Raija Juvonen

RESPIRATORY INFECTIONS AND COLD EXPOSURE IN ASTHMATIC AND HEALTHY MILITARY CONSCRIPTS
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Abstract
The purpose was to study respiratory infections in a cold environment among young Finnish men. The seasonal variation in the occurrence of respiratory tract infections is well-known, but the impact of cold exposure is obscure. The burden of respiratory tract infections is especially apparent during military service, but the possible risk factors for infections are not.

A total of 892 young military conscripts, 224 men with physician-diagnosed asthma, from the intake groups of July 2004 and January 2005 in Kainuu Brigade, were recruited for the study. In Kajaani area, the average daily temperature is above 10°C only from June to August and all conscripts serve during the cold season, too. The previous history of respiratory tract symptoms, infections, smoking habits and cold sensations were obtained with a questionnaire. Blood samples were taken for determination of the markers of inflammation and infection and peak expiratory flow, height and weight were measured. Data on respiratory tract infections requiring a physician consultation and results of a 12-min running test were collected. The temperature data was obtained from the nearest meteorological station located ca. 15 km from the garrison.

At the beginning of the service, asthmatic men reported to have experienced more respiratory tract symptoms and were in poorer physical condition according to the 12-min running test compared to non-asthmatic men. However, 48% of men with asthma were without medication. After the 180–362-day service, both men with and without asthma had enhanced their physical fitness as determined with the 12-min running test. At the same time, the levels of high sensitive C-reactive protein as a marker of low-grade inflammation, decreased.

Infection episodes requiring physician consultation were more common among men with, rather than without, asthma. Chlamydia pneumoniae infections were mostly mild upper respiratory tract infections, common cold and sinusitis, and were as common in asthmatic as in non-asthmatic men. However, prolonged Chlamydia pneumoniae infections were more common among asthmatic men. Obesity and previous respiratory tract infections were independent risk factors for frequent infections among men with 180-day service.

There was a typical seasonal variation in respiratory tract infections among conscripts: most infections occurred in the wintertime. The men with 180-day service had most infections during the first three months of the service, both in the July and January intake groups. Temperature was significantly associated with the occurrence of respiratory infection episodes. The most common temperature for the onset of an episode was in the outdoor temperature range of 0°C to –5°C. Respiratory tract infections were preceded by linearly decreasing outdoor temperature, the coldest day being the day before physician consultation.

Keywords: asthma, Chlamydia pneumoniae, cold exposure, military conscript, respiratory tract infection, risk factor
To my family
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Kajaani, March 2008  Raija Juvonen
List of abbreviations and definitions

AOM  acute otitis media
BDI  Beck Depression Inventory
BMI  body mass index (kg/m^2)
CAP  community acquired pneumonia
COPD  chronic obstructive pulmonary disease
CRP  C-reactive protein (mg/l)
ELISA  enzyme-linked immunosorbent assay
GINA  Global Initiative for Asthma
GP  general practitioner
hsCRP  high sensitive C-reactive protein (mg/l)
IEMA  Immunoenzymometric Assay
IgA  Immunoglobulin A
IgE  Immunoglobulin E
IgG  Immunoglobulin G
IgM  Immunoglobulin M
LRTI  lower respiratory tract infection
MIF  Microimmunofluorescence test
NAEPP  National Asthma Education and Protection Program
NK  natural killer cell
OME  otitis media with effusion
PY  pack-years, number of cigarettes per day x number of years/20
PEF  peak expiratory flow
RSV  respiratory syncytial virus
RTI  respiratory tract infection
T_{avg} °C  average ambient daily temperature
T_{max} °C  maximum ambient daily temperature
URTI  upper respiratory tract infection
List of original publications

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


Some unpublished results will also be presented in the thesis.
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Original publications
1 Introduction

Respiratory tract infections are the most common infectious diseases in the world (Denny Jr 1995). Infections are mainly viral upper respiratory infections and have a typical seasonal variation. In Finland, most respiratory infection epidemics occur in cold wintertime. The impact of cold exposure on the seasonality of respiratory infections is unknown. Different explanations like seasonal variation in host immunity, virulence of pathogens, man’s behaviour and ambient temperature and relative humidity have been suggested for the seasonality (Dowell 2001, Dowell & Ho 2004). The effects of cold exposure to respiratory airways are better known than the effects on immunological defence mechanisms. Theories how cold exposure promotes the spread of infections by interfering with respiratory and general defence mechanisms have been introduced.

Young Finnish men are especially exposed to frequent respiratory infections during their mandatory military service at the age of 18-19 years. Military service with a great amount of mental and physical stress resembles the environment in kindergarten during the first years of life. Military service in a cold environment still adds the burden of infectious diseases (Gray 1995). Risk factors for respiratory infections are well studied among children, and atopy and asthma are known risk factors reported in numerous articles (Benediksdottir 1993, Kvaerner et al. 2000, Doyle 2002, Hak et al. 2003, Chantzi et al. 2006). Over 80 % of asthmatic men complete their mandatory military service (Kajosaari 2004), which gives a chance to study the characteristics as well as infections of asthmatic and non-asthmatic men, although the men with serious asthma have already been discharged at call-up examinations or examinations at the beginning of their service.

The present study was conducted to get further information on respiratory tract infections among young Finnish men: (1) by investigating the impact of asthma on the respiratory and physical health of young men, (2) by evaluating the risk factors for frequent respiratory tract infections during military service, (3) by studying C. pneumoniae infections among asthmatic and non-asthmatic men and (4) by studying the association between objective environmental temperature and occurrence of respiratory tract infection episodes.
2 Review of the literature

2.1 Respiratory tract infections (RTI)

Acute respiratory tract infections are the most frequent illnesses experienced by people of all ages (Denny Jr 1995). They can be divided into upper and lower respiratory tract infections. Common cold, otitis, sinusitis, pharyngitis and tonsillitis are grouped into upper and bronchitis and pneumonia into lower respiratory tract infections.

The common cold is a name for a mild upper respiratory infection. Adults may experience 2 to 4 and children 6 to 10 common cold episodes each year (Puhakka et al. 2000). Although rarely fatal, respiratory infections are a source of significant morbidity and carry a considerable economic burden (West 2002).

Upper respiratory tract infections can be caused by over 200 serotypes of viruses, with rhinovirus being the most common causative agent (Puhakka et al. 2000). Other common etiological viruses include influenza A and B, respiratory syncytial virus (RSV), parainfluenzaviruses and adenoviruses. Recently, new viruses, e.g. metapneumovirus and bocaviruses, causing respiratory infections have also been described (Kahn 2007). The viruses infect the ciliated respiratory epithelium and cause symptoms like fever, nasal obstruction, rhinorrhea (runny nose), sore throat, cough, headache, feverishness and malaise (Gwaltney 1995). Bacterial infections may have the same kind of symptoms as viral infections and, for example, the clinical presentation of sore throat does not accurately predict whether the infection is viral or bacterial. Although the common cold is usually a self-limited illness of short duration, the viral infection can be accompanied by a bacterial complication. Viral respiratory infections are an important factor predisposing individuals to acute otitis media (AOM) (Greenberg 2003). Sinus abnormalities have been detected in patients with common cold syndrome, but only in 0.5–2 % of cases complicated by bacterial infection (Greenberg 2003).

Acute bronchitis is most often associated with respiratory viruses including rhinovirus and coronavirus, in addition to more invasive viruses of the lower respiratory tract such as influenza and adenovirus. Other viral causes of acute bronchitis include RSV, parainfluenza virus and herpes simplex virus. Mycoplasma pneumoniae, Bordetella pertussis and Chlamydia pneumoniae are recognized bacterial causes of acute bronchitis. The etiologic role of Streptococcus pneumoniae and Haemophilus influenzae in acute bronchitis is not clear (Niroumand & Grossman 1998).
Community acquired pneumonia (CAP) occurs in approximately two per 1000 of the adult population per year (Tsirgiotis & Ruffin 2000). In the western world, CAP is the most common infectious disease requiring hospital admission (Pinner et al. 1996). The frequency of different causative agents depends on the age of the patients and the epidemic phase (Korppi et al. 2003). Mostly pneumonia is a bacterial complication of the viral infection. It can also be of viral origin, when upper respiratory tract infection extends to the lower airways. Multiple pathogens may be isolated from the CAP patient (Lieberman et al. 1996, Marston et al. 1997). Mixed pneumonia may occur in 2.5–38 % of cases with an established aetiology (Blanquer et al. 1991, Lieberman et al. 1996). The aetiology of CAP remains undetermined in 50% of the patients (Ravago et al. 2000). The most common bacterial cause of CAP requiring hospitalization is *S. pneumoniae* followed by *C. pneumoniae* and *H. influenzae* (Marrie 1998). *M. pneumoniae* is a more common cause of ambulatory CAP than of CAP requiring hospitalization (Marrie 1998).

2.1.1 Host defence in respiratory tract infections

The risk of airway infection is related to the ability of the microbe to gain access to respiratory epithelium and establish invasive infection. Direct inoculation, haematogenous spread by the vascular system, inhalation of the aerosol and colonization of respiratory surfaces are ways in which pathogens may gain access to the respiratory tract. Colonization followed by aspiration or aerosolization are the most common paths for exposure. Upper airway colonization by potential pathogens may occur seasonally or especially during epidemics. Prevalence of colonization may increase in areas of crowding or cohabitation, such as dormitories and military barracks.

When pathogens have gained entry to the respiratory system, they may be eliminated without a clinical infection. When the microbial challenge is either too large or too virulent, an inflammatory reaction is initiated. Respiratory defences against infection involve a diverse and complex system. The first line of defence is structural. Both non-specific and specific defence mechanisms of the immune system function at mucosal surfaces. The non-specific innate immune system can provide the signals to eliminate the pathogen or direct the activation of the specific adaptive component of host defence. After the failure of the non-specific defences, the antigen is available for immunological processing. In which direction the
immune reaction goes, depends on the specific inciting antigen and the local inflammatory milieu at the time of antigen processing.

The non-specific innate immune system must be able to recognize a variety of invading microbes (Welsh & Mason 2001). Acquired immune defence is the antigen-specific mechanism of the respiratory system host defence and includes cell- and antibody-mediated immunity (Reynolds 1989). It has a unique capability to recognize a specific pathogen, target the defence against it and recognize the same pathogen later. Specific immune responses are particularly important for the effective elimination of virulent encapsulated bacteria, viruses and intracellular pathogens.

2.1.2 Respiratory tract infections and seasonal variation

There is seasonal variation in the occurrence of most human respiratory pathogens (Dowell & Ho 2004). Epidemics of influenza occur between November and April in northern temperate latitudes (Dowell & Ho 2004, Virological statistics 1984–1994). RSV infections occur during winter months: the first cases are noticed in September and usually the peak is from November to March and every other year there is a second peak in the spring time (Anderson et al. 1990, Waris 1991). Parainfluenza viruses usually cause epidemics in Finland in early spring. Rhinovirus infections occur all year round with epidemics from September to October in autumn and another from April to May in spring (Mäkelä et al. 1998). Seasonal variation is also seen with bacterial pathogens. The incidence of invasive pneumococcal diseases has been reported to increase during colder months in temperate regions (Dowell et al. 2003, Watson et al. 2006). The incidence and mortality of sepsis and severe sepsis are also seasonal and highest during winter months, predominantly due to sepsis with a respiratory tract origin (Danai et al. 2007). The rate of colonization with respiratory pathogens also increases in midwinter (Garcia-Rodriguez & Martinez 2002).

The reason why respiratory infections are common in cold wintertime is not completely understood. The seasonal variation in infectious diseases may result from variation in the susceptibility of the human host (Dowell 2001). Crowding favours the spread of respiratory pathogens. In northern latitudes, the cooling of weather in autumn forces people to spend more time indoors. On the other hand, in tropical weather respiratory infections are common during rainy seasons (Nwankwo et al. 1988). The bad weather, but not necessarily so cold, gathers people together. Previous data suggest that exposure of the body surface or the
airways to cold temperatures may contribute to the development of respiratory infections (Mourtzoukou & Falagas 2007). Periods of low environmental temperatures have been shown to increase the incidence of respiratory tract infections (Hajat et al. 2004). Acute cooling of the body surface elicits a reflex vasoconstriction in the nose and upper airways, worsening respiratory defence and converting an asymptomatic subclinical viral infection into a symptomatic clinical infection (Eccles 2002 a). Inspiration of cold air causes a decrease in the temperature of the respiratory epithelium and hence decreases mucociliary clearance and the local immune responses of the airway (Eccles 2002 b).

2.1.3 Chlamydia pneumoniae respiratory tract infections

In the present study, C. pneumoniae infections were studied more thoroughly than other respiratory infections among the conscripts. The study population consists of young men with and without asthma and in previous studies C. pneumoniae has been associated with asthma (Hahn et al. 1991, Allegra et al. 1994, Von Hertzen et al. 1999). C. pneumoniae is also an aetiological agent in 10–20 % of pneumonia cases among adolescents (Korppi et al. 2003). In addition, C. pneumoniae was associated with respiratory infection for the first time among pneumonia patients from Kainuu in 1985 (Saikku et al. 1985) and among conscripts in Kainuu Brigade it was shown to cause epidemics (Kleemola et al. 1988).

C. pneumoniae has been associated with both epidemic and endemic occurrences of acute respiratory disease (Ekman et al. 1993). Infections are more common in the winter than in the summertime (Lim et al. 2001). Primary C. pneumoniae infections mostly occur in children, particularly in schoolchildren (Grayston et al. 1990, Dal Molin et al. 2005), and the majority of adults have serologic evidence of past infection (Kuo et al. 1995). Recurrent or secondary respiratory tract infections can occur even when antibodies induced by a previous infection are still detectable in serum (Verkooyen et al. 1998). Serology, based on the use of paired sera, is the tool most often applied to the routine diagnosis of acute C. pneumoniae infections (Verkooyen et al. 1998, Dowell et al. 2001), although it is useful only retrospectively.

C. pneumoniae can cause both upper and lower respiratory tract infections. Mild and asymptomatic infections are typical for C. pneumoniae (Miyashita et al. 2001, Hahn et al. 2002) and infections are characterized by gradual onset, pharyngitis with hoarseness, mild cough and transient fever. The disease may have a biphasic pattern, with resolution of pharyngitis prior to development of
bronchitis or pneumonia (Saikku et al. 1985, Grayston et al. 1990, Kauppinen & Saikku 1995, Kuo et al. 1995). Cough is very common and is often prolonged.

The role of *C. pneumoniae* in acute bronchitis and pneumonia is well established. *C. pneumoniae* causes 5–20 % of community-acquired pneumonia in children and adults (Hammerschlag 2000). Pneumonias associated with *C. pneumoniae* and other common respiratory pathogens do not differ clinically from each other (Monno et al. 2002). Mixed infections, mainly with *S. pneumoniae*, have been reported (Kauppinen & Saikku 1995). Headache and other central nervous symptoms seem to be common in patients with *C. pneumoniae* pneumonia. In acute pharyngitis, *C. pneumoniae* seems to be mainly a co-pathogen rather than the primary agent (Esposito et al. 2004). Symptoms of sinus infection commonly occur in *C. pneumoniae* infections and the microbe has been isolated from patients with purulent sinusitis and otitis media with effusion (Kuo et al. 1995).

A particular feature of *C. pneumoniae* is its ability to cause prolonged or chronic infections. *C. pneumoniae* infections have been linked to chronic diseases including cardiovascular diseases, chronic obstructive pulmonary disease (COPD) and asthma (Hahn et al. 1991, Saikku 1993, von Hertzen et al. 2002). It has been shown that acute *C. pneumoniae* infection is able to exacerbate asthma (Hahn et al. 1991, Allegra et al. 1994, Hahn & Golubjatnikov 1994). The controlled study of asthmatics with long-standing or recently diagnosed disease revealed that the association between elevated antibody levels to *C. pneumoniae* and the disease was strongest for non-atopic long-standing asthma and much weaker, although also significant, for non-atopic recent asthma (von Hertzen et al. 1999). An association of childhood asthma with *C. pneumoniae* has also been described (Emre et al. 1994, Cunningham et al. 1998). Further evidence of the possible role of *C. pneumoniae* in asthma is derived from observations that some subjects treated with antichlamydial antibiotics report improvement in their asthma symptoms (Emre et al. 1994, Hahn 1995).

### 2.1.4 Exercise and respiratory tract infections

There is a general perception that regular moderate activity enhances resistance to minor illnesses such as upper respiratory tract infections (Mackinnon 2000). Intense exercise and heavy acute exercise is related to an increased incidence of upper respiratory infections in athletes (Konig et al. 2000). Epidemiological data in endurance athletes and limited data from intervention studies using moderate
exercise in previously untrained individuals supports this. Endurance athletes are at increased risk for upper respiratory tract infections during periods of heavy training and the 1–2-week period following race events. Data on upper respiratory tract infection risk between physically inactive and moderately active adults support the hypothesis that moderate levels of physical activity are associated with a reduced risk for upper respiratory tract infections (Matthews et al. 2002). A "J"-shaped model has been proposed to describe the relationship between physical activity and the risk of upper respiratory tract infection (Nieman 1994).

During the past years many groups have investigated the association between changes within the immune system and exercise at different intensity levels. The exercise stress, intense exercise, can be immunosuppressive and increase the risk of infection (Pedersen & Hoffman-Goetz 2000). There is evidence that for several hours subsequent to heavy exertion several components of both the innate and adaptive immune system exhibit suppressed function and this immune response is transient (Nieman 1998). Prolonged periods of intense training may lead to slight impairment in immune parameters such as neutrophil function, serum and mucosal immunoglobulin levels, plasma glutamine concentration and possibly natural killer cell cytotoxic activity (Mackinnon 2000). In contrast, moderate exercise training has either no effect on, or may stimulate, these immune parameters (Mackinnon 2000). Recent investigations suggest that physical activity reduces levels of hsCRP (high sensitive C-reactive protein), a marker of systemic low-grade inflammation (Kasapis & Thompson 2005, Plaisance & Grandjean 2006).

