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Henna Hyrkäs-Palmu

COLD WEATHER-RELATED SENSITIVITY AMONG ASTHMATICS AND DETERMINANTS AFFECTING IT

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Abstract

Asthma is a chronic airways disease affecting 7–9% of the Finnish working-age adults, and it has been reported to become more prevalent in Finland and internationally. Allergic rhinitis is also common among the general population and occurs frequently in the same individuals as asthma. Population studies have found that cold air causes respiratory symptoms commonly among the Finns. Especially those who have chronic lung diseases are sensitive to cold. In addition, the winter season is reported to increase morbidity due to respiratory diseases worldwide, and asthma patients are even at an increased risk of dying on cold days.

The aim of this study was to investigate potential sensitivity to cold air among adults with asthma and/or allergic rhinitis, their perceived functional disability and potential exacerbation of disease symptoms. We applied three population-based epidemiological studies. In two studies, populations with either allergic rhinitis or, asthma, or both were compared with individuals without either of these conditions. In the third study, asthma patients were divided into four groups based on their ACT score for asthma control.

Cold weather-related respiratory symptoms were common already among young asthmatic adults, and allergic rhinitis together with asthma increased the symptom prevalences even more than asthma alone. Among young adults with asthma, 33% reported having cold weather-related shortness of breath, whereas 51% of those who had both asthma and allergic rhinitis reported such symptoms compared with 7% without these diseases. Cold weather-related functional disability was associated with asthma and/or allergic rhinitis, and exacerbation of health problems was associated especially with asthma. Poor asthma control increased the occurrence of cold weather-related symptoms. As many as 84–87% of those who had the poorest asthma control, according to the ACT score, reported cold weather-related shortness of breath.

This study provides new evidence on the occurrence of cold weather-related respiratory symptoms and resulting functional disability in Finnish adults with asthma and/or allergic rhinitis. These results are relevant for populations living and working in cold environments and provide useful information for asthmatics on means to maintain the ability to function and work, even in the cold.

Keywords: allergic rhinitis, asthma, asthma control, cold temperature, respiratory symptoms

Hyrkäs-Palmu, Henna, Astmaa sairastavien kylmään liittyvä oireherkkyys ja siihen vaikuttavat tekijät.
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Tiivistelmä

Astma on kansantauti, jota sairastaa 7–9 % suomalaisista työikäisistä aikuisista, ja se yleistyy niin Suomessa kuin kansainvälisesti. Myös allerginen nuha on yleinen väestössä, ja sitä esiintyy useasti samoilla henkilöillä kuin astmaa. Väestötutkimuksissa on todettu kylmän ilman aiheuttavan hengitystieoireita hyvin yleisesti suomalaisilla, mutta erityisesti niillä, joilla on joku keuhkosairaus. Lisäksi tiedetään, että talvikausi lisää maailmanlaajuisesti hengitystiesairauksista johtuvaa sairastavuutta, ja astmaa sairastavilla on jopa suurentunut riski kuolla kylminä päivinä.

Tutkimuksen tarkoituksena oli tutkia aikuisten astmaa ja/tai allergista nuhaa sairastavien kylmäoireherkkyyttä sekä koettua toimintahaittaa ja sairausoireiden pahenemista kolmea väestöpohjaista kyselytutkimusta hyödyntäen. Kahdessa osajulkaisussa väestöryhmiä, joilla oli joko allerginen nuha, astma tai sekä allerginen nuha että astma, verrattiin henkilöihin, joilla ei ole kumpaakaan näistä sairauksista. Kolmannen osajulkaisun aineistossa astmaa sairastavat jaettiin neljään ryhmään astmatasapainoa kuvaavan ACT-pisteytyksen perusteella.

Kylmän ilman aiheuttamat hengitystieoireet olivat yleisiä jo nuorilla astmaa sairastavilla aikuisilla, ja allerginen nuha yhdessä astman kanssa lisäsi oireiden esiintyvyyttä enemmän kuin pelkkä astman sairastaminen. Astmaa sairastavista nuorista aikuisista 33 % ilmoitti kokevansa kylmän ilman aiheuttamaa hengenahdistusta, ja 51 % astmaa ja allergista nuhaa sairastavista. Kylmän ilman aiheuttama toimintahaitta oli yhteydessä astman ja/tai allergisen nuhan sairastamiseen, ja sairausoireiden paheneminen etenkin astman sairastamiseen. Huono astman tasapaino lisäsi kylmän ilman aiheuttamia hengitystieoireita, jopa 84–87 % ACT-pisteytyksen perusteella huonoimman astmatasapainon ryhmästä koki kylmästä ilmasta aiheutuvaa hengenahdistusta.

Tutkimus tuo uutta tietoa kylmän sään aiheuttamien hengitystieoireiden esiintyvyydestä sekä näistä aiheutuvasta toimintahaitasta astmaa ja/tai allergista nuhaa sairastavilla suomalaisilla aikuisilla. Tutkimustieto on merkityksellinen väestölle, joka asuu ja työskentelee kylmässä ympäristössä, ja jonka avulla voidaan tarjota astmaa sairastaville keinoja ylläpitämään toiminta- ja työkykyään myös kylmässä.

Asiasanat: allerginen nuha, astma, astmatasapaino, hengitystieoireet, kylmä ilma

To my family

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Oulu, October 2020 Henna Hyrkäs-Palmu

Abbreviations

ACQ	The Asthma Control Questionnaire
ACT	The Asthma Control test
aPR	Adjusted prevalence ratio
AR	Allergic rhinitis
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
ECS	The Espoo Cohort Study
EH	Exacerbation of health problems
FD	Functional disability
FINRISK	Finnish population survey on risk factors on chronic, noncommunicable diseases
GINA	The Global Initiative for Asthma
HRQL	Health related quality of life
Ig E	Immunoglobuliini E
NoFAS	The Northern Finnish Asthma Study
PAR	Perennial allergic rhinitis
PR	Prevalence ratio
SAR	Seasonal allergic rhinitis
SHS	Second hand smoke

Original publications

This thesis is based on the following original publications, which are referred to throughout the text by their Roman numerals:

I Hyrkäs H, Jaakkola MS, Ikäheimo TM, Hugg TT, Jaakkola JJK. (2014). Asthma and allergic rhinitis increase respiratory symptoms in cold weather among young adults. Respir Med. Jan;108(1):63-70.

II Hyrkäs-Palmu H, Ikäheimo TM, Laatikainen T, Jousilahti P, Jaakkola MS, Jaakkola JJK. (2018). Cold weather increases respiratory symptoms and functional disability especially among patients with asthma and allergic rhinitis. Sci Rep. Jul 4;8(1):10131.

III Hyrkäs H, Ikäheimo TM, Jaakkola JJK, Jaakkola MS. (2016). Asthma control and cold-related respiratory symptoms. Respir Med. Apr;113:1-7.

Contributions in research for publication: I participated in planning and design of the manuscript in all publications (I-III). I participated in managing the questionnaire data in studies I and III. I performed the statistical analyses for all publications and had a significant role in drafting the manuscripts for publication (I-III).

Contents

1 Introduction

Asthma is a common chronic disease in many parts of the world and its prevalence has been reported to have risen during the past decades (Eder, Ege, & von Mutius, 2006). However, some studies have reported that the prevalence of asthma has reached a plateau in some high-income countries, while in the low- and middle-income countries the prevalence is still rising fast (Borna et al., 2019; To et al., 2012). Allergic rhinitis is even more common than asthma, but it does not have as clear diagnostic criteria as asthma. Thus, many people are likely to have undiagnosed allergic rhinitis (Bousquet et al., 2008; de Marco et al., 2012). In the Finnish population, the prevalence of both asthma and allergic rhinitis has increased during the past decades. The Finnish Allergy Programme 2008-2018 had the main goal to stop the increase in the occurrence of allergies (Haahtela, von Hertzen, Mäkelä, Hannuksela, & Allergy Programme Working Group, 2008; Jousilahti, Haahtela, Laatikainen, Mäkelä, & Vartiainen, 2016). Both asthma control and the severity of asthma indicate how asthma influences everyday life, and how well it is under control with proper medication and lifestyle. Previous studies have indicated that poor asthma control has a negative impact on the quality of life. (Chen et al., 2007; Williams, Wagner, Kannan, & Bolge, 2009).

The United Airways -theory postulates the idea that asthma and allergic rhinitis are two aspects of the same disease. This theory has been introduced based on clinical, epidemiological, functional, and immunological relationships reported previously. (Compalati et al., 2010; Feng, Miller, & Simon, 2012).

People living in the northern hemisphere are frequently exposed to low air temperatures during their leisure time or while working outdoors (Mäkinen et al., 2006). The term “cold weather” does not have a singular specific definition, and there are different views about what is considered as cold weather. Cold weather has usually been defined based on absolute temperatures but could also be defined on the basis of relative temperatures, i.e., temperatures unusually cold with respect to the time and place (Ryti, Guo, & Jaakkola, 2016). According to the Finnish Meteorological Institute, the mean temperature in 2018 was 7.3 °C in Helsinki, which is the capital of Finland and located in the southern part of Finland, and it was 1.4 °C in Sodankylä, which is in the northern part of Finland. These temperatures show that people living in Finland and in other countries which are at the same latitude, are exposed to rather cold temperatures for long time periods.

Population-based epidemiological studies have investigated cold weather-related respiratory symptoms among adult general population and among groups with chronic diseases. These studies have provided evidence that cold weather-related respiratory symptoms are common and that certain groups with chronic diseases are more prone to experience these symptoms than healthy people. (Harju et al., 2010; Näyhä, Hassi, Jousilahti, Laatikainen, & Ikäheimo, 2011; Raatikka, Rytkönen, Näyhä, & Hassi, 2007). Provocation studies have provided evidence that asthmatics are sensitive to cold air (Deal, McFadden, Ingram, Breslin, & Jaeger, 1980; Koskela, H., 2007). There is also empirical evidence from cold air provocation studies that individuals with allergic rhinitis report nasal symptoms and responsiveness to cold exposure more often than those without AR (Graudenz et al., 2006; Hanes, Issa, Proud, & Togias, 2006). Controlled experimental studies and a review of those studies have indicated that exposure to cold and dry air seems to cause physiological changes in the airways. These include narrowing of the respiratory airways and changes in the epithelium of the airways. (Cruz & Togias, 2008; Liener, Leiacker, Lindemann, Rettinger, & Keck, 2003). It has also been found that airway epithelium changes can also induce chronic inflammation and decreasing lung function (Eccles, 2002; Sue-Chu, 2012). Epidemiological studies have suggested that morbidity and mortality from respiratory diseases are greater during wintertime compared to summer (Analitis et al., 2008; Michelozzi et al., 2007).

Experiencing cold weather-related respiratory symptoms and the exacerbation of asthma could lead to the avoidance of outdoor activities in wintertime, and it could also reduce the performance level in the cold environment (Michelozzi et al., 2007; Millqvist, Bengtsson, & Bake, 1987). A cross-sectional epidemiological study showed that exercise or working outside in cold weather further aggravates these symptoms, which was shown also in a review (Kotaniemi et al., 2003; Sue-Chu, 2012). These symptoms may have negative impacts on the quality of life among individuals with asthma or allergic rhinitis.

The overall aim of this thesis was to study whether asthma and allergic rhinitis increase the susceptibility to cold weather when measured in terms of respiratory symptoms and functional disability. Asthmatics have reported that cold weather during the winter has harmful effects on their everyday life. Better understanding of the occurrence of cold weather-related symptoms and their individual and environmental determinants would be useful for health care personnel. Understanding these aspects would support the development of better instruction for asthma management, including planning of asthma medication and behavior in relation to cold weather.

2 Review of the literature

2.1 Climate, weather and human exposure to cold weather and temperatures in Finland

Several epidemiological studies in Europe, including studies in Finland, have provided evidence that cold weather increases morbidity and mortality (Analitis et al., 2008; Harju et al., 2010; Michelozzi et al., 2007; The Eurowinter Group, 1997). A time-series study conducted in 15 European countries provided evidence that a 1 °C decrease in temperature was associated with a 1.35% increase in the daily number of total natural deaths. Increases in cardiovascular, respiratory, and cerebrovascular deaths were 1.72%, 3.30%, and 1.25%, respectively. (Analitis et al., 2008).

