Finnish Institute of
Occupational Health

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REPORT FROM THE RESEARCH PROJECT 108327
FOR THE FINNISH WORK ENVIRONMENT FUND

Irmeli Lindström
Antti Karjalainen
Jouko Karjalainen
Antti Lauerma
Harri Lindholm
Ritva Luukkonen
Paula Pallasaho
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ABSTRACT

Asthma is a complex disorder with many distinct clinical phenotypes and can be manifested in childhood or adulthood. The recent systematic review of epidemiological studies found no overall signs of reduction of asthma prevalence; on the contrary an increasing prevalence in many parts of the world was suggested [1]. Asthma prevalence has also shown an increase in Finland during recent decades [2, 3]. Therefore it can be concluded, that asthma is a significant, growing health problem among working age people and can affect work ability. The majority of asthmatics are thought to have a mild form of the disease, but those with more severe asthma are an important group of sufferers. Their morbidity, disability and use of health care and social resources are increased compared with subjects having milder asthma [4]. Recognizing the modifiable risk factors of asthma severity is important for decreasing the burden of asthma.

The aim was to study the asthma prognosis and effect of asthma on work ability in a study of a population of men aged approximately 40 years old who have had asthma since their youth. The more specific objectives were to study: 1) the effect of asthma on work ability and risk factors for decreased work ability, 2) the effect of current work and workplace exposure on current asthma severity, asthma control and occurrence of exacerbations, 3) the impact of individual characteristics and lung function tests at the age of around 20 as risk factors for current persistent asthma. 4) the characteristics of upper airway inflammation and its association to current asthma status

We used the Finnish Defence Force registers to select the study population. In the 1980s, approximately 90% of young men carried out 8-11 months military service. Subjects with mild asthma and normal lung function or stable, moderate asthma and good lung function were evaluated as fit for service. Subjects with unstable or deteriorating asthma, or clearly decreased lung function, were exempted from military service at call-up examinations. The study basis of this survey was the following: Asthma group 1, (milder asthma, n=505) consisted of all subjects who were referred in 1987-1990 to the Central Military Hospital because of a diagnosis of asthma representing an unselected population of men, who had mild or moderate asthma. Asthma group 2, (more severe asthma, n=393) included men who were exempted from military service in 1986-89 due to asthma, representing men with relatively severe asthma at the age of 18. The control group (n=1500) was randomly selected from the 7433 young men who entered military service in the five big military units in Southern Finland between 1986 and 1990, who had no asthma diagnosis during military service.

A postal questionnaire including validated questions about asthma and work ability was sent out in the spring of 2009, i.e. approximately twenty years after military service or exemption at call-up. After two reminders, 232 men (54%) from asthma group 1 (milder), 161 men (44%) from asthma group 2 (more severe), and 608 (44%) of the control group answered and thus comprised the final study population for the studies I and II. The current occupational exposure was evaluated based on self-reports and the asthma-specific Job Exposure Matrix (JEM)[5]. All 232 respondents of the follow-up questionnaire from asthma group 1 were invited for clinical tests at the Finnish Institute of

Occupational Health (FIOH). A total of 119 (51.3%) respondents accepted and attended the tests between August 2009 and April 2010, i.e. approximately 21 years after their military service and comprised the final study population for the study III and IV.

Results: The self-assessed work ability of both asthma groups was decreased, when compared with the controls. The adjusted odds ratio (OR) of current work ability compared with a lifetime best of below 8 (vs 8-10) was 1.5 (95% CI 1.0-2.2) in the asthma group 1 and 1.6 (95%CI 1.0-2.5) in the asthma group 2, when compared with the control group. In the risk factor analysis current smoking, only basic education, being a manual worker or being self-employed and suffering from current severe asthma associated most strongly with decreased self-assessed work ability among the asthmatics. Occupational exposure to non-asthmogenic irritants according to JEM and self-reported occupational exposure to abnormal temperatures were also significantly related to the same outcome.

Conclusions: Both mild and more severe asthma at the age of around 20 seems to be associated with reduced self-assessed work ability and work life participation in 40-year-old males. Occupational health care professionals should be aware of risk of reduced work ability and support the work ability of men with asthma that began in youth, especially those with a severe form of the disease, sufferers who smoke, have a lower educational level or occupational exposure to respiratory irritants/abnormal temperatures. It also seems to be justified to guide young male asthmatics with a relatively severe form of the disease to pay attention to their future working environment, especially exposure to irritants and abnormal temperatures.

TIIVISTELMÄ

Astma on monimuotoinen sairaus, joka voi ilmetä useina erilaisina taudinkuvina ja alkaa lapsuudessa tai aikuisuudessa. Hiljattain ilmestyneen epidemiologisen katsauksen perusteella astman esiintyvyys ei ole laskussa, vaan päinvastoin se lisääntyy maailman useilla alueilla [1]. Astman esiintyvyys on myös lisääntynyt Suomessa viimeisten vuosikymmenien aikana [2, 3]. Siten astmaa voi pitää merkittävänä ja kasvavana työikäisen väestön terveysongelmana, joka voi myös vaikuttaa työkykyyn. Suurella osalla väestöstä astma on lievää, mutta vaikeampaa taudinmuotoa sairastavat ovat tärkeä ryhmä. Heillä esiintyy lisääntynyttä sairastavuutta, työkyvyttömyyttä sekä terveys- ja sosiaalipalveluiden käyttöä verrattuna lievempää astmaa sairastaviin [4]. On tärkeää tunnistaa sellaiset riskitekijät, joihin voidaan ennaltaehkäisevästi vaikuttaa, jotta astman aiheuttama haitta olisi mahdollisimman vähäinen.

Tämän tutkimuksen tarkoituksena oli selvittää astman ennustetta ja sairauden vaikutusta työkykyyn noin 40-vuotiailla miehillä, jotka ovat sairastaneet astmaa nuoruudesta alkaen. Tarkempina tavoitteina oli tutkia: 1) astman vaikutusta tämänhetkiseen työkykyyn ja riskitekijöitä, jotka liittyivät heikentyneeseen työkykyyn, 2) tämän hetkisen työn ja työssä tapahtuvan altistumisen vaikutusta astman vaikeusasteeseen, hoitotasapainoon ja pahenemisvaiheiden esiintymiseen, 3) n.20 vuoden iässä todettujen tutkittavien ominaisuuksien ja keuhkojen toimintakokeiden tulosten vaikutusta pysyvän astman kehittymiseen, 4) ylähengitysteiden limakalvojen tulehdusta ja sen liittymistä tämänhetkiseen astmatilanteeseen.

Tutkimusaineisto valittiin Puolustusvoimien rekistereistä. 1980-luvun lopussa noin 90% nuorista miehistä suoritti 8-11 kuukautta pitkän varusmiespalveluksen. Lievää ja keskivaikeaa astmaa sairastavat miehet, joiden astma oli hyvässä hoitotasapainossa ja joilla oli hyvät keuhkotilavuudet otettiin palvelukseen. Henkilöt, jotka sairastivat vaikeampaa astmaa, johon liittyi huono hoitotasapaino tai alentuneet keuhkotilavuudet, vapautettiin palveluksesta kutsuntatarkastuksessa. Tutkimusaineistomme muodostui seuraavasti: Astmaryhmään 1 (lievä astma, n=505) valittiin kaikki varusmiehet, joita oli hoidettu Keskussotilassairaala Tilkassa v.1987-1990 astman vuoksi ja nämä miehet edustivat nuoruudessaan lievää/keskivaikeaa astmaa sairastavia. Astmaryhmään 2 (vaikeampi astma, n=393) valittiin miehet, jotka oli vapautettu palveluksesta astman vuoksi v.1986-1989 ja tämä ryhmä edusti nuoruudessaan melko vaikeaa astmaa sairastavia. Verrokkiryhmään (n=1500) valittiin satunnaisotoksella miehiä, jotka olivat astuneet varusmiespalvelukseen v.1987-1990 viidessä eri suuressa varuskunnassa ja jotka eivät sairastaneet astmaa varusmiesaikana.

Keväällä 2009 eli noin 20 vuotta varusmiespalveluksen jälkeen lähetimme postikyselyn, joka sisälsi validoituja astmaa ja työkykyä koskevia kysymyksiä. Kahden muistutuksen jälkeen 232 (54%) miestä astmaryhmästä 1, 161 miestä (44%) astmaryhmästä 2 ja 608 (44%) verrokkiryhmästä vastasi kyselyyn ja nämä miehet muodostivat lopullisen tutkimusaineiston tutkimuksiin I ja II. Tämän hetkinen työssä tapahtuva altistuminen arvioitiin käyttäen työaltistematriisia ja tutkittavien omien arvioiden perusteella. Kaikki 232 astmaryhmään 1 kuuluvaa, jotka vastasivat kyselyyn, kutsuttiin seurantakäynnille Työterveys-

laitokselle. 119 (51.3%) näistä miehistä osallistui kliinisiin tutkimuksiin elokuun 2009 ja huhtikuun 2010 välisenä aikana eli noin 21 vuotta heidän varusmiespalvelunsa jälkeen ja he muodostivat lopullisen tutkimusaineiston tutkimuksiin III ja IV.

