INDOOR DAMPNESS AND MOULD IN PRIMARY SCHOOLS AND RESPIRATORY HEALTH IN CHILDREN

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'…Man must be able to breathe, drink, eat and live in the environment trusting on its safety. This is both an individual's civil right and a prerequisite for a functioning society and economy…'

Environmental Health Department-KTL (Finland)

ABSTRACT

Introduction

Several studies have shown that the occupants of damp or mouldy buildings have an increased risk of respiratory symptoms, respiratory infections and exacerbation of asthma. However, information on the school environment in this context is limited and hence more studies are needed. Dampness-related health effects may be associated with different indoor pollutants, but the causal mechanisms and aetiological agents are still largely unknown. Included in the HITEA project, this thesis aims to assess qualitatively and quantitatively the occurrence of moisture problems in school buildings in three European countries from different climatic regions and to study the respiratory health effects associated with dampness and mould in schoolchildren.

Methods

First, a questionnaire survey and school inspection visits were conducted to assess moisture damage, dampness problems and other indoor air quality issues in primary schools in the three countries under study. The questionnaire, addressed to the principals of the schools, included questions on current and past dampness, moisture, and mould observations and also collected background information on building and ventilation characteristics and renovation plans. Secondly, we carried out an extensive questionnaire survey on respiratory health of pupils aged 6-12 years, in at least eight moisture-damaged and eight non-damaged schools per country. The parent-administered questionnaire assessed the respiratory health status of the pupils using questions from the validated International Study of Asthma and Allergies in Childhood.

Results

(i) Moisture problems were relatively common in schools in all three climatic regions across Europe. Spanish school buildings had the highest prevalence of moisture problems, followed by The Netherlands and Finland (ii) Overall, the data from the questionnaires regarding moisture damage prevalence in school buildings was consistent with the data from the inspections. Nevertheless, the variation in agreement between countries was high (iii) Dampness and mould in schools were associated with adverse respiratory symptoms in pupils (most consistent for nocturnal cough).

Conclusions

Dampness and mould in schools may have respiratory adverse health effects in children, especially in Finland. Finnish school children seem to be at higher risk, possibly due to quantitative and/or qualitative differences in exposure, due to variations in climate and building characteristics. Thus, prevention and remediation measures should be considered to reduce dampness and mould problems in school buildings to protect pupils' health.

RESUMEN

Introducción

Diversos estudios han observado que los ocupantes de edificios con problemas de humedad o moho tienen más riesgo de padecer síntomas respiratorios, infecciones respiratorias y exacerbación asmática. Aún así, la información sobre el entorno escolar en este contexto es limitada y por ello más estudios son necesarios. Los efectos en la salud relacionados con la humedad en los edificios pueden estar asociados con diferentes contaminantes interiores, pero los mecanismos causales y los factores etiológicos siguen siendo desconocidos. Incluida en el proyecto HITEA, esta tesis pretende evaluar cualitativa y cuantitativamente la prevalencia de edificios escolares con problemas de humedad en tres países europeos de tres regiones climáticas distintas y estudiar los efectos en la salud asociados a la humedad y el moho en sus alumnos.

Métodos

En primer lugar, se realizaron cuestionarios e inspecciones en los colegios de los tres países a estudio, para evaluar los posibles daños y problemas relacionados con la humedad y otros factores asociados con la calidad del aire interior. Los cuestionarios dirigidos a los directores de las escuelas incluyeron preguntas sobre observaciones de humedad y moho, en la actualidad y en el pasado. También se recogió información sobre las características de los edificios, su sistema de ventilación y futuros planes de reforma. En Segundo lugar, se llevó a cabo un amplio cuestionario sobre salud respiratoria en los alumnos de entre 6 y 12 años, en al menos 8 escuelas con problemas de humedad y 8 escuelas sin problemas. El cuestionario administrado a los padres de los alumnos evaluó la salud respiratoria de los niños utilizando preguntas del cuestionario internacional validado ISACC(International Study of Asthma and Allergies in Childhood).

Resultados

(i) Los problemas de humedad en los edificios escolares eran relativamente comunes en las 3 regiones climáticas europeas. Las escuelas españolas presentaron una mayor prevalencia de problemas de humedad, seguidas de Holanda y Finlandia. (ii)En general, los datos de los cuestionarios sobre la prevalencia de los daños provocados por la humedad en los colegios fueron consistentes con las inspecciones. Sin embargo, se observó una elevada variación de la concordancia entre países.

(iii)Los problemas de humedad y moho en los edificios escolares se vieron asociados con síntomas respiratorios adversos en los alumnos (de forma más consistente para 'tos nocturna').

Conclusiones

Los problemas de humedad y moho en los edificios escolares podrían tener efectos adversos en la salud respiratoria de los niños, especialmente en Finlandia. Los alumnos finlandeses parecen tener más riesgo, posiblemente debido a diferencias cuantitativas y/o cualitativas en la exposición. Esto podría estar relacionado con las diferentes características de los edificios y con la variabilidad climática. Así pues, para proteger la salud de los alumnos se deberían considerar diversas medidas de prevención y reparación de los problemas de humedad y moho en los edificios escolares.

PREFACE

This thesis represents a compilation of the scientific publications coauthored by the PhD candidate, and supervised by Dr Jan-Paul Zock and Prof. Jordi Sunyer, according to the procedures of the Biomedicine PhD program of the Department of Experimental and Health Sciences of Pompeu Fabra University. The book includes an abstract, a general introduction with a review of the relevant literature, the thesis' rationale and objectives, the research results (two original papers), a global discussion, final conclusions and a third paper included in the annex. Most of the work, that included data gathering, management and analysis, was performed by the PhD candidate at the Centre for Research in Environmental Epidemiology (CREAL) in Barcelona (Spain) and part of it at the Institute for Risk Assessment Sciences (IRAS) in Utrecht (The Netherlands).

The thesis focuses on the respiratory health effects associated with dampness and mould in school children in 3 different climatic regions across Europe : Spain, the Netherlands and Finland. It includes two papers: *1) Occurrence of moisture problems in schools in three countries from different climatic regions of Europe based on questionnaires and building inspections: the HITEA study and 2) Dampness and mould in schools and respiratory symptoms in children: the HITEA study*. These two publications are based on data collected in the framework of the European HITEA project (Health Effects of Indoor Pollutants: Integrating microbial, toxicological and epidemiological approaches), funded by the 7th Framework Program. Apart from the original papers included in this thesis, the PhD candidate has actively participated and co-authored four other papers in the context of the HITEA project. (Annex II)

CONTENTS

1. INTRODUCTION

1.1 Respiratory and allergic diseases in children

1.1.1 Paediatric asthma definition: the clinical and epidemiological approaches

Asthma is a heterogeneous condition with different clinical presentations that can start at any age (Tarlo et al., 2010; Global Initiative for Asthma: GINA, 2015). This is due not only to the absence of a single biological marker or clinical test for asthma, but also to the variety of symptoms, multiple aetiology factors, heterogeneous responses to treatment, and differing outcomes (Sears et al., 1997). Given to the various different phenotypes of childhood asthma that make it difficult to agree on a clear definition of the condition, an operational description is used: 'Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment'(GINA, 2012).

Most cases of chronic asthma start with wheezing during pre-school ages. At these ages, wheezing is typically associated with upper respiratory tract infections and whether these first wheezing episodes are the initial episodes of asthma can only be determined by its evolution. Therefore, having a longitudinal perspective of asthma symptoms during childhood is crucial for the correct assessment of asthma.

Childhood asthma phenotypes have been defined by two different approaches. From a clinically oriented perspective or symptom-based classification that has been based on patient histories, diagnostic techniques, and treatment responses; and from an epidemiologic point of view or time-trend based classification (Depner et al., 2014).

- Symptom-based classification: this is based on whether the child has only episodic viral wheeze (wheezing during discrete time periods, often in association with Upper Respiratory Tract infections, with symptoms absent between episodes) or multiple trigger wheeze (episodic wheezing, being caused by various triggers besides infections, with symptoms also occurring between episodes: during sleep, physical activity…). Another distinct phenotype ('frequent wheeze') has been proposed recently which is related with severity of symptoms and defined by a higher frequency of wheezing episodes (usually more than three per year) (Depner et al., 2014).

- Time-trend based classification: this system was based on the analysis of data from a cohort study (Martinez et al., 1995) and it included three major groups. Early transient wheeze: symptoms began and ended before the age of 3 (wheezing was correlated to maternal smoking but not maternal asthma); persistent wheeze: symptoms began before the age of 3 and continued beyond the age of 6; and late-onset wheeze: symptoms began after the age of 3 and persisted. These last two groups had clinical features of atopy, high IgE levels, positive skin tests and a strong family history of asthma. This classification has been further confirmed and extended in other birth cohort-based studies (Martinez 1995; Depner 2014).

In addition, different studies suggest that most of the deficits in lung function growth observed in children who have asthma occur in children whose symptoms begin during the first 3 years of life and continue beyond the age of 6 (Martinez et al., 1995). The onset of symptoms after 3 years of age is not usually associated with significant deficits in lung function growth. Thus, a promising target for interventions designed to prevent deficits in lung function, and perhaps the development of more severe symptoms later in life, would be children who are 'persistent wheezers' and have higher chances to develop persistent asthma later in life.

The Expert Panel Report (National Heart, Lung and Blood Institute: NHLBI, 2007) have organized recommendations for asthma care around four components considered essential to effective asthma management:

- Measures of assessment and monitoring (obtained by objective tests, physical examination, patient history and patient report) in order to diagnose and assess the characteristics and severity of asthma and to monitor whether asthma control is achieved and maintained.

- Education for asthma care (encouraging physical activity for example) (ERS: European Respiratory Society, 2013).

- Control of environmental factors and comorbid conditions that affect asthma.
- Pharmacologic therapy (NHLBI, 2007).

Related to medication, modern guidelines for treating childhood asthma distinguish between controlling and relieving treatment. Among the controlling treatments, inhaled corticosteroids are the preferred therapy for initiating long-term control therapy in children of all ages (ERS, 2013). Moreover, they are generally safe, especially at low doses and even for extended periods of time. (NHLBI, 2007)

1.1.2 Prevalence of asthma and allergic diseases: geographical variation and time trends

Approximately 30 million children and adults under 45 years of age have asthma in Europe (ERS, 2013), and 300 million people in the World have been diagnosed with the disease (Braman, et al. 2006). Asthma is the most common chronic non-infectious disease in childhood (ERS, 2013). Around the world, there are significant variations in the prevalence of childhood asthma. The ISAAC study investigated worldwide trends in prevalence and severity of asthma and allergies in children and showed variations across regions in the prevalence of asthma, asthma symptoms, rhinitis, and eczema (Asher et al., 1995). In the first phase, the results showed variations across regions in the prevalence of respiratory and allergic disorders and symptoms. In particular, they observed differences in the prevalence of asthma, asthma symptoms, rhinitis, and eczema (ISAAC Steering Committee, 1998a). They concluded that together with New Zealand, Australia and Ireland, the United Kingdom (with around a 20% prevalence) had one of the highest prevalence rates of asthma symptoms in the world (ISAAC Steering committee, 1998b; ERS 2013). In Europe, although childhood asthma has historically been more prevalent in Northern and western European countries, the difference seem to be diminishing as rates in the East are rising (ERS, 2013).

Asthma prevalence increase

Studies on the prevalence of childhood asthma and allergic diseases agree that these diseases have increased during the last decades (Asher et al., 1995; Richardson et al., 2005) in both industrialized and developing countries, although the current tendency is much higher in the latter. This indicates that the global burden of respiratory disorders is continuing to rise and that the global differences in prevalence tend to become smaller

(Asher et al., 2006; Pearce et al., 2007). It has been suggested that the rising number of cases indicates a tendency to over-diagnose childhood asthma; however, some researchers claim that, in fact, asthma is under-treated (Richardson et al., 2005). In Europe, childhood asthma has increased in the second half of the 20th Century, being higher on the whole in Western versus Eastern European countries. For example, published studies of asthma among schoolchildren in Norway report that asthma increased from 0.4% in 1948 to 12.3% in the mid-1990s, and to 20% in 2004. However, the most recent study reported a prevalence of only 17.6% in 2008 (ERS, 2013). Referring to childhood wheezing, the prevalence has also increased in Britain, Australasia, Scandinavia, Israel and Taiwan, although the magnitude of the increase varies considerably between studies (Asher et al., 1995). Thus, although some authors have observed recent trends suggesting that asthma rates have begun to decline or stabilize (Björksten et al., 2008; Williams et al., 2008), this disease remains the leading chronic illness affecting children worldwide (ERS, 2013).

