Indoor Environment in Dwellings and Sick Building Syndrome (SBS)

Longitudinal Studies

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Abstract

People spend most of their time indoors and mostly in the dwelling. It is therefore important to investigate associations between indoor exposure in dwellings and health. Symptoms that may be related to the indoor environment are sometimes referred to as the "sick building syndrome" (SBS). SBS involves symptoms such as eye, skin and upper airway irritation, headache and fatigue. Three longitudinal studies and one prevalence study on personal and environmental risk factors for SBS in adults were performed. The prevalence study included measurements of indoor exposures in the dwellings. The longitudinal studies, with 8-10 years follow-up time, showed that smoking and indoor paint emissions were risk factors for SBS. Moreover, building dampness and moulds in dwellings were risk factors for onset (incidence) of general symptoms, skin symptoms and mucosal symptoms. In addition subjects living in damp dwellings have a lower remission of general symptoms and skin symptoms. Hay fever was a risk factor for onset of skin symptoms and mucosal symptoms, and asthma was a risk factor for onset of general and mucosal symptoms. Biomarkers of allergy and inflammation (bronchial reactivity, total IgE, ECP and eosinophil count) were predictors of onset of SBS symptoms, in particular mucosal symptoms. In the prevalence study, any SBS-symptom was associated with some individual volatile organic compounds of possible microbial origin (MVOC) e.g. 2-pentanol, 2-hexanon, 2-pentylfuran and 1-octen-3ol. Moreover, there were associations between indoor levels of formaldehyde and the plasticizer Texanol and any SBS. The result from the study indicates that individual MVOC are better indicators of SBS than the total value of MVOC. A final conclusion is that smoking, dampness and moulds and emissions from indoor painting may increase the onset of SBS. The indoor environment in dwellings over time has improved, but there is still a need for further improvements of the indoor environment in dwellings. More longitudinal SBS studies are needed.

Keywords: Indoor environment, sick building syndrome (SBS), dwelling, longitudinal cohort study, building dampness, mould, microbial volatile organic compounds (MVOC), biomarkers, asthma, risk factors

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To my family
List of Papers

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


IV. B. Sahlberg, M. Gunbjörnsdottir, A. Soon, R. Jogi, T Gislason, G Wieslander, C Janson, D Norbäck. Airborne moulds and bacteria, microbial volatile organic compounds (MVOC), plasticizers and formaldehyde in dwellings in three North European cities in relation to sick building syndrome (SBS) (submitted).

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Abbreviations and definitions

Atopy  Defined as having either allergy to grass or three pollen (hay fever), allergy to furry animals or a history of childhood eczema.
BHR  Bronchial hyperresponsiveness
CI  Confidence interval
COPD  chronic obstructive pulmonary disease
CRP  High-Sensitivity C-Reactive Protein
ECP  Eosinophilic cationic protein
EOS  Eosinophil counts
ETS  Environmental tobacco smoke
FEV1  Forced expiratory volume in one second
FVC  Forced vital capacity
IgE  Serum immunoglobulin E
IL-6  Interleukin-6
IQR  Inter quartile range
MVOC  Microbial volatile organic compounds
OR  Odds ratio
RR  Relative risk
SBS  Sick building syndrome
SCB  Statistics Sweden
SD  Standard deviation
Slope  The term "slope" is used for log transformed slope for the methacholin test. The transformation 100/ (log slope + 10).
VOC  Volatile organic compounds
Introduction

People in the industrialized world spend about 60% of their time in the dwelling and up to 90% could be spent indoors \(^1\). Consequently, factors in the home environment such as dampness and presence of moulds can have a considerable influence on human health. Concern about possible health effects of indoor air pollution is increasing, both with respect to asthma, allergies, and non-specific symptoms from eyes, upper airways and facial skin \(^2\text{-}^6\). Such non-specific symptoms are common in the general population \(^7\), and even more common among people in buildings with indoor air problems, sometimes called "sick" buildings. These symptoms are occasionally referred to as the "sick building syndrome" (SBS) \(^2\text{-}^8\text{,}^9\). The SBS has been defined empirically on the basis of case reports in which the occupants of a specific building described similar symptoms that were attributed to indoor climate problems \(^10\). The SBS is a group phenomenon, not a syndrome as it is normally defined in medicine, and individual diagnostics is a difficult matter.

Associations between some factors in the indoor environment in dwellings, inflammatory markers and SBS were studied in this thesis.

Gender, allergy, and personality

Female gender has been shown in many studies to be an important risk factor for SBS-symptoms \(^2\text{-}^3\text{,}^5\text{-}^8\text{,}^9\). In office workers females tend to report more SBS symptoms than men \(^11\). Inequalities in social conditions did not explain the sex differential in symptom reporting.

It is generally believed that individuals with atopy are particularly vulnerable to poorer indoor environments. However, this has been shown only in few studies and even fewer have used definitions of atopy based on clinical tests. Atopy defined as a positive prick test to any allergen is a significant independent risk factor for reporting at least one SBS related symptom \(^3\) while in another study atopy did not seem to influence the prevalence of SBS symptoms \(^12\). In a Norwegian study on university staff, positive Phadiatop was used as atopy definition for studies of occupational indoor environmental
effects. Other definitions where used to define atopy such as total IgE, familiar allergy, or ever eczema. Markers of atopy in terms of Phadiatop, total IgE, familiar allergy and “ever eczema” were not associated with symptoms or perceived environments, but to hay fever.

Personality aspects seem to play an important role for reporting medical symptoms. Personality and personal vulnerability should be considered in both indoor environmental epidemiology and practical handling of buildings with suspected indoor problems. Moreover, personality aspects should be considered among subjects with possible vulnerable personality exposed to environmental stress, and the personality diagnosis can be a complementary tool useful when assessing sick building patients in the medical services. A low sense of coherence (SOC), a psychological measure of life attitude, was related to a higher prevalence of tiredness, headache, and ocular, nasal, and throat symptoms. Moreover, there is an association between SBS and personality traits measured by the Karolinska scale of personality.

There are few studies on education level, size of residence town and SBS symptoms. One study tried to evaluate these factors. Size of residence town or education level did not have any impact on reporting SBS symptoms.

Ventilation and indoor climate

Various factors, such as type of ventilation system, high room temperature, low supply of outdoor air, and low air humidity have been shown to influence the prevalence of SBS-symptoms. The impact of ventilation on health, comfort and productivity in non-industrial indoor environments has been reviewed by a multidisciplinary group of scientists called EUROVEN. Based on the available data judged conclusively, the group concluded that ventilation is strongly associated with comfort, health, and SBS. Low building ventilation flow has also been concluded to be associated with an increase in SBS in previous reviews. SBS-symptoms are more common at personal airflow rates below 10 l/s. It has also been concluded that increasing outdoor air supply rates in non-industrial environments improves perceived air quality and that outdoor air supply rates below 25 l/s per person increase the risk of SBS symptoms. In buildings with a CO₂ level lower than 800 ppm the risk for SBS-symptoms decreased.

There are few studies on SBS and ventilation in dwellings. A Swedish study in dwellings showed that subjects in buildings with a mechanical ventilation system had less ocular and nasal symptoms and concluded that mechanical ventilation in dwellings is beneficial from a health perspective. In one intervention study in dwellings of the outdoor ventilation flow during the heating
season was reduced with 25 – 30%. The reason for this was to investigate whether a lower ventilation rate influenced SBS symptoms. However, no influence on SBS symptoms was found.

Indoor air temperatures above 22 °C have been found to be related to SBS symptoms. The average intensity of dryness symptoms and sensations of dryness increased with each unit increase in temperature above 22 °C. Relative air humidity plays an important role in the indoor environment. Epidemiological, clinical, and human exposure studies show that low relative air humidity can lead to an increased reporting of eye irritation symptoms. Air humidification studies have shown that an increase of relative air humidity from 20 - 25% to 30 - 35% may reduce SBS. In addition, the overall intensity of SBS-symptoms only increased when the indoor air was not humidified. There are no studies on associations between relative air humidity in dwelling and SBS, but there are some studies on offices.

Particles, carpets and textiles

There are few studies on particles and carpets in dwellings. However, on offices there are several studies. One intervention study on the effect of cleaning in order to reduce airborne dust showed that comprehensive cleaning reduced airborne dust and decreased mucosal symptoms. In another study on office worker where the relationship between textile wall materials and SBS-symptoms were studied demonstrate more mucosal symptoms. Supporting a hypothesis that textile and other soft-fibre wall material are possible determinants of SBS.

In the Danish town hall study a fleece and shelf factor was defined. The factor is related to the amount of fleece material and open shelves in the rooms and SBS. An association between this factor and SBS was found. In a school study it was concluded that furnishings and textiles in the classroom act as significant reservoirs of irritants and allergens and have an impact on the indoor air quality at school. Wall-to-wall carpeting is a fleecy material that can bind particles that can be released, for example when vacuum cleaning.

Particles from indoor mould contamination are thought of as a cause of SBS symptoms. There is unclear to what extent there is an association between bioaerosols and SBS-symptoms. Furthermore, epidemiological studies suggest an association between bioaerosols and SBS. Evidence for an association between bioaerosol exposure and SBS has come mainly from cross-sectional studies and investigations of ‘sick buildings’. Toxicological studies have provided some evidence supporting biological plausibility.
Dampness

Adverse health effects on inhabitants in buildings with dampness and mould has been the subject of much research. Building dampness is a common indoor exposure, shown to be related to an increased prevalence of SBS. In a review by Bornehag et al. (2001), it was concluded that dampness in buildings is a risk factor for SBS. Also, there are associations between both self-reported and observed dampness and symptoms. The dampness approximately doubles the risk of health effects. A Japanese study on dampness in public apartment houses showed that dampness was associated with all SBS symptoms. Furthermore, dampness was related to SBS symptoms in a study on newly built dwellings in Japan. Building dampness in Swedish multi-family residential buildings has been reported to be related to a pronounced increase of symptoms compatible with SBS symptoms.

Tobacco smoke and environmental tobacco smoke

Tobacco smoke contains more than 4000 compounds that are carcinogenic, toxic and an irritant to humans. Tobacco smoking is related to many diseases such as chronic obstructive pulmonary disease (COPD), lung cancer and ischemic heart disease. Some SBS-symptoms e.g. general symptoms are also related to tobacco smoking.

In the last decades awareness of the damaging effects of environmental tobacco smoke (ETS) has been found to be causally associated with a large number of diseases in various organs. In the 2001 European Community Respiratory Health survey it was reported that 39% are exposed to ETS at home. Other studies have shown that exposure to ETS contributes to the occurrence of SBS-symptoms. Furthermore the study has shown a dose-response relationship between ETS exposure and chronic respiratory tract symptoms on adults in their homes. There are very few studies on ETS in dwellings and SBS-symptoms.

Inflammatory markers

Mechanisms of SBS could be inflammation or sensory effects. Oxidative stress has recently been shown to be important for SBS-symptoms in relation to chemical indoor exposure. One study by Metso et.al in (1993) perceives a relation between serum myeloperoxidase and sick building syndrome. In a study, SBS is considered as part of autoimmune (auto-inflammatory) syndrome induced by adjuvants.
Biomarkers have been used to study ocular and nasal effects of the environment. Some previous studies indicate inflammatory effects of building dampness. One prevalence study found an association between dampness in the dwelling and serum eosinophilic cationic protein (ECP). Other studies have analysed inflammatory biomarkers in nasal lavage. In a study in office workers, it was found that subjects with dampness at home had increased levels of lysozyme in nasal lavage. In a study on office workers in damp buildings showed a had higher levels of ECP in nasal lavage fluid in subjects in damped buildings, compared to those working in buildings without dampness. In a study in hospital workers, those working in damp buildings had higher levels of lysozyme in nasal lavage compared to those in buildings without dampness. These cross-sectional studies indicate that exposure in damp building may cause an inflammatory mucosal response.