Tulokset: Itsearvioitu työkyky oli alentunut molemmissa astmaryhmissä verrattuna verrokkeihin. Käytettäessä itsearvioidun työkyvyn mittarina "työkykyä verrattuna elinaikaiseen parhaimpaan asteikolla 0-10" ja määriteltäessä alentunut työkyky arvoilla 0-7 (verrattuna arvoihin 8-10) oli vakioitu odds ratio (OR) 1.5 (95% CI 1.0-2.2) lievän astman ryhmällä ja 1.6 (95%CI 1.0-2.5) vaikeamman astman ryhmällä verrattaessa verrokkiryhmään. Riskitekijäanalyysissa tämänhetkinen tupakointi, ainoastaan peruskoulutus, työntekijänä tai yrittäjänä toimiminen sekä tämänhetkinen vaikea astma liittyivät kaikkein selviten alentuneeseen työkykyyn astmaa sairastavilla. Myös työaltistematriisiin perusteella tapahtuvaan altistumiseen hengitysteitä ärsyttäville tekijöille ja itsearvioituun altistumiseen poikkeaville lämpötiloille liittyi lisääntynyt riski alentuneelle työkyvylle.

Johtopäätökset: 20-vuoden iässä sekä lievää ja että vaikeampaan astmaa sairastavien miesten koettu työkyky ja työelämään osallistuminen ovat alentuneet noin 40-vuoden iässä. Työterveyshuolloissa tulee tukea miesten, joilla on nuoruudessa alkanut astma, työkykyä. Erityisesti on tuettava niiden miesten työkykyä, joilla on vaikeampi sairaus, jotka tupakoivat, joilla on alhaisempi koulutustaso tai jotka altistuvat työssään hengitysteitä ärsyttäville tekijöille tai poikkeaville lämpötiloilla. Vaikuttaa myös siltä, että on oikeutettua neuvoa vaikeampaa astmaa sairastavia nuoria miehiä kiinnittämään huomiota heidän tulevaisuuden työympäristöönsä ja välttämään töitä, joissa altistutaan hengitysteitä ärsyttäville tekijöille tai poikkeaville lämpötiloille.

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1 INTRODUCTION

Asthma is a complex disorder with many distinct clinical phenotypes, which are manifested in the interaction of genetic predisposition and environmental exposures. Until the 1980s bronchospasm was considered to be a key feature of asthma, but since there increasing knowledge of airway inflammation has changed the definition of asthma. The current Global Strategy for Asthma Management and Prevention Report (GINA) states that "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment [8].

1.1 Epidemiology in working aged

1.1.1 Prevalence

Asthma is the most common chronic respiratory disease in the world and approximately 300 million people in the world currently have asthma [9]. The lack of a golden standard in the definition of asthma in epidemiological studies makes the evaluation of asthma prevalence and incidence a challenge. In the questionnaire both questions about asthma symptoms and physician-diagnosed asthma have been used, however the prevalence rates based on this data are highly dependent on the awareness of asthma in the population studied [10].

1.1.1.1 Worldwide

The prevalence of asthma increased worldwide in the second half of the last century until the 1990s, but since then there has been no clear temporal pattern [10]. Some studies suggest a stabilization or even a decrease in asthma prevalence [11, 12], while others suggest that it is still increasing [1, 13]. The recent systematic review of epidemiological studies found no overall signs of reduction in asthma prevalence; on the contrary an increasing prevalence in many parts of the world was suggested [1]. However the utilization of emergency healthcare reported to be reduced in some economically developed countries, most probably due to an improvement in quality of care.

1.1.1.2 Finland

Asthma prevalence has shown an increase in Finland in recent decades. In 1996, a postal questionnaire survey performed in Southern Finland showed a non-response adjusted asthma prevalence of 4.4% among adults aged 18-65 years [14]. The FinEsS study from Northern Finland reported asthma prevalence of 6.0% in adults aged 20-69 years based on the question about physician-diagnosed asthma. In the same study asthma prevalence was 6.8% in 1996 [15] and 9.4% in 2007 [3] in Helsinki area.

Asthma prevalence among young Finnish men recruited to military service based on the statistics of the Finnish Defence Forces reported to be steady between 0.02% and 0.08% from 1926 to 1961, while from 1961 to 1989 a 20-fold increase was shown [16]. Latvala et al showed a further increase with no signs levelling off and the prevalence of 3.45% was reached in 2003 [2].

1.1.2 Aetiology

Asthma in the working-age population may have persisted from childhood, may have occurred as a relapse of earlier childhood asthma or may be true adult-onset asthma without symptoms in earlier life. Therefore aetiological factors of both childhood-onset and adult-onset asthma need to be taken into account. Both host related factors (eg. genes, sex and obesity) and environmental factors influence the development of asthma in a complex and interactive way.

1.1.2.1 Host related factors

Family and twin studies have indicated that genetics play an important role in the development of asthma and allergies, likely through several genes of moderate effect [17]. Sex affects the development of asthma in a time-dependent manner [18]. Asthma is far more common in boys than girls during early childhood. The prevalence equalizes between the genders during adolescence and then switches to a female predominance in adulthood.

Atopy is strongly associated with asthma, especially with asthma starting at a young age [19, 20]. The role of atopy is more unclear in new-onset asthma in adults and the possible overestimation of its meaning has been argued [21]. Allergic rhinitis has shown to increase asthma risk in adults [3, 22], as well as aspirin intolerance and nasal polyposis [14]. In the recent study chronic rhinosinusitis without nasal allergies was associated with late-onset of asthma [23].

There is increasing evidence relating to being overweight and obese and the prevalence and incidence of asthma in both adults [24] and children [25], although most consistently in adolescent girls [26]. It is considered to be unlikely that the association is attributable due to reverse causation - that is asthma causes reduced physical exercise and weight gain [27].

1.1.2.2 Environmental factors

Environmental factors also play an important role in the development of asthma. According to meta-analyses, parental smoking has been concluded to be very likely to be causally related to childhood asthma [28]. Numbers of studies have also shown that active smoking is associated with the onset of asthma in adolescents and adults [29, 30]. The role of respiratory tract infections in the development of asthma is still poorly understood [31], although physicians have long recognized an association between common respiratory tract illnesses and the onset and worsening of wheezing and asthma. Diet and particularly the role of breastfeeding in the development of asthma have been widely studied. Current data about latter is conflicting [32, 33].Exposure to evident indoor mould or damp in children and adults is associated with asthma development and asthma exacerbations.

The evidence of a causal relationship is however lacking except for asthma exacerbations in children [34]. The impact of the occupational exposure in the development of asthma is described later.

1.1.3 Classification

1.1.3.1 Phenotypes

There is increasing awareness of heterogeneity of asthma and also the overlapping of asthma with chronic bronchitis and emphysema [35]. Recent reviews have highlighted the importance of different asthma phenotypes, their natural history and varying treatment responses [36]. Allergic and non-allergic asthma are probably the most commonly discussed phenotypes.

1.1.3.2 Severity

The definition of asthma severity has evolved in recent years [37]. In the severity evaluation it is important to include both the severity of the underlying disease and its response to treatment. Asthma severity is not a static phenomenon, but can change over months and years. The 2002 version of GINA guidelines classified asthma relying on three dimensions: 1) perceived symptoms, 2) lung function and 3) type of asthma treatment [6]. In this classification the clinical severity is classified in 1 of 4 steps according to the frequency of nocturnal and diurnal symptoms and FEV1% predicted. Treatment is classified in 1 of 4 steps according to the reported daily medication use. Final asthma severity evaluation is a composition of these two independent classifications. The following categories were used: remission, intermittent, mild persistent, moderate persistent and severe persistent. This classification is complex and is poorly suited to clinical practice. According to the current GINA guidelines asthma severity is classified on the basis of intensity of treatment required to achieve good asthma control [8].

1.1.3.3 Control

The 1995 GINA guidelines already introduced the concept of the medication required to maintain control [38]. According to current GINA classification, subjects who have daytime symptoms less than three times a week and/or need of rescue medication, no nocturnal symptoms or limitation of activities and PEF/FEV1 ≥80% or personal best, are currently considered to have clinically controlled asthma [8]. Asthma is considered to be partly controlled if 1 or 2 of the above features are absent and uncontrolled if more than 2 features are absent. An assessment of current asthma control should preferably be done over a four week period. The future risk means expected exacerbations, rapid decline in lung function and the side-effects of medication.

1.1.4 Prognosis

The natural history of asthma is still poorly known and measuring asthma prognosis in a population based framework is challenging and not well established. The methods used are the evaluation of asthma remission, severity and control as well as the occurrence of severe asthma and lung function measurements. The use of asthma medication, mortal-

ity, hospitalization rate, emergency visits, doctor visits and work disability due to asthma have been used as markers of asthma prognosis for example in community-based educational programmes [39]. The age of death of patients with asthma does not differ from the population as whole and death is usually caused by the same diseases as the general population [40].