Rhinitis or hay fever prevalence increase

Rhinitis is characterised by hypersensitivity symptoms from the nose, such as: itching, sneezing, increased secretion, and blockage. This condition can be seasonal or perennial and may be labelled as allergic rhinitis (when immunologically mediated and a causative allergen is identified) or non-allergic (Sibbald et al.,1991; Johansson et al., 2004). The estimated prevalence of hay fever among school children in different countries has been reported to vary between 0.5 and 28%, but much of this variation is likely to be due to the diagnostic criteria and age group chosen (Strachan et al., 1997). The prevalence of reported hay fever has increased in the United States, Sweden, and Britain in recent decades. These trends may reflect changes in the perception and labelling of symptoms, or in presentation for medical diagnosis and treatment. Alternatively, they may reflect an increased propensity to allergic sensitization in successive generations probably related to the urbanization process (Asher et al., 1995).

Eczema prevalence increase

Eczema, an important skin disease worldwide (Williams et al., 2008), 'includes several skin diseases with certain clinical characteristics in common, involving a genetically determined skin barrier defect'. In atopic children (atopic eczema) the underlying inflammation is dominated by an IgE-antibody-associated reaction (Johanson et al., 2004). Geographical variations in the prevalence of eczema in children have been described in Britain, and these closely match the regional variations in hay fever (Asher et al., 1995). Data from British and Danish studies, suggest that eczema has increased and is more common amongst recent generations of children. Studies of children whose parents have migrated from developing to developed countries suggest that eczema, as hay fever, could be related with urbanization and decreased infectious morbidity in childhood; however, the causes are still unclear and are probably multifactorial (Asher et al., 1995; Savilahti et al., 2001).

Savilahti et al. concluded that the prevalence of these atopic conditions (hay fever and eczema) had approximately doubled in recent decades and, suggested that the increase in asthma and wheezing may result from this increase in atopy among children (Savilahti et al., 2001). On the other hand, some authors have stated that the prevalence of these atopic diseases, such as asthma, seems to be levelling or decreasing in developed countries and increasing in low-income countries (Björksten et al., 2008; Williams et al., 2008)

1.1.3 Risk factors for asthma and potential explanations for time trends

Much research has been conducted into the reasons why some individuals rather than others develop asthma and other atopic diseases, such as rhinitis and/or eczema. Both genetic and environmental factors have been proved to be associated with the prevalence and/or attacks of asthma (Asher et al., 1995). These include personal factors such as age, sex, nutritional status, number of siblings, coexisting lung diseases, lifestyle, allergy status, family history, and environmental stimuli such as house dust, animal dander, moulds, respiratory virus, cockroach infestation, environmental tobacco smoke, indoor/outdoor air pollution, cooking fumes, aeroallergens and climate (Lee et al., 2003). According to the US Institute of Medicine, there are eight indoor agents that may be associated with asthma exacerbation in school-aged children. These are cat, dog, dust mite, and cockroach allergens, fungi, rhinovirus, environmental tobacco smoke and nitrogen oxide species (IOM 2004; Cai et al., 2011).

Respiratory virus infections are the major cause of acute bronchiolitis in infancy and of acute asthma attacks among older asthmatic children. More than half of the children under 2 years of age hospitalised due to respiratory syncytial virus (RSV) bronchiolitis, develop asthma later. In addition, it has been observed that the majority of acute asthma attacks are precipitated by respiratory virus infections. (ERS, 2013). Probably related to an increase in virus infections, attendance at a day care centre has been also associated with an increased risk in wheezing illness in children under 2 years of age (Sears et al., 1997). In addition to respiratory infections, exposure to other risk factors related to indoor air quality are associated with increased risk of asthma. More than half percent of all school-age asthmatic children are allergic. From 2 years of age, inhalant allergens have been related to childhood asthma, being animal dander one of the most frequent in Europe. In a warm and humid climate, house dust mites and moulds are also important. Allergen exposure may cause acute asthma exacerbations and may increase airway inflammation and bronchial hyperresponsiveness (ERS, 2013).

In addition, several studies have demonstrated that parental smoking increases the risk of both asthma and poorer lung function during childhood (ERS, 2103). Already in the TUCSON study (Martinez et al., 1995), parental smoking was primarily a risk factor for childhood cough without wheezing, while being male, maternal allergy, wheezing, Low Respiratory Tract Iinfections and high levels of IgE were risk factors for cough with wheezing (Sears et al., 1997). The influence of family income in asthma prevalence has been debated too. While children from poorer families may have a higher prevalence of wheezing, children from better off families are more likely to receive a diagnosis of asthma and treatment for asthma, reflecting different levels of access to health care (Sears et al., 1997). Finally, other studies have confirmed the effects of mould exposure at home, especially when it occurs early in life, on the prevalence of respiratory disorders such as asthma, rhinitis and cough in the paediatric age (WHO 2009, Tischer et al., 2011b).

The reasons for the increasing trends and the enormous geographical variations worldwide in asthma and atopy among children are not entirely understood (Heinrich et al., 2011). The change has been too rapid to be the result of genetic factors. It is also unlikely that the increase is the result of changes in clinical diagnostic patterns or increased recognition of asthma symptoms by the general population (Lee et al., 2003).

This suggests that environmental exposures and/or changes in lifestyle factors may be behind this epidemic. Air pollution and increased exposure to environmental tobacco smoke have been considered environmental risk factors for asthma. Decreased protection against the development of atopy (by reducing breastfeeding and antioxidant intake) and a lower frequency or severity of early childhood infections ('hygiene hypothesis') may have a role too (Sears et al. 1997; Ege et al., 2011). Some previous studies have also stressed the importance of indoor pollutants (such as moisture and mould) as a possible cause of the increase in childhood asthma (Taskinen et al., 1997 and 1999). However, in relation to air pollution as a risk factor for asthma, regions such as China and Eastern Europe, with some of the highest levels of air pollutants generally have had low rates of asthma prevalence and some areas with the lowest levels of air pollution, such as New Zealand, have had high rates of asthma prevalence (ISAAC Steering Committee, 1998b).

Regarding the 'hygiene hypothesis', epidemiological studies on bacterial components have been contradictory. Some have demonstrated protective effects of bacterial exposure both on atopy and respiratory symptoms (Douwes et al., 2004; Radon et al. 2006), while others showed associations with increased asthma symptoms, medication use and degree of airflow obstruction in children and adults with asthma (Michel et al. 1996; Zhao et al., 2008).

According to Heinrich et al. (2011), the "hygiene hypothesis," in concert with the 'western lifestyle factor pattern,' seems to be the best candidate we currently have to explain the trends of this 'asthma epidemic' (Heinrich et al., 2011). If this effect of 'westernization' is confirmed, and the urban population of the world increases as predicted, it is likely that the asthma prevalence will keep increasing worldwide over the next decades (GINA, 2004).

1.2. Indoor dampness and mould

1.2.1 Definitions and sources of moisture, dampness and mould

There is a wide variation in the definition of the term 'dampness' (Bornehag et al. 2001, 2004). But, following the definition of the World Health Organisation (WHO), dampness can be described as "any visible, measurable or perceived outcome of excess moisture that causes problems in buildings, such as mould, leaks or material degradation, mould odour or directly measured excess moisture (in terms of relative humidity or moisture content) or microbial growth" (WHO, 2009). Regarding mould, the WHO defines it as 'all species of microscopic fungi that grow in the form of multicellular filaments, called hyphae'. Moisture is defined as 'water vapour or water in a medium, such as soil or insulation, but not bulk water or flowing water. In addition, moisture problem/damage or water damage is any visible, measurable or perceived outcome caused by excess moisture indicating indoor climate problems or problems of durability in building assemblies'. Moisture damage is a particular problem of building assembly durability and water damage is a moisture problem caused by various leaks of water (WHO, 2009).

Studies performed to date have used numerous indicators to assess dampness: 'Visible mould ', 'Damp stains', 'Condensation on window panes and/or walls ', 'Water damage', 'Smell/odour', indicating different dampness sources. These indicators are related to different problems in the building. 'Visible mould' and 'condensation' are indications of high relative humidity in indoor air in combination with cold surfaces. 'Damp stains and spots', 'damp water damage', 'bad smell and odour' and 'flooding' are often indications of moisture in the construction (Bornehag et al., 2001).

There are four main sources of dampness and moisture in buildings:

1. Leakage of rain and snow into the building construction or moisture from the ground: outdoor sources.

2. Moisture from human and indoor activities, such as cooking, bathing, human expiration, humidifiers: indoor sources.

3. Moisture within the construction materials from when the buildings were erected, due to insufficient protection against rain and snow, or due to insufficient time to dry out (for example humidity in concrete floors).

4. Water leakage from pipes, flooding and other types of accidents or unattended plumbing problems. (Bornehag et al., 2001; Holme et al., 2010; Krieger et al., 2010; Tarlo et al., 2010).

1.2.2 Building characteristics associated with dampness and mould

Different housing characteristics and climate conditions are possible explanations of the wide variation in frequencies and characteristics of moisture problems worldwide. The building characteristics that have been associated with dampness/moisture damage are: age, size and type of building, type of foundation, building frame material, amount of thermal insulation, lack of central heating, use of natural ventilation or poor ventilation and indoor Relative Humidity (Zock et al., 2002; Haverinen-Shaughnessy et al., 2006; Bornehag et al., 2005; Garrett et al., 1998). According to a Swedish study that observed building characteristics and other factors associated with reports on 'dampness' in single-family houses, no particular building characteristic could be pointed as the most important factor responsible for reports of moisture-related problems. But the following factors were frequently associated with different reported signs of moisture and odours: type of house (such as flat-roofed), older constructions, type of foundation (such as concrete slab ground foundation), natural ventilation system, former renovation due to mould or moisture and rented houses. However, more research is needed between the association of different types of moisture problems and building characteristics (Hagerhed-Engman et al., 2009).

Regarding the type of ventilation system, a study found an association between natural ventilation and higher occurrence of mould spores in the indoor air (Holme et al., 2010). A possible explanation was related to a lower ventilation rate in the houses with natural ventilation, compared to the houses with mechanical ventilation (Bornehag et al., 2005). Higher ventilation rate could be associated with decreasing moisture content in indoor air, followed by a lower risk of condensation and mould growth. Another explanation could be that mechanical ventilation usually filters the incoming air. They also found an association between mould and houses with a fireplace for solid fuels. Air contaminated with spores from the basement / cellars might have entered the house through the open fires. Moreover, the wood could be a source for mould growth too (Holme et al., 2010).

1.2.3 Indoor dampness: prevalence and geographical variation

Prevalence of Indoor dampness and mould

Data from the statistical office of the European Union (Eurostat) revealed that 10 to 50% of the European homes had self-reported problems of dampness between 1995-

2001, with huge regional differences across Europe. These data also showed a decrease in the percentage of damp homes in nearly all European countries during this period of time (Heinrich et al., 2011). In addition, a review of studies in several European countries, Canada and the United States in 2004 indicated that at least 20% of buildings in these countries had one or more signs of dampness (Institute of Medicine, 2004). This estimate coincides with a study done in some Nordic and Easter countries, which gave an overall prevalence of indoor dampness of 18%, with the lowest prevalence in Sweden (12.1%), and the highest in Estonia (31.6%) (WHO, 2009).

Although limited data is available for low-income countries, several studies suggest that indoor dampness is also common in this other areas of the world. For example, a dampness self-reported study in rural Taiwan showed that 12.2% of the parents considered their dwelling to be damp and 60% reported visible mould and/or water damage and/or leaks (WHO, 2009). A study in the Gaza Strip, showed that 56% of the dwellings had visible mould on the walls and ceilings, observing the highest prevalence in the refugee camps (WHO, 2009). As dampness is more likely to occur in houses that are overcrowded and lack appropriate heating, ventilation and insulation (Institute of Medicine 2004), the prevalence of indoor dampness in low-income communities in developed countries can also be substantially higher than the national average. For example, a study in eastern Germany showed that the children of parents with a low educational level were almost 5 times more likely to live in damp houses than those of parents with a higher level of education (WHO, 2009). Thus, indoor dampness has to be considered an important public health issue in low-income countries and deprived neighbourhoods from developed countries (WHO, 2009).

Geographical variation of indoor dampness and mould

The NORDDAMP review concluded that the outdoor climate was important for the prevalence of different indicators of dampness (Bornehag et al., 2001). Thus, we can presume that different parts of the world will have different types of dampness problems (Hersoug et al., 2005). In tropical climates, mould and water damage are found in many buildings with a typical prevalence of 23–79%. In cold areas, such as the Scandinavian countries, dampness indicators are typically found in 4–25% of the buildings. However, mouldy odour and hidden moisture problems in the building structure are more frequently reported in the latter (Bornehag et al., 2001; Hagerhed-Engman et al., 2009).

In addition, the cold outdoor climate in Nordic countries generates a low relative humidity indoors during the cold season, often less than 15–30%. On the other hand, visible mould on indoor surfaces in buildings is rare in Scandinavia. In Nordic countries, moisture damage is more often caused by precipitation, leakage from pipes, built-in moisture (Bornehag et al., 2001) or moisture from the ground, and not so often by condensation on indoor surfaces, which is the common case in warmer and more humid climates (Hersoug et al., 2005; Hagerhed-Engman et al., 2009). In relation to mould exposure, some studies observed a big difference in mould spore levels in subtropical and tropical climates compared to cold Nordic climates (Holme et al., 2010). In the latter, mould spore concentrations tended to be low (around 10^2 cfu/m3), as fungal outdoor air concentrations decrease seasonally because of snow cover (Meklin et al., 2002).

