff. A total of 38% were situated in the same building as an ODC. Mostly, allergic or asthmatic children with a certificate issued by a physician had priority of attendance, but only six AADCs (7%) exclusively recruited allergic children. Siblings or other non-allergic or non-asthmatic children were often recruited in order to have a sufficient number of children. Most of the AADCs (61%) had not had any support from an allergy doctor or nurse during the last year, while 23% had regular medical support at least three times a year.

Table 10. *Selected indoor environment characteristics in allergen avoidance day-care sections, when compared with ordinary day-care sections, adjusted for building age*[a]

	OR	95%CI	*P*-value
PVC floor	0.53	0.32-0.87	0.01
Wooden floor	5.00	1.52-16.7	0.008
Textile walls	0.36	0.17-0.76	0.008
Other odor	0.40	0.18-0.93	0.03
Current dampness	0.52	0.24-1.12	ns
Previous dampness	0.56	0.31-1.04	ns
Current or previous dampness	0.55	0.31-0.96	0.04
Cupboards reaching up to ceiling	6.25	4.00-10.0	0.001
Total shelf <1 m	3.03	1.92-4.76	0.001
Short or no window curtains	1.67	1.01-2.77	0.047
Presence of any flowers or pot plants	0.03	0.02-0.06	<0.001
Written cleaning instructions available	2.60	1.31-5.14	0.006
Daytime cleaning	0.43	0.24-0.77	0.005
Daily floor cleaning	19.9	2.68-148	0.004
Central vacuum cleaning	16.6	7.74-35.5	0.001
Wet mopping	0.51	0.31-0.83	0.007
Wiping of furniture at least once/week	11.0	5.10-23.6	0.001
Pillows/mattress washing >2/year	2.74	1.35-5.54	0.005
Curtain washing >2/year	9.07	4.99-16.5	0.001
Water damage	0.70	0.26-1.89	ns
Floor dampness	0.53	0.16-1.82	ns
Basement	1.09	0.54-2.22	ns
Flat roof	0.75	0.41-1.39	ns
Wooden house	0.96	0.56-1.64	ns

[a] OR with 95% confidence interval calculated by logistic regression, adjusting for building age expressed as a continuous variable. Ordinary day-care sections (coded 0) were compared with allergen avoidance day-care sections (coded 1)

Paper II

Potential diagnostic criteria

The criteria asthma diagnosed by a physician and having current symptoms, being on inhalation steroid therapy, ever had asthma and having current symptoms, experienced four or more wheezing episodes during the last 12 months, and experienced any wheezing during the last 12 months, in ODC children were chosen for further analysis. As shown in Table 11, the four first criteria or criteria combinations gave fairly similar age and sex-specific asthma prevalence levels. The fifth criterion, any wheezing during the last 12 months, usually not used as single asthma criterion in studies of pre-school children, gave a 2–3-fold higher prevalence.

Table 11. *Asthma prevalence at ordinary day-care centres (model 1) using five potential diagnostic criteria (baseline data)*

		Prevalence of diagnostic criteria											
		Boys aged						Girls aged					
		1	2	3	4	5	6	1	2	3	4	5	6
N		112	485	503	506	583	287	90	432	472	512	585	319
1	Physician diagnosis and any wheezing last 12 months	8.0	7.9	8.6	8.5	6.2	6.0	1.1	4.9	6.0	5.7	4.7	2.5
2	Being on inhalation steroids	8.0	6.6	6.6	7.9	5.5	5.9	0	3.7	5.3	6.1	5.0	3.1
3	Ever had asthma and any wheezing last 12 months	8.0	9.2	8.6	9.2	6.4	6.4	1.1	6.3	6.8	6.3	5.0	3.2
4	Wheezing $\geq$ 4 times last 12 months	10.7	8.1	6.4	5.4	3.8	5.3	2.3	5.6	3.0	4.1	3.3	2.5
5	Any wheezing last 12 months	34.8	28.1	22.9	18.8	13.5	14.1	19.1	22.0	16.6	14.1	12.9	8.2

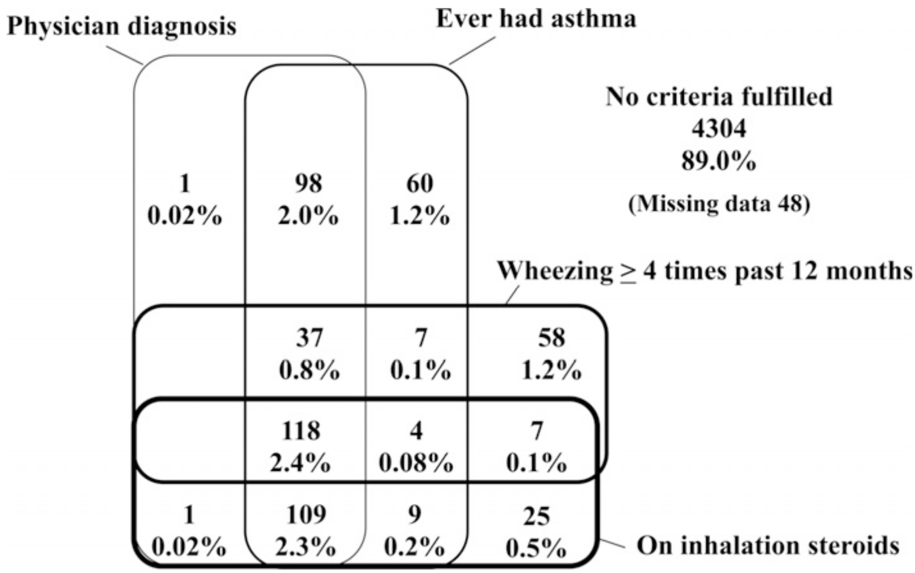

Figure 2. Venn diagram showing overlap between the four diagnostic asthma criteria, asthma diagnosed by physician, ever had asthma, four or more wheezing episodes during the past 12 months, and being on inhalation steroid therapy in ordinary day-care centre children 1-6 years old. Percentages refer to number of children with criterion or criteria combination in relation to total ordinary day-care study population (N=4,886 excluding 48 with missing data)

The overlap between the four first criteria is depicted in Figure 2. Generally, there was a considerable overlap among all criteria. The most common criteria or criterion combinations were all four criteria combined (2.4% of all ODC children), the combination physician diagnosis, ever had asthma and being on inhalation steroids (2.3%) and the combination physician diagnosis and ever had asthma (2%). Other combinations and single criteria were infrequent.

Prevalence calculations

A combination of diagnostic criteria 1 or 2 or 3 or 4 in Table 11 yielded an asthma prevalence across all sex and age groups of 9.0% (model 1). There were no significant asthma prevalence differences between response batches. The age and sex-specific prevalence based on model 1 and smoothed with logistic regression technique is shown in Figure 3. The prevalence among boys fell linearly across age while it was curvilinear among girls. According to model 2 the shape of the relation between prevalence and age was curvi-

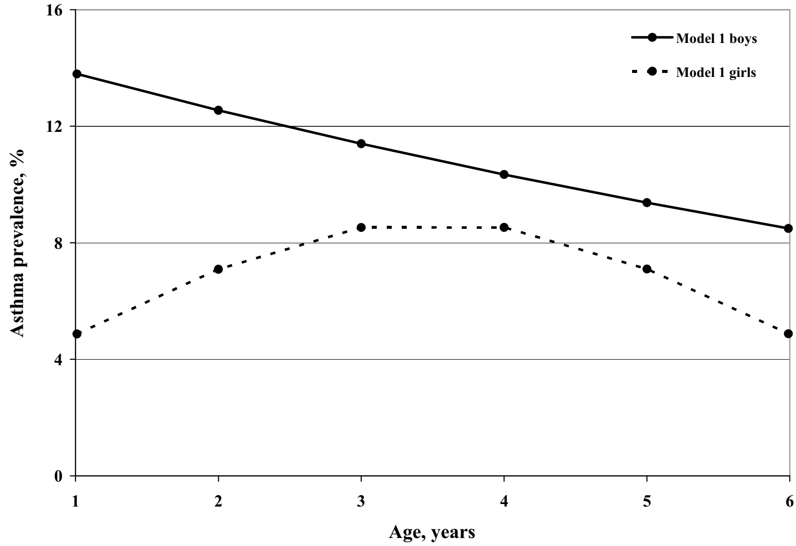

Figure 3. Asthma prevalence (%) in Swedish pre-school children by age and sex, based on the ordinary day-care centre study population data (model 1)

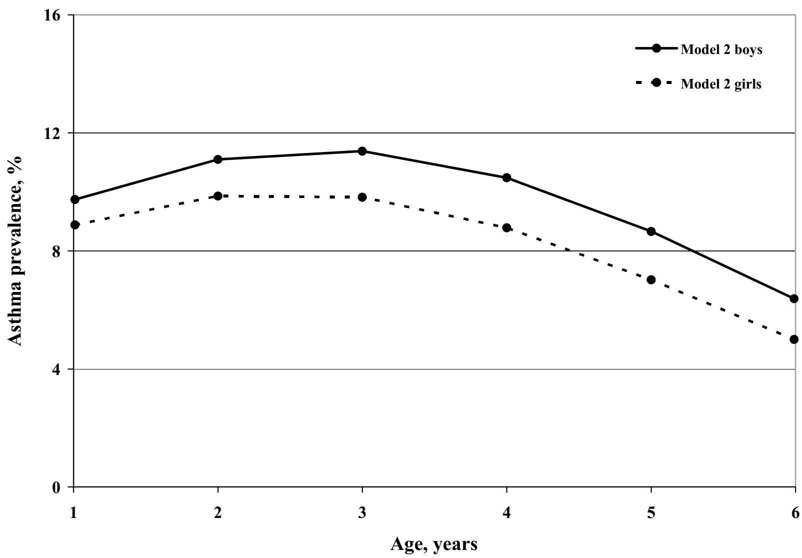

Figure 4. Asthma prevalence (%) in Swedish pre-school children by age and sex, based on calculations of the proportion of children with asthma in the total child population, 1-6 years of age, in the municipalities covered by the study (model 2)