People in the northern areas of the globe are exposed to cold weather more often than people living in the vicinity of the equator. In Finland, the winter season is the longest of the four seasons, as it lasts for about 100-200 days. The temperature variation is also wide during the winter season. According to the Finnish Meteorological Institute, in February 2020 the highest temperature was 9.0 °C and the lowest was -32.3 °C in Finland, and in northern Finland the temperature has gone below -30 °C every winter season for decades now. From the health perspective, a cold environment can be defined as the environmental conditions that activate the human thermoregulatory system. Other weather conditions such as wind, humidity, and snow, can have an additional contribution to cold exposure. An experimental study of eight subjects showed that sensation of facial pain in cold temperatures increased with higher wind speeds (Gavhed, Mäkinen, Holmer, & Rintamäki, 2000). It has been reported that in the northern climate people are likely to experience longer periods of cold temperatures that may be harmful to their health while commuting to work, or during their occupational and leisure time activities (Kotaniemi, Pallasaho, Sovijärvi, Laitinen, & Lundbäck, 2002; Mäkinen et al., 2006). Some studies have reported that cold weather-related health effects may be stronger in the southern countries than in the northern countries, because people are not used to protecting themselves against the cold (Analitis et al., 2008; The Eurowinter Group, 1997). Some population groups, such as the elderly, children, and those with chronic diseases are likely to be especially susceptible to cold weather-related health effects (Harju et al., 2010; Luo, Li, Guo, Han, & Jaakkola, 2019; Michelozzi et al., 2007; Ryti et al., 2016).

2.2 Asthma

Asthma is a chronic inflammatory disease of the airways (The Global Initiative for Asthma, 2020). The diagnosis of asthma is based on the patient's medical history, a physical examination, a history of respiratory symptoms, and an assessment of the reversibility of airway obstruction in lung function measurements. The criteria for asthma diagnosis include at least one documented and reliably measured expiratory airflow limitation as introduced in the GINA guidelines. In Finland, 2 weeks monitoring of the peak expiratory flow and a significant positive bronchodilator reversibility test have been included in the asthma diagnosis (The Global Initiative for Asthma, 2020; To et al., 2012; Working group set up by the Duodecim of the Finnish Medical Society Duodecim, the Finnish Respiratory Society, the Finnish Paediatric Society and the Finnish Society of Clinical Physiology, 2012).

Careful examinations and assessments of medical history are important in evaluating whether the respiratory symptoms experienced by the person are due to asthma rather than some other respiratory disease because the symptoms of asthma are quite non-specific. Because of this, there are no internationally agreed diagnostic criteria for asthma. (Papi, Brightling, Pedersen, & Reddel, 2018). Asthma also has several clinical subtypes which are based on clinical and/or pathophysiological characteristics of the patient. The most common subtypes are allergic and non-allergic asthma, adult-onset asthma, and asthma with persistent airflow limitation. Additionally, asthma with obesity is recognized as one of the most common subtypes of asthma. (The Global Initiative for Asthma, 2020).

The key feature of asthma is airway hyper-responsiveness, which is the enhanced narrowing of the airways in response to various inhaled stimuli (Eder et al., 2006). Sometimes no specific stimuli or exposure can be identified, however. In such a case the term intrinsic asthma has been used (Peters, 2014).

2.2.1 Pathophysiology

The airway smooth muscle is hypercontractile among asthmatics and the epithelium of their airways is swollen due to inflammatory changes. As asthma is an inflammatory disease of the airways, the epithelium contains increased numbers of lymphocytes, mast cells, and eosinophils. (Barnes, 1996; Papi et al., 2018).

Recently, genome-wide association studies have reported a significant association between asthma and polymorphisms of genes, which imply abnormalities in the epithelial barrier function and innate and adaptive immune responses, and these have been suggested as contributing to the development of asthma (Papi et al., 2018). Recently, in a population-based incident case-control study, Lajunen et al. (Lajunen, Jaakkola, & Jaakkola, 2016) identified an association between polymorphisms of IL-6 and the risk of adult-onset asthma using a mechanistically formulated hypothesis as a starting point. They also presented evidence of a gene-environment interaction between these polymorphisms and tobacco smoke exposure (Lajunen, Jaakkola, & Jaakkola, 2018).

2.2.2 Incidence and burden of disease

Asthma is a common chronic disease worldwide (To et al., 2012). Diagnosed asthma has been reported to have increased, especially in high-income countries. However, there is some evidence that this increasing trend has reached a plateau in the high-income countries, while in some low- and middle-income countries the prevalence of asthma is currently increasing rapidly. (Bjerg et al., 2011; Papi et al., 2018; To et al., 2012). A study of Finnish adults showed that the prevalence of physician-diagnosed asthma has levelled off during a 20-year study period from 1996 to 2016 (Hisinger-Mölkänen et al., 2019).

The global prevalence of asthma has been reported to be 4.3%, while in Europe it has been somewhat larger at 5.1%, and some differences between countries have been reported in Europe (To et al., 2012). In Finland, the prevalence of asthma has been 9.4% (Jaakkola, M. S. et al., 2002; To et al., 2012), so it is higher than in Europe on average. A Swedish study showed that the prevalence of asthma increased from 2008 to 2016 statistically significantly. The current asthma prevalences increased from 8.1% to 9.1% among the whole study population, and the prevalence was the highest in 2016 among 16-25 years old being 11.5%. (Borna et al., 2019). A high prevalence of asthma has been reported in some southern European countries. In Italy, the prevalence of asthma was low until the 1990s but has started to rise since then. The prevalence among the Italian adult population was reported to be 6.6% in 2007-2010. (de Marco et al., 2012; Maio et al., 2016). Some of the differences reported in the asthma prevalence between different countries can be explained by the different diagnostic criteria that have been applied. The differences can also be explained by the definition of asthma used in different areas or by different definitions or reporting of respiratory symptoms (Magnus & Jaakkola, 1997). Such differences may lead to either underestimation or overestimation of the ‘true’ prevalence (Eder et al., 2006; To et al., 2012). Eder et al. (Eder et al., 2006) also suggested that the prevalence rates of both symptoms and diagnoses of asthma are likely to be influenced by the awareness of asthma in the population studied.

Asthma is a significant economic burden to many societies, as it causes both direct and indirect costs. Asthmatics require many health care services, including inpatient care and emergency visits, as well as medications and therapeutic devices. These contribute to direct costs. Indirect costs include school or workdays lost due to the exacerbations of asthma, lost productivity and travelling to health care facilities. (Bahadori et al., 2009).

2.2.3 Severity and control

Asthma severity and control are often interrelated but can be seen as two different aspects of asthma (Chen et al., 2007; Mäkikyrö, Jaakkola, & Jaakkola, 2017). It should be noted that asthma severity and asthma control contribute to the quality of health significantly and separately. Those with severe asthma can have good asthma control, and those with asthma under poor control can have mild asthma. (Chen et al., 2007; Mäkikyrö et al., 2017; Peters, Ferguson, Deniz, & Reisner, 2006). European Respiratory Society and American Thoracic Society guidelines define severe asthma as asthma that requires abundant treatment to achieve good asthma control, while The Global Initiative for Asthma (GINA) guidelines define severe asthma as requiring medication steps 4-5 during the past year or oral corticosteroids for at least 50% of the past year, or asthma which remains uncontrolled despite the abundant therapy (Papi et al., 2018). A review introduced another definition of asthma control which included impairment caused by asthma as well as risk related to it. The latter includes the potential for future adverse health events. Impairment includes functional limitations that patients may experience because of asthma symptoms. The review suggested a strategy for identifying risk factors for uncontrolled asthma, and also suggested that controlling such risk factors would improve asthma control, and thus, reduce the burden of disease related to asthma. (Schatz, 2012).

Severe and uncontrolled asthma is associated with higher total costs because of hospitalizations, ED visits, clinic visits, and higher overall treatment costs compared to mild and/or controlled asthma (Bahadori et al., 2009; Williams et al., 2009). Lee et al. (Lee, Obi, Paknis, Kavati, & Chipps, 2018) reported the health and economic burden related to asthma stratified by asthma control. They showed that patients who had poorly controlled or not well-controlled asthma experienced more anxiety disorders, depression and many sleep problems compared to those who had well-controlled asthma. The same study also showed that the estimated annual costs were highest among those with poorly controlled asthma. The costs included both direct and indirect costs. (Lee et al., 2018).

Some questionnaire-based asthma control tests have been reported for use in evaluating the level of asthma control by doctors or by the asthmatics themselves (Jia et al., 2013; Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999). The need for identifying asthmatics whose asthma is poorly controlled has become more urgent because there have been improvements in asthma treatments, and it has become more realistic to focus asthma management efforts on maintaining good asthma control or improving asthma control (Nathan et al., 2004). The most frequently used indices to assess asthma control are the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) (Jia et al., 2013). Development of the ACT was based on giving a set of questions to asthmatics concerning the influence of asthma on their symptoms and their coping in everyday life. After analysing the correlations between questions and different markers indicating asthma control, the ACT was chosen to include five questions. (Nathan et al., 2004). Melosini et al. (Melosini et al., 2012) reported that the ACT can effectively measure the current level of asthma control, but it was not found to be effective in evaluating the pulmonary function level or markers of airway inflammation. The ACT score provides a synthesis of all previously validated asthma control instruments, as its questions include i) the frequency of asthma-related symptoms, ii) the use of rescue asthma therapy, iii) the frequency of nocturnal asthma symptoms or iv) the interference of asthma with sleep, and v) the activity limitations caused by asthma (Schatz, 2012).

Many studies have reported a significant negative relationship between asthma control and health related quality of life (HRQL) (Williams et al., 2009). A similar association was found between the asthma severity and HRQL in an Italian population where asthmatics with more severe asthma experienced worse HRQL than those asthmatics whose asthma was less severe. Such an association was found to be even stronger among those who had allergic rhinitis in addition to asthma. The study based its quality of life assessment on the use of health-care resources, the occurrence of absenteeism from work or school, and daily activity limitations. (Maio et al., 2012). A Swedish study showed the same association between asthma severity and HRQL, as well as between asthma severity and societal costs (Jansson et al., 2020). Boulet and Boulay (Boulet & Boulay, 2011) presented in 2011 a review of the relationship between asthma severity and potential comorbidities.

They showed that comorbidities were more common among those who had severe asthma, and that comorbidities had adverse effects on asthma control.

Asthmatics can aim at achieving good asthma control by avoiding known or strongly suspected asthma triggers and by using regularly appropriate asthma medication. With such an approach, they can enjoy living with relatively few asthma-related symptoms and their need for ED visits and hospitalization caused by asthma is reduced. (Croisant, 2014). The GINA Guidelines (The Global Initiative for Asthma, 2020) present several currently known risk factors for poor asthma control as well as currently known risk factors which exacerbate asthma. Risk factors for poor asthma control include insufficient treatment plans for asthma, several exposures, such as smoking and allergen exposure, and comorbidities such as obesity and rhinitis. It also mentions risk factors that have been reported to lead to development of fixed airflow limitation. Further, major psychological or socioeconomic problems can worsen asthma control. (The Global Initiative for Asthma, 2020).

2.3 Allergic rhinitis

2.3.1 Pathophysiology

Allergic rhinitis has not been reported to have a standard set of diagnostic criteria, but in general it is defined as an immunologic response of nasal mucosa modulated by immunoglobulin E (Ig E) and characterized by nasal symptoms such as sneezing and/or rhinorrea (Ozdoganoglu & Songu, 2012). The allergic response in AR can be divided into an early phase response which occurs within minutes of allergen exposure, and a late-phase response, which occurs 4- to 8-hours after the exposure has taken place (Skoner, 2001). The diagnosis of AR can be confirmed by skin prick tests and testing allergen specific Ig E in serum (Wang et al., 2018). Nasal mucosa brushing has also been identified as a tool for diagnosing local AR (Hamizan et al., 2019). AR can be classified as seasonal (SAR) or perennial (PAR) and this classification is based on the timing and duration of the allergen exposure and the type of allergen and the symptoms occurring. SAR is most often caused by exposure to pollen and/or other outdoor allergens, while PAR has been reported to be caused mainly by indoor allergens, for example dust mites. Most often PAR has been defined as a rhinitis which persists more than 9 months per year and has typical symptoms for PAR, such as nasal blockage caused by swollen nasal mucosa and mucus hypersecretion. (Ciprandi, Cirillo, & Pistorio, 2008; Ozdoganoglu & Songu, 2012; Skoner, 2001). Rhinitis is also often associated with inflammation if the lower airways (Boulay, Morin, Laprise, & Boulet, 2012).

2.3.2 Incidence and burden of disease

An increase in AR prevalence has been reported especially in high-income countries, even though the prevalence of asthma has been suggested to have reached a plateau (Bjerg et al., 2011; de Marco et al., 2012; Maio et al., 2016). Changing global climate conditions, changes in hygienic or dietary conditions, and increase in the occurrence of obesity have been suggested as factors explaining this increase (Bousquet et al., 2008; Kilpeläinen, Terho, Helenius, & Koskenvuo, 2006).

