Indoor Environmental Factors and Chronic Diseases in Swedish Pre-School Children

Risk factors and methodological issues investigated in a longitudinal study on airway diseases and autism spectrum disorders
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Malin Larsson. *Indoor Environmental Factors and Chronic Diseases in Swedish Pre-School Children - Risk factors and methodological issues investigated in a longitudinal study on airway diseases and autism spectrum disorders*

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ABSTRACT

Research has shown a considerable increase in asthma and allergies during the past 40-50 years. Along with this increase, a heightened awareness regarding different neurodevelopmental disorders such as autism spectrum disorders has occurred and it has been proposed that such disorders are also on the increase. It has been suggested that environmental factors, especially in the indoor environments, may be associated with the increase in asthma and allergy, especially among children, who spend more than 90% of their time indoors and environmental exposures are on the list of potential causal factors for neurodevelopmental disorders as well.

The aim of this thesis has been to investigate certain environmental factors in homes and their impact on asthma, rhinitis, eczema as well as autism spectrum disorders in children, and to identify certain methodological difficulties in epidemiological investigations.

The articles in this thesis are based on data from the Dampness in Buildings and Health (DBH) study which started in the year 2000 in the county of Värmland, Sweden. This thesis is based upon findings from questionnaire data from the first phase of the DBH-study, which was a baseline questionnaire study in 2000 to the parents of 14,077 children aged 1-5 years, and data from the third phase of the study, which was a five year follow-up questionnaire study carried out in 2005.

Estimating the incidence of allergic symptoms and disease from questionnaire studies can be assessed by the use of data from birth cohort studies as well as from cohorts established later on in life. When not using birth cohort data the estimated incidence rates are strongly dependent of how the baseline population's health is defined and how the studied health outcome at follow-up is defined. We found that the mean incidence rate per year for doctor diagnosed asthma was in the range of 0.6 to 2.4% and for doctor diagnosed rhinitis in the range of 1.1 to 3.7% depending on different definitions at baseline and health outcome at follow-up. The incidence rate of eczema ever was 2.7%.

Our results show that the associations between parental reported moisture problems in the home and asthma in children, that were revealed in cross-sectional
analyses, decreased or disappeared when longitudinal data were used. Our results therefore indicate that associations between parental reported moisture problems and asthma from cross-sectional questionnaire studies should be interpreted with caution due to the risk for reporting bias.

Finally, our results indicate that children who were living in homes with PVC-flooring in the bedroom when they were 1-3 years of age were more likely to develop asthma during the following 5-year period compared with children living in homes without such flooring material. A similar association was found for children with autism spectrum disorders, where children who were living in homes with PVC-flooring in the bedroom when they were 1-3 years of age were more likely to have a diagnose of autism spectrum disorders five years later when compared with children living in homes without such flooring material. These results indicate that building materials including suspected endocrine disrupting chemicals e.g. phthalates might be of importance for the development of these chronic diseases. Further studies are needed to explore the early life exposure and the mechanisms and contribution of phthalates for the development of chronic diseases.
Astma och allergier har ökat under de senaste 40-50 åren. Under samma tidsperiod har troligen olika neuropsykiatriska tillstånd också ökat, även om en del av ökningen kan bero på mer uppmärksamhet och förbättrad diagnostik. Barn idag tillbringar mer än 90% av tiden inomhus kan exponeringar i sådana miljöer ha betydelse för astma och allergi men kanske även för autism och andra autismliknande tillstånd.

Syftet med denna avhandling är att identifiera miljöfaktorer i bostaden under tidig barndom som är associerade till utvecklandet av astma, rinit och eksem samt autistliknande tillstånd hos barn samt att studera metodologiska svårigheter i epidemiologiska studier som rör sjukdomsutveckling.

Avhandlingen är baserad på enkätdata från Bostad-Barn-Hälsa-studien (DBH) som startade år 2000 i Värmland, Sverige. I den första fasen skickades en enkät ut till alla föräldrar till 14 077 barn i åldern 1-5 år med en svarsfrekvens på 79%. Fem år senare skickades en uppföljande enkät ut till föräldrarna till de tre yngsta årsgrupperna där 73% svarade.

Våra resultat visade att den årliga incidensen av läkardiagnostiserad astma var mellan 0,6 och 2,4%, incidensen av läkardiagnostiserad rinit mellan 1,1 och 3,7% och incidensen av eksem var 2,7%, beroende på beräkningssätt. Beräkning av incidens, d.v.s. nyinsjuknande, påverkas av hur man definierar en frisk baslinjepopulation samt hur man definierar sjukdom i den uppföljande studien.

De samband vi hittade mellan föräldrarapporterade fuktproblem i bostaden och astma hos barnet i tvärsnittsdata minskade eller försvann när vi undersökte longitudinella data från samma population. Slutsatsen är därför att samband mellan föräldrarapporterade fuktproblem i bostaden och astma från tvärsnittsstudier ska tolkas med försiktighet då denna typ av resultat kan vara behäftade med systematiska rapporteringsfel.

PVC-golv i föräldrarnas eller barnens sovrum när barnen var 1-3 år ökade risken för att barnet skulle utveckla astma under den följande femårsperioden jämfört
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I. 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 Paediatrica* 2008; 97: 1210-1215

II. Larsson M, Hägerhed-Engman L, Moniruzzaman S, Janson S, Sundell J, Bornehag CG. “Can we trust cross-sectional studies when studying the risk of moisture related problems indoor for asthma in children?”

*International Journal of Environmental Health Research* 2010 (in press)


*Indoor Air* 2010 (in press)

IV. Larsson M, Weiss B, Janson S, Sundell J, Bornehag CG. “Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age”

*NeuroToxicology* 2009: 30: 822-831

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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>aOR</td>
<td>Adjusted Odds Ratio</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorders</td>
</tr>
<tr>
<td>ASSQ</td>
<td>Autism Spectrum Screening Questionnaire</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DBH</td>
<td>The Dampness in Buildings and Health study</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>The Diagnostic and Statistical Manual of Mental Disorders, 4th Revision</td>
</tr>
<tr>
<td>EDC</td>
<td>Endocrine Disrupting Chemical</td>
</tr>
<tr>
<td>ETS</td>
<td>Environmental tobacco smoke</td>
</tr>
<tr>
<td>HDM</td>
<td>House dust mites</td>
</tr>
<tr>
<td>IAQ</td>
<td>Indoor air quality</td>
</tr>
<tr>
<td>ICD-10</td>
<td>The International Statistical Classification of Diseases and Related Health Problems, 10th Revision</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IOM</td>
<td>The Institute of Medicine</td>
</tr>
<tr>
<td>ISAAC</td>
<td>The International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PCB</td>
<td>Polychlorinated biphenyls</td>
</tr>
<tr>
<td>PGEs</td>
<td>Propylene glycol and glycol ethers</td>
</tr>
<tr>
<td>P-value</td>
<td>A measure of probability that a difference between groups during an experiment happened by chance</td>
</tr>
<tr>
<td>PVC</td>
<td>Poly Vinyl Chloride</td>
</tr>
<tr>
<td>SBS</td>
<td>Sick Building Syndrome</td>
</tr>
<tr>
<td>SELMA</td>
<td>Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study</td>
</tr>
<tr>
<td>SES</td>
<td>Socio Economic Status</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences, a computer program for analyzing statistics</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

During the last decades there has been a remarkable increase of different chronic diseases such as asthma, allergies, obesity, diabetes, male reproductive and neurodevelopmental disorders (Stahlhut et al. 2007, Hertz-Picciotto et al. 2009, Han et al. 2010, Main et al. 2010) where causes are largely unknown but environmental factors are suspected. Part of this increase is probably an artefact based on better diagnostic methods and more attention, but the main increase is believed to be real.

Asthma and allergies are one of the most common chronic diseases in children - at least in western societies - and the prevalence of such diseases has increased considerably over the past 40-50 years (Beasley et al. 2000, Pearce et al. 2007, Lai et al. 2009). Simultaneously, an increased awareness regarding different neurodevelopmental disorders such as autism spectrum disorders (ASD) has occurred (Fombonne 1999, Newschaffer et al. 2003, Rutter 2005). Recent research has proposed that these disorders are also increasing (Hertz-Picciotto et al. 2009). It has been suggested that indoor environmental factors may be of relevance for the rise in asthma and allergies as well as ASD, not at least due to the fact that we spend most of the time in the home.

During the last decades there has been an increase in exposure for certain industrial chemicals in the general population. Several chemicals found in many common consumer products, such as plastics, toys, cleaning products, cosmetics and building materials, have been shown or are suspected to impact human health (Weschler et al. 2006, Rudel et al. 2009, Bornehag et al. 2010). An interaction between a genetic predisposition and environmental factors (exposures) is suspected to play an important role for these diseases, but the biological mechanisms are poorly understood.

The current thesis concerns certain environmental factors in the dwelling and their impact on children’s health, in terms of the development of asthma, rhinitis and eczema as well as autism spectrum disorders.
Chronic disease of public health concern

A chronic disease is a condition that persists over a long period, usually more than three months (Groholt et al. 2003). Asthma, allergies and neurodevelopmental disorders, which are in focus in this thesis, are included in such a definition (Lindbaek et al. 2005). Asthma, rhinitis, eczema, and ASD, are conditions that may lead to long-term health effects. Children who suffer from these conditions may experience frequent exacerbations, leading to interrupted development, missed education, stress and strain on family and community resources. ASD, in particular, is considered a highly debilitating and life-long condition. Understanding risk factors associated with these diseases can help identify effective treatments, and prevention programmes, leading to a better quality of life for affected children, their families, and the communities as a whole (Gillberg et al. 2006, Shaaban et al. 2008).

Asthma, rhinitis and eczema

Asthma is a chronic inflammatory disease in the airways which causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Rhinitis symptoms can be hay fever with blocked nose and/or runny eyes, sneezing and increased mucus secretion. Such symptoms can be seasonal and due to pollen exposure. Eczema is a local inflammation of the skin leading to recurrent itching (Johansson et al. 2004).

Asthma, rhinitis and eczema can either be allergic or non-allergic depending on whether specific immunologic mechanisms are initiating the reaction or not. An immunological reaction means that a person becomes sensitized with a production of IgE-antibodies after contact with certain allergens. The most common allergens in Scandinavia are from cats, dogs, and pollen while allergens from house dust mites and mold spores are quite rare. Allergic diseases can therefore be seen as a hypersensitivity reaction initiated by specific immunologic mechanisms (Johansson et al. 2004).

Sensitization can be influenced by adjuvant factors. An adjuvant is an agent that may stimulate the immune system and increase the response to an allergen, without having any specific antigenic effects in itself. Typical adjuvant agents include certain chemicals, where several studies have investigated exposure to
phthalates in combination with well known allergens, with the aim to examine if the chemical exposure increase the sensitization effect compared with exposure to only allergens (Larsen et al. 2007).

**Autism spectrum disorders**

Autism spectrum disorders is a developmental disorder that commonly involves impairments in social, communicative and behaviour development and is accompanied by abnormalities in cognitive functioning, learning, and sensory processing and is generally regarded as a life-long disorder. Over the past few decades, our understanding of the genesis and character of autism has undergone a series of transformations. It is now viewed, not as a single disorder, but as one with multiple dimensions (hence the term ASD), with sufferers exhibiting a range of severity. Autism spectrum disorders is sometimes a composite diagnosis including one or more other diagnoses, including infantile autism/autistic disorder, Asperger syndrome, disintegrative disorder, other autistic-like conditions and severe autistic features (Gillberg et al. 2006).

The average age at diagnosis has been shown to be 2-4 years for children with autism (Fombonne 2003, Mandell et al. 2005) while Asperger in general is diagnosed later, often when children reach the age of 6-8 years.

**Comorbidity**

Comorbidity between asthma, rhinitis and eczema is frequently found. More than half of the population in U.S. suffering from allergic rhinitis also has asthma. Rhinitis and asthma have similar pathogenic mechanisms and similar treatments (Spector 2001). Comorbidity of asthma with eczema was diagnosed in one third of children in a recent study (Yuksel et al. 2008).

Children who have an allergic predisposition are frequently seen to get eczema in early childhood. Children with eczema are frequently diagnosed with asthma within a few years of age. Later in their childhoods, vulnerable school age children may experience allergic problems that involve symptoms from the nose and eyes, called rhinitis. This process is called “the atopic march” or “the allergic march” and is described in Figure 1 (Spergel 2010).
Some studies have suggested that there might be a relationship between ASD and allergic diseases, including asthma. Becker et al. (2010) found that both diseases share particular aspects of disease etiology, including skewed sex bias towards boys, early childhood age-of-onset, increasing prevalence in the population, and shared molecular and genetic markers. A modest association between autism in the child and maternal asthma and allergy diagnoses recorded during the second trimester has been showed (Croen et al. 2005). These findings raise the question whether gene-environment interactions may be involved in both disorders (Becker et al. 2010).