Volatile organic compounds

Complex mixtures of organic chemicals in indoor air have the potential to invoke subtle effects on the central and peripheral nervous system, leading to changes in behaviour and performance. Volatile organic compounds (VOCs) are emitted as gases from certain solids or liquids. VOCs include a variety of chemicals, some of which may have short- and long-term adverse health effects. Concentrations of many VOCs are consistently, up to ten times higher indoors compared to outdoors.

Indoor VOCs are emitted by a wide array of products. Examples include: paints and lacquers, paint strippers, cleaning supplies, pesticides, building materials and furnishings, office equipment such as copiers and printers, correction fluids and carbonless copy paper, graphics and craft materials including glues and adhesives, permanent markers, and photographic solutions. Office buildings with increased dampness in the construction have large emissions of VOCs.

One common indoor source of VOC is emissions from fresh paint. Two studies have shown that 26-32% of the Swedish population have had the interior of their dwelling painted during the last year. Nowadays most indoor paints in Sweden are water based. Emissions from fresh indoor paint in the dwelling may cause airway symptoms and eye irritation.

There is no consistent association between the total concentration of VOCs (TVOCs) and SBS, but the pattern of individual VOC may vary between buildings with and without SBS. In a new longitudinal study on aldehydes and VOC in association with SBS in new dwellings it was found that ele-
vated levels of aldehydes and aliphatic hydrocarbons increased the risk of SBS in residents living in new homes \textsuperscript{57}.

A reactive chemistry hypothesis has been presented in search of plausible explanations for sensory irritations in office environments. Ozone is one of the reactive chemicals that can have an effect on symptoms \textsuperscript{58-59}. Sensory irritants are produced when ozone reacts with certain alkenes to form gas and aerosol phase of oxidation products. These oxidation products may contribute to eye and airway symptoms under certain conditions and low relative humidity \textsuperscript{60}.

**Microbial volatile organic compounds**

Microorganisms emit VOCs, so-called microbial volatile organic compounds (MVOC), when growing on building materials. Examples of compounds that are considered to be of microbial origin are certain ketones (e.g. 2-heptanone), alcohols (e.g. 1-octen-3-ol), terpenes and terpene derivatives (e.g. geosmin) and sulfur compounds (e.g. dimethyl disulfide) \textsuperscript{61-64}. In a study on MVOC it was reported that the concentrations of 26 different compounds emitted from certain microorganisms, were higher in indoor air than in outdoor air \textsuperscript{65}. An association between MVOC levels and health problems has been sought. It have been reported that the MVOC concentration was higher in buildings that had problems with dampness than in control buildings \textsuperscript{66}. Thus, these compounds may form a link between dampness and building related symptoms. MVOC are also emitted from plants, furniture, furnishing, and building materials \textsuperscript{62,67,68}. Studies have failed to find any strong association between indoor mould concentrations and MVOC \textsuperscript{67}.

In a study on MVOC at school it was found that exposure to several MVOC was associated with asthmatic symptoms such as nocturnal breathlessness in pupils \textsuperscript{69}. An earlier study concluded that the relation to asthma and MVOC is due to exposure to microorganisms \textsuperscript{70}. One study in a home environment reported that children living in dwellings with higher MVOC levels had a higher prevalence of asthma, hay fever, wheezing, and eye irritation, although the increases were not statistically significant \textsuperscript{71}. There are few epidemiological studies on SBS-symptoms in relation to MVOC in the home environment are few. There is only one study available on association between MVOC and SBS \textsuperscript{72}. In that study some MVOC were associated with health effects.
Study design of SBS studies

Most studies on SBS are cross-sectional and have dealt with symptoms among office workers. In addition, there are hardly any longitudinal cohort studies at all and only few studies on SBS in relation to domestic exposures. Moreover only a few studies deal with risk factors for SBS-symptoms in the general population.

Most of these SBS studies are based on questionnaires and few have performed measurements in dwellings. Moreover, no study to our knowledge had combined a questionnaire study of SBS longitudinal with measurement of biomarkers and indoor environment. To my knowledge there are few longitudinal studies on SBS-symptoms in relations to home environmental factors. Since a cross-sectional study does not give strong evidence on casual relations, there is a need for longitudinal studies on SBS, especially in the general population.
Aim

The overall aim of this thesis was to investigate different factors in the indoor environment in dwellings over time and if these factors are associated with SBS. Another aim was to investigate if inflammatory markers are associated with SBS.

The more specific aims were:
- To study changes of SBS and changes of selected types of indoor exposures at home over a follow-up period in a population sample of adults.
- To study associations between selected indoor factors at home and onset (incidence) and remission of SBS.
- To study associations between selected biomarkers and onset (incidence) of SBS.
- To study selected personal factors and onset (incidence) of SBS symptoms.
- To study associations between selected biomarkers and reports on dampness and moulds in homes.
- To study if airborne levels of MVOC, bacteria, moulds, formaldehyde, Texanol, TXIB, temperature and RH in dwellings in Northern Europe are associated with the prevalence of SBS symptoms.
- To study if there is an association between levels of MVOC and reports on dampness and moulds in the dwelling.
Materials and Methods

This thesis comprises three longitudinal studies (Paper I – III) and one prevalence study (Paper IV). The methods used in the respective papers are given below. All the studies were approved by the ethics committee of Uppsala University. In Paper IV local ethics committees at each centre (Reykjavik, Tartu, and Uppsala) approved the study protocols.

Paper I

Study design and population
The study was carried out in a three county region in mid-Sweden (the counties of Gävleborg, Kopparberg and Uppsala). The total population in the age group 20-65 years in the region was 468 000 people (162000 in Gävleborg County, 156000 in Kopparberg County, and 150000 in Uppsala County). During December 1988, a random sample was drawn from the civil registration register by selecting 0.1% of the total population aged 20-65 years. This resulted in a sample of 633 subjects (209 from Gävleborg County, 211 from Kopparberg County, and 213 from Uppsala County). Among those, 466 participated (74%) in the initial questionnaire study, which was performed in March 1989. This cohort was followed up after 8 years (in March 1997) by sending a similar postal questionnaire to the current address of each participant. Totally 348 subjects (75%) of the initial cohort participated in the follow-up study (Figure 1).
Figure 1. Selections of subjects in 1989 and 1997 in Paper I. The numbers of participants are given in the boxes. G=Gävleborg County, K=Kopparberg County, U=Uppsala County.

Paper II

Study design and population

The study population consists of a random sample of 1000 subjects of the general population aged 20 – 65 years in 1991 (figure 2). The sampling was done by Statistic Sweden, which is a central government authority for official statistics and other government statistics and in this capacity also has the responsibility for coordinating and supporting the Swedish system for official statistics. In order to study seasonal effects, the sample was further divided into four sub-samples (250 subjects in each). The subjects in each subsample received the standardized self administered questionnaire during one of the four seasons (September 1991 to August 1992). The response rate was 70%. A follow-up questionnaire was sent 10 years later (September 2001 to August 2002) to all subjects who participated in the first study (N=695),
following the same division into seasonal sub-groups as in the first study. The response rate in the follow-up was 61% (N=427).

Random sample from the Swedish population

Participated 1992

Participated 2002

Figure 2. Selections of subjects 1992 and 2002 in Paper II. The numbers of participants are given in the boxes.

Assessment of symptoms and personal factors in Paper I and Paper II

The same questionnaire was used in Paper I and Paper II, but some additional questions were added to the follow-up questionnaire of the second study. The questionnaires contained questions about age, sex, atopy and smoking habits. Current smoker was defined as subject reporting actual smoking in the interview, more than one cigarette per day, or who reported ceasing smoking less than one year ago.

Atopy was defined as having either allergy to grass or tree pollen (hay fever), allergy to furry animals or a history of childhood eczema. The questionnaire contained questions requiring "yes" or "no" answers on 16 different SBS-symptoms used in earlier investigations. The recall period was three months. Work-related symptoms were not addressed in the studies. There was one question asking whether the symptoms disappeared or improved when being away from the workplace or the home environment. This information, however, was not used in the studies, which covers symptoms regardless of the subject’s opinion of causes. In the first study the questionnaire also included questions about education level and size of residence town. Education level was nine-year compulsory school, upper secondary school or university. Size of residence town was classified as more than 100 000 inhabitants, less than 100 000 inhabitants but more than 10 000 or less than 10 000 inhabitants.
The prevalence of symptoms was calculated for each of the 16 symptoms. The symptoms were classified as eye, nasal, throat, facial dermal, or general symptoms and the prevalence of subjects with at least one symptom in each group was calculated. The prevalence of subjects with at least one symptom in mucosal membrane (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in throat, sore throat or irritative cough), dermal (facial itching, facial rash, itching on the hands, rashes on the hands, eczema) or general (headache, tiredness, sensation of getting a cold, nausea) was calculated. Moreover, in Paper I a symptom score (0 – 16) was calculated, by counting the number of symptoms.

Assessment of information on the dwelling in Paper I and Paper II
The questionnaire requested information on building age, type of building, type of ventilation system, air humidification, presence of wall-to-wall carpets, and four different signs of microbial growth, malodours or building moisture during the last 12 months. The questions on building dampness have been validated in a previous study. The validation was made by comparing self-reported building dampness by the inhabitant of the respective dwelling, with observations of signs of building dampness made by an occupational hygienist visiting dwellings. If presence of at least one observed sign of building dampness was used as golden standard, sensitivity was 74% and specificity was 71%. The questionnaire used in the follow-up of the second study contained three additional questions on any building dampness, any indoor painting, and any wall-to-wall carpeting in any of the dwellings the subjects had lived in during the 10-year follow-up period.

Paper III
Study design and population
Paper III is based on data from the Uppsala part of the European Community Respiratory Health Survey (ECRHS). ECRHS is a multi-centre population study carried out on a random sample of subjects aged 20-44 years during the years 1990-1994. ECRHS I has been described in detail elsewhere.

One random and an additional symptomatic sample of subjects from each centre who had completed the initial screening questionnaire were asked to answer a more detailed interview-led questionnaire and to undergo blood tests for measuring total and specific IgE, a skin prick test, a spirometry and a methacholine challenge. Symptomatic subjects were those who had reported at least one of the following symptoms in the screening questionnaire: attacks of asthma during the past 12 months, nocturnal breathlessness in the past 12 months, or current use of asthma medication.
In the Uppsala part of the ECRHS I, a random sample of 1800 males and 1800 females aged 20–44 years received a brief postal questionnaire about respiratory symptoms (stage 1) in December 1990. From those who responded, a random sample of 400 males and 400 females was selected to undergo a more detailed clinical examination (stage 2), to which all symptomatic subjects not included in the random sample were added (N=216). The random and symptomatic samples were invited to the same clinical tests and face-to-face interview, performed from April 1991 to February 1992. A follow-up study, ECRHS II, was carried out beginning in 2000 and using the same study protocol. In Uppsala it was performed in 2002. The cohort to be followed was defined as all subjects who completed stage 1 or stage 2 of ECRHS I and who also had their smoking status recorded. Paper III is restricted to participants from the Uppsala centre, who participated in both ECRHS I and ECRHS II, and who answered an additional questionnaire with questions on dermal, mucosal and general symptom (SBS symptoms) twice.

Figure 3. Selections of participants in 1992 and 2002 in Paper III. The numbers of participants are given in the boxes. *Participants who had answered the supplementary questionnaire with questions on SBS and the home environment.
Medical history, demographic data and the home environment

Data on age and gender was collected from each center. At ECRHS I (baseline) and ECRHS II (follow-up) subjects answered a detailed questionnaire on smoking, asthmatic symptoms, rhinitis, allergies, occupation, and the home environment. In ECRHS I atopy was defined as positive specific IgE, or a positive skin prick test. Besides the ECRHS questionnaire, an additional questionnaire used in previous SBS studies was answered. Based on this questionnaire, self reported atopy at baseline was defined as having either allergy to grass or tree pollen (hay fever), allergy to furry animals or a history of childhood eczema. This definition of atopy has been used in previous longitudinal SBS studies (Paper I and Paper II). As a validation, the previously used self-reported atopy at baseline was compared to the clinically diagnosed atopy definitions used in ECRHS I.