Subjects with AR have reported experiencing more problems with social activities, difficulties with daily activities and worse mental well-being (including more difficulty in sleeping, more exhaustion during the day, and worse cognitive disturbances, and mood changes) than subjects without AR (Leynaert, Neukirch, Liard, Bousquet, & Neukirch, 2000). AR has a significant negative impact on patients' activities of daily living because of nasal symptoms, related fatigue, and headaches. These can lead to poor concentration and reduced productivity. (Keith, Desrosiers, Laister, Schellenberg, & Waserman, 2012).

Vandenplas et al. (Vandenplas et al., 2018) reported a systematic review of the burden of AR on work productivity. Their results found that 35.9% of subjects with AR reported impairment in their at-work performance and 3.6% lost work time due to AR. They also assessed factors that were associated with a greater impact and found that the severity of AR was most consistently a factor. (Vandenplas et al., 2018).

The World Health Organization and its Impact on Asthma (ARIA) proposed the first extensive review on the relationship between allergic rhinitis and asthma in 1999, and in 2008 the review was updated by Bousquet and colleagues. The review summarized epidemiological results between AR and asthma. It showed that having AR was also a risk factor for developing asthma, especially if the AR is persistent and severe. (Bousquet et al., 2008). A cross-sectional study of 1001 AR patients and 160 physicians who treat AR in Canada showed that common comorbid diseases and conditions, such as asthma and sleep apnea often cause an unrecognized burden of disease among those with AR. The majority of AR patients (72%) reported that AR symptoms impaired their daily lives during the allergy season, and 61% of AR patients also felt that the symptom control of AR was suboptimal during their worst month in the past year. (Keith et al., 2012).

2.4 The united airways –hypothesis

Previous studies have suggested that AR and asthma are two different aspects of the same airway disease that can thus be called the United Airways Disease, or that AR and asthma are one disease in two parts of the respiratory tract (Compalati et al., 2010; Feng et al., 2012). Compalati and colleagues carried out a review of previous studies which evaluated the link between AR and asthma, and they showed that the upper and lower airways have clinical, epidemiological, functional, and immunological relationships (Compalati et al., 2010). Feng and colleagues (Feng et al., 2012) added chronic sinusitis in their review of the united allergic airway theory. The review showed the same connection between the disorders as the review by Compalati et al., but they also addressed future study suggestions to define this theory more precisely. (Feng et al., 2012).

Similar allergens can cause or trigger AR and asthma (Feng et al., 2012). Both diseases are Ig E mediated immunological diseases and studies have suggested that AR and asthma should be approached concomitantly. AR is a significant risk factor for asthma and it often occurs before the onset of asthma. (Boulay et al., 2012; Feng et al., 2012). The presence of AR increases the risk of asthmatic attacks, as well as ER visits and hospitalizations due to asthma (Ozdoganoglu & Songu, 2012). Several reviews have summarized the evidence of the connection between AR and asthma. These have shown that appropriate treatment of AR has beneficial effect on asthma outcomes, or that it may help to prevent the occurrence of asthma. However, any direct evidence that AR therapy would prevent the development of lower airway inflammation has not been clearly shown, and there is still a lot to study to get a better view of the relationship between these diseases. (Boulay et al., 2012; Boulet & Boulay, 2011; Vignola, Chanez, & Bousquet, 2003).

Some studies have suggested several mechanisms underlying the relationship between upper and lower airway disease in AR and asthma. A review of asthma-related comorbidities suggested that AR impairs the filtering and air-conditioning functions of the nose, and this can lead to increased exposure of the lower airways to allergens and other asthma causes and triggers. (Boulet & Boulay, 2011).

2.5 Functional disability

Functional disability (FD) can include both mental and physiologic disability, and most of the previous studies have focused on occupational disability. FD is related to environmental factors, chronic diseases, or individual factors, as well as their combinations. Occupational disability can include a change in job or job responsibilities due to health reasons, lost workdays, or decreased occupational effectiveness because of illness. A cohort study of 68,686 Finnish employees studied the risk of long-term work disability among employees who had asthma and/or other chronic diseases. The study included 2,332 asthmatic employees and 66,354 without asthma, and it showed that asthma increased the risk of all-cause work disability nearly twofold. The study also reported that comorbidities increased the risk of work disability according the number of comorbidities. (Hakola et al., 2011).

The previously mentioned cold weather-related effects on performance and health may also result in FD and complaints such as musculoskeletal pain and reduced performance. A Finnish population-based cross-sectional study of 6,591 adults, aged 25-74 years showed that a substantial portion of the Finnish adults suffer from musculoskeletal pain in cold weather. (Pienimäki et al., 2014; Raatikka et al., 2007). Studies on cold weather-related cognitive performance have reported controversial results on whether cold weather has positive or negative effects on it. The results suggest that moderate cold exposure negatively affects cognitive performance by causing a distraction, but it can affect cognitive performance both positively and negatively through the mechanisms of arousal caused by the cold exposure. (Mäkinen et al., 2006).

2.6 Effects of cold climate on the respiratory system

The nasal region of the airways warms and humidifies inhaled air efficiently. Cold air is also usually very dry, and hence, inhaling cold air both lowers the temperature of the airways, as well as dries the mucosal membrane. These can lead to sensorineural stimulation and mast cell activation in order to achieve homeostasis and can cause nasal symptoms such as a runny or stuffy nose and the sensation of an itchy nose, as shown in controlled experiments in climate chambers. (Assanasen, Baroody, Naureckas, Solway, & Naclerio, 2001; Cruz & Togias, 2008; Koskela, H., 2007). Physical exercise in cold environments increases cooling and drying of the airway. Nasal breathing shifts to mouth breathing as the minute ventilation reaches

35-40 L/min, and the warming and humidification of the inhaled air shifts to lower airways (Sue-Chu, 2012). Two recent systematic reviews have summarized the evidence of the adverse health effects of cold weather (Luo et al., 2019; Ryti et al., 2016). Luo and colleagues (Luo et al., 2019) conducted a systematic review and meta-analysis of 45 epidemiological studies on the association of daily temperature and mortality conducted in China. For every 1°C increase or decrease beyond reference points, non-accidental mortality increased by 4% for cold. The rate of cardiovascular mortality increased 6%, the rate of respiratory mortality increased 2% and the rate of cerebrovascular mortality increased 3% for cold. The latitude of the residential area influenced the people's capability to adapt to the cold. (Luo et al., 2019). Ryti and colleagues (Ryti et al., 2016) reviewed studies on the health effects of cold spells. Random-effects models in their meta-analysis showed an association between cold spells and increased mortality from all nonaccidental causes (summary rate ratio 1.10, 95% CI: 1.04-1.17), cardiovascular diseases (1.11, 95% CI: 1.03-1.19) and respiratory diseases (1.21, 95% CI: 0.97-1.51). Increased morbidity related to cold spells was not possible to quantitatively summarize because of the limited number of studies suggesting it. (Ryti et al., 2016).

A report on experimental studies suggested that there are individuals whose airways are unusually sensitive to cold air exposure. One possibility can be that this reflects a failure of the mucosa to compensate for water loss. That could lead to epithelial shedding and long-term consequences of mucosal dysfunction. This effect is likely to be stronger among patients with asthma because of their increased nasal responsiveness to cold air. (Cruz & Togias, 2008). A controlled study of eight healthy subjects compared the effects of light, intermittent work done in controlled cold air and in normal indoor air. The study showed that exposure to cold air increased the numbers of inflammatory cells in the lower airways among these healthy subjects aged 20 to 43 years. (Larsson, Tornling, Gavhed, Muller-Suur, & Palmberg, 1998). A previous experimental study of 25 adults aged 21-53 years showed that facial cooling induces bronchoconstriction rapidly after the onset of exposure and that bronchoconstriction is greatest during the exposure to cold but vanished soon after the cessation of exposure. Bronchoconstriction was seen irrespective of whether the inhaled air was cold or warm if the ambient air was cold. (Koskela, H. & Tukiainen, 1995).

In a review Eccles (Eccles, 2002) hypothesised that exposure to cold air increases the risk of upper respiratory tract infections. The study suggested that inhaling cold air causes a fall in the temperature of the respiratory epithelium and this reduces the effectiveness of local respiratory defences against respiratory viruses (Eccles, 2002). Repeated and prolonged exposure to cold dry air is a significant stress to airways, but it is uncertain whether cold air is a causal factor initiating lung disease. Cold air exposure is more likely a trigger of symptoms. However, the mechanisms underlying such a triggering effect depend on individual susceptibility and ventilation level. (Koskela, H., 2007; Sue-Chu, 2012).

Cold weather-related symptoms have been studied previously among adult populations and in occupational studies. Population-based studies of 6,591 Finnish adults aged 25-74 years reported that cold air provoked symptoms, especially respiratory symptoms. The prevalence of symptoms was found to be higher among individuals with some chronic disease, and it was suggested that subjects with chronic diseases may be at a higher risk of developing adverse health effects compared to healthy subjects. (Harju et al., 2010; Näyhä et al., 2011). The quality of life may also be diminished because of cold weather-related symptoms as such symptoms can reduce the time spent engaged in outdoor activities (Harju et al., 2010). An occupational study compared 12 subjects (mean age 47 ± 2 years) and 6 controls (mean age 44 ± 2 years) before beginning new jobs, and after 6 months and 12 months working periods. At the baseline subjects started to work in a cold environment (6 days per week for 6 hours per day), while the controls worked at normal room air temperature. This study showed that 1 year of daily occupational exposure to a cold environment increased respiratory symptoms and changes in lung function. For example, the central airway resistance increased statistically after 6 months among subjects. (Jammes et al., 2002).

2.6.1 Asthma and cold exposure

Asthmatics' ability to condition (i.e. warm and moisten) inhaled air is reduced. Hence, inhaling cold and dry air into the lower airways of subjects with asthma will induce inflammation (Assanasen et al., 2001). Exposure to cold air can be mediated also indirectly through cooling of skin. An experimental study of 10 adult asthmatics reported that skin cooling introduced mild airway obstruction among these patients. (Skowronski, Ciufo, Nelson, & McFadden, 1998). Furthermore, a clinical provocation study investigated the effects of cold exposure and high altitude by comparing indoor skiing where the temperature was ≤ -5°C, and an expedition test where the measurements were taken at 7 different altitudes from 750 m to 5963 m, while the temperatures were from 24°C to -12°C. They showed that cold exposure itself increased airway obstruction as well as neutrophilia in the sputum as a marker of inflammation, and some subjects also reported an increased occurrence of asthmatic symptoms. (Seys et al., 2013).

Cold air induces hyperpnea, which can lead to bronchoconstriction among individuals with asthma. When the ventilation level exceeds the level where the breathing switches from nasal to mouth breathing, cold air is no longer properly conditioned. Sensitive asthmatics may react to this by bronchoconstriction irrespective of the level of asthma control. A literature review and one experimental study have shown that whole-body cold air exposure does not have as severe effects when the inhaled air is warm compared to when cold air is inhaled. (Koskela, H. & Tukiainen, 1995; Koskela, H., 2007).

Experimental studies have shown that breathing cold air affects the pulmonary function. They have reported significant decreases in FEV_1 among both asthmatics and subjects who did not have asthma. (Koskela, H., Tukiainen, Kononoff, & Pekkarinen, 1994; Sandsund, Reinertsen, Holand, & Bjermer, 2007). Sandsund et al. (Sandsund et al., 2007) reported that bronchoconstriction was observed when the subjects took an exercise test in the cold regardless of the temperature of the inhaled air. The subjects performed a similar exercise in the same climatic temperature twice, and the inhaled air was either cold or warm in a randomly assigned order. The results suggests that the reflex mechanism could be more relevant than previously thought. (Sandsund et al., 2007).

Two population-based epidemiological studies have shown that adult subjects with asthma report more cold weather-related symptoms, especially respiratory symptoms, than those without asthma (Kotaniemi et al., 2003; Näyhä et al., 2011). A study of 6,633 Finnish adults aged 20-69 years living in the central and southern parts of Finnish Lapland reported that shortness of breath in cold weather increased substantially if they had asthma. Shortness of breath was reported for 3.2-14.2% of healthy adults, and for asthmatics shortness of breath was reported by 51.3-77.8%. (Kotaniemi et al., 2003). Another study of 6,951 Finnish adults aged 25-74 years showed that the prevalence of cold weather-related respiratory symptoms ranged from 18.2 to 21.3% among healthy adults and increased to 69.2-77.5% among those with asthma. (Näyhä et al., 2011).