![Figure 1. An overall picture of allergic disease development in children that most often starts with eczema and followed by asthma and rhinitis later on in life (Spergel 2010)](image)

**Burden of disease**

In Sweden, asthma and allergies have high prevalence rates, especially among children. In childhood, boys are consistently reported to have more asthma and rhinitis than girls (Anderson et al. 1992, Peroni et al. 2003). However, in the teenage there is a shift towards more asthma diagnosed in girls (Larsson 1995). Almost one third of all children between the ages of 4 to 12 years suffer from asthma or allergies which make this an essential public health problem (Wickman 2009). In Sweden, prevalence rates of 8% of ever having asthma and 6.9% of current rhinoconjunctivitis have been found (Asher et al. 2006). Furthermore, in 2009, 22.3% children were reported to have current eczema and 38.6% were reported to have ever been diagnosed with eczema, which is one of the highest rates in the world (Odhiambo et al. 2009).
ASD is not as commonly diagnosed as allergic diseases, with about 1% of the children in Sweden having this diagnosis (Gillberg et al. 2006), compared with a Norwegian study found 1.8% (Posserud et al. 2006).

There are heavy economic burdens associated with asthma, allergy and ASD. For asthma and allergies the most obvious cost is medication and hospitalization, but these conditions also lead to costs related to work and school losses (Bahadori et al. 2009). The costs are greater than supposed, due to comorbidity of asthma, rhinitis and eczema. These diseases may also contribute to decreased physical and social functioning, such as disrupts in sleep, leading to fatigue, irritability, memory deficits and depression (Shaaban et al. 2008). For a child with ASD, the health and medical costs are only a small part of the total economic burden, which include costs for community support and schooling (Jarbrink 2007). ASD also affects the family because it is a lifelong and complex disorder which involves difficulties in social, behavioural and sometimes physical development (Levy et al. 2009).

It is essential to develop both primary and secondary prevention strategies for asthma, allergy and ASD. The primary prevention targets the incidence of these diseases and would optimally occur at the prenatal, perinatal and postnatal stages, where avoidance or limited exposure of different risk factors decreases the risk of affecting the developing immune system of the fetus, and decreases the likelihood of symptoms to arise after infants are born. The secondary prevention is aimed to reduce the risk for children who are already sensitized to develop symptoms. The tertiary prevention is focused on reducing complications caused by severe disease and also to minimize the need of medication (Lorente et al. 2007, StoLoff 2008). When greater understanding about risk factors at each level of disease prevention are understood, this knowledge can be translated into public health policy and clinical practice (Milgrom 2006).

World wide time trends

Increase in allergic diseases during the last decades

Although asthma patterns are varying around the world, there is considerable evidence that there has been an increase globally in both the prevalence and severity of asthma over the recent decades (Pearce et al. 2000, Bach 2002).
Figure 2 shows the increasing prevalence of asthma from 1956 to 2000. While the studies referenced to in this figure use disparate methodology, the combined evidence shows that increasing trends over time amongst populations in countries of widely differing lifestyles and ethnic groups is generally consistent (Beggs et al. 2005). Studies have also shown that there has been an increase in the prevalence of both rhinitis and eczema (Bach 2002, Beasley 2002). Industrialised countries have mainly been the settings for research on asthma and allergies in children, but during the last decade studies have shown an increase in developing countries as well (Lai et al. 2009).
One of the most comprehensive estimates of world wide asthma and allergies is the International Study of Asthma and Allergies in Childhood (ISAAC), which is mainly based on parental reports. With high response and participation rates, ISAAC studies have provided valuable data on the prevalence of asthma and allergies for international comparisons from countries all over the world, incorporating responses from populations with different socioeconomic backgrounds and over different points of time (Asher et al. 1995).

The first phase of the ISAAC study was conducted during the early to mid 1990s using a questionnaire measuring the prevalence of asthma and allergies in more than 700 000 school-children aged 6-7 and 13-14 years in more than 50 international settings (Asher et al. 1995). In a second phase, a more extensive medical and technical investigation was conducted including 30 000 children, with more detailed questionnaires, blood sampling, skin-prick testing of sensitization and indoor environmental sampling (Weiland et al. 2004). The third phase was conducted 5-10 years after the first questionnaire. The aim of this last study was to investigate time trends in the prevalence of the three conditions in a population of 1.2 million children and to include new centers in this investigation, in order to expand the coverage of world prevalence studies (Ellwood et al. 2005).

Broadly speaking, the results of the first ISAAC study, assessing children ages 6 and 7, found that the prevalence of asthma was highest in English speaking countries, such as Australia, United Kingdom, New Zealand and Canada. The study also found high prevalence in some countries in the Latin America (Costa Rica and Panama). Among the non-English-speaking European countries, the first ISAAC study found that asthma prevalence was higher in Western Europe compared to populations living in Eastern and Southern Europe. Furthermore, Africa and Asia showed generally low asthma prevalence rates (Asher et al. 1998). The countries showing the highest prevalence rates for rhinitis were found in different parts of the world, while the highest prevalence rates for eczema was generally found in countries lying on high altitude, such as New-Zealand, Eastern Europe and Scandinavia (Asher et al. 2006).

Figure 3 show a general picture of the changes of the prevalence rates for asthma, allergic rhinoconjunctivitis, and eczema in children aged 6–7 year from phase one to phase three in the ISAAC study with data from 64-66 centers. The figure show
that asthma has increased in 25 centers (mainly in East Mediterranean and Western Europe) with a decrease seen in 14 centers (mainly in Asia Pacific) and no major changes in 27 centers. The figure shows that over time, countries with lower mean prevalence rates of asthma were likely to experience increases in mean change while higher prevalence centers showed a lower mean change (Asher et al. 2006).

Prevalence rates for allergic rhinoconjunctivitis increased in 44 centers and a decrease in nine centers. No major changes were seen in 13 centers. The same trend was seen for eczema symptoms where an increase in prevalence was reported in 44 centers and a decrease in eight centers and no major change in 12 centers (Asher et al. 2006).

There are speculations that the asthma prevalence has leveled out or plateaued in the past ten years (Anderson et al. 2004, Robertson et al. 2004). If so, these results would indicate that the saturation point for diagnoses has been reached. Regardless of increase or not during recent years, asthma rates in particular are high in most countries (Burr et al. 1989, Yunginger et al. 1992, Asher et al. 1995, Burr et al. 2006, Pearce et al. 2006, Lai et al. 2009) and in many cases one of the most common health problems in children and young adults.

**Incidence of allergic diseases**
In contrast to the well documented prevalence of asthma, there are less data on the incidence of asthma. The incidence of a disease is measured by how many new persons develop the disease under a certain period of time in a specified population (Bonita et al. 2006). International studies have shown an incidence rate for asthma in the range of 1.3-2.6 children/100 children/year (Anderson et al. 1992, Dik et al. 2004, Jaakkola et al. 2005).

Studies in Sweden have showed a yearly incidence rate for asthma of 1.1% in young adults aged 16-19 years (Larsson 1995), with the same rate found in another study of children aged 7-13 years old (Smedje et al. 2001). Another Swedish study of children aged 7-9 years, an incidence rate of 0.9% was found for doctor diagnosed asthma. This study also estimated an incidence rate of 1.6% for a child reporting ever asthma (Rönmark 2002). While rhinitis and eczema are known to be co-morbid conditions, unfortunately, there is a lack of valid information on incidence rates of these conditions in children.
Figure 3. Mean change in prevalence per year of symptoms of asthma, allergic rhinoconjunctivitis, and eczema for children aged 6-7 years versus mean prevalence of ISAAC phase one and phase three for each center (Asher et al. 2006)
**Has autism spectrum disorders increased?**

There are suspicions that ASD has increased during recent decades (Rutter 2005). ASD prevalence rates from international studies published before 1990 are ranged from 0.4-0.5% (Yeargin-Allsopp et al. 2003, Rutter 2005), while more recent studies have shown higher prevalence estimates in the range of 0.3 to 1.2% (Bertrand et al. 2001, Fombonne 2005, Baird et al. 2006, Gillberg et al. 2006). Scandinavian studies have shown prevalence rates of 0.2 to 0.8% (Kadesjö et al. 2000, Kielinen et al. 2000, Gillberg et al. 2006, Atladottir et al. 2007).

It is highly controversial if ASD has actually increased or not. Increased awareness of the disorder, changes in definitions, more complete diagnostic criteria, younger age at diagnosis, greater funding for services and an increased desire of parents to seek services for affected children may have confounded the interpretation of prevalence estimates in studies of ASD. However, recent publications argue that the huge increase in the number of children born with ASD can not be attributed simply to changes in diagnostic criteria or record-keeping. Such a large increase could only possibly account for a quarter of the published increase in ASD with the remaining increase based on real growth in this diagnosis category (Rutter 2005, Hertz-Picciotto et al. 2009).

**Interaction between exposures and genetic predisposition**

Human health is affected by different types of exposures from the environment and from psychological and social factors (Figure 4). There is a general understanding that such factors interact with our genetic disposition influencing human health (Martinez 2008).

**Genetic predisposition**

The risk with different kinds of environmental exposures to lead to adverse health effects, such as asthma, allergy and ASD, is most probably influenced by genetic predisposition. Multiple studies have found that genetic factors (often expressed as asthma and allergic problems in the family) is the strongest individual risk factor for the development of asthma and allergies in children (Åberg 1993, Norman et al. 1998, Rönmark 2002, Peroni et al. 2003, Jaakkola et al. 2005). It has been estimated that the odds of having a child with asthma were three times higher in
families with one asthmatic parent, and six times higher in families with two parents with allergic symptoms, compared to those families without allergic symptoms (Litonjua et al. 1998). Although a family history of asthma is a strong risk factor, it is neither sufficient nor necessary cause for the development of asthma (Burke et al. 2003).

There is also accumulating evidence showing that ASD is related to genetic factors with complex inheritance factors coming into play (Monaco et al. 2001, Levy et al. 2009). It has been suggested that a family with a child with ASD have 20-50% higher risk of having a second child with ASD is 20-50% compared with the population base rate (O’Roak et al. 2008). However, there is still little known about the biological basis of the disorder and the specific genes that are associated with ASD (Monaco et al. 2001, Daniels 2006).

During this short time period which the prevalence of asthma has increased, as well as the pronounced disparities of asthma prevalence in populations with the same ethnic background but diverging environmental exposures, indicate that
genetic factors alone can not explain such an increase (Pearce et al. 2006, Wong et al. 2008). This is probably true for ASD, as well. As recent research has not identified a specific set of genes for autism and as rates for ASD seem to have increased, the increases in this diagnosis might be associated with changes in the environment (Daniels 2006), with genes interacting with environmental exposure (Daniels 2006, Kinney et al. 2008, Martinez 2008).

Environmental exposures

There has been a concern about outdoor pollutants and this field has been extensively studied and debated. Outdoor air is a main source of exposure to airborne allergens such as pollen from plants and molds. It has also been suggested that different types of compounds, such as particulate matter, vehicle pollutants and ozone, increases the risk of asthma and allergies or act as triggers in already asthmatic persons (Asher et al. 1998, Brauer et al. 2007).

Another environment of importance for asthma in the population is occupational settings, both industries and non-industrial workplaces such as offices, hospitals, school, day care centers etc. Studies have shown that industrial workplace exposures are important causes of both new-onset asthma and exacerbations of pre-existing disease. Occupational exposures from industrial environments have been proposed to cause 10-15% of new-onset asthma in adults (Stenton 2010). In occupational environments different allergens such as flour and grain dusts, wood dusts and latex allergens are present, along with chemical agents (Lombardo et al. 2000).

Even though the occupational environment is an important setting in terms of risk factors associated with adult-onset asthma, the environment in which most people spend 90% of their time are non-industrial indoor environments (Figure 5). Such environments include the home environment besides offices, hospitals etc. Children spend even more time indoors, especially in the home, but also in indoor settings at schools and in day care centers (Leech et al. 2002, Brasche et al. 2005). Children are suspected to be more vulnerable to environmental exposures than adults (Landrigan et al. 2003, Grandjean et al. 2006).
Over the past decades the indoor environment has changed for most children living in affluent countries. Before 1950 most houses were built with natural materials such as wood and bricks; and the technical installations for heating and ventilation were relatively uncomplicated. During the 1960’s building technology changed to emphasize the use of new composite building materials and new construction designs. A decade later the energy crises appeared and energy saving became a priority. Energy savings in buildings called for more insulation and reduced ventilation rate which in turn impacted indoor air quality. These standards also resulted in higher relative indoor humidity which increased the risk for moisture related problems. Along with the trend toward such constructions, a tremendous number of consumer products and articles made from synthetic materials and/or chemical compounds have been introduced to our daily life. Many products such as plastics, toys, cleaning products, cosmetics, packages, textiles, electronic equipments etc. includes chemicals of health concern that may leak into the surrounding environment. Since many of these products are used indoors such environments are important when assessing exposure and subsequent disease (Hwang et al. 2008, Weschler et al. 2008).