1.1.4.1 Remission

There is no universally accepted definition for asthma remission. Most studies include the absence of respiratory symptoms and asthma medication used [41], whereas others also include normal lung function and/or absence of BHR [42, 43]. The time period required without asthma symptoms and asthma medication has varied from one to three years in different studies [42-45]. In unselected population-based or preselected cohorts the proportion of subjects with childhood asthma being in remission varies from 10-70% being however in most studies between 20-30% [43]. In the RHINE study, the young adult population of Northern Europe was studied and the remission rate of 20.2 per 1000 person years was found, i.e. about 20% of the subjects recovered from their asthma during a 10year period [46]. Stopping smoking [45, 46], having a mild form of the disease [45, 47], a shorter duration of disease [41], and having normal lung function [42, 48] have all been shown to predict asthma remission. Additionally in children male gender has shown to be a predictor of asthma remission [48]. In the studies of young adults, an earlier age of asthma onset is associated with asthma remission [41, 49] and a negative association with a change in body mass index (BMI) has also been found [47].

1.1.4.2 Asthma severity

As described earlier, the evaluation of severity in population-based studies has been mainly based on different versions of GINA guidelines [6, 8, 38] In the prospective part of the second survey (ECRHS II) 856 young adults with asthma were followed for 9 years and then asthma severity was evaluated based on the 2002 GINA classification. At the end of the follow-up, 11.9% of the subjects were in remission (no symptoms, no exacerbations, no asthma medications in the last year), and 45.3% had intermittent, 8.1% had mild persistent, 16.7% moderate persistent and 18.0% severe persistent asthma [47]. A similar distribution of asthma severity has also been reported by other authors [50].

In the cross-sectional studies of ECRHS I and II sensitization to moulds (Alternaria alternata or Cladosporium herbarum) is associated with severe asthma [51, 52]. Associations between persistent asthma and sensitization to house dust mite, non-seasonal asthma, an older age of asthma onset and chronic cough and phlegm were also reported, while sensitization to cats was related to severe asthma only [52]. In the prospective part of ECRHS II at baseline levels a lower FEV1% predicted a poorer symptom control, higher IgE levels and a higher prevalence of chronic cough/mucus hypersecretion predicted moderate or severe persistent asthma, when compared with subjects with intermittent asthma [47]. No gender difference in asthma severity has been found in ECRHs studies [53]. Smoking, airway hyperresponsiveness, atopy and decreased forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio in young adults has been shown to predict persistence of wheezing [48, 54] in older age.

1.1.4.3 Asthma control

Asthma control reflects the extent to which the various asthma manifestations can be reduced by treatment. The definition of asthma control is described in detail earlier. Although poor asthma control may be due to the underlying severity of the disease or resistance to therapy, it is far more frequently due to poor compliance, poor inhaler technique, under-prescribing or environmental factors, such as allergen exposure or smoking [37].

In the ECRHS II, the distribution of asthma control was evaluated in a population based setting with 1042 adult asthmatics. Overall 32% of asthmatics had completely controlled asthma, 36% partly controlled and 32% uncontrolled [55]. Probably reflecting the severity of the underlying disease, asthma was more often uncontrolled among the subjects using inhaled corticosteroids during last year: only 15% of them had controlled asthma, 49% had uncontrolled asthma and 36% partly controlled asthma.

Smoking, female gender and a body mass index of greater than 30 kg/m2 have been shown to be independent determinants of poor asthma control [56] as well as long-term exposure to air pollution [57]. Chronic cough and phlegm [55, 58], female gender [58], overweight [55] and sensitisation to Cladosporium [55] have been shown to be associated with poor asthma control in subjects using inhaled corticosteroids. The reported risk factors of non-ICS users for poor asthma control were partly different including high total IgE [55, 58], non-seasonal asthma [55], sensitization to moulds [59] and a chronic cough and phlegm [55].

1.1.4.4 Occurrence of severe refractory asthma

The term severe refractory asthma applies to patients who remain difficult to control despite an extensive re-evaluation of diagnosis, management and an observational period of at least 6 months by an asthma specialist [60]. The prevalence of severe asthma is poorly known partly due to a variation in definitions of this disorder. However, it is estimated that 10% to 20% of the population with asthma has the symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs [61]. Typical characteristics of these subjects include the occurrence of frequent exacerbations, low baseline lung function, reliance of high dose corticosteroids and near daily symptoms. Subjects with severe refractory asthma represent a heterogeneous group of asthmatics, some of whom have a more severe form of allergic asthma, whereas many others do not. The risk factors identified for severe asthma are female gender, neutrophilic inflammation and being less atopic [62] as well as reporting less family history of allergies [63].

1.2 Impact of work on asthma

1.2.1 Incidence

Over the past few years, work-related asthma has increasingly been recognized as a public health concern due to its high prevalence. Accordingly to systematic analysis ~16% of adult-onset asthma is estimated to be caused by the workplace environment [64]. In the Finnish population-based study with 49,575 incident cases of asthma, the attributable

fraction of occupation was as high as 29% for men and 17% for women [65]. The risk was increased especially in agricultural work, manufacturing work and service work.

However the impact of occupational exposure on asthma can still be underestimated. The healthy worker effect is the potential bias caused by the phenomenon that sicker individuals may choose work environments in which exposures are low; they may be excluded from recruitment, or once hired; they may seek transfer to less exposed jobs or leave work [66]

1.2.2 Occupational asthma and work related asthma

The evidence-based guidelines on occupational asthma give the following definitions [67] "Asthma is "work-related" when there is an association between symptoms and work. The different types of work-related asthma should be distinguished since the implications for the worker and the occupational health management of the disease differ. Work-related asthma includes two distinct categories:

- work-aggravated asthma, i.e. pre-existing or coincidental new onset adult asthma which is made worse by non-specific factors in the workplace e.g. cold, dry air, dust and fumes
- occupational asthma, i.e. asthma induced by exposure in the work environment to airborne dust, vapours or fumes, in workers with or without pre-existing asthma.

1.2.2.1 Work-aggravated asthma

Aggravation of asthma symptoms at work has been shown to be common among employed adults with asthma. Half of the low-income urban population reported work-aggravated asthma symptoms in their current or most recent job [68] and in another hospital-register based study 25% of asthmatics reported a worsening of symptoms at work [69].

In the Finnish population-based survey, 21% of the currently employed 969 respondents reported work-aggravated asthma symptoms at least weekly during the past month [70]. The prevalence of those with work-aggravated symptoms increased by age, self-reported occupational exposure to dust, abnormal temperatures or poor indoor air quality, physically strenuous work and expert-evaluated probability of daily occupational exposure to airborne dust, gases or fumes.

1.2.2.2 Occupational asthma

Occupational asthma can be subdivided into sensitizer-induced or irritant-induced occupational asthma. A latency period between first exposure to a respiratory sensitizer at work and the development of allergy symptoms is characteristic to sensitizer-induced occupational asthma. Irritant-induced occupational asthma occurs typically within few hours of a high concentration exposure to an irritant gas, fume or vapour at work.

In the Finnish register-based study, the annual incidence of occupational asthma was 17.4 cases/100,000 employed workers [71]. The incidence rate of occupational asthma was highest in bakers, painters and lacquerers, veterinary surgeons, chemical workers, farmers, animal husbandry workers, other food manufacturing workers, welders, plastic product workers, butchers and sausage makers, and floor layers. Cases caused by animal epithelia, hairs and secretions or flours, grains, and fodders accounted for 60% of the total cases.

1.2.3 Asthma severity and exacerbations

There is conflicting data on the influence of occupational exposure on asthma severity. In a study by Gaga et al, 155 subjects having severe asthma were compared with subjects having milder asthma [63]. A larger proportion of severe asthma patients reported symptoms at work or changes of jobs, while exposure at work to gas, dust or fumes did not differ between the groups. Le Moual et al reported based on a hospital-based population an association between exposure to occupational asthmogens and more severe adult-onset asthma [72]. In the European Community Respiratory Health Survey high-level exposure to gases dusts and fumes at work increased the risk of severe asthma exacerbations 3-fold and a total of one of seven asthma exacerbations was estimated to be of occupational origin [73]. In a Swedish study of work-related exposure to gas, dust and fumes was linked to multi-symptom asthma, which was considered to be a sign of more severe asthma [74].

1.3 Work ability

1.3.1 Conceptual framework and definition

The diversity of work ability makes its evaluation a challenge. Cessation of employment and disability pension are the most severe consequences of reduced work ability. Temporary sick leave, change of employer, job or work tasks and reduced self-assessed work ability are more common and have an impact on work productivity. Subjective assessment has proved to be a good predictor of future work ability or disability [75].