### 2.1.5 Contributing factors for respiratory tract infections

The cause of current upper respiratory tract infections is multifactorial and results from interactions between environmental, immunological (adaptive and innate) and genetic factors (Rovers et al. 2004). Genetic variation of the host has a significant role in susceptibility to infectious disease (Hill 2001). It has been suggested that there might exist a common cold constitution, whereby some people are more susceptible to infections and/or the expression of clinical symptoms when infected than are others (Ball et al. 2002).

Risk factors associated with increased incidence or severity of respiratory infections are very young or old age, crowding, male sex, inhaled pollutants, anatomic, metabolic, genetic or immunologic disorders and malnutrition (Denny Jr 1995). Psychosocial factors and health-related behavior have been related to subsequent susceptibility to upper respiratory tract illness (Smith & Nicholson
Psychological stress is associated with susceptibility to the common cold (Cohen et al. 1991). People with depression may have a weaker immune system and be prone to many diseases compared with non-depressed people (Kiecolt-Glaser et al. 1996). Military trainees are particularly prone to respiratory epidemics because of the crowded living conditions, stressful working environment, frequent travel and exposure to novel strains of respiratory pathogens (Gray et al. 1994, Gray 1995, Gaydos & Gaydos 1995, Gray et al. 1999). Training during the winter months, when most viral epidemics occur, add to the risk of catching an infection (Gray 1995).

Smoking is a well-known risk factor for respiratory infections (Arcavi & Benowitz 2004). Smokers have the same or higher frequency of colds, but the colds are more severe than in nonsmokers (Gwaltney Jr et al. 1966, Cohen et al. 1993). Smoking is an important risk factor for CAP through alterations in mechanisms of the host defense (Almirall et al. 1999). Several earlier studies have shown an association between cigarette smoking and reported or recorded acute respiratory illness also among military personnel and recruits (Finklea et al. 1971, Crowdy & Langmuir 1975, Kark et al. 1981, Kark et al. 1982). Moderate alcohol consumption appears to have no influence on the incidence rates in smokers, but is associated with both decreased incidence and risk of illness in nonsmokers (Cohen et al. 1993). Tonsillectomy does not seem to affect the prevalence of colds (Dingle et al. 1964).

Incidence and severity of specific types of infections have been shown to be higher in obese than in lean persons (Marti et al. 2001). Overweight children (BMI $\geq 20$ kg/m$^2$) have been reported to be more susceptible to acute respiratory infections than non-obese children (Jedrychowski et al. 1998). Obesity has been associated with alterations in various measures of the immune function (Nieman 1994), which may explain the elevated risk for infections. In addition, obesity itself is an inflammatory state and is associated with elevated hsCRP, a marker of systemic low-grade inflammation (Visser et al. 1999). A diet with multiple deficiencies of nutrients may also impair the immunocompetence of obese people (Jedrychowski et al. 1998).

The evidence of the increased susceptibility to respiratory infections in people with allergies and asthma is contradictory. There are studies showing no difference in frequency or severity of upper respiratory tract infections between allergic or non-allergic subjects (Hinriksdottir & Melen 1994, Doyle et al. 1992) and no difference in the rates of rhinovirus infection between asthmatic and healthy individuals (Pattermore et al. 1992, Corne et al. 2002). On the other hand, more
severe cold symptoms in atopic than nonatopic subjects have been reported (Bardin et al. 1994) and in addition, severity of atopic condition and extent of dermatitis, has been related to frequent respiratory infections (Rystedt & Strannegard 1986). Allergy and asthma in addition to age, sex, family history of frequent upper respiratory tract infections and the form of day care have been the major factors affecting the frequency of upper respiratory tract infections in pre-school children (Benediksdottir 1993). Among children, respiratory allergy is also an independent risk factor for the development of otitis media with effusion (Chantzi et al. 2006). Perennial allergy has been reported to associate with recurrent acute and chronic rhinosinusitis (Gutman et al. 2004). In addition, experimental studies have shown that asthmatic individuals have more severe and long lasting lower respiratory tract symptoms and greater falls in PEF twice as frequently as do healthy individuals when infected with rhinovirus (Corne et al. 2002). Epidemiological studies indicate the important role of viral respiratory infections in asthma exacerbations (Busse & Gern 2000).

2.2 Cold exposure

2.2.1 Cold exposure and respiratory system

Major responses on cold exposure include peripheral vasoconstriction, increased oxygen uptake, increased cold sensations, muscular in-coordination and shivering. In a cold environment the respiratory system is either affected in response to direct cooling of the airways or secondarily to neural and hormonal reflex responses to cooling of other body structures (i.e. skin or central structures) (Giesbrecht 1995). The face and upper respiratory system are trigger sites for cold air-provoked respiratory symptoms (Koskela & Tukiainen 1995). At rest and during light exercise, the inhaled air is warmed and humidified to near body temperature when passing through the nasal cavity (Cole 1954, Ingelstedt 1956). During exercise with nose- and -mouth breathing at ventilation levels >30 l/min (Anderson & Togias 1995), incompletely conditioned air can reach the lower airways ((McFadden Jr et al. 1985). Thus in military conscripts with strenuous exercise the lower airways are exposed frequently to incompletely conditioned air.

Acute and chronic cold exposures have several effects on the respiratory system (Giesbrecht 1995). The most common problem is cold-induced rhinitis, ”athlete’s nose” or ”skier’s nose”, which was first described in the literature by Silvers (Silvers 1991). Cold-induced rhinitis is a distinct clinical syndrome
involving rhinorrhea, congestion and sneezing (Silvers 1991). An engorgement of the venous sinuses in the submucosa induced by cold air leads to the symptoms (Cole et al. 1983). Allergic patients seem to experience greater nasal congestion and sneezing than those without allergy on cold exposure (Silvers 1991). The response is also greater in people with rhinitis and asthma than people with rhinitis alone (Hanes et al. 2006).

During cold exposure, pulmonary mechanisms are worsened due to bronchoconstriction, airway congestion, secretions and decreased mucociliary clearance (Giesbrecht1995). Stimulus of airway cooling and/or drying is translated into airflow limitation via the generation of bronchoactive mediators, neural reflexes or hyperaemia and oedema that result in a net narrowing of the airway (Andersson et al. 1989, McFadden & Gilbert 1994).

2.2.2 Cold exposure and defence mechanisms

Both anecdotal and experimental reports and seasonal epidemiology have suggested that cold exposure may increase susceptibility to infection (Shephard & Shek 1998). Upper respiratory infections appear to be the main cause of illness in cross-country skiers (Berglund & Hemmingson 1990). Studies of sustained military operations in the Canadian Arctic also have reported an increased incidence and severity of upper respiratory tract infections during patrols involving high levels of energy expenditure and exposure to cold conditions during both day and night (St. Rose et al. 1972, Sabiston & Livingstone 1973). It is unclear what part the cold exposure and what part the other incidental consequences of the cold environment play in human susceptibility to infection during and after cold exposure. Such incidental consequences may be drying of mucosal surfaces and decreased ciliary movement in respiratory airways. Further work is also needed to examine interactions between cold exposure and exercise.

Inhalation of cold air is a specific and local type of cold stress. The airway mucosa is directly exposed to cooling and drying (Koskela 2007). Cooling the airway mucosa is potentiated when the inhaled air is further cooled or dried, or when the ventilation increases (McFadden et al. 1982). A reduction in temperature decreases ciliary beat frequency (Konietzko et al. 1981). Inspiration of cold air causes a decrease in the temperature of the respiratory epithelium and hence decreases mucociliary clearance and the local immune responses of the airway (Proctor 1982, Eccles 2002 b). In humans, dry air reduces clearance in the nose (Salah et al. 1988), but there is no evidence concerning lower airways (Daviskas et
On the other hand, it has been shown that mucociliary clearance is reduced during, and increased after, isocapnic hyperventilation with dry air comparable with cold air (Daviskas et al. 1995). Mechanisms stimulating the ciliary beat frequency like hyperventilation of dry air by causing hypeosmolarity of the periciliary fluid layer and by releasing mediators are thought to stimulate mucociliary clearance (Daviskas et al. 1995). Additional mediators due to inflammatory cells of the asthmatic airways can cause a prolonged stimulation to mucociliary clearance (Daviskas et al. 1995). Inhalation of air at -20° C may cause inflammatory responses of the mucosal membrane (Gavhed et al. 1998) and in sensitive individuals the drying of the mucosa may lead to an epithelial damage (Cruz et al. 2006).

Data obtained mainly from small mammals suggest that the acute effect of severe cold exposure is a suppression of several cellular and humoral components of the immune response (Shephard & Shek 1998). These include a decrease of lymphocyte proliferation (Goundashova et al. 1994, Shu et al. 1993), a down-regulation of immune cascade, a reduction of natural killer (NK) cell count and cytolytic activity (Aarstad et al. 1983, Won & Lin 1995), activation of complement and the increased expression of heat shock proteins (Shephard & Shek 1998). After several days of cold exposure there is an enhanced production of proinflammatory cytokines (Jiang et al. 1990). Adaptation to a given cold stimulus appears to develop over the course of 2–3 weeks in animal studies (Shephard & Shek 1998).

There are a few reports on the effects of cold exposure on the immunological functions in humans and the results have shown divergent results with no conclusive support for either decreasing or enhancing the response (Castellani 2002). Cold exposure may have stimulating effects on the immunological functions and the response is enhanced with physical exercise (Brenner et al. 1999). Immersion of healthy young men in cold (14°C) water induces a leukocytosis (Jansky et al. 1996). Cold exposure may also initiate changes in a nonspecific acute phase reaction (Dugue & Leppänen 2000, Fairchild et al. 2000). On the other hand, in heat exposure passive heating and exercise both recruit leukocytes into the circulation (Brenner et al. 1995). Neurotransmitters and neuroendocrine hormones can modify the functioning of immune cells and conversely cytokines produced by immune cells can alter brain homeostasis (Klein 1993).
## 2.3 Asthma

Asthma is a chronic disease characterized by recurrent breathing problems and symptoms such as breathlessness, wheezing, chest tightness and coughing, particularly at night and in the early morning (www.ginasthma.org). Local inflammation with various cells, mediators and cytokines play the main role. Airflow obstruction is often reversible either spontaneously or with treatment. Recent findings suggest that systemic inflammation also exists in bronchial asthma (Jousilahti et al. 2002). There is growing evidence on the association of hsCRP, a marker of low-grade systemic inflammation, and asthma (Kony et al. 2004, Sävykoski et al. 2004, Olafsdottir et al. 2005, Takemura et al. 2006). A clinical diagnosis of asthma is made by physicians on the basis of a careful medical history, a physical examination, and tests of lung function (Eder et al. 2006, www.ginasthma.org). Spirometry provides an assessment of airflow limitation and peak flow measures the maximum speed at which air can flow out of the lungs (www.ginasthma.org).

Asthma cannot be cured but it can be controlled (Humbert et al. 2007). With treatment the person with asthma does not experience asthma symptoms, does not have to use quick-relief medication or visit the emergency room, is able to engage in normal physical activity and has normal lung function. Medications used are controller (anti-inflammatory agents) and reliever medications (rapid-acting bronchodilators), www.ginasthma.org. Over 90% of patients with asthma can lead a normal life as a result of modern therapy (Martinez 2003).

The severity of asthma has been classified by objective measures of lung function and the frequency of clinical symptoms by the National Asthma Education and Prevention Program (NAEPP 1997) and the Global Initiative for Asthma (GINA 1995), introduced by Naureckas & Solway 2001 in Table 1. Mild asthma, which includes intermittent and persistent mild asthma according to the Global Initiative for Asthma (GINA) classification, affects between 50 and 75% of asthmatic patients (Dusser et al. 2007). Mild asthma is more frequent, more symptomatic and less well controlled in children than adults (Dusser et al. 2007).
Table 1. Classification of the severity of asthma* (Naureckas & Solway 2001).

<table>
<thead>
<tr>
<th>Severity of asthma</th>
<th>Clinical features before treatment</th>
<th>Night-time symptoms</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe persistent asthma</td>
<td>Continual symptoms Physical activity limited Frequent exacerbations</td>
<td>Frequent</td>
<td>FEV1 or PEF ≤ 60 % of predicted value Variability in PEF &gt; 30 %</td>
</tr>
<tr>
<td>Moderate persistent asthma</td>
<td>Daily symptoms Daily use of inhaled β2-agonists Activity affected with by exacerbations Exacerbations &gt; 2 times/wk</td>
<td>&gt; 1 time/wk</td>
<td>FEV1 or PEF 61–79 % of predicted value Variability in PEF &gt; 30 %</td>
</tr>
<tr>
<td>Mild persistent asthma</td>
<td>Symptoms &gt; 2 times/wk but &lt; 1 time/ day Activity may be affected by exacerbations</td>
<td>&gt; 2 times/mo</td>
<td>FEV1 or PEF ≥ 80 % of predicted value Variability in PEF 20–30 %</td>
</tr>
<tr>
<td>Mild intermittent asthma</td>
<td>Symptoms ≤ 2 times/wk No symptoms and normal level of activity between exacerbations Exacerbations brief</td>
<td>≤ 2 times/mo</td>
<td>FEV1 or PEF ≥ 80 % of predicted value Variability in PEF &lt; 20 %</td>
</tr>
</tbody>
</table>

*Data are from the National Asthma Education and Prevention Program, Expert panel report II: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Asthma Education and Prevention Program, 1997. (NIH publication no. 97–4051) Patients with asthma can have mild, moderate, or severe exacerbations separated by long periods of normal function and no symptoms. FEV1 denotes forced expiratory volume in one second, and PEF peak expiratory flow. †The presence of any one feature is sufficient to place a patient in that category. A patient should be classified as having the most severe grade in which any feature occurs. The characteristics given for each category are general and may overlap, because asthma is highly variable. Furthermore, a patient’s classification may change over time.

However, instead of the classification in table 1 nowadays the asthma severity is defined according to revised GINA guidelines 2006. Asthma severity has been defined to depend on the clinical features, pulmonary function and the current treatment of the patient (GINA 2006), introduced in table 2.
Table 2. Levels of asthma control in the GINA revision (2006).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled</th>
<th>Partly controlled (any measure present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (or minimal)</td>
<td>More than twice/week</td>
<td>Three or more features of partly controlled asthma present in any week</td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue treatment</td>
<td>None (or minimal)</td>
<td>More than twice/week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF FEV1)</td>
<td>Normal or near-normal</td>
<td>&lt; 80 % predicted or personal best (if known) on any day</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>None</td>
<td>One or more/year*</td>
<td>One in any week†</td>
</tr>
</tbody>
</table>

*Exacerbations occurring more than once a year should prompt review of maintenance treatment to ensure that it is adequate
†By definition, an exacerbation in any week makes that an uncontrolled asthma week

2.3.1 Asthma in adolescence

In most patients asthma starts in the first years of life. In childhood the occurrence of asthma has been found to be higher than at other ages (Chipps 2004). Asthma symptoms reduce with age. According to longitudinal cohort studies 40–75 % of children with asthma have complete resolution of symptoms by adulthood (Zeiger et al. 1999, de Marco et al. 2002, Taylor et al. 2005, Vonk et al. 2004). Asthma is still the most common chronic disease in adolescence (de Benedictis & Bush 2007), the prevalence being 4–7 % (ISAAC 1998, Kilpeläinen et al. 2000). There is large international variation in the prevalence of asthma (ISAAC 1998) and the rates vary also within countries (Migliore et al. 2007). The prevalence rates tend to be highest in economically developed countries with a temperate climate (Janson et al. 1997, ISAAC 1998). Among young Finnish men, the prevalence of asthma recorded at call-up examinations has increased from 0.3 % in 1966 to 1.8 % in 1989 (Haahtela et al. 1990). According to Latvala and co-workers the prevalence of asthma has not reduced in young Finnish men by 2003, but nowadays asthma is milder than earlier (Latvala et al. 2005). During puberty and adolescence new cases of asthma occur (de Benedictis & Bush 2007), but many cases of asthma in adults represent the relapse of childhood asthma (Bronniman & Burrows 1986, Radford et al. 1992, Strachan et al. 1996). The relapse rate after a remission ranges between 12 % and 35 % (Taylor et al. 2005, Vonk et al. 2004, Sears et al. 2003).
The rate of clinical remission with no symptoms and no use of inhaled corticosteroids is high, in 57% of asthmatics according to Vonk and co-workers, whereas complete remission, defined as no symptoms, no use of inhaled corticosteroids, normal lung function and no bronchial hyper-responsiveness was present in 22% of asthmatics (Vonk et al. 2004). Even in the absence of asthma symptoms subjects may have obstructed air flow limitation and increased bronchial responsiveness.

Table 3 shows some studies which have evaluated the natural history of asthma from childhood to adolescence or adulthood.
### Table 3. Studies Which Evaluated the Natural History of Asthma from Childhood to Adolescence or Adulthood.