Humans are in general constantly exposed to microbiological organisms and chemical components and sometimes to radiation. Microbiological exposures consist of e.g. allergens, bacteria, mold, virus, dust mites etc. Exposure to indoor allergens has been found to cause asthma symptoms (Gina 2006). However, the
importance of allergen exposure for sensitization and the risk with such exposure for development of allergy-related diseases is complex in the sense that not all exposures result in sensitization (Johansson et al. 2004, Henderson 2008). It has also been proposed that certain exposures early in life may protect from developing asthma and allergy, the so-called the hygiene hypothesis (Strachan 1989). This hypothesis has been driven by the results of several epidemiological studies showing that unhygienic conditions including pet exposure, farming life, overcrowding, more siblings, and day care attendance among other factors are associated with a lower prevalence of rhinitis and eczema in children, although the evidence for such factors resulting in lower prevalence rates for asthma is less consistent (Strachan 1989, Strachan 2000, von Mutius 2007).

Different chemical exposures may affect asthma and ASD. Studies show that asthma, wheezing and ASD in the child are strongly associated with pre- and postnatal parental smoking (Henderson et al. 2001, Hultman et al. 2002, Linnet et al. 2003, Lannerö et al. 2006, Pattenden et al. 2006). Exposure to environmental tobacco smoking consistently exacerbates asthma symptoms and is a risk for severe asthma (James et al. 2005). Other factors that are associated with asthma or allergy include various building materials, pesticides, cleaning agents, and personal care products. Industrial chemicals that serve as additives in flooring materials (e.g. phthalates) and formaldehyde have been suggested to increase the risk for asthma (Mendell 2007, Wang et al. 2007). Different chemical exposures to pesticides, have been associated with ASD, along with prenatal exposure to maternal use of alcohol and thalidomide (Mendola et al. 2002, Rodier 2004).

**Psychological and social factors**

To this date, relatively little has been done to identify the psychological and social factors related to asthma, allergy and ASD. A Swedish study found that psychological and social factors such as occupation as a manual worker (which was used as a proxy for low socioeconomic status) increased the risk for asthma and respiratory symptoms in adults and their children (Almqvist et al. 2005, Ekerljung et al. 2010). Other studies have demonstrated that stress symptoms and depression during pregnancy and the presence of psychiatric illness in the mother were associated with increased rates of asthma diagnoses in children (Kozyrskyj et al. 2008, Barreto do Carmo et al. 2009, Cookson et al. 2009). Stress during pregnancy
has also been associated with increased risk for the development of cognitive and emotional disorders, including autism, in offspring (Wadhwa 2005, Previc 2007).

**Indoor environmental risk factors**

The causes behind the increase in asthma and allergies are largely unknown. The reasons for growth in rates for ASD are still unclear as well and very little is known regarding indoor environmental risk factors for these diseases. The following section of this document will discuss the knowledge regarding the relationship between indoor moisture problems and respiratory diseases. The section will also discuss indoor exposure for certain chemicals and resultant diagnoses for both asthma and autism spectrum disorders.

**Moisture related problems and asthma**

Moisture related problems in buildings - also called dampness - have been associated with respiratory problems in a large number of epidemiological studies. The Nordic interdisciplinary review, NORDDAMP, conducted a multidisciplinary meta-analysis of 61 studies and found that living or working in buildings with dampness problems increased the risk for respiratory symptoms for people (Bornehag et al. 2001). This result was further confirmed in the EUROEXPO review (Bornehag et al. 2004a). Furthermore, in 2004 the Institute of Medicine (IOM) concluded in their review that “excessive indoor dampness is a public health problem” and that dampness problems in buildings are common (IOM 2004). Recently, the World Health Organization (WHO) published a report showing that dampness and moisture related problems in buildings are associated with respiratory symptoms such as cough, wheeze and asthma (WHO 2009).

These reviews, involving large numbers of participants, show that dampness in buildings appears to increase the risk of respiratory problems with odds ratios in the range from 1.4 to 2.2. These adverse effects are similar for infants, children and adults and are similar in different types of buildings and in different parts of the world. However, there is a lack of studies explaining the biological mechanisms for such a relationship and there is no consistent scientific evidence that exposure to mold is the causal factor. Both microbiological and chemicals exposures are suggested as possible causal factors for respiratory diseases (Bornehag et al. 2001, Bornehag et al. 2004a, IOM 2004, WHO 2009).
Bacteria, fungi, and mycotoxins all flourish in indoor environments. The main sources of bacteria in indoor environments are people, outdoor air and indoor bacterial growth. To this date, little is known about how specific bacteria indoor affect health (WHO 2009). Fungi producing allergens such as *Cladosporium, Alternaria, Penicillium* and *Aspergillus* are known to develop in the presence of moisture (Bloom et al. 2009). Mycotoxins, which are toxic fungi, have been hypothesized to cause adverse health effects, but evidence showing such relationship is weak (WHO 2009). Mold appears to have limited predictive value for the development of allergic symptoms, and studies have failed to show associations between mold or fungi and asthma and allergy in children at least in Scandinavia and regions with about the same climate (Bornehag et al. 2001, Bornehag et al. 2004a, IOM 2004, WHO 2009). Due to variations in study design, methodology, the lack of standardized procedures for environmental assessments of mold and the sheer number of mold found in indoor environment, health problems are complicated to evaluate (WHO 2009). Furthermore, the specific mechanisms by which these health outcomes are created (microbiological or chemical exposure or both), is still not known.

However, there is a general problem to make risk assessment of mold exposure on a global basis. In general, the exposure indoor is low in e.g. Scandinavian countries when compared with regions with a more hot and humid climate. This implies that mold exposure differ in risk between different regions globally.

Recent reviews conclude that moisture related problems in buildings are associated with respiratory problems in children. However, such studies are often designed around questionnaires, using a cross-sectional design which limits the possibility of establishing temporality between exposure and health outcome and increasing the risk for reporting bias. Due to these methodological concerns, one of the questions at issue in this thesis is to investigate the health risk with moisture related problems indoor using a longitudinal study design where problems with reporting bias can be reduced.
**Chemical exposure and asthma**

During the last decades in Europe more than 100,000 new chemicals have been introduced to the entire environments (Commission of the European Communities: White paper 2001). However, a majority of these chemicals are most probably not harmful to humans under normal circumstances. Sources for chemical contamination in indoor environments include building materials (Bornehag et al. 2005a), water based paints and cleaning agents (Choi et al. 2010), personal care products (Sathyanarayana et al. 2008) etc. Some of these chemicals may persist from several months to years in the indoor environment (Weschler et al. 2008).

Some chemicals have been shown to be toxic in animal studies and an increasing body of evidence suggests that they are also impacting human health. There are suggestions that the increase in exposure for suspected endocrine disrupting chemicals (EDCs) might explain the increase in several chronic diseases/disorders including asthma and allergies (Bornehag et al. 2010). EDCs have in animal tests shown to be able to mimic or block the endocrine activity (Rudel et al. 2009). EDCs during developing stages may affect the endocrine system with potential impact on the immune system (Chalubinski et al. 2006).

One group of chemicals that has been suggested to have endocrine disrupting properties are phthalates, used in soft poly vinyl chloride (PVC) material and in a huge number of consumer products such as toys, cleaning products, cosmetics, and hygiene products. Phthalates are not chemically bound to the polymers or the products where they are used, which means they can migrate to the surrounding environment (Wormuth et al. 2006). Phthalates are also routinely found in indoor dust and air which is to be expected since very many potential sources are used indoor (Oie et al. 1997, Becker et al. 2004, Bornehag et al. 2004c) and identified sources are e.g. flooring materials of PVC (Bornehag et al. 2005a). Metabolites of phthalates are furthermore routinely found in human fluids such as urine, blood, breast milk and amniotic fluids meaning that the general population is exposed including pregnant women, foetus and infants (Stahlhut et al. 2007). This trail of markers means that we can follow phthalates from their sources to human uptake. This means that studies should be possible to examine if such exposure is associated with asthma and other conditions (diseases) in children.
A dose response relationship between asthma, rhinitis and eczema and different phthalates in indoor dust have been reported (Bornehag et al. 2004c). A Bulgarian study, using the same methodology as Bornehag’s study, found that phthalates in indoor dust were associated with airway symptoms in children (Kolarik et al. 2008b). In the Bulgarian study, PVC was not identified as a source for phthalates in indoor dust - rather, furniture polish was strongly associated as a source of phthalates in indoor dust (Kolarik et al. 2008a). Other epidemiological research indicates that phthalates and/or sources for phthalates are related to respiratory diseases in children. A Norwegian case-control study showed that the risk of bronchial obstruction was related to the presence of PVC-flooring (Jaakkola et al. 1999, Oie et al. 1999). Furthermore, three cross-sectional studies from Finland, Russia and Sweden showed associations between plastic wall materials and/or PVC-flooring and airway symptoms in children (Jaakkola et al. 2000, Jaakkola et al. 2004, Bornehag et al. 2005c).

There are suggestions that phthalates may act as potential modulators of the immune system in humans, with allergic responses as a possible result. Experimental studies present support for an adjuvant effect on basic mechanisms in allergic sensitization by high doses of phthalates. Thus, phthalate exposure could possibly affect fundamental mechanisms in the pathophysiology, responsible for asthma and allergy. However, there is still limited knowledge about this relationship and there is a need to look at real life exposure of phthalates and to identify molecular targets that can explain this interaction (Bornehag et al. 2010).

Another recent study show that bedroom air concentrations of propylene glycol and glycol ethers (PGEs) was significantly associated with multiple allergic symptoms as well as sensitization (IgE) in pre-school children (Choi et al. 2010). PGEs are volatile organic compounds that can be found in e.g. water based paint and water based cleaning products. This finding indicates again that common household products may be of health relevance.

In conclusion, while the relationship between PVC or phthalate exposure and airway diseases is becoming better known, there are still methodological shortcomings that limit our knowledge on this subject. The available data is primarily from cross-sectional studies, which means that we can not determine the
exposure involved in the development of these diseases. Longitudinal studies are needed in order to investigate the relationship between exposure and development of disease. This is one of the questions at issue in the current thesis; to investigate if PVC-flooring is related to the incidence of asthma.

Chemical exposure and autism spectrum disorders

Theories regarding the vulnerability of the human central nervous system to environmental chemicals have been developed. There is clear evidence that the developing nervous systems in foetuses and children are more vulnerable to many chemical agents than adult nervous systems (Tilson 1998). Exposure to chemicals such as pesticides, PCBs, along with exposure to alcohol during gestation, have been associated with adverse neurodevelopmental outcomes in children (Grandjean et al. 2006). Some of these chemicals are also considered to be potential endocrine disruptors and such exposure can result in a spectrum of adverse health outcomes depending on the timing and doses of these chemical agents (Mendola et al. 2002). Other environmental factors that are associated with autistic behaviours are prenatal exposures to thalidomide (Stromland et al. 1993, Rodier 2004) or valproic acid (Christianson et al. 1994). Although lead is a known neurotoxin and studies have found adverse effects of prenatal exposure on growth and development, surprisingly little research regarding chemical exposure has been done with respect to autism (Banks et al. 1997, Mendola et al. 2002).

Exposure to modern chemicals, commonly occurring in indoor environments has been suggested as a possible causal factor for neurodevelopmental disorders including ASD (Grandjean et al. 2006). There are suspicions that EDCs can interfere with brain development and might cause a wide range of developmental disabilities in children (Weiss et al. 2000). However, the contribution of such exposures to ASD remains uncertain and scientific evidence to support this theory is lacking (Grandjean et al. 2006). Due to this uncertainty, one of the questions at issue in the current thesis is to investigate if ASD is related to certain indoor environmental factors, such as PVC-flooring, a known source for indoor phthalate exposure.
Methodological problems in epidemiology

The incidence of asthma in Swedish children estimated with questionnaire studies varies widely, from 0.9 to 1.6%. This variation may be due to true differences in incidence rates; but might also be due to methodological problems. Estimating the incidence of allergic diseases from questionnaire studies can be done by the use of data from birth cohort studies as well as from cohorts established later on in life (Figure 6).