The supplementary questionnaire contained a number of questions on current home environment that were not available in the ECRHS questionnaire but have been used in previous SBS studies (Paper I and II). The studies included information on building age, type of building, type of ventilation system, pet keeping, ETS, recent indoor painting (redecoration), any wall-to-wall carpeting, four different signs of microbial growth (any building dampness, water leakage, sign of floor dampness and visible moulds), and malodorous or building moisture during the last 12 months (the same questions as in Paper I and II). The same questions were repeated in the follow-up study.

Assessment of symptoms

The supplementary questionnaire contained questions on 16 different mucosal, dermal and general symptoms. There were three alternatives for each question ‘no,-never’, ‘yes, sometimes’, and ‘yes, often’(every week). In the statistical analysis, ‘no,-never’ and ‘yes, sometimes’ where coded 0 and ‘yes, often’ (weekly symptoms) was coded 1. The recall period was three months. One additional question concerning whether any of the symptoms improved when away from home was not used in this study as very few subjects reported improvement of symptoms when away from home. The prevalence of weekly symptoms was calculated for each symptom. Symptoms were classified as mucosal, dermal or general, and calculations were made for the prevalence of subjects with at least one weekly symptom in each group. The same questions were repeated in the follow-up study.

Clinical investigation

The same procedure for the clinical investigations was used at both baseline and follow-up, but some biomarkers in blood where only analysed on one occasion. Blood and serum samples were collected and stored at -20° C for the measurement of total serum IgE, specific serum immunoglobulin E (IgE)
at a central laboratory and additional biomarkers locally. Specific serum levels against cat, timothy grass, the *Cladosporium herbarium*, mould and the house dust mite *Dermatophagoides pteronyssinus*, were determined by using Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden) in both ECRHS I and ECRHS II. A level above 0.35 kU/L was considered a positive reaction. Skin prick tests were only performed in ECRHS I. A prick test reaction to at least one of the allergens (*Dermatophagoides pteronyssinus*, cat, birch, dog, *Cladosporium*, olive, ragweed, mugwort, timothy grass and *Alternaria*) was defined as a mean wheal diameter of $\geq 3$ mm. A negative control was used and its diameter was subtracted from the diameter of the challenge allergens. Additional biomarkers in Uppsala at base line were ECP (eosinophil cationic protein) and EOS (eosinophil counts). Additional biomarkers at follow-up were CRP (C-reactive protein) and IL-6 (interleukin-6) which were analysed at the Department of Clinical Biochemistry, Landspitali-University Hospital, Iceland. The total levels of serum (IgE) were measured on both occasions.

Lung function measures, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were taken at baseline and follow-up. In Uppsala a dry rolling seal spirometer system (Sensor Medics 2130, Sensor Medics, Anaheim, California, USA) was employed. The same method for bronchial responsiveness was used at both occasions (methacholine challenge). Log transformation of slope was used to satisfy the assumptions of standard statistical analyses, *i.e.* normality and homogeneity of variance. The transformation $100/(\log \text{slope} + 10)$ was used as in previous publications from ECRHS 79. The term ‘slope’ is used for transformed log slope from here on. A low value of slope means a higher degree of bronchial responsiveness.

**Paper IV**

**Study design and population**

Paper IV is based on data from the Uppsala, Reykjavik and Tartu centres of the European Community Respiratory Health Survey (ECRHS II) 44. Of totally 1238 subjects from ECRHS II in these centres, 510 included in the random sample had not moved to another house since the ECRHS I survey. Sixty of these were randomly selected from each centre and invited to participate in the present study with air measurements in the home environment, as previously described 80. In addition all subjects who had reported that they had dampness or indoor moulds, but were not included in the 60 randomly selected subjects, were invited as well. A total of 129 subjects from the random sample (42 in Reykjavik, 46 in Uppsala and 41 in Tartu) and 48
subjects from the additional dampness sample participated. However, technical problem resulted in failure to analyse 18 MVOC samples (14 from Reykjavik, 3 from Uppsala and 1 from Tartu, all from the random sample) and these subjects were therefore not included. Finally 159 subjects were included with MVOC data available (28 random samples and 3 additional dampness samples from Reykjavik, 43 random samples and 20 additional dampness samples from Uppsala, and 40 random samples and 25 additional dampness samples from Tartu).

![Diagram](image)

**Figure 4.** Selections of participants in Paper IV. The numbers of participants are given in the boxes. R=Reykjavik U=Uppsala T=Tartu. a, A random sample of subject who had not moved where selected. b, Subjects who had dampness in the dwelling and were not in the random samples.
The subjects’ homes were visited between March 2001 and January 2002 in Reykjavik, between February 2001 and December 2001 in Uppsala and between April 2001 and June 2002 in Tartu. Most home visits were performed during the winter months, early spring or late autumn. All subject participating in this study also participated in the ECRHSII indoor study. Also, an additional questionnaire on SBS symptoms and five questions on dampness and indoor moulds were used. These questions were not included in the ECRHS questionnaire (Paper III).

**Measurement of indoor microbial and chemical exposure**

Indoor measurements included temperature, relative humidity, airborne moulds and bacteria, MVOC, Texanol and TXIB. Temperature and relative air humidity was measured with an Assman Psychrometer type SK-RHG (Sato Keiryoky Mfg. Co., Tokyo, Japan). Airborne microorganisms were sampled on 25 mm nucleopore filters with pore size 0.4 µm (2.0 l/min; 2.5 h). The total concentration of airborne moulds and bacteria were determined by the CAMNEA method. The detection limit for viable organisms was 30 colony-forming units per m³ of air and 11 000/m³ for total bacteria and moulds. Airborne MVOC and the two plasticizers were sampled on a charcoal tubes (Anasorb 747; SKC Inc., Eighty Four, PA, USA) and analysed by selective ion monitoring (SIM) gas chromatography mass spectrometry (GC-MS). The following compounds were measured: 3-methylfuran, 3-methyl-1-butanol, dimethyl disulfide, 2-hexanone, 2-heptanone, 1-octen-3-ol, 3-octanone, 2-metyl-1-butanol, ethyl-2-methylbutyrate, 2-pentylfuran, isobuty- lactate, isobutanol, 2-pentanol, ethylisobutyrate, 2-ethyl-1-hexanol, Texanol and TXIB. The detection limit was 1 ng/m³ for all MVOC and 0.1 µg/ m³ for 2-ethyl-1-hexanol. The total concentration of the selected MVOC (total MVOC) was defined as mass summation excluding the butanols and 2-ethyl-1-hexanol. Indoor concentrations of formaldehyde were measured with glass fiber filters impregnated with 2,4-dinitrophenylhydrazine (Andersson et al., 1981) with an air sampling flow of 0.2 l/min during 2.5 h. The detection limit for formaldehyde was 6 µg/m³.

**Assessment of Symptoms and Personal Factors**

Information on age, sex, and smoking habits was collected from the screening and interview questionnaires. A current smoker was defined as a subject who, during the interview, reported current smoking, or who had ceased smoking less than one year ago. Information on sixteen symptoms compatible with SBS was obtained from the self-administered questionnaire (Paper III). The recall period was 3 months. For each symptom, an answer could be given according to one of three options: 'no, never,' 'yes, sometimes', and 'yes, often' - often meaning every week. The prevalence of weekly symptoms was calculated for each symptom as well as the prevalence of at
least one weekly symptom, and at least one mucosal, general or dermal symptom.

**Blood samples**

Blood and serum samples were collected and stored at -20° C for the measurement of total serum IgE, specific serum immunoglobulin E (IgE) at a central laboratory and additional biomarkers locally. Specific serum levels against cat, timothy grass, the *Cladosporium herbarium*, mould and the house dust mite *Dermatophagoides pteronyssinus*, were determined by using Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden). A level above 0.35 kU/L was considered a positive reaction. The definition of atopy was one positive sign on the RAST-test.

**Statistical methods**

Changes in prevalence of health parameters or building characteristics were tested by McNemar test. For each individual, weekly occurrence of any mucosal, dermal or general symptom was calculated both in the beginning and end of the follow up period. Onset of any mucosal symptom was defined as presence of at least one mucosal symptom at the end of the follow up period, but absence of any mucosal symptom in the beginning. Onset of any dermal or any general symptom was defined in a similar way. In the remission analysis, only subjects with the particular type of symptoms at baseline were included.

Multiple binominal regression was used to analyse onset of symptoms and remission of symptoms as well as for analysing education levels and regional differences, changes of biomarkers and SBS. Log-transformed data was used for the biomarkers in the regression analysis. A symptom score (SC) was calculated at both occasions by counting the number of weekly symptoms (0-16). Symptom score difference (SCD) in relation to personal factors and exposure indicators was analysed by multiple linear regression. Logistic regression was use for analysing association between MVOC, bacteria, moulds, formaldehyde, plasticizers, temperature, RH and prevalence of symptoms. In the regression models control was made for possible confounders such as age, gender, current smoking, and hay fever by keeping them at the same time in the model together with the home exposure variables. Log transformation of MVOC and chemical data was done.

Associations between biomarkers and dampness were analysed by the Mann-Whitney U-test. Differences in levels of MVOC, bacteria, moulds, formaldehyde and the plasticizers between buildings with and without a history of dampness and moulds, according to the participant, were analysed by the
Mann-Whitney U-test. Lastly, Kruskal-Wallis test was used to examine if there was any difference in total MVOC level between different centres. Chi-square analyses (2*3 contingency tables) were used to examine if there was any centre difference in weekly SBS symptoms. In all statistical analyses two-tailed tests and a 5% level of significance were used. Calculations were performed using SAS® system version 9.1 and SAS® system version 9.2.
Results

Paper I
The follow-up study was restricted to those 348 subjects who participated in both the initial study in 1989 and the follow-up study in 1997. A comparison between participants (N=348) with non-participants (N=118) gave the following results: The non-participants did not differ significantly from the participants with respect to age, gender, hay fever, doctors’ diagnosed asthma, or smoking habits, in 1989. The initial mean age was 42 years in 1989. The cumulative incidence of asthma (ever had asthma) had numerically increased. The prevalence of current smoking had decreased considerably. Prevalence of a few SBS-symptoms had decreased, e.g. nasal catarrh and sensation of getting a cold, but overall the symptoms remained unchanged (Table 1).

Some improvements of the home environment were observed concerning building dampness and indoor moulds. Water leakage during the last year had decreased and visible indoor mould, and any sign of building dampness had decreased. The proportion of dwellings with mechanical ventilation either in living rooms or in bedrooms increased (Table 2). The prevalence of any building dampness, water leakage, sign of floor dampness and visible moulds reported the last 12 months had decreased. Many of the subjects had painted indoors and nearly one third of them had used solvent-based paints. The 8-year onset of at least one symptom in each group was 14% for skin symptoms, 10% for mucosal symptoms and 21% for general symptoms. The incidence of headache and tiredness was 12 and 15%, respectively. No increased risk for onset of any skin, mucosal or general symptoms in relation to building factors (building age, type of building, type of ventilation system, air humidification, presence of wall-to-wall carpets, and four different signs of microbial growth, malodours or building moisture) and any personal factors (age, sex, atopy and smoking habits) at baseline was found in the binomial regression analysis (Table 3).

When analysing the change of symptom score in relation to home exposure during the follow-up period, or personal factors at baseline, it was found that smokers at baseline reported a significant increase of 0.7 units in symptom score (0 – 16) as compared to non-smokers. Moreover, subjects with any
indoor painting during follow-up reported a significant net increase of 0.6 units in symptom score.