1.3.1.1 Work Ability Index

Our main indicator for work ability was self-assessed current work ability compared with lifetime best on a scale of 0-10, which is one of the parameters in the Work Ability Index (WAI) [76]. The internal validity of WAI has shown a satisfactory relationship between the subjects' WAI results and more objective measurements [77, 78], and the test-retest reliability has proved to be good [79]. The single question of current work ability compared with lifetime best was used because it appears to associate strongly with WAI and predict the future degree of sick leave [80]. Other more objective outcomes such as not being currently employed, having been unemployed or having changed jobs is also used.

1.3.1.2 Asthma and work ability

Previous cross-sectional [81] and prospective population-based [82] studies have shown that job changes due to respiratory problems at work are common, and that occupational exposure to irritants and dusts contribute to respiratory work disability. Clinically-assessed asthma severity [83-85], smoking [83], workplace exposures [83], lower educational level [84], presence of comorbidity [84], workplace-associated asthma symptoms [85] and bronchial hyperresponsiviness [85] have also predicted decreased work ability.

The effect of asthma on work ability has only been studied in a longitudinal setting in a few studies [82, 86]. Due to the variable character of asthma and asthma treatment, as well as the current societal challenge to extend careers, there is a further need for evaluation of asthma-related work disability in a longitudinal and multivariate setting.

2 AIMS

The aim was to study the asthma prognosis and the effect of asthma on work ability in a study population of men aged approximately 40 years old who have had asthma since their youth.

The more specific objectives were to study:

1) The effect of asthma on work ability and risk factors for decreased work ability (Study I)

2) The effect of current work and workplace exposures on current asthma severity, asthma control and occurrence of exacerbations (Study II)

3) The impact of individual characteristics and lung function tests at the age of around 20 and smoking as risk factors for current persistent asthma (Study III)

4) The characteristics of upper airway inflammation and its association to current asthma status (Study IV)

3 MATERIALS AND METHODS

3.1 Study population and design

We used Finnish Defence Force registers to select the study population. In Finland it is obligatory for all young men of sufficiently good health to participate in either military or civil service. Up to 98% of all men undergo a medical examination at the age of 18-19. Subjects who have mild asthma with normal lung function, possibly using inhaled anti-inflammatory drugs but using sympathomimetics only rarely are evaluated as fit for most service duties. Men with stable moderate asthma and good lung function, using inhaled corticosteroids and needing sympathomimetics on a weekly or daily basis are evaluated as fit for restricted duties. Subjects with unstable or deteriorating asthma, or clearly decreased lung function, are exempted from military service. We used this information when estimating the severity of asthma of the study subjects at baseline. At the end of the 1980s, about 90% of young men carried out 8-11 months military service.

Two groups of asthmatics and a control group without asthma were included in the study. *Asthma group 1* (n=505) consisted of all subjects who were referred in 1987-1990 to the Central Military Hospital due a diagnosis of asthma (including both men in military service with asthma already diagnosed before the service, and men with a new onset of asthma during service). This group represented an unselected population of men, who had mild or moderate asthma and were living in southern and central parts of Finland at the age of 18-27 and were 39-44 years old at the time of the study. The subjects being not conscripts (n=22), having another lung disease (1), being not alive (n=12) and having unknown address or living abroad (n=38) were excluded.

Asthma group 2 (n=393) included men who were exempted from military service in 1986-89 due to asthma, representing an unselected population of Finnish men with relatively severe asthma at the age of 18, and who were 39-44 years old at the time of the study. The subjects having unknown address or living abroad (n=23) were excluded.

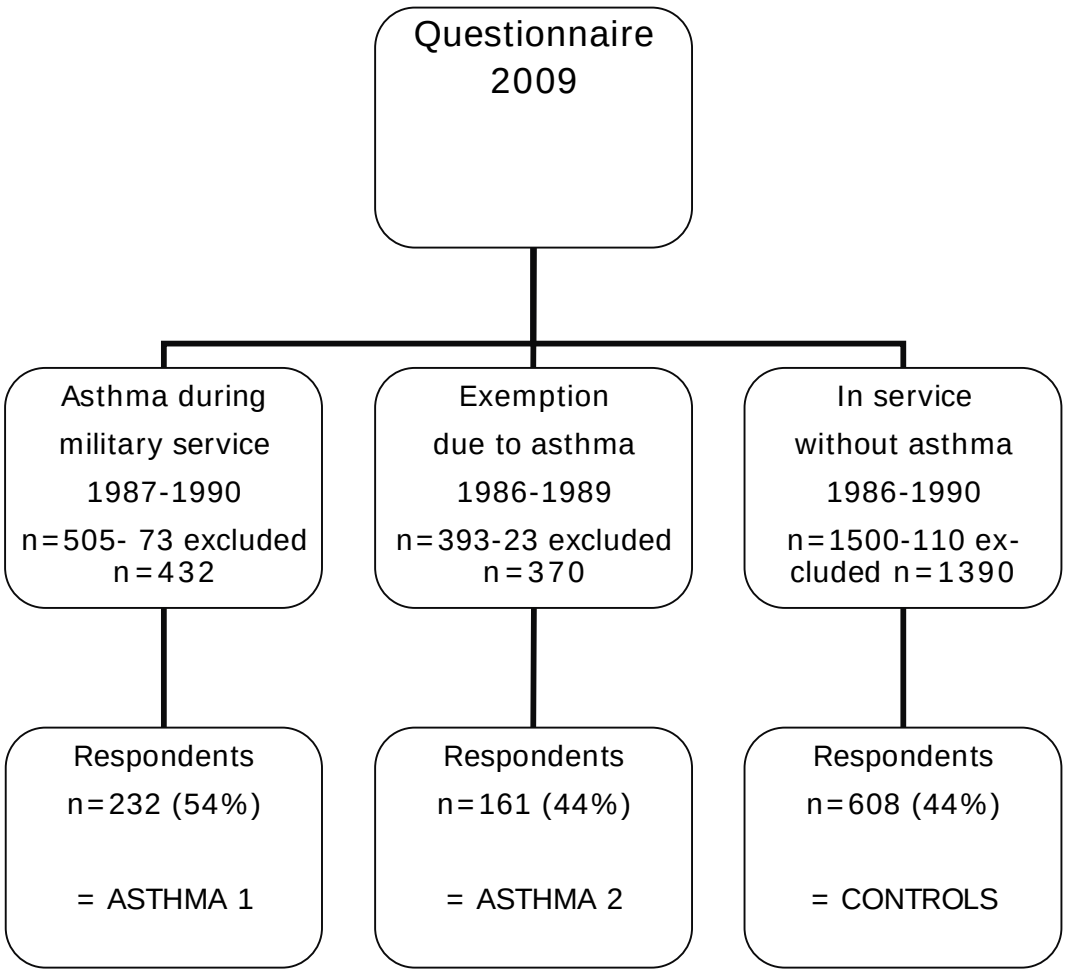
The control group (n=1500) was randomly selected from the 7433 young men who entered military service in five big military units in Southern Finland between 1986 and 1990, who had no asthma diagnosis during military service according to Defence Force register. The subjects having unknown address or living abroad (n=81) and being not alive (n=1) were excluded. After the completion of the study, the 28 subjects who, in the study questionnaire, had reported having an asthma diagnosis during their military service were excluded. The controls represented an unselected population of men, without asthma or any other disabling illness in their youth and who lived in southern or central parts of Finland. Figure 1 shows the description of the study in more detail.

A postal questionnaire was sent out in the spring of 2009, i.e. approximately twenty years (18-23 years) after military service or exemption at call-up. After two reminders, 232 men (54%) from the first study group, 161 men (44%) from the second study group, and 608 (44%) of the controls answered and thus comprised the final study population for studies I and II.

All 232 respondents of the follow-up questionnaire were invited to clinical tests at the Finnish Institute of Occupational Health (FIOH). A total of 119 (51.3%) respondents accepted and attended the tests between August 2009 and April 2010, i.e. approximately twenty years (18–23 years, mean 21.1 years) after their military service. These 119 men comprised the study population for the studies III and IV.

The study was approved by the Ethical Committee of the Department of Medicine of Helsinki University Central Hospital. Written informed consent was collected from the study subjects.

Figure 1 The description of the study



3.2 Information on the non-respondents

We used the nationwide registers of the Finnish Social Insurance Institution to obtain information on the non-respondents of the questionnaire. The following data was attended of the respondents and the non-respondents in both asthma groups: 1) having special medication reimbursement rights for asthma medication in 1992 and in 2009 (see for details [70] of the definition and criteria of these rights), 2) having asthma medication purchased in 2008, 3) the number of periods on sick leave due to respiratory illness of more than nine days of duration in 2009.

3.3 Questionnaire

Questions on personal characteristics, education, lifetime work history, current exposures at work, aggravation of asthma symptoms at work, work ability, lifestyle, weight, and length were included. We used the previously validated Finnish questions of the Tuohilampi questionnaire [87] to evaluate current asthma symptoms, the presence of other atopic disorders, the current use of asthma medication and the age of asthma onset.