Table 12. *Effects of age, sex, municipality population density, and geographical location (latitude and longitude) on asthma prevalence1-6 years old attending ordinary day-care centres in Sweden in multivariate logistic regression analysis (baseline data)*

	OR	95%CI	Wald's chi^2	*P*-value
Municipality population density[a]	1.02	1.02-1.02	1720.6	<0.0001
Age, years	1.39	1.33-1.44	271.3	<0.0001
Age squared	0.94	0.94-0.95	456.7	<0.0001
Male sex	1.19	1.16-1.23	159.7	<0.0001
Latitude, degree north	1.07	1.06-1.09	147.3	<0.0001
Longitude, degree east	0.97	0.96-0.98	30.7	<0.0001

[a] Number of residents, divided by 100, per square kilometre municipality area

linear and similar for boys and girls, but boys had on average 1.5 per cent units higher prevalence than girls and the maximum prevalence occurred somewhat later, Figure 4. For boys, the prevalence was 9.7% at age 1, reached a maximum of 11.4% at age 3 and then fell to 6.4% at age 6. The corresponding prevalence levels for girls were 8.9%, 9.8% (at age 2-3), and 5.0%. The mean prevalence, irrespective of age, was 9.6% for boys and 8.2% for girls, altogether 8.9%.

Asthma prevalence determinants

Based on the prevalence calculation by municipality according to model 2 an analysis of the influence of municipality population size, population density and geographical location on the asthma prevalence adjusted for municipality differences in age and sex distribution was made. Municipality population size, as well as population size at the municipality part where the DCs were located, was tested. Both variables gave the same result. For this reason municipality population size was used in the analyses.

In a first, preliminary age and sex adjusted logistic regression analysis with asthma prevalence as the dependent variable, municipality population density caught 98.5% (Wald's chi-square 598.9) of the demographic variable impact on asthma prevalence whereas municipality population size caught 1.5% (Wald's chi-square 9.1). For this reason population density was used in further analyses. As determined from model 1 parental education had a marginal negative impact (chi-square test, $p < 0.05$) on asthma prevalence, whereas smoking in the child's home during the first year of life or during pregnancy had no significant effect. For this reason these variables were not used in the final analysis model.

The result of the final determinant analysis is shown in Table 12. The asthma prevalence increased by 2% for each 100 residents per municipality square kilometre area, was 19% more common in boys than girls, increased

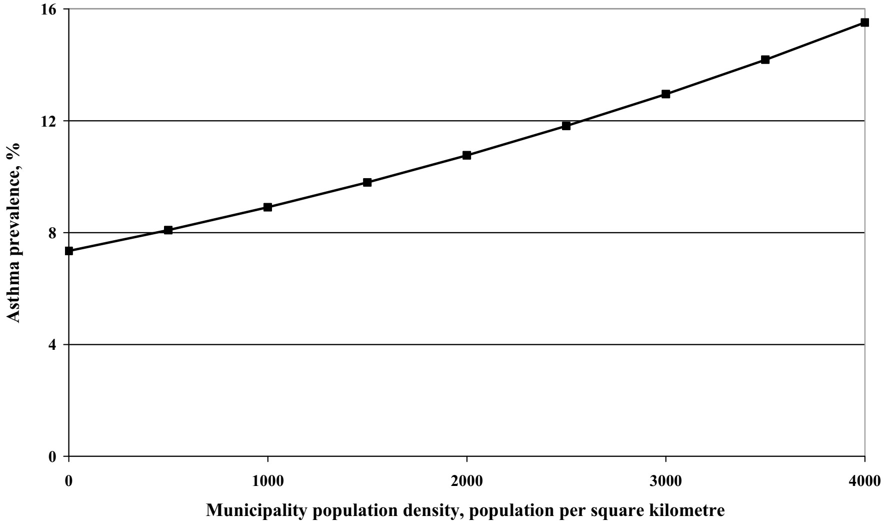

Figure 5. Relationship between asthma prevalence in Swedish pre-school children 1-6 years of age and municipality population density in their home municipality, expressed as number of residents regardless of age per square kilometer municipality area

by 7% for each degree north and decreased by 3% for each degree east. The strongest determinants, as measured by Wald's chi-square, were in ranking order municipality population density, age, sex, latitude, and longitude. Population density had nearly twice as large impact than all the other determinants together. As shown in Figure 5 asthma prevalence increased in a slowly accelerating pace with population density. Latitude and longitude were still highly significant but had a fairly limited importance over and above that of population density.

Paper III

Asthma, rhinitis, eczema, and food, furred pet, and pollen allergy

Asthma, rhinitis and eczema manifestations are presented in Table 13. Boys had a higher prevalence of all asthma manifestations than girls, 10.7% versus 7.3%. The same was true for rhinitis manifestations, 9.2% versus 7.1%. Although the differences in eczema manifestations were inconclusive, the total prevalence of any eczema criterion was somewhat higher in girls than in boys, 23.1% versus 21.2%.

The prevalence of food, furred pets and pollen allergies is shown in Table 14. There were small and inconclusive differences regarding food allergies with the exception of nut allergy, where boys had a significantly higher

Table 13. *Prevalence of asthma, rhinitis, and eczema manifestations in boys and girls 1-6 years old attending ordinary day-care centres (baseline data)*

	Boys		Girls		
	n	%	n	%	*P*-value
N	2476	50.7	2410	49.3	
Asthma manifestation					
Ever had asthma and current[a] symptoms	197	8.0	131	5.5	<0.0005
Wheezing 4 times or more last 12 months	147	6.0	88	3.7	<0.0005
Physician's diagnosis of asthma and current[1] symptoms	185	7.5	114	4.8	<0.0001
Being on inhalation steroids	163	6.6	111	4.6	<0.005
Any asthma criterion	265	10.7	176	7.3	<0.0001
Rhinitis manifestation					
Ever had hay fever and current[a] symptoms	134	5.5	100	4.2	<0.05
Rhino-conjunctivitis without cold last 12 months	143	5.8	97	4.1	<0.005
Physician's diagnosis of rhinitis and current[a] symptoms	66	2.7	37	1.6	<0.01
On anti-allergy medication and current[a] symptoms	79	3.2	45	1.9	<0.005
Allergy to pollen and/or furred pets and current[a] symptoms	142	5.8	95	4.0	<0.005
Any rhinitis criterion	227	9.2	171	7.1	<0.01
Eczema manifestation					
Itchy rash ever, coming and going for $\geq$6 months, and itchy rash in typical eczema localisations last 12 months	492	20.0	531	22.3	0.06
Physician's diagnosis of eczema and current[a] symptoms	252	10.2	231	9.7	0.52
Steroid ointments last 12 months and current[a] symptoms	186	7.6	170	7.1	0.54
Any eczema criterion	525	21.2	557	23.1	0.11

[a] Current indicates symptoms any time during the last 12 months of the specific disease

prevalence than girls, 2.1% versus 1.3%. There was a similar tendency regarding allergies to furred pets, but boys had a higher prevalence of pollen allergy than girls, 6.7% versus 4.0%.

Co-occurrence of asthma, rhinitis, eczema and allergies

Measures of co-occurrence between prevalent asthma, rhinitis, eczema, and allergies to food, furred pets and pollen in logistic regression analyses are displayed in Table 15. Presence of asthma (dependent variable) was highly significantly related to the presence of rhinitis, eczema and all the allergy variables (independent variables), after adjustment for the influence on asthma prevalence of age and sex (co-variates), indicating a relationship between the presence of asthma and presence of all the other variables. The

Table 14. *Prevalence of food allergy, furred pet, and pollen allergy in boys and girls 1-6 years old attending ordinary day-care centres (baseline data, N = 4,886)*

	Boys		Girls		
	n	%	n	%	*P*-value
Reported food allergies					
Milk allergy	106	4.3	97	4.0	0.64
Egg allergy	67	2.7	51	2.1	0.18
Fish allergy	23	0.9	22	0.9	0.95
Peanut allergy	55	2.2	37	1.5	0.08
Nut allergy	52	2.1	31	1.3	<0.05
Soy allergy	20	0.8	10	0.4	0.08
Stone fruit allergy	21	0.9	32	1.3	0.11
(Miscellaneous[a])	243	8.1	235	8.3	0.85
Any food allergy	201	8.2	167	7.0	0.11
Allergy to furred pets					
Cat allergy	86	3.5	67	2.8	0.16
Dog allergy	68	2.8	43	1.8	<0.05
Horse allergy	30	1.2	23	1.0	0.38
Rodent allergy	38	1.6	31	1.3	0.45
Any allergy to furred pets	118	4.8	89	3.7	0.06
Pollen allergy	164	6.7	96	4.0	<0.0001

[a] Not included in 'Any food allergy' prevalence

variables with the largest impact on asthma prevalence, as indicated by Wald's chi-square, were in ranking order furred pet allergy, rhinitis, food allergy, eczema and pollen allergy.

A corresponding analysis (Table 15, mid-section) showed that presence of asthma, eczema, and food, furred pet and pollen allergy were all highly significantly related to presence of rhinitis. Pollen allergy was the far most important determinant, with a Wald's chi-square value more then four times that of all other variables combined. For eczema presence (Table 15, right hand section) the most important determinant was food allergy, Wald's chi-square measure being larger than that of all other variables combined.