It was found that subjects with a middle level of education (upper secondary school but no university education) had a significant increase of onset of dermal symptoms. Finally, the remission of different types of symptoms was studied in relation to home exposure during the follow-up period, or personal factors at baseline. Remission of skin symptoms was more common in older subjects and in subject with hay fever at baseline. Moreover, remission of mucosal symptoms was less likely in subjects that were current tobacco smokers at baseline (Table 4).

Table 1. The prevalence of asthma, allergies, chronic bronchitis, smoking habits and symptom groups among subjects who participated both in the initial study in 1989 and in the follow-up in 1997 (N=348).

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>P-value^d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1989</td>
</tr>
<tr>
<td>Asthma (cumulative incidence)</td>
<td>5.2</td>
</tr>
<tr>
<td>Any type of allergy</td>
<td>26</td>
</tr>
<tr>
<td>Hay fever</td>
<td>14</td>
</tr>
<tr>
<td>Nickel allergy</td>
<td>17</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>4.9</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>23</td>
</tr>
<tr>
<td>Any mucosal (7 symptoms)^a</td>
<td>16</td>
</tr>
<tr>
<td>Any general (4 symptoms)^b</td>
<td>44</td>
</tr>
<tr>
<td>Any skin (5 symptoms)^c</td>
<td>21</td>
</tr>
</tbody>
</table>

a. The prevalence of subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).
b. The prevalence of subjects with at least one symptom classified as general (headache, tiredness, sensation of getting a cold, nausea).
c. The prevalence of subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
d. Differences tested by McNemar statistical test
Table 2. The prevalence of environmental factors in the current dwelling of subjects who participated both in the initial study in 1989 and in the follow-up in 1997 (N=348).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence (%) Study I</th>
<th>Prevalence (%) Study II</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of pet at home</td>
<td>44</td>
<td>41</td>
<td>0.37</td>
</tr>
<tr>
<td>Indoor painting the last 12 months</td>
<td>24.0</td>
<td>19.4</td>
<td>0.15</td>
</tr>
<tr>
<td>General mechanical ventilation (in bedroom or living room)</td>
<td>11.8</td>
<td>16.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Other type of odour (mouldy odour excluded)</td>
<td>4.7</td>
<td>5.4</td>
<td>0.64</td>
</tr>
<tr>
<td>Water leakage the last 12 months</td>
<td>11.2</td>
<td>4.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Signs of floor dampness the last 12 months</td>
<td>6.0</td>
<td>5.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Visible moulds the last 12 months</td>
<td>4.7</td>
<td>1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Mouldy odour the last 12 months</td>
<td>2.5</td>
<td>1.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Any type of building dampness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16.1</td>
<td>9.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subjects reporting at least on factor regarded as dampness  
<sup>b</sup> Differences tested by McNemar statistical test

Table 3. Relationship between onset of symptoms, building factors and personal factors.

<table>
<thead>
<tr>
<th>Type of symptoms</th>
<th>General&lt;sup&gt;a&lt;/sup&gt; (RR95%CI)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Skin&lt;sup&gt;b&lt;/sup&gt; (RR95%CI)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Mucosal&lt;sup&gt;c&lt;/sup&gt; (RR95%CI)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1.16 (0.83-1.62)</td>
<td>1.05 (0.81-1.38)</td>
<td>1.08 (0.84-1.40)</td>
</tr>
<tr>
<td>Age (10y)</td>
<td>0.99 (0.85-1.15)</td>
<td>1.02 (0.91-1.15)</td>
<td>1.01 (0.89-1.14)</td>
</tr>
<tr>
<td>Hay fever</td>
<td>1.02 (0.63-1.66)</td>
<td>1.03 (0.68-1.55)</td>
<td>0.94 (0.64-1.36)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.91 (0.61-1.35)</td>
<td>0.96 (0.71-1.31)</td>
<td>1.00 (0.76-1.33)</td>
</tr>
<tr>
<td>Any type of building dampness</td>
<td>0.92 (0.60-1.41)</td>
<td>0.91 (0.63-1.33)</td>
<td>1.05 (0.74-1.48)</td>
</tr>
<tr>
<td>Any indoor painting</td>
<td>0.97 (0.68-1.37)</td>
<td>1.00 (0.76-1.23)</td>
<td>1.06 (0.80-1.40)</td>
</tr>
<tr>
<td>Any wall-to-wall carpet</td>
<td>1.00 (0.72-1.38)</td>
<td>0.95 (0.73-1.23)</td>
<td>0.95 (0.73-1.23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subjects with at least one symptom classified as general (headache, tiredness, sensation of getting a cold, nausea).  
<sup>b</sup> Subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).  
<sup>c</sup> Subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).  
<sup>d</sup> Relative risk (RR) and 95% confidence interval.
Table 4. Adjusted RR for remission of symptoms, building factors and personal factors.

<table>
<thead>
<tr>
<th></th>
<th>Any type&lt;sup&gt;e&lt;/sup&gt;</th>
<th>General&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Skin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mucosal&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR(95%CI)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>RR(95%CI)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>RR(95%CI)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>RR(95%CI)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.96 (0.48-1.91)</td>
<td>0.62 (0.30-1.28)</td>
<td>1.33 (0.42-4.22)</td>
<td>0.33 (0.08-1.41)</td>
</tr>
<tr>
<td>Age (10year)</td>
<td>0.90 (0.60-1.02)</td>
<td>1.34 (1.00-1.97)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.79 (1.00-3.39)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.73 (0.39-1.34)</td>
</tr>
<tr>
<td>Hay fever</td>
<td>2.13 (0.76-5.95)</td>
<td>1.52 (0.54-4.30)</td>
<td>4.91 (1.09-22.1)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>3.78 (0.55-25.8)</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>1.00 (0.45-2.19)</td>
<td>0.62 (0.29-1.33)</td>
<td>0.42 (0.12-1.39)</td>
<td>0.17 (0.03-0.90)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any type of building dampness</td>
<td>0.85 (0.33-1.17)</td>
<td>1.32 (0.51-3.38)</td>
<td>1.44 (0.42-4.93)</td>
<td>0.41 (0.09-1.83)</td>
</tr>
<tr>
<td>Any indoor painting</td>
<td>0.65 (0.30-1.40)</td>
<td>1.09 (0.50-2.34)</td>
<td>1.77 (0.50-6.30)</td>
<td>1.22 (0.30-4.88)</td>
</tr>
<tr>
<td>Any wall-to-wall carpet</td>
<td>1.76 (0.84-3.67)</td>
<td>1.28 (0.61-2.69)</td>
<td>0.40 (0.13-1.24)</td>
<td>1.38 (0.36-5.28)</td>
</tr>
</tbody>
</table>

a, Subjects with at least one symptom classified as general (headache, tiredness, sensation of getting a cold, nausea).
b Subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
c, Subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).
d. Relative risk (RR) and 95% confidence interval.
e. Subjects with onset of at least one symptom.
* P<0.05
(*) P=0.05

Paper II

The follow-up study was restricted to those 427 subjects who participated in both the initial study and the follow up-study. A comparison between participants (N=427) and non-participants (N=268) gave the following results: The non-participants did not differ significantly from the participants with respect to age, gender, hay fever, doctors’ diagnosed asthma, or smoking habits at baseline. The initial mean age was 42 years. The prevalence of current smoking had decreased (Table 5). The prevalence of mucosal symptoms remained unchanged while any general and any skin symptom had decreased (Table 5). The prevalence of hay fever had increased (Table 5).

Some improvements of the home environment concerning building dampness and indoor moulds were observed. Visible indoor mould during the last year had decreased. Also mouldy odour and any sign of building dampness had decreased. Other types of odour, excluding mouldy odour had decreased.
The prevalence of any type of building dampness had decreased, and water leakage, sign of floor dampness and visible moulds had decreased during the study period. A large proportion of the subjects (70%) had painted indoors during the follow-up period and nearly a third of them had used solvent-based paints. Furthermore 31% of the subjects had had any wall-to-wall carpets and a third of them had had any type of building dampness in their homes.

The onset (incidence) of subjects with at least one symptom in each group was 12% for skin, 28% for mucosal and 25% for general symptoms. For headache the onset was 10% and for tiredness 15%. An increased onset of any skin, mucosal or general symptoms was found among those who had any type of building dampness in the dwelling at base line. Among personal factors hay fever at baseline was positively related to onset of skin and mucosal symptoms, and age was related to onset of general symptoms (Table 7). Also the relationship between specific mucosal symptoms (such as eye, nose and throat) and building factors and personal factors were analysed. Onset of eye symptoms (RR 2.41 CI, 1.38-4.35) and throat symptoms (RR 2.33 CI, 1.10 – 4.95) was significantly more common in damp dwellings.

In the stratified analysis, the associations between symptoms and dampness in the dwelling were analysed. Smokers at baseline had a consistently higher RR for onset of general, skin and mucosal symptoms in relation to dampness as compared to non-smokers. The RR was 2-8 times higher for smokers, but confidence intervals were partly overlapping.

Remission from general symptoms or skin symptoms was less likely in subjects with dampness in the dwelling, and remission from general symptoms was less likely if the dwelling had been painted indoors during follow-up. Moreover, remission from skin symptoms was less likely in subjects with hay fever at baseline (Table 8).
Table 5. The prevalence of asthma, allergies, chronic bronchitis, smoking habits and
type of symptoms among subjects who participated in both studies.

<table>
<thead>
<tr>
<th>Type of symptom</th>
<th>Prevalence (%)</th>
<th>1991 (N=427)</th>
<th>2001 (N=427)</th>
<th>P-value&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>7.8</td>
<td>9.7</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Any type of allergy</td>
<td>27</td>
<td>27</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Hay fever</td>
<td>12</td>
<td>16</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>6.9</td>
<td>6.2</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>28</td>
<td>19</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22</td>
<td>32</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Type of symptom</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mucosal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41</td>
<td>43</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Any general&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48</td>
<td>42</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Any skin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21</td>
<td>16</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>, The prevalence of subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).

<sup>b</sup>, The prevalence of subjects with at least one symptom classified as general (headache, tiredness, sensation of getting a cold, nausea).

<sup>c</sup>, The prevalence of subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).

<sup>d</sup>, Differences tested by McNemar statistical test

Table 6. The prevalence of environmental factors in the current dwelling of subjects
who participated both in the initial study in 1991 and in the follow-up in 2001.

<table>
<thead>
<tr>
<th>Environmental factor</th>
<th>Prevalence (%)</th>
<th>1991 (N=427)</th>
<th>Prevalence (%)</th>
<th>2001 (N=427)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of pet at home</td>
<td>40</td>
<td>36</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor painting the last 12 months</td>
<td>30</td>
<td>25</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General mechanical ventilation (in bedroom or living room)</td>
<td>20</td>
<td>22</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other type of odour (mouldy odour excluded)</td>
<td>7.9</td>
<td>1.8</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water leakage the last 12 months</td>
<td>11</td>
<td>7.3</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of floor dampness last 12 months</td>
<td>5.8</td>
<td>3.3</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible moulds last 12 months</td>
<td>5.3</td>
<td>1.5</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouldy odour last 12 months</td>
<td>2.8</td>
<td>0.5</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type of building dampness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
<td>18</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>, Subjects reporting at least one factor regarded as dampness

<sup>b</sup>, Differences tested by McNemar statistical test
Table 7. Relationship between onset of weekly symptoms, building factors and personal factors at baseline.

