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SMOKING ASSESSMENT AND WORK ABILITY TRENDS IN ASTHMA PATIENTS

Prospective and Retrospective Study Approach

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To my Family

UNIVERSITY OF TURKU
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ABSTRACT

Smoking increases the risk of asthma and impairs the prognosis of the disease and therapeutic response. Smoking cessation is an essential part of the treatment of asthma. The comprehensive treatment of asthma is also important for the patient's work ability. The prevalence of asthma has grown, and an increasing number of workers have to cope with the disease in their working lives.

The present study aimed to evaluate how reliably asthmatics reported their smoking status and the changes in smoking habits over the last 15 years. We investigated how actively physicians discuss and document patient's smoking status. The study also examined the development of the work ability score (WAS) in asthma patients to find risk factors for poor development of WAS.

This study included two cohorts. The Finnish obstructive airway disease (CAD) cohort included 1,329 asthma patients and 959 chronic obstructive pulmonary disease patients. Their smoking habits, work ability, and general health were followed by questionnaires during 10-years. The register-based cohort included 35,650 patients, whose electronic health records (EHR) were analysed with a combination of rule-and deep learning (ULMFiT)-based algorithms.

Only 6% of asthmatics had unreliability in the self-reported smoking data. Pack years can be considered only a rough estimate of the comprehensive consumption of tobacco products. Based on the algorithmic analysis, 61% of asthma patients had documented smoking status, and 55% of current smokers had discussed smoking cessation with the clinician during the two-year follow-up. In the future, smoking cessation care should be activated in hospitals. The performance of the ULMFiT-based classifier was good and showed that deep-learning-based models can create efficient tools for utilising the Finnish EHR. Over 90% of the patients' WAS remained stable throughout the 10-year study period, but 8% of the patients who had more severe asthma, higher BMI, and multiple comorbidities showed significantly poorer outcomes. To support asthma patients' work ability, comprehensive treatment of asthma and comorbidities, regular controls, and weight management are needed.

KEYWORDS: Asthma, smoking, smoking cessation, smoking intervention, work ability, work ability score, artificial intelligence, deep learning, ULMFiT

TIIVISTELMÄ

Tupakointi lisää astmariskiä, heikentää sairauden ennustetta ja terapeuttista vastetta. Tupakoinnin lopettaminen on tärkeä osa astman hoitoa. Astman kokonaisvaltainen hoito on oleellista myös potilaan työkyvyn kannalta. Astman esiintyvyys on kasvanut ja yhä useamman täytyy selviytyä sairauden kanssa työelämässä.

Tutkimuksen tavoitteena oli selvittää kuinka luotettavasti astmaatikot raportoivat tupakointitietojaan ja mitkä ovat tupakointitottumusten muutokset viimeisten 15 v aikana. Tutkimme myös kuinka aktiivisesti lääkärit keskustelevat tupakoinnista ja dokumentoivat potilaan tupakointistatuksen sairaskertomukseen. Lisäksi tavoitteena oli tutkia työkykypisteiden (WAS) kehitystä astmapotilailla, jotta löydettäisiin riskitekijöitä työkyvyn heikolle kehitykselle.

Tutkimus sisälsi kaksi kohorttia. Astman ja keuhkoahtaumataudin yksilöllinen hoito -tutkimuskohortti (AST) koostui 1329 astma- ja 959 keuhkoahtauma-tautipotilaasta. Heidän tupakointitapojaan, työkykyään ja yleistä terveyttään seurattiin 10 vuoden ajan kyselylomakkeiden avulla. Rekisteripohjainen kohortti koostui 35 650 aikuispotilaasta, joiden sairauskertomustekstejä analysoitiin sääntöpohjaisten ja syväoppimiseen (ULMFiT) perustuvien algoritmien avulla.

Vain 6 %:lla astmapotilaista itseraportoidut tupakkatiedot olivat epäluotettavia. Askivuosia voidaan käyttää vain karkeana arviona tupakointitaakasta. Algoritmisten analyysien pohjalta 61 %:lla astmapotilaista oli tupakointistatus merkittynä sairauskertomukseen ja 55 % nykyisistä tupakoitsijoista oli keskustellut lopetta-misesta lääkärin kanssa. Tulevaisuudessa tupakka- ja nikotiiniriippuvuuden hoitoa tulee aktivoida sairaaloissa. ULMFiT:iin perustuvan tupakointiluokittelijan toimivuus oli hyvä ja osoitti, että syväoppimiseen perustuvat mallit voivat luoda tehokkaita työkaluja suomalaisen sairauskertomuksen hyödyntämiseen. Yli 90 %:lla potilaista työkykypistemäärä pysyi vakaana 10 vuoden seuranta-ajan, mutta 8 %:lla potilaista, joilla oli vaikeampi astma ja enemmän oheissairauksia, tulokset olivat selkeästi heikommat. Astmapotilaiden työkyvyn tukemiseksi tarvitaan astman ja oheissairauksien kokonaisvaltaista hoitoa sekä ohjausta painonhallinnan.