![Diagram](image)

Figure 6. Different principles for estimating the incidence rate of asthma in a cohort study

When not using birth cohort data, as in the current study, the estimated incidence rates depends on how the baseline population is defined from a health point of view and how the studied health outcome is defined in the follow-up. For example, should subjects reporting wheezing or other airway symptoms (but not asthma) at baseline be excluded? Some studies using established cohort designs excluded both doctor diagnosed asthma and asthma ever from the baseline population (Larsson 1995, Smedje et al. 2001, Rönmark 2002) while other only excluded doctor diagnosed asthma (Dik et al. 2004, Jaakkola et al. 2005). It is also important to consider that studies have investigated different health outcomes at follow-up, e.g. doctor diagnosed asthma (Larsson 1995, Rönmark 2002, Dik et al. 2004), parental reported asthma or wheezing ever (Anderson et al. 1992), or parental reported asthma ever (Larsson 1995, Rönmark 2002, Jaakkola et al. 2005). As a result it is difficult to compare results between investigations.
Studies that employ a cross-sectional design may also limit the possibility for establishing temporality between exposure and health outcome due to the risk for reporting bias. Reporting bias occurs when those affected by the outcome are more likely to report the exposure than the unaffected. This makes it difficult to interpret associations between exposure and outcome in cross-sectional studies. This particular source of reporting bias occur to a lesser degree in longitudinal studies where exposure is reported separately from the disease that is studied (Bonita et al. 2006).

These two issues, one regarding how to estimate the incidence rate of asthma, rhinitis and eczema and one regarding reporting bias, are elaborated in the current thesis.
AIMS AND OBJECTIVES

The aim of this work has been to investigate certain environmental factors in the dwelling and their impact on children's health, in terms of asthma, rhinitis, eczema as well as autism spectrum disorders and to identify certain methodological difficulties in epidemiological studies.

The thesis includes four major objectives:

I To estimate the incidence rates for asthma, rhinitis and eczema symptoms during a 5-year period among Swedish pre-school children. A further objective was to investigate the importance of the baseline health status and the definition of the health outcome for the incidence rates and identification of different influential factors for the incidence of asthma, rhinitis and eczema.

II To investigate if the association between reported moisture related problems indoor and asthma in children found in cross-sectional data can be confirmed in longitudinal analyses.

III To examine the association between exposure to PVC-flooring in the home during early childhood and the incidence of asthma, rhinitis and eczema in children.

IV To investigate associations between certain indoor environmental factors and autism spectrum disorders in children.
MATERIALS AND METHODS

The DBH-study

The Dampness in Buildings and Health (DBH) study started in the year 2000 in the county of Värmland, Sweden with an overall aim to investigate the importance of indoor exposures for asthma and allergy in children. The study was divided into four phases (Figure 7). The first phase was a questionnaire study in 2000 to the parents of 14,077 children aged 1-5 years (Bornehag et al. 2004b). One and a half years later, the second phase of the study was conducted including an analysis of subpopulation, using a nested case-control design (Bornehag et al. 2004c). In the third phase, a five year follow-up questionnaire study was carried out in 2005 and a ten year follow-up questionnaire was conducted during spring 2010 in the fourth phase. This thesis is based upon questionnaire data from the first and the third phase of the DBH-study.

Figure 7. Overview of the four conducted phases of the Dampness in Building and Health study

**DBH Phase I**

The first step was carried out in March 2000 as a cross-sectional questionnaire study. This baseline questionnaire was distributed to the parents of all children aged 1–5 years (n=14,077) in the Swedish county of Värmland, with about 273,000 inhabitants. The county is divided into 16 municipalities where the county capital is Karlstad with almost 84,000 inhabitants.

The questionnaire was distributed by post, with three postal reminders sent to potential participants. Of the study population, parents of 100 randomly selected children participated in a pilot study for development of the questionnaire. Of the potential respondents, 200 children could not be found by post. In total, the
parents of 10,851 children responded to the questionnaire, corresponding to a response rate of 79% (Figure 9). These children lived in 8,918 homes as siblings were included in the study.

**DBH phase II**

The second phase of the study was based on 400 children (198 cases and 202 healthy controls) living in 390 homes, since there were ten pairs of siblings. The cases and the healthy controls were selected from the baseline questionnaire, described further elsewhere (Bornehag et al. 2004c). From October 2001 to April 2002 medical examinations of the 400 children and technical investigations of the homes were performed. The medical examinations were focused on asthma, rhinitis and eczema and included collection of biological samples (blood, nasal secretions, condensed breath). The aim of the technical inspection and measurements in the dwellings was to perform visual inspections (by professional inspectors) and indoor air quality (IAQ) assessments, including collection of dust and air, and measurements of ventilation rate, temperature and relative humidity. These samples were further analyzed for the content of microbiological and chemical agents. Data from this phase in not included in this thesis, but discussed in some sections.

**DBH phase III**

In the third phase of the study, a follow-up questionnaire was conducted five years after the baseline questionnaire. This phase included the children of the first three year cohorts, who were 1-3 years at baseline and consequently 6-8 years in 2005 (n=7,509). The parents of 5,483 children responded, corresponding to a response rate of 73%.

**DBH phase IV**

During spring 2010, a ten year follow-up investigation with focus on chronical diseases was conducted including all children in Värmland, who were part of the original study population, or also those who had moved to Värmland during the period, now between the ages of 11-15 years (n=15,043). The response rate was 53%.
In order to examine selection problems in the baseline material (DBH-phase I), 200 families were randomly selected from those who did not answer the questionnaire. Of these, 116 were reached by telephone and asked to respond to five questions related to their children’s health (Figure 8). There were no significant differences in prevalence of symptoms in the child between responding and non-responding families, i.e. “wheezing ever” (24.3 vs. 23.1 for responders and non-responders, respectively) and “doctor diagnosed asthma” (5.4 vs. 4.3%). Participating families reported 23.5% “eczema ever” while non-responding families reported 12.1%. However, the difference was not significant. Neither was there any significant difference between responders and non-responders regarding type of building “single family house vs. multifamily house” (82.0 vs. 81.0%), and “suspected mold problem in the dwelling” (7.8 vs. 9.5%). A relatively high response rate (79%) in combination with minor differences between participating and non-participating families means that the risk for selection bias in this the first phase investigation is limited.

It was not possible to do an analysis of the 2,026 families that did not respond to the follow-up questionnaire (Figure 8). However, we can compare the health status of the children who were participants on both questionnaires (n=4,779) with the children who did not respond to the DBH-I questionnaire (n=704). Analyses showed that there were no significant differences in prevalence of symptoms between these two groups (4,779 vs. 704), i.e. “wheezing ever” (24.1 vs. 22.0%), “doctor diagnosed asthma” (8.7 vs. 8.3%), “doctor diagnosed rhinitis” (6.3 vs. 7.5%) and “eczema ever” (23.2 vs. 23.3%). Reports of “visible dampness” were almost the same in the two groups (1.0 vs. 1.1%) as was housing status, living in a single family house (88.2 vs. 83.4%).

**The study population**

The population investigated in this thesis is 4,779 children who participated in both the baseline and the follow-up questionnaire (Table 1). The children were between 1-3 years of age in the baseline study 2000 and 6-8 years in the follow-up 2005. The population was equally distributed between boys and girls and more than half of the children had at least one family member (mother, father, siblings) who had asthma, rhinitis or eczema symptoms at baseline. Baseline data in 2000 showed that most of the families lived in single family houses and almost 22% of the children...
had at least one smoking parent at baseline, with a slight decrease during the 5 year follow-up period. A more detailed description of the studied population is given in the different papers included in the thesis.

Figure 9. Description of participating and non-participating families in the baseline (phase I) and the follow-up (phase III) of the DBH-study
Table 1. Description of the study population participated in the baseline and follow-up study

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline questionnaire 2000 (n=4,779)</th>
<th>Follow-up questionnaire 2005 (n=4,779)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline questionnaire</td>
<td>2000</td>
<td>2005</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>2388</td>
<td>2388</td>
</tr>
<tr>
<td>Boys</td>
<td>2391</td>
<td>2391</td>
</tr>
<tr>
<td><strong>Age of the child (y)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>1557 (32.6)</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>1568 (32.8)</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>1654 (34.6)</td>
</tr>
<tr>
<td><strong>Type of building</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SH</td>
<td>3871 (81)</td>
<td>4090 (85.6)</td>
</tr>
<tr>
<td>MH</td>
<td>793 (16.6)</td>
<td>546 (11.4)</td>
</tr>
<tr>
<td><strong>Size of the home (m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>326 (6.8)</td>
<td>135 (2.8)</td>
</tr>
<tr>
<td>75-150</td>
<td>3389 (70.9)</td>
<td>3240 (67.8)</td>
</tr>
<tr>
<td>&gt;150</td>
<td>1013 (21.2)</td>
<td>1332 (27.9)</td>
</tr>
<tr>
<td><strong>Divorce</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>324 (6.8)</td>
<td>960 (20.1)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Economical problems</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Allergy in family</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2167 (45.3)</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>2563 (53.6)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Smoking in family</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any smoker</td>
<td>1044 (21.8)</td>
<td>909 (19.0)</td>
</tr>
<tr>
<td>Smoking mother</td>
<td>673 (14.1)</td>
<td>605 (12.7)</td>
</tr>
<tr>
<td>Smoking father</td>
<td>497 (10.4)</td>
<td>398 (8.3)</td>
</tr>
</tbody>
</table>

1) SH = single family house, MH = multi family house

Descriptions of the used questionnaires

The questionnaire from phase I is described in Appendix A and the phase III questionnaire is described in Appendix B. Information on allergic symptoms among children and their parents was collected with the same validated questions as used in the ISAAC-studies (Table 2)(Pearce et al. 2007).

Data on background factors such as age, sex, birth weight, gestation length, and length of breastfeeding period as well as the number of family members, and smoking habits in the home were collected. Moreover, information regarding day care attendance, sick building syndrome (SBS) symptoms of one parent, pet-keeping, cleaning frequency, and food habits was collected. There were further questions about the dwelling e.g. type of house, type of surroundings and type of construction, surface material on walls and floors.
Table 2. Description of used questions in the questionnaire regarding symptoms and diseases

<table>
<thead>
<tr>
<th>Health definitions</th>
<th>Yes vs. No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing ever</td>
<td>“Has your child ever had wheezing or whistling in the chest at any time in the past?”</td>
</tr>
<tr>
<td>Wheezing during last 12 months</td>
<td>“Has your child had wheezing or whistling in the chest in the last 12 months?”</td>
</tr>
<tr>
<td>Cough</td>
<td>“In the last 12 months, has your child had a dry cough at night for more than two weeks, apart from a cough associated with a cold or chest infection?”</td>
</tr>
<tr>
<td>Doctor diagnosed asthma</td>
<td>“Has your child been diagnosed with asthma by a doctor?”</td>
</tr>
<tr>
<td>Rhinitis ever</td>
<td>“Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or a flu?”</td>
</tr>
<tr>
<td>Rhinitis during last 12 months</td>
<td>“In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?”</td>
</tr>
<tr>
<td>Rhinitis on pets</td>
<td>“In the past 12 months, has your child had a problem with sneezing, a runny or a blocked nose, or itchy-watery eyes after been in contact with furred animals?”</td>
</tr>
<tr>
<td>Rhinitis on pollen</td>
<td>“In the past 12 months, has your child had a problem with sneezing, a runny or a blocked nose, or itchy-watery eyes after been in contact with pollen?”</td>
</tr>
<tr>
<td>Doctor diagnosed rhinitis</td>
<td>“Has your child been diagnosed with hay fever or allergic rhinitis by a doctor?”</td>
</tr>
<tr>
<td>Eczema ever</td>
<td>“Has your child ever had an itchy rash (eczema), which was coming and going for the last 6 months?”</td>
</tr>
<tr>
<td>Eczema during last 12 months</td>
<td>“Has your child had this itchy rash at any time in the last 12 months?”</td>
</tr>
</tbody>
</table>

Data on moisture related problems were collected both regarding the current dwelling as well as the home where the child was born (Table 3). In the baseline questionnaire thirteen questions on moisture problems in different rooms in the home were used. Answers to these single questions were “Yes”, “No” or “Don’t know”. With the single questions as a ground, different dampness indices were calculated where “Yes” and “No” were used and the answer “Don’t know” was excluded. In the baseline questionnaire, there were further retrospective questions about moisture related problems in the child’s birth residence. However, these questions were not specified to what room the moisture problem existed and the parents could only answer “Yes, at least one problem” or “No such problems”. In the follow-up questionnaire (2005) only three indices were asked for.
### Table 3. Description of different moisture related indices in the questionnaire