2.6.2 Allergic rhinitis and cold exposure

There is some evidence from controlled experimental human studies that exposure to cold air leads to experiencing more symptoms such as nasal congestion and sneezing among those with AR and asthma compared to healthy individuals (Cruz

& Togias, 2008; Koskela, H., 2007). Cruz and Togias (Cruz & Togias, 2008) discussed the upper airways reactions to cold air in their review. They hypothesized that cold air breathing may cause long-term mucosal dysfunction in subjects whose ability to condition inhaled air is reduced (Cruz & Togias, 2008). A review by Koskela (Koskela, H., 2007) provided evidence that nasal breathing in cold air causes rhinorrhea, congestion and sneezing, and these responses are suggested to be greater among those with AR than healthy subjects. These are considered to be short-term responses to cold air and the trigger site is the nasal cavity. Long-term responses of exposure to cold air occurs as damage in the airway epithelium and changes in the airway's wall structure and function. Asthma enhances the cold weather-related responses even more, with or without AR. (Koskela, H., 2007). Hanes and colleagues (Hanes et al., 2006) conducted nasal provocation tests with a cold dry air stimulus. The study groups consisted of 24 subjects with AR and asthma, and 17 subjects with AR alone. All the subjects were aged 21-68 years. They studied nasal symptoms using visual analogue scales and determined the histamine and lysozyme levels from nasal lavages. The study showed that the cold dry air stimulus caused significantly increased scores for nasal symptoms among the subjects with AR and asthma compared to the subjects with AR only. The histamine and lysozyme levels also increased significantly among the subjects with AR and asthma, whereas among the subjects with AR alone the levels of histamine and lysozyme did not increase significantly. (Hanes et al., 2006). An intervention study of adults aged 18 to 55 years, living in Austria and Germany, had contrasting results. This controlled intervention study had 18 participants in an exercise group and 22 participants in a control group. The exercise group did eight recreational guided winter exercise during the ten-day study period. The study showed that the allergic airway inflammation, measured as the fractional exhaled nitric oxide (FENO) value, reduced and improvements in allergic symptoms were seen after the winter exercise period. (Prossegger et al., 2019). A cross-sectional study of 6,633 adults aged 20-69 years compared healthy adults to those with AR or conjunctivitis, and it reported that the prevalence of cold weather-related shortness of breath was higher among adults with AR (10.3-23.6%) compared to healthy subjects (3.2-14.2%) (Kotaniemi et al., 2003).

A case-control study of 32 patients with AR and 16 controls assessed the nasal mucosa's response to sudden temperature change. The results suggested that hyperreactivity of the nasal mucosa started immediately after the temperature change had occurred in the AR group, and the inflammatory nasal response was more pronounced in the AR group compared to the control group. This study showed epithelial shedding and an inflammatory response after exposure had taken place. (Graudenz et al., 2006).

2.6.3 Other chronic respiratory diseases and cold exposure

Donaldson et.al. (Donaldson, Goldring, & Wedzicha, 2012) studied cold weather-related health effects among 307 chronic obstructive pulmonary disease (COPD) patients. In the wintertime, these patients experienced more severe exacerbations, which involved symptoms of common cold and cough, compared to during the warm season. These exacerbations needed longer recovery times and were more likely to result in hospital admissions compared to during the warm season. 8.4% of the exacerbations which occurred in the cold season resulted in hospital admissions, compared to 4.6% of the exacerbations which occurred in the warm season. (Donaldson et al., 2012). Experimental studies have also shown that high ventilation level of cold air induces bronchoconstriction among COPD patients and their exercise capacity decreases in cold environments (Koskela, H. O., Koskela, & Tukiaineu, 1996; Koskela, H., Pihlajamäki, Pekkarinen, & Tukiainen, 1998). A review has shown a higher COPD mortality in winter compared to in the spring and summer and COPD patients have also reported lower health-related quality of life scores in the winter than in the spring and summer. (Donaldson & Wedzicha, 2014).

2.7 Questionnaires as a study tool

Questionnaires are widely used in health and epidemiologic research. In respiratory epidemiology, questionnaires have been used since 1960s when the Medical Research Council first developed a standardized questionnaire (Cotes & Chinn, 2007). Since then several questionnaires which reflect the main focus areas within respiratory research have been developed based on the Medical Research Council Questionnaire (Bellia et al., 2003).

The mode of questionnaire administration affects the data quality and different modes have different level of bias. Postal self-administrated questionnaires can achieve a high population coverage and they are easier to conduct than interviews. Self-administrated questionnaires are also useful for longitudinal research where it is necessary that answers are comparable between different research periods. However, questionnaires may be sensitive to information bias, and self-administrated questionnaires are considered to cause the recipients a degree of cognitive burden. (Bowling, 2005).

A review showed that there are differences in reporting disease symptoms or health problems between women and men. These differences can be seen in different study populations regardless the study format or whether the symptoms are inquired prospectively or retrospectively. Women also seem to be more willing to answer health related questionnaires and participate health research. (Barsky, Peekna, & Borus, 2001; Mindell et al., 2015). Participation rates in population-based epidemiologic studies have been declining during past decades which has to be taken into account when interpreting the results (Borodulin et al., 2015; Galea & Tracy, 2007). A review of European studies showed that older age groups are more willing to participate to health surveys than younger age groups (Mindell et al., 2015).

2.8 Gaps in the knowledge

It is well known from previous studies that individuals with chronic respiratory diseases are more susceptible to cold weather-related health problems. Provocation studies have shown that inhaled cold air induces changes in the upper and lower airways which can cause substantial health effects in subjects with asthma or AR (Cruz & Togias, 2008; Koskela, H., 2007). Previous population-based studies have had a wide age range (Kotaniemi et al., 2003; Näyhä et al., 2011), but there are no studies that have focused on young adults and how much they experience cold weather-related health effects. The united airways -hypothesis is established based on clinical and provocation studies which have indicated that asthma and AR are two aspects of the same disease (Boulay et al., 2012; Compalati et al., 2010; Feng et al., 2012). Population-based studies have not yet assessed the connection between asthma and AR widely, and there is a lack of studied knowledge on cold weather-related health problems among this group.

Occupational studies and studies of athletes have reported cold weather-related functional disabilities and health problems (Mäkinen & Hassi, 2009). A Finnish study of 68,686 employees showed that having asthma increased the risk of long-term all-cause work disability and the risk increased further with chronic co-morbidities, but AR was not among the studied co-morbidities (Hakola et al., 2011). Cold weather-related functional disability and health problems have not been studied more widely in the general population and especially among those who have asthma and/or AR.

Asthma control and severity are assessed on the impact of asthma on an individual's everyday life and the level of medication which is needed to maintain the quality of life so it is as good as it can be with the disease (Papi et al., 2018; The Global Initiative for Asthma, 2020). Previous studies have reported the connection between asthma control and overall quality of life, but the connection between asthma control and cold weather-related respiratory symptoms has not been studied before.

3 Aims and hypotheses of the study

The overall aim of this research project was to investigate whether asthma and/or allergic rhinitis increase the susceptibility to cold weather manifested as the increased occurrence of respiratory symptoms and functional disability. The specific objectives were:

1. To study the relations between the presence of asthma and/or allergic rhinitis and the occurrence of cold weather-related respiratory symptoms among young adults. (Study I)
2. To study the relations between the presence of asthma and/or allergic rhinitis and the occurrence of cold weather-related functional disability and exacerbation of health problems among adults. (Study II)
3. To study the relations between the level of asthma control and the occurrence of cold weather-related respiratory symptoms. (Study III)

The main hypotheses of this study were:

1. Young adults with asthma and/or allergic rhinitis are more susceptible to experiencing cold weather-related respiratory symptoms than subjects without these conditions. (Study I)
2. Adults with asthma and/or allergic rhinitis experience more cold weather-related functional disability than subjects without these underlying diseases. (Study II)
3. Cold weather exacerbates health problems more among subjects with asthma and/or allergic rhinitis than subjects without these diseases. (Study II)
4. Subjects with poor asthma control are more susceptible to experiencing cold weather-related respiratory symptoms than subjects with good asthma control. (Study III)

4 Methods

4.1 Study populations

This thesis used data from three Finnish population-based epidemiological studies to examine the objectives presented in the previous chapter. Table 1 presents the summary of these studies.

Table 1. Description of the study populations, and determinants of interest, outcomes and covariates which were used in the analyses.

Study descriptions	The Espoo Cohort Study	FINRISK 2007 & 2012	The Northern Finnish Asthma Study
Study design	Population-based cross-sectional study	Population-based cross-sectional study	Population-based cross-sectional study
Age	20-27	25-74	17-73
Study area	Local (City)	National	Regional (Hospital District)
Data collection	Self-administrated questionnaire	Self-administrated questionnaire and physical measurements	Self-administrated questionnaire
Determinants of interest	Asthma, allergic rhinitis asthma+allergic rhinitis	Asthma, allergic rhinitis asthma+allergic rhinitis	Asthma control, measured by ACT
Outcomes	Shortness of breath, phlegm production, wheezing, prolonged cough, chest pain	Functional disability, exacerbation of health problems	Shortness of breath, phlegm production, wheezing, prolonged cough, chest pain
Covariates	Gender, age, cohabitation, education, having children, smoking, SHS, cold exposure time (in hours per week	Age, BMI, cohabitation, education, type of work, smoking, SHS, other chronic diseases	Age, BMI, smoking, cohabitation, education, SHS, COPD, AR, CVD

4.1.1 The Espoo Cohort Study, ECS

The source population for the Espoo Cohort Study included all children living in the city of Espoo born between January 1, 1984 and December 31, 1989. Espoo is the second largest municipality in Finland, with a population of 279,044 in 2017, located across the western border of Helsinki (60°N, 24°E). A parent administered baseline questionnaire was distributed in March 1991 to a random sample of children drawn from the roster of Finland's Statistical Center (Jaakkola, J. J., Jaakkola, & Ruotsalainen, 1993). The baseline study population included 2568 children whose parents filled in the questionnaire (response rate 80.3%). We conducted a 20-year follow-up in 2010-2011 directed at 2534 members of the cohort for whom the Population Registry provided a contact address. Subjects were 20-27 years old when the data collection was conducted. A total of 1623 subjects answered the self-administered follow-up questionnaire (response rate 64.0%) and these subjects form the study population for Study I.

4.1.2 The FINRISK 2007 and FINRISK 2012 studies

The data analysed in this study consisted of the National FINRISK 2007 and FINRISK 2012 studies conducted by the National Institute for Health and Welfare in Finland. The FINRISK 2007 and 2012 surveys were carried out for a stratified random sample of the population aged 25-74 years drawn from the Finnish population register (Borodulin et al., 2015). A random sample of the main study population was invited to participate in sub-studies exploring weather and temperature related health phenomena conducted during each survey. Those who agreed to participate also answered The Oulu Cold and Health Questionnaire, which was designed by a specialist study team (Ikäheimo et al., 2014). This questionnaire data was linked to the FINRISK main study containing questionnaire information on health and lifestyles on an individual basis.

4.1.3 The Northern Finnish Asthma Study, NoFAS

The Northern Finnish Asthma Study (NoFAS) is a population-based cross-sectional study of 17-73 year old adults with asthma living in Northern Finland. The source population consisted of subjects who had received reimbursement for asthma medication from the Social Insurance Institution of Finland and who lived in the Oulu University Hospital District (= the Northern Ostrobothnia Hospital District) in 2012. The Oulu University Hospital District is geographically the largest hospital district in Finland, covering 51.5% of the overall area. A random sample of 5,000 subjects with an asthma diagnosis received two self-administrated questionnaires, the basic NoFAS questionnaire and the St George's Respiratory Questionnaire (Jones, Quirk, & Baveystock, 1991). A total of 1995 subjects (40.0% response rate) form the study population for Study III.

4.2 Determinants of interest

In Studies I and II, the determinant of interest was the presence of AR and/or asthma. The determinant had four categories according to the presence of asthma and/or AR: 1. asthma and AR, 2. asthma without AR, 3. AR without asthma, and 4. neither asthma or AR. The latter formed the reference category. In Study I, we used definitions of current asthma and current AR to form the categories of the determinants. Current asthma was defined based on having "doctor-diagnosed asthma ever" AND ("the use of any asthma medication" OR "the occurrence of asthma-related symptoms" during the past 12 months) (Fig. 1). Current AR was defined in a similar way using AR specific questions (Fig. 2). In Study II, the groups were defined based on question: "Have you ever been diagnosed as having asthma?" and "Have you ever had hay fever or other allergic nasal symptoms?".