AVAINSANAT: Astma, tupakointi, tupakoinnin lopettaminen, tupakkaintervention, työkyky, työkykypistemäärä, tekoäly, syväoppiminen, ULMFIT

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Abbreviations

15D	15 dimension
ACQ	Asthma control questionnaire
ACT	Asthma control test
AI	Artificial intelligence
ANN	Artificial neural networks
AQ20	Airway Questionnaire 20
ATS	American thoracic society
CAD	the Finnish chronic obstructive airway disease cohort
CAT	Complementary and alternative therapies
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular diseases
DLPFC	Dorsolateral prefrontal cortical region
DPI	Dry powder inhaler
EBMEDS	the Finnish Evidence-Based Medicine electronic Decision Support
EHR	Electronic health records
ERS	European respiratory society
Fe_{NO}	Fractional concentration of exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence
FVC	Forced vital capacity
FWA	Future work ability
GINA	Global initiative for asthma
GOLD	Global initiative for chronic obstructive lung disease
HFA	Hydrofluoroalkane
HRQoL	Health related quality of life
HIS	Heaviness of smoking index
ICC	Intraclass correlation coefficient
ICD	International classification of diseases
ICS	Inhaled corticosteroids

IgE   Immunoglobulin E
IHD   Ischemic heart diseases
IL   Interleukin
ILC2   Innate lymphoid cells group 2
LABA   Long-acting beta$_2$ agonist
LAMA   Long-acting muscarinic antagonist
LTRA   Leukotriene receptor antagonist
MDI   Metered-dose inhaler
nAChR   Nicotine acetylcholine receptor
NLP   Natural language processing
NRT   Nicotine replacement therapy
OCS   Oral corticosteroids
PEF   Peak expiratory flow
QoL   Quality of life
rTMS   Repetitive transcranial magnetic stimulation
SAMA   Short-acting muscarinic antagonist
SABA   Short-acting beta$_2$ agonist
SD   Standard deviation
T1   Type 1
T2   Type 2
Th   T-helper cell
WAI   Work ability index
WAS   Work ability score

List of Original Publications

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

I   Hirvonen E, Stepanov M, Kilpeläinen M, Lindqvist A, Laitinen T. Consistency and reliability of smoking related variables: longitudinal study design in Asthma and COPD. *European Clinical Respiratory Journal*, 2019; 6 (1); 1591842.

II   Hirvonen E, Karlsson A, Kilpeläinen M, Lindqvist A, Laitinen T. Development of self-assessed work ability among middle-aged asthma patients – a 10 year follow-up study. *Journal of Asthma*, 2020; 1-9.

III   Hirvonen E, Karlsson A, Saaresranta T, Laitinen T. Documentation of the patient's smoking status in common chronic diseases - analysis of medical narrative reports using the ULMFiT based text classification. (Submitted)

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1   Introduction

Asthma is a common, chronic inflammatory airway disease, the prevalence of which has increased in adults worldwide, being 10% in Finland (Hisinger-Mölkänen et al. 2019; Jousilahti et al. 2016; Lundbäck et al. 2016). Smoking has many adverse effects on asthma. It increases the severity of the disease (Eisner et al. 2006), accelerates lung function decline (Tommola et al. 2016) and impairs therapeutic outcomes (Chalmers et al. 2002). Despite this, the prevalence of smoking has been reported to be similar in asthma patients and healthy population (Polosa et al. 2011). In 2018, 14% of Finnish people were active smokers, which was 6% less than in 2008 (S. Virtanen et al. 2019). However, the declining trend has discontinued. As known, smoking cessation is an essential part of the treatment of asthma and many other chronic diseases. All clinical guidelines suggest that the harmful effects of smoking should be discussed with patients (GINA 2020; Asthma. Current Care Guidelines 2012). Healthcare professionals play a key role in delivering smoking cessation assistance. However, while two-thirds of smokers want to quit, only less than half of them get help from physicians (Babb et al. 2017; Helldán et al. 2015). A 2–3 minute discussion with a smoker has been shown to increase the likelihood of quitting (Stead et al. 2008; West et al. 2015). The most effective way for smoking cessarion is to combine behavioural support and pharmacotherapy (Stead et al. 2015).

The growing prevalence of asthma and the prolongation of working careers means that more and more asthma patients have to cope with their disease in work life. Asthma often has a negative effect on work ability (Blanc et al. 1996; Eisner et al. 2006; Hansen et al. 2012; Lindström et al. 2011; Toren et al. 2009). Work-related respiratory symptoms are common and can prevent the employee to fully perform the job-related duties. Poorly treated or unstable asthma can lead to the loss of workdays, job changes, or even unemployment. Asthma is often a contributing factor, but not the only reason, for serious forms of work disability, such as disability pensions and long-term sickness absence (Nyman 2018). In prior studies, both work- and asthma-related factors, such as workplace exposures and the severity of the disease, have been reported to increase the risk of work disability (Blanc et al. 1996;

Eisner et al. 2006; Fell et al. 2016; Lindström et al. 2011; Saarinen et al. 2003; Toren et al. 2009).

The present study aimed to evaluate smoking and work ability trends in asthma patients. We studied how reliably patients reported their smoking status and whether their smoking habits changed over the 10-year study period. We also examined how clinicians document patients' smoking status and, in the case of current smokers, deliver smoking cessation care. The work abilities of asthma patients were evaluated in a longitudinal setting to find asthma and other health-related risk factors for the poor development of work ability.

2 Review of the Literature

2.1 Asthma

2.1.1 Definition and Pathogenesis

Asthma is a common chronic respiratory disease that causes cough, wheeze, shortness of breath, mucus secretion, and episodes of expiratory airflow limitation (GINA 2020; McCracken et al. 2017). Asthma is usually characterised by chronic airway inflammation, bronchial hyperresponsiveness, and reversible airflow obstruction. Symptoms are variable and recurring, typically due to fluctuating inflammatory activity, but airflow limitation may become later persistent (GINA 2020). Exposure to allergens or irritants, physical exercise, and viral respiratory infections are typical factors that trigger symptoms (McCracken et al. 2017).