<table>
<thead>
<tr>
<th>References</th>
<th>Type of study population</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phelan et al. 2002</td>
<td>Prospective study, 374 subjects with wheezing in childhood and 105 controls followed prospectively at 7-year intervals until adulthood</td>
<td>Symptoms and lung function.</td>
<td>The more severe the asthma at the age 7 yrs, the more likely the asthma persistence at the age of 42 yrs. Hay fever, eczema and positive skin prick test predispose severe adult asthma.</td>
</tr>
<tr>
<td>Vonk et al. 2004</td>
<td>Prospective study, 119 asthmatic subjects evaluated at 5–14 years, 21–33 years, and 32–42 years</td>
<td>Asthma symptoms, use of inhaled corticosteroids, lung function were examined to define clinical and complete remission</td>
<td>Clinical remission is present in half, but complete only in a small subset. Higher lung function level in childhood predicts remission.</td>
</tr>
<tr>
<td>Panhuysen et al. 1997</td>
<td>Prospective study, 181 asthmatic subjects evaluated at 13–44 years and 25 years later</td>
<td>Determinants of the outcome of asthma</td>
<td>In substantial proportion of symptomatic asthmatics disease improves. Improving associated with a younger age and less severe airway obstruction at first testing.</td>
</tr>
<tr>
<td>Sears et al. 2003</td>
<td>Prospective study, 1139 asthmatic subjects evaluated repeatedly from 9 to 26 years</td>
<td>Risk factors for persistence and relapse of asthma.</td>
<td>Sensitization to house dust mites, airway hyper-responsiveness, female sex, smoking and early age at onset predict persistence or relapse of asthma.</td>
</tr>
<tr>
<td>Limb et al. 2005</td>
<td>Prospective study, 85 asthmatic subjects evaluated at 5–12 years and 17–30 years</td>
<td>Clinical features and exposures associated with persistence of childhood asthma</td>
<td>Lower total serum IgE in childhood, fewer positive allergy skin tests and milder childhood asthma associated with remission.</td>
</tr>
<tr>
<td>Morgan et al. 2005</td>
<td>Birth cohort prospective study, 18559 subjects evaluated repeatedly from birth to age 33 years</td>
<td>Incidence and prognosis of wheezing illness, and relationship to different factors.</td>
<td>Wheezing prevalence and levels of lung function established at age 6 yr and do not change by age 16 yr.</td>
</tr>
<tr>
<td>Strachan et al. 1996</td>
<td>Prospective study, 718 subjects evaluated at 8–10 years, six times at 2 yearly intervals and then 5 years later</td>
<td>Factors influencing onset and prognosis of asthma during adolescence and young adulthood</td>
<td>Adopy and active cigarette smoking major contributors to incidence and recurrence of wheezing during adulthood.</td>
</tr>
<tr>
<td>Roorda et al. 1993</td>
<td>Prospective study, 2289 subjects evaluated at 6–8 years and 14–16 years</td>
<td>Association between potential risk factors and natural history of respiratory symptoms</td>
<td>Childhood symptom severity and degree of bronchial responsiveness with a low % FEV1 related to outcome of asthma in adulthood.</td>
</tr>
<tr>
<td>References</td>
<td>Type of study population</td>
<td>Outcome measure</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Withers et al. 1998</td>
<td>Birth cohort prospective study, 15712 subjects evaluated at birth, 5 years and 16 years</td>
<td>Risk factors in the etiology and persistence of wheezing illness</td>
<td>Personal and family history of atopy, active and passive smoking risk factors for persistence of symptoms. More than half of children with symptoms in early childhood suffer symptoms in adolescence.</td>
</tr>
<tr>
<td>Dodge et al. 1993</td>
<td>Prospective study, 408 subjects examined at 7–17 years and then after a 6-year interval</td>
<td>Relation of various factors to the growth of pulmonary function</td>
<td>Subjects with either wheezing or cough and positive skin allergy test at highest risk for subsequent asthma</td>
</tr>
<tr>
<td>Yunginger et al. 1992</td>
<td>Retrospective, case-control study, population-based survey on 18659 subjects from birth to 44 years</td>
<td>Age- and sex-specific incidence of asthma, and factors influencing asthma incidence in young adults</td>
<td>Asthma begins in early childhood with a higher incidence and earlier onset in males.</td>
</tr>
<tr>
<td>Kokkonen &amp; Linna 1993</td>
<td>Prospective study, 108 asthmatic subjects evaluated at the age of 20–24 yr</td>
<td>The clinical state of the disease, ventilatory lung function and hyper-reactivity of the airways</td>
<td>Atopic dermatitis, severe early disease and impaired lung function at school age significant risk factors for a severe asthma in young adult.</td>
</tr>
<tr>
<td>Gustafsson &amp; Kjellman 2000</td>
<td>Prospective study, 55 asthmatic children evaluated 5 times from childhood to adulthood (age 30)</td>
<td>Lung function, bronchial challenge, serum IgE antibodies to furred animal dander, asthma severity</td>
<td>Initial lung function and gender, but not asthma severity or sensitization to perennial allergens significant influence on lung function development.</td>
</tr>
</tbody>
</table>
The clinical manifestations of asthma in adolescence are variable (de Benedictis & Bush 2007). Persisting asthma over adolescence and young adulthood is influenced by many factors. Features of childhood asthma often predict the course of asthma in later life: The severity of childhood asthma predicts later lung function. Longer duration of the disease means greater decline in lung function in adulthood. Children with bronchial hyper-responsiveness have significantly more respiratory symptoms in later life. Children with episodic asthma generally have good prognosis (Koh & Irving 2007). Positive asthma heredity and individual atopy are factors most often associated with asthma in adolescence. Asthma and airway hyper-responsiveness both among children and adults are strongly related to serum IgE level and skin test reactivity (Zimmerman et al. 1988, Burrows et al. 1989, Sears et al. 1991). Atopy has been shown to be a risk factor for relapse after remission (Taylor et al. 2005) and sensitization to perennial allergen for asthma persistence (Sears et al. 2003). Over 80% of the allergic asthma patients have concomitant rhinitis symptoms (Danielsson & Jessen 1997, Greisner et al. 1998, Braunstahl & Fokkens 2003). Asthmatic patients with allergic rhinitis have more asthma symptoms and increased need for β-agonist medication than asthmatics without rhinitis (Bousquet et al. 2004). Extrinsic factors like exposure to active and passive smoke, greater time in closed environments, change in feeding habits and greater exposure to chemical substances influence the pattern of asthma (de Benedictis & Bush 2007). Common factors provoking asthma are allergens, respiratory tract infections, exercise, perfume, fumes and changes in temperature and humidity, less frequently drugs, food and drinks (Tattersfield et al. 2002).

Cigarette smoke is toxic for the lungs, reduces lung function and may trigger asthma exacerbations (Zimlichman et al. 2004). Current smoking is a risk factor for relapse of asthma (Strachan et al. 1996) and persistence of wheeze (Sears et al. 2003). Smoking asthmatics have poorer asthma control and increase need for acute care (Boulet et al. 2006). Smoking also attenuates the therapeutic response to inhaled corticosteroids (Chalmers et al. 2002). Regardless of the adverse effects cigarette smoking is almost as common among adult asthmatics as it is in non-asthmatic subjects (Price 1996). In addition, asthmatic adolescents are more likely to be daily smokers than non-asthmatic adolescents (Hublet et al. 2007).

Asthmatic adolescents often deny their respiratory symptoms. In addition, adolescents are less likely to seek medical help. Chest pain and shortness of breath on exercise, during infections and with allergy contacts are ignored. Young asthma patients often limit exercise and lifestyle activities (Mancuso et al. 2006) to avoid respiratory symptoms rather than seek medical help for respiratory problems. A
sedentary lifestyle in asthmatic subjects has been accused for obesity (Epstein et al. 2000), but the opposite conclusions have been made, too (Chen et al. 2001a, Thomsen et al. 2005). Both in children and adults, the diagnosis of asthma has been associated with obesity (Figueroa-Munoz et al. 2001, Tantisira & Weiss 2001).

2.3.2 Respiratory tract infections and asthma

The relationship between asthma and respiratory infections is important in three respects. Firstly, respiratory infections caused by viruses and atypical bacterial agents such as M. pneumoniae and C. pneumoniae are frequent causes of exacerbations of asthma both in children and adults. Secondly, some respiratory tract infections such as those caused by RSV and Chlamydia have been proposed as possible causes of asthma. (Isaacs & Joshi 2002). Thirdly, patients with asthma may have increased susceptibility to both viral and bacterial infections (Johnston 2006). In addition, respiratory infection in the small airways of infants and little children cause oedema and wheezing, a condition which resembles asthma.

Clinical and experimental evidence has shown an important role for respiratory infections in the development of asthma attacks. Viral respiratory infections are the most common precipitating factor of acute asthma. Cross-sectional, prospective and case-control studies have shown that virus infections trigger asthma attacks both in children and adults (Pattermore 2003). In a prospective epidemiologic study by Nicholson and co-workers, 57 % of adult asthma attacks were associated with viral respiratory infections (Nicholson et al. 1993). The study by Johnston and co-workers shows that 80 to 85 % of asthma exacerbations in school age children are associated with upper respiratory viral infections (Johnston et al. 1995). Two thirds of the viral infections were caused by picornaviruses (mostly rhinoviruses), coronavirus being the next common cause with less severe asthma exacerbations (Johnston et al. 1995). Rhinoviruses have been noticed to be important inducers of wheezing even in infancy (Kotaniemi-Syrjänen et al. 2003). Other viral types associated with asthma exacerbations include influenza, parainfluenza, RSV and human metapneumovirus. Prospective studies on the association of viral infections and asthma attacks in adults have been collected in Table 4 by Pattermore (Pattermore 2003).
Hospitalization for severe asthma episodes has been linked with viral respiratory infections (Johnston \textit{et al.} 1996). The major spike in hospitalizations due to asthma exacerbations and upper respiratory tract infections has been seen in early September, which is the peak time for rhinovirus infections (Traves & Proud 2007). School-age children experience the earliest peaks of hospitalizations after school return in September in the Northern hemisphere and children are the primary vectors of agents causing asthma exacerbations in older and younger people (Johnston \& Sears 2006).

Atypical bacteria \textit{C. pneumoniae} and \textit{M. pneumoniae} have been linked to asthma also in various ways: an infection with these organisms may precede asthma onset, exacerbate asthma or make asthma control more difficult (Daian \textit{et al.} 2000). Streptococcus pneumoniae, Hemophilus influenzae and Moraxella catarrhalis have been linked to asthma exacerbations, especially in sinusitis (Kraft 2000).

Several studies have demonstrated an association between severe respiratory infections, particularly RSV bronchiolitis, in early life and later development of wheezing, asthma and atopic sensitization (Busse 1993, Sigurs \textit{et al.} 2000, Gern 2000). RSV infections probably do not cause asthma, but are potent triggers of wheezing, with the result that RSV infection often reveals underlying asthma in

\begin{table}[h]
\centering
\begin{tabular}{lccccccll}
\hline
\textbf{Study} & \textbf{People with asthma No.} & \textbf{Age (y)} & \textbf{Any virus} & \textbf{Rhin} & \textbf{Cor} & \textbf{RSV} & \textbf{Para} & \textbf{Inf} & \textbf{Ad} & \textbf{Ent} & \textbf{H.S.} & \textbf{M.P.} & \textbf{C.P.} & \textbf{other dual} \\
\hline
Huhti \textit{et al.} 1974 & 63 & 15–77 & 19.0 & 4.2 & 4.2 & 7.7 & 0.7 & 0.7 & 3.5 & 0.7 & (2.8) \\
Hudgel \textit{et al.} 1979 & 19 & 24–67 & 10.5 & 2.6 & 2.6 & 1.3 & 2.6 & 3.9 & & & & & \\
Clarke 1979 & 51 & adult & 14.8 & 11.1 & & & & 3.7 & & & & & \\
Clarke 1979 & 51 & adult & 3.9 & & & 2.9 & 1.0 & & & & & & \\
Beasley \textit{et al.} 1988 & 31 & 15–56 & 10.0 & 2.2 & 4.5 & 1.7 & 1.1 & 0.6 & & & & & \\
Nicholson \textit{et al.} 1993 & 138 & 19–46 & 44.3 & 27.8 & 8.2 & 1.6 & 6.6 & 3.3 & & & & (1.6) & \\
\hline
\end{tabular}
\end{table}

*Atmar did not allow calculation of individual virus rates, viruses found are shown

Abbreviations: Rhin, Rhinovirus; Cor, Coronavirus; RSV, Respiratory syncytial virus; Para, Parainfluenza virus; Inf, Influenza virus; Ad, Adenovirus; En, Enterovirus; H.S., Herpes Simplex virus; M.P., Mycoplasma pneumoniae; C.P., Chlamydia pneumoniae
children (Wang & Forsyth 1998). The incidence of later asthma is higher in infants with RSV bronchiolitis requiring hospitalization compared with controls (Wang & Forsyth 1998) but not for infants with milder RSV bronchiolitis that can be managed at home (McConnachie et al. 1985). It has been suggested that RSV bronchiolitis in infancy is associated with increased risk of recurrent wheeze up to six years of age, but the risk decreases markedly after that age (Stein et al. 1999).

A recent prospective follow-up study shows that also infants with non-RSV bronchiolitis requiring treatment in hospital are at an increased risk for asthma in adulthood (Piippo-Savolainen et al. 2007). There are also opposite results. A large epidemiologic study shows a protective effect of frequent upper respiratory infections during the first year of life on the risk of later development of atopy and asthma even in children with a family history of atopic diseases (Illi et al. 2001).

Ball and co-workers also demonstrate that increased respiratory infections early in life protect against the development of asthma (Ball et al. 2000).

Adults with asthma have increased susceptibility to rhinovirus infections with increased severity and duration of lower respiratory symptoms and reduction in lung function when compared with infected non-asthmatic individuals (Corne et al. 2002). The mechanisms concerning this issue are poorly understood. The impaired innate immunity in asthmatic patients has been suggested to be the key mechanism (Mallia & Johnston 2006). Respiratory viruses may exacerbate asthma by causing epithelial damage and airway inflammation. Acute asthma attacks are characterized by increased levels of neutrophils and lymphocytes in the airways as in cases of human rhinovirus infections (Proud 2007). Rhinoviruses have been detected in lower airway cells during experimental rhinovirus infection (Gern et al. 1997) and it has been suggested that the bronchospasm mechanism is likely to involve cytokine production in response to viral replication in the lower airways.

Viruses may also potentiate the underlying allergic response. Increased susceptibility to bacterial infections can be derived from the report that asthma is also a risk factor for invasive pneumococcal disease (Talbot et al. 2005).

### 2.3.3 Cold exposure and asthma

In Finland the occurrence of asthma is similar in the southern and northern part of Finland (Kotaniemi et al. 2002). International studies on the prevalence of asthma among children and adults does not associate a high occurrence of symptoms with a cold environment (the European Community Respiratory Health Survey 1996, Worldwide variations in the prevalence of asthma symptoms 1998). In a large
epidemiological study daily exposure to cold occupational environment increase nonspecific respiratory symptoms and airflow limitation, but recreational skiing and outdoor work in cold weather seem not to increase the risk of asthma (Kotaniemi et al. 2003).

However, cross-country skiers who repeatedly breathe cold air at high ventilation rates for a long time, have a much greater prevalence of bronchial hyper-responsiveness and bronchial asthma compared to a control group of non-skiers (Larsson et al. 1993). Other endurance athletes like swimmers and long-distance runners have also a high prevalence of respiratory symptoms and airway hyper-responsiveness (Helenius et al. 2005). The cold-weather athletes have been found to have significantly more airway inflammation than their sedentary counterparts despite the absence of a comparable difference in atopy (Sue-Chu et al. 1998). It has been found that cross-country skiers have a minor to moderate degree of macroscopic inflammation in the proximal airways at bronchoscopy and a bronchoalveolar lavage fluid profile and these findings differ in several respects from healthy persons lacking cross-country skiing activity (Sue-Chu et al. 1999). The mucosal cellular infiltrate in a skier’s airways differs from that in asthmatics: a greater number of neutrophils and a lesser number of eosinophils, mast cells and macrophages (Karjalainen et al. 2000). The term ”athlete” airway disorder may be better than ”ski asthma” (Koskela 2007).

In asthmatic subjects cold air hyperventilation provokes bronchoconstriction by cooling and drying of the airways (Deal Jr et al. 1980, Naureckas & Solway 2001). Exercise in cold or even temperate environments may trigger symptoms in asthmatic people (McFadden & Gilbert 1994). Exercise itself is capable of inducing bronchodilatation both in healthy and asthmatic subjects (Lefcoe 1969, Gelb et al. 1985, Crimi et al. 2002). Bronchoconstriction usually develops after the cessation of exercise and maximal symptoms usually appear in 5 to 10 minutes after stopping activity and vanish within 45 min (Bar-Yiashay & Godfrey 1995). Post-exercise obstruction increases at higher levels of exertion and when inspiring cold air (Caplan 1999). Exercise-induced symptoms are present in 80–90 % of all patients with asthma (Gotshall 2002). Tobacco smoke can enhance the effect of cold air and exercise in provoking respiratory symptoms (Kotaniemi et al. 2003). In cold air provocation airway resistance increases most in asthmatics, then in non-asthmatics and least in healthy non-smokers (Decramer et al. 1984). The use of inhaled corticosteroids reduces exercise-induced bronchoconstriction (Koh et al. 2007). Pre-treatment with an inhaled short-acting β2-agonist is traditionally used before exercise or cold exposure.
2.4 Military service in Finland

In Finland, all healthy young men are called up for mandatory military service for 6 to 12 months (Lehmuskallio et al. 1995). Military service started on a voluntary basis also for women in 1995. About 98% of all men aged 18–19 are examined to establish their fitness for service (Latvala et al. 2005). Altogether 80–85% of the men and also over 80% of asthmatic young men complete their service (Kajosaari 2004). The medical examination is a two-stage procedure before entering the service: clinical examination by a local general practitioner during the spring of the year of the 18th birthday and re-examination at call-up by an army physician. Specialists are consulted if necessary. Young men enter the service two times a year, in January or in July. At the beginning of the service they are examined by an army physician. According to their tasks they continue service for 180, 270 or 362 days. The number of conscripts in the intake group in July 2004 was 13895 and in the intake group January 2005 14320, in Kainuu Brigade 1836 and 1861, respectively. Despite profound medical check-ups of draftees, approximately 8% of conscripts discontinue their military service for medical reasons (Sahi & Korpela 2002). Mental problems are the main reason, the second being locomotor diseases and injuries (Koskinen & Puustinen 2005). The number of conscripts discharged was 1373 (9.7%) from the July 2004 intake group and 1391 (9.7%) from the January 2005 in Finland, in Kainuu Brigade 164 (8.9%) and 128 (6.9%) respectively. Most of the discharges occur during the first two weeks with the entrance medical screening, the discharge percents were 4.7% in July 2004 and 4.6% in January 2005. From the whole Finnish intake groups, 45 asthmatics were discharged in July and 70 in January groups, from which 17 and 8 in Kainuu Brigade, respectively. (Statistics of military medicine, unpublished data.) The majority of the men serve 180 days either from January to June or from July to December.