<table>
<thead>
<tr>
<th>Moisture related indices in the home collected in the baseline questionnaire</th>
<th>Moisture related indices in birth residence collected retrospectively in the baseline questionnaire</th>
<th>Moisture related indices in the home collected in the follow-up questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water leakage</strong>&lt;sub&gt;BL&lt;/sub&gt;</td>
<td>No such indices vs. Yes at least one indices during the past 12 month, Yes at least one earlier</td>
<td>“Have you had flooding or other types of water damages in the child’s and/or parent’s bedroom and/or in kitchen and/or bathroom?”</td>
</tr>
<tr>
<td></td>
<td>“Is there loosening, bubbling or discoloured flooring material in the child’s and/or parent’s bedroom and/or in the bathroom?” and/or “Is there miscoloured plastic cork or parquet in the dwelling?”</td>
<td>“Was there flooding or other types of water damages in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Floor moisture</strong>&lt;sub&gt;BL&lt;/sub&gt;</td>
<td>No such indices vs. Yes at least one</td>
<td>“Is there visible mold on the floor, wall or roof in the parent’s and/or child’s bedroom?” and/or “Is there visible damp stains on the floor, wall or roof in the parent’s and/or child’s bedroom?”</td>
</tr>
<tr>
<td><strong>Visible dampness</strong>&lt;sub&gt;BL&lt;/sub&gt;</td>
<td>No such indices vs. Yes at least one</td>
<td>“Is there condensation on the inside of the windows during winter time in the parent’s and/or child’s bedroom?”</td>
</tr>
<tr>
<td><strong>Condensation on window</strong>&lt;sub&gt;BL&lt;/sub&gt;</td>
<td>No condensation vs. Yes, less than 5 cm, Yes, more than 5 cm</td>
<td>“Was there condensation on the inside of the window during winter time in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Moldy odor</strong>&lt;sub&gt;BL&lt;/sub&gt;</td>
<td>No odor vs. Yes, sometimes; Yes, often</td>
<td>“Did you perceived mold odor in the dwelling in the child’s birth residence?” and/or “Did you perceive earthy odor in your dwelling in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Visible dampness</strong>&lt;sub&gt;BR&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Was there flooding or other types of water damages in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Floor moisture</strong>&lt;sub&gt;BR&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Was there loosening, bubbling or discoloured floor carpets in the child’s birth residence?” and/or “Was there miscoloured plastic cork or parquet in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Visible dampness</strong>&lt;sub&gt;BR&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Was there visible mold or damp stains on the floor, wall or roof in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Condensation on window</strong>&lt;sub&gt;BR&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Was there condensation on the inside of the window during winter time in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Moldy odor</strong>&lt;sub&gt;BR&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Did you perceived mold odor in the dwelling in the child’s birth residence?” and/or “Did you perceive earthy odor in your dwelling in the child’s birth residence?”</td>
</tr>
<tr>
<td><strong>Visible dampness</strong>&lt;sub&gt;FU&lt;/sub&gt;</td>
<td>No such problems vs. Yes, at least one problem</td>
<td>“Is there visible mold on the floor, wall or roof in the parent’s and/or child’s bedroom?” and/or “Is there visible damp stains on the floor, wall or roof in the parent’s and/or child’s bedroom?”</td>
</tr>
<tr>
<td><strong>Condensation on window</strong>&lt;sub&gt;FU&lt;/sub&gt;</td>
<td>No condensation; Yes, less than 5 cm vs. Yes, more than 5 cm</td>
<td>“Is there condensation on the inside of the windows during winter time in the parent’s and/or child’s bedroom?”</td>
</tr>
<tr>
<td><strong>Floor moisture</strong>&lt;sub&gt;FU&lt;/sub&gt;</td>
<td>No such problems vs. Yes, floor moisture</td>
<td>“Is there loosening, bubbling or discoloured flooring material in the child’s and/or parent’s bedroom and/or in the bathroom?”</td>
</tr>
</tbody>
</table>
In both the baseline and the follow-up questionnaire there were questions on different flooring materials (PVC, plastic cork, wood, linoleum, stone, wall-to-wall carpet). The flooring material “plastic cork” has been grouped together with PVC-material in the analyses. The reason for this was that an earlier validation study showed that 40 out of 55 parental reports of “plastic cork” was PVC when evaluated by the professional inspectors (Engman et al. 2007). Furthermore, “plastic cork” material has traditionally not been used in bedrooms.

The follow-up questionnaire also had an additional question on different chronic disorders. The question used in this thesis was if the child had “autism, Asperger or Tourette’s syndrome”, also described as the composite definition of ASD (Gillberg et al. 2006).

**Estimation of incidence rates for asthma, rhinitis and eczema**

The impact of different health status of the baseline population as well as different health outcomes at follow-up on the incidence of asthma, rhinitis and eczema was investigated in paper I. The different baseline and follow-up definitions are also described in Table 4.

Table 4. Description of different baseline and follow-up definitions to be used for estimation of incidence rates of asthma, rhinitis and eczema in children

<table>
<thead>
<tr>
<th>Definition of the baseline group</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
</tr>
<tr>
<td>No doctor diagnosed asthma</td>
<td>Doctor diagnosed asthma</td>
</tr>
<tr>
<td>No doctor diagnosed asthma and No wheezing ever</td>
<td>Doctor diagnosed asthma</td>
</tr>
<tr>
<td>Wheezing, but No doctor diagnosed asthma</td>
<td>Doctor diagnosed asthma</td>
</tr>
<tr>
<td>No doctor diagnosed asthma and No wheezing ever</td>
<td>Doctor diagnosed asthma and/or wheezing ever</td>
</tr>
<tr>
<td><strong>Rhinitis</strong></td>
<td></td>
</tr>
<tr>
<td>No doctor diagnosed rhinitis</td>
<td>Doctor diagnosed rhinitis</td>
</tr>
<tr>
<td>None of the following symptoms; doctor diagnosed rhinitis, rhinitis ever, rhinitis during last 12 month, rhinitis to pollen and rhinitis to pets</td>
<td>Doctor diagnosed rhinitis, rhinitis ever, rhinitis during last 12 month, rhinitis to pollen and rhinitis to pets</td>
</tr>
<tr>
<td><strong>Eczema</strong></td>
<td></td>
</tr>
<tr>
<td>No eczema ever</td>
<td>Eczema ever</td>
</tr>
</tbody>
</table>
The incidence of doctor diagnosed asthma was estimated for four different groups of children. In the first baseline definition children with doctor diagnosed asthma were excluded. In the second baseline definition also wheezing ever were excluded. In the third group the incidence was estimated in those children that had wheezing at baseline, but not doctor diagnosed asthma. When estimating the incident of doctor diagnosed asthma and/or wheezing ever, such symptoms were excluded from the baseline population.

When estimating the incidence of doctor diagnosed rhinitis, children with such symptoms were excluded from the baseline population. The incidence of any of the symptoms--; diagnosed rhinitis, rhinitis ever, rhinitis during last 12 month, rhinitis to pollen and rhinitis to pets--; was estimated by excluding such symptoms from the baseline population.

Finally, the incidence of eczema ever was only calculated in one way, where children with eczema ever were excluded from the baseline population.

**Statistical methods**

Since we collected questionnaire data for a 5-year period, we had no information of the yearly incidence during the intervening years. The yearly incidence was therefore estimated by dividing the 5-year incidence by the number of years in the period (5), meaning a mean incidence rate per year during the period.

Differences in frequencies, prevalence and incidence have been tested with Chi-square test ($\chi^2$) and trends in data have been tested with linear by linear associations.

Associations between different environmental and lifestyle factors and symptoms have been estimated by crude and adjusted odds ratios (ORs and aORs), and are expressed as estimated odds ratios and 95% confidence intervals. Adjusted odds ratios were computed using logistic regression models. In Paper I a stepwise method was used (forward: conditional) where only factors remaining statistically significant in the final model are reported. The specific adjustment variables used in each analysis are further described in each paper, but commonly used potential confounders were age (6, 7 or 8 years of age) and sex of the child as well as allergy...
in family (history of symptoms of asthma, rhinitis and/or eczema in other family members; yes vs. no). Also type of dwelling (multi family house vs. single family house) and smoking in the family (any smoker in the dwelling vs. no smoker) was used. In order to even further avoid confounders, stratifications where done.

The associations were considered to be statistically significant when the p-value was below 0.05. Statistical analyses were carried out using SPSS for Windows (version 14.0, 15.0 and 18.0).

Ethics

The DBH phase I study was approved by the regional ethical committee in Örebro, Sweden. Phase III was approved by the regional ethical review board at Uppsala University, Uppsala, Sweden.
RESULTS AND DISCUSSION

Prevalence and incidence rates of asthma, rhinitis and eczema

The cumulative prevalence of doctor diagnosed asthma increased from 5.2% for children aged 1-3 years to 8.7% for children aged 6-8 years (Figure 9). The cumulative prevalence of wheezing ever was surprisingly lower in the follow-up questionnaire compared to baseline (24.9% in baseline vs. 24.1% in the follow-up), which could be due to recall bias. Furthermore, the cumulative prevalence for doctor diagnosed rhinitis increased from 1.4% to 6.3%. Rates for rhinitis ever (12.0% to 20.4%) and eczema ever were found to increase from 21.9% to 23.2%.

The cumulative prevalence rates have been compared with two other Swedish studies. Björksten et al. (1998) investigated asthma and allergies in 3,029 children aged 6-7 years in Stockholm, and Bjerg et al. (2010) studied 2,585 children 7-8 years old in northern Sweden. Both these studies have shown that the cumulative prevalence of doctor diagnosed asthma, wheezing ever, and rhinitis are in line with our results from the follow-up study, with children who were between 6 and 8 years old. The prevalence of eczema ever was higher (35.7%) in the study in Stockholm (Björksten et al. 1998) compared with our rate (23.2%).

Figure 9. Cumulative prevalence of doctor diagnosed asthma, rhinitis and eczema ever at baseline (n=10,851) and at follow-up (n=5,483) in the current DBH study and data from two other Swedish studies on children in the age of 6-8 years (Björksten et al. 1998, Bjerg et al. 2010) *Prevalence’s that was not estimated in these studies
The prevalence of wheezing during the previous 12 months declined significantly from 22.2% at baseline to 10.0% at follow-up in our study. Prevalence rates for rhinitis during the previous 12 months increased slightly from 11.4% to 14.8%, while the prevalence of eczema during the previous 12 months was about the same at baseline and follow-up (18.7% and 18.3%) as seen in Figure 10.

Prevalence rates for wheezing during the previous 12 months and rhinitis during the previous 12 months are similar to results from the two other Swedish studies while the prevalence rates for eczema during the previous 12 months in our study was lower than these other two studies.

Figure 10. Prevalence of wheezing, rhinitis and eczema during the last 12 months at baseline (n=10,851) and at follow-up (n=5,483) in the current DBH study as well as in two other Swedish studies on children aged 6-8 years (Björksten et al. 1998, Bjerg et al. 2010)

*Prevalence that was not estimated in this study

**Health status at baseline and follow-up and incidence rates**

In cohort studies that are established after participants are born, children in the baseline population may already have developed allergic symptoms and/or disease. Therefore, when estimating the incidence of asthma, rhinitis and eczema a study population of healthy subjects must be defined, from which incidence can be
calculated. In paper I there is a discussion how incidence rates of asthma, rhinitis and eczema change, when calculating the incidence with different formulae.

**Incidence of asthma**

We found that the mean incidence rate per year for doctor diagnosed asthma ranged between 0.6 and 2.4% depending on different definitions of the baseline group and health outcome at follow-up (Table 5).