Asthma is a heterogeneous disease with varying mechanisms of pathogenesis. Airway inflammation plays an important role in pathophysiology. The typical cells identified in airway inflammation include T-helper cells (Th1, Th2), mast cells, eosinophils, neutrophils, epithelial cells, and macrophages (McCracken et al. 2017). Th2 lymphocytes (CD4+) play an important role in asthma inflammation and secrete proteins such as interleukin (IL)-4, IL-5, IL-13, and immunoglobulin E (IgE), resulting in eosinophilic inflammation (McCracken et al. 2017). Recently, the identification of non-classic cells other than Th2 CD4+ cells, such as innate lymphoid cells group 2 (ILC2), has changed the terminology from "Th2 high" to "T2 high" inflammation (Sze et al. 2020). Non-T2 asthma is non-eosinophilic asthma without the presence of type 2 inflammation markers (Sze et al. 2020). Overall, the interaction of inflammatory cells and mediators leads to bronchial inflammation, airflow limitation, airway hyperresponsiveness, and the presentation of typical asthma symptoms. Later, the progression of the disease and prolonged inflammation can cause permanent structural changes and remodelling of the airway, such as mucus gland hyperplasia and hypersecretion, injury to epithelial cells, thickening of the sub-basement membrane, sub-basement fibrosis, smooth muscle hypertrophy, and angiogenesis (McCracken et al. 2017). These changes increase airway obstruction even more and lead to a less favourable response to the usual treatment.

Bronchial hyperresponsiveness means an exaggerated bronchoconstrictor response to non-specific stimuli, which results in bronchospasm and airway obstruction (McCracken et al. 2017). Multiple mechanisms influence hyperresponsiveness, including inflammation, dysfunctional neuroregulation, and structural changes. More severe airway hyperresponsiveness is commonly associated with the clinical severity of asthma, but even patients with mild and moderate asthma can be at risk of developing exacerbations that require urgent health care (K. Larsson et al. 2020).

2.1.2 Epidemiology

The prevalence of asthma has increased in Finland and other industrialised nations over the last decades (Hisinger-Mölkänen et al. 2019; Jousilahti et al. 2016; Kankaanranta et al. 2017a; Kuruvilla et al. 2019; Lundbäck et al. 2016). Based on the Finnish National FinHealth 2017 study, 10% of men and 14% of women aged over 30 years reported having physician-diagnosed asthma (Koponen et al. 2018). In the 1990s, only 6% of adults reported having asthma (Hisinger-Mölkänen et al. 2019; Erkki Vartiainen et al. 1998). The prevalence is higher among children, decreases in early adulthood, and begins to increase again after 30–35 years of age (Kankaanranta et al. 2017b). Asthma is the most common chronic disease in childhood. The prevalence among Finnish children is 6–10 % (Jalanko 2017).

2.1.3 Risk Factors

Asthma is a complex disease that is determined by the interaction between genetic predisposition and environmental factors (Mims 2015). Family history of asthma and atopy, and allergic multimorbidities are common risk factors, especially for childhood asthma (Räsänen 2000; Toppila-Salmi et al. 2019). Several genes have been associated with asthma, but the disease is not fully understood at the genetic level (Ober et al. 2011). However, genetic factors have been proven to affect the onset, severity, and treatment of asthma.

A sharp rise in the prevalence of asthma indicates the importance of epigenetic and environmental factors in the development of asthma (Harb et al. 2015; Mims 2015). Both indoor (e.g., airborne particulate matter, nitrogen dioxide, mould, and animal dander) and outdoor pollution (pollens, moulds) are important risk factors for the onset of asthma and worsening of symptoms (Tischer et al. 2021). A Finnish population-based study found that polysensitisation was associated with a risk of asthma in adults (Toppila-Salmi et al. 2015). There is also evidence that overweight patients are more susceptible to reacting to air pollution (Toskala et al. 2015). Moreover, obesity alone is a considerable risk factor for asthma and its prognosis

(Kilpeläinen et al. 2006; Sivapalan et al. 2015; Sutherland 2014). Occupational exposures have an important effect on asthma; the work environment can cause asthma, or asthma symptoms can worsen at work. The typical sensitisers at work have been classified into high–molecular weight compounds (e.g., gums, enzymes, flour dust, animal allergens) and low–molecular weight compounds (e.g., polyisocyanates, metals, and chemical substances) (Malo et al. 2011).

Active smoking and second-hand smoke seem to increase the risk for asthma (Accordini et al. 2012; Burke et al. 2012; Flodin et al. 1995; Toskala et al. 2015). The evidence is suggestive but not sufficient in adult-onset asthma (Smoking Cessation: A Report of the Surgeon General. 2020). By contrast, an association between pre- and postnatal exposure to tobacco smoke and the risk of developing asthma in children is clear (Burke et al. 2012; J. J. K. Jaakkola et al. 2004; B. Wang et al. 2020). A recent study showed that maternal smoking during pregnancy can also affect adult-onset asthma in offspring (Toppila-Salmi et al. 2020).