3.4 Assessment of work ability

3.4.1 Self-assessed work ability

The participants were asked to compare their current work ability with their best lifetime work ability so that 0 represented full work disability and 10 indicated work ability at its best. This validated question was the main indicator for self-assessed work ability, and belonged to the Work Ability Index (WAI) questionnaire as did all other questions about self-assessed work ability (Table 3) [76]. The subjects with current work ability ≤7 compared with lifetime best were classified as having decreased work ability, and those with values of 8-10 as having normal work ability. Based on the Finnish Health 2000 Survey, 88% of men in the entire Finnish population aged 30-44 had a work ability of 8-10 compared with lifetime best [77].

3.4.2 Work life participation

The subjects were asked if they were currently full-time employed, part-time employed, unemployed, temporarily dismissed, studying, on sick leave, on disability pension, on some other pension, or if they took care of households or children. Because it was possible to choose many alternatives, the answers were classified by selecting the following groups in the following order: 1. The men who answered that they were either full-time or part-time employed were by default classified as employed, 2. The men who answered that they were unemployed or on temporary dismissal were classified as unemployed, 3. Those who answered that they received disability pension were classified as on disability pension, and 4. All the rest were classified as being temporarily out of work for other reasons. The subjects classified as unemployed, on disability pension or temporarily out of work for other reasons were defined as not employed. Information on ever having been

unemployed or having changed occupation after military service and the number of such periods was also elicited.

3.5 Occupational exposure assessment

3.5.1 Self-reported exposure

The respondents were asked about exposure to each of the following factors in their current job using previously established questions: dusts, chemical agents or factors, abnormal temperatures (cold and heat), poor indoor air quality, mental stress, and physically strenuous work [70].

3.5.2 Expert evaluation

The current or last occupation of the respondents was first coded according to the 1997 Classification of Occupations of Statistics Finland [88], which is based on the European Community revision of the International Standard Classification of Occupations (ISCO-88 (COM)). The coded occupational history was matched with the asthma-specific Job Exposure Matrix (JEM) developed by Kennedy et al [89] in order to assign the study subjects to exposure risk groups based on ever having had a job that places them at high risk of developing occupational asthma or having been exposed to some other non-specific respiratory irritants. The asthmogens were classified into three groups as follows: high-molecular-weight agents (HMW), low-molecular-weight agents (LMW) or mixed environment; and the non-asthmogenic irritants were grouped in one separate group, as in the previous study [72]. Latex exposure was ignored in our study, as non-powdered low-latex gloves have been used in Finland for many years.

3.6 Other explanatory variables

3.6.1 Education

Subjects having completed only comprehensive school, high school or vocational school were classified as having basic education. Those with college or other upper secondary education were classified as having mid-level education. Subjects with a university degree were classified accordingly.

3.6.2 Professional status

Professional status was categorized as self-employed or farmer, upper level non-manual worker, lower level non-manual worker, manual worker, and other or unknown.

3.6.3 Smoking

According to the questionnaire data, the respondents were classified as either current smokers, or ex-smokers/non-smokers.

3.6.4 Alcohol consumption

Subjects who reported drinking six or more standard units of alcohol at a time once a week or more often were categorized as frequently consuming multiple alcohol units.

3.6.5 Physical activity

Those who reported taking part in exercise that results in at least mild breathlessness and sweating for at least half an hour at a time, only once a week or less in their free time, were classified as physically inactive.

3.6.6 Release of asthma symptoms on days off

The subjects answering to the question: Are your asthma symptoms releasing on days off (no symptoms on current job/yes, frequently/yes, sometimes/no) yes, frequently or yes, sometimes were defined to have release of asthma symptoms on days off. In the risk factor analyses these subjects were compared with those choosing the last mentioned answer alternative (no).

3.6.7 Change of occupation

Information on ever having been changed occupation after military service and if asthma was a reason for the change of occupation (no/ yes, partly/yes, mainly) was elicited.

3.7 Assessment of asthma severity

A chest physician (IL) estimated the current severity of asthma according to the information on asthma symptoms, night time symptoms and their frequency, medication used, and asthma exacerbations. The classification was based on the modified GINA guidelines [6] without forced expiratory volume in one second (FEV1) values. The categories were as follows: remission, intermittent, mild persistent, moderate persistent and severe persistent. Remission was defined as having no asthma symptoms and not using asthma medication for the last three years.

3.8 Assessment of asthma control

The asthma control test (ACT, Finnish version of the Asthma Control Test(tm) The Asthma Control Test(tm) is a trademark of Quality Metric Incorporated © 2002 GlaxoSmithKline) was used to evaluate current asthma control [7]. This self-administered questionnaire assesses key components of asthma control over the prior 4 weeks, including asthma symptoms, everyday functioning, use of rescue medications, and night time awakenings. The ACT scale ranges from 5 to 25, with higher scores indicating better asthma control and the subjects having less than 20 scores are identified to have poorly controlled asthma.

3.9 Occurrence of asthma exacerbations

The subjects were classified having an asthma exacerbation, if they reported at least one of the following during the past 12 months: 1) an unscheduled office visit or an emergency department visit for asthma, 2) a hospitalisation for asthma or 3) an oral corticosteroid burst for asthma.

3.10 Clinical investigations

3.10.1 At baseline

All clinical investigations were carried out in the Central Military Hospital between 1987 and 1990. Information on height, weight, the results of pulmonary function tests and allergy tests, the use of asthma medication, and asthma symptoms and exacerbations were collected from the medical records. The medical records of four subjects were not available; these individuals also did not participate in the follow-up visit.

3.10.1.1 Spirometer

Ventilatory function was measured by a flow-volume spirometer (Pneumoscreen, Eric Jaeger, Germany) according to the guidelines [90], using predicted values for the Finnish population [91]. In this study, the cut-off values for decreased spirometric parameters were based on the lower limits of normal, and were for FEV1% predicted <81, FEV1/FVC% predicted <88, and FEF50%% predicted <62. A significant reversibility of airway obstruction was defined as an increase of at least 12% and 200ml in FEV1 after bronchodilator administration.

3.10.1.2 Histamine challenge

Airway hyperresponsiveness to histamine was assessed using Laitinen's method [92]. It was classified as severe if the concentration of histamine causing a 15% decrease in the FEV1 or peak expiratory flow (PEF) values (PD15) was ≤ 0.10 mg, moderate for PD15 values of 0.11 to 0.39 mg, and mild for PD15 values of 0.40 to 1.60 mg.

3.10.1.3 Exercise test

A field exercise test was performed standardized using an eight minute freerunning test outdoors on a 150 metre circular track between 9 and 11 AM [93]. The running speed was adjusted by monitoring the subject's heart rate with a Sport Tester TM PE 3000 heart rate meter (Polar Electro Ky, Kempele, Finland). Subjects raised their heart rate to 85% of the predicted maximal rate during a two minute warm up and maintained at that level for the remaining six minutes of the test. The PEF values were measured just before the exercise and immediately, 5, 10, 20 and 30 minutes after the exercise. Of the three successive PEF measurements obtained on each occasion, the highest value was recorded for analysis. A positive exercise reaction was defined by at least 15% PEF fall in the 30-minute follow-up after exercise. The response to exercise challenge was maximum percentage fall in PEF (ΔPEF%) after exercise: % fall in PEF=[PEF(baseline) -PEF(after)]/ PEF(baseline) x100].

Air temperature ranged from -19°C to + 24°C, mean 5.4°C. Therefore, for all exercise challenges, ΔPEF% was adjusted to temperature of 5.4°C by using regression coefficient (-0.327) between air temperature (°C) and ΔPEF% as has been done in a previous study [94]. Regression coefficient was obtained by linear regression from similar outdoor exercise tests in 1809 conscripts with asthma [17]. Those exercise tests were performed during years 1985-1998 in temperatures ranging from -25°C to +26°C.

3.10.1.4 Serial PEF recordings

Serial PEF recordings showing either a diurnal variation of ≥20% or a bronchodilatation effect of ≥15% at least three times were considered diagnostic for asthma.

3.10.1.5 Skin prick tests

Skin prick tests (SPT) were performed using both a negative and positive control and a panel of 10 common perennial and seasonal allergens with standardized allergen extracts (ALK Abello). A wheal diameter of at least 3 mm and at least 50% histamine control in SPT was considered positive.

3.10.1.6 Asthma diagnosis

According to the 1986–1990 Military Hospital medical records, all 119 follow-up participants had been diagnosed with asthma in the Internal Medicine Unit of the Central Military Hospital. A total of 48 men (40.3%) were already suffering from asthma when they entered the military service, and were admitted to the Central Military Hospital for restarting or increasing medication, or for evaluation of service ability. Sixty-seven men (56.3%) had a new onset of asthma and came for confirmation of diagnosis, while in four cases it was unclear whether asthma had started during or before military service. Asthma was verified by a significant reversibility of bronchial obstruction in spirometry (n=2), moderate/severe airway hyperresponsiveness to histamine challenge (n=7), a positive exercise test (n=48), a diagnostic PEF recording (n=1), more than one of these tests being diagnostic for asthma (n=24), or clinical evidence of earlier diagnosed asthma (n=6). In 31 men (26.1%) asthma diagnosis was based on borderline diagnostic findings such as mild hyperresponsiveness (n=11), PEF decrease of 10-14% in exercise test (n=9), both of these (n=4), obstructive spirometry (n=2) or a history of childhood asthma or typical asthma symptoms (n=5).