<table>
<thead>
<tr>
<th>Type of symptoms</th>
<th>General[^a^] (RR[^d^] 95%CI[^d^])</th>
<th>Skin[^b^] (RR[^d^] 95%CI[^d^])</th>
<th>Mucosal[^c^] (RR[^d^] 95%CI[^d^])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1.45 (0.96-2.21)</td>
<td>1.59 (0.88-2.89)</td>
<td>1.33 (0.88-2.02)</td>
</tr>
<tr>
<td>Age (10 years)</td>
<td>0.90 (0.74-1.11)</td>
<td>1.11 (0.90-1.48)</td>
<td>1.11 (1.00-1.34)*</td>
</tr>
<tr>
<td>Hay fever</td>
<td>1.46 (0.78-2.73)</td>
<td>2.76 (1.30-5.84)*</td>
<td>2.30 (1.22-4.32)*</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>0.95 (0.57-1.59)</td>
<td>1.67 (0.86-3.21)</td>
<td>073 (0.44-1.22)</td>
</tr>
<tr>
<td>Any type of building dampness</td>
<td>2.32 (1.37-3.93)*</td>
<td>3.17 (1.69-5.95)*</td>
<td>2.18 (1.29-3.70)*</td>
</tr>
<tr>
<td>Indoor painting</td>
<td>1.42 (0.91-2.21)</td>
<td>1.23 (0.68-2.23)</td>
<td>1.11 (0.71-1.73)</td>
</tr>
<tr>
<td>Any wall–to-wall carpet</td>
<td>0.64 (0.40-1.01)</td>
<td>0.72 (038-1.38)</td>
<td>0.79 (0.50-1.24)</td>
</tr>
</tbody>
</table>

[^a^] Subjects with onset of at least one symptom classified as general (headache, tiredness, sensation of getting a cold, nausea).
[^b^] Subjects with onset of at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
[^c^] Subjects with onset of at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).
[^d^] Relative risk (RR) and 95% confidence interval.
* P<0.05

Table 8. Relationship between remission of weekly symptoms, building factors and personal factors at baseline.

<table>
<thead>
<tr>
<th>Type of symptoms</th>
<th>General[^a^] (RR[^d^] 95%CI[^d^])</th>
<th>Skin[^b^] (RR[^d^] 95%CI[^d^])</th>
<th>Mucosal[^c^] (RR[^d^] 95%CI[^d^])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.79 (0.43-1.47)</td>
<td>0.62 (0.18-2.05)</td>
<td>0.80 (0.41-1.55)</td>
</tr>
<tr>
<td>Age (10 years)</td>
<td>1.11 (0.82-1.48)</td>
<td>1.00 (0.43-1.22)</td>
<td>0.90 (1.00-1.86)</td>
</tr>
<tr>
<td>Hay fever</td>
<td>2.18 (0.99-4.19)</td>
<td>0.18 (0.05-0.70)*</td>
<td>0.47 (0.19-1.14)</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>1.28 (0.59-2.79)</td>
<td>0.74 (0.20-2.74)</td>
<td>0.92 (0.39-2.16)</td>
</tr>
<tr>
<td>Any type of building dampness</td>
<td>0.48 (0.23-0.99)*</td>
<td>0.24 (0.07-0.83)*</td>
<td>0.46 (0.21-1.02)</td>
</tr>
<tr>
<td>Indoor painting</td>
<td>0.43 (0.21-0.86)*</td>
<td>0.51 (0.15-1.69)</td>
<td>1.13 (0.56-2.27)</td>
</tr>
<tr>
<td>Any wall–to-wall carpet</td>
<td>1.57 (0.80-3.10)</td>
<td>1.42 (0.41-4.97)</td>
<td>1.21 (0.58-2.53)</td>
</tr>
</tbody>
</table>

[^a^] Subjects with remission of all symptoms classified as general (headache, tiredness, sensation of getting a cold, nausea).
[^b^] Subjects with remission of all symptoms classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
[^c^] Subjects with remission of all symptoms classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness in the throat, sore throat, irritative cough).
[^d^] Relative risk (RR) and 95% confidence interval.
* P<0.05
Paper III

The follow-up study was restricted to those subjects who (a) participated in the clinical investigation both in the initial study and the follow-up study, and (b) answered the SBS questionnaire twice (N=452). Totally 43% had clinically diagnosed atopy at baseline, and 45% had self-reported atopy. When validating the definition of self-reported atopy (hay fever, furry pet allergy, childhood eczema) at baseline, using the ECRHS I definition of atopy (either a positive skin prick test or at least one elevated specific IgE) as the golden standard, the sensitivity was 75% and specificity was 74% for self-reported atopy.

Some improvements in the home environment were observed over time. The prevalence of ETS, visible indoor moulds, mouldy odour and other types of odour, as well as any type of building dampness had decreased (Table 9). The prevalence of hay fever had increased.

The prevalence of current smokers had decreased and there was a decrease in the median slope value indicating increased bronchial responsiveness (BR). Moreover, there was an increase in the total levels of serum IgE (Table 10). There was no significant change in the prevalence of any general, any mucosal or any skin symptoms. The 10-year onset (incidence) was 12.7% for any general symptom, 8.5% for any mucus membrane symptom and 6.8% for any skin symptom. Subjects with medical doctor diagnosed asthma at baseline had a higher onset of mucosal and general symptoms.

Subjects living in buildings with any type of building dampness at baseline had a higher onset of any mucosal, any general and any skin symptom. Moreover, females had a higher onset of general and mucous membrane (mucosal) symptoms, and those who had their home re-painted at baseline had a higher onset of general symptoms (Table 11).

As a next step, the associations between remission of SBS and personal factors and home environment at baseline were analysed. The 10-year remission was 65% for any general symptom, 63% for any mucus membrane symptom and 69% for any skin symptom. No personal or environmental factors were associated with remission of SBS.

As a third step, the associations between the onset of SBS and levels of biomarkers at baseline or at follow-up were analysed. Among baseline biomarkers, low slope (higher BR) was a predictor of the onset of general and mucosal symptoms. Total IgE was a predictor of the incidence of mucosal and skin symptoms, ECP was a predictor of onset of general and mucosal symptoms, and EOS was only a predictor of mucosal symptoms.
follow-up biomarkers, low slope (higher BR) was only associated with a higher onset of mucosal symptoms. Total IgE was associated with incidence of skin symptoms, and CRP was associated with higher onset of mucosal symptoms (Table 11).

Finally, associations were studied between dampness at home (yes on at least one of the four questions) and biomarkers. Dampness at baseline was positively associated with higher levels of CRP (p=0.02) and negative associated with IL-6 (p=0.04) at follow-up. No other associations between dampness at baseline or follow-up, and other biomarkers were found.

Table 9. Prevalence of environmental factors in the dwelling of subjects who participated in both the initial study in 1992 and the follow-up in 2002.

<table>
<thead>
<tr>
<th>Environmental Factor</th>
<th>1992 (N=452)</th>
<th>2002 (N=452)</th>
<th>P-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of pet at home</td>
<td>40.1</td>
<td>35.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Indoor painting during last 12 months</td>
<td>30.2</td>
<td>24.8</td>
<td>0.10</td>
</tr>
<tr>
<td>General mechanical ventilation (in bedroom or living room)</td>
<td>20.3</td>
<td>22.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Environmental tobacco smoke</td>
<td>15.4</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other type of odour (mouldy odour excluded)</td>
<td>7.9</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Water leakage during the last 12 months</td>
<td>11.3</td>
<td>7.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Signs of floor dampness during the last 12 months</td>
<td>5.8</td>
<td>3.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Visible moulds during the last 12 months</td>
<td>5.3</td>
<td>1.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Mouldy odour during the last 12 months</td>
<td>2.8</td>
<td>0.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Any type of building dampnessa</td>
<td>16.2</td>
<td>9.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

a. Subjects reporting at least one factor regarded as dampness
b. Differences tested using McNemar statistical test
Table 10. Prevalence of asthma, hay fever, chronic bronchitis, smoking habits and inflammatory markers among subjects

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1992 (n=452)</td>
<td>2002 (n=452)</td>
<td>P-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>52.0</td>
<td>52.0</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Asthma&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18.1</td>
<td>19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hay fever&lt;sup&gt;e&lt;/sup&gt;</td>
<td>30.4</td>
<td>36.6</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>6.9</td>
<td>6.2</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>25.1</td>
<td>15.3</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Any mucosal&lt;sup&gt;g&lt;/sup&gt;</td>
<td>19.9</td>
<td>14.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any general&lt;sup&gt;h&lt;/sup&gt;</td>
<td>16.5</td>
<td>17.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any skin&lt;sup&gt;i&lt;/sup&gt;</td>
<td>10.3</td>
<td>10.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>Median value and IQR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>7.9 (6.3-9.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Total IgE (kU/l)</td>
<td>28 (11-80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.0 (0.5-2.4)</td>
</tr>
<tr>
<td>IL-6 (ng/l)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.6 (5.6-10.9)</td>
</tr>
<tr>
<td>ECP (µg/l)</td>
<td>12.1 (8.4-18.4)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>EOS (µg/l)</td>
<td>150 (90-231)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Differences tested using McNemar statistical test
<sup>b</sup> IQR, inter-quartile range
<sup>c</sup> NA, not analysed
<sup>d</sup> Doctor diagnosed asthma
<sup>e</sup> Defined as having allergy to either grass or tree pollen.
<sup>f</sup> Wilcoxon
<sup>g</sup> Prevalence of subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness of the throat, sore throat, irritative cough).
<sup>h</sup> Prevalence of subjects with at least one symptom classified as general (headache, tiredness, sensation of catching a cold, nausea).
<sup>i</sup> Prevalence of subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
Slope. The term “slope” is used for log transformed slope for the methacholin test. The transformation 100/ (log slope + 10).
IgE. Serum immunoglobulin E
CRP. High-Sensitivity C-Reactive Protein
IL-6. Interleukin-6
ECP. Eosinophilic cationic protein
EOS. Eosinophil counts
Table 11. Predictors at baseline for onset of symptoms.