Viral and bacterial infections play an important role in the development and progression of the disease (Fuchs et al. 2013; Jartti et al. 2020). Several studies have found a link between early viral lower tract infections, such as respiratory syncytial virus infection, and childhood wheeze and asthma (Jartti et al. 2020, 2017; Kieninger et al. 2013). The possible mechanism behind this association is that viruses might trigger wheeze and asthma in patients with impaired mucosal and systemic immune defence and/or atopy. However, childhood exposure to certain infections and microorganisms protects against autoimmune and allergic diseases (Ege 2017; Heikkinen et al. 2013). This phenomenon is called the hygiene hypothesis and contributes to the development of the immune defence (Brooks et al. 2013; Strachan 1989). Hygiene hypothesis was presented first in the 1980s when David Strachan suggested that allergic sensitisation and hay fever might be prevented by viral infections transmitted by "unhygienic contact" to siblings in early childhood (Strachan 1989). The observation was confirmed later in several populations (Von Mutius 2000). Over the years, the epidemiological observation changed from siblings to day care, faecal-oral and other infections, and to farm exposures. Various studies around the world have proven the protective effect of traditional farm environments on the development of childhood asthma and allergies, mainly in terms of exposure to farm animals and the consumption of raw cow's milk (Von Mutius et al. 2010). Compared to urban environments, the farm environment often has a richer and more diverse microbial population, which enables the development of a more auspicious microbiome, both in the gut and in the airways. This further affects the development of the immune system and protects against inflammatory diseases (Kääriö et al. 2016; Roponen et al. 2005; Von Mutius et al. 2010). The protective effect of the farm environment in utero and during early childhood seems to prevent allergic diseases and polysensitisation in adulthood (Karvonen et al. 2021;

Kilpeläinen et al. 2002; Lampi et al. 2011, 2015). There is also some evidence that microbial exposure at home may protect against asthma in adults (Pekkanen et al. 2018).

Low socioeconomic status has been proven to increase asthma risk (Kozyrskyj et al. 2010; Poowuttikul et al. 2019). Also, nutritional factors may alter the immune response and influence the development of asthma (Nagel et al. 2010; Shen et al. 2018; L. G. Wood 2017). Consumption of fruit, vegetables, and whole grains seems to have a protective effect, while fast food can enhance inflammation, leading to an increased risk of many chronic diseases, including asthma (L. G. Wood 2017). Moreover, higher food diversity during the first year of life decreases the risk of asthma and allergies in childhood (Nwaru et al. 2017; Sozańska et al. 2021).

2.1.4 Diagnosis

Asthma is diagnosed based on a history of typical symptoms (e.g., wheeze, shortness of breath, chest tightness, and cough), a history of allergic rhinitis or eczema, family history (e.g., atopic disease), and lung function tests. Symptoms can vary in severity and intensity over time. Typically, symptoms are worse in the morning or at night. Diagnosis is confirmed by a lung function test showing variable airway obstruction. Diagnostics must be carefully conducted to ensure appropriate treatment for every patient.

The diagnostic tests used in Finland are shown in Table 1 (GINA 2020; Asthma. Current Care Guidelines 2012). A positive finding in any of these tests indicates asthma. Primary health care has the main responsibility of diagnosis, except histamine and methacholine tests.

Additional tests include fractional concentration of exhaled nitric oxide (Fe_{NO}), which is associated with the levels of sputum eosinophils and increases typically in (eosinophilic) airway inflammation (Korevaar et al. 2015). Both Fe_{NO} and blood eosinophilic count are biomarkers for type 2 (T2) inflammation and are used to assess asthma phenotype (discussed in more detail in chapter 2.1.6). Eucapnic voluntary hyperventilation test is used to show exercise-induced bronchoconstriction (Hull et al. 2016).

The physical examination of an asthma patient can be normal. Expiratory wheezing may be heard in lung auscultation as a sign of bronchial obstruction. Chest X-ray is used in differential diagnostics to exclude other diseases, such as tuberculosis and lung cancer. Allergic status can be diagnosed by skin prick testing or by measuring the specific IgE level in serum. Taking a basic blood count and a blood eosinophil count has also been recommended.

Table 1. Diagnosis of asthma over 12 years of age in Finland.

Lung function test	Diagnostic criteria
Spirometry	Increase in FEV1[1] or FVC[2] of >12% and >200 mL from baseline, 10–15 minutes after 200–400 mcg salbutamol
PEF[3] (twice-daily 14 days)	- PEF variability before and after SABA[4] (salbutamol 0.4mg) >15% and 60l/min at least three times during 14 days OR - PEF (taken before SABA[4]) variability between morning and evening values >20% and 60l/min at least three times during 14 days
Anti-inflammatory treatment test (e.g. budesonide 800-1600ug/day 4-8 weeks or prednisolone 20mg/day 1-2 weeks)	Increase in FEV1 by >15% or PEF by >20% from baseline after treatment, outside respiratory infections
Exercise challenge test	Fall in FEV1 or PEF from baseline of ≥15%
Histamine or methacholine test	Fall in FEV1 from baseline of ≥15% when histamine dose ≤ 0.4mg or methacholine dose ≤ 0.6mg

[1] Forced expiratory volume in one second [2] Forced vital capacity [3] Peak expiratory flow [4] Short-acting β2 agonist. Modified from Asthma. Current care guidelines 2012.

2.1.5   Differential diagnostic for asthma and COPD

Asthma and COPD are both obstructive lung diseases with similar symptoms, such as shortness of breath and cough. In COPD, cough is often associated with an increase in sputum production. Asthma patients usually experience shortness of breath periodically, while COPD patients report persistent and progressive dyspnoea, especially during physical exertion (GOLD 2020). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is "a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (GOLD 2020). COPD is characterised by chronic bronchitis and chronic airflow limitation caused by a mixture of small airway disease and emphysema (GOLD 2020). In Finland, the prevalence of COPD is estimated to be between 2% and 4% (Axelsson et al. 2016; Kainu et al. 2016).