3.10.1.7 Asthma severity

Asthma severity during military service was evaluated according to modified GINA guidelines and classified as intermittent, mild persistent or moderate/severe persistent. Treatment step classes were not used, because most subjects had no treatment, and the medication used differed from the current treatment guidelines.

3.10.2 At follow-up

All clinical investigations were carried out at FIOH. A period of four weeks without respiratory infections and exposure to seasonal allergens before the visit was required.

Flow-volume spirometry and a bronchodilation test were performed using a Medikro-spirometer according to the guidelines [95] and the same predicted values were used as those on baseline.

The patients filled in the *questionnaire*, which included validated questions about asthma symptoms and medications used.

Skin prick tests were performed similarly to those at baseline, using corresponding allergen extracts.

Serum total IgE was measured using Phadia UniCAP System (Phadia, Uppsala, Sweden). Total IgE <110 kU/l and specific IgE <0.35 kU/l were regarded as normal.

Nasal nitric oxide (nNO) was measured using on-line chemiluminescence analyser (NIOX, Aerocrine AB, Solna, Sweden) in compliance with ATS/ERS recommendations [96].

3.10.2.1 Histology of nasal biopsies

Nasal biopsies obtained from the anterio-superior part of inferior conchae were fixed in 10% buffered formalin and embedded in paraffin. Sections of 2.5 µm were cut and stained with haematoxylin and eosin (H&E) and examined under light microscopy (Leica DM LB, Wetzlar, Germany). Inflammatory cell types were counted in 3 high-power fields (HPF) at 400x magnification.

3.10.2.2 Assessment of asthma severity

A respiratory physician (IL/HS) examined every subject. We used the Global Initiative for Asthma (GINA) [6] to evaluate current asthma severity. Two independent GINA classifications were combined, the first based on symptoms and FEV1 and the second on current medication, in order to construct a final "symptom-FEV1-medication" classification as described earlier. Clinical severity was classified as one of four grades according to the frequency of diurnal and nocturnal symptoms in the last 12 months and the prebronchodilator FEV1 of predicted values. Treatment was also classified as one of four grades, according to reported daily medication use. Finally, asthma severity was based on the independent classifications of clinical severity and medication, according to GINA. The following categories were used: remission, intermittent, mild persistent, moderate persistent, and severe persistent. Remission was defined as having no asthma symptoms and using no asthma medication for the last three years. Classification was carried out by two physicians (IL and HS) separately, and the results proved congruent with each other. The kappa coefficient between the two observations was 0.90.

3.11 Statistical analyses

Our data set consisted of both continuous and categorical variables. In our preliminary study, we wanted to find out if the study groups, i.e. the two asthma groups and one control group, differ from each other. When comparing the differences between groups. We applied the Chi-squared tests for categorical variables and one-way ANOVA for continued variables. A p-value of <0.05 was considered statistically significant.

Logistic regression analyses were used when examining the associations between potential risk factors and decreased work ability (Study I). We then calculated the odds ratios (OR) and their 95% confidence intervals (95% CI).

Logistic regression analyses were used while examining the associations between determinants at follow-up and poorly controlled asthma and asthma exacerbations (Study II). The odds ratios (OR) with 95% confidence intervals (95% CI) were counted.

In the risk factor analyses, the subjects with mild, moderate and severe persistent asthma were categorised as having persistent asthma, and were compared with those with asthma in remission or intermittent asthma (Study III). Our data set consisted of both continuous and categorical variables. In our preliminary study, we wanted to check if those who participated in examinations differed from those who did not participate in examinations. We then applied Chi-squared tests for categorical variables and one-way ANOVA for continued variables. The same tests were applied when examining the associations between potential predictors and asthma severity. When comparing the baseline results to the follow-up results of those who had participated in both examinations, we used statistical tests for repeated measurements. A p-value of <0.05 was considered statistically significant. We used logistic regression analyses when examining the associations between different spirometry values, exercise test results, and asthma severity. We then calculated the odds ratios (OR) and their 95% confidence intervals (95% CI).

All analyses were carried out using the Statistical Analysis System 9.1 programme (SAS Institute Cary, USA).

4 RESULTS

4.1 Study participants

Table 1 shows the characteristics of the study groups. The socioeconomic status of asthma group 2 differed from the other groups: these men were less educated, worked more often as manual workers and a greater proportion of them were not currently employed.The men in asthma group 1 had changed more often occupation than those in asthma group 2 and control group (67.0% vs. 55.7% vs. 57.1%, p=0.025). The change of occupation due to asthma was relatively uncommon being reported only 13.8% of the subjects in asthma group 1 and 16.8% of the subjects in asthma group 2. Smoking was as common among the asthmatics as among the controls. About 80% of the asthmatics had doctor diagnosed allergic rhinitis.

4.2 The current asthma status

The subjects in the asthma group 2 had currently more severe asthma as the men in the asthma group 1. A total of 40.5% of the subjects in asthma group 2 had currently moderate or severe persistent asthma, while only 17.7% of the men in asthma group 1 had this severe asthma (p= <.0001).

4.3 The current occupational exposure

There was no significant difference in self-reported occupational exposures in current work between the groups (Table 2). According to JEM, exposure to LMW asthmogens in current work was more common among the controls (p=0.009), while no significant difference in exposure to other asthmogens or non-asthmogenic irritants between the study groups was detected.

Table 1 Characteristics of the study population at the time of the follow-up questionnaire. Data are presented as n (%) unless otherwise stated.

	Asthma group 1 n=232	Asthma group 2 n=161	Controls n=608	P-value
Mean age, years (SD)	40.9 (1.7)	40.6 (1.9)	41.0 (1.9)	0.0481
Education				0.0324
Basic	126 (57.0)	95 (63.3)	320 (56.2)	
Mid-level	66 (29.9)	36 (24.0)	134 (23.6)	
University	29 (13.1)	19 (12.7)	115 (20.2)	
Professional status				0.0334
Self-employed	43 (18.5)	24 (14.9)	101 (16.7)	
Upper-level non-manual worker	58 (25.0)	25 (15.5)	169 (27.9)	
Lower-level non-manual worker	33 (14.2)	23 (14.3)	71 (11.7)	
Manual worker	76 (32.8)	66 (41.0)	215 (35.5)	
Other or unknown	22 (9.5)	23 (14.3)	49 (8.1)	
Current smoker	82 (35.3)	48 (29.8)	173 (28.5)	0.1498
BMI kg/m^2				0.1527
< 25	68 (29.4)	64 (39.8)	223 (37.3)	
25.0-29.9	110 (47.6)	65 (40.4)	266 (44.5)	
≥30.0	53 (22.9)	32 (19.9)	109 (18.2)	
Doctor diagnosed allergic rhinitis	177 (77.6)	130 (82.3)	182 (30.1)	<.0001
Mean asthma duration years (SD)	27.0 (7.5)	31.1 (6.5)	7.2 (5.0)	<.0001
Current asthma severity				<.0001
Remission	17 (8.3)	6 (3.8)	-	
Intermittent	119 (58.3)	47 (29.7)	-	
Mild persistent	32 (15.7)	41 (26.0)	-	
Moderate persistent	24 (11.8)	38 (24.0)	-	
Severe persistent	12 (5.9)	26 (16.5)	-	

Table 2 Current occupational exposure of the study population. Data are presented as n (%), p-values for χ^2-test

	Asthma group 1 n=232	Asthma group 2 n=161	Controls n=608	P-value
Occupational exposure based on JEM				
HMW asthmogenss	8 (3.5)	7 (4.4)	17 (2.8)	0.5909
LMW asthmogens	10 (4.3)	9 (5.6)	62 (10.2)	0.0089
Mixed environment asthmogens	13 (5.6)	8 (5.0)	51 (8.4)	0.1852
Any asthmogen	22 (9.5)	20 (12.4)	96 (15.8)	0.0518
Non-asthmogenic irritants	86 (37.1)	51 (31.7)	232 (38.2)	0.3162
Self-reported occupational exposure				
Dust, chemical agents, gases or fumes	153 (66.0)	114 (70.8)	496 (65.1)	0.3976
Abnormal temperatures	99 (42.7)	66 (41.0)	249 (41.0)	0.8981
Bad indoor quality	56 (24.1)	39 (24.2)	127 (20.9)	0.4741
Mental stress	152 (65.5)	105 (65.2)	390 (64.1)	0.9200
Physically strenuous work	117 (50.4)	80 (49.7)	307 (50.5)	0.9716

4.4 Comparison of work ability

Self-assessed work ability was reduced among the asthmatics: current work ability compared with lifetime best was ≤7 in 28.9% of asthma group 1, in 31.1% of asthma group 2, and in 19.7% of the controls (p=0.0007) (Table 3). Work ability as regards physical job demands was moderate or bad in the groups, at 32.0%, 34.2% and 23.4%, respectively (p=0.004), and 17.3%, 24.0% and 15.4% (p=0.037) as regards mental job demands. No significant difference in the mean number of sick leave days during the last 12 months and the self-assessed estimate of work ability two years from now were found between the groups.