1.2.4 Indoor exposure assessment of building dampness

Exposure can be defined as 'an event during which people come into contact with a pollutant at a certain concentration during a certain length of time'. In most cases, however, exposure defined in this way cannot be determined with any confidence, and exposure indicators are used instead (WHO, 2009).

Methods to estimate the presence of moisture damage, dampness and mould in buildings include the use of questionnaires, visual inspection of buildings, and environmental sampling. The use of questionnaires is a relatively easy and economic method to use (Haverinen-Shaughnessy et al., 2005). Moreover It can be considered an efficient method as demonstrated by a study of moisture problems in Finnish dwellings. The authors found that about two thirds of moisture problems in the buildings could be found by non-destructive methods, such as careful visual inspection (WHO, 2009). A more objective approach (but not necessarily a more valid one) might be to measure the airborne or surface concentrations of indoor pollutants, such as the amount of pollutant per cubic metre of air or per gram of house dust. These are, however, generally relatively crude proxies of the true exposure and thus can lead to at least some misclassification of exposure and subsequent bias reference. In addition, air sampling methods have major limitations (for example spatial and temporal variance of fungal levels) in assessing exposure to mould and other biological agents that may interfere with the demonstration of associations of microbial exposure with health (WHO, 2009).

Qualitative methods: questionnaires and inspections

Self-reported data are the basis used for assessing house dampness in most epidemiological studies, and questionnaires are therefore the method chosen. The questions typically ask for information on whether conditions such as leaks, flooding, wet basements, window condensation, extent of water damage and dampness, visible fungal growth or mouldy odours are or have been present. Depending on the type of questions, the level of detail requested and the judgement of the people filling in the questionnaire, prevalence estimates may vary widely (Haverinen-Shaughnessy et al., 2005). Self-reporting, which is subjective, may be a source of report bias in cross-sectional studies (Dales et al.,1997). Although other studies have shown that such error is unlikely to happen (Verhoeff et al., 1995; Zock et al., 2002). To overcome the problems associated with the bias of self-reporting, trained inspectors have been used in several studies to visit houses and assess indoor dampness. A study confirmed that studies assessing moisture damage in buildings should preferably include standardised inspections by trained staff (Haverinen-Shaughnessy et al., 2001a and 2005). This method has the advantage of being more objective; nevertheless, it often lacks the longer perspective provided by occupants.

Semi-quantitative methods

The semi-quantitative dampness/mould exposure indexes offer an alternative to the questionnaires described above that only provide yes/no answers. These last studies often dichotomize exposures in entire buildings, or in rooms within buildings into damp/not damp (Bornehag et al., 2001). However, semi-quantitative methods of assessing exposure to dampness/mould based on visual and olfactory classifications may provide a more adequate information to assess possible exposure–response relationships (Haverinen-Shaughnessy et al., 2003). Haverinen-Shaughnessy et al. (2001b) described the advantages of a three-level classification of water-damage for entire residential buildings, using both the number of damaged sites and the damage severity. This index better predicted health symptoms than a two-level (no/minor versus moderate/severe water damage) classification. Another study, used a four-level classification of water-damage index, based on the percentage of area stained in different parts of each room and measuring the time spent in different areas. They observed that this exposure index was able to predict building-related respiratory symptoms and diseases (Park et al., 2004). Thus, for future exposure assessments in epidemiologic studies, the extent of these dampness factors and the time spent exposed (a part from the presence of dampness, visible mould, mould odour, or moisture) should also be considered as they seem important factors for predicting building-related respiratory diseases (Park et al. 2004).

Quantitative methods

Measuring instruments (including hand-held moisture detectors, relative humidity and temperature monitoring devices) are useful to complement visible observations. Some investigators tend to use a borescope to look for mould growth behind walls without significantly damaging the drywall. A borescope is 'an optical probe, inserted through a small hole drilled into a wall, that lets an investigator inspect a small portion of the wall without causing extensive damage'. Humidity gauges may be also useful for checking or monitoring humidity throughout the building. In addition many inspectors also use moisture meters to find wet areas. These meters measure the moisture in many types of building materials, such as wood, brick or concrete. They can also have a thin probe that can be inserted into the material to be tested or pressed directly against its surface (US Environmental Protection Agency: EPA).

The assessment of indoor concentrations of microorganisms (mainly fungi and bacteria) presents distinct challenges. The microbial levels needed to cause health problems can be different depending on the microorganism. Certain fungal spores are easily identified and counted, while many bacteria are difficult to characterize (WHO, 2009). Of the wide range of fungal and bacterial groups in the indoor environment, *Aspergillus, Stachybotrys, Penicillium and Cladosporium* are commonly found in moisture damaged buildings (IOM, 2004). Sensitive, specific methods are available for quantifying some microbial agents, while there are no good methods for others. Many of the newly developed methods have not been well validated and are often unavailable commercially. Even with some well-established methods (e.g. the Limulus amoebocyte lysate assay for measuring bacterial endotoxins in dust), significant variations in concentrations have been found (WHO, 2009).

As the possible health effects caused by indoor fungal exposure are mainly suspected to be respiratory symptoms, **air sampling** is one of the most common methods used to assess fungal levels in indoor environments. However, this sampling method may not reflect long term exposure levels. Therefore, the interpretation of airborne sampling data should be based on multiple samples, as space–time variation in the environment is high. Due to these limitations, **dust samples** may represent a better exposure over a long period of time. The **culture-based analysis,** also called a viable method, which allows colonies to be identified at a species-level, is useful to detect fungi indicators in mouldy buildings. However, this method can overlook fungal species that are not easily culturable and that grow slowly. In addition, dead microorganisms and microbial components are not detected, while they may have toxic and/or allergenic properties (Holme et al., 2010).

Another recently developed quantitative method is the **Quantitative Polymerase Chain Reaction (qPCR)**. This is a new method for measuring indoor fungi and bacteria that can detect both general and specific DNA sequences irrespective of the viability of the organisms. Gas and high performance liquid chromatography-tandem mass spectrometry (GC- and HPLC-MSMS) is an easy-to-use method that provides a high degree of detection specificity. Analysis of fungal and bacterial DNA by qPCR collected by a Petri dish seems also to be a promising method for monitoring indoor mould exposure in epidemiological studies (Cai et al., 2011). Only a few epidemiological studies measuring fungal DNA by qPCR have been carried out so far, but it has recently been used successfully in epidemiological studies on asthma in relation to mould exposure in homes and schools (Zhang et al., 2011). Thus, this method for assessing microbial constituents appear more promising, although the experience with it is generally limited (WHO, 2009).

Endotoxins and glucans

Endotoxins are a ‘component of the wall of gram-negative bacteria, which are commonly used as a surrogate for microbial exposure’ (Heinrich et al., 2011). In the environment, airborne endotoxins are usually associated with dust particles or aqueous aerosols. Environmental air and dust samples may be collected and analysed using the endotoxin-specific LAL assay. Endotoxins represent a very bio-active component with a lot of stimulating properties (Heinrich et al., 2011). Thus, heavy exposure to endotoxins can cause respiratory symptoms, including non-allergic asthma, but moderate-to-low exposure may protect against allergies and asthma. Indoor concentrations may be higher in damp houses, but a study conducted in Louisiana, after the hurricane Katrina and the subsequent flooding, did not confirm this. Other studies also found no evidence for a relationship between endotoxins in house dust and observed dampness or mould (WHO, 2009).

Other important bio-active components are the glucans, which are also cell-wall components, but indicative of fungal growth (Heinrich et al., 2011). These microbial agents, present in dust, are non-allergenic, water-insoluble structural cell-wall components of most fungi, some bacteria, most higher plants and many lower plants (WHO, 2009). Glucans also have inflammatory properties (but less severe than endotoxins) including an irritation of the airways and immune-stimulating characteristics (Heinrich et al., 2011) that may affect respiratory health (WHO, 2009). Environmental air and dust samples may be collected and analysed using the glucan-specific LAL assay. The question of the association between fungal spore concentration and visible mould and dampness is controversial. One Swedish study could not find any association between the fungal spore concentration in indoor air and signs of dampness and mouldy odour (Holme et al., 2010). On the other hand, several other studies have reported an association between fungal levels in indoor air, and visible mould and water damage (Holme et al., 2010).

In conclusion, measurement of mould spores in indoor air is insufficient on its own to decide whether there is a moisture problem in a building. Indirect measures such as visible moulds or mildew on surfaces have been commonly used for assessment of mould exposure, and may better represent long-term exposure to moulds than measurements during a short sampling time (Antova et al., 2008). Risk assessment is seriously impeded by the absence of valid methods for quantitative assessment of exposure. This may explain the relatively large number of studies that have failed to demonstrate a direct association between microbial components and health effects in damp indoor environments. Therefore, more research is needed to establish better exposure assessment tools, and newly developed methods must undergo rigorous validation. Moreover, it is possible that not all the biological agents that might be associated with damp indoor environments and their health effects have been identified.

This is why epidemiological evidence today is still mainly based on qualitative assessment of dampness related factors, such as visible dampness, mould, water damage or mould odour (WHO, 2009; Cho et al., 2015).

1.2.5 Indoor air quality in schools

Although residential indoor air quality has been described fairly well, it is unclear whether that data can be applied to school buildings that differ from residential buildings in size, design, construction, ventilation, activities, and occupant density (Meklin et al., 2002). Apart from dwellings, schools are the most important indoor environments for children, which may contribute considerably to their total daily exposure to microbial agents and allergens, as exposure levels in schools may be higher than in homes (WHO, 2015). Moreover, several studies have observed that indoor microbial levels and allergens at school environment varies considerably between and within countries and schools (tropical versus cold climate, rural versus urban) (Simoni et al., 2011; Jacobs et al., 2014a and 2014b ; Csobod et al., 2014; WHO, 2015). The SINPHONIE Project (Schools Indoor Pollution and Health: Observatory Network in Europe) conducted in 23 European countries, was conceived to assess the quality of indoor air in schools and outdoor air in the school vicinity, and to establish a European observatory network focused on school indoor air pollution and health. They observed that on average visible mould growth was present in 7% of classrooms, mould odour in 3%, visible damp in 9%, condensation on window frames in 17% and roof leaks were detected in 21% of the school buildings (Csobod et al., 2014).

There are several factors that can affect indoor air quality and are related with dampness and mould in schools. These are: the ventilation system, indoor air humidity, levels of settled dust and indoor allergens.

The type of ventilation system and season affect indoor microbial levels in schools (WHO, 2015). Thus, well-balanced ventilation is fundamental in maintaining thermal comfort and high indoor quality. The primary role of ventilation is to remove airbone pollutants and supply the building with clean air (Tarlo et al., 2010).

Indoor air humidity is dependent on outdoor humidity, room ventilation, vapour built into the construction materials and emissions from humans and their activities. Increased humidity can be the origin of mould and dust mites' growth, Volatile Organic

Compounds accumulation and indoor pet allergens that can affect schoolchildren's respiratory health (Tarlo et al., 2010).

The concentration of **settled dust** is normally higher in schools than in work places for adults. We can find higher concentrations in rooms with: textile carpets, open shelves, or other storage in the room. It is probable that the majority of the dust comes from indoor sources, as the concentration of particles tend to be higher in classrooms than outdoors (Tarlo et al., 2010).

Indoor allergens, such as dander from cats and dogs, dust mites, cockroaches, rodents, and fungal allergens, are also commonly found in school buildings (WHO, 2105; Salo et al., 2009). However, the data shows that levels of allergens are very variable. Allergen levels can vary by time, location, and type of room within the building. This is not surprising because a variety of physical (humidity, temperature), structural (age and type of building), and behavioural factors (pet ownership among children and staff, cleaning and maintenance practices) can influence indoor allergen levels. For example, several studies have observed that building dampness can increase some indoor allergen levels (Salo et al., 2009). The highest **dust mite allergens** concentrations have been found in humid regions as these allergens are strongly associated with high humidity levels (>55%). In contrast, very low dust mite allergen levels have been found in colder and drier climates (such as Nordic countries). Several studies have observed lower mite allergens levels in schools compared with homes (Salo et al., 2009; Tarlo et al. 2010, Hauptman et al., 2015). Furthermore, standing water and dampness may attract cockroaches and rodents, which are also a source of indoor allergens. Some studies have suggested that exposure to **cockroach and mouse allergen**s in schools may be similar or higher to what occurs in homes (Salo et al, 2009). Finally, as discussed above, one major limitation in assessing exposure to **fungal allergens** has been the difficulty in quantifying exposure accurately. The complexity of fungal exposure assessment and lack of clearly defined threshold levels for fungi and substances derived from fungi has limited the number of studies of fungal allergen exposures in school settings (Salo et al., 2009). Among the fungi, the most important school indoor allergenic moulds are *Penicillium* and *Aspergillus* species. Outdoor moulds, as *Cladosporium* and *Alternaria*, can also be found at high levels indoors (Jones et al, 2011).