The co-occurrence is illustrated in a more quantitative way in the Venn diagram, Figure 6. 33% had any of the manifestations. The most common manifestation or manifestation combinations were asthma only, or rhinitis, or eczema, or food allergy, and various combinations of eczema, asthma and rhinitis (195 children, 4%), or combinations of eczema and food allergy (198 children, 4.1%).

Age specific prevalence

The age-specific prevalence of asthma, rhinitis, eczema and food allergy, adjusted for sampling municipality size is presented in Figure 7. The mean

Table 15. *Effects on the prevalence of asthma, rhinitis, and eczema in logistic regression analyses among boys and girls 1-6 years old, attending ordinary day-care centres (baseline data, N = 4,886)*

	Asthma				Rhinitis				Eczema			
	OR	95%CI	Wald's chi^2	*P*-value	OR	95%CI	Wald's chi^2	*P*-value	OR	95%CI	Wald's chi^2	*P*-value
Age	0.86	0.80-0.92	16.3	<0.0001	0.94	0.86-1.04	1.50	0.22	1.00	0.95-1.05	0.02	0.89
Sex	1.44	1.17-1.78	11.5	<0.001	0.98	0.75-1.28	0.03	0.87	0.82	0.71-0.95	7.4	<0.01
Asthma	-				2.69	1.90-3.81	31.0	<0.0001	1.47	1.16-1.85	10.4	<0.005
Rhinitis	2.72	1.93-3.81	33.3	<0.0001	-				2.06	1.55-2.75	24.7	<0.0001
Eczema	1.47	1.17-1.86	10.6	<0.005	2.11	1.58- 2.81	26.1	<0.0001	-			
Food allergy	1.81	1.32-2.46	13.9	<0.0005	1.81	1.21-2.69	8.5	<0.005	3.45	2.74-4.36	108.8	<0.0001
Furred pet allergy	2.98	2.06-4.31	33.8	<0.0001	3.17	2.00-5.03	23.9	<0.0001	2.15	1.54-3.00	19.9	<0.0001
Pollen allergy	1.83	1.23-2.73	8.8	<0.005	49.51	34.71-70.63	463.7	<0.0001	1.46	1.02-2.07	4.4	0.04

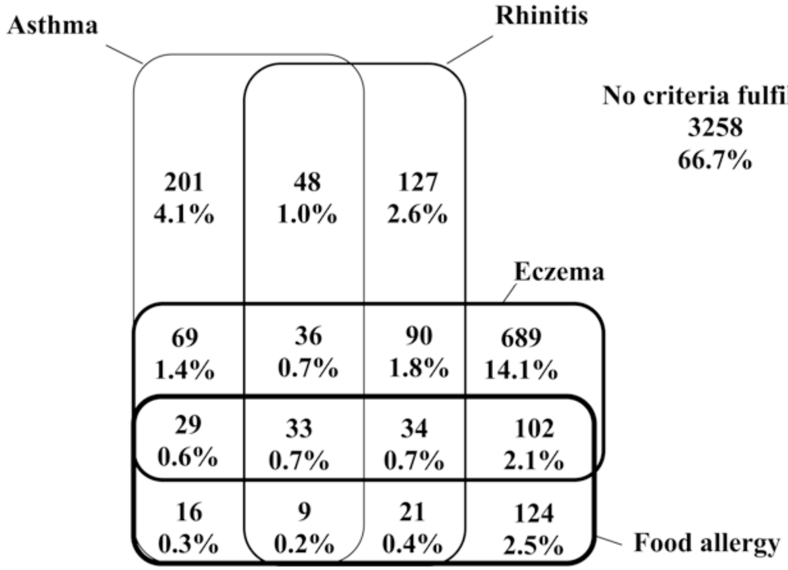

Figure 6. Venn diagram showing overlap between prevalent asthma, rhinitis, eczema, and food allergy in children 1-6 years old attending ordinary day-care centre. Percentages refer to number of children with criterion or criteria combination in relation to total ordinary day-care study population (N = 4,886)

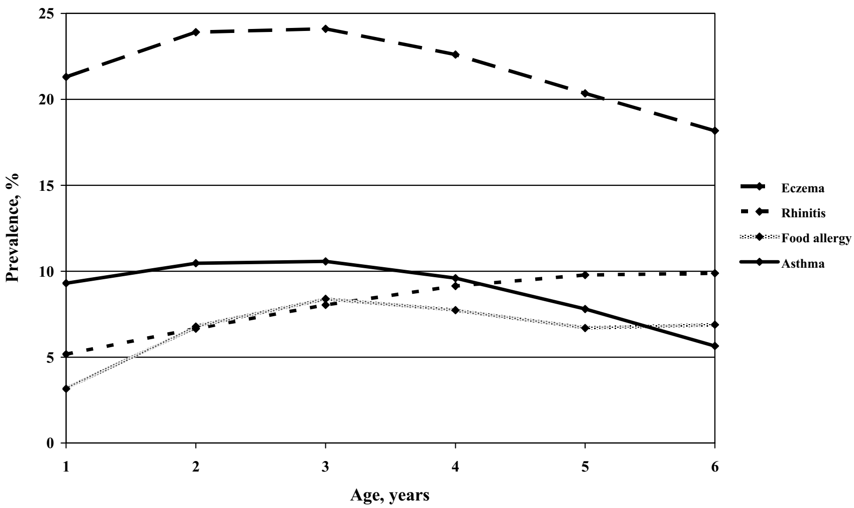

Figure 7. Age-specific prevalence of asthma rhinitis, eczema, and food allergy among Swedish pre-school children (N = 4,886)

Table 16. *Effects of baseline characteristics on incident asthma (n=200) during five years of follow up in bivariate logistic regression among AADC[a] and ODC children free from asthma at baseline (N = 3,715)*

	Effect on asthma incidence			
	OR	90%CI	Wald's chi^2	*P*-value
Food allergy	4.82	3.63-6.40	83.3	<0.0001
Rhinitis	3.96	2.89-5.41	52.0	<0.0001
Furred pet allergy	4.64	3.13-6.89	40.9	<0.0001
Eczema	2.47	1.93-3.16	36.1	<0.0001
Parental asthma	2.50	1.94-3.22	35.5	<0.0001
Parental rhinitis	2.58	1.98-3.37	34.3	<0.0001
Parental furred pet allergy	2.25	1.77-2.86	30.7	<0.0001
Wheezing last 12 months	2.67	1.99-3.57	30.6	<0.0001
Ever wheezing	1.92	1.53-2.41	22.6	<0.0001
Pollen allergy	3.08	2.07-4.59	21.5	<0.0001
Parental eczema	1.62	1.27-2.06	10.7	<0.005
Type of day-care centre	0.97	0.96-0.99	10.1	<0.005
Ever asthma	2.83	1.64-4.89	9.8	<0.005
Age	0.87	0.80-0.95	7.3	<0.01
Physician asthma diagnosis	2.54	1.15-5.64	3.7	<0.10
Cat during first year of life	0.66	0.46-0.95	3.5	<0.10
Ever moisture problems	1.22	0.96-1.57	1.8	0.18
Sex	1.20	0.95-1.53	1.6	0.21
Dog during first year of life	0.77	0.53-1.13	1.3	0.26
Total breast-feeding time, months	1.01	0.99-1.03	1.2	0.27
Ever indoor painting	1.27	0.84-1.93	0.9	0.34
Age at day-care centre introduction	0.85	0.63-1.15	0.8	0.38
Exclusive breast-feeding time, months	1.02	0.98-1.05	0.6	0.43
Ever had wall-to-wall carpets	1.28	0.59-2.77	0.3	0.60
Smoking during pregnancy	0.90	0.58-1.40	0.1	0.70
Parental education	1.03	0.90-1.18	0.1	0.72
Number of older siblings	1.03	0.90-1.17	0.1	0.75
Smoking at home	1.03	0.70-1.52	0.01	0.91

[a] AADC=allergen avoidance day-care centre, ODC=ordinary day-care centre

prevalence across age was 21.7% for eczema, 8.9% for asthma, 8.1% for rhinitis, and 6.6% for food allergy. The prevalence of the most common condition, eczema, increased during the first years of life to 24.1% at age 3 and then decreased to 18.2% at age 6. The asthma prevalence increased until age 3 (10.6%) and then decreased to 5.7% at age 6. The rhinitis prevalence increased throughout the whole age span from 5.2% at age 1 to 9.9% at age 6. Food allergy prevalence increased from 3.2% at age 1 to 8.4% at age 3, and was then fairly stable.

Paper IV

Asthma incidence and its determinants

At the end of the five-year follow-up period 200 new asthma cases were identified among the 3,715 children not fulfilling the asthma definition at baseline. As shown in Table 16 baseline presence of food allergy, rhinitis, furred pet allergy, eczema, parental asthma, parental rhinitis, parental furred pet allergy, wheezing last 12 months, ever wheezing, pollen allergy, parental eczema, type of DC, ever asthma, age, physician asthma diagnosis, and cat at home during first year of life were all significantly related with incident asthma in bivariate analyses, whereas ever moisture problems, sex, dog during first year of life, indoor painting, age at day-care centre entry, wall-to-wall carpets, breast-feeding, smoking during pregnancy or at home, parental education, and number of older siblings were not.

The significant variables were then entered in a multivariate logistic regression analysis with backward elimination of non-significant variables. The result is shown in Table 17, where the significant variables are shown in order of importance, as indicated by the Wald chi-square level. The most important baseline determinants, or risk factor, for incident asthma at end of follow up was to have a food allergy, wheezing last 12 months, rhinitis, parental rhinitis, parental asthma, ever asthma, age, and eczema, whereas all other variables were eliminated. These are shown in the table footnote with their p-level at elimination. The significant variables together explained 73% of the incident asthma variation.