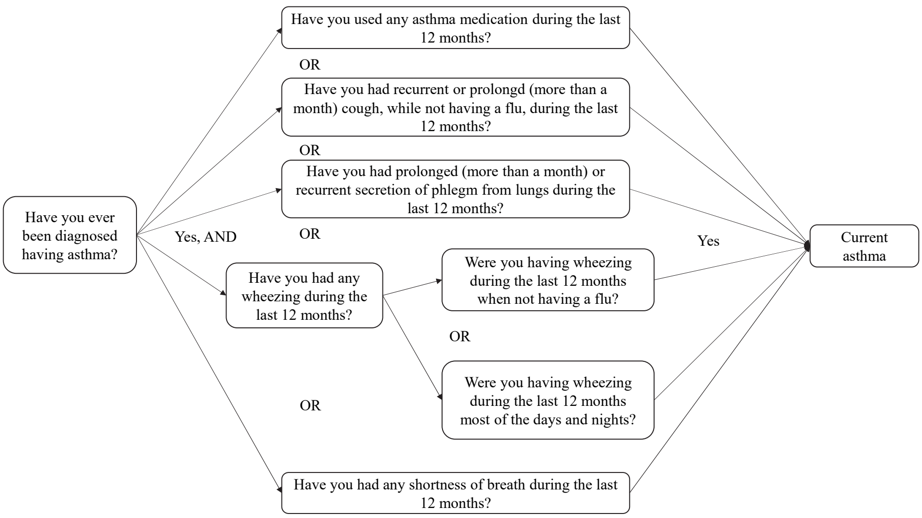

Fig. 1. The definition of current asthma based on questionnaire answers. Modified from Study I.

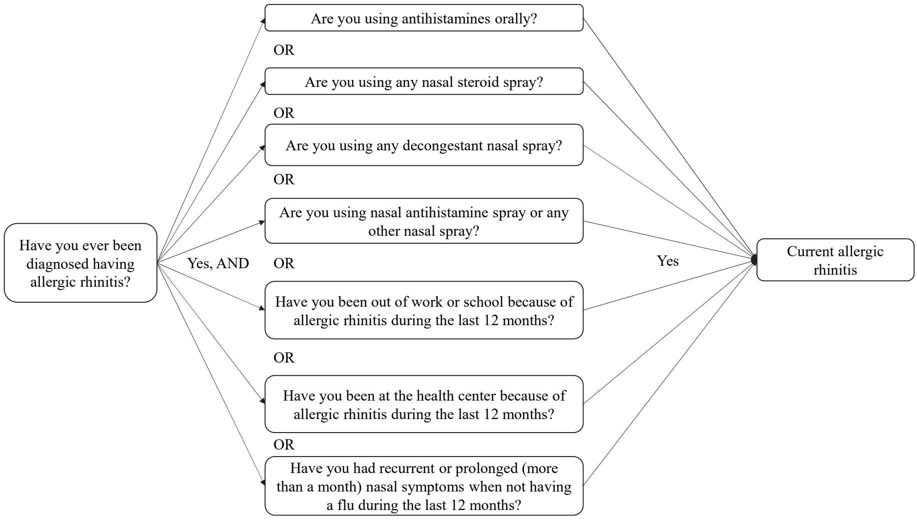

Fig. 2. The definition of current allergic rhinitis based on questionnaire answers. Modified from Study I.

In Study III, the determinant of interest was asthma control. We used the Asthma Control Test (ACT) to measure the subjects' asthma control (Nathan et al., 2004). ACT is a sum of five questions which are listed as follows. 1. During the past 4 weeks, how much of the time did your asthma keep you from achieving much at work, school or at home? 2. During the past 4 weeks, how often did you experience shortness of breath? 3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning? 4. During the past 4 weeks, how often have you needed your rescue inhaler or nebulizer asthma medication (such as salbutamol)? 5. How would you rate your asthma control during the past 4 weeks? Every question has 5 answering choices which provides 1 to 5 points so the ACT can have scores ranging from 5 to 25. An ACT score of 5 indicates uncontrolled asthma and a score of 25 indicates totally controlled asthma. Subjects were divided into quartiles based on the ACT scores, as: Q1 = 18 or lower, Q2 = 19-21, Q3 = 22-23 and Q4 = 24-25.

4.3 Outcomes

The outcomes of interest in Studies I and III were five cold weather-related respiratory symptoms. These symptoms were shortness of breath, cough, wheezing, phlegm production and chest pain. The subjects could indicate as many of these symptoms that they experienced in cold weather.

In Study II the outcomes of interest were cold weather-related functional disability (FD) and worsening of disease symptoms or exacerbation of health (EH). FD and EH were defined based on questions: “In which situations do you feel cold to be a disadvantage in wintertime? (home inside, home outside, commuting, work outside, work inside, during hobbies or leisure time, or never)”. If cold was felt as a disadvantage in some situation, the following details were sought: “How serious are these disadvantages? a) feeling uncomfortable, b) experiencing functional disadvantage, and/or c) feeling that cold air impairs health or exacerbates symptoms of the disease”. For our analyses, we decided to use replies b and/or c because feeling uncomfortable can include any kind of uncomfortable feeling and for example the feeling could be due to too little or too much clothing.

4.4 Covariates

The covariates used in all the studies are introduced in Table 1. The following covariates were adjusted in all of the included studies as potential confounders of the examined relations: age, marital status, education, smoking and second hand smoke (SHS) exposure.

4.5 Ethical considerations

The Espoo Cohort study and the Northern Finnish Asthma study were given a statement by the Ethics Committee of the Oulu University Hospital (ECS:EETTMK: 8/2009; NoFAS: EETTMK: 89/2011). The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District had given a statement for the FINRISK studies. The participants of all studies signed informed written consent, and the results were presented at the group level only.

4.6 Statistical methods

In Study I, we estimated the relations between the presence of asthma and/or allergic rhinitis and the occurrence of cold weather-related symptoms using prevalence ratios (PR) and their 95% confidence intervals (95% CI) as the measure of association. In the crude analyses, we estimated the prevalence ratio of each cold weather-related respiratory symptom for all the disease groups of interest.

In Study II we examined the relations between the presence of asthma and/or allergic rhinitis and the occurrence of cold weather-related FD and EH, by applying PR and their 95% CI. We also conducted stratified analyses by excluding 3275 subjects with a cardiovascular disease.

In Study III we estimated the relations between the level of asthma control and the occurrence of cold weather-related respiratory symptoms applying PR and their 95% CI. In the crude analysis we compared the prevalence of the outcomes in four categories of asthma control, i.e. Q1, Q2, Q3 and Q4. These were formed based on the quartiles of the ACT distribution, using the fourth category Q4 representing the best asthma control as the reference category. We also explored whether BMI or smoking influenced the relations between asthma control and the occurrence of cold weather-related respiratory symptoms by stratified analyses.

Statistical analyses were carried out separately for men and women, apart from in Study I. Multivariate analyses were conducted applying a Poisson regression using a logarithmic link function and the analyses were carried out using the GENMOD-procedure in the SAS software. SAS version 9.3 was used in Studies I and III and version 9.4 in Study II (SAS Institute, Inc., Cary, North Carolina).

5 Results

The main results from Studies I-III are presented here. More detailed results are found in the original articles given as appendices to this thesis.

5.1 Characteristics of the study populations

The characteristics of the study populations are presented in Table 2. The distributions of men and women were similar in Studies I and II. In Study III the proportion of women was slightly larger than in Studies I and II.

Table 2. Characteristics of the study populations in studies I-III.

Characteristic	ECS N (%)	FINRISK 2007 &2012 N (%)	NoFAS N (%)
Total	1623	7330	1995
Gender			
Men	754 (46.5)	3369 (46.0)	692 (34.7)
Women	869 (53.5)	3961 (54.0)	1303 (65.3)
Age			
<30	1623	573 (7.8)	212 (10.6)
30-39	N/A	1151 (15.7)	268 (13.4)
40-49	N/A	1394 (19.0)	354 (17.7)
50-59	N/A	1649 (22.5)	646 (32.4)
>60	N/A	2563 (35.0)	515 (25.8)
BMI			
<20	N/A	240 (3.3)	83 (4.2)
20-≤25	N/A	2464 (33.6)	637 (32.5)
25-≤30	N/A	2916 (39.8)	706 (36.1)
30-≤35	N/A	1180 (16.1)	367 (18.7)
>35	N/A	529 (7.2)	165 (8.4)
Marital status			
Single	1003 (61.9)	961 (13.1)	276 (13.9)
Marriage/ Cohabitation	610 (37.7)	5314 (72.6)	1461 (73.3)
Divorced, separated or widowed	6 (0.4)	1046 (14.3)	255 (12.8)
Education			
Low	877 (54.2)	2141 (29.3)	503 (25.3)
Medium	326 (20.1)	3417 (46.8)	1021 (51.4)
High	415 (25.7)	1742 (23.9)	462 (23.3)

Characteristic	ECS N (%)	FINRISK 2007 &2012 N (%)	NoFAS N (%)
Smoking			
Current smoker	460 (28.4)	1382 (19.0)	365 (18.5)
Ex-smoker	174 (10.7)	1877 (25.8)	591 (30.0)
Never smoker	986 (60.9)	4030 (55.3)	1014 (51.5)
No asthma or allergic rhinitis	1127 (69.4)	4343 (59.5)	N/A
Allergic rhinitis without asthma	332 (20.5)	2248 (30.8)	N/A
Asthma without allergic rhinitis	54 (3.3)	190 (2.6)	1127 (58.2)
Asthma with allergic rhinitis	110 (6.8)	524 (7.2)	811 (41.9)

5.2 Asthma, allergic rhinitis, and cold weather-related respiratory symptoms among young adults

The results of Study I show that asthma was strongly related to experiencing cold weather-related respiratory symptoms in the population of young adults. The prevalence ratios of cold weather-related symptoms followed three patterns (Table 3). First, cold weather-related shortness of breath and wheezing were slightly increased among subjects with AR only, substantially increased among asthmatics without AR (adjusted PR shortness of breath 4.53, wheezing 10.70), and even more strongly increased among asthmatics with AR (shortness of breath 7.16, wheezing 13.05). Second, the occurrence of cold weather-related phlegm production was related to asthma about equally strongly among those with and without AR (2.51 for asthma without AR and 3.69 for asthma with AR). Phlegm production was the only symptom that showed a statistically significant increase when having AR alone (1.66, 95% CI 1.15-2.38). Finally, asthma was related to increased occurrence of cold weather-related cough and chest pain, while AR only showed marginally increased risks of cold weather-related symptoms (cough: PR 3.41 for asthma without AR and 4.18 for asthma with AR; chest pain: PR 2.53 for asthma without AR and 2.62 for asthma with AR).

Table 3. Prevalences (%) and prevalence ratios (PR) and their 95% confidence intervals (CI) of cold weather-related respiratory symptoms among 20-27-year old women and men (ECS-study) according to having asthma with or without allergic rhinitis, and allergic rhinitis alone. Modified from Study I.