Each intake group has part of their service time during the cold season. The autumn season in Finland begins in September, when average daily temperatures are below 10 °C. Winter temperatures below 0 °C come in November and continue until spring in April. At the latitude of Kainuu the average daily temperature is above 10 °C only from June to August. The military service often takes place in severe weather conditions. It involves physically strenuous outdoor working including long marches, skiing and field exercises, especially during the period of basic training. The incidence of respiratory infections among conscripts is high. The prevalence of infection symptoms is high especially during the period of basic
training, the cumulative prevalence of cough amounting to 95% (Jormanainen et al. 1994). Acute respiratory infections are the leading cause of sick days during the service (Gray et al. 1999). Among asthmatics physical training in cold weather provoke asthma symptoms and the role of asthma tends to increase during military service (Haahela & Jokela 1979). According to Harju and co-workers the peaks of asthma-induced hospitalizations among conscripts were located during the first months of the military service in February, July and November in the years 1982–1989 and in April and August in 1992 (Harju et al. 1997).
3 Aims of the study

The general aim of the present study was to study respiratory infections in a cold environment among young Finnish men. Military conscripts suffer from frequent respiratory tract infections and all men also serve during the cold season, especially in the central and northern parts of Finland. Asthmatic men are not automatically exempted from the service and a study population composed of asthmatic, mainly men with mild asthma, and non-asthmatic men is possible. The specific aims of the study were the following (the numbers in parenthesis refer to the original papers):

1. To compare characteristics of young men with and without asthma at the beginning, at the end and during the military service. (I).
2. To study risk factors for frequent respiratory tract infections during 180-day military service (II).
3. To study acute *C. pneumoniae* respiratory tract infections among conscripts with 180-day service (III).
4. To study the association between cold exposure and respiratory infections (IV).

In addition, some unpublished data is presented.
4 Materials and Methods

4.1 Protocol of the study

The respiratory and physical health of 224 asthmatic and 668 non-asthmatic men were studied during their military service in Kainuu Brigade, Kajaani, between July 2004 and January 2006. Each man was followed to the end of his service time lasting 6 to 12 months according to military duties. Factors affecting respiratory health were collected with a questionnaire (Appendix 1) at the beginning of the service. The information on education was collected. Height and weight were measured for calculating BMI at the beginning of the service. PEF and hsCRP were measured at the beginning and end of the service, total IgE values at the beginning. *C. pneumoniae* serology was studied at the beginning and end of the service and during each infection episode with convalescent samples. Data on respiratory infections requiring a physician consultation was collected at the primary care clinic in Kainuu Brigade. Physical fitness was followed with the results of 12-min running tests at the beginning and end of the service. CRP was analyzed during each infection episode.

4.2 Study subjects

The study population included 892 military recruits collected from two intake groups for military service in July 2004 and in January 2005 in Kajaani garrison, northern Finland. The total number of recruits in Kainuu Brigade was 1836 in July 2004 and 1861 in January 2005. All men with a previous diagnosis of asthma and randomly chosen men without asthma were recruited for the study. The asthma diagnosis was based on questionnaire responses for physician-diagnosed asthma, which is the most commonly used and validated method (Sunyer *et al.* 1999). The self-reporting of asthma was assured by register data on previous health checks at call-up and at the beginning of the service. Asthmatic men in the present study had mild or moderately severe asthma, because men with severe asthma had already been discharged at the call-up examination or at the examination during the two first weeks of military service. The response rate in July was 82% and in January 75%. A flow chart of recruitment is shown in Fig. 2. After agreement to participate in the study and signing of an informed consent form, men with medical problems were discharged from the service and from our study population. Three new cases of asthma were diagnosed during the first weeks of the service in July (change
from non-asthmatic to asthmatic group). All together, 420 men in July and 472 men in January took part in the study (Table 5). The age of the respondents ranged from 17.4 to 29.6 years. At the beginning of the military service, the conscripts filled a questionnaire concerning their allergies, respiratory tract symptoms and respiratory tract infections during the preceding 12 months, subjective cold sensations and smoking habits, and went through a clinical examination including laboratory tests. The service time was 180, 270 or 362 days according to duties. The study protocol was approved by the Medical Ethics Committee of the Kainuu Central Hospital and written informed consent was obtained from all participants.

In studies I and IV, the study population consisted of the whole recruited population. At the beginning the study, there were 892 men, of whom 224 were asthmatics. The service was discontinued by 26 (11.6 %) asthmatic and 38 (5.7 %) non-asthmatic men (p=0.003). At the end of the study, there were 818 men, of which 623 were non-asthmatic and 195 asthmatic. Six men quit the study and 4 men were moved to another garrison. In study I, characteristics of 224 asthmatic and 668 non-asthmatic men were compared. In study IV, acute infection episodes requiring physician examination among these 892 men were analyzed and associated with outdoor temperature. In study II and III, the study population consisted of 518 men, 55.4 % of the asthmatic and 59.0 % of non-asthmatic men, who completed 180-day service. In study III, 6 men lacked data on C. pneumoniae antibodies and the population in this study was 512. The study populations with 180-day and with 362-day service did not differ significantly from each other considering asthma, atopy, smoking, education and BMI (data not shown) indicating that the smaller group was also suitable for risk factor analyzing.
4.3 Methods

4.3.1 Questionnaire at the beginning of the service

The questionnaire in Appendix 1 was used at the beginning of the service to get information on respiratory tract symptoms, previous respiratory tract infections and cold sensations. Allergic disorders/symptoms, subject’s own knowledge of results of skin prick or serological tests, physician-diagnosed asthma and asthma medication, smoking habits and the information of previous adenoidectomy/tonsillectomy were inquired about with the same questionnaire.

The questions concerning asthma, respiratory tract symptoms, previous respiratory infections, allergic disorders/symptoms, smoking habits and cold sensations were based on the questionnaire of Tuohilampi (Susitaival & Husman 1996), on the Finriski-questionnaire of the year 1997 (Vartiainen et al. 1998) and
on the Finriski questionnaire for cold exposure of the year 1997 (Hassi et al. 1998). The Tuohilampi-questionnaire has been created by a group of Finnish researchers from The Finnish Institute of Occupational Health, the National Public Health Institute and several universities for environmental studies of asthma and respiratory disease. It includes questions, which are based on several different questionnaires (Medical Research Council (MRC) 1960, 1966 and 1986; European Community for Coal and Steel (ECCS) 1987; American Thoracic Society, National Heart, Lung and Blood Institute, Division of Lung diseases (ATS-DLD-78) 1978; International Union against Tuberculosis and Lung Diseases (IUATLD) 1986) (Samet 1987, Minette 1989, Burney & Chinn 1987). The original international questionnaires have been validated in several studies (Toren et al. 1993).

Depressive symptoms at the beginning of the service were assessed by a Finnish modification of the 13-item Beck Depression Inventory (R-BDI) in Appendix 2 (Raitasalo 1995, Kaltiala-Heino et al. 1999, Kurki et al. 2000). R-BDI is based on the 13-item Beck Depression Inventory (Beck & Beck 1972), which is a shortened version of an originally 21-item questionnaire designed by Beck and co-workers (Beck et al. 1961). The 13 items of R-BDI consist of statements showing increasing intensity of depressive emotions and conditions, each scored on a scale ranging from 0 to 3 and the item scores are summarized a total score with ranges 0–39. Scores 0–4 were classified as no depressive symptoms. The severity of depressive symptoms was categorized as follows: 5–7 as mild, 8–15 as moderate, and ≥ 16 as severe.

4.3.2 Measurements

Body mass index (BMI). Body height and weight of the men were measured at the beginning of the service. BMI was calculated as weight in kilograms divided by the square of height in metres. Overweight was defined as BMI ≥ 25 kg/m² and obesity as BMI ≥ 30 kg/m².

Peak expiratory flow (PEF). PEF was measured using a Wright Peak Flow Meter at the beginning and end of the service. The best of three readings was recorded. The predicted PEF values have been introduced by Quanjer and co-workers (Quanjer et al. 1993). At beginning of the service PEF measurements were done before strenuous exercise just after physician examination which was also permission for exercise and at the end measurements were done along with the service and physical exercises. Results of PEF were considered low if the
measured PEF was < (predicted value -80) l/min or measured PEF < 80 % of predicted PEF value.

**Endurance performance.** Endurance performance was tested with the 12-min running test (distance in m), i.e. Cooper test, during the first weeks of the service and at the end of service. The Cooper test is a test of physical fitness, designed by Kenneth H. Cooper in 1968 for military use (Cooper 1968), in which the person runs as far as possible within 12 minutes. The result gives a rough estimate of a person’s condition, general endurance. The distance < 2200 m is considered poor and distance ≥ 2600 m is considered a good result.

**Temperature in the environment.** The temperature data was obtained from the meteorological station (Kajaani Airport Meteorological Station, 64° N, 27 °E) located ca. 15 km from the garrison and linked to the data. Means of the average (T_{avg} °C) and maximal (T_{max} °C) temperatures of the preceding three days and two weeks of the onset of an infection were calculated and included to the analyses. The maximal temperatures were included because they usually occur during the active phase of the day. The temperatures of the three preceding days were included because of the time-course of acute rhinovirus infections with symptoms within 10–16 hours after virus entrance and peak on days 2–3 of infection (Gwaltney 2002). Furthermore, the temperature of the preceding two weeks of receiving an infection were also used in the analyses to include e.g. the biphasic development of bacterial pneumonia.

### 4.3.3 Laboratory methods

**Highly sensitive C-reactive protein (hsCRP).** A non-fasting venous blood sample was collected from all participants for measurement for hsCRP at the beginning and end of the service. The samples were stored at -80 ºC until analysis. The hsCRP levels were determined by the Immunoenzymometric Assay (IEMA) test (Medix Biochemica, Kauniainen, Finland) (Taponen *et al.* 2004 and according to the manufacturer’s instructions). The assay range was from 0.3 to 30 mg/l, and the sensitivity of the test was 0.08 mg/l. The lowest hsCRP level of the highest quartile was used as a cut-off value for elevated hsCRP levels. Normal CRP concentrations were measured during infectious episodes by enzyme immunoassay (IBL Immunobiological Laboratories, Hamburg, Germany) according to the manufacturer’s instructions (Gewurz *et al.*1982). The concentration of CRP in a serum sample was determined by interpolation from the standard curve. The CRP
standard solutions ranged from 0 mg/l to 100 mg/l. The minimal detectable concentration of the test was 1 mg/l.

*C. pneumoniae antibodies.* The sera were collected from all participants at the beginning and the end of the service. In addition, acute and convalescent serum samples were collected during respiratory tract infections for the measurement of CRP and *C. pneumoniae* antibodies. The samples were stored at -80 °C until analysis. The sera were tested for IgG, IgA and IgM antibodies to *C. pneumoniae* by the MIF test using purified elementary bodies of Kajaani 6 as previously described (Wang 2000, Wang & Grayston 1970). All the sera from one subject were tested in the same series to minimize interassay variation. Fourfold serum dilutions were used, starting from 1/32 in IgG and 1/10 in IgA and IgM antibodies. The serum dilutions were incubated in a moisturized chamber for one hour at +37°C for IgG, overnight at +8 °C for IgA and for three hours at 37 °C for IgM antibodies. IgA- and IgM-positive sera were retested after treatment with Gullsorb reagent (Gull Laboratories, Salt Lake City, Utah) to avoid false-positive reactions (Jauhiainen et al. 1994, Verkooyen et al. 1992). The presence of IgM antibodies in titres of ≥ 10 after Gullsorb treatment was used to define evidence of primary infection, and seroconversions suggesting acute infection were based on a fourfold titre rise in IgG and/or IgA between consecutive sera. Prolonged *C. pneumoniae* infections were defined as prolonged symptoms with elevated IgG antibodies over period ≥ 2 months after an acute rise.

*Total IgE.* Quantitative determination of immunoglobulin E (IgE) in sera was done by Total IgE ELISA (IBL Gesellschaft für Immunochemie MBH, Hamburg, Germany) at the baseline.

### 4.3.4 Definitions

*Definition of asthma, atopy and allergic rhinitis.* Asthma was defined as physician-diagnosed asthma, self-report of medically diagnosed asthma in the questionnaire. Data on previous health and call-up examinations was used to confirm the person’s own opinion.

Each person was asked to give his own estimate of the presence (yes/no/don’t know) of the following allergic disorders/symptoms: asthma, allergic rhinitis, atopic eczema, allergic conjunctivitis. They were also asked to give their own information on the positive results on skin prick or serological tests. Atopy was considered to be present, if the person had at least one of the following allergic disorders/symptoms: asthma, allergic rhinitis, atopic eczema and allergic
conjunctivitis and a history of positive results on skin prick or serological tests to certain allergen(s). In study I when comparing asthmatic and nonasthmatic men, atopy was considered to be present also, if the person had at least one of the inquired allergic disorders/symptoms combined with a history of positive results on skin prick or serological tests with regard to allergens or positive levels of IgE ≥ 100 kU/l according to the manufacturer’s recommendations. Quantitative determination of immunoglobulin E (IgE) in sera was done by Total IgE ELISA (IBL Gesellschaft für Immunochemie MBH, Hamburg, Germany) at the baseline.

Allergic rhinitis was considered to be present, if the person had hay fever or other nasal allergic symptoms and positive skin prick or serological tests for common allergens. Allergic rhinitis was defined only with symptoms without tests.

Definition of smoking. Smoking habits were classified based on four questions: 1. Have you ever smoked? 2. Do you smoke daily (cigarettes, cigars or pipe)? 3. How many cigarettes per day do you smoke or smoked before stopping? and 4. How many years have you smoked (deduct breaks over 6 months)? Smokers were current daily smokers. Non-smokers had never smoked or had stopped smoking or smoked only occasionally. The cumulative lifetime consumption of cigarettes for smokers was calculated as pack-years (PY, number of cigarettes per day x number of years/20).

Definition of depressive symptoms. The 13 items of R-BDI consist of statements showing increasing intensity of depressive emotions and conditions, each scored on a scale ranging from 0 to 3 and the item scores are summarized a total score with ranges 0–39. Scores 0–4 were classified as no depressive symptoms. The severity of depressive symptoms was categorized as follows: 5–7 as mild, 8–15 as moderate, and ≥ 16 as severe.

Definition of education. The information on education was collected from the conscripts’ personal data forms: 1. comprehensive school and 2. any further education after comprehensive school (senior secondary school or vocational education).

4.3.5 Determination of acute episodes of respiratory tract illness

The conscripts with acute or acutely aggravated respiratory tract symptoms were first checked by a nurse in the military primary care clinic in Kainuu Brigade. The nurse made a decision on physician consultation and asked the sick conscript to fill in a questionnaire concerning his work and cold sensations during the previous
three days. The episode was included in the database if a respiratory tract infection or an exacerbation of asthma was diagnosed by the physician. Mild episodes not referred to a physician were not included in the analyses. Respiratory tract infection was defined with a combination of respiratory tract symptoms, physical findings and if necessary laboratory and radiological examinations. The men were examined by the physician: ears, nose, throat and neck were examined and auscultation was done, fever and PEF were measured. Sinus ultrasound and sinus and chest radiography, blood tests (CRP and leukocytes) and throat swabs for bacterial culture were methods to differentiate bacterial infections from viral ones. Consultations within two weeks were considered as one episode.

Respiratory tract infections were categorized as common cold (= upper respiratory tract infection), otitis, tonsillitis, sinusitis, bronchitis, pneumonia or exacerbation of asthma and antibiotics were prescribed for bacterial infections according to Finnish national current care guidelines. Mild upper respiratory tract infection or common cold was diagnosed in a patient with acute illness characterized by symptoms and signs related primarily to the nasal passages with, or without, fever, irritation of the throat and cough. In clinical practice, the key decision was whether or not to prescribe antimicrobials. Bacterial infections were diagnosed according to the recommendations of the national guidelines (Honkanen et al. 2002). Acute otitis media was diagnosed with respiratory infection symptoms and findings of the tympanic membrane and effusion in tympanum and acute sinusitis with a history of respiratory tract infection over 1 week, findings of nasal discharge and positive finding in ultrasound or x-ray. Streptococcal tonsillitis was based on tonsillopharyngeal exudates with a positive throat culture for group A Streptococcus. Acute bronchitis was diagnosed with prolonged infection with cough after an acute respiratory infection, worsening of the disease and elevated level of C-reactive protein over 50 mg/l. Chest radiography was used for differential diagnosis of pneumonia. Pneumonia was based on clinical symptoms and findings, but the reference standard for the diagnosis was a new infiltrate on a chest radiograph. Asthma exacerbation was defined as an increase of asthma symptoms (cough, breathlessness) or an increase in bronchodilator use and/or a reduced peak expiratory flow rate and/or wheezing on clinical examination. In the office there were results of peak expiratory flow rates for each conscript at the baseline at the beginning of the service. Asthma exacerbation without infection was diagnosed if no signs of respiratory tract infection were found.

Symptoms, clinical findings, clinical diagnosis and drug prescriptions were recorded. One episode could have records with several clinical diagnoses such as
sinusitis with asthma exacerbation. There could also be a common cold with bronchitis or tonsillitis meaning viral infections with local findings. In study IV, the infections were further grouped into upper respiratory tract infections (URTI) including common cold, otitis, pharyngitis and sinusitis. The lower respiratory tract infections (LRTI) included bronchitis and pneumonia.

4.4 Statistical analyses

The statistical analysis was performed using the SPSS 13.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were compared using Student’s t test for independent samples. Age comparison was performed using Student’s t test. The distributions of pack-years of smoking and hsCRP concentration were skewed, and comparisons were therefore made with the non-parametric Mann-Whitney U-test. Categorical variables were analyzed with Chi-squared test or Fisher’s exact test, as appropriate. Logistic regression analysis was used to identify the independent risk factors among the variables that showed statistically significant associations (p < 0.05) with frequent respiratory tract infections in univariate analyses. The trend was analyzed with Chi-squared test for trend. Student’s t test for paired samples was used to analyze individual changes between arrival and departure values.

The Generalized Additive model (GAM) procedure (Hastie et al. 1990) with the binomial link function and logit link was used to provide a graphic representation of the relationship between respiratory tract infections and daily average temperature available in the R software, release 2.50 (R Development Core Team, 2007).