The differential diagnosis of asthma and COPD is based on symptoms, smoking history, physical examinations, and lung function tests. Usually, asthma patients have a smoking history of under 10 years, while COPD patients report a smoking history of over 20 years. Occupational dusts, vapours, gases, fumes, and other chemicals can also cause COPD. Host related factors, such as abnormal lung development, can also increase the risk of COPD (GOLD 2020). In spirometry, the presence of a post-bronchodilator FEV1/FVC <0.70 confirms the presence of persistent airflow limitation and COPD (GOLD 2020). Patient can also have features of both asthma and COPD, which Chapter 2.3.6.1 discusses in more detail.

COPD is a progressive and incurable disease. Smoking cessation is the most effective way to slow down the progression of COPD (Smoking Cessation: A Report of the Surgeon General. 2020). Non-pharmacological treatments also include physical exercise and physical rehabilitation, education, and self-management, and pneumococcal and influenza vaccination (COPD. Current Care Guidelines 2019). Pharmacological treatments are used to reduce symptoms, reduce the severity and frequency of exacerbations, and improve exercise tolerance and health status. The most commonly used classes of medication in COPD are short-acting beta-agonist (SABA), long-acting beta-agonist (LABA), short-acting muscarinic antagonist (SAMA), and long-acting muscarinic antagonist (LAMA). Inhaled corticosteroids (ICS) are used if the patient also has asthma, blood eosinophil count is over 0.3×10^9 cell/l or patient has a history of moderate to severe exacerbations(COPD. Current Care Guidelines 2019).

2.1.6 Treatment

The primary, long-term goals of asthma management are to achieve and maintain good symptom control and activity levels, to minimise the risk of asthma exacerbations, persistent airflow limitation, mortality, and side effects of treatment using the lowest treatment level to achieve these goals (GINA 2020). Effective asthma management requires patient education in asthma self-management, which includes self-monitoring (PEF, symptoms), a written action plan, and knowledge of the factors that trigger and worsen symptoms (Gibson et al. 1999). Asthma patients should have regular controls with the physician and/or asthma nurse, where symptoms, inhalation techniques, medication, and comorbidities are assessed and adjusted (GINA 2020).

The pharmacological treatments include *controller medications* that reduce airway inflammation and control symptoms, and *reliever medications* that are taken as required for prevention and relief of symptoms. The guidelines recommend a stepwise approach to the treatment (Figure 1)(GINA 2020; Asthma. Current Care Guidelines 2012). ICSs are first-line controller medications for the majority of

patients. Previously, intermittent and very mild asthma were treated with SABA alone (GINA 2020). However, SABA relieves bronchoconstriction effectively but does not cure the underlying inflammation, which is usually also present in mild asthma. Overreliance on SABA may potentially worsen respiratory inflammation and even increase the risk of hospitalisation and exacerbations (FitzGerald et al. 2017; GINA 2020). Currently, the updated version of the GINA guideline recommends replacing SABA with low dose ICS/formoterol as a preferred reliever in mild asthma and also at the higher treatment steps. In the second step, asthma is controlled with low dose ICS. Asthma of moderate severity requires low- or moderate-dose ICS and one extra medicine, usually LABA (Ducharme et al. 2010a, 2010b, 2011). Severe asthma is usually treated with the addition of other controller medications, leukotriene inhibitors (Kelloway 1997), theophylline (P. J. Barnes 2003), or biologic drugs (Normansell et al. 2014). Oral corticosteroids are used to treat exacerbated asthma if the symptoms are severe (GINA 2020).

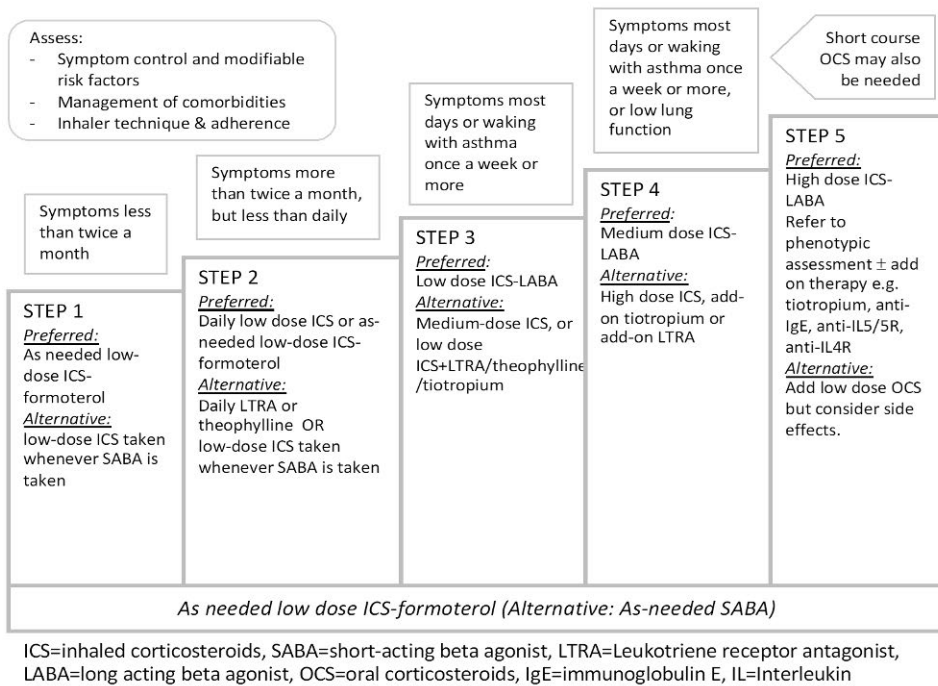**Figure 1.** Step-up therapy of asthma in patients over 12 years of aged. Modified from GINA 2020.