Cold weather-related symptoms	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
Shortness of breath			
Healthy	73 (6.8)	1.00	1.00
Allergic rhinitis without asthma	22 (6.9)	1.02 (0.64-1.62)	1.03 (0.65-1.62)
Asthma without allergic rhinitis	17 (32.7)	4.84 (3.09-7.57)	4.53 (2.93-6.99)
Asthma with allergic rhinitis	54 (51.4)	7.61 (5.70-10.16)	7.16 (5.30-9.67)
Phlegm production			
Healthy	76 (7.0)	1.00	1.00
Allergic rhinitis without asthma	39 (12.3)	1.74 (1.21-2.51)	1.66 (1.15-2.38)
Asthma without allergic rhinitis	10 (19.2)	2.73 (1.50-4.97)	2.51 (1.37-4.62)
Asthma with allergic rhinitis	27 (25.7)	3.65 (2.47-5.40)	3.69 (2.49-5.47)
Wheezing			
Healthy	22 (2.0)	1.00	1.00
Allergic rhinitis without asthma	10 (3.1)	1.54 (0.74-3.23)	1.59 (0.77-3.28)
Asthma without allergic rhinitis	12 (23.1)	11.33 (5.94-21.61)	10.70 (5.38-21.29)
Asthma with allergic rhinitis	27 (25.7)	12.62 (7.46-21.36)	13.05 (7.75-22.00)
Prolonged cough			
Healthy	63 (5.8)	1.00	1.00
Allergic rhinitis without asthma	18 (5.7)	0.97 (0.58-1.61)	0.97 (0.58-1.62)
Asthma without allergic rhinitis	12 (23.1)	3.96 (2.28-6.86)	3.41 (1.97-5.87)
Asthma with allergic rhinitis	27 (25.7)	4.41 (2.94-6.60)	4.18 (2.73-6.41)
Chest pain			
Healthy	27 (2.5)	1.00	1.00
Allergic rhinitis without asthma	6 (1.9)	0.75 (0.31-1.81)	0.76 (0.33-1.77)
Asthma without allergic rhinitis	3 (5.8)	2.31 (0.72-7.36)	2.53 (0.82-7.79)
Asthma with allergic rhinitis	6 (5.7)	2.29 (0.97-5.41)	2.62 (1.09-6.28)

5.3 Asthma, allergic rhinitis and cold weather-related functional disability and exacerbation of health

5.3.1 Cold weather-related functional disability in relation to allergic rhinitis and/or asthma

Figure 3 presents results showing that among the total study population, 20.3% of the participants reported FD related to cold weather. Men reported it slightly more commonly (23.4%) than women (17.6%). The prevalence of FD was lowest in the reference group among both men (21.9%) and women (15.3%). Subjects with allergic rhinitis alone experienced cold weather-related FD more commonly (25.1% and 19.2%) with an adjusted PR of 1.19 (95% CI 1.04-1.37) among men and 1.26 (95% CI 1.08-1.46) among women, as shown in Table 4. The presence of asthma alone increased cold weather-related FD slightly more, giving an adjusted PR of 1.29 (95% CI 0.93-1.80) for men and 1.36 (95% CI 0.92-2.02) for women. The presence of allergic rhinitis in addition to asthma did not increase the effect estimates among men, resulting in similar adjusted PR for those who had allergic rhinitis only, the estimate being 1.16 (0.90-1.50) for men, or for those who had asthma only, the estimate being 1.40 (1.12-1.76) for women.

Table 5 presents the results of sensitivity analyses in which we excluded those with a cardiovascular disease. Even among this sub-population, the pattern of results followed the same trend as the men's results in the total population. The adjusted PRs were of the same magnitude as in the total population.

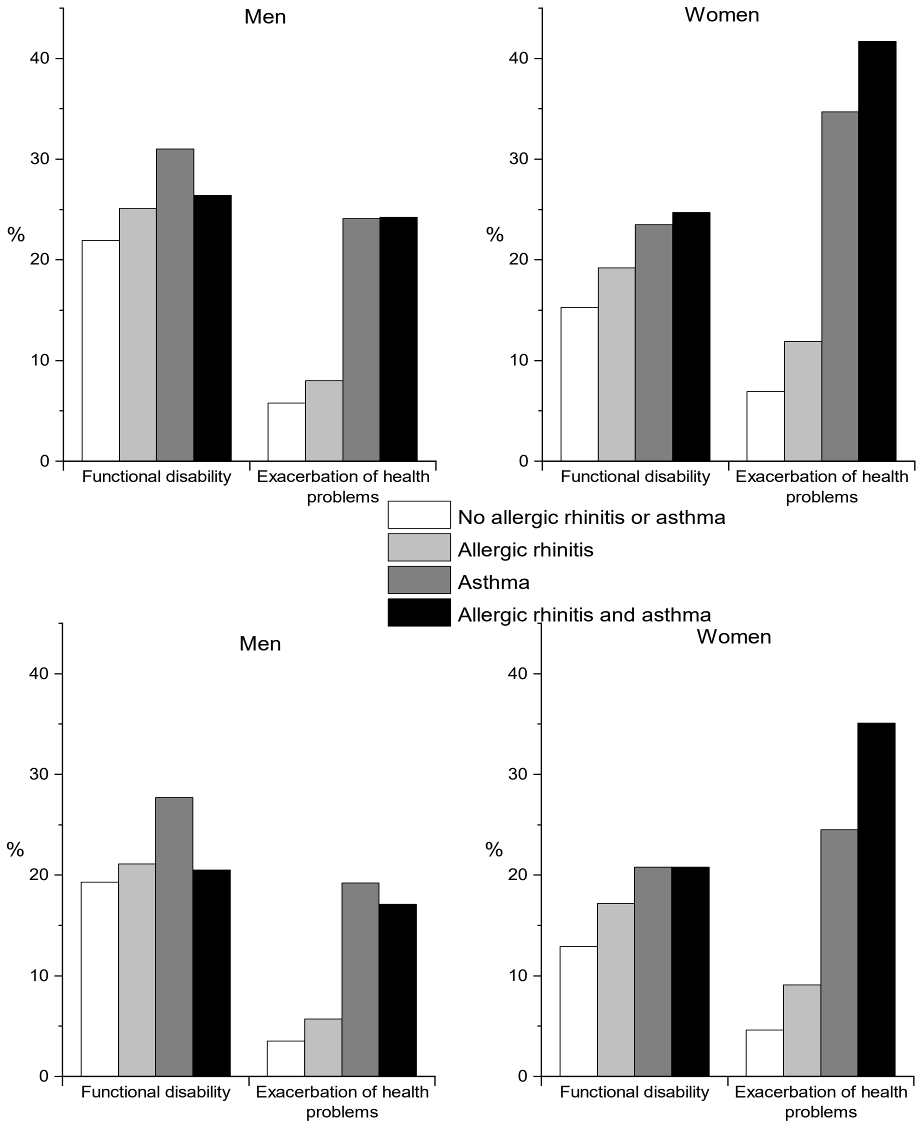

Fig. 3. Reported cold weather-related FD and EH according to having asthma and/or AR or neither of these. Results from the whole study population (upper figures) and from the stratified population (lower figures) which did not include subjects with any CVD. Modified picture from Study II.

Table 4. Cold weather-related FD among the 25-74-year old women and men (FINRISK ColdHeat-substudy). Modified from Study II.

Determinant category	Men			Women		
	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
No asthma or allergic rhinitis (reference)	462 (21.9)	1.00	1.00	330 (15.3)	1.00	1.00
Allergic rhinitis without asthma	233 (25.1)	1.15 (1.00-1.32)	1.19 (1.04-1.37)	249 (19.2)	1.26 (1.08-1.46)	1.26 (1.08-1.46)
Asthma without allergic rhinitis	27 (31.0)	1.42 (1.03-1.96)	1.29 (0.93-1.80)	23 (23.5)	1.54 (1.06-2.23)	1.36 (0.92-2.02)
Asthma with allergic rhinitis	48 (26.4)	1.21 (0.94-1.55)	1.16 (0.90-1.50)	83 (24.7)	1.62 (1.31-2.00)	1.40 (1.12-1.76)

Table 5. Cold weather-related FD among the 25-74-year old women and men (FINRISK ColdHeat-substudy), subjects with CVD excluded. Modified from Study II, supplementary Table S1.

Determinant category	Men			Women		
	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
No asthma or allergic rhinitis (reference)	218 (19.3)	1.00	1.00	166 (12.9)	1.00	1.00
Allergic rhinitis without asthma	104 (21.1)	1.10 (0.89, 1.35)	1.12 (0.91, 1.38)	132 (17.2)	1.33 (1.08, 1.65)	1.32 (1.06, 1.64)
Asthma without allergic rhinitis	13 (27.7)	1.44 (0.89, 2.32)	1.48 (0.93, 2.37)	11 (20.8)	1.61 (0.93, 2.76)	1.68 (0.99, 2.85)
Asthma with allergic rhinitis	18 (20.5)	1.06 (0.69, 1.63)	1.13 (0.74, 1.74)	32 (20.8)	1.61 (1.14, 2.26)	1.44 (0.98, 2.10)

5.3.2 Cold weather-related impairment of health and exacerbation of disease symptoms in relation to allergic rhinitis and/or asthma

The overall prevalence of cold weather-related EH was 10.3%, 7.9% among men and 12.3% among women (Fig. 3). Allergic rhinitis alone increased the experience of cold weather-related EH significantly with an adjusted PR of 1.53 (1.15-2.04) for men and 1.78 (1.43-2.21) for women. The presence of asthma without allergic rhinitis was a substantially stronger determinant, with an adjusted PR of 4.28 (2.88-6.36) for men and 3.77 (2.67-5.34) for women. As shown in Table 6, allergic rhinitis in addition to asthma did not influence the effect estimate much among men (adjusted PR of 4.02 (2.89-5.59)), but among women the adjusted PR was 4.60 (3.69-5.73) i.e. stronger than in relation to asthma only.

Table 6. Cold weather-related EH among the 25-74-year old women and men (FINRISK ColdHeat-substudy). Modified from Study II.

Determinant	Men			Women		
category	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
No asthma or allergic rhinitis (reference)	123 (5.8)	1.00	1.00	149 (6.9)	1.00	1.00
Allergic rhinitis without asthma	74 (8.0)	1.37 (1.04-1.81)	1.53 (1.15-2.04)	155 (11.9)	1.73 (1.40-2.14)	1.78 (1.43-2.21)
Asthma without allergic rhinitis	21 (24.1)	4.14 (2.75-6.24)	4.28 (2.88-6.36)	34 (34.7)	5.04 (3.69-6.89)	3.77 (2.67-5.34)
Asthma with allergic rhinitis	44 (24.2)	4.15 (3.05-5.65)	4.02 (2.89-5.59)	140 (41.7)	6.05 (4.96-7.39)	4.60 (3.69-5.73)

The results of the sensitivity analyses showed greater effect estimates in the sub-population of subjects without any cardiovascular diseases except among men who had allergic rhinitis alone (Table 7). The results followed the same trend as in the pattern for the whole population.

Table 7. Cold weather-related EH among the 25-74-year old women and men (FINRISK ColdHeat-substudy), subjects with CVD excluded. Modified from Study II, supplementary Table S2.

Determinant category	Men			Women		
	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects with symptoms and prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
No asthma or allergic rhinitis (reference)	40 (3.5)	1.00	1.00	59 (4.6)	1.00	1.00
Allergic rhinitis without asthma	28 (5.7)	1.61 (1.01, 2.58)	1.53 (0.95, 2.49)	70 (9.1)	1.99 (1.42, 2.78)	2.07 (1.47, 2.92)
Asthma without allergic rhinitis	9 (19.2)	5.42 (2.80, 10.50)	5.46 (2.77, 10.78)	13 (24.5)	5.34 (3.13, 9.10)	5.61 (3.20, 9.82)
Asthma with allergic rhinitis	15 (17.1)	4.82 (2.77, 8.39)	4.15 (2.30, 7.49)	54 (35.1)	7.63 (5.50, 10.58)	6.40 (4.41, 9.29)

5.4 Asthma control and cold weather-related respiratory symptoms

Worsening of asthma control was associated with a trend of higher occurrence of all studied cold weather-related respiratory symptoms among both men and women (Fig. 4). However, there were some differences in the magnitude of PR according to gender, with men showing somewhat stronger PRs for breathlessness, wheezing and chest pain (Table 8). When comparing the adjusted PRs, poor asthma control was the strongest determinant for chest pain, for both men (aPR 4.47; 95% CI 1.89-10.56), and women (aPR 2.60; 95% CI 1.64-4.12), and the weakest for cough, for men (aPR 1.10; 95% CI 0.91-1.34) and women (aPR 1.18; 95% CI 1.08-1.30), and shortness of breath for women (aPR 1.18; 95% CI 1.07-1.30). The effect estimates were of the same magnitude for wheezing (aPR 1.91; 95% CI 1.31-2.78), phlegm production (aPR 1.51; 95% CI 1.06-2.14) and shortness of breath (aPR 1.47; 95% CI 1.22-1.77) for men and for phlegm production (aPR 1.62; 95% CI 1.27-2.08) and wheezing (aPR 1.48; 95% CI 1.17-1.87) for women.