The estimated risk by infection type and temperature was analysed by logistic regression analysis. Model fitting was based on the generalized estimating equation (GEE) approach with exchangeable correlation matrix. Temperature trends preceding the infection was analysed by the repeated measures ANOVA for either a three-day or two-week period. Significance was set at p < 0.05.

4.5 Ethical considerations

The study protocol was approved by the Medical Ethics Committee at Kainuu Central Hospital. At the beginning of the military service the participants were informed about the study. They were given an opportunity to ask questions about the study and they were asked to give a written consent. Written informed consent
was obtained from all study subjects. The participants were voluntary, and they were able to withdraw from the study at any time. Privacy was protected during the whole work. The data and samples were preserved in the National Public Health Institute, in Oulu. The samples have been coded so that they cannot be connected to persons. Only the research group can know the person behind each code.
5 Results

5.1 Characteristics of asthmatic and non-asthmatic young men

The respiratory and physical health of 224 asthmatic and 668 non-asthmatic men were studied during the military service in Kainuu Brigade, Kajaani between July 2004 and January 2006. Characteristics for the whole study population and separately for each intake group are shown in Table 5. Each man was followed to the end of his service time lasting 6 to 12 months according to military duties. Factors affecting respiratory health were collected with a questionnaire (Appendix 1) at the beginning of the service. Data on respiratory infections requiring a physician consultation was collected at the primary care clinic in Kainuu Brigade. PEF and hsCRP were measured at the beginning and end of the service. Physical fitness was followed with the results of a 12-min running tests. Height and weight was measured for calculating BMI and total IgE was measured at the beginning of the service.

Table 5. Characteristics of the conscripts included in the analysis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All N=892</th>
<th>July 2004 N=420</th>
<th>January 2005 N=472</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean) (sd)</td>
<td>19.6 (0.8)</td>
<td>19.6 (0.9)</td>
<td>19.6 (0.6)</td>
<td>0.834</td>
</tr>
<tr>
<td>Asthma n (%)</td>
<td>224 (25.1)</td>
<td>116 (27.6)</td>
<td>108 (22.9)</td>
<td>0.103</td>
</tr>
<tr>
<td>Atopy* n (%)</td>
<td>223/416 (53.6)</td>
<td>232/469 (49.5)</td>
<td>0.219</td>
<td></td>
</tr>
<tr>
<td>Current smoker† n (%)</td>
<td>161/414 (38.9)</td>
<td>217/463 (46.9)</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Pack-years of smoking median (range)</td>
<td>2.5 (0.1–15.8)</td>
<td>2.3 (0.1–9.0)</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>BMI‡ mean (SD)</td>
<td>21.8 (3.8)</td>
<td>22.0 (3.7)</td>
<td>21.6 (3.8)</td>
<td>0.056</td>
</tr>
<tr>
<td>Education&amp; % (n)</td>
<td>90.9 (758)</td>
<td>89.9 (357)</td>
<td>91.8 (401)</td>
<td>0.357</td>
</tr>
</tbody>
</table>

* Chi-squared test or Fisher’s exact test for categorical variables, Student’s t-test or Mann-Whitney U-test for continuous variables
*knowledge of atopy missing for four subjects in July 2004 and for three subjects in January 2005
†smoking status missing for six subjects in July 2004 and for nine subjects in January 2005
‡BMI missing for one subject in July 2004
& further education after comprehensive school, education data missing for 23 subjects in July and for 35 subjects in January 2005

Altogether 55.4 % of asthmatic and 59.0 % of non-asthmatic men completed 180-day service, 5.8 % and 6.3 % completed 270-day service, and 25.9 % and 28.0 % completed 362-day service, respectively. The service was discontinued 38 (5.7
%) non-asthmatic and 26 (11.6 %) asthmatic men (p=0.003). 14 non-asthmatic and 3 asthmatic dropped out, but continued in civil service. 24 non-asthmatic (3.6 %) and 23 asthmatic (10.3 %) men were discharged from service because of health problems (p < 0.001), including 14 men discharged because of severe asthma (accounting for 58 % of the asthmatic men discharged because of health problems), and 2 of these also had depression, 1 was obese, and 1 had episodes of syncope. In addition, 3 were discharged because of atopic eczema.

Characteristics of the 224 asthmatic and 668 non-asthmatic men were compared according to answers on the questionnaire at the beginning of the service. Results are introduced in tables 6 and 7.

Table 6. The presence (%) of atopy, allergic rhinitis, smoking, previous respiratory infections and previous adenoidectomy or tonsillectomy among men with and without asthma at the beginning of the service.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Asthmatics N=224</th>
<th>Non-asthmatics N=668</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy *</td>
<td>90.6</td>
<td>38.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atopy&quot;</td>
<td>37.5</td>
<td>8.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Allergic rhinitis+</td>
<td>77.7</td>
<td>38.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Allergic rhinitis#</td>
<td>33.9</td>
<td>8.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>37.4</td>
<td>45.0</td>
<td>0.051</td>
</tr>
<tr>
<td>Smoking history ≥ 6 pack years</td>
<td>22.2</td>
<td>23.5</td>
<td>0.802</td>
</tr>
<tr>
<td>Education°</td>
<td>10.5</td>
<td>8.6</td>
<td>0.412</td>
</tr>
<tr>
<td>Recurrent respiratory tract infections before the service</td>
<td>17.5</td>
<td>9.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A common cold without fever during the preceding year</td>
<td>88.4</td>
<td>82.5</td>
<td>0.024</td>
</tr>
<tr>
<td>Adenoidectomy or tonsillectomy</td>
<td>18.8</td>
<td>16.5</td>
<td>0.442</td>
</tr>
<tr>
<td>Tympanostomy</td>
<td>8.5</td>
<td>8.2</td>
<td>0.912</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>20.2</td>
<td>15.9</td>
<td>0.137</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>4.0</td>
<td>3.6</td>
<td>0.762</td>
</tr>
</tbody>
</table>

* at least one of the inquired allergic disorders/symptoms combined with a history of positive results on skin prick or serological tests with regard to allergens or positive levels of IgE ≥100 kU/l
"at least one of the inquired allergic disorders/symptoms combined with a history of positive results on skin prick or serological tests without IgE determination
# hay fever or other nasal allergic symptoms
°no further education after elementary school

Based on the questionnaire survey, respiratory tract symptoms were very frequent among asthmatics, being clearly more common than in non-asthmatics (Table 7). Almost half (48 %) of the men with asthma reported having no medication for
asthma. Respiratory symptoms, including cold-induced symptoms, were statistically significantly more common among asthmatic men both with and without medication compared to non-asthmatic men at the beginning of the service. Sputum and cough during the previous year were significantly more common in asthmatic men with medication (57.5 %) than in those without medication (42.1 %) compared to non-asthmatics (34.9 %), p < 0.001 vs. p= 0.435. Cold sensation was also more frequent among asthmatics than non-asthmatics (24.1 % vs. 15.4 %, p=0.003), but asthmatics with medication were more often sensitive to cold than asthmatics without medication (30.1 % vs. 18.3 %).

During the service, men with asthma had an average of 0.2 and men without asthma 0.1 respiratory tract infections requiring a physician care per month (p < 0.001).

Table 7. The presence (%) of respiratory tract symptoms among men with, and without, asthma at the beginning of the military service.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Asthmatics N=224 %</th>
<th>Non-asthmatics N=668 %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, wheeze during infections</td>
<td>67.6</td>
<td>47.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough, wheeze without infections</td>
<td>53.9</td>
<td>15.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough or dyspnea during previous 12 months</td>
<td>52.2</td>
<td>21.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough at night during previous 12 months</td>
<td>38.4</td>
<td>38.1</td>
<td>0.946</td>
</tr>
<tr>
<td>Cough, wheeze and dyspnea on exercise</td>
<td>69.6</td>
<td>30.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough, wheeze and dyspnea in cold</td>
<td>43.4</td>
<td>13.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dyspnea, wheeze and cough in cold and on exercise</td>
<td>76.3</td>
<td>39.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dust-induced cough, wheeze and dyspnea</td>
<td>54.0</td>
<td>28.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pollen-induced cough, wheeze and dyspnea</td>
<td>46.0</td>
<td>12.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Animal-induced cough, wheeze and dyspnea</td>
<td>44.1</td>
<td>8.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough and sputum during previous year</td>
<td>49.5</td>
<td>34.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cold sensation</td>
<td>24.1</td>
<td>15.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Arrival and departure percentages of men with low PEF results (PEF < (predicted -80) l /min or PEF < (80 % of predicted)), with poor (< 2200 m) or good results (≥2600 m) in 12-min running test (Cooper test) and, in addition, median levels of hsCRP concentration among asthmatic and non-asthmatic men at the beginning and the end of the service are shown in table 8.

A decrease in PEF values between departure and arrival was shown in both groups, but the decrease was only statistically significant in non-asthmatics. The
mean difference between PEF values and the percentage difference from predicted PEF at the end and at the baseline were -4.3 l/min and -0.7 %, respectively, in non-asthmatics (both values being statistically significant p=0.010 and p=0.009). The corresponding figures for asthmatics were -3.9 l/min and -0.6 % (not statistically significant p=0.197 and p=0.191). The mean Cooper test result at the beginning was 2470 m (1050–3610 m) in non-asthmatic and 2404 m (1300–3450 m) in asthmatic men, and the corresponding figures at the end were 2597 m (1165–3420 m) and 2545 m (1700–3320 m). The difference between the results at the beginning and at the end was statistically significant in both groups (p< 0.001), but the increase in running distance did not differ between the groups (p=0.863). The mean decrease in hsCRP levels among asthmatics was 1.5 and that among non-asthmatics 1.6 (the decrease was significant in both groups, p = 0.001 and p < 0.001, respectively).

Table 8. Arrival and departure percentages of men with low PEF results, poor and good 12-min running test results, and arrival and departure median levels of hsCRP concentration. Comparison between asthmatic and non-asthmatic men.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At the beginning</th>
<th></th>
<th>p-value</th>
<th>At the end</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthmatics</td>
<td>Non-asthmatics</td>
<td></td>
<td>Asthmatics</td>
<td>Non-asthmatics</td>
<td></td>
</tr>
<tr>
<td>PEF &lt; (predicted -80) l/min</td>
<td>22.9 %</td>
<td>18.1 %</td>
<td>0.119</td>
<td>30.9 %</td>
<td>21.5 %</td>
<td>0.008</td>
</tr>
<tr>
<td>PEF &lt; (80% of predicted)</td>
<td>7.6 %</td>
<td>4.5 %</td>
<td>0.070</td>
<td>10.5 %</td>
<td>6.4 %</td>
<td>0.061</td>
</tr>
<tr>
<td>Cooper &lt; 2200m</td>
<td>25.8 %</td>
<td>19.1 %</td>
<td>0.050</td>
<td>11.7 %</td>
<td>9.7 %</td>
<td>0.434</td>
</tr>
<tr>
<td>Cooper ≥ 2600m</td>
<td>31.7 %</td>
<td>38.8 %</td>
<td>0.081</td>
<td>50.8 %</td>
<td>55.8 %</td>
<td>0.243</td>
</tr>
<tr>
<td>hsCRP (median, IQR)</td>
<td>0.8</td>
<td>1.0</td>
<td>0.185</td>
<td>0.7</td>
<td>0.6</td>
<td>0.097</td>
</tr>
</tbody>
</table>

*p predicted values for PEF at the age of 20 by Quanjer et al. 1993

5.2 Risk factors for acute respiratory tract illness in military conscripts

Factors contributing to susceptibility to respiratory tract infections were studied among 518 military conscripts, 124 men with and 394 without asthma, who completed 180-day service in Kainuu garrison, Kajaani. Characteristics of the conscripts are introduced in table 9.
Fifteen factors potentially contributing to respiratory tract illness were evaluated (Table 10). The conscripts with one or more respiratory tract infections were compared to those with no infections, and those with frequent (≥3) episodes were compared to those with 0–2 episodes.

A total of 417 respiratory tract illness episodes were diagnosed among these 518 conscripts. 252 conscripts had no recorded respiratory tract disease episodes. Only 8 asthma exacerbations were noticed without a clinical diagnosis of respiratory infection. There was obvious seasonal variation in the frequency of respiratory tract illness. Both asthmatic and non-asthmatic men from the January intake group had more infections than men from the July group. At least one infectious episode was diagnosed in 97 men in the July intake group and 169 men in the January intake group (p< 0.001). Three or more infections were recorded for 11 conscripts in the July group and 26 in the January group (p=0.047). Fig.3 shows the distribution of men (%) with infection episodes in different months. The highest percentages in both the asthma and the non-asthma groups were seen during the month following the entry into service.
The presence of the fifteen contributing factors for respiratory tract infections among conscripts with 0 infections, with $\geq 1$ infections, with 0–2 infections and $\geq 3$ infections are shown in table 10.
Table 10. Comparison of conscripts with a service time of 180 days with or without respiratory tract infections.

<table>
<thead>
<tr>
<th>Factors</th>
<th>no infections</th>
<th>≥1 infection</th>
<th>p-value</th>
<th>0–2 infections</th>
<th>≥3 infections</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking#</td>
<td>111 (44.6%)</td>
<td>117 (44.8%)</td>
<td>0.955</td>
<td>210 (44.3%)</td>
<td>18 (50.0%)</td>
<td>0.508</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²ª</td>
<td>40 (15.9%)</td>
<td>50 (18.9%)</td>
<td>0.369</td>
<td>78 (16.2%)</td>
<td>12 (33.3%)</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²ª</td>
<td>9 (3.6%)</td>
<td>8 (3.0%)</td>
<td>0.725</td>
<td>14 (2.9%)</td>
<td>3 (8.3%)</td>
<td>0.107</td>
</tr>
<tr>
<td>Depressive symptoms: (R-BDI ≥ 5)</td>
<td>23 (9.2%)</td>
<td>45 (17.2%)</td>
<td>0.007</td>
<td>62 (13.0%)</td>
<td>6 (17.1%)</td>
<td>0.443</td>
</tr>
<tr>
<td>Education (only comprehensive school)*</td>
<td>19 (8.2%)</td>
<td>28 (11.6%)</td>
<td>0.207</td>
<td>43 (9.7%)</td>
<td>4 (12.5%)</td>
<td>0.544</td>
</tr>
<tr>
<td>Previous respiratory tract infections =</td>
<td>21 (8.4%)</td>
<td>43 (16.2%)</td>
<td>0.007</td>
<td>53 (11.0%)</td>
<td>11 (29.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous adenoidectomy/tonsillectomy©</td>
<td>31 (12.4%)</td>
<td>51 (19.2%)</td>
<td>0.032</td>
<td>72 (15.0%)</td>
<td>10 (27.0%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Atopy</td>
<td>33 (13.1%)</td>
<td>55 (20.7%)</td>
<td>0.022</td>
<td>75 (15.6%)</td>
<td>13 (35.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>29 (11.5%)</td>
<td>52 (19.5%)</td>
<td>0.012</td>
<td>69 (14.3%)</td>
<td>12 (32.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Asthma (medically diagnosed)</td>
<td>47 (18.7%)</td>
<td>77 (28.9%)</td>
<td>0.006</td>
<td>106 (22.0%)</td>
<td>18 (48.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any medication for asthma&gt;</td>
<td>21 (8.3%)</td>
<td>46 (17.4%)</td>
<td>0.002</td>
<td>57 (11.9%)</td>
<td>10 (27.0%)</td>
<td>0.018</td>
</tr>
<tr>
<td>HsCRP ≥ 3.2 mg/l &amp;</td>
<td>62 (24.7%)</td>
<td>71 (26.7%)</td>
<td>0.605</td>
<td>123 (25.6%)</td>
<td>10 (27.0%)</td>
<td>0.851</td>
</tr>
<tr>
<td>PEF &lt; (80 % of predicted) ^</td>
<td>11 (4.4%)</td>
<td>10 (3.8%)</td>
<td>0.733</td>
<td>20 (4.2%)</td>
<td>1 (2.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>12-min running test &lt; 2200 m÷</td>
<td>44 (19.2%)</td>
<td>71 (29.5%)</td>
<td>0.010</td>
<td>103 (23.6%)</td>
<td>12 (35.3%)</td>
<td>0.127</td>
</tr>
<tr>
<td>12-min running test ≥ 2600 m+</td>
<td>74 (32.3%)</td>
<td>69 (28.6%)</td>
<td>0.386</td>
<td>133 (30.5%)</td>
<td>10 (29.4%)</td>
<td>0.894</td>
</tr>
</tbody>
</table>

# smoking status missing for 8 subjects
ª BMI missing for 1 subject
± depressive symptoms missing for 5 subjects
* education missing for 44 subjects
= previous respiratory infections missing for 1 subject
© adenoidectomy/tonsillectomy missing for 2 subjects
> medication for asthma missing for 2 subjects
& highest quartile, CRP missing for 1 subject
^ PEF missing for 1 subject
+ 12-min running test missing for 48 subjects

Overweight (BMI ≥ 25 kg/m²) (p=0.009) and previous respiratory tract infections (p=0.003) were more frequent among the conscripts with 3 infection episodes compared to the men with 0–2 episodes. Obesity (BMI ≥ 30 kg/m²) was not found to be a contributing factor for infections. The men with atopy (p=0.002), allergic rhinitis (p=0.004) or asthma (p=0.001) were prone to frequent infections. The men with depressive symptoms (p=0.007) and those who did <2200 m in a 12-min running test (p=0.010) were more prone to have at least one infection episode, but these factors were not more frequent among the men with 3 episodes. Elevated levels of hsCRP did not predict future respiratory infections. No association between current smoking and frequent respiratory infections could be found. With regard to smoking history as package years, there was no difference between the
groups with 0 vs. more than 1 infection episodes (the medians were 2.2 (max 16) and 2.5 (max 12), nor between the groups with 0–2 vs. more than 3 infection episodes (the medians were 2.2 (max 16) and 3.2 (max 12)).