Table 5. The yearly incidence rate of different symptoms based on different baseline and follow-up definitions of the studied disease

<table>
<thead>
<tr>
<th>Definition of the baseline group</th>
<th>Follow-up</th>
<th>Mean yearly incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No doctor diagnosed asthma</td>
<td>Doctor diagnosed asthma</td>
<td>1.0%</td>
</tr>
<tr>
<td>No doctor diagnosed asthma and No wheezing ever</td>
<td>Doctor diagnosed asthma</td>
<td>0.6%</td>
</tr>
<tr>
<td>Wheezing, but No doctor diagnosed asthma</td>
<td>Doctor diagnosed asthma</td>
<td>2.4%</td>
</tr>
<tr>
<td>No doctor diagnosed asthma and No wheezing ever</td>
<td>Doctor diagnosed asthma and/or wheezing ever</td>
<td>2.4%</td>
</tr>
<tr>
<td><strong>Rhinitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No doctor diagnosed rhinitis</td>
<td>Doctor diagnosed rhinitis</td>
<td>1.1%</td>
</tr>
<tr>
<td>None of the following symptoms; doctor diagnosed rhinitis, rhinitis ever, rhinitis during last 12 month, rhinitis to pollen and rhinitis to pets</td>
<td>Doctor diagnosed rhinitis, rhinitis ever, rhinitis during last 12 month, rhinitis to pollen and rhinitis to pets</td>
<td>3.7%</td>
</tr>
<tr>
<td><strong>Eczema</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No eczema ever</td>
<td>Eczema ever</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

When children with doctor diagnosed asthma at baseline were excluded from baseline, the five year incidence of doctor diagnosed asthma became 4.9%, and the mean incidence per year was 1.0 child/100 children/year (1.0%). This incidence rate is similar with other studies in Sweden. Larsson (1995) found an incidence of 1.1% in young adults aged 16-19 years, while Smedje et al. (2001) found similar rates in children aged 7-13 years. However, the most comparable study, due to study definitions and the studied age group, conducted by Rönnmark et al. (2002) who reported an incidence rate of doctor diagnosed asthma of 0.9% in children aged 7-9 years. Our study had the same outcome definition for new cases (doctor diagnosed asthma) as the other studies when estimating the incidence of asthma.
but we had different baseline definitions. Our study excluded solitary doctor
diagnosed asthma from the baseline population while the other three studies
excluded both doctor diagnosed asthma and ever asthma from baseline. In our
study, we did not have a specific question on “ever asthma”, so an exact
comparison could not be done.

When excluding both doctor diagnosed asthma and wheezing ever from the
baseline population, the incidence of doctor diagnosed asthma decreased to 0.6%.
This finding indicates that children with wheezing are at risk for developing
asthma. Furthermore, children who are reported to have wheezing or other
asthma-associated symptoms (but not doctor diagnosed asthma) at baseline may
have an increased risk to develop asthma. In fact, they may already have asthma,
but have not yet been diagnosed.

The incidence rate for asthma in our study was also related to how the health
outcomes at follow-up were defined (Table 5). When we excluded children with
doctor diagnosed asthma and wheezing from the baseline population, we found a
large variation for the incidence of doctor diagnosed asthma (0.6%) or the
incidence of any of the two outcomes; doctor diagnosed asthma and/or wheezing
ever (2.4%). Our study showed that the vast majority of children having doctor
diagnosed asthma were also reported to have wheezing (95%). Yet, out of children
with wheezing only about 20-35% had doctor diagnosed asthma. A possible
explanation for this discrepancy has been proposed by Rönmark et al. (2000) who
found different incidence rates when using two different definitions of asthma.
The incidence of doctor diagnosed asthma in that study was found to be 0.9%
while the incidence of ever asthma was 1.6%. This shows that different definitions
of asthma, both at baseline and as outcome, have a considerable impact of the
reported incidence rates in different studies.

**Incidence of rhinitis and eczema**

In contrast to many studies on the prevalence of rhinitis and eczema in children,
only a few have investigated the incidence rates using questionnaire studies. We
found the mean annual incidence of doctor diagnosed rhinitis to be 1.1%, while
the incidence of any rhinitis symptom was 3.7% (Table 5). We found only one
other Swedish study studying the incidence of rhinoconjunctivitis in teenagers aged
13-16 years (Norrman et al. 1998). That study reported an incidence rate of 1.1% which was comparable to the incidence rate of doctor diagnosed rhinitis in our study. Even though the rates are similar, the age of the children in Norrman et al.’s study differs from the age of children in our study and both baseline and outcome definitions at follow-up were different from our study.

The incidence of eczema was estimated in only one way with an yearly incidence of 2.7%, which is slightly lower than another Swedish study in children aged 5.5 years showing an incidence rate of 3.8%/year (Broberg et al. 2000).

Our study used the definitions below for the baseline group and health outcomes. These definitions were used in paper II and III in the thesis:

- The incidence of parental reported doctor diagnosed asthma during the five year period (2000-2005) was estimated by excluding children reported to have “doctor diagnosed asthma” and/or “wheezing ever” at baseline and calculating the incidence of “doctor diagnosed asthma” in the follow-up questionnaire.
- The incidence of rhinitis was estimated by excluding “doctor diagnosed rhinitis” at baseline and calculating the incidence based on those that were reported to have “doctor diagnosed rhinitis” in the follow-up questionnaire.
- Finally, the incidence of eczema was calculated by excluding children with “eczema ever” at baseline and calculating the incidence based on those that reported “eczema ever” in the follow-up questionnaire.

Factors associated with incidence of asthma, rhinitis and eczema
The following section provides a summary of study results of factors that are significantly associated with the incidence of asthma, rhinitis and eczema.

We found that allergic problems in the family were strongly associated with an incidence of asthma, rhinitis and eczema, a finding which also has been shown in many other studies (Norrman et al. 1998, Rönmark 2002, Jaakkola et al. 2005, Willemsen et al. 2008). Our data show that allergic symptoms in the mother were more strongly associated with the incidence of asthma and eczema in the child (adjusted odds ratio (aOR) for asthma 2.16; 95% CI 1.27-3.66 and aOR for eczema
than such symptoms in the father (aOR for asthma 1.33; 0.72-2.45 and aOR for eczema 1.28; 0.96-1.71). Overall, the highest incidence rates were found in children where both parents were reported to have allergic symptoms.

Another factor related to the incidence of asthma in children in our data was male sex, (aOR 1.99; 1.29-3.06), a finding which also has been reported in several other studies (Roel et al. 1999, Rönmark 2002, Dik et al. 2004). Our results also showed that male sex was associated with the development of rhinitis, another finding which also has been stated before (Peroni et al. 2003). Girls were more inclined to develop eczema in our study population. This is a finding which was also shown to be the case in both a study including data from Germany, Denmark and Sweden (Schultz Larsen et al. 1996) and another Swedish study (Broberg et al. 2000).

Other studies have shown that asthma and wheezing in children up to 3 years of age are strongly associated with parental smoking (Lannero et al. 2006, Moshammer et al. 2006, Pattenden et al. 2006). In our study, however, we could not find any significant relationship between smoking in the family and the incidence of asthma, rhinitis or eczema in the child. About 22% of the children in the baseline population live with at least one smoking parent, which is a low rate compared with many other countries (Warren et al. 2008). The low rate of parental smoking may be due to successful prevention actions regarding smoking during recent decades. Moreover, our data show that even if parents are reporting that they smoke, most of them report that they don’t smoke indoor. An outdoors smoking habit is probably due to the fact that Swedish parents are well informed about the risks of exposing their children to tobacco smoke.

Our study shows that breastfeeding during the first three months after birth reduced the risk of developing asthma in the child. This finding has also been shown in other studies (Oddy et al. 1999, Rönmark 2002, van Odijk et al. 2003, Kull et al. 2005). It is possible that parents’ reports on the extent of breastfeeding is underestimated since there is a broad public opinion in Sweden that breastfeeding protects small children from developing asthma and allergy. A mother in a family with allergic symptoms may tend to breastfeed the child for a longer period compared to a mother in a family with no allergic problem, due to the belief that breastfeeding protects against development of allergy in the child.
The study show that 97% of the mothers had breastfed their children but there were no difference in breastfeeding patterns between families with allergic symptoms and families without such problems. Moreover, both groups reported that they continued breastfeeding at the same length of time.

We found that proxies for lower SES were associated with the development of asthma, rhinitis and eczema. Children living with one parent were more often reported to develop asthma and eczema than children living with both parents. Furthermore, living in a multifamily house was associated with the incidence of rhinitis and eczema, when compared with living in a single family house. Other Swedish studies have also shown that childhood asthma and rhinitis are more common in families with low SES (Lindbaek et al. 2003, Almqvist et al. 2005, Bråbäck et al. 2005). It has further been discussed that these differences might be related to differences in lifestyle and environmental exposures between different SES groups (Almqvist et al. 2005). However, one limitation with the DBH phase I and III study is that we don’t have specific data on socioeconomic status of the family.

**Moisture related problems indoor and asthma**

Results in paper II show that different moisture related problems are rather frequently reported in the homes in this study (Figure 11).

Water leakage was reported in 6.9% of the birth residences. The reports of water leakage were more than doubled in houses where respondents lived at the study’s baseline (17.8%). One explanation for such a discrepancy could be that at baseline the parents could report if they ever had water leakage, a category that included both the current dwelling and the birth residence while reports in the birth residence was limited to the birth residence (Table 3). Questions about water leakage were not included in the follow-up questionnaire. Our study findings can be compared to a Swedish 8-year follow-up study of 348 persons aged 20-65 years (Sahlberg et al. 2009) who found a water leakage prevalence rate of about 11%, a value that lies between our findings.
Figure 11. Frequencies of self reported moisture related problems in the birth residence (n=8,918), the home at baseline (n=8,918) and in the home at follow-up (n=5,483)

*There were no questions for water leakage and moldy odor in the follow-up study

The reported frequencies of parents’ perception of moldy odor in the birth residence are somewhat higher than reports of moldy odor from the baseline home (6.3 and 4.3% respectively). Both reports were somewhat higher than found in Sahlberg’s study, which showed a report rate of moldy odor of 2%. A comparison between the data in our study show that the reporting criteria for the time periods for moldy odor were defined slightly differently regarding the birth and the baseline dwelling. Moldy odor at baseline was reported only over the previous three months while the reporting period for moldy odor in the birth residence could take in a longer period of time, depending on how long the family had lived in the child’s birth residence. Questions about moldy odor were not included in the follow-up questionnaire of our study.

Floor moisture was reported to be present in 6.5% of birth residences and 8.3% of residences at the baseline study period. Sahlberg et al. (2009) described a respondent-reported rate for floor moisture of 6%. The respondents’ reports of floor moisture index at our study’s follow-up was somewhat lower (4.7%) than
reports at birth and baseline, which might be due to different inclusion criteria in the index definitions (see Table 3 in the method section).

Parent reports of visible dampness in the birth residence was much higher (7.2%) compared with both baseline (1.5%) and follow-up (1.0%) reports. One possible explanation for this might be that visible dampness in the birth residence included dampness signs in the whole dwelling including cellar, bathrooms, etc., while reporting criteria for visible dampness at baseline and at follow-up only included the child’s or parent’s bedroom. In comparison, Sahlberg’s study (2009) found a frequency of visible mold of 3%.

Reports of condensation on windows in the birth residence are more than doubled (32.3%) compared to reports from baseline (14.3%) and follow-up (10.6%). One possible explanation for this variation is that reports on condensation on windows in the birth residence included reports from anywhere in the home, while data from the baseline only included reports for the parent’s or the child’s room.

In conclusion, our data show that parental reports of moisture problems varied when comparing reports from birth residence, the baseline and the follow-up home. Some of the variation is due to discrepancy in definitions, but it may also involve recall bias. What can be speculated from our study’s findings is that retrospective reports regarding moisture problems might be more biased than reports involving present-day conditions in one’s current home. This bias might occur when families report more problems retrospectively, i.e. in the home where they don’t live, which would result in over reporting of moisture problems in the birth residence.

**Moisture related problems and incidence of asthma**

In paper II, the focus was to investigate the importance of moisture related problems in the home on the development of asthma in children. The overall aim was to investigate if the associations between parental reported moisture related problems in the home and asthma in children found in our cross-sectional data could be confirmed in longitudinal analyses. Analyses between moisture related problems in the birth residence and in the baseline home and asthma was
estimated in both cross-sectional data (n=10,851) and longitudinal data five years later (n=4,779).

Adjusted associations between moisture related problems in the birth residence and asthma in both cross-sectional and longitudinal data are showed in Figure 12. Adjustments were made for possible confounders (age, sex, allergic symptoms in family and smoking in family). In the cross-sectional analyses, significant associations were found between all moisture indices in the birth residence and asthma at baseline with aOR in the range of 1.4-2.1. However, we also analyzed longitudinal data, meaning that we examined the relationship between moisture indices in the birth residence and the incidence of asthma during the five years after the baseline study. Our longitudinal data showed that all associations that were significant in cross-sectional analyses disappeared.

![Figure 12. Associations between moisture related problems in the birth residence and asthma in cross-sectional (n=10,851) and longitudinal analyses (n=4,779)](image)

When analyzing moisture related problems in the home at baseline, cross-sectional data showed that visible dampness and floor moisture were associated with asthma but after longitudinal analyses these associations decreased and was found to be non-significant (Figure 13). Reports of condensation on windows and water leakage were associated with asthma in cross-sectional analyses but after analysis of longitudinal data these associations disappeared. However, the association between
moldy odor and asthma found from cross-sectional data were also found in longitudinal analyses - in fact the risk was increased.