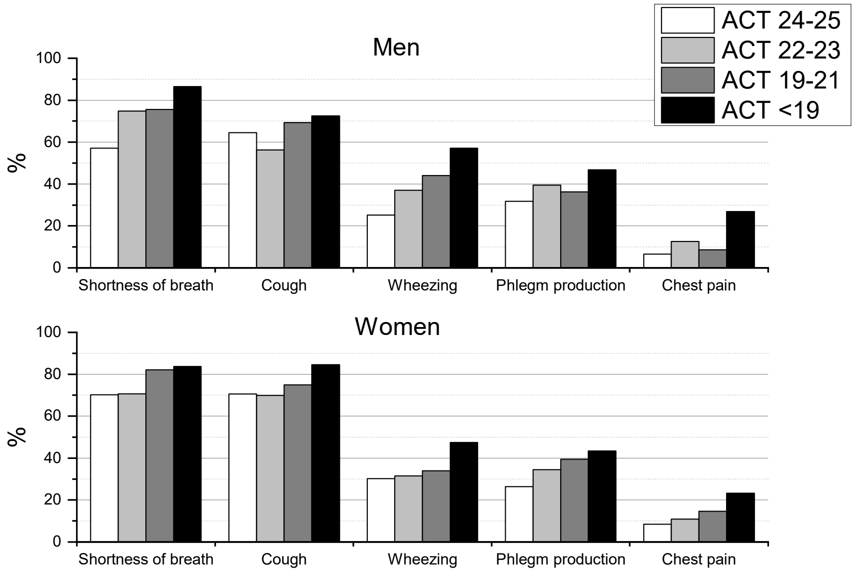

Fig. 4. The occurrence of cold weather-related symptoms according the ACT, separately for men and women. Modified from Study III.

Table 8. Prevalence, PRs and aPRs of cold weather-related symptoms according the ACT separately for women and men. Modified from Study III.

Respiratory symptoms and ACT	Men			Women		
	Number of subjects and symptom prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects and symptom prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
Shortness of breath						
ACT ≥ 24	61 (57.0)	1.00	1.00	181 (70.2)	1.00	1.00
21 < ACT < 24	89 (74.8)	1.31 (1.08-1.59)	1.28 (1.05-1.55)	162 (70.7)	1.01 (0.90-1.13)	1.01 (0.90-1.13)
18 < ACT ≤ 21	96 (75.6)	1.33 (1.09-1.61)	1.36 (1.12-1.65)	226 (82.2)	1.17 (1.06-1.29)	1.15 (1.04-1.27)
ACT ≤ 18	135 (86.5)	1.52 (1.27-1.81)	1.47 (1.22-1.77)	256 (83.7)	1.19 (1.09-1.31)	1.18 (1.07-1.30)
Cough						
ACT ≥ 24	69 (64.5)	1.00	1.00	182 (70.5)	1.00	1.00
21 < ACT < 24	67 (56.3)	0.87 (0.71-1.08)	0.86 (0.69-1.07)	160 (69.9)	0.99 (0.88-1.11)	1.00 (0.90-1.13)
18 < ACT ≤ 21	88 (69.3)	1.07 (0.90-1.29)	1.05 (0.86-1.27)	206 (74.9)	1.06 (0.96-1.18)	1.05 (0.94-1.17)
ACT ≤ 18	113 (72.4)	1.12 (0.95-1.33)	1.10 (0.91-1.34)	259 (84.6)	1.20 (1.09-1.32)	1.18 (1.08-1.30)
Wheezing						
ACT ≥ 24	27 (25.2)	1.00	1.00	68 (26.4)	1.00	1.00
21 < ACT < 24	44 (37.0)	1.47 (0.98-2.19)	1.39 (0.93-2.08)	72 (31.4)	1.04 (0.80-1.36)	1.00 (0.77-1.33)
18 < ACT ≤ 21	56 (44.1)	1.75 (1.19-2.56)	1.62 (1.10-2.39)	93 (33.9)	1.12 (0.88-1.44)	1.10 (0.85-1.42)
ACT ≤ 18	89 (57.1)	2.26 (1.59-3.22)	1.91 (1.31-2.78)	145 (47.4)	1.57 (1.26-1.95)	1.48 (1.17-1.87)
Phlegm production						
ACT ≥ 24	34 (31.8)	1.00	1.00	68 (26.4)	1.00	1.00
21 < ACT < 24	47 (39.5)	1.24 (0.87-1.77)	1.29 (0.90-1.85)	79 (34.5)	1.31 (1.00-1.72)	1.28 (0.97-1.69)
18 < ACT ≤ 21	46 (36.2)	1.14 (0.79-1.64)	1.17 (0.81-1.69)	108 (39.4)	1.50 (1.16-1.92)	1.49 (1.16-1.93)
ACT ≤ 18	73 (46.8)	1.47 (1.06-2.04)	1.51 (1.06-2.14)	133 (43.5)	1.65 (1.30-2.10)	1.62 (1.27-2.08)

Respiratory symptoms and ACT	Men			Women		
	Number of subjects and symptom prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)	Number of subjects and symptom prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
Chest pain						
ACT ≥ 24	7 (6.5)	1.00	1.00	22 (8.5)	1.00	1.00
21 < ACT < 24	15 (12.6)	1.93 (0.82-4.55)	1.99 (0.82-4.82)	25 (10.9)	1.28 (0.74-2.21)	1.32 (0.77-2.28)
18 < ACT ≤ 21	11 (8.7)	1.32 (0.53-3.30)	1.60 (0.62-4.12)	40 (14.6)	1.71 (1.05-2.80)	1.66 (1.01-2.72)
ACT ≤ 18	42 (26.9)	4.12 (1.92-8.81)	4.47 (1.89-10.56)	71 (23.3)	2.73 (1.74-4.28)	2.60 (1.64-4.12)

6 Discussion

6.1 Main findings

The overall objective of this research project was to investigate whether subjects with asthma and/or AR are more prone to experience cold weather-related respiratory symptoms and functional disability than those subjects who do not have these conditions. According to our results young adults with asthma experience more cold weather-related symptoms than healthy young adults, and there is an additional effect when a young adult has both asthma and AR (Study I). Cold weather-related FD and EH also occurred more commonly among those who had asthma and/or AR than among subjects of adult age without these conditions. However, we did not find similar additional effects as we detected in young adults in Study I (Study II). Our findings among those adults with asthma in Northern Finland were consistent with the hypothesis that adults with poor asthma control are more susceptible to experiencing cold weather-related respiratory symptoms than subjects with good asthma control (Study III).

6.2 Validity issues

This project included study populations from three Finnish population-based studies. These study populations represented subjects from different age groups covering young adulthood, working-aged adults and older adults. Thus, we were able to address potential susceptibility to cold weather-related respiratory symptoms and FD in relation to a wide age range, including young adults that have not been studied earlier with respect to cold weather-related symptoms or health problems.

Study I included a study population consisting of young adults that had originally been studied in the city of Espoo in Southern Finland in 1991 when the subjects were children from 1 to 7 years (the Espoo Cohort Study) (Jaakkola, J. J. et al., 1993). The current study was based on the 20-year follow-up of the ECS. The follow-up rate was 64%, which is considered good for the age group studied and the long follow-up period. The comparison between the baseline and the follow-up population showed no major differences between these study populations, so there was no indication of any major selection bias. The results of Study I are generalizable for this age group.

Study II was based on the National FINRISK Studies in 2007 and 2012 which have a wide geographical coverage in Finland. The FINRISK study included a wide age range of adults living in Finland. In the 2007 and 2012 studies the age range was 25 to 74 years. These studies have been conducted every five years since 1972, and the latest National FINRISK study took place in 2012. The study populations have been selected randomly from the Finnish adult population, and the sample was selected to have same number of men and women from each area and each 10-year age groups. The FINRISK study has been reported to be representative of the Finnish population because of the sample stratification. Participation rates have declined over the years, but they were still at an acceptable level in the 2007 and 2012 studies, being 60% among men and 70% among women in 2007, and in 2012 the rates were 57% and 67%, respectively. Comparison between participants and non-participants have shown that non-participants were more often from larger cities, men and younger, and they had a poorer health status than participants based on the administrative register. This kind of selection in participation may have resulted in selection bias to some extent in the health-related associations by underestimating the studied relations. (Borodulin et al., 2015).

Study III included a population of adults hypothesized to be potentially susceptible to the effects of cold air on their respiratory health. We studied possible effects of asthma control on cold weather-related symptoms. The study population of Study III included subjects with asthma who were randomly selected by the Social Insurance Institution of Finland based on data on their reimbursements for asthma medication. The response rate in Study III was lower than in our other studies (40%), but we considered it to be satisfactory considering that the National Social Insurance Institution sent the invitation letters and questionnaires. When subjects are identified through the Social Insurance Institution of Finland reimbursement files, as under the law, the researchers of the study are not allowed to approach the participants directly. Neither were we allowed to send any reminder letters. This might have influenced the response rate to some extent. In addition, we cannot exclude the possibility that there was some association between asthma control and participation activity. Those who are not that interested in their health and factors that might influence it, may not have been so interested in answering to health-related questionnaires. This would lead to some underestimation of the studied relations. On the other hand, the strength of this approach was that the diagnosis of the study subjects had been verified in a rigorous manner, as the Social Insurance Institution of Finland requires that the diagnosis is made according to the national official guidelines for the diagnosis asthma before it warrants the special reimbursement right for asthma medications, which was how the study subjects were identified.

The determinants of interest were self-reported doctor-diagnosed asthma and AR in Studies I and II. Subjects with asthma and AR were hypothesized to be more susceptible to the effects of exposure to cold, which would manifest as a higher prevalence of symptoms related to cold weather. Doctor-diagnosed asthma is a valid way of confirming the diagnoses, because the reimbursement system in Finland requires that the diagnosis for patients has been made using clearly verified methods that are in line with national guidelines, before the subject gets a special, higher reimbursement percentage for medication. The assessment of AR, on the other hand, can be more vulnerable to information bias, due to possible measurement error as no such national guidelines existed for AR at the time of data collection (Ozdoganoglu & Songu, 2012). We considered that our study could be influenced by some underdiagnosis because AR does not have as clearly verifiable criteria as asthma. For example, it is not always easy to distinguish allergic rhinitis from non-allergic rhinitis if allergy skin prick testing has not been performed. Previous studies have reported that subjects with asthma often also have AR (Boulay et al., 2012; Compalati et al., 2010), but it is not known whether subjects with asthma experience nasal symptoms more easily than healthy subjects and because of that are more frequently tested for AR. If this were the case, it could lead to the underdiagnosis of AR among non-asthmatic subjects, thus weakening the relation estimated among those with only AR. This could be one feature explaining why we detected weaker effects among those who had only AR.

In Study III the determinant of interest was asthma control, which was assessed based on replies by the study subjects to the questions in the ACT. Validated ACT questions (Nathan et al., 2004) were included in the main questionnaire. Some previous studies have verified the validity of the ACT in assessing asthma control (Jia et al., 2013; Schatz et al., 2006).

Identical outcomes, i.e. cold weather-related symptoms in the previous 12 months, were applied in both Studies I and III. The questions were asked using an identical form for the studied comparison groups. The symptoms are subjective per definition, which may introduce some random misclassification. A bias would have been introduced if the outcome information were related to the determinant of interest. However, the observed differences between the compared groups in the prevalence of symptoms were so great that they are not likely to be explained by moderate differences in the subjective assessment of the symptoms. Additionally, the season when the subject answered the questionnaire may have had some degree of influence on how well the symptoms and their connection to cold weather were remembered. These two elements could have caused some degree of non-differential misclassification. In Study I, we compared the prevalence of cold weather-related symptoms between subjects with and without asthma and/or AR, and in Study III between subjects with good and poor asthma control. Those who have some chronic disease may be more aware of their symptoms and thus pay more attention to their symptoms. Healthy subjects are not as used to paying attention to respiratory symptoms as the subjects who have asthma or AR, so this may have caused some overestimation of the prevalence of the symptoms and may have led to the introduction of information bias.

In Study II we studied cold weather-related functional disability and the exacerbation of health problems as the outcomes of interest, which were based on the self-reported perception of cold. The questions were assigned to reflect psychological, environmental, somatic, and motivational factors behind cold weather-related effects. The self-assessment of outcomes was retrospective and the season the subjects answered the questionnaires was unknown, so these might have caused non-differential misclassification, which may have introduced some underestimation of the real effects.

Men and women can experience cold weather and its unpleasant health effects differently, as a previous review showed that women report more somatic symptoms than men and the genders experience physical health differently (Barsky et al., 2001). In studies II and II we conducted stratified analyses separately for men and women. In Study I the group sizes would have been too small for statistical analyses if the analyses had been carried out separately for men and women, so gender was one of the covariates in the Poisson regression model and was noted as a possible confounder in the stratified analyses. Women also tend to answer questionnaires more readily than men. This was seen in Study III, so with stratified analyses we excluded the potential bias which could occur because of more answers from women.