Biologic drugs have recently been developed for the treatment of patients with severe asthma (Godar et al. 2018). Individuals with a specific subtype of asthma may benefit from biologics if conventional therapy and optimal treatment of comorbidities do not result in adequate asthma management. There are currently five approved biologics:

omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Omalizumab targets immunoglobulin E (IgE), whereas mepolizumab (anti interleukin (IL)-5), reslizumab (anti IL-5), and benralizumab (anti-IL5 receptor α) reduce eosinophilic inflammation. Dupilumab binds to IL-4 receptor alpha and blocks both IL-4 and IL-13 signalling. All biologics reduce either eosinophilic or type 2 inflammation, leading to better asthma control and reduced exacerbation rates (Godar et al. 2018).

2.1.7   Asthma Phenotypes and Endotypes

Asthma is increasingly defined as a heterogeneous disease characterised by a variety of clinical presentations, pathophysiological pathways, and outcomes. It can be divided into clinically similar subgroups, called phenotypes, based on different pathophysiological mechanisms, called endotypes. The assessment of a clinical or inflammatory phenotype is essential for patients with severe asthma to provide appropriate target treatment (Wenzel 2020). According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines, severe asthma can be defined based on the medication and evaluation of asthma control (Table 2) (Chung et al. 2014).

Table 2.   Definition of severe asthma for patients aged over 6 years of age.

Asthma which requires treatment with high dose ICS[1] plus a second controller[2] for the previous year or OCS[3] for ≥50% of the previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy

Uncontrolled asthma defined as at least one of the following:
1. Poor symptom control: ACQ[4] consistently ≥1.5, ACT[5] <20 (or "not well controlled" by GINA guidelines)
2. Frequent severe exacerbations: two or more bursts of OCS (≥3 days each) in the previous year
3. Serious exacerbations: at least one hospitalisation or mechanical ventilation in the previous year
4. Airflow limitation: after appropriate bronchodilator withhold FEV1[6] <80% predicted (in the face of reduced FEV1/FVC[7] defined as less than the lower limit of normal)

Controlled asthma that worsens when high dose treatment is reduced.

[1] Inhaled corticosteroid (Fluticasone propionate ≥1000 ug when age ≥12 years) [2] leukotriene receptor antagonist, theophylline, cromones, OCS, or biological drug [3] Oral corticosteroids [4] Asthma control questionnaire [5] Asthma control test [6] Forced expiratory volume in 1 second [7] Forced vital capacity. Modified from Chung et al. 2014.

Traditionally, asthma has been classified based on observable characteristics, such as triggers (occupational, exercise-induced, atopic), symptoms (wheeze), and response to treatment (sensitive/insensitive to ICS). The classification can be made relatively easy, but it does not accurately predict patient response to the treatment accurately. The classification of asthma severity has contributed to identifying patients with increasing symptoms and a substantial need for medication. However, this approach may lead to inappropriate polypharmacy and side effects for some patients. To better understand asthma heterogeneity, the concepts of phenotyping and endotyping have emerged (Anderson 2008).

Phenotyping utilises clinical and biological features to identify subgroups, whereas endotyping also aims to understand the different underlying mechanistic pathways (Chung et al. 2014). The ultimate goal is to move towards personalised therapy. Several large multicentre studies have been conducted to identify asthma phenotypes, but the concept is still not fully understood (Haldar et al. 2008; Lefaudeux et al. 2017; Moore et al. 2010). Different phenotypes share the same clinical characteristics and biomarkers making the subgrouping challenging. To precisely manage asthma, novel and specific biomarkers are needed.

The current knowledge of the phenotypes of asthma is summarised in Table 3 and Figure 2. At the moment, the key discriminators are the age of onset, lung function, atopy, and the presence of eosinophils (P. Ilmarinen et al. 2015; Kaur et al. 2019; Nadif et al. 2020). Other asthma-related characteristics, such as sex
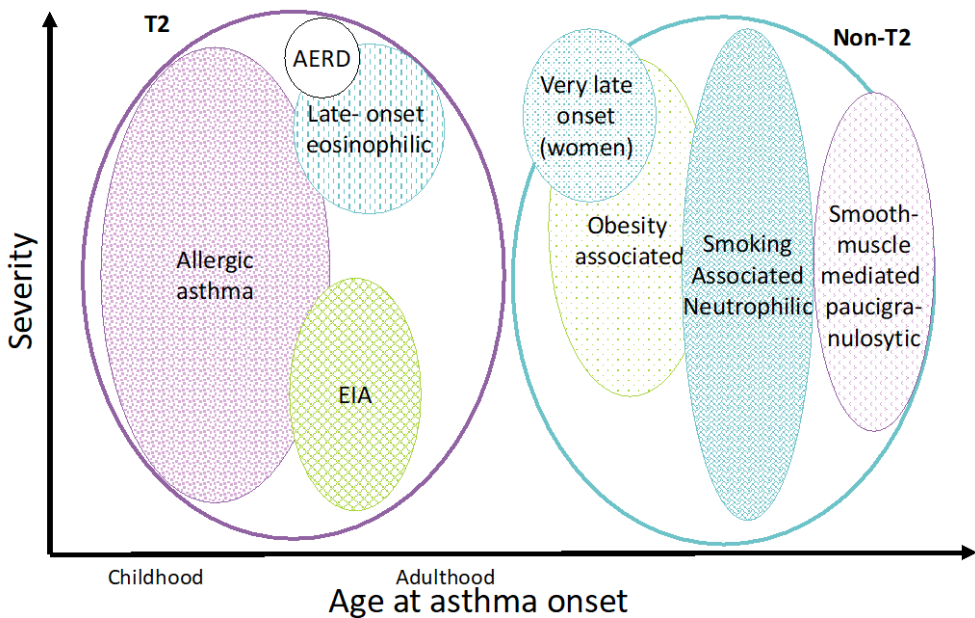
Figure 2. Asthma phenotypes. EIA=Exercise induced asthma. AERD= aspirin induced asthma. Modified from Wenzel et al 2012.