The variables that showed statistically significant associations with frequent respiratory tract infections in univariate analyses (atopy, allergic rhinitis, asthma, BMI and predictive previous respiratory infections) were further analyzed by logistic regression analysis. The results confirmed that BMI ≥ 25 kg/m² (OR = 2.27, 95 % CI 1.05, 4.9) and history of previous respiratory infections (OR= 2.9, 95 % CI 1.3, 6.48) were independent risk factors for frequent respiratory tract infections. The more these two contributing factors were present, the higher was the number of conscripts with frequent respiratory infections: 4.8 % of the conscripts with neither BMI ≥ 25 kg/m² nor previous respiratory infections, 10.3 % of the conscripts with one contributing factor and 35.7 % of those with two contributing factors had frequent respiratory tract infections (test for trend p< 0.001).

5.3 Acute *C. pneumoniae* infections in asthmatic and non-asthmatic military conscripts during a non-epidemic period

*C. pneumoniae* respiratory tract infections were studied among 512 military conscripts, 123 asthmatics and 389 non-asthmatics men, in 180-day service between July 2004 and July 2005 in Kainuu garrison. All respiratory tract infections requiring a physician examination at a primary care clinic were analyzed prospectively. Blood samples for measurement of *C. pneumoniae* antibodies were obtained at the beginning and the end of the service and in the acute and convalescent phases of each infection episode.

A recent *C. pneumoniae* infection was serologically diagnosed in 34 (6.6 %) of the 512 conscripts. The characteristics of these 34 men are shown in table 11 in comparison with the characteristics of all 512 conscripts included in the study. Twenty-two of the men with recent *C. pneumoniae* infection were non-asthmatic and 12 were asthmatic, with no significant difference between the non-asthmatic and asthmatic groups (5.7 % vs. 9.8 %, p=0.111).
Table 11. Characteristics of the 512 conscripts in 180-day service with available data concerning acute *C. pneumoniae* antibodies.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire study population</th>
<th>Conscripts with recent <em>C. pneumoniae</em> infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>512</td>
<td>231</td>
</tr>
<tr>
<td>Age years, mean (sd)</td>
<td>19.6 (0.7)</td>
<td>19.6 (0.8)</td>
</tr>
<tr>
<td>Asthmatic, n (%)</td>
<td>123 (24.0)</td>
<td>63 (27.3)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>226 (44.8)</td>
<td>95 (41.7)</td>
</tr>
</tbody>
</table>

a Student’s t test  
b Chi squared test

Acute primary infections with the presence of IgM titres of ≥ 10 were seen in 13 men, nine without and four with asthma. In five men, IgM antibodies were present at the beginning of service, suggesting scars from a previous infection, and another 5 men had IgM antibodies in the sera taken at the end of service, but these ten men had no clinical illness. A clinical illness was diagnosed in the other three men with IgM ≥ 10. In addition, acute primary infection with clinical illness was diagnosed in two conscripts on the basis of IgG antibody response, as no IgG antibodies were present in the acute phase.

Acute re-infections or reactivations of chronic infection, with a fourfold or greater rise in IgG antibodies, were found in 19 conscripts, including 12 (3.1 %) of the 389 non-asthmatic and seven (5.7 %) of the 123 asthmatic men (p=0.180), (one with two episodes), and all of the subjects had a clinical illness. Primary infections were diagnosed in five men, three in non-asthmatic men and two in asthmatic men. Prolonged infections were diagnosed in one (0.3 %) of 389 non-asthmatic men and in six (4.9 %) of 123 asthmatic men (p=0.001).

The clinical picture was compatible in 24 men (one with two episodes) with laboratory-confirmed *C. pneumoniae* infection. The clinical symptoms and the diagnoses of these 25 episodes are shown in tables 12 and 13. One episode could have one or more clinical diagnosis, e.g. common cold with tonsillitis. Sixteen of the clinical episodes occurred between September 2004 and April 2005, ten in the July 2004 intake group and 24 in the January 2005 intake group.
Body temperature was ≤ 38 °C in 22 and > 38 °C in three infectious episodes. CRP was ≤ 10 mg/l in nine, 11–50 mg/l in 12 and > 50 mg/l in four episodes. Three men with upper respiratory tract infections and two men with sinusitis also experienced exacerbation of asthma. Three cases of pneumonia were diagnosed, two of which were primary infections. Antimicrobial agents were prescribed for 12 episodes, including the three men with pneumonias, who were prescribed roxithromycin for 14 days. Men with prolonged infections were treated for common cold and sinusitis. The following antimicrobial agents were prescribed for sinusitis: amoxycillin, amoxycillin-clavulanate and trimetophrim-sulphamethoxazole.

### Table 12. Occurrence of clinical symptoms in 25 cases of acute *C. pneumoniae* infection.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No (%) of episodes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Earache</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Sputum</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Chest soreness</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*One episode could have more than one associated symptom

### Table 13. Clinical diagnoses associated with 25 cases of acute *C. pneumoniae* infection.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>No (%) of episodes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Exacerbation of asthma</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>1 (12)</td>
</tr>
</tbody>
</table>

*One episode could have more than one associated diagnosis
5.4 Cold temperature and respiratory tract infections

The association between daily-monitored ambient temperature and occurrence of respiratory tract infections was studied among the military conscripts from July 2004 to January 2006. Among the initial examinations for RTI episodes (n=720), a total of 643 respiratory infection episodes were diagnosed, 595 (93 %) were URTI (common cold, sinusitis, pharyngitis and otitis) and 87 (14 %) LRTI episodes (bronchitis and pneumonia). Some episodes were with upper and lower RTI diagnosis like pneumonia with sinusitis. Most episodes of URTI were diagnosed as common cold, n=354. Pharyngitis was diagnosed in 99 episodes.

Table 14. Mean of the average (Tavg °C) and maximum (Tmax °C) during the preceding three days of the onset of a respiratory infection.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Tavg °C mean±SD (n)</th>
<th>95% CI</th>
<th>Tmax °C mean±SD (n)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>-4.1±10.6 (595)</td>
<td>-5.0; -3.3</td>
<td>-0.1±9.8 (595)</td>
<td>-0.9; +0.7</td>
</tr>
<tr>
<td>LRTI</td>
<td>-1.1±10.0 (87)</td>
<td>-3.2; +1.0</td>
<td>2.9±9.7 (87)</td>
<td>0.8; +4.9</td>
</tr>
<tr>
<td>Common cold</td>
<td>-4.5±10.5 (354)</td>
<td>-5.6; -3.4</td>
<td>-0.4±9.7 (354)</td>
<td>-1.4; +0.6</td>
</tr>
<tr>
<td>All RI</td>
<td>-3.7±10.6 (643)</td>
<td>-4.5; -2.8</td>
<td>0.3±9.9 (643)</td>
<td>-0.4; +1.1</td>
</tr>
</tbody>
</table>

The GAM analysis revealed a significant linear association between temperature and infection type. The association between temperature and RTIs (common cold and LRTI) is presented in Fig. 3. The average temperature in the preceding three days was associated with the occurrence of URTI (p=0.055) and LRTI (p=0.0475) episodes and separately with common cold (p=0.0172) and pharyngitis (p=0.0109). A 1 °C decrease in temperature increased the estimated risk for URTI by 4.3 % (OR 0.96, p<0.0001), common cold by 2.1 % (OR 0.98, p=0.0040) and pharyngitis by 2.8 % (OR 0.97, p=0.019). The association between temperature and LRTI was nonlinear (p=0.0475). The estimated risk for LRTI for a 1 °C decrease in temperature was 2.1 % (OR 1.02, p=0.038, n=87). For RTI episodes among asthmatic conscripts mean daily temperature was significantly associated with URTI (p=0.0212) and pharyngitis (p=0.0465). The association between RTI episodes and temperature did not differ between the asthmatic and non-asthmatic conscripts.
Fig. 3. The association between temperature and RTIs (common cold and LRTI). Relative odds (logarithmic scale) on common cold (upper panel) and LRTI (lower panel) by the mean of the average daily temperature of the preceding three days before the onset of an infection. The shaded area represents the 95% confidence interval of the relative odds curve. Based on a generalized additive model with binomial error and identity link.

The outdoor average temperature decreased linearly during the preceding three days before the onset of an infection separately for any RTI (F=58.4, p<0.001), URTI (F=56.8, p<0.001), LRTI (F=4.2, p=0.042) and common cold (F=28.0, p<0.001) being lowest one day before seeking medical consultation. Also when examining the temperature trend for a longer period (14 days) significant linear decreases in temperatures were observed for all infections (F=26.4, p<0.001), URTI (F=17.2, p<0.001) and common cold (F=12.9, p<0.001), but not for LRTI.
6 Discussion

6.1 Study population

The study population consisted of young healthy men capable for military service in Kainuu Brigade, Kajaani. In Finland, military service is obligatory for all healthy men and about 15 000 young men enter the service twice a year. In July 2004, 1836 and in January 2005, 1861 conscripts entered the service in Kainuu Brigade. Men for Kainuu Brigade come mainly from the central part of Finland, mostly from rural area with small cities. The examination for military service is a two-stage procedure: a clinical examination by a local practitioner and re-examination at call-up by an army physician. The men are examined a third time during the first two weeks at the beginning of their service. Chronic illnesses except asthma are generally a reason for exemption. The study population represents ordinary healthy young Finnish men. Men with asthma were collected according to their own opinion of having a physician-diagnosed disease. The questionnaire based information of physician-diagnosed asthma is a largely accepted and validated method (Toren et al. 1993). In addition, the diagnosis was confirmed with data on previous medical appointments and data on the first examination in the service. Men with serious asthma were not participants in the study, because they were exempted either at call-up examinations or were discharged during the first two weeks. Features appearing among asthmatic men in the present study concern mainly mild or moderately severe disease.

In Finland, asthma is diagnosed according to national guidelines. Asthmatic men were diagnosed in the past. The onset of asthma or grounds for the diagnosis were not available. No pulmonary function testing except PEF measurement was done to ensure the diagnosis. Neither skin prick nor serological tests for common allergies were carried out and the results rely on the conscripts’ own opinion. There were many conscripts who did not know if they were tested for their allergic symptoms or if their tests were positive.

In studies II and III, risk factors for respiratory tract infections and C. pneumoniae infections were studied among men with 180-day service. These men were better controlled for their infections, because they served only in Kainuu Brigade. From the original study population 55.4 % of asthmatic and 59.0 % of non-asthmatic men were in these analyses. The study populations with 180-day and with 362-day service did not differ from each other when considering asthma,
atopy, smoking, education and BMI and so indicated that the smaller group was also suitable for risk factor analysis.

6.2 Methods

6.2.1 Questionnaires

The medical history and many other variables used in this study were self-reported. Validity and reliability are general problems with questionnaires. Validity is the strength of conclusions, inferences or propositions. Validity is concerned with the study's success to measure what the researcher set out to measure. Reliability is the extent to which an experiment, test, or any measuring procedure yields the same result on repeated trials. Reliability is associated with the generalizability of the research.

Measures on self-reported health status have been shown to be reasonably realistic and correlate considerably well with the health status assessed by a physician (Nagi 1969, Maddox & Douglass 1973, Hunt et al. 1980, Kivinen et al. 1998). Questionnaires are also the only available method to get information on subjective health. The strength of self-reported health lies in its subjectivity; it is based on a person’s own opinion (Ware 1987, Blaxter 1989). The questionnaires formulated for this study were based on previous questionnaires for similar purposes. The Tuohilampi -questionnaire has been created by Finnish experts for epidemiological studies concerning respiratory, eye and skin symptoms and screening for allergic patients (Susitaival & Husman 1996) and is based on international questionnaires, which have been validated in several studies (Toren et al. 1993). The questionnaire of depressive symptoms was a Finnish modification of the 13-item Beck Depression Inventory (R-BDI) (Raitasalo 1995, Kurki et al. 2000). BDI is a state measure and it is not possible to assess the duration of depressive symptoms. However, an adolescent’s severe depressive symptoms are likely to be relatively persistent (Charman 1994). Rates of depressive symptoms in newly recruited young adult men have been shown to be higher than rates found in non-military populations (Tekbas et al. 2003). Questions on smoking habits and cold sensations were based on the Finriski questionnaire from the year 1997 with a questionnaire of cold exposure (Vartiainen et al. 1998, Hassi et al. 1998). The validity of self-reported smoking has been shown to be high in a study, in which questionnaire-based smoking was compared to cotinine measurements in serum (Vartianen et al. 2002). According to a review and meta-analysis by Patrick and
co-workers, the self-reported smoking is very reliable in a general population (Patrick et al. 1994). The possible under-reporting has been the main concern in questionnaires concerning smoking habits. In the present study, smoking prevalence was high both in asthmatic and non-asthmatic young men and over-reporting instead of under-reporting may be the problem. The high smoking prevalence is in agreement with the previous FinEsS study, which showed current smoking by Finnish men to be most common in Lapland, where 48% of men were smokers (Kotaniemi et al. 2001).

6.2.2 Data on respiratory tract infections

The data on respiratory tract infections was collected at the primary care clinic in Kainuu Brigade. The appointment was arranged so that examination was first done by a nurse and if necessary afterwards by a physician. Respiratory tract infections or exacerbations of asthma were included in the database only after diagnosis by physician. Mild episodes not referred to a physician were not included in the analyses. In the present study, data from all the respiratory infections diagnosed by physician could not be collected to the database. The majority of the men travelled to their home district during weekends and acute illnesses during that time are missing from the data, if the infectious episode did not last over the weekend. The same problem was noticed during the peak of an influenza epidemic. There were so many men attending the clinic that the men with an infectious episode belonging to the study group may have visited a physician without records being entered into the data base. The men could also have been too busy with their intensive service that they did not come for blood test 2 weeks after the first visit without a reminder.

Definition of respiratory infection in the present study is based on the clinical experience of the study physician. Etiological analyses were not available. The study population was mainly examined by one physician and the others made their notes according to her advice. An infection was searched for and if none was noticed, the visit was not included in the data on respiratory tract infections. Respiratory tract infection was defined with a combination of respiratory tract symptoms, physical findings and, if necessary, laboratory and radiological examinations. Upper respiratory tract infection/ common cold was diagnosed in a patient with acute illness characterized by symptoms and signs related primarily to the nasal passages with or without fever, irritation of the throat and cough. An asthma exacerbation was defined by an increase of asthma symptoms or an
increase in bronchodilator use and/or a reduced peak expiratory flow rate and/or wheezing on clinical examination. For comparison, information on the results of peak expiratory flow rates for each conscript at the baseline at the beginning of the service was available. The clinician’s main problem is usually whether or not the existing infection is viral or bacterial and whether to prescribe antimicrobials. For this purpose it was possible to take laboratory and radiological tests. Infections were categorized and antibiotics were prescribed for bacterial infections according to current Finnish national care guidelines. In the works II, III and IV all physician-diagnosed respiratory infections including common cold, otitis, sinusitis, pharyngitis, bronchitis and pneumonia were collected for the analysis. It has been proposed that in primary care it would be better to define a single clinical entity than anatomically specific diagnoses (Hueston et al. 2000). For example sinusitis and bronchitis are probably manifestations of the same clinical condition. Influenza-like illness was not defined separately and most cases were included in the common cold entity.

The possibility of non-infective aetiology is possible in some of the patients who presented complaints of respiratory tract infection. Thus far, laboratory specimens for defining different viruses as etiological agents for the episodes have not been analyzed. The fact is that conscripts can avoid unpleasant duties by aggravating symptoms and visiting a clinic. The medical services are easily accessible and it may lead conscripts to get rest in the clinic when waiting for the appointment. This may also affect the greater frequency of infections in cold periods. Careful examination and objective means like fever measurement and laboratory tests help to reveal acting. Data on the service programme may have also helped to analyze the eagerness to avoid service demands.

Respiratory infections with more severe symptoms are also more likely to lead to medical consultations than minimally symptomatic or asymptomatic infections. Men with asthma could be more vulnerable to respiratory infection agents, experience more intense symptoms and seek medical attention and so they were sent to a physician consultation more easily than men without asthma. That is why, in the present data there may be more common cold episodes in asthmatic than in non-asthmatic men. However, it seems possible that the presence of an inflammatory condition in the airways predisposes patients to develop more frequent and/or more severe respiratory tract infections (Bardin et al. 1994, Chen et al. 2001 b, Corne et al. 2002). Chronic inflammation of the airways may contribute to impaired immunity and to a predisposition to bacterial and viral infections (Message & Johnston 2004). At any rate, conscripts with atopy, allergic rhinitis or
asthma need more medical attention for their respiratory tract infections than men without these diseases during military service.

6.3 Results

6.3.1 Characteristics of asthmatic and non-asthmatic young men

Asthma in young adulthood is a variable disease. Men in the present study had mild or moderately severe asthma, because men with severe asthma had already been discharged at the first examination on the suitability for military service. However, men with asthma reported to experience significantly more respiratory tract symptoms than men without asthma. Considering the high prevalence of respiratory symptoms, the proportion of asthmatics using medication was quite low, 52% of the group. Respiratory symptoms provoked by stress factors like exercise, exercise in a cold and dusty environment are emphasized during the service, especially during respiratory infection epidemics in winter. It can be assumed that medication could help in these situations, inhaled corticosteroids have been shown to reduce exercise-induced bronchoconstriction (Koh et al. 2007). A drawback of the present study is that there is no information on the type of drugs used by asthmatics with medication. Although young asthmatic men reported to have more respiratory symptoms than their healthy counterparts, we really do not know how much they had lifestyle restrictions. In our questionnaires there were not any questions concerning their ability for different activities and lifestyle limitations.