1.3. Indoor dampness and mould and respiratory symptoms in children

1.3.1 Health effects associated with dampness and mould

The associations observed between indoor dampness and mould and respiratory health problems are consistent throughout the literature. As much as 30–50% of respiratory health symptoms have been linked to moisture-related problems in homes (Fisk et al., 2007). Sufficient epidemiological evidence is available from studies conducted in different countries (Zock et al., 2002; Antova et al., 2008) and under different climatic conditions (Spengler et al., 2004; Tham et al., 2007) to show that the occupants of damp or mouldy buildings, both houses and public buildings, are at increased risk of respiratory health problems, including current asthma, development and exacerbation of asthma, respiratory infections (except otitis media), upper respiratory tract symptoms, cough, wheezing and dyspnoea (Bornehag et al., 2001 and 2004; IOM 2004; Fisk et al. 2007 and 2010; Antova et al.,2008; WHO, 2009; Jones et al., 2011; Mendell et al. 2011; Kennedy et al., 2013). These effects occur among adults and children, and among atopics and non-atopics (Bornehag et al., 2004; WHO, 2009). In the case of allergic rhinitis and bronchitis, the epidemiological evidence linking it to indoor dampness or mould is limited (WHO, 2009; Fisk et al, 2010). Similarly, in the case of lung function, allergy or atopy and "asthma, ever" the evidence to date is inadequate or insufficient (WHO, 2009). The WHO (2009) and the Institute of Medicine (2004) concluded that, in the case of asthma exacerbation, there was almost enough evidence to meet the criteria of causality for dampness-related agents. For the rest of the health outcomes reviewed, they considered that there was insufficient evidence of a causal relationship (WHO, 2009**)**. Knowledge of which agents in indoor air or dust can cause reported health effects is limited. Both chemical and biological pollutants, as well as house dust-mites, have been suggested (Holme et al., 2010). In addition to the previous cross-sectional studies, several surveys, most of them longitudinal, have shown that early life exposure to indoor dampness seem to have adverse effects on asthma onset and respiratory and allergic symptoms in the paediatric age (Simoni et al. 2005; Iossifova et al., 2009; Tischer et al. 2011b; Reponen et al., 2011 and 2012; Karvonen et al., 2009 and 2015). Moreover a more recent systematic review and meta-analysis from 2012, evaluating different longitudinal studies, concluded that dampness and mould in the home was associated with an increased risk of developing asthma (Quansah et al., 2012).

Most of the surveys studying dampness-related health effects have considered qualitative exposure assessment of dampness and mould. And studies with a quantitative evaluation have been done mostly in dwellings. Several of these quantitative studies have shown that exposure to mould spores in homes tend to increase asthma and wheezing symptoms in children (Stark et al., 2005; Gent et al., 2012; Jones et al., 2011). In addition, a quantitative meta-analysis observed (except for the highest glucan concentrations in dust that decreased wheezing), that fungal and bacterial markers were associated with increase in asthma and wheeze (Mendell et al., 2011). Other studies have not found any clear relation between microbial components and health (Holme et al., 2010). In relation to early life exposure, longitudinal studies have suggested that exposure in early life to endotoxins or fungal agents could protect against atopy and allergic diseases (WHO, 2009, Tischner et al., 2010). This potentially protective effect is consistent with the hygiene hypothesis, which postulates that growing up in a microbiologically hygienic environment might increase the risk of developing allergies. Thus, It's possible that some of the inconsistency related with microbial exposure and health, may be due to the timing of exposure, being protective in early life and being a risk factor later in life. Alternatively, exposure to endotoxins may prevent allergic asthma, but at higher exposure may cause non-allergic asthma (Douwes et al., 2002). If in fact exposure to certain microbiological agents early in life protects against atopy and asthma, it should be noticed that no similar pattern is seen for dampness-related risk factors in infants. Overall, the available evidence is not consistent, and further research is needed. However, there is no indication that living in a damp building could prevent the development of allergies and respiratory disease (WHO, 2009).

On the other hand, only a few studies, mainly carried out in homes, have investigated the effects of dampness and mould on objective health outcomes, such as lung function (LF) and the results are not conclusive. A Dutch study found a small but significant decrease of LF parameters in Dutch children exposed to home dampness (Cuijpers et al., 1995). In a more recent study also done in dwellings, with asthmatic children, they observed a consistent association between reported moulds and dampness and an increased risk for airway hyperresponsiveness (Hagmolen et al., 2007). However, another study done in The Netherlands, didn't found any association between home dampness and LF (Dijkstra et al.,1990). Moreover, other authors that studied the association between LF and self-reported home dampness in children, didn't found any statistically significant association, except for the presence of mouldy spots and decreased maximal mid expiratory flow (Brunekreef et al., 1989).

Other health symptoms such as tiredness, headache, memory and concentration problems, fatigue, and dizziness and mucous membrane irritation have also been reported to be associated with dampness in buildings. However, several personal factors such as: asthma, hay fever, recent upper airways infections and female gender, have been found to be even stronger risk factors for these health symptoms (Meyer et al., 2004 and 2005).

1.3.2 The school environment

Research on the adverse health effects associated with moisture and mould problems in buildings has mainly been focused on home environments. However, some studies have revealed that the same risks can occur in water-damaged non-residential buildings (WHO, 2009). Thus, a mouldy school environment, where children spend a large part of their time, can be considered a health risk for both pupils. In the case of younger children, the timing of exposure to allergens can be critical, because IgEmediated sensitivity to specific aeroallergens develops in early childhood. In daycare and elementary school classrooms, which often have a variety of potential allergen reservoirs (pillows, stuffed animals) and where children are more active, the inhaled dose of indoor pollutants can increase (Salo et al., 2009). Thus, these factors make schools, which sometimes have poor ventilation and inadequate building maintenance, a unique microenvironment of indoor air pollutants and particles (Huffaker et al., 2014). Indeed, respiratory symptoms (such as wheezing and nocturnal cough), asthma and infections, as well as general symptoms such as headache, eye and throat irritation, tiredness and nausea, have been found to be higher among pupils and teachers in moisture damaged schools than in non-damaged ones (Savilahti et al, 2000 and 2001; Meklin et al, 2002 and 2005; Haverinen-Shaughnessy et al., 2004; Meyer et al., 2004; Zhao et al, 2008; Cai et al., 2011; Simoni et al., 2011; WHO, 2015) but findings are not conclusive. Most of the studies performed in schools have been performed in Nordic countries (Meklin et al., 2002; Haverinen-Shaughnessy et al., 2004) and are almost all based on relatively small samples (Smedje et al., 1997; Rylander et al., 1998; Savilahti et al, 2000 and 2001; Meyer et al., 2004). Although, it has been suggested that the health risks are greatest among children who are exposed to moisture and mould both at school and at home (Taskinen et al., 1997; Meklin et al. 2005), only a small number of the studies reviewed assessed dampness status simultaneously in school and home environments (Salo et al, 2009).

Microbial exposure at school

As we have already mentioned, few studies have performed quantitative measurements of microbial levels at schools and have related them to health (Zhao et al. 2008; Cai et al. 2011; Simoni et al, 2011; Zhang et al., 2011). Most of these quantitative studies have shown an association between microbial components and respiratory health, but the results are not conclusive. A recent European study (The HESE study) that assessed the effects of indoor air quality in schools on the respiratory health of children, showed an association between viable moulds and fungal DNA levels in classrooms and respiratory symptoms, including decrease in lung function, but no country-specific results were given (Simoni et al, 2011). This association with lung function was not seen in another school study that looked at dampness and mould as exposure (Immonen et al., 2004). In addition, there are several Asian studies on this topic. For example, a study by Cai et al (2011), that measured selected fungal DNA, furry pet allergens and mycotoxin levels in schools and looked at their associations with respiratory symptoms in children, did not find an association between total fungal DNA and respiratory health, but found a positive association with specific DNA from the fungal species. These findings illustrate the importance of analysing specific microbes when studying effects on respiratory health (Cai et al., 2011). In two cross-sectional studies, where they studied associations between microbial components in school dust (bacteria and fungi) and asthmatic symptoms in school children, they found mainly negative associations for bacterial components and positive associations for fungal markers (Zhao et al., 2008; Chen et al., 2014). Similar results were found by the first Chinese longitudinal study looking at associations between selected microbial components in dust, selected fungal DNA, and furry pet allergens in schools and Sick Building Symptoms among children.

This study found that bacterial compounds seemed to protect against the development of mucosal and general symptoms, but fungal exposure, measured as fungal DNA, could increase the incidence of school-related symptoms (Zhang et al., 2011).

School building characteristics and health

Some studies have observed that building characteristics could be a possible risk factor for respiratory problems among schoolchildren. The study by Smedje et al. (1997) found that there were more pupils with current asthma in schools that were: larger, had more open shelves, lower room temperature and higher relative air humidity. Another study that reviewed the literature on indoor air quality, ventilation and building-related health problems in schools, observed that ventilation in school buildings may affect pupils health (Daisey et al., 2003). Moreover, a Finnish study observed that the association between moisture damage and respiratory symptoms in children was more clear in the case of concrete/brick buildings than in the case of wooden school buildings, concluding that a wooden, organic frame may behave differently from a concrete frame. These results emphasize the importance of the building frame as a determinant of exposure and symptoms. Moreover, age and construction of buildings may have an effect on indoor spores levels, which can cause respiratory symptoms (Meklin et al., 2002).

1.3.3 Possible causes of dampness-related health effects

There is a direct link between relative humidity (RH) and respiratory problems (Richardson et al., 2005). Indoor RH levels >45% (dampness) can increase microbial growth and may enhance sensitization to allergens. On the other hand, RH levels below 30% (dry air) can cause dry skin, eye irritations and tiredness (Richardson et al., 2005). The amount of water or dampness, on or in materials, is the most important trigger of the growth of microorganisms (fungi and bacteria) and allergens. Microbes propagate rapidly wherever water is available (WHO, 2009). Thus, the presence of many biological agents in the indoor environment is related to dampness, condensation, moisture and inadequate ventilation. Microbial growth may result in a greater numbers of spores, cell fragments, fungal allergens, mycotoxins, endotoxins, β-glucans and volatile organic compounds in indoor air. Existing studies indicate that both biological and chemical substances are suspected to be the causative agents of adverse health effects related to indoor dampness and mould. These biological and chemicals substances are: microbiological agents (such as bacteria, moulds and various components from these organisms), allergens (such as dust mites), or emissions of organic chemicals from degraded building materials (Bornehag et al., 2001, 2004; IOM, 2004; Richardson et al., 2005; WHO, 2009; Zhang et al., 2011). Although an excess level of any of these agents in the indoor environment is a potential health hazard, the causative agents of adverse health effects related to indoor dampness and mould have not been identified conclusively (WHO, 2009). The difficulty in identifying these causal agents is probably due in part to the lack of valid exposure assessment methods.

Dust mite allergens seem to be the indoor allergen that is more influenced by moisture. Although we can find different degrees of mite infestation worldwide, the level of association between indoor dampness and health seems to be almost the same all over the world. Therefore, we could conclude that mite exposure alone cannot explain completely the health effects related to damp buildings (Bornehag et al., 2004). **Microorganisms** and derived components are considered among the most likely cause of respiratory health problems associated with indoor dampness. Nevertheless, conventional quantitative measurements of such exposure, based on counts of total culturable airborne microorganisms (endotoxins, glucan), have shown less consistent associations with health effects than have more qualitative assessments, such as visible dampness or water damage, visible mould or mould odour (WHO, 2009; Holme et al., 2010). Jarvis and Morey (2001) have suggested that the lack of a standardized methodology is a primary cause for the poorly understood relationship between fungal exposures and health outcomes (Holme et al., 2010). These controversial results could also be associated with the lack of evidence to associate mould components with visible mould. This is in agreement with a recent cohort study which did not observe a correlation between fungal components and visible mould (Iossifova et al, 2007 and 2009). Nevertheless, other studies observed associations between mould odour, water damage and visible mould growth, and microbial exposure (Dales et al., 1997; Garrett et al., 1998). In sum, although It appears that the causal link between microbiological exposures and respiratory health problems is strong, the evidence is still inconclusive (Douwes et al., 2003; Bornehag et al., 2004). Another possible causative agent for adverse health effects related to indoor dampness and mould could be attributed to

viruses. Respiratory viruses have been identified in the majority of cases of asthma or exacerbations of asthma. The infectious effectiveness of respiratory viruses depends strongly on the environment where the viruses are spread. For respiratory viruses, survival and infectivity are dependent on temperature and relative humidity. Therefore, a more effective spreading of viral infections in damp indoor climates is likely to represent one of the possible causes for the increased prevalence of asthma in these environments (Hersoug et al., 2005). In the case of **organic chemicals** from degraded building materials, high humidity content in materials can give rise to degradation processes, with emission of chemical compounds as a result. Such compounds can produce irritation and maybe allergic reactions (Bornehag et al., 2004; WHO, 2009). A study from Kim et al. (2007) concluded that exposure to volatile organic compounds of possible microbial origin (MVOC) at school could be a risk factor for asthmatic symptoms in children. Despite generally good ventilation and no visible signs of mould growth, they found an association between respiratory symptoms and indoor MVOC concentration. As MVOC were positively correlated to health respiratory symptoms, while indoor viable moulds and bacteria were negatively correlated, it is unclear if indoor MVOC is an indicator of microbial exposure (Kim et al., 2007). In addition, another study observed that some MVOCs could cause mucosal symptoms. Unlike the study from Kim et al, they observed that concentrations of airborne moulds, bacteria and some other MVOCs were slightly higher in homes with reported dampness and mould (Sahlberg et al., 2013).