<table>
<thead>
<tr>
<th></th>
<th>General\textsuperscript{a} Symptoms (RR95%CI\textsuperscript{d})</th>
<th>Mucosal\textsuperscript{b} Symptoms (RR95%CI\textsuperscript{d})</th>
<th>Skin\textsuperscript{c} Symptoms (RR95%CI\textsuperscript{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1.74 (1.15-2.65)*</td>
<td>1.71 (1.12-2.62)*</td>
<td>1.08 (0.64-1.81)</td>
</tr>
<tr>
<td>Age (10y)</td>
<td>0.99 (0.96-1.01)</td>
<td>1.05 (0.98-1.03)</td>
<td>0.99 (0.95-1.02)</td>
</tr>
<tr>
<td>Current tobacco smoker</td>
<td>0.82 (0.50-1.33)</td>
<td>0.99 (0.62-1.58)</td>
<td>0.89 (0.48-1.67)</td>
</tr>
<tr>
<td>Any type of building dampness \textsuperscript{e}</td>
<td>1.98 (1.27-3.09)*</td>
<td>2.28 (1.46-3.55)*</td>
<td>1.91 (1.06-3.44)*</td>
</tr>
<tr>
<td>Any indoor painting\textsuperscript{e}</td>
<td>1.62 (1.06-2.47)*</td>
<td>1.50 (0.97-2.31)</td>
<td>1.24 (0.69-2.20)</td>
</tr>
<tr>
<td>Any wall-to-wall carpet</td>
<td>0.72 (0.36-1.44)</td>
<td>0.94 (0.50-1.76)</td>
<td>1.09 (0.52-2.32)</td>
</tr>
<tr>
<td><strong>Baseline biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.85 (0.77-0.93)**</td>
<td>0.87 (0.79-0.95)**</td>
<td>0.88 (0.78-1.00)</td>
</tr>
<tr>
<td>Total IgE\textsuperscript{j} (kU/l)</td>
<td>1.23 (0.62-2.45)</td>
<td>1.69 (1.00-2.84)*</td>
<td>2.17 (1.30-3.63)**</td>
</tr>
<tr>
<td>ECP\textsuperscript{f} (µg/l)</td>
<td>1.22(1.01-1.48)*</td>
<td>1.30 (1.09-1.56)*</td>
<td>1.00 (0.75-1.33)</td>
</tr>
<tr>
<td>EOS\textsuperscript{h} (µg/l)</td>
<td>1.05 (0.95-1.17)</td>
<td>1.17 (1.07-1.28)**</td>
<td>1.10 (0.93-1.29)</td>
</tr>
<tr>
<td><strong>Follow-up biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.94 (0.83-1.07)</td>
<td>0.90 (0.82-0.98)**</td>
<td>0.87 (0.74-1.02)</td>
</tr>
<tr>
<td>Total IgE\textsuperscript{j} (kU/l)</td>
<td>1.50 (0.74-3.07)</td>
<td>1.30 (0.94-1.816)</td>
<td>2.52 (1.50-4.22)**</td>
</tr>
<tr>
<td>CRP\textsuperscript{g} (mg/l)</td>
<td>1.07 (0.80-1.44)</td>
<td>1.19 (1.08-1.32)*</td>
<td>0.96 (0.55-1.69)</td>
</tr>
<tr>
<td>IL-6\textsuperscript{h} (ng/l)</td>
<td>1.03 (0.85-1.25)</td>
<td>0.99 (0.84-1.17)</td>
<td>1.15 (0.95-1.41)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Subjects with at least one symptom classified as general (headache, tiredness, sensation of catching a cold, nausea).
\textsuperscript{b} Subjects with at least one symptom classified as mucosal (eye irritation, swollen eyelids, nasal catarrh, nasal obstruction, dryness of the throat, sore throat, irritative cough).
\textsuperscript{c} Subjects with at least one symptom classified as skin (facial itching, facial rash, itching on the hands, rashes on the hands, eczema).
\textsuperscript{d} Relative risk (RR) and 95% confidence interval.
\textsuperscript{e} 12-month recall period.
\textsuperscript{f} Relative risk expressed as change of coefficient by 10 µg/l
\textsuperscript{g} Relative risk expressed as change of coefficient by 10 mg/l
\textsuperscript{h} Relative risk expressed as change of coefficient by 10 ng/l
\textsuperscript{i} Relative risk expressed as change of coefficient by 100 µg/l
\textsuperscript{j} Relative risk expressed as change of coefficient by 1000 kU/l

* P<0.05 ** P<0.01 *** P<0.001

All analyses were controlled for age, sex and smoking habits.

Slope. The term "slope" is used for log transformed slope for the methacholin test. The transformation 100/ (log slope + 10).

IgE. Serum immunoglobulin E
CRP. High-Sensitivity C-Reactive Protein
IL-6. Interleukin-6
ECP. Eosinophilic cationic protein
EOS. Eosinophil counts
Paper IV

The prevalence of weekly general symptoms was 11.3%, for mucosal symptoms 20.1%, and for skin symptoms 7.6%. The most common SBS-symptom was nasal catarrh. Prevalence of female gender was 57%, atopy 24%, and hay fever 35%. The proportion of current smokers was high, 31%. Prevalence of any type of building dampness during the last 10 years was 41%, and for 12 month dampness 20%. The level of specific MVOC, formaldehyde and the plasticizers as well as temperature, relative air humidity, mould, and bacteria in the dwellings are presented in table 12.

The distribution of subjects by centre was 19% from Reykjavik, 40% Uppsala, and 41% from Tartu, in total 159 subjects. Of these were 57% females. The prevalence of any weekly SBS symptom was 19% for Reykjavik, 33% for Uppsala and 29% for Tartu, a significant difference (p<0.001). Moreover, the total MVOC differed between the centres (p<0.001) (11.64 ng/m$^3$ in Reykjavik, 13.69 ng/m$^3$ in Uppsala, and 11.34 ng/m$^3$ in Tartu). Associations between each exposure variable and any weekly SBS were analysed by multiple linear regression analysis, keeping age, gender, smoking and atopy in the models. Significant positive associations were found for six compounds (formaldehyde, 2-pentanol, 2-hexanone, 1-okten-3-ol, 2-pentylfuran and Texanol) (Table 13). A significant negative association was found between level of ethyl-2-methylbutyrat and any SBS symptoms. As a next step, analyses of associations between the six significant exposure variables and any general and any mucosal symptoms was done. 1-okten-3-ol was found to be associated with mucosal symptoms, OR 1.80 (95% CI 1.14-2.83). When comparing levels of the six significant variables between centres, there were significant differences for all six compounds (p<0.05), with lowest levels in Reykjavik and highest levels in Uppsala.

Finally, levels of exposure variables between those with and without a history of dampness and moulds (either during the last 10 years or the last 12 months) were compared. The levels of total bacteria, total moulds, viable moulds, 3-methylfuran and ethyl-isobutyrate were significantly higher in dwellings with a history of dampness and microbial growth the last 10 years (Table 14). If restricting the dampness variable to reports of dampness or moulds last 12 months (current dampness or moulds), only 2-ethyl-1-hexanol, 2-methylfuran and relative air humidity were significantly elevated. Levels of 2-ethyl-1-hexanol (GM with 95% CI) were (2.80; 95% CI 2.22-3.69) in damp dwellings and (1.85; 95% CI 1.40-2.44) (p=0.03) in non-damp dwellings. Levels of 3-methylfuran (GM with 95% CI) were (35 ng/m$^3$; 95% CI 20-50) in damp dwellings and (17 ng/m$^3$; 95% CI 11-26) (p=0.03) in non-damp dwellings. Relative air humidity in damp dwellings was 43% (95% CI 40-46) and in non damp dwellings 40% (95% CI 37-42) (p=008).
Table 12. Concentrations of Indoor MVOC, other specific compounds, microorganisms, temperature and relative air humidity.

(N=159) | DR(%) | AM | GM | 95% CI | MAX
--- | --- | --- | --- | --- | ---
**MVOC (ng/m³)**
Sum of MVOC | 12330 | 9160 | 8160 -10270 | 88000
3-methylfuran | 99 | 40 | 20 | 20 – 30 | 690
isobutanol | 100 | 2340 | 1560 | 1370 – 1790 | 18000
1-butanol | 100 | 8600 | 5840 | 5110 – 6660 | 78000
2-pentanol | 99 | 30 | 10 | 9 – 10 | 220
3-methyl-1-butanol | 98 | 460 | 270 | 200 – 360 | 5320
dimethylsulfid | 99 | 340 | 30 | 20 – 40 | 5780
2-hexanone | 100 | 80 | 50 | 50 – 60 | 320
2-heptanone | 100 | 440 | 320 | 280 – 360 | 3170
1-okten-3-ol | 100 | 90 | 50 | 40 – 60 | 2330
3-octanone | 100 | 50 | 40 | 40 – 50 | 350
2-methyl-1-butanol | 99 | 110 | 70 | 60 – 90 | 940
ethylisobutyrate | 68 | 5 | 1 | 1 – 2 | 70
isobutyric acetate | 84 | 530 | 60 | 30 – 100 | 17250
ethyl-2-methylbutyrate | 93 | 130 | 30 | 20 – 40 | 2390
2-pentathylfuran | 100 | 400 | 40 | 30 – 50 | 46000
**Other specific compounds (µg/m³)**
2-ethyl-1-hexanol | 100 | 2.99 | 2.37 | 2.12 – 2.67 | 14.2
Formaldehyde | 99 | 26.03 | 19.95 | 17.79 – 22.39 | 233
Texanol | 99 | 5.07 | 1.07 | 0.83 – 1.37 | 246.80
TXIB | 100 | 2.68 | 1.47 | 1.26 – 1.73 | 22.8
**Microorganisms**
Viable bacteria | 99 | 899 | 227 | 299 – 1500 | 42000
Total bacteria | 99 | 34269 | 16358 | 14045 – 19050 | 610000
Viable moulds | 99 | 467 | 216 | 186 – 251 | 20000
Total moulds | 99 | 17165 | 12830 | 11573 – 14224 | 110000
Temperature (°C) | 100 | 20.8 | 20.7 | 20.4-21.1 | 25
Relative air humidity | 100 | 43 | 41 | 39-43 | 76

a. DR = Detection rate (the samples where the compound be detected if possible to analysed)
b. Arithmetic mean
c. Geometric mean
d. 95% Confidence interval of geometric mean
e. Maximum value of analyzed Mvoc, other specific compounds, bacteria, moulds, temperature and relative air humidity
f. Colony forming unit, cfu/m³
g. Number / m³
Table 13. Indoor MVOC significantly associated with any SBS.

<table>
<thead>
<tr>
<th>MVOC and other specific compounds</th>
<th>OR$^a$</th>
<th>95% CI$^b$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>1.61</td>
<td>1.00-2.62</td>
<td>0.05</td>
</tr>
<tr>
<td>2-pentanol</td>
<td>1.49</td>
<td>1.16-1.92</td>
<td>0.002</td>
</tr>
<tr>
<td>2-hexanone</td>
<td>2.30</td>
<td>1.47-3.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-octen-3-ol</td>
<td>1.91</td>
<td>1.28-2.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-pentylfuran</td>
<td>1.43</td>
<td>1.09-1.88</td>
<td>0.009</td>
</tr>
<tr>
<td>ethyl-2-methylbutyrate</td>
<td>0.80</td>
<td>0.67-0.96</td>
<td>0.02</td>
</tr>
<tr>
<td>Texanol</td>
<td>1.23</td>
<td>1.00-1.52</td>
<td>0.05</td>
</tr>
</tbody>
</table>

a. Odds ratio (OR)
b. 95% confidence interval.
Odds ratio expressed as change of coefficient by 1. Odds ratios were calculated using log-transformed variables.
All analyses were controlled for age, sex atopy and smoking habits.

Table 14. Indoor variables that differ significantly between homes which has dampness or no dampness.

<table>
<thead>
<tr>
<th></th>
<th>Any dampness</th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES (GM$^a$, 95%CI$^b$)</td>
<td>NO (GM$^e$, 95%Cl$^e$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bacteria$^e$</td>
<td>19200(14800-24800)</td>
<td>14600(12100-17600)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Viable moulds$^e$</td>
<td>264(200-347)</td>
<td>186(158-220)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Total moulds$^e$</td>
<td>13700(11600-16200)</td>
<td>12200(11000-14000)</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>3-methylfuran$^d$</td>
<td>29(22-38)</td>
<td>18 (15-24)</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>2-methyl-1-butanol$^d$</td>
<td>80(52-120)</td>
<td>67(50-89)</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Ethylisobutyrate$^d$</td>
<td>2(0.16-3.3)</td>
<td>1.3(1.0-1.6)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>ethyl-2-methylbutyrate$^d$</td>
<td>40(25-64)</td>
<td>22(14-34)</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>43 (40 -46)</td>
<td>40(37-42)</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

a. Geometric mean
b. 95% Confidence interval of geometric mean
c. Colony forming unit, cfu/m$^3$
d. ng/m$^3$
e. number/m$^3$
This thesis provides evidence of an association between dampness in dwellings and the onset of mucosal, general, and dermal symptoms in prospective studies. In addition subjects living in damp dwellings have a slower remission of general symptoms and skin symptoms.

It was found in the prevalence study (Paper IV) that levels of four specific MVOC, formaldehyde and the plasticizer Texanol in dwellings were positively associated with SBS symptoms. Moreover, certain MVOC, as well as airborne moulds and bacteria, were measured at higher levels in dwellings with a history of dampness and moulds, as compared to dwellings without such reports. However, the compounds that were associated with SBS were not the same compounds that were associated with dampness and indoor moulds.