Most of the significant determinants may be regarded not only as determinants, or risk factors, but also as representing an underlying atopic predisposition. This means that the asthma incidence is highly dependent on the presence of such variables at baseline. This is illustrated in Figure 8. Among those who had none of the variables present at baseline, the 5-year asthma incidence was 2.9% among those one year of age at baseline to 1.4% in those aged 6. Presence of eczema only at baseline increased the incidence by 1.1 percent units, presence of parental asthma only increased the incidence by 1.5 percent units, parental rhinitis by 1.6 percent units, *etcetera*. The top incidence in was associated with baseline presence of food allergy, or ever had asthma that increased the incidence by 4.3 percent units.

This means that the asthma 5-year incidence may vary from 2.9% to 8.5% among those one year old, and from 1.4% to 4.4% among those 6 years old at baseline, depending on presence or absence of underlying factors. The mix of these factors in the study population gave an asthma incidence variation from 5.8% (95% CI 2.0-9.6) among one-year-olds to 2.9% (95%CI 1.4-4.5) among six-year-olds at baseline, Table 18. The average 5-year incidence across all ages was 4.1% (95%CI 3.5-4.7). This corresponds to an annual asthma incidence of 0.6% to 1.2%. Having no such determinants at baseline was associated with a low annual asthma incidence, 0.3% to 0.6%.

Table 17. *Effects of baseline characteristics on incident asthma (n=200) during five years of follow up in multivariate logistic regression with backward elimination of non-significant variables*[a] *among AADC*[b] *and ODC children free from asthma at baseline (N = 3,715)*

	Effect on asthma incidence			
	OR	95%CI	Wald's chi^2	*P*-value
Food allergy	3.02	2.08-4.39	33.4	<0.0001
Wheezing last 12 months	2.00	1.37-2.90	13.1	<0.0005
Rhinitis	2.14	1.41-3.26	12.7	<0.0005
Parental rhinitis	1.77	1.26-2.49	10.9	<0.001
Parental asthma	1.71	1.24-2.38	10.4	<0.005
Ever asthma	3.12	1.56-6.24	10.3	<0.005
Age	0.87	0.78-0.96	6.9	<0.01
Eczema	1.53	1.10-2.12	6.5	<0.05

[a] The following non-significant variables were eliminated (p-value at elimination): physician asthma diagnosis (0.99), age at day-care introduction (0.94), dog at home first year (0.87), parental eczema (0.87), ever wheezing (0.85), parental education (0.83), smoking during pregnancy (0.70), type of day-care centre (0.69), cat at home first year (0.63), smoking at home (0.50), number of older siblings (0.49), sex (0.49), pollen allergy (0.48), parental furred pet allergy (0.47), total breast-feeding, time (0.43), ever moist problem (0.38), ever wall-to-wall carpets (0.32), furred pet allergy (0.24), and ever indoor painting (0.23)

[b] AADC=allergen avoidance day-care centre, ODC=ordinary day-care centre

Table 18. *Five-year asthma incidence by age among AADC*[a] *and ODC children free from asthma at baseline (n=3,715)*

	N	5-year incidence, %	95%CI
Age at baseline, years			
1	145	5.8	2.0-9.6
2	713	5.3	3.6-6.9
3	738	4.6	3.1-6.1
4	768	3.9	2.5-5.2
5	882	3.3	2.1-4.5
6	469	2.9	1.4-4.5
All ages	3715	4.1	3.5-4.7

[a] AADC=allergen avoidance day-care centre, ODC=ordinary day-care centre

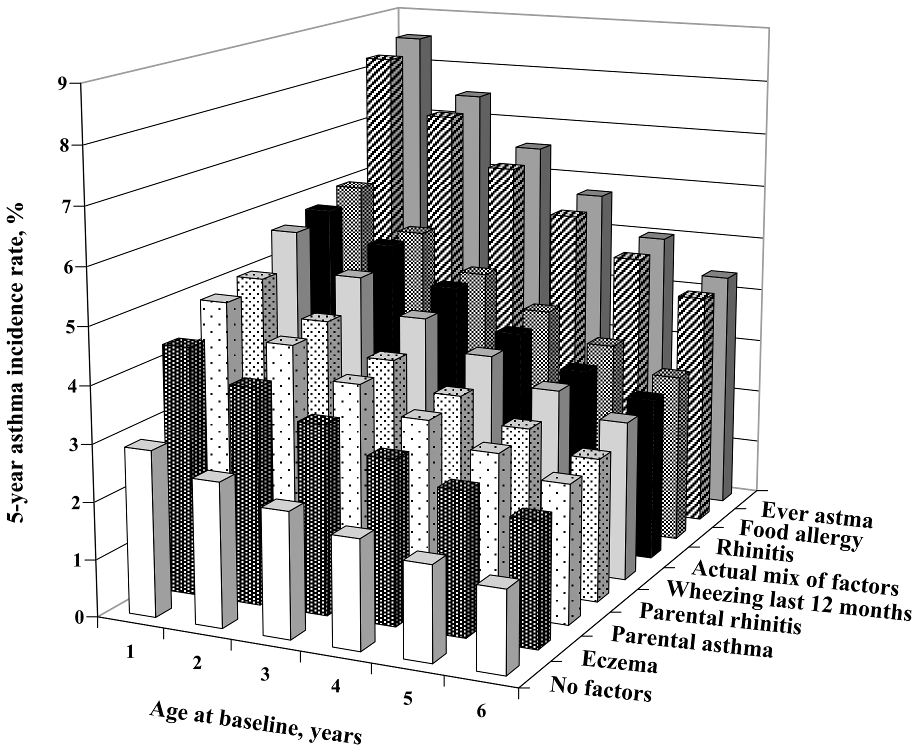

Figure 8.. Effects on asthma incidence during 5-year follow up of baseline presence of eczema, parental asthma and rhinitis, wheezing last 12 months, rhinitis, food allergy or ever asthma, or none of these factors. In addition, the effect of the actual mix of these factors in the study population is shown

Discussion

Major findings

Swedish DCs, like all buildings, have a number of environmental factors that could be associated with allergen and irritant exposure, e.g. furnishing and fixtures that could accumulate dust and allergens, insufficient cleaning, and outdoor factors such as proximity to stables, horses or animal farms, heavy trafficked roads, and smoke from wood heating in winter. Moreover, 39% of the ODCs had a history of mould growth or building dampness. Most of these risk factors (proxy variables for exposure) were less common in AADC.

The diagnostic criteria commonly used for asthma in childhood all produced fairly similar prevalence levels, as did criteria combinations. Of the two models used to estimate asthma prevalence, model 2, based on adjustment for municipality size and thereby being the most reliable, yielded fairly similar age-specific prevalence for boys and girls. However, boys had on average 1.5 percent units higher age-specific prevalence levels than girls. The strongest asthma prevalence determinant in this study was municipality population density, whereas latitude and longitude had less importance.

There was considerable co-occurrence between prevalent asthma, rhinitis, eczema and food allergy. The prevalence of all conditions peaked at the age of 3 with the exception of rhinitis, where the prevalence increased throughout the whole age span 1-6. Eczema was by far the most common of the conditions. The mean prevalence across age of the others was about the same.

The asthma incidence was highly dependent of the absence or presence of asthma incidence determinants at baseline. The 5-year asthma incidence ranged from 1.4% among those 6 years old at baseline and with none of the other determinants, to 8.5% among those 1 year old at baseline and with ever had asthma present. Given the same mix of determinants as in the study population, the 5-year asthma incidence would be 2.9% to 5.8%.

Study design and methodological consideration

The study on DC environment included about 1.6% of all Swedish ODCs. The participation rate was high and similar from both types of DCs. Thus, selection bias is less likely. The ODCs were recruited as controls for the AADCs and do not represent a random sample of DCs in Sweden. However, as the ODCs came from all parts of Sweden, and from various sizes of cities/towns/villages, they may be consided to be reasonably representative of DCs in Sweden in general.

Another methodological problem is possible information bias (response bias) in relation to awareness of exposure. The staff at the AADCs was aware that the study focus was on this type of DCs, while the ODCs were not informed that they served as controls. A general recall bias is most likely to result in general over-reporting of expected risk factors in the AADCs: building characteristic, indoor factors, and outdoor exposure. As the AADCs and ODCs were situated close to each other, the general outdoor environment would be expected to be similar. However, most of the outdoor factors did not differ, only some specific factors differed significantly, differences in both directions were found, and many building characteristic did not differ. Thus, we do not believe that our conclusions in Paper I are seriously biased by selection or information bias, or due to chance findings.

Papers II, III and IV were based on a large sample of pre-school children covering all of Sweden. A possible source of bias might have been the sampling frame, for instance that children attending DCs were more or less healthy than non-attending children. Koopman *et al.* found that children attending DC had more physician diagnosed lower respiratory tract infections during their first year of life than children cared for at home [14]. Nafstad *et al.* found no differences in wheeze, chest tightness or current asthma between four-year-old children cared for in DCs or at home [15]. Hägerhed-Engman *et al.* found a somewhat higher prevalence of wheezing among 1-to-4-year-old children in day-care centres as compared with children cared for at home, but there were no differences in older children and no significant difference regarding physician diagnosis [17]. The most comparable variable in their and our data was having a physician diagnosis. Based on their differences in physician diagnosis between children in DC and children care at home, the physician diagnosis proportion in all children in our data set, whether in DC or at home, would have been 7.1% versus the observed 7.5% among DC children.

Another potential bias might have been the non-random sampling procedure. However, more than 20% of the Swedish municipalities, covering the whole populated part of the country and covering a wide range of population density were included in the study. The potential bias owing to the sampling frame is therefore probably small.