Potential mechanisms involved

The mechanisms by which non-infectious microbial exposures contribute to adverse health effects associated with indoor air dampness and mould are largely unknown. It is clear, however, that no single mechanism can explain the wide variety of effects associated with these exposures (See figure 1). The available epidemiological and clinical evidence suggests that both atopic and non atopic people are susceptible to adverse health effects from exposure to dampness and mould, even if some outcomes are more common in atopic people. Therefore, both allergic and non-allergic mechanisms may be involved in the biological response (WHO, 2009).

In vitro and in vivo studies have demonstrated diverse **inflammatory, cytotoxic and immunosuppressive responses** after exposure to the spores, metabolites and components of microbial species found in damp buildings, lending plausibility to epidemiological findings (WHO, 2009; Salo et al., 2009; Antova et al., 2008). Many dampness-associated conditions are likely to involve **inflammation**, as inflammatory responses to many microbiological agents have been found (WHO, 2009). Moreover, fungal spores associated with damp buildings produce metabolites with demonstrated acute **cytotoxicity.** Activation of the immune defences, exaggerated **immune responses**, prolonged production of inflammatory mediators and tissue damage, leading to chronic inflammation and inflammation-related diseases, can cause dampness-associated asthma, allergic sensitization and associated respiratory symptoms (WHO, 2009). On the other hand, the observed increase in respiratory infections associated with damp buildings might be explained by the immunosuppressive effects of dampness associated microbes. An alternative explanation might be that inflamed mucosal tissue provides a less effective barrier, increasing the risk of infection (WHO, 2009). Moreover, various microbial are present simultaneously with other airborne compounds, inevitably resulting in interactions in indoor air. Therefore, the detection of individual exposures, such as certain microbial species, toxins or chemical agents, cannot always explain any associated adverse health effects (WHO, 2009).

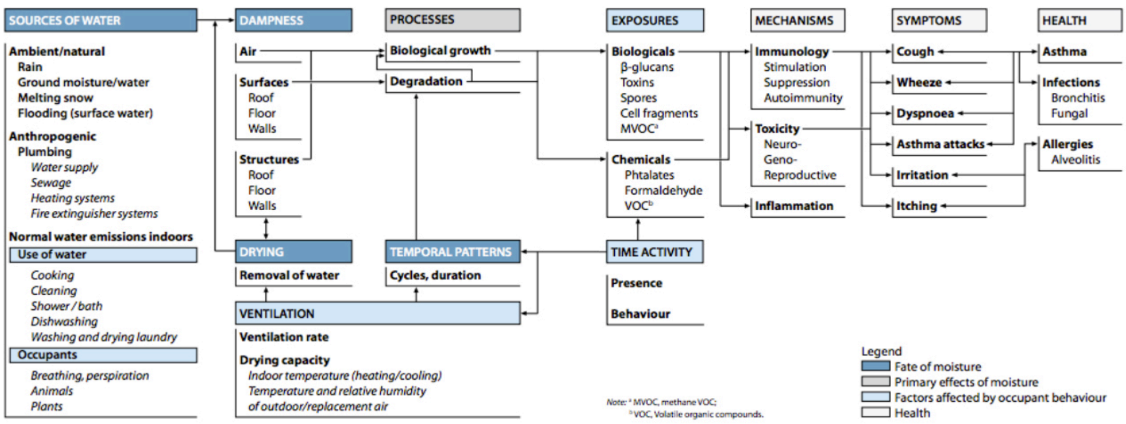

Figure 1. Pathways linking sources of dampness with health (from WHO, 2009)

1.3.4 Remediation studies and respiratory health

A number of different interventions have been proposed to reduce exposure to dampness and moisture in homes and school buildings (Haverinen-Shaughnessy et al, 2004 and 2008; Savilahti et al, 2000; Patovirta et al., 2004; Meklin et al., 2005; Lignell et al., 2007; Huffaker et al. 2014). The type of interventions can vary, and may range from simple replacement of a ventilation filter to extensive structural repairs (Meklin et al., 2005). If intervention studies show a positive effect of the remediation (that is the removal of the source of moisture problems) on the occupants' health, this would strengthen the assumption of the causal link between moisture problems and associated health problems (Meklin et al., 2005). However, the results of the different intervention studies carried out are diverse and sometimes contradictory. Krieger et al. (2010) observed that a strategy that combined elimination of moisture intrusion and leaks, and removal of mouldy items reduced mould levels and respiratory symptoms. In a previous study done by Haverinen-Shaughnessy et al. (2004) they observed that students health improved after comprehensive repairs of moisture damage in the school. Meklin et al. (2005) conducted a study in a damaged school in Finland and observed a significant decrease in indoor air fungi and respiratory health problems among children after full renovation of the building. No change in microbial conditions and only a slight improvement was observed in symptom prevalence after partial repairs in another damaged school (Meklin et al., 2005). Other studies that looked at the effects of moisture and mould damage repairs on school children's health concluded that the renovation of the buildings was associated with improvements in the occupants' symptoms and reduction of microbial levels (Savilahti et al, 2000; Salo et al., 2009). As well as full or partial repairs, improvements in ventilation may also affect, in a positive way, relative humidity and concentrations of airborne viable moulds (Salo et al., 2009). A study conducted in schools found that new ventilation systems improved indoor air quality and reduced asthma symptoms among students in intervened schools (Smedje et al., 2000). On the other hand, Sauni et al. (2011) studied the effectiveness of repairing dampness and mould damaged buildings in order to reduce or prevent respiratory tract symptoms, infections and symptoms of asthma. They found that there was very "low-quality evidence" that pupils' respiratory health based on doctor's consultations, were less frequent after remediation of the schools. They concluded that due to a wide range of outcome measures and variation in study designs, it was difficult to draw any conclusion and further research was needed, preferably with a clinical trial design (Sauni et al., 2011). In summary, multifaceted approaches may be needed to lower indoor pollutant levels in schools: combining allergen-avoidance measures (such as improving ventilation systems, controlling excess moisture, reducing potential dust reservoirs, regular and thorough cleaning and maintenance, pest control, and use of special school clothing), plus extensive structural repairs of the moisture damage and improvements in ventilation. However, there is limited information on how to choose and implement the most cost-effective intervention and the extent to which reductions in indoor pollutants exposure, by remediation, in these environments influence allergy and asthma symptoms (Salo et al., 2009; Krieger et al. 2010).

2. RATIONALE

People spend a large part of their time indoors. The quality of the air they breathe in indoor environments is an important factor in determining their health and well-being as well as a potential public health issue. The composition of indoor air is extremely complex and its quality can be influenced by many factors, such as the type of building materials used, outdoor sources, the number of people and animals in the building, dampness and mould, the use of certain fuels for heating and cooking, indoor temperature, ventilation and humidity. Air inside homes and other buildings may be more seriously polluted than outdoor air, even in the largest and most industrialized cities. In addition, people exposed to indoor air pollutants for the longest periods of time are often those most susceptible to their effects: children, the elderly and the chronically ill, especially those suffering from respiratory or cardiovascular diseases.

Asthma, one of the most common chronic non-infectious diseases in the World, is an important health problem among children and adults everywhere, and in many countries prevalence rates are high and on the increase. Exposure to pollutants in indoor environments can influence the development and morbidity of asthma. One of the possible risk factors is dampness and mould.

The presence of dampness problems in buildings is difficult to assess. In epidemiological studies, these problems are usually self-reported by building occupants or assessed by a trained inspector (qualitative assessment). Risk assessment is hampered by a limited availability and/or feasibility of valid methods for quantitative assessment of exposure. Nevertheless, the World Health Organization has concluded that there is sufficient evidence to show that the occupants of damp or mouldy buildings are more likely to suffer respiratory symptoms, respiratory infections and exacerbation of asthma. These dampness-related health effects may be associated with different indoor pollutants such as fungi, bacteria, allergens, chemical pollutants, products of microbiological activity (Microbial Volatile Organic compounds: MVOC) and toxins. However, the causal mechanisms and aetiological agents are still largely unknown.

Children are especially vulnerable to indoor air pollutants as their lungs are still growing. Public places where children spend substantial periods of their time, such as schools, may be important sources of exposure. Thus, the study of the health effects of indoor pollutants in these settings is of great relevance for Public Health. Identifying determinants of dampness and mould in school buildings will help developing measures to control these exposures and hence reduce the burden of respiratory disorders related to dampness and mould.

3. OBJECTIVES

The overall aim of this thesis is to identify the role of indoor agents that lead to respiratory, inflammatory and allergic health problems among schoolchildren. The main focus is on microbial exposures due to dampness and mould in school buildings.

Specific objectives:

1. To assess qualitatively and quantitatively the occurrence of moisture problems in school buildings in three European countries from different climatic regions: Spain, the Netherlands and Finland.
2. To study which building characteristics are associated with dampness and mould problems in schools in these three countries.
3. To study the respiratory health effects associated with dampness and mould in schoolchildren in these 3 climatic regions across Europe.

4. METHODS

In 2008, the HITEA study ('Health Effects of Indoor Pollutants: Integrating microbial, toxicological and epidemiological approaches') was started. The aim of the project was to clarify the health impacts of indoor exposures on children and adults by providing comprehensive exposure data on biological and chemical factors in European indoor environments, both homes (from existing population cohorts) and European schools (school study). The overall structure of the Project is shown in Figure 2.

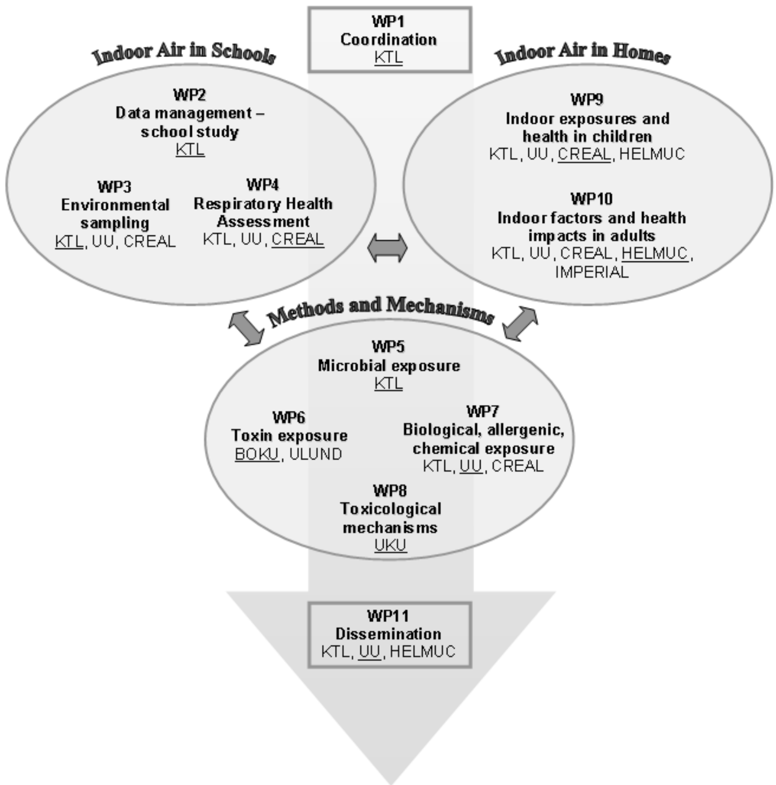

Figure 2. Overall structure of the HITEA project

4.1 The HITEA field study in schools

This thesis focuses on the school study arm of the HITEA Project (See figure 3), which studied dampness, mould and moisture problems and associated exposures to biological and chemical agents in schools across Europe. An extensive longitudinal field survey in schools was implemented during two school years in identical set-ups in Finland, The Netherlands and Spain to reveal the role of the dampness-related multiple exposures in school environment for children's and teachers' respiratory health. This study provides data on short term health effects that may potentially lead to long term and chronic health impacts.