Certain biomarkers were also found to be associated with increased onset of symptoms, particularly mucous membrane symptoms. Subjects with increased levels of eosinophilic markers at baseline had an increased risk of developing general and mucosal symptoms. Increased bronchial responsiveness (reduced slope), total IgE and CRP were other biomarkers related to the onset of SBS. Furthermore, asthma at baseline was a predictor of onset of general symptoms and mucosal membrane symptoms. In addition subjects with hay fever had a higher incidence for skin symptoms and mucosal symptoms. Moreover, those who were tobacco smokers at baseline reported a higher net increase of the number of SBS-symptoms during the follow-up, as compared to non-smokers. Tobacco smoking was a risk factor for onset of SBS. Subjects who had lived in a home where indoor painting had occurred had a significantly higher increase of the number of SBS-symptoms.

Internal validity

Selection bias
Selection bias can occur, both because of an incorrect study design and as a result of a low response rate. The response rate in Paper I was 75% initially as well as in the follow-up study. The response rate in Paper II was 70%, of
these subjects 64% participated in the follow-up study. An analysis of the participants who were lost to follow-up did show that they did not differ from the participants in baseline characteristics concerning age, gender, hay fever, doctors’ diagnosed asthma, or smoking habits. Thus, no major bias due to drop-outs was expected.

The subjects in Paper III were randomly selected from the adult population in Uppsala, but with an addition of subjects with respiratory symptoms. This method of selecting subjects results in an enhanced number of subjects with asthma or other respiratory symptoms. However, an advantage of an enriched sample is that the power is increased due to higher levels of biomarkers. A problem may be that subjects with asthma or other respiratory symptoms are more sensitive compared to those in the normal population, and hence they will report more symptoms.

In Paper IV the study population was those subjects who lived in the same dwelling during the follow-up. An additional sample of subjects with dampness in their dwelling and who had not been selected in the random selection was added. The enrichment of dwellings with dampness increases the power of the study.

**Information bias**

The first two papers are solely based on self-reported data with no objective measurement and the information on cumulative indoor exposure was collected retrospectively. The questions on dampness and indoor mould used in this study have been validated in an earlier study with regard to the relationship between observed and self-reported dampness. If presence of at least one observed sign of building dampness was used as golden standard, sensitivity was 74% and specificity was 71%, respectively. In another study regarding building characteristics, mouldy odour, and signs of moisture problems in Swedish homes, it was found that the questionnaire response was a quite reliable source regarding technical parameters in the home. However, regarding dampness problems the questionnaire response was not so reliable. This indicates that sometimes, but not always, there is an agreement between observed and self-reported dampness.

The same questionnaire was used for measuring both exposure and SBS. This is a weakness and it may lead to possible recall bias. In this thesis, baseline data was chosen for exposure to reduce the risk of recall bias. To use follow-up data for exposure increases the risk for recall bias. A potential problem is the possibility that the subjects report more dampness if they have symptoms. However, earlier studies found no difference in the reporting rate of indoor dampness between symptomatic and asymptomatic sub-
jects and both groups tended to underestimate the true observed indoor dampness.

One limitation in the longitudinal studies is the long follow-up period as compared to the short recall period. Since the questionnaire asked for symptoms that occurred at least once per week during the last three months, it is likely that the follow-up will mainly capture symptoms with some persistence, and transient symptoms will be missed. This will most likely lead to non-differential misclassification.

There should be minor problems with information bias concerning biomarkers and the environmental measurements. It may well be consider as double blinded as the investigators did not know the results from the questionnaire and the laboratories that analysed the samples did not know where the samples came from. Furthermore, in the analyses of biomarkers and in the exposure in the dwelling the analyses of biomarkers were done in the same batch. However for practical reasons the analyses of microbial data and MVOC was done in different batches. Some batches could not detect a few substances so often but this should not be connected to symptoms since there are arbitrary sequences of the samples. The prevalence study is based on both questionnaire and measured exposures in the dwelling which is a strength with respect to the recall bias issue. The questionnaire has been used in other studies such as ECRHS and previous SBS studies.

External validity

The external validity is considered to be good, since all studies are based on a random sample from defined geographical areas. Paper I and Paper II are similar in many ways and the result should mainly agree. However, the results differ in some aspects. No relation between onset of symptoms and dampness in the dwelling was found in Paper I. The cross-sectional study for the baseline data for this sample performed by Norbäck and Edling found an association between indoor painting and prevalence of SBS. No association for other residential factors such as age of building, type of building, degree of crowding, mechanical ventilation, or signs of dampness or mould growth were related to symptoms. In contrast, associations between building dampness and onset of symptoms could be demonstrated in Paper II. Other inconsistent results were connections between SBS and hay fever or age.
Trends of exposures in the dwelling

Some improvements of the home environment were observed, concerning building dampness and indoor moulds. The number of water leakages and visible indoor moulds had decreased notably, possible due to better maintenance and other improvements in the dwellings. Moreover, the number of dwellings with mechanic ventilation had increased. These improvements may lead to a better indoor environment, and possibly a reduced risk of impaired health. A trend was shown in the 12 months prevalence of any building dampness, water leakage, sign of floor dampness and visible moulds since all these factors had decreased from the baseline study to the follow up. Another explanation to the improvements in the dwellings could be that subjects have moved and upgraded to an improved dwelling. In the longitudinal studies many of the dwellings had been painted indoors, and nearly a third of these had been painted indoors with solvent-based paints. The participants reported that solvent-based paint was commonly used, which is in contrast with data from professional painters who report that over 95% of the paint they use is water based 54. One explanation could be that solvent-based paint was still used in the dwellings for specific applications, e.g on wood or metal surfaces. Another explanation for the relative common use of solvent paint could be that the subjects had been doing the paint work by themselves. Also they may not know that they could use water-based paint instead of solvent-based paint.

Changes of SBS, biomarkers, hay fever, and smoking over time

The prevalence of hay fever and any type of allergy remained unchanged over time in Paper I. In contrast, the prevalence of these symptoms increased in Paper II and Paper III. This finding is not in accordance with other studies on allergy in the adult population 86 87. A major health problem in Europe is allergic diseases. These are increasing in prevalence and severity 88. There has been an increased prevalence of symptoms of rhinitis, but not of asthma, between 1990 and 2008 in Swedish adults 89. There seems to be a general trend toward a plateau in asthma in Westernised countries89.

Changes of SBS in the longitudinal studies were found in Paper II where any general symptom and any skin symptom had decreased. Overall the symptoms remained unchanged. There was no change in the prevalence of any general, any mucosal or any skin symptoms in the other studies.

There was a significant reduction of prevalence of current smokers in the follow-up of subjects. The considerable reduction of tobacco smoking in
Sweden is expected to have a positive impact on public health, with less exposure to ETS and fewer smoke-related diseases in the future. A similar trend of a decrease in smoking and ETS exposure was found in all of the three longitudinal SBS studies in this thesis. No other longitudinal study on smoking and SBS in dwellings has been found. One study has shown that exposure to ETS contributes to the prevalence of SBS-symptoms. ETS could not be studied because there were too few subjects who were smoking at home.

One of the longitudinal studies measured biomarkers and reports on exposures in the dwelling. Among the baseline biomarkers in that study, low slope (higher BR) was a predictor of the incidence of general and mucosal symptoms. Total IgE was a predictor of the incidence of mucosal and skin symptoms, ECP was only a predictor of general and mucosal symptoms, and EOS was a predictor of mucosal symptoms. Among follow-up biomarkers, low slope (higher BR) was only associated with a higher incidence of mucosal symptoms. Total IgE was associated with incidence of skin symptoms, and CRP was associated with higher incidence of mucosal symptom. There are no previous studies combining a questionnaire study of SBS longitudinally with measurements of biomarkers and indoor environments in dwellings. These findings indicate that the incidence of SBS may be related to inflammatory processes.

Personal risk factors

Age was one of the personal factors that was analysed. Only in Paper II could an association between age and mucosal symptoms be observed. However, in all the other papers there were no association between age and SBS. The evidence concerning age and SBS is not consistent in the literature. Negative association but also positive association has been found. In contrast to these, other studies have shown no association at all between age and SBS. It has been shown that persons in the age of 21 to 40 years report more symptoms than either younger or older subjects. In contrast, there are results showing that very old subjects report more symptoms than younger ones.

Females have higher incidence of general and mucosal symptoms. In many prevalence studies the female gender has been shown to be an important risk factor for SBS-symptoms. In a study on office workers females tend to report more SBS symptoms compared to men. Inequalities in social conditions did not explain the sex difference in symptom reporting. In a study on personal and psychosocial factors and symptoms compatible with SBS sit was shown that female gender was a main predictor of SBS symptoms.
Among personal factors, hay fever at baseline was positively related to onset of skin and mucosal symptoms, asthma at baseline, biomarkers of allergy and inflammation at baseline and follow-up, were related to an increased incidence of SBS, in particular mucous membrane symptoms. These findings indicate that the incidence of SBS may be related to inflammatory processes and allergy.

Other studies have found that self-reported atopy was found to be associated with SBS-symptoms, mainly with general symptoms. However, clinical diagnosed atopy and SBS-symptoms have not been shown to have any association at all. Atopy have also been shown to be a predictor of SBS-symptoms in a study on personal and psychosocial factors.

Smoking at base-line also showed to be important regarding the number of reported SBS-symptoms. In Paper I it was found that smokers at baseline reported a higher increase of symptom scores as compared to non-smokers. In addition the remission was less common in smokers. In one prevalence study some SBS-symptoms, e.g. general symptoms were related to tobacco smoking.

Building dampness

The dampness in buildings was studied. It was found that dampness in the dwelling can be a risk factor for new onset of SBS-symptoms. In one of the longitudinal studies (Paper II) it was found that any type of building dampness was associated with onset of general, mucosal, and skin symptoms. Also onset of eye symptoms and throat symptoms were much more common in damp dwellings. Moreover, an association between building dampness at home at baseline and levels of some biomarkers (CRP and IL-6) at follow-up was found (Paper III). The result was not consistent because the level of CRP was positively associated with dampness while IL-6 was negatively associated with dampness. This indicates that dampness at home may lead to mild systemic inflammation.

Onset of eye symptoms and throat symptoms was more common in damp dwellings. There are relatively few studies on dampness and SBS in dwellings. Two Japanese studies on dampness among adults in public apartment houses showed that dampness was associated with all SBS symptoms. Also, a study on newly built dwellings in Japan showed that dampness was related to SBS symptoms.
**MVOC and microbial exposure**

In the prevalence study of this thesis, total bacteria, total moulds, viable moulds, and three chemical compounds (2-ethyl-1-hexanol, 2-methylfuran and ethylisobutyrate) were positively associated with a history of building dampness and indoor moulds. The associations were stronger if including retrospective information about dampness and moulds during the last 10 years and as compare to reports on dampness and moulds the last 12 months. This shows the importance of asking retrospectively for the history of dampness and moulds over several years in dwellings, not just the last year, if the exposure is to be assessed in the best way. Positive associations with SBS were found for six of the compounds (formaldehyde, 2-pentanol, 2-hexanone, 1-octen-3-ol, 2-pentylfuran and Texanol).

There are few epidemiological studies on SBS symptoms in relation to MVOC in the home environment. There is only one Japanese study. In that study presence of some MVOC were associated with health effects 72. The compounds that were associated with SBS were not the same ones that were associated with dampness and indoor moulds. The summation of MVOC, which is used by indoor consultant companies to evaluate the dampness status of buildings, was neither associated with SBS symptoms nor with reports on dampness or moulds. This shows that summation of MVOC is no good indicator for dampness status of buildings, moulds or SBS symptoms.