The response rates (68% in 2002 and 72% in 2007 of those who responded to the baseline questionnaire) were satisfactory. The possible bias caused by non-response may be estimated based on the assumptions that non-respondents had asthma diagnosis criteria on average either five standard error units more often or five standard error units less often then the respondents, *i.e.*, a considerable difference. In model 1 the overall asthma prevalence in respondents and non-respondents combined would then have been 9.7% if non-respondents had higher prevalence than respondents, and 8.3% if they had lower prevalence, as compared with the 9.0% we found among respondents. The corresponding prevalence levels in model 2 were 9.0%, 8.8% and 8.9%. The potential bias owing to non-response is therefore small.

The strengths of the present study include that it was based on a large sample with a national coverage, that well-known instruments were used, and that the attrition rate was moderate and appears to have had little effect on the results. The weaknesses include that the sample was not strictly random, that although the study has a longitudinal nature the results in Papers II and III were based on the baseline survey and therefore cross-sectional, and that the results, like those in most other similar studies, were based on questionnaire data only with no access to medical examination data. In Paper IV longitudinal data were used. Exactly the same definitions of asthma and the atopic condition were used at baseline and at the follow-up investigation, minimizing bias in the incidence rate calculations.

Discussion by findings

Paper I

A high proportion of ODC sections (39%) had a history of building dampness and mould growth, and 18% had current dampness/mould growth in the last year. The most common problems were water leakage (10%) and dampness in the floor construction (6.6%), while visible indoor moulds (0.6%), mouldy odor (3.5%), and window condensation in the winter was rare (4.6%). In a study of 175 randomly selected DCs in Oslo, dampness problems (signs of moulds, water leakage, dampness-related damage to floor/wall) were observed in 51% of all DCs [16]. Even high prevalence of water damage (70%) and mould odor (17%) were found in a random sample of 30 DCs in Espoo, Finland [68]. Finally, a study of 28 DCs in Taipei, Taiwan reported dampness in 72.3% of all DCs, visible moulds in 23.3%, water damage in 40.8% and flooding in 51.2% [5]. As dampness and mould growth are risk factors for asthma, allergy and sick building syndrome [35], there is an obvious need to take preventive measures against building dampness and moulds in DCs, both in Sweden and other countries.

Building age and flat roof were associated with a higher prevalence of building dampness and mould growth. It is well known that flat roofs may increase the risk of water leakage from the roof, and one previous study has demonstrated that teachers in a school with flat roof and water leakage had an increase of biomarkers for inflammation in the nasal mucosa [69]. Older DCs, constructed before 1975, had more dampness problems and newer buildings built after 1983 had fewer dampness problems. We have no detailed data of the type of previous dampness in the buildings, but the risk of water leakage may increase with age. Older building may have poor ventilation, causing condensation dampness, but window condensation was rare. One third of the DCs were built in the period 1975–83, and there was borderline significance for current dampness in this group. During this period, several risk constructions were introduced in Sweden [70, 71], but in our study the oldest buildings seemed to have the most dampness problems.

In addition, we identified several potential outdoor pollution sources for the DCs. A total of 12% of ODC sections were situated <500 m from stables, horses, or animal farms. The general recommendation in Sweden is that the distance between farms/stables and dwellings should be at least 500 m [72]. A total of 23% were situated <50 m from a heavily trafficked road, which indicates that the children and staff could be significantly exposed to air pollution from traffic. Moreover, 18% were situated <1 km from an industry with emission to air, and 13% reported weekly smell from wood heating in winter. This indicates that the locations of Swedish DCs are not optimal, and when new DCs are built, outdoor risk factors should be considered.

The ODC sections had indoor factors that could contribute to unnecessary accumulation of dust and allergens. Textile wall coverings were common (23%), 81% had cupboards not reaching up to the ceiling, 67% had more than 1 m of open bookshelves, and 71% had long window curtains. In addition, the cleaning routines could be improved. Day-time cleaning was prevalent (86%), and vacuum cleaning was quite common (36%), which could cause unnecessary dust exposure. In 27% of the ODC sections, the furniture was wiped less than once a month, and in only 8% were the curtains washed more than twice a year. Assuming that these factors can be used as proxy variables for dust and allergen exposure, several improvements could be made. Previous studies from schools suggest that such assumptions may be valid [73, 74], but there is a need for validation studies of these proxy variables at DCs.

There are a few intervention studies from DCs evaluating effects of environmental improvements. One long-term study of two Swedish DCs showed that use of electrostatic air cleaners during a 2-year period reduced particle exposure at the DCs, and that the absenteeism was also reduced [75]. Another intervention study of one CD showed that the levels of cat and dog allergens were reduced 6- and 10-fold respectively [76]. Use of school uniforms as well as a ban on pets at home reduced the allergen levels in schools, and both measures were equally efficient [77]. Another school study did not demonstrate any significant effects on cat allergen levels from allergen avoidance measures such as increased cleaning and reduction of dust collecting materials in the classrooms [78].

AADCs differ from ODC in many respects, not just for proxy variables possibly related to allergen exposure. On average, the AADCs were newer, but adjusting for building age did not change the findings. Numbers of children per section were lower, none used perfumes, pets at home were very rare, and there were less tobacco smokers in these sections. Moreover, the buildings less often had a history of dampness and indoor moulds, and there were fewer complaints about indoor odours in general. Finally, furnishing and fixtures that could accumulate dust were less common, pot plants were rare, and the frequency of floor cleaning, wiping of furniture, and washing of pillows, mattresses and curtains was higher. To our knowledge, there are no international publications available on large-scale surveys of allergen avoidance (allergy adapted) day-care centres. Two smaller studies from Stockholm, comparing the indoor environments at allergen avoidance and ODC have demonstrated that AADC sections have lower total dust concentrations in indoor air [79], six times lower levels of cat allergens and nine times lower levels of dog allergens in settled dust [9].

Paper II

In Paper II two methods were used for the prevalence calculations. The results based on model 1, *i.e.,* based on the study population data analysed straightforwardly, are probably not representative for Swedish children in general. However, the results based on model 2, adjusted for municipality population distribution, are approximately equivalent to those from a random sample, as shown by results from other studies. Model 2 was therefore used also in Paper III.

The results from Paper II indicate that the prevalence of asthma in childhood increases until approximately three years of age and then decreases gradually until age 6. A number of studies have investigated the asthma prevalence in childhood, but none has presented age and sex specific prevalence data for each year in the 1–6 year age range. Bornehag *et al*. presented age specific data for boys and girls combined, showing the same trends as in this study [44]. Caudri *et al*. showed trends similar to our model 1 among children in the Netherlands [57]. The BAMSE study reported 8.5% prevalence among 4-year-old boys and 5.3% among girls [80]. The BMHE study reported prevalence in 4-year-old children of approximately 9% among boys and 6% among girls [81]. A number of other studies have reported prevalence among 6–8 year old children with estimates similar to our 6-year estimates [82, 83].

Prevalence across age should, however, be interpreted with caution, since there may be secular trends, or cohort effects, involved. However, Swedish ISAAC data indicate that only small changes have occurred over time in specific age groups, indicating small secular effects [40]. The sex and age specific asthma prevalence shown in this report indicates either that a considerable part of asthma in childhood disappears before age 7, as shown by others, or that some asthma cases in reality are attacks of wheezy bronchitis (transient wheezing), that cannot be distinguished from asthma other than by following the course [34, 57, 84]. However, given the similarities of our results with those of other studies [44, 57, 80, 81] and the fairly low prevalence among the youngest children, where the diagnostic problems are largest, the bias owing to the latter is probably moderate to small.

Highly significant geographical gradients with increasing prevalence towards the north and the west were found. However, the importance of these gradients was to a large extent attenuated by municipality population density, indicating that a substantial part of the importance of geographical gradients was linked to population density. This is a novel finding not reported before. BMHE reported increasing prevalence towards the north for 12-year-old children but no east-west gradient was presented [81]. Forsberg *et al.* reported on childhood asthma in four regions of Scandinavia but found no significant difference between suburban and rural areas [85], but in other parts of the world urban-rural prevalence differences have been found [86, 87]. As far as we know no previous study in this field has used population density as a pre-school asthma prevalence determinant.

Population density was in this study used as a proxy for degree of urbanisation. Population size and density were strongly correlated. We tested not only municipality population size but also population size in the part of the municipality where the DCs were located. Both variables gave similar results. However, municipality sub districts are troublesome to handle because they are not legally defined units in the same way as municipalities, and their borders and areas are thereby defined less strictly than those of the municipalities, resulting in less analysis precision. For these reasons we decided to use only municipality based data.

The results could not be explained by differences in parental education or smoking habits. They could neither be explained by climate, since the population density gradient does not follow the latitude or longitude very closely. However, an association has been shown between population density or degree of urbanisation on the one hand and air pollution or traffic flow density on the other [37, 38, 88]. Degree of urbanisation may also coincide with other degree of urbanisation related factors.

There was a residual importance of latitude and longitude when the importance of population density was accounted for. This residual importance might reflect climate factors, such as temperature and humidity. The climate in northern Sweden is sub arctic, whereas the climate in the south resembles that of northern continental Europe. The east-west gradient might reflect air humidity, with more humidity in the west than in the east. However, Weiland *et al.* found a negative effect on asthma symptom prevalence of altitude, annual temperature variation, and outdoor relative humidity, and no relationship to latitude [89]. De Marco *et al*. found similar results regarding outdoor temperature [38].