In the initial phase of the study, a questionnaire survey was conducted to assess moisture damage/dampness problems and other indoor air quality issues in primary schools in the three study countries (phase 0). The screening questionnaire was first developed in English and then translated into Spanish, Catalan, Dutch, and Finnish, using an Internet-based platform. The questionnaire contained ten key questions on current and past dampness, moisture, and mould observations and also collected background information on building and ventilation characteristics and renovation plans (the latter relevant for appropriateness of follow-up studies). The questionnaire was addressed to the principals of the schools, with support - where needed - from the person responsible for school building maintenance. Using this questionnaire, information from 236 school buildings in the three countries were collected. Of the schools that participated in the screening phase, between 20 and 24 schools per country were selected for on-site building inspections (phase Ia; summer 2008). Approximately half of these represented schools did not report any signs of dampness problems, moisture or water damage, or mould growth in the building nor a history with such problems ('reference schools'). The other half represented schools with such problems that were considered severe (i.e. either widespread, and/or located in classrooms, and/or including reports of visible mould; 'index schools'). The inspections of a total of 66 schools (95 school buildings) included walkthroughs utilizing pre-designed checklists and non-destructive measurements by trained research personnel. The research personnel were centrally trained by senior members of the research group with extensive experience in building investigations. Complementing the visible observations, measuring instruments included hand-held moisture detectors, relative humidity, temperature and CO2 monitoring devices.

Based on the location, extent and severity of moisture damage/dampness/visible mould observations derived from the school building inspections, schools were categorized as case or control schools and selected for subsequent phases of the study. The methodology of both screening questionnaire, and selection of study schools based on walkthrough building inspections have been published in the first paper of this thesis.

In autumn 2008, phase Ib facilitated the administration of an extensive respiratory health questionnaire to pupils and teachers in a minimum of eight moisture-damaged (index) and eight non-damaged (reference) schools per country. For pupils aged 6-12 years, the parent administered questionnaire assessed the respiratory health status using questions from the validated International Study of Asthma and Allergies in Childhood, translated into three languages. Information from more than 9400 pupils from 57 schools in Finland, The Netherlands and Spain was collected (paper II). The questionnaire developed for teachers included items on demographic characteristics, relevant exposures and respiratory health, partly based on the European Community Respiratory Health (ECRHS) protocol. In total, more than 650 teachers from 55 schools in the three countries provided information on their respiratory health in this phase.

From all schools categorized as case or control schools, a minimum of 4 case and 2 control schools were selected per country, with emphasis on biggest possible contrast in observations on moisture damage, dampness and visible mould in the school buildings. In total, 23 schools were defined for more detailed exposure and health characterization in the subsequent study phases. During phase II in late winter/early spring 2009, lung function measurements were conducted in all consented pupils from the study schools, yielding lung function tests from more than 3500 pupils in the three countries. Measurements from 2736 children were considered valid and reproducible and were used for respiratory health analyses (paper III annex).

Phases III to V represented a longitudinal health and exposure assessment in the selected study schools. The first two of these phases were conducted before and immediately after the school vacation, to define the effect of the school exposure on pupils' and teachers' health. Lung function testing, exhaled nitric oxide measurements and health diaries were completed for more than 500 pupils with symptoms indicative for asthma. Data on sickness absence and school performance were collected where available. In addition to pupils, also 175 teachers from these schools participated in the health study, providing - in addition to lung function and lung inflammation measurements - peripheral blood and nasal lavage samples for determination of markers of inflammation and immunological parameters. Exhaled breath condensate was collected from a subset of Finnish teachers to follow changes in inflammatory markers during one school week. Moreover, we collected the school absence data and academic performances of the children during 2009-2010 school term.

In parallel to the longitudinal health assessment, extensive exposure assessments and sample collection campaigns were performed during phases 2, 3 and 5 in the study schools. The focus in these assessments was on biological agents that were measured from airborne settled dust that was collected in more than 1000 locations in the 23 study schools over three assessments. In addition, selected chemical and physical parameters were monitored in the HITEA schools, including sampling for PM2.5 and NO2, monitoring of CO, CO2 (for modelling of ventilation rates), temperature and relative humidity. Outdoor environmental characteristics as well as cleaning procedures were assessed via questionnaire.

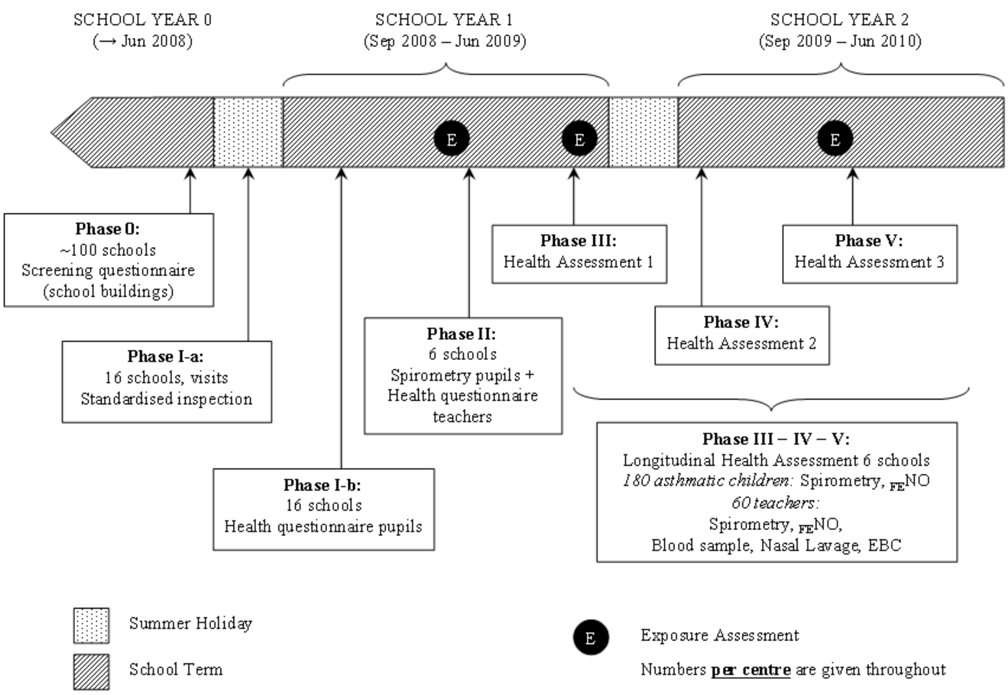

Figure 3. Overview and timing of the different phases of the school study.

5. RESULTS

Paper I

Occurrence of moisture problems in schools in three countries from different climatic regions of Europe based on questionnaires and building inspections - the HITEA study

Paper II

Dampness and mould in schools and respiratory symptoms in children: the HITEA study

5.1. PAPER I

Haverinen-Shaughnessy U, Borras-Santos A, Turunen M, Zock JP, Jacobs J, Krop EJ, et al. Occurrence of moisture problems in schools in three countries from different climatic regions of Europe based on questionnaires and building inspections - the HITEA study. Indoor Air. 2012 Dec;22(6):457-66.

http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0668.2012.00780.x/abstract

doi: 10.1111/j.1600-0668.2012.00780.x

5.2 PAPER II

Borràs-Santos A, Jacobs JH, Täubel M, Haverinen-Shaughnessy U, Krop EJ, Huttunen K, Hirvonen MR, Pekkanen J, Heederik DJ, Zock JP, Hyvärinen A. Dampness and mould in schools and respiratory symptoms in children: the HITEA study. Occup Environ Med. 2013 Oct;70(10):681-7.

http://oem.bmj.com/content/70/10/681.long

doi:10.1136/oemed-2012-101286

6. DISCUSSION

This section provides a global discussion of the results presented in the articles that make up the body of this thesis. The aim is to provide a broader and more integrated interpretation of the entire study project.

6.1 What does this thesis add to current knowledge in the field?

The HITEA study was designed to clarify the health impacts of indoor exposures on children and adults. This was to be achieved by collecting comprehensive exposure data on biological and chemical factors in European indoor environments (homes and schools) and by combining this information with extensive health data obtained from a field study in schools and from existing general population cohorts. As part of the HITEA study, the overall aim of this thesis was to study the association between building dampness in primary schools and respiratory symptoms in children.

An initial analysis (Paper I) in the HITEA school study investigated the occurrence of moisture problems in schools in three European countries with different climates (Spain, the Netherlands, and Finland), based on questionnaires and on-site building inspections. Then, the agreement between the results obtained by these two methods was evaluated for validation purposes. We also aimed to study building factors that may contribute to dampness and mould related exposures in different climates or regions, and create a consistent exposed-nonexposed setting for a subsequent, large-scale epidemiological study among pupils and teachers relating respiratory health to exposure to dampness and mould in schools in the course of the HITEA study (paper II).

Thus, this first paper was motivated by the need for comparable data related to occurrence of moisture problems in schools, laying the basis for detailed exposure and health impact assessments. To our knowledge this is the first large-sacale study to assess the prevalence of moisture problems in schools in different climatic regions across Europe.

6.1.1 Moisture problems in schools in three climatic regions across Europe

Based on the questionnaire assessment, different types of moisture problems were reported in 24-47% of all school buildings at the time of the study. Extrapolating from the inspection data, the prevalence of moisture problems in school buildings was 20% in the Netherlands, 41% in Spain, and 24% in Finland. This prevalence range is similar to European data published by other authors in dwellings (Bornehag et al, 2001; IOM, 2004; WHO, 2009; Heinrich et al., 2011) and higher than data published in the Sinphonie European school study (Csobod et al., 2014). The most commonly reported moisture problems in Dutch, Spanish and Finnish schools were dampness, moisture damage and mould odour, respectively. As described in the literature, both current and past mould odour were commonly reported in Finland, which could be attributed to (hidden) microbial growth in parts of the buildings (Bornehag et al., 2001). The most common causes of problems identified were water from outside sources in all three countries. In Finland, the school buildings were older and occupant density was overall lower. Renovation activity in the past was more prevalent in Finnish schools, and their school buildings were more likely to be detached from any other buildings. Most prevalent window types were triple glass in Finland, double glass in the Netherlands and single glass in Spain. Single glass windows could be related to the higher prevalence of moisture problems observed in Spanish schools because this type of windows do not insulate (Hagerhed-Engman et al., 2009). Observations of condensation on the windowpanes were more widely reported in Dutch schools and hardly at all in the Finnish ones. These low levels of condensation in Finnish schools have been previously reported (Bornehag et al., 2001). Higher condensation levels in the Netherlands could be attributed to the type of windows as well as to insufficient ventilation and the relatively high occupancy observed in schools. The predominant ventilation system in Finland was mechanical exhaust and support air. On the other hand, in Spanish and Dutch school buildings natural ventilation predominated. The higher moisture occurrence in Spanish schools could also be related to this type of ventilation.

6.1.2 Association between building characteristics and dampness in schools

Housing characteristics and climate conditions are possible explanations of the wide variation in frequency and characteristics of moisture problems worldwide.

According to several studies, the building characteristics that have been associated with dampness or moisture damage are: age, size and type of building (such as flat-roofed), type of foundation (such as concrete slab ground foundation), building frame material, amount of thermal insulation, lack of central heating, use of natural ventilation or poor ventilation, indoor Relative Humidity, former renovation due to mould or moisture and rented houses (Zock et al., 2002; Haverinen-Shaughnessy et al., 2006; Bornehag et al., 2005; Garrett et al., 1998, Hagerhed-Engman et al., 2009). The results from our first paper showed (borderline) statistically significant associations between any signs of dampness, moisture or mould damage and the main frame structure material or the type of windowpane. However, the associations were not statistically significant when both frame material and windowpane were included in the same model. Although a significant association was not observed with the construction period, the size or with the type of ventilation system, results similar to the cited studies were found in association with the main frame structure and type of windowpane (that can be related to insulation characteristics). Some of the differences between our study and the previous studies may be due to the type of buildings studied, dwellings or schools, due to the particular maintenance characteristics of the latter.

6.1.3 Building questionnaires versus inspectors' visits

On-site building inspections by trained research staff in a sub-sample of schools from the questionnaire survey showed a good overall agreement between questionnaire and inspection data (kappa-value 0.62). However, big differences (0.39-0.91) were observed across the three countries: 0.39 for the Netherlands, 0.66 for Spain and 0.91 for Finland. On the other hand, a previous study in Finnish residential buildings (Haverinen-Shaughnessy et al., 2005) concluded that the overall agreement between inspectors and occupants was poor (average kappa 0.23), while the agreement between two inspectors was higher (average kappa 0.41). In a study conducted in Bulgarian residences, kappa-values between dampness and mould indicators reported by parents and inspectors varied between 0.21-0.47 (Naydenov et al., 2008). Possible explanations for the better agreement obtained in this study involving school buildings include the fact that questionnaire respondents were all school principals and therefore presumably a more homogenous group than occupants of residential buildings. School principals may also have sought help from the school technical personnel, who usually know a lot about the technical matters and conditions of the schools.