The high number of men with asthma with a poor result in 12-min running at the beginning of the service, 25.8% of asthmatic compared with 19.0% of non-asthmatics, p=0.050, may be related to their lifestyle. There is evidence that asthma patients limit their exercise and healthy lifestyle activities to avoid respiratory symptoms (Lucas & Platts-Mills 2005). The appearance of symptoms and poor physical fitness may imply that the asthmatic inflammation is not adequately controlled. Sedentary life without physical demands does not reveal the reality and many adolescents tend to consider that their asthma is better controlled than it actually is. On the other hand, 31.7% of asthmatics and 38.8% of non-asthmatics had a good result ≥ 2600 m in 12-min running (p= 0.081). The physical activity among adolescents with and without asthma is still quite similar. In general, the physical activity among adolescents is at a low stage, both among healthy and asthmatic ones (Ford et al. 2003). The poor aerobic fitness among men
with asthma may be rather due to their decreased levels of habitual activity than obstruction (Lucas & Platts-Mills 2005). However those asthmatic men, who completed their service, could enhance their physical fitness according to the 12-min running test just like non-asthmatic ones. The increment of distance was not big in metres, but the increase was statistically significant in both groups. The proportion of men with the result < 2200 m also decreased among both asthmatic and non-asthmatic groups. The most serious asthma cases with continuous symptoms were discharged and this may affect the fact that the difference between asthmatic and non-asthmatic men in poor result < 2200 m disappeared at the end. With the service the hsCRP levels decreased both in asthmatic and non-asthmatic men. This may reflect the effect of continuous physical exercise on the levels of hsCRP, as reported earlier (Kasapis & Thompson 2005).

The reason for a minor decrease in PEF values in both asthmatic and non-asthmatic group with the service remains ambiguous. 10.3 % of asthmatic men were discharged, mostly because of inadequate asthma control. So, the most serious asthma cases were discharged from the service and the assumed lowest PEF values were taken away from the analysis at the end and still there was fall between start and end in PEF values among the asthmatic. It has been shown that young men gain more weight with the service (Tähtinen et al. 2000). Obese subjects have been shown to have lower PEF values than the non-obese (Ulger et al. 2006), but among these conscripts the effect of possible weight gain cannot be analyzed. The weight of the conscripts was not measured at the end of the service. However, the baseline PEF measurements were taken during the first two ‘easy’ weeks of the service without physical exercise and the end measurements were taken throughout the service. Post-exercise fall in PEF values has been shown in previous studies (van Helden et al. 2001, Helenius et al. 2002). Reduced PEF values have also been associated with passive smoking (van Helden et al. 2001) and the exposure to cigarette smoke has been great among these intake groups.

Asthmatic men were more sensitive to the cold and experienced more cold-related respiratory symptoms than non-asthmatics. In an adult population living in a cold climate, the rates of cold- and exercise-induced shortness of breath are higher among subjects with asthma, allergic rhinitis and conjunctivitis than in healthy subjects (Kotaniemi et al. 2003). Especially asthmatics with medication reported being sensitive to cold. Their asthma may be more serious than the asthma in men without medication, or their medication predisposes them to the cold. In addition, tobacco smoke can enhance the effect of cold air and exercise in provoking respiratory symptoms both in healthy and in asthmatic persons.

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(Kotaniemi et al. 2003). In the present study, smoking was prevalent both among asthmatic and non-asthmatic men: 37.4% of the men with and 45.0% of the men without asthma were current smokers, and 22.2% and 23.5%, respectively, had a smoking history of ≥ 6 pack years. The prevalence of smoking is even higher than previously reported. According to national smoking statistics in the year 2004 21% and in the year 2005 20% of men aged 15 to 24 years and 31% and 30% of men aged 25 to 44 years smoked daily (Statistics Finland, tobacco statistics). Previously the FinEsS study by Kotaniemi has reported a similar high prevalence of current smoking, 48% of men aged 20–29 years were current smokers (Kotaniemi et al. 2002). In previous studies, the smoking prevalence of asthmatics has been similar or even higher than that of non-asthmatics (Precht et al. 2003).

Results in the present study showed that 10.3% of asthmatic men were discharged because of medical problems. The number is high compared with non-asthmatic men with a 3.6% discharge percentage for medical reasons. All men had gone through a 3-stage procedure with physician examinations, so it can be assumed that the control of asthma has been assessed. In addition, during the service men can seek medical help and also new asthma-related symptoms are controlled and medicated. Unfortunately the role of new descriptions to medicate asthma during the service has not been analyzed. Men with an increasing amount of asthma symptoms get medication. Still, it is not easy to get good asthma control in a military environment. Asthmatic men may not be able to bear the physical and mental stress of the service. Previous evidence shows that the full effects of treatment with inhaled corticosteroids are not seen immediately. Symptoms and lung function have been shown to improve relatively quickly, whilst airway hyper-responsiveness will continue to improve with treatment over many months and even years (Lundback & Dahl 2007).

6.3.2 Risk factors for respiratory tract infections

In the present study, men with atopy, allergic rhinitis or asthma were prone to frequent respiratory tract infections during their 180-day military service. Overweight (BMI ≥ 25 kg/m²) and previous respiratory tract infections appeared to be risk factors for recurrent respiratory illness independently of the other factors considered. Asthmatic and non-asthmatic men suffered more respiratory infections during the winter than during the summer.

Overweight (BMI ≥ 25 kg/m²), which is a growing problem among young men in Finland (Kautiainen et al. 2002, Lahti-Koski et al. 2002), was statistically
significantly and independently associated with frequent respiratory tract infections (≥ 3 infections). Previous data indicate that the incidence and severity of specific types of infectious illnesses are higher in obese persons than in lean persons (Marti et al. 2001). Overweight children (BMI ≥ 20 kg/m²) have been shown to be more susceptible to acute respiratory infections than non-obese children (Jedrychowski et al. 1998). A diet with multiple deficiencies in nutrients may impair the immunocompetence of obese people (Jedrychowski et al. 1998). Obesity has been associated with alterations in various measures of the immune function (Nieman 1994), which may also explain the elevated risk for infections. In addition, obesity itself is an inflammatory state and associated with hsCRP, a marker of systemic low-grade inflammation (Visser et al. 1999). In the present study, however, slightly elevated CRP levels did not predict frequent respiratory tract infections.

The data showed that conscripts with frequent respiratory infections had suffered frequent infections also earlier. Previous adenoidectomy or tonsillectomy was also common in men with at least one and frequent respiratory infections. These may reflect a general susceptibility to respiratory infections and suggest the presence of an infection-prone condition. In both intake groups most infections occurred during the first three months of the service. Mixing young men from different regions, some carrying unique strains of regional pathogens and crowding may increase the risk of infections (Gray 1995). Psychophysical stress during the first months may also influence the immune system of the conscripts depressively and predispose to infections (Gray 1995). It can be assumed that after the first three months men have adapted to their new environment.

In the present study there was no association between smoking and respiratory tract infections. This finding is contrary to previous evidence (Murin & Bilello 2005). There are, however, other reports showing no association between the frequency of respiratory tract infections and smoking (Monto & Ross 1977). In our series, the prevalence of smoking in both the July and the January intake groups was high (41 % and 47 %, respectively) and passive exposure to smoking among nonsmoking conscripts may have been huge. Previously, it has been reported that more frequent and more prolonged colds are seen in persons exposed to passive smoking (Bensenor et al. 2001). However, our study sample differs from the general population regarding the living environment shared by the participants, the large army unit as a working place, the high levels of psychological stress and numerous social ties, and the effect of smoking on the infection rate may hence disappear. Based on smoking history as pack-years, we could not find any
statistically significant differences, but the smoking histories may also have been shorter than in other studies concerning the frequency of respiratory infections in smokers. In young men, smoking had not possibly yet caused irreversible lung damage, leading to vulnerability to respiratory infections.

6.3.3 Acute *C. pneumoniae* infections in asthmatic and non-asthmatic military conscripts during a non-epidemic period

The clinical picture of *C. pneumoniae* infection has been studied primarily during epidemic periods (Kleemola *et al.* 1988, Ekman *et al.* 1993, Miyashita *et al.* 2002, Lee *et al.* 2006, Nakashima *et al.* 2006). The present study period (July 2004 to July 2005) can be considered to be a non-epidemic period with respect to *C. pneumoniae* infections in Finland. The number of laboratory-confirmed *C. pneumoniae* infections in Finland has varied from 90 to 430 cases annually during the past decade, being highest in 2003 and lowest in 2006. In 2004, 245 *C. pneumoniae* infections were registered in Finland, and 32.2 % (79/245) of the infections occurred between June and December (National Public Health Institute, Infectious diseases register). In 2005, 113 infections were registered, 62.8 % (71/113) of which between January and July. Usually, over 50 % of *C. pneumoniae* infections occur in Finland during winter. In the present study, 16 (47.1 %) of the clinical episodes occurred between September 2004 and April 2005.

Primary infections occur mostly during childhood. In the present study, primary clinical illnesses were diagnosed in 5 (14.7 %) young men. A fourfold rise in *C. pneumoniae* IgG antibodies, suggesting re-infection or reactivation of a persistent infection, was naturally more common, being verified in 19 men (one with two episodes). Since *C. pneumoniae*, like other *Chlamydia* spp., tends to cause persistent infection, serological tests do not differentiate between re-infections and reactivation of chronic infection during acute episodes in adults. *C. pneumoniae* infections during epidemics may involve a combination of both primary and secondary infections, and further molecular or typing investigations are required to determine whether a strain represents a reactivated strain or a new infection.

*C. pneumoniae* has been associated with asthma in various ways: an infection may precede the onset of asthma, exacerbate asthma or make the management of asthma more difficult (Johnston & Martin 2005). The present data revealed no statistical difference in the number of serological diagnoses of recent *C. pneumoniae* infections, or in the number of *C. pneumoniae* re-infections or
reactivation episodes, between asthmatic men and non-asthmatic men, but prolonged clinical infection with persistently elevated IgG antibodies after an acute *C. pneumoniae* episode was diagnosed in six asthmatic men and one non-asthmatic man (4.9 % vs. 0.3 %, p=0.001). However, the number of prolonged infections was small, and further research is required to confirm the suggestion that asthmatic individuals are prone to prolonged *C. pneumoniae* infection, although similar findings have been published previously (File et al. 1998).

As reported previously, nonproductive cough is a common symptom, and fever is of low grade (File et al. 1998). In the present study, most infections were mild, with fever of ≤ 38°C in 22 episodes and CRP values of ≤ 50 mg/l in 21 episodes. The occurrence of mild infections may have been much greater, if all episodes have been collected and not only those requiring physician consultation. It has been estimated that c. 70 % of all *C. pneumoniae* infections are asymptomatic (Miyashita et al. 2001). In the present study, asymptomatic infections were evidently present in five men with IgM titres 10 at the end of their service. These individuals may have had an actual subclinical disease, or may have been so eager to complete their service that they ignored their symptoms.

Pneumonia and bronchitis are the most frequently recognized clinical illnesses associated with *C. pneumoniae*, although asymptomatic or mild symptomatic illness is the most common feature of infection (Kuo et al. 1995). In the present study, 13 of 25 *C. pneumoniae* infections were diagnosed as upper respiratory tract infections, with the next most common diagnosis being sinusitis (seven cases). Pneumonia and bronchitis were both diagnosed in three subjects. According to previous studies, 5 % of the cases of bronchitis and sinusitis in adults are associated with *C. pneumoniae* infection (Kuo et al. 1995), and this organism has been isolated from patients with purulent sinusitis and from patients with otitis media with effusion (Hammerschlag 2000). It has also been suggested previously that more than one apparent etiological agent can be demonstrated in a majority of cases of *C. pneumoniae* pneumonia (Kauppinen et al. 1995). Evidently, acute or chronic infections caused by intracellular pathogens such as *C. pneumoniae* may pave the way for invasion by other bacteria, e.g., *S. pneumoniae* (Kauppinen et al. 1995) and *Haemophilus influenzae* (Monno et al. 2002), and some of the patients in the present study, e.g. those with sinusitis, might have been affected by a combination of various etiological agents. *C. pneumoniae* can contribute to respiratory infections by decreasing the ciliary activity of ciliated bronchial cells (Shemer-Avni & Lieberman 1995).
In the majority of respiratory tract infections, the etiological diagnosis remains obscure and empirical antibiotic therapy is prescribed. Coverage against atypical pathogens should be provided for community-acquired pneumonias. Macrolides, tetracyclines, ketolides and fluoroquinolones demonstrate both \textit{in vitro} and \textit{in vivo} activity against \textit{C. pneumoniae} (Miyashita et al. 2003), but this organism is not treatable with penicillin, ampicillin or sulphonamides. In the present study, men with pneumonia were treated with roxithromycin, but those with prolonged infection and sinusitis were prescribed antimicrobials according to the recommendations for sinusitis (Finnish otolaryngological Association. Sinusitis: Best Practices in Treatment 1999) none of which provide coverage against \textit{C. pneumoniae}. It is possible that these men could have recovered sooner with antibiotics effective against \textit{C. pneumoniae}, but the use of antimicrobial agents poses a risk for the development of antibiotic resistance, particularly with respect to macrolide resistance among \textit{S. pneumoniae} (Plouffe 2000). The current treatment guidelines should be followed, but additional coverage against \textit{C. pneumoniae} should be provided in the case of prolonged infections.

\subsection*{6.3.4 Cold temperature and respiratory tract infections}

The most common temperature for the onset of a respiratory infection episode was in the outdoor temperature range of 0 to -5 °C. According to the general additive model, daily average temperature was significantly associated with episodes of RTI. URTI showed an inverse linear association with temperature, where especially the occurrence of common cold was higher in cold temperatures. The association between LRTIs and temperature was nonlinear and the susceptibility was highest at temperatures between 0 to 10 °C, after which the risk again decreased with both colder and warmer temperatures.

Aetiologically viral infections dominate in URTI infections and rhinovirus has been traditionally considered an upper airway pathogen frequently associated with symptoms of the common cold (Gwaltney 2002). In a cold environment the temperature of the upper airways (nasal cavity) may be favourable to rhinovirus. Rhinovirus is known to replicate best at airway temperatures of 33 to 35 °C (Papadopoulos \textit{et al.} 1999) which approximates the temperature of the upper airways (McFadden \textit{et al.} 1985). On the other hand, local hyperthermia (43 °C for 20–30 min) reduces the symptoms of naturally acquired as well as experimental colds (Tyrrell \textit{et al.} 1989). During cold seasons the frequent indoor-outdoor change common in military service may also affect on the epithelium of the upper airways.
and be favourable to viruses. In addition, in cool and dry air some viruses, like the influenza virus, seem to be more stable (Hemmes et al. 1960, Lowen et al. 2007). A recent experimental animal study showed that both cold temperature and low humidity favour the spread of the influenza virus (Lowen et al. 2007). In this study housing animals in the cold prolonged the viral growth and that viral transmission was highly efficient when the relative humidity is low. The results would provide support for the fact that the low relative humidity observed frequently in cold environmental temperatures is a contributing factor for respiratory infections.

The different impacts of cold weather on URTI and LTRI can partially be explained by the different cooling patterns of the upper and lower airways in cold weather. Although, the long-term responses of cold air inhalation have been shown to extend to the lungs causing inflammation (Larsson et al. 1998), it has been shown mainly in cases of heavy physical exercise (and oronasal breathing) when also the lower respiratory tract is more affected by the cold. Other reasons for the different effect of cold on LRTI could be the different aeti ological pattern and often biphasic nature of the development of LRTI. The episode begins as a mild viral infection and the host factors such as the action of immunological defence mechanisms and genetic susceptibility may predetermine the outcome which is not as temperature-sensitive as the primary viral infection.

In the present study, the ambient temperature decreased significantly during the preceding three days of the onset of an acute respiratory infection (all infections, URTI, LRTI). The decrease in temperature ranged between 1.3–1.4 °C. Also the temperature trend for a longer period demonstrated a significant decrease (any RTIs, URTI, common cold) of approximately 0.4–1.3 °C. This could indicate that the temperature decrease itself is associated with the onset of an infection.

There are only a few previous studies where the association between temperature and RTIs has been demonstrated. Danielides and co-workers (Danielides et al. 2002) conducted a retrospective study on medical records and showed that several meteorological parameters (including low temperatures) were associated with increased occurrence of acute laryngitis. Though, this research was conducted in a temperate, southern climate (Greece), where the occurrence of sub-zero cold temperatures is not as frequent, as in the present study. The results in the present study are in accordance with a previous study conducted in Greece where GP consultations for respiratory tract infection were studied and compared with outdoor temperatures (Nastos & Matzarakis 2006). In this study a 15-day lag between \( T_{\text{min}} \) and the peak of GP consultation was found; a decrease of 10 °C in \( T_{\text{min}} \) increased GP consultations by 28 %. Consistent with our findings, the study
also revealed a three day lag effect. Similarly, Hajat and co-workers (Hajat et al. 2004) observed an increased amount of GP consultations, especially for LRTIs, with cold temperatures in the UK, but this study was restricted to elderly people. Similarly studies on respiratory mortality have demonstrated a 12 day lag after a cold spell (Donaldson & Keatinge 1997).

The reasons for the seasonality and peak winter incidence of many of the respiratory pathogens have remained controversial (Dowell & Ho 2004). There are several proposed mechanisms for the increased occurrence of RTIs during the winter months. Indoor crowding promotes transmission, and has likely affected the numbers of observed RTIs in this study as well. Military trainees are at particularly high risk for infection epidemics due to the crowded living conditions, harsh exercise and environmental conditions (Gray et al. 1999). Free weekends in the home district still increase the contact with different infection agents.

It has been suggested that acute cooling of the body surface could elicit a reflex vasoconstriction in the nose and upper airways, which may inhibit the respiratory defence and convert an asymptomatic sub clinical viral infection into a symptomatic clinical infection (Eccles 2002a, Johnson & Eccles 2005). A recent study examining the effects of acute cooling of the feet showed common cold symptoms in 4 to 5 days in 10% (Johnson & Eccles 2005), suggesting that chilling is in fact associated with the onset of the common cold. However, the study did not include any objective evidence, such as virological analyses to support this observation. Breathing cold air causes cooling of the upper respiratory tract (Giesbrecht 1995, Koskela 2007) and subsequent drying of the mucosal membrane (Liener et al. 2003). In sensitive individuals the drying of the mucosa may lead to epithelial damage (Cruz et al. 2006). Furthermore, an in vitro study showed that cooling enhances the norepinephrine response of the nasal mucosa, which could indicate an increase vasoconstriction (Chu et al. 2006). These effects could depress the ciliary movements in the respiratory tract and affect the susceptibility to infections.