Paper III

The total prevalence of asthma, rhinitis, eczema or food allergy across the age span 1-6 years was 33.3%. A previous Swedish study found a total prevalence of 32% [41], not very different from our total prevalence estimate. The 8.9% asthma prevalence is similar to what others have found [41, 44, 82]. We found a total rhinitis prevalence of 8.1%. Other western and northern European studies have reported a similar prevalence levels [40, 41]. The eczema prevalence found in this study, 21.7%, is similar to results from other Swedish studies [40, 45], but higher than results reported from other European and non-European countries in the ISAAC study [40]. The food allergy prevalence in the present study was 6.6%. Other Scandinavian and British studies reported 8%-15% based on questionnaires [90-92] but only 2%-3.5% after oral provocation [90-94]. The results from this study are thus similar to those from other Scandinavian studies, but differ to some extent from data collected in other parts of the world.

We found a highly significant co-occurrence between the various atopic manifestations. The effect of the allergy manifestations on the presence of asthma was of a similar magnitude except for pet allergy, which had the largest effect. Regarding rhinitis, pollen allergy had by far the largest impact, and for eczema food allergy had the unquestionably largest impact. These findings are well in line with clinical observations. Results from other studies are usually based on two-by-two manifestation comparisons, with a few exceptions [42, 60, 61, 90, 95] and with only partial adjustments, which means that the extent of the co-occurrence is only partially shown.

There are two interesting issues linked to co-occurrence, its cause or causes and consequences. It is unlikely that the various atopic manifestations cause or trigger each other. It is much more likely that there are common underlying factors that trigger the onset of manifestations. These are presently incompletely known. A commonly held view is that the manifestations become prevalent in some sort of ordered sequence, the 'atopic march', for instance, first gastro-intestinal symptoms, then eczema, then asthma, then rhinitis, etcetera. However, in a German birth cohort study, children with moderate to severe early eczema often had early wheeze. Of these children half had wheeze before the onset of eczema and half had eczema before or concomitant with wheezing [62]. As early as at two years of age, 6.5% of the children in a Swedish birth cohort study had at least three of five atopic manifestations [96]. In the present study co-occurrences were common as early as before three years of age, especially the impact of pollen allergy on rhinitis as compared with that of furred pet allergy was larger than expected in these young children.

According to the age-specific prevalence shown in Figure 2, all but one manifestation has its peak prevalence at three years of age. Although the present study is based on cross-sectional data, where the manifestations among individual children were not followed over time, Figure 2 gives no impression that the manifestations appear in an ordered sequence. Instead they appear to have their onset at about the same time, possibly with the exception of rhinitis.

Paper IV

In another Swedish study the 5-year incidence of physician diagnosed asthma was 3.5%, or 0.7% annually, at 1-3 years of age [45], and in northern Sweden 0.8%-0.9% annually at 7-8 years of age [97], close to the incidence levels found in the present study. A somewhat higher incidence, 1-2% yearly of wheeze that was followed by an asthma diagnosis at 8 years of age was found in the Netherlands [58].

The reason why the asthma incidence is inversely related to age is not well known. However, the finding has been reported also from other studies [32, 58, 59, 98]. The same relation to age is found in prevalence studies [57], with peak prevalence in some studies at age 3, in boys as well as girls [98, 99]. It may be that the asthma disease process is most active at very young age and is then retarded. If so, the youngest children among those still not afflicted by the condition would have a higher incidence rate than older children, who may already have passed the most intense asthma triggering age. Another explanation could be that some of the asthma cases in reality were attacks of wheezy bronchitis (transient wheezing) [28].

It is easier to understand why the other determinants affect asthma incidence. Most of these determinants may reflect an underlying atopic predisposition, even though their asthma triggering effect may vary. Having one or more such determinants may mean that the child already at baseline is on its way towards an asthma onset. The potential asthma incidence determinants in this study may be classified either as indicating an atopic predisposition, or as potential trigger factors causing an asthma onset. Only one of the potential triggers were significantly associated with incident asthma in bivariate analysis, and none in the multivariate analysis.

It is well known that if these factors form a chain of causation the statistical relationship between the outcome and a variable in the chain decreases with the distance between the variable and the outcome. If the variables analysed in this study form a chain of causation it may be that atopic predisposition is located fairly close to the outcome, whereas heredity in the form of parental disease, or potential triggers like moisture problems, painting, wall-to-wall carpets, parental smoking, etcetera, are more early factors in the chain of causation. If so, a more detailed analysis is required in order to disclose their importance.

Since even children with none of the determinants in this study may develop asthma, there must be determinants other than those analysed in this study. However, the degree of explanation, 73%, indicates that the strongest determinants most probably are identified. The scope for other, still unidentified, powerful determinant is limited.

Conclusions

In conclusion, there is a need to improve the indoor environment at DCs, to reduce exposure to allergens, irritants, and building dampness. The experience of AADCs in Sweden has demonstrated that it is possible to reduce a number of environmental risk factors at DCs. Data suggest indirectly that AADCs have lower levels of pet allergens, which is beneficial to children with pet allergy. The effects of these improvements on indoor exposures and the health of the children need to be further evaluated.

The diagnostic criteria commonly used for asthma in childhood all produced fairly similar prevalence levels, as did criteria combinations. Of the two models used to compute age and sex-specific asthma prevalence, the model based on adjustment for municipality population size yielded fairly similar prevalence by age in boys and girls. However, boys had on average 1.5 per cent units higher age specific prevalence levels than girls. The most important asthma prevalence determinant was population density, as a proxy for degree of urbanisation, catching up more than twice the importance of all other determinants combined. Geographical location affected asthma prevalence only marginally.

There was considerable co-occurrence between prevalent asthma, rhinitis, eczema and food allergy. One third of the children had at least one of the manifestations. The prevalence of all conditions peaked at the age of 3 with the exception of rhinitis, where the prevalence increased throughout the whole age span of 1-6 years. Eczema was by far the most common of the conditions. There was a similar mean prevalence of the others manifestations across age.

The determinants of the 5-year asthma incidence were in ranking order of importance presence of food allergy, wheezing last 12 months, rhinitis, parental rhinitis, parental asthma, ever had asthma, age, and eczema. The five-year asthma incidence was highly dependent on presence or absence of these determinants at baseline, with a possible range of 1.4%-8.5%, and a probable range of 2.9% to 5.8%, depending on age at baseline.

Acknowledgements

This work was performed at the Department of Public Health and Caring Sciences, Family Medicine and Clinical Epidemiology Section, Uppsala University, Sweden

I would like to express my sincere gratitude to all those who supported me during the work with this thesis. In particular, I wish to thank:

- Kurt Svärdsudd, my main supervisor and co-author, for outstanding and generous scientific teaching and for always being an eternal optimist with everlasting enthusiasm introducing new challenging ideas and finding suitable statistical tests in advanced epidemiology and methodology.
- Dan Norbäck, my supervisor and co-author, for generous support, sharing of knowledge especially about indoor environment and for helping with the development of the project and the questionnaires.
- Margaretha Eriksson, my supervisor and co-author, for all her support, guidance and encouragement, and for invaluable help with monitoring and formatting of the thesis.
- Claes Sundelin, my supervisor and co-author, for generous support and valuable advice and for helping with personal contacts that were necessary for the progress of the study.
- The County Council of Gävleborg for generous support and grants during my research.
- Centre for Research Uppsala University Gävleborg County Council (CFUG) for generous support and grants during my research, especially former head Vivi-Ann Rahm, co-ordinator Inga-Lill Stenlund, present head Marieann Högman, and research colleagues.
- Anna-Lena Blom, Karin Modin, and Annie Lundberg, for excellent monitoring of the day-care study, and for their support and friendship.

- Björn Ställberg och Karin Lisspers at the Department of Public Health and Caring Sciences, Family Medicine and Clinical Epidemiology Section for support and friendship.
- My many co-workers and research colleges at the Family Medicine and Clinical Epidemiology Section and at other sections of the Department of Public Health and Caring Sciences.
- Linda Schenck, for valuable help with the linguistic revision of manuscripts.
- My colleagues at Södertull Health Care Centre and my former head Kristina Granewåg for their support and friendship.
- All parents of the children participating in this study.
- Last but not least my beloved family Gunnar, Malin, Åsa and Maria.

The study was supported by grants from The Vårdal Foundation for Health Care Sciences and Allergy Research, the Swedish Asthma and Allergy Association, Max Mathiessen Foundation, Bror Hjerpstedts Foundation, CFUG Gävleborg County/Uppsala University, the Gästrikland Primary Health Care Administration, and Uppsala University

Summary in Swedish (Svensk sammanfattning)

Förekomsten av astma, eksem och hösnuva har fördubblats under de senaste decennierna. Ökningen har skett framför allt hos barn och unga vuxna. Ett antal teorier om varför allergierna har ökat har presenterats, t ex exponering för inomhus- och utomhusmiljöfaktorer, livsstilsfaktorer, och sociala faktorer. Avhandlingsarbetet är baserat på en kohort om nästan 6000 förskolebarn från hela Sverige och grundar sig på fyra delarbeten.

Syftet med delarbete 1 var att kartlägga i vilken utsträckning allergiförskoleavdelningarna skiljer sig från vanliga förskoleavdelningar vad gäller fysisk allergenbekämpning via regelverk, städrutiner, ventilation och andra omgivningshygieniska faktorer. Under hösten 1998 identifierades Sveriges samtliga astma-allergiförskolor och de två närmaste vanliga förskolorna (kontrollförskolor). Studiepopulationen kom så småningom att bestå av 70 allergiförskolor med 91 avdelningar och 140 vanliga förskolor med 440 avdelningar. Varje avdelning fick besvara en miljöenkät med frågor om struktur (antal barn, deras åldersfördelning, personalsammansättning, etc,) om byggnaden (inredning, fuktskador, ommålning, städning, etc.), samt regelverk (djurinnehav, rökning, starka dofter, etc).