The presence of a cardiovascular disease may influence the response to cold exposure (Näyhä et al., 2011). Therefore, we conducted analyses in Study II which were stratified according to the cardiovascular diseases that the subjects reported. In the additional analyses we excluded those who reported at least one cardiovascular disease, because the presence of CVDs can have an additional effect on cold weather-related FD and EH. The prevalence of having asthma and/or AR within those without any CVDs were similar compared to the whole study population, so we could see that our studied determinants of interest were not associated with CVDs. The results of the stratified analyses showed that the effect estimates of cold weather-related FD and EH were similar or slightly stronger than in the total study population. These results showed that the effect of cold weather could not be explained by having a CVD.

We conducted additional stratified analyses also in Study III because there were some indications that BMI and smoking might modify the effect estimates of cold weather-related symptoms. Stratified analyses according to BMI suggested that overall slightly overweight subjects, with a BMI of 25-30, showed a lesser occurrence of cold weather-related symptoms than normal and overweight subjects. The trend according to the ACT within the BMI groups was similar to the overall study population. The analysis model worked with a crude analysis, but with an adjusted analysis the groups became too small for the highest BMI groups among those who reported cold weather-related chest pain. The stratified analyses according to smoking suggested that there was some difference between the groups. For example, for wheezing, phlegm production and chest pain the trend indicated that the smallest prevalence rate was among those who had never smoked and the highest among current smokers. For shortness of breath and cough the trend was not as clear as it was with the former symptoms. The trend according to the ACT within the smoking groups was similar to the whole study population except for cough and chest pain among ex-smokers, and shortness of breath and wheezing among current smokers. The differences between the trends could be a consequence of smaller group sizes in the stratified analyses than for the whole study population.

One strength of this series of studies is that we used a Poisson regression analysis in all three publications included in this thesis to adjust for potential confounding. In these analyses we could adjust for a large set of potential confounders which excludes them as potential explanations for our results. The measure of effect in a Poisson regression is a risk or prevalence ratio, which is more meaningful for interpretation of the effect size than an odds ratio estimated in a logistic regression.

6.3 Synthesis with previous knowledge

6.3.1 Asthma, allergic rhinitis, and cold weather-related respiratory symptoms among young adults

Study I showed that the five studied cold weather-related symptoms are rather uncommon (2.0-7.0%) among healthy young adults. However, the prevalence of each symptom increased substantially if the subject had asthma and/or AR (19.2-51.4%). Our systematic literature search showed that cold weather-related symptoms had been assessed only in a few studies. In addition, young adults had not been specifically studied in those studies. Respiratory symptoms in general have been studied and one study showed that they impaired HRQL regardless of any respiratory disease (Voll-Aanerud et al., 2010). One study showed that the overall prevalence of cold weather-related symptoms was manifold if a person has any chronic disease (Näyhä et al., 2011). In addition, one population-based study of 25-74 years old adults showed that subjects with asthma experienced more cold weather-related symptoms (69-78%) than those without these diseases (18-21%) (Harju et al., 2010). Another population-based study investigated 20-69 years old Finnish adults living in Helsinki or Lapland. In this study, the prevalence of cold weather-related shortness of breath, wheezing and/or severe coughing were 11.1-13.1%. (Kotaniemi et al., 2002). With regards to symptoms related to shortness of breath, the prevalence in cold weather was 3.2-12.8% among healthy adults. In this context, the group of healthy adults was defined as those without asthma, chronic bronchitis, or allergies. The prevalences increased for those who had AR or conjunctivitis (prevalences being 10.3-23.6%) and they were more augmented among subjects who had asthma alone (prevalences being 47.1-77.8%). (Kotaniemi et al., 2003). Our results among young adults follow a similar pattern, although the increased amount of symptom reporting is lower than in the previous studies.

6.3.2 Asthma, allergic rhinitis and cold weather-related functional disability and exacerbation of health

Study II showed that a considerable number of Finnish adults experience cold weather-related FD, its prevalence being 23% among men and 18% among women. Subjects without AR or asthma reported less cold weather-related disability compared to the whole study population (prevalences being 22 and 15%, respectively). Having AR increased the prevalence of FD to 25 and 19%, respectively. The prevalence was even higher among subjects with asthma (31 and 24%, respectively). However, Study II did not find any added effect on reporting cold weather-related FD if the subject had both AR and asthma (26 and 25%, respectively). Cold weather-related EH was less common than FD. In the whole study population 8% of men and 12% of women reported cold weather-related EH. Asthma increased the prevalence of EH more than AR. One quarter of men and a third of women who had asthma alone reported EH.

There are physiological changes that occur in the airways (Cruz & Togias, 2008; Seys et al., 2013), as well as in cardiovascular (Näyhä, 2005) and muscular systems (Pienimäki et al., 2014) related to cooling of the body. These changes can influence the perceived cold weather-related FD and have been reported to cause impaired cognitive (Mäkinen et al., 2006) and/or physical performances (Castellani & Tipton, 2015). Some occupational studies have reported that daily exposure to cold air among cold workers, for example in the food industry, has adverse health effects on lung function (Jammes et al., 2002) and the musculoskeletal system (Pienimäki et al., 2014).

The term "functional disability" has not been defined with specific, strict criteria, so there may be some differences between individuals concerning how they interpret FD. FD can influence either physiological or cognitive performance, or both. According to our literature search, cold weather-related FD has not been studied before among subjects who have AR and/or asthma. The exacerbation of health problems (impairment of health and the exacerbation of disease symptoms) is likely to be more clearly understood by the study subjects than FD. Two previous population-based studies investigated respiratory symptoms among the adult population. They found that those reporting at least one respiratory disease also reported more respiratory symptoms in the cold than healthy subjects (Harju et al., 2010; Näyhä et al., 2011). The results of Study II are consistent with previous studies, although we did not specify the perceived disease symptoms as respiratory symptoms. Previous studies have shown that subjects with diseases of other systems than the respiratory system are also susceptible to cold weather (Ikäheimo et al., 2014). Because of this, we performed stratified analyses, in which we excluded subjects who had at least one CVD. Our stratified analyses showed that CVD did not influence the reporting of the studied outcomes.

Previous cross-sectional questionnaire studies have provided evidence that subjects with asthma report a worse quality of life compared to those who do not have asthma. Coexisting AR has been shown to impair the quality of life even more than asthma alone. (Maio et al., 2012). Some studies have shown that AR can cause frequent symptoms year-round which can lead to functional disability, and this can influence everyday life (Feng et al., 2012; Keith et al., 2012).

6.3.3 Asthma control and cold weather-related respiratory symptoms

Study III showed that poor asthma control increases the risk of cold weather-related respiratory symptoms both in men and women. Furthermore, we found that there was a dose-response pattern between worsening asthma control and perceived cold weather-related symptoms. The strongest effect of asthma control on cold weather-related respiratory symptoms was seen in relation to chest pain for both men and women. The effect of asthma control was weakest for those who were slightly overweight (BMI 25-30) and strongest for those who were overweight (BMI 30-35). However, the corresponding association between cold weather-related respiratory symptoms and asthma control by BMI was observed as for the whole population. On phlegm production and chest pain the trend was not that clear, which may be due to a lack of statistical power due to the small population strata. Previous epidemiological studies have shown that a high BMI reduces asthma control and increases the respiratory symptoms (Bildstrup, Backer, & Thomsen, 2015; Celebi Sozener, Aydin, Mungan, & Misirligil, 2016; Dixon & Peters, 2018). On the other hand, some studies have shown that a higher BMI may have a protective effect against cold temperature, explained by improved insulation of subcutaneous adipose tissue and related reduced heat loss (Castellani & Young, 2016; Stocks, Taylor, Tipton, & Greenleaf, 2004). These two competing mechanisms can explain the somewhat contradictory results we found in the analyses stratified by BMI in Study III.

Our results indicate that poor asthma control is a stronger determinant of cold weather-related symptoms among current smokers than among non- and ex-smokers. There is accumulative evidence that smoking influences asthma causing airway irritation (Rom, Avezov, Aizenbud, & Reznick, 2013). Among persons with poor asthma control and related structural and functional changes in the airways, smoking can further irritate and sensitize them to the effects of cold weather.

Four of the queried respiratory symptoms are considered to be typical asthma symptoms which could indicate worsening asthma control. These symptoms are shortness of breath, cough, wheezing and phlegm production, and they could indicate the presence of an obstruction due to inflammatory processes in the airways (Ferris, 1978). In our questionnaire we asked the subjects to indicate the respiratory symptoms in cold weather, which was the outcome of Study III. The respiratory symptoms occurring in everyday life were included in the ACT questions.

Based on our systematic literature search, our study is the first study that investigates the relations between asthma control and the mentioned respiratory symptoms triggered by cold weather. The level of reported cold weather-related symptoms among asthmatics whose asthma was under good control was comparable with previous studies in which symptoms have been assessed. In our study, the reports of cold weather-related symptoms of subjects who had good asthma control were comparable to previous studies that involved separate analyses for asthmatic subjects. (Harju et al., 2010; Näyhä et al., 2011). However, for those with poor asthma control the occurrence of respiratory symptoms was substantially higher than reported in the earlier studies. We found that age did not modify the association between reported cold weather-related symptoms and asthma control.

6.4 Biological plausibility of the health effects of exposure to cold air

We observed that asthma and allergic rhinitis increased the risk of cold weather-related symptoms and functional disability. A series of controlled experiments provide findings that support biological plausibility of our observations.

Koskela (Koskela, H., 2007) provided evidence in a review that nasal breathing in cold air causes short-term responses like rhinorrhea, congestion and sneezing, and these responses are suggested to be greater among those with AR than healthy subjects. Damage in the airway epithelium and changes in the airway's wall structure and function are considered long-term responses, and asthma enhances these responses even more, with or without AR. (Koskela, H., 2007). Our results in Studies I and II showed a similar trend, but in Study I the effect related to having both AR and asthma on reported cold weather-related respiratory symptoms was more considerable than in Study II.

Previous controlled experiments have reported that exposure to cold air can be mediated directly by inhaling cold air (Hanes et al., 2006) or indirectly by the cooling of the skin (Skowronski et al., 1998). Cold air contains only a small amount of humidity. Hence, the adverse effects of inhaling cold air are mediated both by the effects of the low temperature, as well by the drying of the airways. Inhaling cold air can trigger unfavourable functional changes, such as a reduction in the respiratory function in the upper and lower airways (Cruz & Togias, 2008; Koskela, H. & Tukiainen, 1995; Koskela, H., 2007; Seys et al., 2013). Inhaled cold air has also been shown to increase inflammatory markers (Larsson et al., 1998; Seys et al., 2013). There is also some evidence that repeated exposure of the airways to cold air can lead to permanent damage on the airways (Koskela, H., 2007; Sue-Chu, 2012). Skin cooling alone can cause functional changes in the respiratory system, for example mild airway obstruction among asthmatic subjects (Skowronski et al., 1998).

A clinical provocation study has further studied the effects of cold exposure and high altitude (Seys et al., 2013). Some subjects reported an increased prevalence of asthmatic symptoms, which was in line with our results in Studies I and II. Additionally, exposure to high altitude and cold air increased asthma symptoms and reduced asthma control according to the ACT. However, the increase in the sputum neutrophil percentage was not as considerable as that observed after cold exposure alone.

7 Conclusions

The aim of this thesis was to investigate whether asthma and/or allergic rhinitis increase the individual's susceptibility to cold weather manifested as the increased occurrence of respiratory symptoms and functional disability. The thesis used three population-based study populations to study different age groups and to ensure a wide study group of asthmatics. The conclusions of the thesis are:

1. Young adults with asthma experience substantially more cold weather-related symptoms, whereas these symptoms are only slightly elevated among subjects with allergic rhinitis alone compared to healthy young adults. Having both asthma and allergic rhinitis has an additional effect on cold weather-related symptoms.
2. Adults with asthma or allergic rhinitis experience more cold weather-related functional disability and exacerbation of health problems compared to heathy adults.
3. Poorly controlled asthma in adults increases experiencing cold weather-related symptoms. Even a slight worsening of asthma control seems to increase these symptoms.

The findings of this thesis are important to subjects with asthma or allergic rhinitis, because they are susceptible to cold weather manifested as an increased occurrence of respiratory symptoms and functional disability. Good asthma control will reduce cold weather-related health problems. Health care personnel and clinicians can use this knowledge to inform these patients about the risks related to cold weather and to advise the medication changes needed to improve asthma control, and to keep nasal cavities moisturized because of the cold, dry air. They can also advise asthmatics to protect themselves properly, by covering their airways and face with a scarf or a mask to reduce inhaling cold air, during wintertime to reduce adverse health effects and to maintain their quality of life. The results of this thesis are useful especially to populations living in the northern hemisphere. They are exposed to cold temperatures for long periods because of the long and cold winter season, and the exposure times can be prolonged during daily activities.

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