smoking, and obesity have been studied, but the results are not consistent. Several cluster analyses have been carried out to define the phenotypes of asthma. The results varied depending on the type of cohort and the variables used in clustering. Efforts have been made to aggregate these studies, and four primary phenotypes have been suggested: early-onset allergic asthma, early-onset moderate-to-severe remodelled asthma, late-onset nonallergic eosinophilic asthma, and late-onset nonallergic, non-eosinophilic asthma (Kaur et al. 2019). Moreover, many studies have defined obesity-associated asthma as a unique phenotype (Amelink et al. 2013; P. Ilmarinen et al. 2015; Miethe et al. 2020). It is usually described as difficult to treat neutrophilic asthma with a low eosinophilic count. However, a recent review showed that the obesity-asthma phenotype shares heterogeneous pathology and is not only a classical phenotype in women with late onset and corticosteroid resistance (Miethe et al. 2020). Similarly, smoking has a clear influence on phenotypic expression, but asthma patients who smoke are often excluded from studies (P. Ilmarinen et al. 2015, 2017). Smoking-related asthma is usually described as neutrophilic, more severe/uncontrolled and patients are often less responsive to ICS treatment (P. Ilmarinen et al. 2017; Wenzel 2012). Obesity- and smoking-associated phenotypes have similar features to non-eosinophilic asthma, and may also be regarded as subtypes of non-eosinophilic asthma. In addition to previous phenotypes, studies have suggested several other phenotypes in adults, such as aspirin-induced asthma, exercise-induced asthma, and paucigranulocytic asthma (Schatz et al. 2014; Wenzel 2012). Lately, phenotype overlap has also gained the attention of clinicians and researchers. A recent study by Han et al. found that phenotype overlap is common in asthma and underlined the importance of a multidimensional asthma assessment (Han et al. 2021).

In childhood, boys have a higher risk of asthma (Hugg et al. 2008). The recognised phenotypes in childhood are infection-related asthma (Th1), mild allergic asthma, severe asthma with multiple allergies, severe non-allergic, neutrophilic asthma, and late-onset non-allergic asthma (Just et al. 2017).

Table 3. The common identified phenotypes of asthma

Phenotype	Clinical and physiological features	Response to therapy and other treatment	Exacerbations	Severity	Comorbidities	REF
Early-onset mild allergic asthma (Th2)	Eos (blood, sputum), IgE ↑ FE_{NO} norm. or high FEV1 normal Strong family history	Responsive to ICS and anti-IgE (omalizumab)	Fewer	Mild to moderate	Allergic rhinitis Allergic dermatitis	(Kaur et al. 2019; Nadif et al. 2020)
Early-onset moderate to severe allergic asthma (Th2)	Eos (blood, sputum), IgE ↑ FE_{NO} norm. or high FEV1 low	Responsive to ICS and anti-IgE (omalizumab)	Recurrent	Moderate to severe	Allergic rhinitis Allergic dermatitis	(Kaur et al. 2019)
Late onset, non-allergic, eosinophilic asthma (T2)	Eos (blood, sputum), FE_{NO} ↑ Low IgE FEV1: ↓ (despite short disease duration)	Difficult to treat ICS-refractory, requires higher doses of ICS or OCS Responsive to anti-T2 biologic therapy	Recurrent	Moderate to severe	Chronic rhinosinusitis Nasal polyps	(Kaur et al. 2019)
Late onset, non-allergic, non-eosinophilic, neutrophilic asthma (non-T2)	Women Sputum neutrophils ↑ Eos. count, FE_{NO} Norm IgE, sputum eos. Neg Airway obstruction ↑ More air trapping hs-CRP, IL6 +	Not sensitive to ICS Responsive to anti-LTB4 Remission: rare	Recurrent symptom control ↓	Moderate to severe	Many comorbidities and medication Respiratory infections	(Kaur et al. 2019; Nadif et al. 2020)
Obesity-associated, non-eosinophilic asthma (usually neutrophilic)	Often older women Low eos and FE_{NO} hs-CRP, IL6 + FEV1: ↓ or Norm	Weight loss Management difficult Less sensitive to steroids Add-on medication	Recurrent use of health care↑↑	Different levels- often severe	Many; often reflux, sinus disease. High depression score.	(P. Ilmarinen et al. 2015; Miethe et al. 2020)
Smoking-associated, neutrophilic asthma	Often males with smoking history. Less atopic. Neut, macrophages↑ hs-CRP, IL6 + FEV1: ↓ or Norm	Management difficult, poor response to ICS Smoking cessation	Recurrent use of health care↑↑	Moderate to severe	Many; often COPD	(P. Ilmarinen et al. 2015)

Eos=eosinophilic count. FE_{NO}= Fractional concentration of exhaled nitric oxide. FEV1=Forced expiratory volume in 1 second. ICS=inhaled corticosteroids. IgE=Immunoglobulin E. IL=Interleukin. Neut=Neutrophils. T2=type 2 inflammation.