A total of 9.2% of the subjects in asthma group 1, 14.3% of the subjects in asthma group 2, and 9.4% of the controls were not currently employed (p=0.165). Having ever been unemployed was most common in asthma group 2, and having ever changed occupation in asthma group 1.

Table 3 Current self-assessed work ability. Data are presented as n (%), p-values for χ^2-test

	Asthma group 1 n=232	Asthma group 2 n=161	Controls n=608	P-value
Current work ability compared with lifetime best (0-10)				0.0011
8-10	165 (71.1)	111 (68.9)	488 (80.3)	
0-7	67 (28.9)	50 (31.1)	120 (19.7)	
Work ability in relation to the demands of the job in relation to physical demands				0.0040
Very or quite good	157 (68.0)	104 (65.8)	462 (76.6)	
Moderate or bad	74 (32.0)	54 (34.2)	141 (23.4)	
Work ability in relation to the demands of the job in relation to mental demands				0.0372
Very or quite good	191 (82.7)	120 (76.0)	511 (84.6)	
Moderate or bad	40 (17.3)	38 (24.0)	93 (15.4)	
Sick leave during past 12 months, mean number of days (SD)	13.1 (36.0)	12.2 (26.3)	12.3(40.9)	0.9651
Self-reported estimate of being fit to work in 2 years from now				0.1852
Quite surely	209 (90.9)	138 (88.5)	550 (92.4)	
Not surely	16 (7.0)	10 (16.4)	34 (5.7)	
Hardly	5 (2.2)	8 (5.3)	11 (1.9)	

In the univariate analysis, the OR of current work ability compared with a lifetime best of 7 or below was 1.7 (95%CI 1.2-2.3) in asthma group 1, and 1.8 (95%CI 1.2-2.7) in asthma group 2. The increased risk remained in the multivariate models when adjusted with professional status and education as well as with life style factors consisted of BMI classes, current smoking, frequent use of multiple alcohol doses and physical inactivity. In the final model adjustments were done for both education and professional status and life style factors. In this model, the OR of current work ability compared with a lifetime best of 7 or below was 1.5 (95%CI 1.0-2.2) in asthma group 1, and 1.6 (95%CI 1.0-2.5) in

asthma group 2. These models also showed an increased risk of reduced work ability in relation to the physical demands of the work in both asthma groups, while in relation to the mental demands of the work; the risk was only significant in asthma group 2.

4.5 Risk factors for decreased work ability among asthmatics

In the logistic regression analysis, current smoking (OR 2.5), only basic education (OR 2.6), being a manual worker (OR 2.7) or being self-employed (OR 2.5), and suffering from current severe asthma (OR 3.8) associated most strongly with decreased work ability among the asthmatics (table 4). Occupational exposure to nonasthmogenic irritants according to JEM (OR 1.7) and self-reported occupational exposure to abnormal temperatures (OR 1.7) were also related to the same outcome. The association with smoking strengthened in the logistic model including all listed variables, while others weakened, becoming no longer significant.

Table 4 The odds ratios (ORs) for decreased self-assessed current work ability compared with lifetime best (<8 vs 8-10) among asthmatics and controls. Statistically significant results are shown in bold. JEM= Job exposure matrix.

Risk factor	Asthma group 1 and 2		Controls	
	OR	95% CI	OR	95% CI
Long lasting rhinitis	1.8	1.0 - 3.1	1.6	1.1 - 2.4
Current smoking	2.5	1.6 - 3.9	1.5	1.0 - 2.4
BMI over 30	1.7	0.9 - 3.0	2.8	1.6 - 4.9
Education				
Basic	2.6	1.1 - 5.8	3.2	1.6 - 6.2
Mid-level	1.8	0.7 - 4.3	2.1	1.0 - 4.4
University	1	reference	1	reference
Professional status				
Self employed	2.5	1.1 - 5.6	1.5	0.7 - 3.0
Upper level non-manual worker	1	reference	1	reference
Lower level non-manual worker	1.6	0.7 - 3.9	1.6	0.7 - 3.5
Manual worker	2.7	1.4 - 5.6	2.0	1.1 - 3.5
Other or unknown	9.7	4.1 - 23.0	11.4	5.4 - 24.1

Table 4 continues

Risk factor	Asthma group 1 and 2		Controls	
	OR	95% CI	OR	95% CI
Occupational exposure based on asthma -JEM				
Any asthmogen	1.1	0.5 - 2.1	0.8	0.4 - 1.4
Nonasthmogenetic irritants	1.7	1.1 - 2.7	1.3	0.9 - 2.0
Self reported occupational exposure				
Dusts, chemic agents, gases or fumes	1.3	0.8 - 2.1	1.3	0.8 - 1.9
Abnormal temperatures	1.7	1.1 - 2.7	1.2	0.8 - 1.8
Bad indoor air quality	1.6	0.9 - 2.5	1.7	1.1 - 2.7
Mental stress	1.2	0.8 - 1.9	1.3	0.8 - 1.9
Physically strenuous work	0.6	0.4 - 1.0	0.9	0.6 - 1.3
Current asthma severity				
Remission	1	reference	1	reference
Intermittent	2.1	0.7 - 6.5		
Mild persistent	1.8	0.5 - 5.9		
Moderate persistent	2.1	0.6 - 7.0		
Severe persistent	3.8	1.1 - 13.5		

5 DISCUSSION

At population level most asthmatics have a mild form of the disease and the treatment options for asthma have evolved markedly during recent decades. The Finnish Asthma Programme in 1993-2003 had the goal of teaching primary care doctors to treat asthma with inhaled corticosteroids, which are considered to be the most important medication for asthma [39]. The results of this Programme showed that despite the increasing incidence of asthma the morbidity of the disease had decreased considerably. The number of hospital days has fallen by 69% in relation to the number of asthmatics. In 1993, 7,212 patients of working age (9% of 80,133 asthmatics) received a disability pension from the Finnish Social Insurance Institution compared with 1,741 in 2003 (1.5% of 116,067 asthmatics). The decrease of 83% in relation to the number of asthmatics was shown in asthmatics receiving disability pension.

It can be assumed that asthma is currently a relatively mild disease with good treatment options and only has a minor effect on work ability. Additionally asthma treatment can potentially keep the disease stable in most cases despite exposure to irritants or asthmogens at work. Asthma starting in childhood or early adulthood usually presents as an atopic phenotype of asthma and is generally milder than non-atopic adult-onset asthma [97].

In this study we followed approximately 400 young men with mostly atopic asthma from the late 1980s to 2009. These men have suffered from asthma for their whole or almost whole career and being males they relatively often are working in dusty environments. During the 20-year follow-up period inhaled corticosteroids were widely used in Finland and at population level asthma treatment was well executed. However we found that the work ability of the asthmatics at the age of 40 was reduced and the current occupational exposure was related to asthma exacerbations in subjects with relatively severe asthma in youth. Therefore it can be concluded that asthma starting at a young age can still be a relevant cause for work disability. The occupational exposure to asthma aggravating factors can increase the occurrence of asthma exacerbations, which have been shown to be related to worsened asthma outcomes. Recognizing the modifiable risk factors of poor asthma outcome is important for decreasing the burden of asthma.

5.1 Advantages

The study population was homogenous regarding age and sex, and represented unselected men from Southern and Central parts of Finland. The asthma groups had a clinically verified disease at the age of 19-21 and represented all severity forms of asthma, while the control group had no asthma in their youth. The asthma severity in youth of all asthmatics could be roughly evaluated based on the Defence Forces exemption criteria from military service. This longitudinal setting allowed us to study the effect of early-onset asthma on work ability 20 years later and asthma prognosis. The influence of asthma on

work ability is a relevant issue in this subgroup of asthmatics, because they have suffered from asthma during their entire or almost entire career and being male they more likely to work in dusty workplaces. Work ability was evaluated with many different outcomes representing both self-assessed work ability and participation in work life.

The occupational exposure evaluation was based on self-reports and the asthma specific Job Exposure Matrix information on occupational exposure [5]. In a previous study the specificity of self-reported occupational exposure has been shown to be relatively high among asthmatics, approximately 0.83, but the sensitivity has been relatively low (0.48), when compared with the JEM evaluation [98].

One advantage is that the study was conducted in Finland, where inhaled corticosteroids for the treatment of asthma were first adopted in the world. During the 20-year follow-up period inhaled corticosteroids were extensively used as first line therapy for persistent asthma in Finland, because treatment practices were influenced by National Asthma Programme [39]. Therefore it is probable, that the associations we found are relevant also for young men whose asthma is treated according to current recommendations [8].