Previous results in small mammals suggest that acute cold stress could also suppress several cellular and humoral components of the immune system (Shephard & Shek 1998). However, the results concerning the effects of cold exposure on the human immune function have shown divergent results with no conclusive support in either direction (Castellani et al. 2002).

Additional studies on the association between environmental temperature and occurrence of RTI are needed. The results in the present study show the association between temperature and occurrence of RIs, but the causality is
obscure. Further analyses to minimize the confounding caused by crowding and annually occurring respiratory infection epidemics are needed. The winter peak in infections recurs annually, in the year 2005 the peak in the epidemic activity of influenza was observed in the Finnish armed forces during week 6 (Pyhälä et al. 2005). So the number of infections grows at the same time as the temperature normally falls. A study on the association between temperature and infections should be carried out in different brigades coincidently and for many years to get more reliable results. In the future, virological and bacterial analyses may give further information on the association between temperature and microbes. The military environment is optimal for examining the association between cold temperatures and RTIs, because compared with the general population, where cold exposures are usually recurrent but short (Mäkinen et al. 2006), the conscripts are frequently exposed to the cold for prolonged periods. Although, the population of military conscripts might be considered a selected group, in Finland with mandatory military service, they represent a normal population of young men and the effects of indoor crowding are similar to those observed in schools and kindergartens in winter.
7 Conclusions

In the present study, asthmatics reported to have experienced frequent exercise- and cold-related asthma symptoms and 48 % of them had no medication for asthma on entering military service. In the beginning, a higher proportion of asthmatic men had a poor result of < 2200 m in the 12-min running test than non-asthmatics, although in both groups the proportion of men with a poor result was high: 25.8 % in men with and 19.1 % in men without asthma. With 180–362 day-service both asthmatic and non-asthmatic men could enhance their physical fitness in the 12-min running test.

During the service young men had frequent respiratory tract infections and as expected, men beginning their service in the winter experienced more infections than men entering military service in the summer. The independent risk factors for respiratory tract infections among men with 180-day service were overweight (BMI ≥ 25 kg/m^2) and previous respiratory tract infections. Men with atopy, allergic rhinitis or asthma were also more prone to have ≥ 3 infections compared to non-asthmatic men in univariate analysis. Recent *C. pneumoniae* infections were mostly mild upper respiratory tract infections and were equally common in asthmatic and non-asthmatic men, while asthmatic men were more susceptible to prolonged *C. pneumoniae* infections than non-asthmatic men.

RTIs occurred most often when the ambient temperature was at or below 0 °C. Average daily temperature in the preceding three days was significantly associated with common cold, pharyngitis and LRTI episodes. The outdoor average temperature decreased linearly during the preceding three days separately for all infections and especially for the common cold, being lowest one day before seeking medical consultation. Also when examining the temperature trend for a longer period (14 days) significant linear decreases in temperatures were observed for all respiratory infections. The results show that the occurrence of the common cold increases in cold temperatures, but does not bare the causality. The future aim will be to analyze the microbes in the background of these infections and study the relationship between temperature and different microbes.

The goal of asthma treatment is to achieve asthma control without symptoms and variability in lung function. Awareness of the significance of respiratory symptoms and achievable control should be improved among young people with asthma. Asthmatic men should be examined better and treated if necessary before entrance to military service. Recommendations for physical exercise, smoking cessation and normal weight are part of health promotion of young men.
Asthmatic men can exercise and enhance their physical fitness like non-asthmatic ones. Overweight is not only a risk factor for locomotor diseases and traumas, but also for frequent infections during military service.

The common cold constitution, men with frequent infections reported to have had frequent infections previously, may reflect the genetic susceptibility to infections. Influenza is nowadays the only vaccine-preventable respiratory infection and the vaccine can be recommended for asthmatics to attenuate the total burden of infections. The benefits of blanket influenza vaccination among conscripts have not been established. Studies on specific susceptibility and resistance genes responsible for infectious diseases are future aims. Developing new vaccines for viral infections is another challenge among investigators.
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Appendices
Appendix 1.

Information on respiratory tract symptoms, previous respiratory tract infections and cold sensations was inquired with the following questions with reply alternatives: yes, no or don’t know:

1. Have you ever had “hay fever” or other allergic nasal symptoms?
2. Have you ever had cough with wheezing?
3. When did this cough with wheezing occur?
   a) Only during respiratory tract infections (for example flu or bronchitis)?
   b) Also without respiratory tract infection?
4. Have you had cough or attacks of shortness of breath with wheezing during the preceding 12 months?
5. Have you woken up because of cough during the preceding 12 months?
6. Do you have dyspnea, wheezing or serious attacks of cough?
   a) during exercise
   b) in cold
   c) during exercise in cold
   d) induced by dust
   e) induced by smoking
   f) induced by exhaust fumes
   g) induced by pollen
   h) induced by animals
7. Have you had prolonged cough and/or sputum without respiratory tract infections during the preceding year?
8. Have you had the following respiratory tract infections during the preceding 12 months?
   a) flu without fever
   b) flu with fever
   c) tonsillitis
   d) otitis
   e) sinusitis
   f) bronchitis
   g) pneumonia
   h) I have not had any respiratory tract infections during the preceding 12 months?
9. Are you especially sensitive to cold?
Allergic disorders/symptoms were inquired with the following questions with answer alternatives yes/no:
1. Have you ever had asthma?
2. Has your asthma been diagnosed by a physician?
3. Have you ever had hay fever or other allergic nasal symptoms?
4. Have you ever had allergic eye symptoms?
5. Have you ever had itching eczema, which has been called infantile eczema (infantile atopic dermatitis), Besnier’s prurigo or atopic eczema?

Subject’s own knowledge of positive results on skin prick or serological tests was inquired with following questions with answer alternatives: yes/no/don’t know:
1. Have you ever been tested with skin testing (prick-test) or allergic immunological tests (blood tests for example Rast tests) because of rhinitis, conjunctivitis, eczema or asthma?
2. Were there positive results in skin testing or in blood tests?

Asthma medication was inquired with the following question with reply alternatives: yes or no:
1. Do you have any medication, such as a metered dose inhaler, dry powder inhalers or tablets, for asthma?

Smoking habits were classified by three questions with answer alternatives: yes/no:
1. Have you ever smoked?
2. Do you smoke daily (cigarettes, cigars or pipe)?
3. How much do you smoke nowadays daily or smoked before cessation: how many cigarettes per day?

Information on previous adenoidectomy/tonsillectomy was asked with the question and answer alternatives: yes/no/don’t know:

Have you had adenoidectomy or tonsillectomy because of infections?

Appendix 1 in Finnish.

Hengitystieoireet ja aiemmat hengitystieinfektiot.
1. Onko sinulla koskaan ollut heinänhauaa tai muita allergisia nenäoireita? Kyllä 2 Ei
2. Onko sinulla koskaan ollut yskää, johon on liittynyt hengityksen vinkumista? 1 Kyllä 2 Ei
3. Milloin sinulla on ollut yskää, johon on liittynyt hengityksen vinkumista?
   a) vain hengitystietulehduksen (esim. flunssan tai keuhkoputkentulehduksen) yhteydessä
      1 Kyllä 2 Ei
   b) muulloinkin
      1 Kyllä 2 Ei

4. Onko sinulla viimeisten 12 kuukauden aikana ollut yskää tai hengenahdistuskohtauksia, joihin on liittynyt hengityksen vinkumista? 1 Kyllä 2 Ei

5. Oletko joutunut viimeisten 12 kuukauden aikana heräämään yöllä yskän takia? 1 Kyllä 2 Ei

6. Esiintyykö sinulla hengenahdistusta, hengityksen vinkunaa tai vaikeita yskänpuuskia?
   a) rasituksessa
      1 Kyllä 2 Ei
   b) kylmässä
      1 Kyllä 2 Ei
   c) pakkasessa rasituksen yhteydessä
      1 Kyllä 2 Ei
   d) pölyisissä olosuhteissa
      1 Kyllä 2 Ei
   e) tupakansavusta
      1 Kyllä 2 Ei
   f) autojen pakokaasuista
      1 Kyllä 2 Ei
   g) voimakkaista tuoksustä
      1 Kyllä 2 Ei
   h) kasvien ja puiden siitepölyistä
      1 Kyllä 2 Ei
   i) ollessasi tekemisissä eläinten kanssa
      1 Kyllä 2 Ei

7. Onko sinulla ollut viimeisen vuoden aikana pitkäaikaista yskää ja/tai limannousua keuhkoista ilman hengitystietulehduksia? 1 Kyllä 2 Ei

8. Onko sinulla ollut seuraavia hengitystietulehduksia viimeisten 12 kuukauden aikana?
   a) flunssan ilman kuumetta
      1 Kyllä 2 Ei
   b) kuumeinen flunssan, nuhakuume
      1 Kyllä 2 Ei
   c) nielurisatulehdus, angiina
      1 Kyllä 2 Ei
   d) välikorvatulehdus (keskikorvatulehdus)
      1 Kyllä 2 Ei
   e) poskiontelotulehdus
      1 Kyllä 2 Ei
   f) keuhkoputkentulehdus
      1 Kyllä 2 Ei
   g) keuhkokuume
      1 Kyllä 2 Ei
   h) olen ollut terve hengitystietulehduksen suhteen viimeisten 12 kuukauden aikana
      1 Kyllä 2 Ei

9. Oletko mielestäsi epätavallisen kylmäherkkä? 1 Kyllä 2 Ei

10. Onko sinulla koskaan ollut astmaa? 1 Kyllä 2 Ei

   Onko astma lääkärin toteama? 1 Kyllä 2 Ei
Allergiset oireet ja tutkimukset.
1. Onko sinulla koskaan ollut heinänuhaa tai muita allergisia nenäoireita? 1 Kyllä 2 Ei
2. Onko sinulla koskaan ollut allergisia silmäoireita? 1 Kyllä 2 Ei
3. Onko sinulla koskaan ollut kutisevaa ihottumaa, jota on sanottu maitoruveksi, taiveihottumaksi tai atooppiseksi ihottumaksi? 1 Kyllä 2 Ei
4. Onko sinulle tehty nuhan, silmätulehduksen, ihottuman tai astman tutkimiseksi ihopistokokeita (prick-testejä) tai allergiavasta-ainetutkimuksia (verikokeita esim, Rast-kokeita)? 1 Kyllä 2 Ei 3 En tiedä
5. Todettiinko sinulla positiivisia ihopistokokeet tuloksia tai allergiavastaaineita verikokeissa? 1 Kyllä 2 Ei 3 En tiedä

Asthmalääkitys.
1. Käytätkö nykyään astman hoitoon mitään lääkkeitä kuten sumutinta, inhalatiojauhetta tai tabletteja? 1 Kyllä 2 Ei

Tupakointi.
1. Oletko koskaan tupakoinut elämäsaikana? 1 Kyllä 2 Ei
2. Oletko koskaan tupakoinut säännöllisesti (=lähes joka päivä ainakin yhden vuoden ajan)? 1 Kyllä 2 Ei
3. Minkä ikäinen olt aloittaessasi säännöllisen tupakoinnin? ______vuoden ikäinen
4. Kuinka monta vuotta olet tupakoinut yhteensä? (vähennä tupakointivuosista yli 6 kuukautta kestäneet tupakkalakot) _______vuotta
5. Miten paljon polttat nykyisin tai pollit ennen tupakoinnin lopettamista keskimän päivässä? Vastaa jokaiseen kohtaan. Kuinka paljon / vuorokausi?
   a) savukkeita _______ savuketta vuorokaudessa
   b) piippua _______ piipullista vuorokaudessa
   c) C sikareita _______ sikaria vuorokaudessa
6. Tupakoitko nykyisin (savukkeita, sikareita tai piippua)? 1 Kyllä, päivittäin 2 Kyllä, satunnaisesti 3 En lainkaan
1. Onko sinulta poistettu kitarisa tai nielurisat tulehdusten vuoksi  
   1 Kyllä  2 Ei  3 En tiedä

2. Onko sinulla joskus ollut putket korvissa korvatulehdusten vuoksi?  
   1 Kyllä  2 Ei  3 En tiedä
Appendix 2

Seuraavat kysymykset käsittelevät mielialan erilaisia piirteitä. Vastaa kuhunkin kysymykseen siten, millaisenä tänään tunnet itsesi.

Valitse kustakin kysymyksestä vain yksi vaihtoehto äläkä jätä yhtään kysymystä välillä.

1. Minkälainen on mielialasi?
   1 mielialani on melko valoisa ja hyvä
   2 en ole alakuloinen tai surullinen
   3 tunnen itseni alakuloiseksi ja surulliseksi
   4 olen alakuloinen jatkuvasti enkä pääse siitä
   5 olen niin masentunut ja alavireinen, etten kestä enää

2. Miten suhtaudut tulevaisuuteen?
   1 suhtaudun tulevaisuuteen toiveikkaasti
   2 en suhtaudu tulevaisuuteen toivottomasti
   3 tulevaisuus tuntuu minusta melko masentavalta
   4 minusta tuntuu, ettei minulla ole tulevaisuudelta mitään odotettavaa
   5 tulevaisuus tuntuu minusta toivottomalta, enkä jaksa uskoa, että asiat muuttuisivat parempaan päin

3. Miten katsot elämäsi sujuneen?
   1 olen elämässäni onnistunut huomattavan usein
   2 en tunne epäonnistuneeni elämässä
   3 minusta tuntuu, että olen epäonnistunut pyrkimysissäni tavallisista useammin
   4 elämäni on tähän saakka ollut vain sarja epäonnistumisia
   5 tunnen epäonnistuneeni täydellisesti ihmisenä

4. Miten tyytyväiseksi tai tyytymättömäksi tunnet itsesi?
   1 olen varsin tyytyväinen elämäni
   2 en ole erityisen tyytymätön
   3 en nauti asioista samalla tavalla kuin ennen
   4 minusta tuntuu, etten saa enää tyydyttystä juuri mistään
   5 olen täysin tyytymätön kaikkeen

5. Minkälaisena pidät itsesi?
   1 tunnen itseni melko hyväksi
   2 en tunne itseni huonoksi ja arvottomaksi
   3 tunnen itseni huonoksi ja arvottomaksi melko usein
   4 nykyään tunnen itseni arvottomaksi melkein aina
   5 olen kerta kaikkiaan huono ja arvolon

6. Onko sinulla pettymyksen tunteita?
   1 olen varsin tyytyväinen itseeni ja suorituksini
   2 en ole pettynyt itseni suhteen
   3 olen pettynyt itseni suhteen
   4 minua ihottaa oma itseni
   5 vihaan itseni

7. Onko sinulla itseäsi vahingoittamiseen liittyviä ajatuksia?
   1 minulla ei ole koskaan ollut itsemurha-ajatuksia
   2 en ajattele enkä halua vahingoittaa itseni
   3 minusta tuntuu, että olisi parempi jos olisin kuollut
   4 minulla on tarkat suunnitelmat itsemurhasta
   5 tekin itsemurhan, jos siihen olisi mahdollisuus

8. Miten suhtaudut vieraiden ihmisten tapaamiseen?
   1 pidän ihmisten tapaamisesta ja juttelemisesta
   2 en ole menettänyt kiinnostustani muihin ihmisiin
3 toiset ihmiset eivät enää kiinnosta minua niin paljon kuin ennen
4 olen melkein kokonaan menettänyt mielenkiintonsa sekä tunneen toisia ihmisiä kohtaan
5 olen menettänyt mielenkiintontoni muihin ihmisiin, enkä välitä heistä lainkaan
9. Miten koet päätösten tekemisen?
1 erilaisten päätösten tekeminen on minulle helppoa
2 pystyn tekemään päätöksiä samoin kuin ennenkin
3 varmuuteni on vähentynyt ja yritän lykätä päätösten tekoa
4 minulla on suuria vaikeuksia päätösten teossa
5 en pysty enää lainkaan tekemään ratkaisuja ja päätöksiä
10. Minkälaisena pidät olemustasi ja ulkonäköäsi?
1 olen melko tyytyväinen ulkonäkööni ja olemukseeni
2 ulkonäössäni ei ole minua haittaavia piirteitä
3 olen huolissani siitä, että näytän epämiehitys-vääriltä
4 minusta tuntuu, että näytän ruumalta
5 olen varma, että näytän ruumalta ja vastenmieliseltä
11. Minkälaisista nukkumisesi on?
1 minulla ei ole nukkumisessa minkäänlaisia vaikeuksia
2 nukun yhtä hyvin kuin ennenkin
3 herätessäni aamuisten olen paljon väsyneempi kuin ennen
4 minua haittaa unettomuus
5 känin unetomuudesta, nukahamisvaikeuksista tai liian aikaisiin kesken unien heräämisestä
12. Tunnetko väsymystä ja uupumusta?
1 väsynen on minulle lähes täysin vierasta
2 en väsy helpommin kuin tavallisessa
3 väsyn nopeammin kuin ennen
4 vähäninen työväsyn vuoksi ja uuvuttaa minua
5 olen liian väsynyt tehdäkseni mitään
13. Minkälainen ruokahalusi on?
1 ruokahalussani ei ole mitään hankaluksia
2 ruokahaluni on ennallaan
3 ruokahaluni on huonompi kuin ennen
4 ruokahaluni on nyt paljon huonompi kuin ennen
5 minulla ei ole enää lainkaan ruokahalua
14. Oletko ahdistunut ja jännittynyt?
1 pidän itseäni melko hyvähemoisena enkä ahdistu kovinkaan helposti
2 en tunne itseäni ahdistuneeksi tai "huonohermoiseksi"
3 ahdistun ja jännityn melko helposti
4 tulen erityisen helposti tuskaiseksi, ahdistuneeksi tai jännityneeksi
5 tunnen itseni jatkuvasti ahdistuneeksi ja tuskaiseksi kuin hermoni olisivat "lopun kuluneet"
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950. Anttonen, Vuokko (2007) Laser fluorescence in detecting and monitoring the progression of occlusal dental caries lesions and for screening persons with unfavourable dietary habits


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