Thirteen out of seventy inspected schools changed status defined by the survey when the inspection was taken into account. Moreover, overall specificity and sensitivity were moderate to high for all three countries, except for specificity in The Netherlands that was moderate (50%). There were a total of 6 false negative (i.e. schools originally classified as references based on the questionnaires but as index based on the inspections), mostly from Spain. Also, we identified 7 false positive (i.e. buildings with reported moisture problems that were not confirmed by the inspections) all of them from the Netherlands. It could be speculated that these variations were related to the inspector's perception of moisture problems, or to differences in awareness of the responding school personnel. On the one hand, false negative schools could be related to the unawareness of the school personnel regarding the presence of dampness and mould related issues in their school. On the other hand, the seven false positive schools in the Netherlands could be explained by an increased sensitization of the school personnel regarding moisture damage problems in buildings, linked to recent media attention to this topic. Four of the Dutch false positive schools were new buildings and it is possible that these buildings, at the moment of administering the questionnaires, were still experiencing some off-gassing from buildings materials resulting in odours and, possibly, complaints related to indoor air quality. Such characteristics are specific to newly built buildings and not always easy to distinguish from dampness and mould issues. The primary purpose of the on-site inspections was to discern false negative and false positive schools amongst the actual "index" and "reference" schools selected on the results of the questionnaire study. Given that almost 20% of the schools inspected were discovered to have been given a false status, it would seem that inspections could overcome a potential bias and provide reasonably objective results. Without the inspections, these biases may have produced uncorrect health related conclusions.

6.1.4 Dampness and mould in primary schools and respiratory health in children

In the second stage of the thesis (paper II) we conducted a cross-sectional study to evaluate the associations between dampness and mould in school buildings and respiratory symptoms among 6 to 12 years old pupils in 3 European countries with different climates.

The exposure assessment was addressed at school-level, using a semi-quantitative method. This method has shown more consistent associations between dampness problems and health outcomes than quantitative estimates. We considered all the pupils from a damaged school as exposed and all the pupils from a non-damaged school as non-exposed. Three "heterogeneous" schools consisted of one building that was classified as damaged, and another that was classified as non-damaged. The degree of exposure was defined based on different concepts using data from the standardised inspection checklists. High severity of damage in the classroom was based on a severity score of 3, 4 or 5. A large area of moisture damage in the classrooms was defined as being larger than 5 m^2. Finally, the observed presence or absence of visible mould in at least one of the classroom of the school was taken into account.

Dampness and mould and respiratory health

Our results suggest that children attending damp schools had a higher odds of nocturnal dry cough. This is consistent with results reported in previous studies that focused on dampness at home (Antova et al., 2008) or at school (Meklin et al., 2002 and 2005; Simoni et al., 2011) using quantitative exposure methods. Finnish children attending moisture damaged schools showed higher prevalence of wheeze, nasal symptoms and respiratory-related school absence. These findings were more evident when mould was present. These results are consistent with previous studies for wheezing and nasal symptoms (IOM 2004;Tham et al., 2007; WHO 2009; Mendell et al., 2011;Simoni et al., 2011). No significant associations of moisture damage with wheeze, nasal symptoms or respiratory-related school absence were found in The Netherlands or Spain. However, we observed additional significant associations of moisture damage with nasal symptoms in Spain in sensitivity analyses including only schools with the highest response rates (>60%).

This heterogeneity between countries could be related to both quantitative and qualitative differences in dampness related exposures in the schools. Absence from school, as an indicator of the severity of the underlying respiratory illness, has not been documented in other studies. In addition, most previous studies only included one region (Meklin et al., 2002; Haverinen-Shaughnessy et al., 2004). Only one European study published in 2011 assessed effects of indoor air quality in schools on respiratory health of children living in several European countries (Simoni et al., 2011) This study showed an association between viable moulds and fungal DNA levels in classrooms and respiratory symptoms, including decrease in lung function. Levels of viable moulds higher than 300 cfu/m^3 were associated with dry cough at night, rhinitis and persistent cough, while fungal DNA levels were associated with wheeze symptoms, rhinitis and cough supporting the hypothesis that microbial exposure related to moisture damage in school buildings can cause respiratory health effects in pupils. However, no country-specific results were shown for associations between exposure and respiratory health and home exposure was not considered. Moreover, in line with previous studies (Bornehag et al., 2001 and 2004; IOM 2004; Douwes et al. 2005; Hersoug et al., 2005; Fisk et al. 2007; Antova et al, 2008; WHO 2009; Jones et al., 2011; Mendell et al. 2011; Kennedy et al, 2013) we found an association between dampness at home and asthma attack in the last year, but it was not related to dampness in the school. Other studies found an association between respiratory infections and dampness at home and at school, but we only found clear associations with moisture damage in dwellings (Antova et al, 2008; Fisk et al., 2010; Kennedy et al, 2013). These apparent inconsistencies between schools and homes may be explained by differences in duration, quality and quantity of the dampness related exposures. Concerning socioeconomic variables, Finnish and Spanish children of parents with low educational levels were statistically more likely to attend damp schools. Moreover, in Finland, school absence for respiratory illness was also associated with building dampness. Thus, pupils' health and absenteeism might be affected in an inequitable way across the socioeconomic gradient (Kreiss, 2013).

Sensitivity analysis

We carried out several sensitivity analyses. First of all, visible mould, degree of severity and damage extent were used as additional criteria to further subgroup school buildings, confirming more associations between dampness and health in Finnish schools. These analyses were also done for Spain and the Netherlands, but the results were not significant. In addition, we explored the respiratory health effects of dampness at school among pupils with and without self-reported dampness at home. One may expect that the health effects of exposure to dampness in the school are not detected when the prevalence of dampness at the child's home is high or if dampness in the two micro-environments is correlated. However, excluding children with damage at home did not change the results. We also limited the analyses to pupils who had attended the school for more than 2 years to focus on long-term exposure and the results were tending towards the same direction. Finally, we repeated all the analyses excluding the schools with a response rate below 60% in order to avoid a possible differential response bias across countries and additional significant associations of moisture damage with nasal symptoms in Spain were seen.

Dampness-related health effects only in Finnish schools?

In this study, the respiratory health effects of the exposure to moisture damage in schools are mostly evident in Finland. These inconsistencies across countries can be explained by differences in climatic conditions (e.g. relative humidity), building materials and indoor microbiome, or differences in potential misclassification and report biases; or in the response rate.

The indoor relative humidity in Finland is low and this is generally considered a non-favourable condition associated with respiratory irritation (Richardson et al., 2005). High relative humidity is associated with high prevalence of moisture damage in buildings. Consistently with this, the prevalence of dampness and mould in Finish schools was low (paper I).

Another possible hypothesis relates to the differences in building types and building materials used. Mould odour in Finnish buildings may be related to active microbial growth. Buildings in Finland might contain more moisture in their construction materials, for instance due to excessive moisture and insufficient drying during construction or due to moisture accumulating during their use.

Misclassification of the exposure may also explain the inconsistencies observed. We assumed that all children in a damp school had the same exposure. However, microenvironments exist within buildings. Unlike in Spanish and Dutch schools, the majority of school buildings in Finland are equipped with mechanical ventilation systems. In this country, natural ventilation via opening windows is rare. Perhaps mechanical ventilation present in Finnish schools homogenises exposures from structural dampness and reduces misclassification of exposure by school within the country. In addition, misclassification of the health outcomes could also be an issue in between-country comparisons, especially regarding language and health care services differences. What in Finland is considered as a respiratory problem may be different in Spain or the Netherlands. Nevertheless, the ISAAC questionnaire has been use in previous multicenter studies and international consistency has been well accepted.

Moreover, people in Finland are highly aware of the dampness issue and its relation to adverse health and that could lead to a reporting bias. However, other symptoms like hay fever, typically not linked with dampness in buildings, were significantly more present in damaged schools in Finland, as compared to the other two countries.

The effect of dampness at home could mask the effect of moisture in the damaged schools in Spain and The Netherlands. But the sensitivity analysis did not show different tendencies to those observed in the overall dataset.

The school building microbiome may be different in the three countries. Some European studies have (Casas et al., 2013, Chen et al., 2012) observed a large variability of indoor microbial exposure in relation to climate zone. A recent study included in the HITEA project (Jacobs et al., 2014a) observed that school endotoxins levels differed significantly between the 3 countries and could be higher than in the home environment (Jacobs et al., 2013). Dutch schools had the highest levels while Finnish schools showed the lowest levels. In each country differences in endotoxin levels were observed among schools and over the sampling periods. Factors affecting endotoxin levels in schools differed in each country. In general, endotoxin levels were higher in lower grades (reflecting differences in physical activity) and in classrooms with higher occupancy. Another HITEA study (paper in annex I: Jacobs et al., 2014b) investigated associations between school dampness, microbial exposure and respiratory health in children, including lung function (Jacobs et al., 2014b). This study revealed that the prevalence of respiratory symptoms was higher in moisture damaged schools, showing the same tendency as paper II. On the other hand, effects on lung function were not apparent. Levels of microbial markers (endotoxins and glucans) were generally higher in moisture damaged schools, varied by season and were lower in Finnish schools. Also variation over time was considerable in Finland, with low measurable exposure in summer and no exposure during winter period. Possibly, patterns of exposure (continuous versus intermittent), or higher microbial levels and diversity in Spain and The Netherlands, protected children to some extent from developing respiratory and allergic symptoms, as was noted in earlier studies (Braun-Fahrlander et al., 2002; Ege et al, 2011). Wheeze tended to be inversely associated with microbial levels. All other respiratory symptoms were not consistently associated with microbial marker levels. Their results indicated that associations between moisture, microbial exposure and health may vary between regions and countries. But microbial markers levels could not clearly explain the more pronounced health associations in Finland. It was hypothesized that the exceptional exposure pattern in Finland, low and intermittent, might have contributed to symptom occurrence.

Finally, another possible explanation for the Finland specific observations could be that the effects are present in all the countries but are not observed in Spain and the Netherlands due to a bias related to the lower response rates found in the damaged schools in these 2 countries. This hypothesis was explored in the sensitivity analysis including only schools with a higher response rate (>60%). The schools with lowest response rates in Spain and The Netherlands were damaged ones. It is possible that the response rate was lower among parents from lower socio-economic status. Low socio-economic status was more prevalent in moisture damaged schools and children attending such schools are at a higher risk of respiratory symptoms. This could have biased the results.

6.2 Strengths

In paper I, the Internet-based method we used allowed a relatively fast distribution and collection of the questionnaires, and different language options had been built into the service. Also the data management was less time consuming as the Internet responses were already in an electronic format. This electronic format reduced the data entry errors that would have been higher with a manual procedure.

Our study showed a relatively good overall correlation between questionnaire and inspection assessment. Thus, this relatively good agreement gives reliability to our exposure assessment.

The use of a semi-quantitative method to assess moisture exposure in schools was a positive asset because it included exposures more widely than strictly quantitative methods. In terms of exposure assessment, although misclassification bias is possible, the study of large numbers of persons in one building or school should be more efficient than studies of occupants of many dwellings, allowing increased precision in exposure classification for individuals.

In the second paper we also considered a large number of possible confounders (such as dampness at home) and adjusted for these to avoid any possible residual confounding. And finally, one of the major strengths for the two studies included in this thesis was the large number of observations from different countries sharing the same protocol that provided comparable data and increased the power of statistical analysis.

6.3 Limitations

Some general limitations of the work presented in this thesis should be considered.

The procedure for school selection was different across countries; in Spain only those schools willing to participate, all the schools in the selected area in Finland, and a random sample in a selected area in The Netherlands. This heterogeneity in the data collection may have led to some bias, as for example that the schools willing to participate might have had less moisture damage. Nevertheless, Spanish schools ended up having the highest prevalence of moisture problems. Related to the questionnaires, translation of the questionnaire into several languages is naturally challenging. Certain technical terminology might not be applicable in different countries and is difficult to translate verbatim, considering both lingual and cultural differences. These issues should be considered when attempting to explain the differences observed among the countries.

As explained in paper I of this thesis the assessment of the occurrence of moisture damage in schools has also been different in the three countries, combining Internet-based questionnaires, telephone interviews and postal questionnaires. This could have led to a lower response rate (as happened in Spain) related to accessibility to the Internet or to a concern about confidentiality. In Finland, two different data collection methods were used. Data collected from the second phase (phone interviews) in Finnish school buildings (larger and newer buildings located in more urban areas) may not be comparable to that collected in the first phase with a larger sample collected from the national Internet based survey. However the rest of the building characteristics and reported moisture problems appear to be comparable between the two data sets.

Due to self-reporting, the screening questionnaire results should be interpreted with caution. Some of the questions included in the questionnaire are relatively simple to answer and readily known by the school personnel, who in most cases also have the most long-term knowledge of their school and its condition. However, some of the questions are more difficult to answer, requiring personal judgement to some degree. Such questions include the existence of moisture problems, their location and extent. A part of the problems may also be hidden and their discovery is therefore dependent on the other types of manifestations, such as odour. In any case, these responses are always somewhat subjective, and variation can be expected even among trained personnel, depending on their background and experience. Nevertheless, we observed a good agreement between school personnel screening questionnaires and inspectors visits. In addition, the research team that performed the on-site inspections was not blinded to the results of the questionnaires administered to the school personnel regarding moisture damage problems. Subsequently, this may have influenced their observations and ratings in the course of the inspections.

Finally, although the school sample used in paper I was one of the biggest samples used in publications on this topic, our sample size may not have been sufficiently large to verify some of the associations between building characteristics and occurrence of moisture problems, such as frame material and type of windows.