Allergiförskolorna hade färre barn per avdelning, nästan alla hade restriktioner mot pälsdjur, rökning i hemmet samt parfym, vilket var ovanligt i kontrollförskolorna. Allergiförskolorna hade mer skåp som gick upp till taket, färre öppna hyllor, mindre gardiner samt mycket frekventare städning och rengöring av textilier. 39% av kontrollförskolorna och 25% av allergiförskolorna hade tecken på aktuell eller tidigare fuktskada. Någon liknande undersökning av miljön i förskolor över hela landet har tidigare inte gjorts.

Syftet med delarbete 2 var att undersöka betydelsen av ålder, kön och befolkningstäthet för astmaprevalensen. Adresslistor till barnen i förskolorna från delarbete 1 erhölls från kommun-förvalningarna. Föräldrarna till 1412 barn i allergiförskolor och 7345 i kontrollförskolor fick år 2002 en enkät med frågor om barnens hälsa vad avser förekomsten av astma, eksem, allergisk snuva (rhinit) eller födoämnesallergi samt bakgrundsfaktorer. Enkäten var baserad på tidigare använda och validerade frågeformulär.

Av de svarande var 1000 föräldrar till allergiförskolebarn och 4884 till kontrollförskolebarn 1-6 år gamla. Uppgifter om antal barn i olika åldrar i de ingående kommunerna samt befolkningstäthet erhölls från Statistiska Centralbyrån. Astmaförekomsten ökade fram till 3 års ålder och minskade därefter hos båda könen. Pojkarna hade 1,5 procentenheter högre astmaprevalens än flickorna, och vid 3 års ålder var pojkarnas prevalens 11,4% och flickornas 9,8%. Befolkningstätheten var den starkaste determinanten och astmaprevalensen ökade med 2% per 100 invånare/km^2, vilket inte visats tidigare.

Bakgrunden till delarbete 3 är 'the atopic march' hypotesen, dvs att vissa barn får än den ena, än den andra atopiska manifestationen. Syftet med delarbete 3 var att undersöka om det finns en 'atopic march' vad gäller astma, rhinit, eksem, pollen- och pälsdjursallergi och födoämnesallergi och hur ordningsföljden i så fall ser ut.

Studiepopulation och datamaterial var desamma som i delarbete 2. Astma, rhinit och allergi mot hund och nötter var vanligare hos pojkar. För eksem, pälsdjursallergi och födoämnesallergi som helhet fanns ingen skillnad. Prevalensen av astma, eksem och födoämnesallergi ökade fram till 3 års ålder och minskade därefter, medan rhinit ökade successivt från 1 till 6 års ålder. För astma var samtidig pälsdjursallergi den faktor som hade störst samband med astmaprevalensen. Pollenallergi hade mer än fyra gånger så stor effekt på rhinitprevalensen än de övriga faktorerna tillsammans och för eksem hade födoämnesallergi störst betydelse. De atopiska manifestationerna hängde således samman, men det fanns inga belägg för att de kommer i en viss ordning.

Syftet med delarbete 4 var att studera astmaincidensen och dess determinanter baserat på en 5-årsuppföljning av barnen i delarbete 2 och 3. De föräldrar som besvarade enkäten 2002 fick en närmast identisk enkät 2007, som föräldrarna till 4255 barn besvarade. En lång rad potentiella determinanter (eller riskfaktorer) för att få astma undersöktes, varav nio signifikanta identifierades. Astmaincidensen varierade kraftigt beroende på förekomst av determinanter med mer än tre gånger så hög incidens vid närvaro av jämfört med avsaknad av determinanter. Dessutom var incidensen åldersberoende med kraftigt sjunkande incidens med åldern.

Vår tolkning av fynden är att det största astmaincidenstrycket finns i mycket tidig ålder och att trycket därefter sjunker. Övriga determinanter kan betraktas som del i astmautvecklings-mekanismen, vilket innebär att de som har determinanter har hunnit längre på vägen mot astma än de som saknar determinanter.

References

1. The Swedish National Agency for Education: *www.skolverket.se. Volume 2010*. The Swedish National Agency for Education, 2010.
2. Swedish Asthma and Allergy Association; Advice on Allergy Adapted School and Nursery School (Astma- och Allergiförbundets råd för allergi-anpassad skola och förskola, 1998-11-23). Stockholm, 1998.
3. Cai GH, Bröms K, Mälarstig B, Zhao ZH, Kim JL, Svärdsudd K, Janson C, Norbäck D. Quantitative PCR analysis of fungal DNA in Swedish day care centers and comparison with building characteristics and allergen levels. *Indoor Air* 2009;19(5): 392-400.
4. Instanes C, Hetland G, Berntsen S, Lovik M, Nafstad P. Allergens and endotoxin in settled dust from day-care centers and schools in Oslo, Norway. *Indoor Air* 2005;15(5):356-62.
5. Li CS, Hsu CW, Tai ML. Indoor pollution and sick building syndrome symptoms among workers in day-care centers. *Arch Environ Health* 1997;52(3):200-07.
6. Koskinen OM, Husman TM, Hyrvärinen AM, Reponen TA, Nevalainen AI. Two moldy day-care centers:a follow- up study of respiratory symptoms and infections *Indoor Air* 1997;7:262-68.
7. Andersson AM, Weiss N, Rainey F, Salkinoja-Salonen MS. Dust-borne bacteria in animal sheds, schools and children's day care centres. *J Appl Microbiol* 1999;86(4): 622-34.
8. Munir AK, Einarsson R, Dreborg SK. Mite (Der p I, Der f I), cat (Fel d I) and dog (Can f I) allergens in dust from Swedish day-care centres. *Clin Exp Allergy* 1995;25(2):119-26.
9. Wickman M, Egmar A, Emenius G, Almqvist C, Berglind N, Larsson P, Van Hage-Hamsten M. Fel d 1 and Can f 1 in settled dust and airborne Fel d 1 in allergen avoidance day-care centres for atopic children in relation to number of pet-owners, ventilation and general cleaning. *Clin Exp Allergy* 1999;29(5):626-32.
10. Arbes SJ, Sever M, Mehta J, Collette N, Thomas B, Zeldin DC. Exposure to indoor allergens in day-care facilities: results from 2 North Carolina counties. *J Allergy Clin immunol* 2005;116(1):133-39.
11. Smedje G, Norbäck D. Incidence of asthma diagnosis and self-reported allergy in relation to the school environment - a four-year follow-up study in schoolchildren. *Int J Tuberc Lung Dis* 2001;5(11):1059-66.
12. Almqvist C, Wickman M, Perfetti L, Berglind N, Renström A, Hedren M, Larsson K, Hedlin G, Malmberg P. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001;163(3 Pt 1):694-98.

13. Celedon JC, Litonjua AA, Weiss ST, Gold DR. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. *Pediatrics* 1999;104(3 Pt 1):495-500.
14. Koopman LP, Smit HA, Heijnen ML, Wijga A, van Strien RT, Kerkhof M, Gerritsen J, Brunekreef B, de Jongste JC, Neijens HJ. Respiratory infections in infants: interaction of parental allergy, child care, and siblings - The PIAMA study. *Pediatrics* 2001;108(4):943-48.
15. Nafstad P, Hagen JA, Oie L, Magnus P, Jaakkola JJ. Day care centers and respiratory health. *Pediatrics* 1999;103(4 Pt 1):753-58.
16. Nafstad P, Jaakkola JJ, Skrondal A, Magnus P. Day care center characteristics and children's respiratory health. *Indoor Air* 2004;15(2):69-75.
17. Hägerhed-Engman L, Bornehag CG, Sundell J, Åberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006;61(4):447-53.
18. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343(8):538-43.
19. de Meer G, Janssen NA, Brunekreef B. Early childhood environment related to microbial exposure and the occurrence of atopic disease at school age. *Allergy* 2005;60(5):619-25.
20. Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999;353(9151):450-54.
21. Mutius v. Environmental factors influencing the development and progression of pediatric asthma. *J Allergy Clin Immunol* 2002;109:525-32.
22. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *J Allergy Clin Immunol* 2008;122(3):500-06 e505.
23. Caudri D, Wijga A, Scholtens S, Kerkhof M, Gerritsen J, Ruskamp JM, Brunekreef B, Smit HA, de Jongste JC. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med* 2009;180(6):491-98.
24. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P *et al*. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56(9):813-24.
25. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J *et al*. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113(5):832-36.
26. Global strategy for asthma management and prevention. *www.ginasthma.org.*
27. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *www.ginasthma.org.*
28. Matricardi PM, Illi S, Gruber C, Keil T, Nickel R, Wahn U, Lau S. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32(3):585-92.

29. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, Gern JE, Gerritsen J, Hamelmann E, Helms PJ *et al*. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372(9643):1100-06.
30. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest* 2005, 127(2):502-08.
31. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD: A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-06.
32. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312(7040):1195-99.
33. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002:19(5):899-905.
34. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-38.
35. Bornehag CG, Blomquist G, Gyntelberg F, Jarvholm B, Malmberg P, Nordvall L, Nielsen A, Pershagen G, Sundell J. Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP). *Indoor Air* 2001;11(2):72-86.
36. Jaakkola JJ, Knight TL. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environ Health Perspect* 2008;116(7):845-53.
37. Chang J, Delfino RJ, Gillen D, Tjoa T, Nickerson B, Cooper D. Repeated respiratory hospital encounters among children with asthma and residential proximity to traffic. *Occup Environ Med* 2009;66(2):90-98.
38. de Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, Villani S, Ponzio M, Bono R, Carrozzi L *et al*. The impact of climate and traffic-related NO2 on the prevalence of asthma and allergic rhinitis in Italy. *Clin Exp Allergy* 2002;32(10):1405-12.
39. Asher MI. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12(2):315-35.
40. Asher MI, Montefort S, Björksten B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368(9537):733-43.
41. Wickman M, Lilja G, Söderström L, van Hage-Hamsten M, Ahlstedt S: Quantitative analysis of IgE antibodies to food and inhalant allergens in 4-year-old children reflects their likelihood of allergic disease. *Allergy* 2005;60(5):650-57.
42. Rönmark E, Perzanowski M, Platts-Mills T, Lundbäck B. Different sensitization profile for asthma, rhinitis, and eczema among 7-8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol* 2003;14(2):91-99.