Figure 13. Associations between moisture related problems at baseline and asthma in cross-sectional (n=10,851) and longitudinal analyses (n=4,779)

**Can cross-sectional associations be due to reporting bias?**

In Sweden there is a common opinion that moisture related problems in homes are related to respiratory health effects. This might influence results in cross-sectional studies which can lead to reporting bias. This means that families with symptomatic children might be more prone to remember and report moisture damages in their dwelling compared to families without such health problems. It could also be that families living in homes with signs of moisture problems might be more inclined to systematically remember and report symptoms in the children. Such reporting bias does not occur to the same extent in longitudinal studies, where exposure and disease are not reported at the same point in time and where the diseased children at baseline are excluded.

Based on our findings, we believe that reporting bias may explain at least part of the associations found in cross-sectional data in the baseline material. However, the findings pose another question: why did we find an association between moldy
odor in the baseline residence and incidence of asthma when such an association couldn’t be found regarding moldy odor in the birth residence?

We showed earlier that there were slightly more reports of moldy odor in the birth residence compared with the baseline dwelling (Figure 11), which could indicate that retrospective reports may lead to over-estimation. Retrospective reports from cross-sectional data showed stronger association between the prevalence of asthma and moisture problems in the birth residence compared to reports regarding the residence at baseline. This could mean that parents who had a child with asthma at baseline were perhaps trying to attribute health problems to moisture problems in an earlier residence, compared to their current home.

Other studies have investigated the association between moisture problems, including moldy odor, and the incidence of asthma. A population-based questionnaire study of Finnish children aged 1-6 years also showed a discrepancy between results from cross-sectional and longitudinal data. They found in cross-sectional analyses that visible mold, moisture, water damage and moldy odor anywhere in the dwelling were all significantly associated with wheezing in separate analyses (Jaakkola et al. 1993). However, the longitudinal analyses six years later showed that the association between visible mold, moisture or water damage at baseline and asthma incidence had disappeared, but moldy odor remained as a significant risk factor in the longitudinal analyses (Jaakkola et al. 2005), which is in line with our data. Another Finnish study also found associations between moldy odor and incidence of asthma (Karvonen et al. 2009). These results raise the question if moldy odor could be of importance for the development of asthma in the child.

In the second phase of the DBH-study, which is not reported in detail in this thesis, a nested case-control study was conducted. Trained inspectors visited 390 dwellings looking for moisture related problems. The analyses did not indicate that case children were over-represented in homes where the inspectors perceived a general moldy odor. However, it was found that case children were over-represented in the group of homes where the inspector perceived moldy odors along the skirting board when compared with homes without such odor. It was suggested that moldy odor along the skirting board could be seen as an indicator of
moisture related problems inside the building structure, which might be of importance for the development of asthma in the child (Hagerhed-Engman et al. 2009).

A problem observed in the study's second phase was the low concordance between parent's report of moldy odor in the home and inspectors' observations of moldy odor (Engman et al. 2007). These diverse findings between parent's and inspectors reports show the complexity in measuring and interpreting perceptions of odor in different kind of studies.

Our data indicates that moldy odor in homes might be seen as a risk factor for developing asthma in children, but the results are not conclusive since there are such differences in reports between odor in the birth residence and odor in the baseline dwelling. Furthermore, even if moldy odor in the home is related to the development of asthma in children, such exposures can explain very little of the onset of asthma in the current study population since moldy odor were reported from less than 4% of the homes and the attributable fraction can be estimated to about 6%. This means that elimination of the exposure (moldy odor in the baseline home) will reduce the number of children developing asthma during the five year period from 100 to about 94 children.

In conclusion, significant associations between parental reported moisture problems in the dwelling and parental reported asthma in children were found in cross-sectional data but these associations disappeared or decreased in longitudinal analyses. A significant association between moldy odor reports in the home at baseline and the incidence of asthma was found in the longitudinal analyses but odor reports from birth residence were not associated with development of asthma. Our results therefore suggest that cross-sectional associations between moisture related problems in homes and asthma in children at least in part can be explained by reporting bias, and this problem might be even stronger when reporting exposure problems retrospectively. This means that cross-sectional data have to be interpreted with caution.
PVC-flooring and development of asthma

There are accumulating scientific data supporting the hypothesis that exposure to PVC-materials indoor may be linked to asthma and allergies, as presented in two recent reviews (Jaakkola et al. 2008, Bornehag et al. 2010). It has been suggested that such a relationship could be due to phthalate exposure as it is known that PVC-materials include phthalates and that PVC-materials emit phthalates to the surrounding environment. However, the biological mechanism for such a relationship is not at all obvious. Furthermore, most of the studies on the relationship between PVC-flooring and asthma are cross-sectional (Bornehag et al. 2010). There is need for longitudinal data investigating if exposure to PVC is associated with the incidence of asthma in children. With these factors serving as motivation, paper III examined the associations between PVC-flooring in the bedrooms at baseline and the incidence of asthma during the following 5 years.

The results in paper III show that children living in homes with PVC-flooring in the bedroom of residences where they lived when they were 1-3 years old were more likely to develop asthma during the following 5-year period when compared with children living without PVC-flooring (the child’s bedroom aOR 1.52; 0.99-2.35 and parent’s bedroom aOR 1.46; 0.96-2.23). There were also findings of a positive relationship between the number of rooms in a home with PVC-flooring and the incidence of asthma (p=0.01); the more rooms with PVC-flooring, the higher risk of developing asthma (Figure 14).

Other epidemiological studies have reported an association between PVC-material and airway symptoms. The Norwegian Oslo birth cohort study employed a case-control design and found that the presence of PVC-flooring significantly increased the risk for bronchial obstruction in children (Jaakkola et al. 1999, Oie et al. 1999). Within five years after this study, three other cross-sectional studies reported that plastic wall materials and/or PVC-flooring increased the risk of airway symptoms in children (Jaakkola et al. 2000, Jaakkola et al. 2004, Bornehag et al. 2005c). Up to now there has only been cross-sectional data on the relationship between respiratory symptoms and PVC-material. To our knowledge, our results were the first showing an association using longitudinal data. Although the available number of studies of the risk with PVC-material for airway diseases are few, all studies
point in the same direction; PVC-materials seems to increase the risk of airway symptoms and diseases.

We found a stronger association between PVC-flooring and development of asthma among families living in multi-family houses (e.g. PVC in the child’s bedroom: OR 4.19; 0.96-18.28) compared with those living in single family houses (PVC in the child’s room: OR 1.32; 0.83-2.11). One possible explanation for these findings could be due to the fact that most multi-family houses in Sweden are built with a concrete floor structure while the single family houses most often have a wooden structure. PVC-flooring in multifamily houses is often glued directly on the concrete floor. If PVC-flooring material is glued on a concrete structure with high moisture and high alkalinity content, there is a risk for chemical degradation of the PVC-material and adhesives followed by increased emissions of degradation products, e.g. phthalates (Wengholt Johnsson 1995, Gustafsson et al. 1997, Sjoberg et al. 2007).

Furthermore, asthma has been shown to be more common in lower socioeconomic groups (Lindbäck et al. 2003, Almqvist et al. 2005, Bråbäck et al. 2005). As shown in the current study, PVC-flooring was associated with incidence

![Figure 14. Number of bedrooms in the home with PVC-flooring at baseline and the risk for doctor diagnosed asthma at follow-up five years later among 4,779 children aged 6-8 years. The bars express the five year incidence rate of asthma (left y-axis) and the adjusted ORs including a 95% confidence interval on the right y-axis](image-url)
of asthma, but PVC-flooring was also correlated with proxies for lower SES such as living in multi-family houses, divorce in the family (Lindbaek et al. 2003) and parental smoking. It is therefore possible that the reported associations between PVC-flooring and asthma in the current study are confounded by socioeconomic factors. However, we made adjustments and stratifications for SES factors and could not find any substantial reduction in the estimated risks between PVC-flooring and incidence of asthma in the affected children.

Our study indicated an association between PVC-flooring in the bedroom and development of asthma in children, but data has to be interpreted with caution due to methodological limitations. The data are based on questionnaire reports on environmental factors and health which may be a source for confounding problems. There is a risk for misclassification of flooring materials. We have earlier showed that parental reports of flooring materials are frequently in error (Engman et al. 2007), i.e. people are in general quite bad in judging the source of some flooring material (this is true for PVC and linoleum, while people in general are good judging wooden flooring). Consequently, families often misclassify types of flooring. However, we have no reason to believe that such misclassification errors differ between groups of parents who had children with and without asthma, especially because the type of flooring was assessed before the onset of asthma.

In conclusion, most studies of the relationship between PVC and/or phthalates and asthma are of a cross-sectional design. Our data show an association between PVC-flooring in the bedrooms and incidence of asthma as well as a relationship between the number of rooms with PVC-flooring and the incidence of asthma. Limitations with the study are the use of questionnaire reports on environmental factors and health outcomes and the risk for misclassification of flooring materials. Further, we only found borderline significance for associations. This means that our data should be interpreted with caution and warrants confirmation in a prospective cohort design including early life exposure during pregnancy and infancy period. Further investigation will require measurements of the phthalate exposure in the environment as well as human uptake of such compounds.
Autism spectrum disorders and indoor environmental factors

Many studies in the past few decades have shown that the developing brain may be vulnerable to a variety of environmental chemicals, such as metals, pesticides, phthalates, solvents etc. (Weiss et al. 2000, Hertz-Picciotto et al. 2009). Hypotheses have been proposed that fetal and early childhood exposures to industrial chemicals in the environment could lead to neurodevelopmental disorders such as ASD (Grandjean et al. 2006). However, while many investigators believe that an environmental component is involved in the etiology of ASD, there is still a tremendous lack of evidence for such a relationship. With this background, paper IV examined if different indoor environmental factors, such as PVC-flooring, was associated with ASD.

Our study showed that the presence of PVC-flooring material in the bedroom of a home when the child was 1-3 years was associated with an ASD diagnoses five years later (Figure 15). It was found that PVC-flooring in the parent’s bedroom showed a slightly stronger association with ASD compared to PVC-flooring in the child’s bedroom. One explanation for such a difference in association could be that children with ASD more often sleep in a parent’s bedroom when they are in the age 1-3 years compared with children without ASD. This was in fact true for our study population, as 47.9% of the children with ASD did sleep in the parents’ bedroom compared with 43.2% of the children without an ASD diagnosis. However, this finding was not significant. Another speculation could be that maternal exposure to PVC during the pregnancy is more critical than later on, when the child him- or herself is exposed. Our data had limitations that did not allow for further exploration.

In the follow-up questionnaire in phase III of the DBH-study we found that 72 children out of 4,779 had parents who reported that the child had ASD, corresponding to a prevalence of 1.5%. Our prevalence figure for ASD is slightly higher than those reported in several other studies where rates range between 0.3-1.2% (Bertrand et al. 2001, Fombonne 2005, Rutter 2005, Baird et al. 2006, Gillberg et al. 2006). These studies have defined ASD according to the classification system DSM-IV or ICD-10, which refer ASD as a composite diagnosis including infantile autism/autistic disorder, Asperger syndrome, disintegrative disorder, other autistic-like conditions and severe autistic features.
Our ASD index included reports of diagnoses of at least one of the following: autism, Asperger syndrome and Tourette’s syndrome.

Our slightly higher prevalence could therefore be ascribed to our inclusion of Tourette’s syndrome in the definition of ASD, unlike the definitions of most other studies, which did not include Tourette’s syndrome. This indicates that our prevalence rate is in accordance with other studies investigating ASD. Our study is also in accordance with other studies in that we found that ASD was five times more common among boys compared with girls (Fombonne 1999, Honda et al. 2005, Gillberg et al. 2006, Hertz-Picciotto et al. 2006, Landa 2008).

![Figure 15. Type of flooring in the child’s and parent’s bedroom at baseline and the risk for ASD at follow-up five years later among 4,779 children aged 6-8 years. The bars express the prevalence of ASD (left y-axis) and the adjusted ORs including a 95% confidence interval on the right y-axis.](image)

Another environmental factor that was shown by our data to be associated with ASD was condensation on the window. Condensation may serve as a proxy for low air exchange rate in the home. A low ventilation rate in the building might increase many indoor-generated exposures and different pollutants and act as an effect modifier (Seppanen et al. 2004, Bornehag et al. 2005b, Hägerhed-Engman et
al. 2009). However, earlier results in the DBH-study did not lead to a conclusion that low ventilation rate was associated with higher concentration of phthalates in dust (Bornéhag et al. 2005a). There are very few papers published discussing how ventilation rates influence indoor contaminant levels. However, there are suggestions that phthalates have long indoor persistency and that if ventilation is the only removal mechanism, these compounds may persist for years in areas with low ventilation (Weschler et al. 2008).