**Indoor painting**

Indoor painting was associated with SBS in Paper I and II. Subjects in Paper I who lived in a home where indoor painting had occurred during the 8-year follow-up period had a significantly higher increase in number of SBS-symptoms. Furthermore, subjects in Paper II who had been painting indoors had a lower remission of general symptoms. This demonstrates that indoor painting can play an important role for remission of general symptoms and a higher increase of number of SBS-symptoms. Moreover, in Paper III an association between indoor painting and incidence of general symptoms was found, which is in agreement with the results of Paper I and II. Solvent based paint was commonly used in study I, which is in contrast with data from professional painters who report that more than 95% of the paint used is water based 54.
Conclusions and implications

The home environment is important to our health because we spend most of our time indoors and symptoms included in the SBS are common. However, little has been known about the change of these symptoms over time, or which risk factors that predict onset or remission of such symptoms. By following cohorts of adults from the general Swedish population, and by combining the longitudinal study design with questionnaire data as well as measurements of biomarkers and certain exposures in the dwelling, new knowledge has been generated. Regarding the understanding of environmental risk factors in the dwelling it also gives new knowledge of the relationship of personal factors as well as inflammatory markers and SBS. In many cases, the longitudinal studies in this thesis confirms associations reported in previous prevalence studies on SBS, e.g. for hay fever, female gender, dampness, mould and indoor paint emissions. However, for biomarkers and SBS there were few data previously, even from prevalence studies.

Within the studied cohorts it was found that the indoor environment in dwellings had improved with respect to dampness and indoor moulds, mechanical ventilation, and less tobacco smoking. Further studies are needed to clarify if this improvement is because people move to better dwellings when getting older, or if it is a real improvement in the building stock. The substantial reduction of tobacco smoking in Sweden is expected to have a beneficial impact on public health, with less exposure to ETS and fewer smoke-related diseases in the future. Despite these improvements, it was possible to demonstrate associations between certain risk factors in the dwelling, such as dampness, indoor moulds, indoor painting, and certain chemical compound in the dwelling, including some MVOC, and SBS. Some results were not consistent between the different cohorts, e.g. with respect to age, hay fever, and dampness and moulds. The partial inconsistency cannot always be easily explained, but in most cases the 95% confidence intervals were overlapping. The discrepancy illustrates a need for further longitudinal studies on risk factors for SBS in different geographical areas and countries. In the future, meta-analysis or a multi-centre approach for longitudinal SBS studies would be helpful in drawing final conclusions on the significance of different risk factors, both personal factors and environmental exposure indicators. Moreover, the studies in this thesis have only focused on adults, but recent studies from Asia have investigated SBS in children and reported significant associ-
lations for environmental and personal risk factors. This indicates a need for SBS studies on children in Europe as well. Different indoor environments for children, such as dwellings, schools and day care centers would be of particular interest.

Associations between biomarkers of allergy and inflammation and onset of SBS have been demonstrated in this thesis. The mechanism of the SBS has been unclear, and it has been suggested to be related to sensory effects as well as personal disposition and psychosocial factors. Further research is needed to study the link between inflammation and SBS. Measuring indoor exposure and biomarkers in combination with questionnaires generates a better understanding of any correlation between SBS, indoor exposures and biomarkers.

There has been considerable focus on building dampness and indoor moulds in the Swedish building stock the last decades. It is important to repair damp damages and to prevent dampness in the dwelling. There is still a need to inform the population on this issue since several studies in Sweden, the studies of this thesis as well as the large national BETSIE study have shown that building dampness and moulds are still common, both in multifamily- and single-family houses.

Studies on health associations longitudinally for self-reported dampness in dwellings, and cross-sectional associations between SBS and concentrations of some chemical compound, e.g. MVOC were performed in this thesis. However, further studies are needed for evaluation of health associations longitudinally to get a broader spectrum of dampness-related exposure indications in indoor environments.

Indoor painting is common in dwellings in Sweden and some associations between paint emissions and SBS were found in the studies of this thesis. The composition of paints have changed over time in Sweden since solvent based paints are less common nowadays, and new “solvent-free” or “low emission” water-based paints have been developed. A reduction of emissions from painting would benefit inhabitants in the dwelling. However, since baseline exposure data was used in the studies of this thesis, the results from exposure conditions 10-20 years ago are presented. There is a need for new studies on health effects of paint emissions for currently used indoor paints, both in Sweden and in other countries.

In conclusion, the indoor environment in dwellings still requires improvements. A better understanding of the indoor environments and SBS are essential. Longitudinal SBS studies could be useful for that purpose.
Sammanfattning (summary in Swedish)


Den första studien är baserad på ett slumpmässigt urval (0,1 %) av befolkningen i en 3-läns region i mellansverige (Gävleborgs, Kopparbergs och Uppsala län), inledningsvis i åldern 20-65 år (n= 466). De fick en postenkät skickad till sin bostad. Denna kohort följes upp efter 8 år genom att en liknande postenkät skickades till den aktuella adressen. Totalt svarade 348 personer (75 %) på den uppföljande enkäten. Syftet med denna studie var att undersöka förändringar av SBS och förändringar av olika typer av inomhusexponering i hemmet under en 8-års perioden (1989-1997) i ett populationsurval av vuxna från mellansverige. Därutöver undersöktes om det fanns någon skillnad i debut av SBS-symtom i förhållande till storleken på bostadsort och utbildningsnivå.

Vattenläckage eller vattenskada i bostaden under det senaste året hade minskat från 11,2 % till 4,8 %, synligt mögel inomhus hade minskat från 4,7 % till 1,6 %, och något tecken på fukt eller mögel i bostaden minskade från 16,1 % till 9,5 % under uppföljningsperioden. Prevalensen av aktuell rökning hade minskat från 30 % till 19 %. De som var rökare från början rapporterade i högre grad debut (incidens) av SBS-symtom än icke-rökare. Därtill var tillfrisknande (remission) av slemhinnesymtomen mindre vanligt hos rökare. Personer som bodde i bostäder som målats om någon gång under uppföljningsperioden hade en högre incidens av SBS-symtom, och de med mellannivå av utbildning (gymnasium men inte universitet) hade oftare debut av hudsymtom. Sammanfattningsvis hade rökning minskat drastiskt under uppföljningsperioden och inomhusmiljön i bostäderna hade förbättrats. Detta kan ha bidragit till en förbättrad folkhälsa. Rökning och målning inomhus var signifikanta riskfaktorer för SBS. Ytterligare longitudinella studi-
er av SBS behövs som kan identifiera andra riskfaktorer än de som hittills identifierats i prevalensstudier av SBS.


**Den tredje studien** är baserad på data från Uppsaladelen av Europastudien över Luftvägar och Hälsa (European Community Respiratory Health Survey: ECRHS). ECRHS är en multicenterstudie som omfattar ett slumpmässigt urval av personer i åldern 20 - 44 år. I Uppsala påbörjades studien 1992. Ett slumpmässigt och ett symtomatiskt urval av personer från varje centrum gjordes av de som hade besvarade den inledande postala enkäten. De fick sedan svara på ett mer detaljerat och intervjuaserat frågeformulär. De fick också genomgå olika typer av kliniska undersökningar såsom att lämna blodprov för mätning av den totala och specifika IgE, pricktest mot allmänna allergen, spirometri och metakolintest. Det primära syftet med studien var att undersöka incidens och remission av SBS-symtom hos vuxna i Uppsala kommun i förhållande till (a) astma vid baseline, (b) biomarkörer vid baseline och uppföljning och (c) utvalda hemexponeringsfaktorer vid baseline, inklusive fukt och mögel i byggnaden. Ett andra syfte var att analysera förändringar i inomhusexponeringar i hemmet under 10 års uppföljning (1992
till 2002). Slutligen studerades samband mellan de analyserade biomarkörerna och fukt och mögel i hemmet.

Den 10-åriga incidensen av allmänna, slemhinnor och hudsymtom var 12.7 %, 25 % respektive 7.7 %. Fukt och mögel inomhus vid baseline var en prediktor för debut av allmännsymptom, slemhinnesymptom och hudsymptom. Kvinnor hade högre incidens av allmännsymptom och slemhinnesymtom än män. Ommåling av bostaden inomhus gav ökad incidens av allmännsymtom. Bronkiell reaktivitet (BR), eosinofila granulocyter i blod, och totalt IgE och eosinofilt kationiskt protein (ECP) i serum vid studiestart var prediktorer för incidens av SBS. BR, total-IgE och C-reaktivt protein (CRP) i slutet av studieperioden hade samband med ökad incidens av SBS. Dessutom hade personer med läkardiagnosticerad astma vid baseline en högre incidens av allmännsymptom och slemhinnesymtom.

Studien kunde visa att fukt och mögel i bostaden och vissa biomarkörer för allergi och inflammation var oberoende prediktorer för incidens av SBS-symtom, i synnerhet slemhinnesymtom. Dessutom visade studien att kemiska emissioner från inomhusmåling kan påverka incidens av allmänna symtom. Den betydande förbättringen av inomhusmiljön i bostäder i Uppsala tillsammans med den minskade förekomsten av rökning visar att det pågående förebyggande miljörarbete har haft en positiv effekt. Det finns dock fortfarande ett behov av ytterligare förbättringar, bland annat genom en minskning av förekomst av fukt och mögel i svenska hem.

**Den fjärde studien** bygger på data från Uppsala, Reykjavik och Tartu från ECRHS II-studien. Fördelningen av personer per centrum var 40 % från Uppsala, 19 % från Reykjavik och 41 % från Tartu, totalt 159 personer. Av dessa var 57 % kvinnor.

Syftet med denna studie var att undersöka om luftburna nivåer av flyktiga ämnen av mikrobiellt ursprung (MVOC), bakterier, mögel, formaldehyd, Texanol och TXIB i bostäder i norra Europa har ett samband med förekomsten av SBS. Dessutom undersökt om det fanns ett samband mellan nivåerna av MVOC och rapporterad fukt och mögel i bostaden.


Totalt rapporterade 30,8 % något SBS (20 % slemhinnesymtom, 10 % generella symtom och 8 % hudsymtom) och i 41 % av bostäderna hade det före-
kommit fukt och mögel Det fanns positiva samband mellan något SBS och halter av 2-pentanol, 2-hexanon, 2-pentylfuran, 1-okten-3ol, formaldehyd och 2,2,4-trimethyl-1, 3-pentandiol monoisobutyrat (Texanol). Endast 1-okten-3ol hade ett samband med slemhinnesymptom, OR= 1,80 (1,14–2,83). I bostäder med fukt och mögel var de totala halterna av bakterier, total mögel, levande mögel, 2-metylfuran och ethyl-iso-butyrat högre jämfört med i torra bostäder.

Inomhushalter av 2-pentanol, 2-hexanon, 1-octene-3-ol och 2-pentylfuran hade ett positivt samband med SBS-symtom. Eftersom ingen av dessa föreningar hade något samband med rapporter om fukt och mögel, är det osäkert om de kom från bakterier under tillväxt eller fuktigt byggnadsmaterial. Därutöver kan formaldehyd och mjukgöraren Texanol vara riskfaktorer för SBS. Inomhuskoncentration av luftburet mögel, bakterier, 2-ethyl-1-hexanol, 3-metylfuran och etylisobutyrat var förknippade med rapporterad fukt och mögel, vilket illustrerar att det finns en signifikant men svag korrelation mellan enkätens uppgifter om fukt och mögel i bostäder och uppmätta halter av vissa mikrobiella föroreningar.

Sammanfattningsvis har inomhusmiljön förbättrats över tiden, men ytterligare förbättringar behöver göras för att minska förekomsten av fukt och mögel. Incidensen för allmänna symtom, hudsymtom och slemhinnesymtom är högre om man har fukt och/eller mögel i bostaden. Även vissa biomarkörer för allergi och inflammation är obberoende prediktorer för incidens av SBS-symtom, i synnerhet slemhinnesymptom. Inomhushalter av vissa MVOC har ett positivt samband med något SBS symtom. Rökning och målning inomhus är riskfaktorer för SBS. Longitudinella studier av samband mellan SBS och olika typer av inomhusexponering identifierar andra riskfaktorer än de som hittills identifierats i prevalensstudier av SBS.
Acknowledgement

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1. WHO. Strategic approaches to indoor air policy-making. WHO European Centre for Environment and Health, Bilthoven 1999.


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.