43. Hedman L, Bjerg A, Perzanowski M, Rönmark E. Good agreement between parental and self-completed questionnaires about allergic diseases and environmental factors in teenagers. *J Clin Epidemiol* 2009;(Dec 1).
44. Bornehag CG, Sundell J, Hägerhed-Engman L, Sigsggard T, Janson S, Åberg N. 'Dampness' at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study. *Indoor Air* 2005;15 Suppl 10:48-55.
45. Larsson M, Hägerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. *Acta Paediatr* 2008;97(9):1210-15.
46. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, Aalberse R, Koopman L, Kerkhof M, Wilga A *et al*. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13 Suppl 15:55-60.
47. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002;32(1):43-50.
48. Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B, Bischof W, Weiss M, Borte M, Wichmann HE. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. *Eur Respir J* 2002;20(3):617-23.
49. Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I, Lodrup Carlsen KC, Carlsen KH, Smit HA, Wijga AH *et al*. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs - a GALEN initiative. *Allergy* 2006;61(2):221-28.
50. Laubereau B, Brockow I, Zirngibl A, Koletzko S, Gruebl A, von Berg A, Filipiak-Pittroff B, Berdel D, Bauer CP, Reinhardt D *et al*. Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life - results from the GINI-birth cohort study. *J Pediatr* 2004;144(5):602-07.
51. Lodrup Carlsen KC. The environment and childhood asthma (ECA) study in Oslo: ECA-1 and ECA-2. *Pediatr Allergy Immunol* 2002;13 Suppl 15:29-31.
52. Nickel R, Lau S, Niggemann B, Gruber C, von Mutius E, Illi S, Kulig M, Wahn U. Messages from the German Multicentre Allergy Study. *Pediatr Allergy Immunol* 2002;13 Suppl 15:7-10.
53. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998, 101(5):587-93.
54. Wright AL. Epidemiology of asthma and recurrent wheeze in childhood. *Clin Rev Allergy Immunol* 2002;22(1):33-44.
55. Östblom E, Lilja G, Pershagen G, van Hage M, Wickman M. Phenotypes of food hypersensitivity and development of allergic diseases during the first 8 years of life. *Clin Exp Allergy* 2008;38(8):1325-32.
56. Bjerg-Backlund A, Perzanowski MS, Platts-Mills T, Sandström T, Lundbäck B, Rönmark E. Asthma during the primary school ages--prevalence, remission and the impact of allergic sensitization. *Allergy* 2006;61(5):549-55.
57. Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, Hoekstra M, Gerritsen J, de Jongste JC. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med* 2007;175(10):1078-85.

58. Kerkhof M, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Aalberse RC, Hoekstra MO, Gerritsen J, Postma DS. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy* 2009;64(8):1202-08.
59. King ME, Mannino DM, Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med* 2004;46(2):97-110.
60. Peroni DG, Piacentini GL, Alfonsi L, Zerman L, Di Blasi P, Visona G, Nottegar F, Boner AL. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy* 2003;33(10):1349-54.
61. Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *J Asthma* 2009;46(5):429-36.
62. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113(5):925-31.
63. Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B. Different pattern of risk factors for atopic and nonatopic asthma among children - report from the Obstructive Lung Disease in Norden Sweden Study. *Allergy* 1999;54:926-35.
64. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW *et al*. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8(3):483-91.
65. Mata Fernandez C, Fernandez-Benitez M, Perez Miranda M, Guillen Grima F. Validation of the Spanish version of the Phase III ISAAC questionnaire on asthma. *J Investig Allergol Clin Immunol* 2005;15(3):201-10.
66. Statistics Sweden: www.ssd.scb.se. Statistics Sweden; 2010.
67. SAS Institute Inc: *www.sas.com*. 9.1 edition. Cary, NC; SAS Institute Inc., 2003.
68. Ruotsalainen R, Jaakkola N, Jaakkola JJ. Dampness and molds in day-care centers as an occupational health problem. *Int Arch Occup Environ Health* 1995;66(6):369-74.
69. Wålinder R, Norbäck D, Wieslander G, Smedje G, Erwall C, Venge P. Acoustic rhinometry and lavage biomarkers in relation to some building characteristics in Swedish schools. *Indoor Air* 2001;11(1):2-9.
70. Lundholm M, Lavrell G, Mathiasson L. Self-leveling mortar as a possible cause of symptoms associated with "sick building syndrome". *Arch Environ Health* 1990;45(3):135-40.
71. Norbäck D, Wieslander G, Nordström K, Wålinder R. Asthma symptoms in relation to measured building dampness in upper concrete floor construction, and 2-ethyl-1-hexanol in indoor air. *Int J Tuberc Lung Dis* 2000;4(11):1016-25.
72. The National Board of Health and Welfare: Hästhållning (Horse and Stables and Horse Enclosures). The National Board of Health and Welfare, Stockholm, Sweden 2004.
73. Smedje G, Norbäck D. Irritants and allergens at school in relation to furnishings and cleaning. *Indoor Air* 2001;11(2):127-33.
74. Wålinder R, Norbäck D, Wieslander G, Smedje G, Erwall C, Venge P. Nasal patency and lavage biomarkers in relation to settled dust and cleaning routines in schools. *Scand J Work Environ Health* 1999;25(2):137-43.

75. Rosen KG, Richardson G. Would removing indoor air particulates in children's environments reduce rate of absenteeism - a hypothesis. *Sci Total Environ* 1999;234(1-3):87-93.
76. Munir AK, Einarsson R, Dreborg S. Allergen avoidance in a day-care center. *Allergy* 1996;51(1):36-41.
77. Karlsson AS, Andersson B, Renström A, Svedmyr J, Larsson K, Borres MP. Airborne cat allergen reduction in classrooms that use special school clothing or ban pet ownership. *J Allergy Clin Immunol* 2004;113(6):1172-77.
78. Karlsson AS, Renström A, Hedren M, Larsson K. Allergen avoidance does not alter airborne cat allergen levels in classrooms. *Allergy* 2004;59(6):661-67.
79. Christensson B, Juringe L. Partikulära luftföroreningar på allergianpassade barndaghem. In: *National Institute for Working Life. Volume 1995:23*:1-18. National Institute for Working Life, Stockholm, Sweden, 1995.
80. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004;114(4):755-60.
81. The National Board of Health and Welfare: Environmental Health Report 2005 [Miljöhälsorapport, in Swedish]. The National Board of Health and Welfare. Stockholm 2005.
82. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007;62(9):758-66.
83. Rönmark E, Lundbäck B, Jonsson E, Platts-Mills T. Asthma, type-1 allergy and related conditions in 7- and 8-year-old children in northern Sweden: prevalence rates and risk factor pattern. *Respir Med* 1998;92(2):316-24.
84. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357(9271):1821-25.
85. Forsberg B, Pekkanen J, Clench-Aas J, Martensson MB, Stjernberg N, Bartonova A, Timonen KL, Skerfving S. Childhood asthma in four regions in Scandinavia: risk factors and avoidance effects. *Int J Epidemiol* 1997;26(3):610-19.
86. Dagoye D, Bekele Z, Woldemichael K, Nida H, Yimam M, Venn AJ, Hall A, Britton JR, Lewis SA, McKeever T *et al*. Domestic risk factors for wheeze in urban and rural Ethiopian children. *Qjm* 2004;97(8):489-98.
87. Odhiambo JA, Ng'ang'a LW, Mungai MW, Gicheha CM, Nyamwaya JK, Karimi F, Macklem PT, Becklake MR. Urban-rural differences in questionnaire-derived markers of asthma in Kenyan school children. *Eur Respir J* 1998;12(5):1105-12.
88. Carbajal-Arroyo L, Barraza-Villarreal A, Durand-Pardo R, Moreno-Macias H, Espinoza-Lain R, Chiarella-Ortigosa P, Romieu I. Impact of traffic flow on the asthma prevalence among school children in Lima, Peru. *J Asthma* 2007, 44(3):197-202.
89. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N: Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 2004;61(7):609-15.

90. Östblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr* 2008;97(1):85-90.
91. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16(7):567-73.
92. Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006;17(5): 356-63.
93. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy* 2009;64(7):1023-29.
94. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Södergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlström J *et al*. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120(3):638-46.
95. Hamelmann E, Beyer K, Gruber C, Lau S, Matricardi PM, Nickel R, Niggemann B, Wahn U. Primary prevention of allergy: avoiding risk or providing protection? *Clin Exp Allergy* 2008;38(2):233-45.
96. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G: Breast feeding and allergic diseases in infants-a prospective birth cohort study. *Arch Dis Child* 2002, 87(6):478-81.
97. Rönmark E, Perzanowski M, Platts-Mills T, Lundbäck B. Incidence rates and risk factors for asthma among school children: a 2-year follow-up report from the obstructive lung disease in Northern Sweden (OLIN) studies. *Respiratory Med* 2002;96(12):1006-13.
98. De Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol* 2002, 110(2):228-35.
99. Hederos CA, Hasselgren M, Hedlin G, Bornehag CG: Comparison of clinically diagnosed asthma with parental assessment of children's asthma in a questionnaire. *Pediatr Allergy Immunol* 2007, 18(2):135-41.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 542

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-121426

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2010