Smoking around children is a well-documented risk factor for child behavior problems, including ASD (Fergusson et al. 1998, Williams et al. 1998, Hultman et al. 2002, Wakschlag et al. 2002, Indredavik et al. 2007). Our data show that maternal smoking (during pregnancy, during the child’s first year and/or current smoking) was associated with ASD. When calculating smoking and its association with ASD, this factor is difficult to sort from other SES-related factors. Furthermore, families with an ASD child reported more socioeconomic problems and displayed more proxy indicators for lower SES, such as living in a multi-family house, having a smaller living area of the home, and comprising family units where parents were divorced, compared with families without an ASD child. Since these SES proxies showed a stronger association to ASD in the cross-sectional data from 2005 compared to data from 2000, there are indications that economic problems are more likely a result of ASD rather than a risk factor.

Our results showed that children with ASD reported twice as many airway symptoms (i.e. doctor diagnosed asthma and wheezing) compared with children without ASD. Our study showed that allergic symptoms in the mother were weakly associated with ASD in the child. Similar results have been reported from a study in U.S. where the risk for ASD doubled in the offspring of mothers with allergic diseases during pregnancy (Croen et al. 2005). These findings that asthma and allergy could be associated with ASD are not at all obvious. An hypothesis has been expounded that postulates that early infections activate the immune system and may affect brain structure or function contributing to the development of ASD (Becker 2007, Fatemi et al. 2008).

A limitation of this study is also that we only have diagnosed ASD via parental reports. We interviewed ten randomly selected families who had reported children
with ASD from the study population and found that the parental reports of ASD were matched by clinical diagnoses of ASD by medical professionals. Our experience tells us that there is no reason to believe that the parents would report autism, Asperger or Tourette’s syndrome without a clinical diagnosis or other relevant information as a basis for their reports but it is possible that such reporting errors can occur.

In conclusion, we have found an association between ASD and PVC-flooring in the home during early childhood, which we presume to reflect exposure to phthalates in air and dust. Even though this study was not designed specifically to address ASD, and confirmation would require further efforts, this suggests that chemical contaminants with suspected endocrine disruptor properties might yield useful insights into the genesis of ASDs.

**Similarities in risk pattern for asthma and autism spectrum disorders**

Our data related to asthma and ASD seem to covariate, meaning that children with ASD were reported to have more asthma and airway symptoms. We also find similarities in the pattern of risk factors, both environmental exposures and background factors, in both conditions.

Our results show that boys who were enrolled in our study were twice as likely to have doctor diagnosed asthma compared with girls (6.8% vs. 3.6% <0.001), a finding that has been replicated elsewhere (Anderson et al. 1992, Almqvist et al. 2008, Bjerg et al. 2010). Our study found a similar pattern for ASD (boys 2.5% vs. girls 0.5% <0.001), a finding that is also replicated in other studies (Honda et al. 2005, Gillberg et al. 2006, Landa 2008).

Environmental exposures that were associated with ASD in our study included maternal smoking during pregnancy, which is a well-documented risk factor for child behavior problems, such as ASD (Wakschlag et al. 2002, Linnet et al. 2003, Indredavik et al. 2007). Other studies have found associations between maternal smoking and asthma (Lannerö et al. 2006, Moshammer et al. 2006, Pattenden et al. 2006), even though this was not found in the study we conducted.
The data from our research showed that different indoor environmental factors were associated with both asthma and ASD. PVC-flooring in the bedroom of participants when they were between 1 and 3 years old was shown to be related to both ASD and asthma five years later. Earlier findings in the DBH-study show that PVC-flooring was a source for phthalate emission (Bornehag et al. 2005a) which was related to asthma in the child (Bornehag et al. 2004c).

Our work and other research have described other similarities related to risk factors between the two diseases/disorders. There is data indicating that both asthma (Pearce et al. 2006) and ASD (Rutter 2005) have increased during the last few decades. Both diseases are often diagnosed in early childhood; 3-6 years for children with asthma (Morgan et al. 2005) and 2-4 years for autism (Mandell et al. 2005), which indicates that the early life period is important and similar for both diseases.

The striking similarities in risk factors are worth focusing on in coming studies. The findings presented here raise the issue that there could be common etiological factors behind both these diseases. There have been suggestions that there might be a tight connection between development of the immune system and the central nervous system, and that the disruption of critical events in immune development may play a role in neurodevelopmental disorders. Of specific concern is that exposure to different environmental agents such as chemicals might be highly detrimental during critical developmental stages such as the prenatal and early post-natal period and may lead to long-term health effects (Hertz-Picciotto et al. 2008).

**Limitations in the current study**

To conduct epidemiological studies and to establish relationships between environmental exposures and health effects is an adventure in that it involves many assumptions and has inherent uncertainties which most often limit the possibilities for conclusive results.

Epidemiological studies may generate hypotheses about a causal relationship between an exposure and a health effect, nothing more. To decide whether our results are causal or not is impossible, as a completely reliable criterion for causality
does not exist. The findings from epidemiological research are, at best, only tentative formulations of a description of nature (Rothman et al. 2005). If one risk factor has been identified in several studies one may suppose that a causal relationship is more likely. But the same type of bias can be present in all studies without investigators being able to identify it. One can see hints of this problem within review studies, where manuscripts with positive findings are more likely to get published than those with negative findings, a so-called publication bias.

To establish understanding of the subject matter, a fair interpretation of the results should be obtained. It is of greatest importance that epidemiologic results are looked upon critically and that study strengths and weaknesses as well as limitations are highlighted.

One of the weaknesses of our study is how we defined the study problem and population when estimating the incidence. Children who had already developed asthma during their infancies and early childhood (the first year of life for the youngest children and the first three years for the oldest children) were excluded from the baseline population in order to estimate the incidence (that is, new cases) of asthma. This means that we have not investigated the importance of different exposures for the development of asthma during infancy.

Our data suggest that the association between moisture related problems and asthma in cross-sectional analysis might be biased, as we used self-reports for some of the data. The results may be skewed due to common opinion in the general population that such exposure is a risk for airway problems. Another reporting bias from parents, which has already been documented in this study, was reporting bias due to misclassification of types of flooring (Engman et al. 2007).

Another problem affecting our study is the loss of statistical power in the longitudinal analyses. When estimating the association between the incidence of asthma and certain moisture indices, the number of cases became small. When the study measured visible dampness or moldy odor at baseline, only 2 and 10 children, respectively, were found to have developed asthma in the exposed group. Even if these exposures is related to the development of asthma in children, such
exposures can explain very little of the onset of asthma in the current study population since these exposures where reported from less than 4% of the homes.

A further problem in the current study is that we can not distinguish between the three disorders; autism, Asperger and Tourette’s syndrome because they were included in the same category in the questionnaire that was used in the current study.

There are also other factors that may contribute to an appearance of a cause-effect relationship that in reality does not exist. Confounding in epidemiological studies can occur when another factor exists and is associated both with the disease and exposure that are being studied. The collection of detailed information about confounding risk factors, such as SES, is a way to limit this confounding. In our study adjustments and stratifications were conducted for SES factors such as single parenthood, smoking in the family and type of dwelling. However, as the most efficient proxies of SES, such as parental occupation, occupation status, income, and education level, or a combination of these (Liberatos et al. 1988, Lindback et al. 2003, Eagan et al. 2004) were not measured in this study, there is still the possibility of residual confounding.

**Further studies**
The two first phases of the Swedish DBH-study are being replicated in seven other countries from different global regions (Figure 16). These studies have been conducted with similar questionnaires and protocols in order to establish comparable data sets. The first country to carry out a DBH-study after Sweden was Bulgaria, followed by Singapore, Taiwan, Denmark, USA, China and South Korea. The overall aim with such global mapping is to establish comparable data on the prevalence of asthma and allergy in children as well as collecting information on the characteristics of homes and indoor environmental exposures. A further aim is to identify general risk and protection factors for asthma and allergy but also region specific factors due to climate, culture, traditions etc.
Dampness in Buildings and Health worldwide
Sweden, Bulgaria, Singapore, Taiwan, Denmark, USA, China, South Korea

Furthermore, findings from the DBH-study will be tested in an ongoing longitudinal birth cohort study; the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study (SELMAs) presented in Figure 17. The overall aim with the SELMAs-study is to investigate the importance of early life exposure to environmental agents, such as suspected EDCs, as risk factors for different chronic diseases/disorders in children later on in life. In that study both questionnaires are used and medical examinations including bio-sampling will be conducted, as well as environmental exposure measurements.

One way to establish knowledge about a causal relationship between exposures and health effects is to combine epidemiological investigations with controlled experimental in-vitro and in-vivo studies. Findings from the DBH-study and the SELMAs-study will be tested in experimental in vitro investigations at Biomedical Science at Karlstad University.
DBH phase I
Cross-Sectional study
Baseline
March 2000
Questionnaire
n=14 077 children, 1-5y (rr=79%)

DBH phase II
Case-Control Study
October 2001-April 2002
Professional inspections
Exposure measurements
Clinical examinations
n=7 052 children, 6-8y (rr=73%)

DBH phase III
1st Follow-up Study
March 2005
Questionnaire
n=7 509 children, 6-8y (rr=73%)
(incidence of chronic diseases)

DBH phase IV
2nd Follow-up Study
March 2010
Questionnaire
n=15 043 children, 11-15y (rr=53%)
(incidence of chronic diseases)

Experimental studies
Biomedical studies
Karlstad University

Birth Cohort Study incl. 2 500 mother-child pairs
September 2007- March 2010

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MAIN CONCLUSIONS AND RECOMMENDATIONS

The incidence of allergic symptoms from questionnaire studies can be estimated by the use of data from birth cohort studies as well as from cohorts established later on in life. When not using birth cohort data the estimated incidence rates are strongly dependent of how the baseline population is defined from a health point of view and how the studied health outcome at follow-up is defined. We found that, for our study’s participants, the mean incidence rate per year for doctor diagnosed asthma was in the range of 0.6 to 2.4% and incidence of doctor diagnosed rhinitis in the range of 1.1 to 3.7% depending on different definitions of baseline and health outcome at follow-up. The incidence rate of eczema ever was 2.7%.

Recommendations: Our results show that wheezing could be an indicator of that the child already has asthma, not yet diagnosed, and therefore suggests that children with asthma and wheezing should be excluded from the baseline population when estimating the incidence of asthma.

The associations between parental reported moisture problems in the home and asthma in children that was found in cross-sectional analyses decreased or disappeared when longitudinal data were used. No association between moldy odor in the birth residence and incidence of asthma was found but moldy odor in the home at baseline was associated to the incidence of asthma.

Recommendations: Our results indicate that associations between parental reported moisture problems and asthma from cross-sectional questionnaire studies should be interpreted with caution due to the risk for reporting bias. This might be due to the fact that there is a general opinion that moisture problems at home are a risk factor for airway problems in many regions in the world.
Children living in homes with PVC-flooring in the bedroom when they were 1-3 years of age were more likely to develop asthma during the following 5-year period when compared with children living in homes without such flooring material.

Recommendations: Our findings regarding associations in a longitudinal design warrant confirmation in a prospective birth cohort study including early life exposure during pregnancy and infancy period as well as measurements of the phthalate exposure in the environment and human uptake of such exposures.

Children living in homes with PVC-flooring in the bedroom when they were 1-3 years of age were more likely to have a diagnosis of autism spectrum disorders five years later compared with children living in homes without such flooring material.

Recommendations: Our study is one of only a few linking ASD with indoor environmental factors such as building materials including suspected endocrine disrupting chemicals such as phthalates. There is a need for more extensive studies focusing on this problem.
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Indoor Environmental Factors and Chronic Diseases in Swedish Pre-School Children

The aim of this thesis has been to investigate environmental factors in homes and their impact on asthma, rhinitis, eczema as well as autism spectrum disorders in children, and to identify certain methodological difficulties in epidemiological investigations.

We found that the mean incidence rate per year for doctor diagnosed asthma was in the range of 0.6-2.4% and for doctor diagnosed rhinitis in the range of 1.1-3.7%. The incidence rate of eczema ever was 2.7%. The results show that when establishing a cohort after birth the estimated incidence rates are dependent of how the baseline population’s health and how the studied health outcome at follow-up is defined.

Our results show that the associations between parental reported moisture problems in the home and asthma in children, which were revealed in cross-sectional analyses, decreased or disappeared when longitudinal data were used. Our results therefore indicate that associations between parental reported moisture problems and asthma from cross-sectional questionnaire studies should be interpreted with caution due to the risk for reporting bias.

Finally, the results indicate that PVC-flooring in the bedrooms was associated to development of asthma as well as autism spectrum disorders. These results indicate that environmental factors such as building materials including suspected endocrine disrupting chemicals such as phthalates might be of importance for the development of these chronic diseases. Further studies are needed to explore early life exposure and the mechanisms and contribution of phthalates in the development of diseases.