In relation to the second paper of this thesis, an important study limitation is related to exposure assessment (misclassification of exposure). In our analysis, school exposure was assumed to be the same for all the pupils in the same school building. Although microenvironments could exist within buildings, we assumed that exposure in a damaged building would affect all the children using this building in a similar way. To improve the exposure assessment, the study used a semi-quantitative method (assessing extension and location of the damage) that has proven to be more related to health symptoms than a quantitative method.

Secondly, the relatively low response rate, in particular in damaged schools in Spain (54%) and The Netherlands (59%), was one of the limitations of this second paper. Nevertheless, frequencies of health symptoms reported by our study population in the last year were similar to the ones listed in other epidemiological studies (ref 30 paper II), which indicates that the population studied was a representative sample of the population.

Finally, the fact that this study is a cross sectional study could have led to the problem of reverse causation and selection bias due to avoidance of damaged schools by (the parents of) children with respiratory conditions. We consider this bias to be unlikely or only occur for severe asthma cases. Nevertheless, our results are in line with previous longitudinal studies focusing in moisture damage in homes. These prospective studies observed that exposure to moisture and dampness indoors during early life was associated with an increased risk of respiratory problems (asthma symptoms as wheezing and allergic rhinitis symptoms) later in life (Karvonen et al., 2009; Tischer et al., 2011b; Kennedy et al, 2013). Few prospective studies in schools have been carried out (Smedje et al., 2001; Zhang et al., 2011) and moisture was not their principal exposure. Moreover, due to the cross sectional nature of the study, we can only establish an association and not a causal relationship between the variables studied, that's why more prospective studies should be undertaken in schools.

6.4 Implications for public health

Healthy housing and good indoor air quality are important goals of public health. Biological indoor pollution due to dampness, moisture and mould is recognized as an emerging environmental health issue. Prevalence of dampness worldwide is remarkable, and may still increase. Climate change and its effects on the weather (i.e. storms and heavy rainfall), the subsequent rise in sea level and increased frequency and duration of floods are likely to further increase the proportion of buildings with damp problems. In addition, high energy costs will cause inadequate heating in winter in many houses (so-called fuel poverty), leading to increased condensation and indoor dampness. As problems of damp are more common in deprived neighbourhoods, a substantial proportion of that population is at higher risk of adverse health effects associated with damp indoor environments (WHO, 2009). The insufficient understanding of the causes of the dampness related health problems impair efficient control and regulation. So, even if the mechanisms are unknown and current evidence does not support measuring specific indoor microbiological factors to guide health-protective actions, there is sufficient evidence to take preventive measures against dampness in buildings.

Thus, whereas moisture damage is a recognized risk factor for health problems, there is limited knowledge on exposures to these problems in school environments and their health effects across the different climate zones in Europe. These data are urgently needed, as there is increasing concern about the indoor air quality in schools. As postulated in our results, dampness and mould in schools may have adverse respiratory health effects on children, in particular in Northern Europe. Considering the prevalence of such problems, moisture damage and dampness in schools need to be considered a serious public health issue. Avoidance or remediation of damaged schools should be attempted in efforts to provide healthy indoor environments for pupils and teachers. Moreover, these health effects are more likely to affect asthmatic children, thus specific preventive measures should be implemented in this subgroup of population, in relation to dampness and mould in school buildings. In addition, moisture exposures in school may compromise the effectiveness of dampness avoidance measures employed at home.

As the relationship between dampness, microbial exposure and health effects in schools cannot yet be quantified precisely, no health-based guideline values or thresholds can be recommended. Instead, as we stated, it is recommended that dampness and mould-related problems should be prevented (WHO, 2009; WHO, 2015). Nevertheless, we should bear in mind that intervention to reduce damp or mould in schools is expensive and requires a large commitment. This means that whenever possible, buildings should be specifically designed for primary prevention of respiratory problems associated with indoor allergen proliferation, rather than using post hoc procedures to improve indoor air quality (Peat et al., 1998). Due to the increased concern about indoor mould exposures in schools and knowing that the prevalence of dampness and mould, poor indoor air quality and inadequate ventilation in European buildings, including schools, is relatively high, a variety of programs and guidelines have been launched over the past decades. For example, the US Environmental Protection Agency has provided guidance and tools for schools in addressing mould and remediation related issues. In the European Community, 18 countries (58%) have policies to prevent exposure to mould in schools and five countries (16%) have provisions for regularly inspecting school buildings. On the other hand, twenty-eight countries (90%) have policies for minimum indoor temperature and a total of 25 countries (83%) have a policy on ventilation (WHO, 2015).

Also, although the effect sizes of building dampness exposures in health are not high and may have a small impact at the individual level, the impact at the population level is important because the prevalence of exposure to mould is common. Moreover, the range of effect sizes is consistent with the measured effects of other environmental exposures that are considered important to health, such as environmental tobacco smoke or outdoor air pollutants. In addition, the studies that have been conducted in children are probably the most reliable because the confounding effects of active smoking or occupational exposures are absent.

In relation to the study protocol, several review studies related to dampness and mould in buildings concluded that the main difficulty in drawing conclusions was that the projects have all used different protocols. A study protocol like the one proposed in this project will provide a useful assessment methodology across Europe, both from a scientific and practical point of view. Therefore, potential users of the knowledge generated in this thesis include researchers, environmental and health authorities, school management personnel, and environmental consultants. Knowledge created under this thesis (in particular considering aspects of school building investigations) is already contributing to a European wide survey on indoor air quality in schools as a part of ENHIS (Environment and Health Information System), guided by the WHO Regional Office in Europe.

Recommendations on Indoor Air Quality in school buildings (WHO, 2015)

Specific recommendations to be considered related to indoor air quality (associated with dampness and mould) in schools are:

- Elimination of moisture/mould and allergen sources in the school building.
- Proper maintenance of buildings to prevent water leaks and accumulation of moisture.
- Repair moisture building damage.

- Control the levels of dust in schools, especially with regard to asthmatic pupils and teachers (such as use of entrance mats to reduce tracked-in soil, decreasing the number of occupants per room, minimizing dust-collecting areas: such as open shelves, proper cleaning and maintenance of school building).
- Develop a strategy for heating and cooling to ensure satisfactory temperature, relative humidity and ventilation in classrooms.
- Establish and enforce maximum permitted occupation densities in classrooms.
- Periodical monitoring and assessment of Indoor Air Quality (IAQ) in schools and of pertinent health parameters in school pupils.
- Informing students, their parents and teachers about the importance of maintaining good IAQ in schools (education about exposure to dampnes and mould harmful effects).

6.5 Future research

There are several gaps in current knowledge about the characterization of exposure to dampness and mould in schools and their effects on child respiratory health. The aspects that require further research include the following.

Exposure assessment

- Risk assessment is seriously hampered by an absence of valid methods for quantitative assessment of exposure. The usual culture methods for quantifying exposure to microbes have major limitations. Non-culture methods for assessing microbial constituents, such as qPCR, appear more promising, although experience with these methods is generally limited. Therefore, more research is needed to establish better exposure assessment tools, and newly developed methods must undergo rigorous validation.
- Studies are needed that better trace long-term and individual children exposure. Experimental studies where children wear individual air samplers to trace their microbial exposure will be interesting although difficult to implement.
- Future research into the mechanisms of dampness-related asthma is recommended. A study that would join exposure assessment of all the possible dampness-related causal factors studied such as: allergens, MVOCs, microbial

markers, viruses will be challenging.

- When choosing a qualitative assessment of the dampness building exposure more studies with semi-quantitative indeces are needed using more than a two-level (no/minor versus moderate/severe water damage) classification. These studies should include in the classification the percentage of area stained in different parts of each room and the time spent in the classrooms by the pupils.
- A more accurate study is required only in Finland of the microbial exposure pattern (low and intermittent) that might have contributed to symptom occurrence in Finnish schoolchildren.

Health assessment

- Few projects have studied the association between lung function and microbial indoor exposures in pupils in schools and their results are not consistent. Moreover, studies that imply invasive health measures with children (such as blood samples) are complicate but are necessary too. To reduce recall bias, health objective outcome measures such as lung function, exhaled nitric oxide, and biomarker assessment in matrices such as blood and nasal lavage are needed.

Design

- More longitudinal studies (carried out in various geographical regions) are needed to observe the association between dampness and mould and microbial markers on long and short-term health respiratory effects on children in schools.

In this sense, the HITEA Group is working on new analyses:

1) Longitudinal analysis based on pupils diaries (conducted before and immediately after the school vacation) recording the daily presence and severity of respiratory and other symptoms among asthmatic pupils of damaged and non-damaged schools.

2) Longitudinal analysis based on lung function tests and exhaled nitric oxide measurements (conducted before and immediately after the school vacation) among asthmatic pupils of damaged and non-damaged schools.

- Renovation and repair of moisture damaged classrooms and buildings have been found to be effective at reducing mould exposure in schools and associated with improvement in building occupants' symptoms. Improvements in ventilation (e.g., increased air-exchange rates) may also affect relative humidity and concentrations of airborne viable moulds. More research is needed (preferably with a clinical trial design) on how dampness remediation and ventilation improvement can influences schoolchildren's respiratory health. Moreover, due to the limited information, studies are needed on how to choose and implement the most cost-effective intervention approach.

- Data from low and low-middle income countries in Europe on indoor dampness and mould in schools are scarce. More studies are needed in these countries. A multicenter study could be planned including data collection on schools from these European countries.

7. CONCLUSIONS

Overall, the results presented in this thesis suggest that building dampness and mould exposure in schools may affect respiratory health in children. More specifically, the following conclusions result from this thesis:

Moisture problems in schools in three climatic regions across Europe:

- Moisture problems are relatively common in schools. The prevalence of moisture problems in school buildings was 41% in Spain, 24% in Finland, and 20% in the Netherlands.
- The overall agreement between questionnaire and inspection data on moisture damage prevalence in school buildings was relatively good, but the variation in agreement between countries was large. Thus, questionnaire-based surveys can be used to assess moisture problems in school buildings, but because of large variation in agreement with inspection data, the questionnaire needs to be validated by on-site inspections in a subsample of the surveyed buildings
- The occurrence and severity of moisture problems in schools may vary across geographical areas, which can be partly explained by building characteristics. However, the estimated risk for health effects is in the same range regardless of the prevalence of such dampness indicators

Exposure to Dampness and mould in primary schools and respiratory health in children:

- Dampness and mould in schools may have adverse respiratory health effects in pupils (mostly dry cough at night). Finnish school children seem to be at higher risk, possibly due to quantitative and/or qualitative differences in exposure due to variations in climate and building characteristics.
- Associations between moisture, microbial exposure and health may vary between countries, meaning that future studies on microbial exposure across different regions and countries should also take into account differences in culture, climate and building use.
- Finnish and Spanish pupils in families where parents have low educational levels were statistically more likely to attend damp schools. Moreover, in Finland, school absence for respiratory illness was also associated with building dampness.

Thus, pupils' health and absenteeism might be affected in an inequitable way across the socioeconomic gradient. Moreover, we should keep in mind that parents are not always able to choose the school setting for their children. Thus school environments should be a Public Health priority.

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ANNEX I: Paper III

Jacobs J, Borràs-Santos A, Krop E, Täubel M, Leppänen H, Haverinen-Shaughnessy U, Pekkanen J, Hyvärinen A, Doekes G, Zock JP, Heederik D. Dampness, bacterial and fungal components in dust in primary schools and respiratory health in schoolchildren across Europe. Occup Environ Med. 2014 Oct;71(10):704-12.

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ANNEX II

Apart from the original papers included in this thesis, the PhD candidate has actively participated and co-authored four other papers in the context of the HITEA Project.

Other papers as co-author:

1. Casas L, Espinosa A, Borràs-Santos A, Jacobs J, Krop E, Heederik D, Nemery B, Pekkanen J, Hyvärinen A, Täubel M, Zock JP.Domestic use of bleach and infections in children: a multicentre cross-sectional study. Occup Environ Med. 2015 Aug;72(8):602-4.

2. Font-Ribera L, Villanueva CM, Gràcia-Lavedan E, **Borràs-Santos A**, Kogevinas M, Zock JP. Indoor swimming pool attendance and respiratory and dermal health in schoolchildren--HITEA Catalonia.Respir Med. 2014 Jul;108(7):1056-9.

3. Jacobs JH, Krop EJ, **Borràs-Santos A**, Zock JP, Taubel M, Hyvarinnen A, Pekkanen J, Doekes G, Heederik DJ; HITEA schools study consortium. Endotoxin levels in settled airborne dust in European schools: the HITEA school study. Indoor Air. 2014 Apr;24(2):148-57.

4. Peitzsch M, Sulyok M, Täubel M, Vishwanath V, Krop E, **Borràs-Santos A**, Hyvärinen A, Nevalainen A, Krska R, Larsson L. Microbial secondary metabolites in school buildings inspected for moisture damage in Finland, The Netherlands and Spain. J Environ Monit. 2012 Aug;14(8):2044-53.