In study III we used the results of lung function tests and allergy tests as predictors for current asthma status. All lung function tests at baseline were performed by qualified technicians with uniform and validated methods in the clinical physiology laboratory of Central Military Hospital, which had strict quality control procedures. The repeatability of manoeuvres in spirometry was always controlled according to the guidelines [90, 95] and measurements with too large a variability were not accepted.

5.2 Limitations

The greatest limitation of this study was the low response rate and the further loss of many subjects in the follow-up visit. Although the register-based information on the non-respondents' characteristics differed only slightly from the respondents, the possibility of selection bias cannot ruled out. In questionnaire studies it is common that men in younger age-groups respond infrequently. A recent Swedish study with a male response rate of 56% showed no difference in respiratory symptoms between responders and non-responders [99]. In our study, the majority of the men had milder forms of asthma: 82.3% of the subjects in asthma group 1 and 59.5% of the subjects in asthma group 2 had remitted, mild intermittent or mild persistent asthma. These factors do not indicate the selection of the subjects having more severe asthma, which could overestimate the difference in work ability between the asthmatics and the control group. Our results cannot be generalized to cover the female population or asthma which begins after the age of 20.

The second limitation is that, the healthy worker effect [66] is possible in this type of setting and might have led to an underestimation of associations between occupational exposures and asthma as well as work ability. Dumas et al reported that the subjects having more severe asthma in childhood tended to choose less exposed jobs [100]. However, in our study current occupational exposure to asthma aggravating factors based on asthma-JEM and self-reports differed only slightly between the asthmatics and the control group and a change of occupation due to asthma was relatively uncommon in both asthma

groups. Based on these factors it seems unlikely that a significant proportion of asthmatics had chosen cleaner jobs.

The other limitation is that we were not able to evaluate the occupational exposure during the whole career. The whole working history was included in the questionnaire, but due to a significant amount of missing and conflicting data we were not able to obtain reliable information.

5.3 The main results:

5.3.1 Asthmatics are not avoiding jobs with exposure to asthma aggravating factors

One interesting finding was the clearly lower socioeconomic status of subjects having relatively severe asthma in youth, when compared with subjects having milder asthma and controls. This may have affected their work ability and the exposure to asthma aggravating factors in their current job. These men also currently had more severe asthma. The severity of childhood asthma has been shown to predict asthma severity in adulthood [101] allowing us to assume that the asthmatics in group 2 also had more severe asthma in their youth. Nevertheless the link between more severe asthma and low socioeconomic status has previously been shown among children [102] and adults [103]. Based on this we conclude that the asthmatics in group 2 were exempted from the military service mainly due to asthma, while socioeconomic factors and motivation had less effect.

The age of asthma onset was before 18 years in subjects with relatively severe asthma in youth and mostly before 20 years in milder asthma group. Therefore a large proportion of our study subjects suffered from asthma already when career choices were made. One could expect that asthma could lead the asthmatics choosing less exposed jobs. However, in our study current occupational exposure to asthma aggravating factors based on asthma-JEM and self-reports differed only slightly between the asthmatics and the control group. A change of occupation was most common in subjects having milder asthma in youth, ie. those with a later onset of the disease

Smoking was as common among the asthmatics as among the controls, which is in line with earlier reports [104].

5.3.2 Asthmatics have reduced self-assessed work ability and work life participation

We found that asthma which begins in childhood or early adulthood reduces both self-assessed work ability and work life participation in men around the age of 40. Our first asthma group had mild to moderate asthma, and the second relatively severe asthma in their youth. The work ability of the severe asthma group was worst and their current participation in work life was reduced. However, the mild asthma group also had decreased self-assessed work ability compared to the control group.

Among the asthmatics, current severe asthma, currently smoking, lower educational level and a blue collar occupation had the strongest associations with decreased work ability.

Exposure to irritants, based on JEM, and self-reported occupational exposure to abnormal temperatures, was also associated with reduced work ability.

Previously self-assessed work ability among subjects with recent-onset asthma was found to be normal in most subjects [85], but different durations of asthma makes comparison with our study difficult. A French cohort study with a five-year follow-up showed no difference in the employment situation of working-age male asthmatics with childhood-onset asthma compared with non-asthmatics. These asthmatics worked in blue-collar jobs less often [86]. The somewhat different results in our study may indicate that choices concerning career and other selection mechanisms play different roles among French asthmatics than among the Finnish survey participants. It is noteworthy that nearly all subjects in our study currently have active asthma, while in the French study over 70% of the subjects with childhood-onset asthma were classified as having asthma in the past. Whether these differences are due to selection processes or a different overall severity or phenotype of asthma at baseline level is difficult to judge. Other population-based studies have shown that asthma reduces employment [105, 106]. Most of the risk factors for decreased work ability that we found have also been reported previously, such as the severity of the disease [83, 84], smoking [83], workplace exposures to irritants [82, 83] and a lower educational level [84].

6 CONCLUSIONS AND FUTURE ASPECTS

The main purposes of this study were to evaluate the effect of asthma starting at a young age on work ability and the influence of occupational exposure on asthma outcome. Both of these goals have been achieved. Additionally we have also obtained information on 20-year prognosis of asthma starting at a young age. The current challenge to extend careers and the increasing prevalence of asthma make this study relevant.

The first conclusion is that both mild and more severe asthma at around 20 years of age seems to be associated with reduced work ability in 40-year-old males. The self-assessed work ability in particular was reduced, which has shown to predict future sick leave and disability [80]. The highest risk for decreased work ability is in asthmatics having a severe form of the disease, smoking or working in blue-collar jobs with exposure to irritants. Therefore occupational health care professionals should pay attention to the work ability of men with asthma from youth, especially those with currently severe symptoms of the disease and support the work ability by:

- Following frequently those male asthmatics, who are exposed to respiratory irritants or abnormal temperatures or have physical strenuous jobs.Motivating in smoking cessation
- Reducing the occupational exposure to irritants. This can be achieved through taking care of occupational hygiene, promoting the use of respiratory masks and modifying work tasks. In some subjects the re-training for occupations with less respiratory exposure might be necessary.
- It seems to be justifiable to guide young male asthmatics with a relatively severe form of the disease to pay attention to their future working environment, especially exposure to irritants and abnormal temperatures.

The results of the study II, III and IV are still unpublished and cannot be shown in this report.

Based on our findings the following aspects should be developed in order to reduce the burden of asthma and extend careers of asthmatics:

- Occupational health services should have tools to find asthmatics with reduced work ability. Validated questionnaire instruments to identify these subjects would be useful. Awareness of interactions of occupational exposure and asthma should be increased with education of occupational health physicians and nurses.
- In order to extend careers of asthmatics it would be favourable to develop the practices to help asthmatics to cope at work including modification of work tasks, guidance of suitable work tasks and occupations as well as re-education.
- The systemically organized vocational guidance of young asthmatics at schools, school health services and paediatric policlinics would be beneficial. Subjects having relatively severe disease should avoid exposure to irritants and abnormal temperatures.

The following articles or abstracts of this study have been published:

- Lindström I, Pallasaho P, Luukkonen R, Suojalehto H, Karjalainen J, Lauerma A and Karjalainen A: Asthma in youth reduces work ability of men in middle-age- a 20-year follow-up study. Respir Med 2011;105:950-955
- Lindström I et al: Young adult men with and without asthma - Work-ability 20 years later, European Respiratory Society Annual Congress, Barcelona 2010
- Lindström I et al: Risk factors for decreased work ability among middle-aged men having asthma from youth, European Respiratory Society Annual Congress, Amsterdam 2011

The following articles or abstracts have been submitted:

- Lindström I, Suojalehto H, Lindholm H, Pallasaho P, Luukkonen R, Karjalainen J, Lauerma A and Karjalainen A: Positive exercise test and obstructive spirometry in young men associated with persistent asthma 20 years later
- Lindström I et al: The effect of work on asthma in middle-aged men having asthma from youth, European Respiratory Society Annual Congress, Wien 2012

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Young men with asthma
–Prognosis and effect on work ability

Asthma is a significant growing health problem of the working-age population and may start already in childhood or early adulthood. Therefore, despite current treatment options, asthma can potentially affect work ability, and occupational exposure to dust gases and fumes can influence asthma prognosis. The main aim of this study was to evaluate the impact of asthma on work ability and the effect of occupational exposure on current asthma status in approximately 40-year-old men with asthma since youth. The current goal to extend careers makes this study highly relevant.

We found that both men with mild asthma and men with relatively severe asthma in youth had diminished self-reported work ability, and decreased work life participation, compared with men without asthma in youth. Among the asthmatics currently smoking, lower educational level, a blue-collar occupation and current severe asthma had the strongest associations with decreased work ability. Exposure to irritants, based on Job Exposure Matrix, and self-reported occupational exposure to abnormal temperatures also associated with poorer work ability. Occupational health care professionals should pay attention and support the work ability of those with asthma since youth.

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Finnish Institute of Occupational Health
Topeliuksenkatu 41 a A, 00250 Helsinki
www.ttl.fi

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