2.2   Asthma and Work Ability

The relationship between work and asthma is multidimensional and complex (Table 4). Work can worsen asthma symptoms or even cause occupational asthma, although this is rarely confirmed. Patients with poorly controlled or more severe asthma can have an impaired ability to fully perform their job-related duties. In general, asthma can affect work productivity (Blanc et al. 2001), which is an important reason for the high economic burden of the disease (Ehteshami-Afshar, FitzGerald, Doyle-Waters, et al. 2016).

Work ability describes the balance and compatibility between an employee's mental and physical resources and the work. There are also several other components that affect a person's work ability, such as professional competence, attitudes towards work, meaningful, and appropriately challenging work, and age. By contrast, work disability can be described as a physical or mental impairment that results in substantial limitations. In asthma patients, milder forms of work disability are common, such as job changes, loss of workdays, reduction in work hours, and limitation in job duties due to asthma symptoms (Blanc et al. 1996; Eisner et al. 2006; Hansen et al. 2012; Lindström et al. 2011). The most serious outcomes of disability are long-term sickness absences and disability pensions. In these cases, severe respiratory symptoms are often contributing factors in decreased work ability but seldom the main or only reason. For example, in 2015, only 0.4% of all disability pensions in Finland were granted due to asthma (Nyman 2018).

Both work- and asthma-related factors can increase the risk of work disability. Typical work-related risk factors for decreased work ability include occupational exposures, physical demands, social climate, and temperature changes (Blanc et al. 1996; Eisner et al. 2006; Toren et al. 2009), while common asthma-related factors are the severity of the disease and age of asthma onset (Blanc et al. 1996; Eisner et al. 2006; Hansen et al. 2012; Karvala et al. 2014; Saarinen et al. 2003). Furthermore, lifestyle and general health-related factors, such as smoking and comorbidities, can affect the work ability of asthma patients (Eisner et al. 2006; Hakola et al. 2011). In the end, personal, and psychosocial factors define how a person experiences the disease and his or her ability to work. Hence, there is a difference between having a health condition and being disabled (Verbeek et al. 2008).

The majority of previous studies on asthma and work ability have been cross-sectional studies (Table 4). The follow-up times in longitudinal studies have varied, and a small number of studies have had a follow-up period of over five years (Karvala et al. 2014; Lindström et al. 2011; Taponen et al. 2019; Toren et al. 2009).

Early recognition of decreased work ability is essential to supporting patients and maintaining their ability to work. In general, subjective assessment has proven to be a valuable method in predicting possible future work disability (J. Ilmarinen et al. 1997). There are several tools for assessing work ability, such as the work ability

score (WAS), future work ability (FWA), and the work ability instrument (WAI) (Tuomi et al. 1998). WAI questionnaire was developed by the Finnish Institute of Occupational Health and is used both in research and in occupational health care to assess work ability during workplace surveys and health examinations. It includes seven items that take into consideration the employee's health status, the resources, and the demands of work. WAS and FWA are single WAI instruments. WAS is scored from 0 (completely unable to work) to 10 (work ability at its best).

Table 4. Description of studies on asthma and work ability (WA) or work disability (WD) performed in the last 20 years

Study	Patients with asthma (severe)	Study cohort description	Follow-up	Asthma diagnosis	Asthma onset	Used definition for WA/WD	Main findings
(Larbanois et al. 2002) Eur Respir J	157	Prospective cohort study	Median 43 months	Doctor-diagnosed	NA	Job change, work loss due to asthma, income loss	A high proportion of patients with occupational asthma (72%) and work-related asthma (54%) had work disability defined as any job change or work loss due to asthma. Authors concluded that work-related asthma symptoms may have a considerable socio-economic impact.
(Nathell et al. 2002) Respir Med	237	Cross sectional	No	Physician diagnosed	NA	Sick leave period >15days	Obesity was significantly more common in asthma patients who were on sick leave because of respiratory problems (21%) compared to the non-specific pain patients on sick leave (14%) and general population (7%). Causality between asthma and obesity remains unclear.
(Saarinen et al. 2003) Eur Respir J	969	Population-based cross sectional	No	Physician diagnosed	73% adult onset 27% child onset	Frequency of asthma symptoms caused or made worse by work during the last month	21% reported work-aggravated asthma symptoms weekly. Symptoms increased by age, self-reported occupational exposure to dusts (OR 3.1), abnormal temperatures or poor indoor air (OR 2.2), physically strenuous work (OR 2.0), and chemicals (OR 1.5), and expert-evaluated probability of daily occupational exposure to dusts, gases or fumes (OR 2.0).
(Blanc et al. 2003) Chest	2424	Population-based cross-sectional study	No	Self-reported	42 % ≥18 yrs. 58% <18 yrs.	Job change due to breathing difficulties at work	11% of patients with childhood-onset asthma and 13% of patients with adult-onset asthma reported WD whereas only 3% of patients without asthma had reported WD. WD was associated with exposures at work: High-risk jobs increased the risk 3.4-fold and intermediate-risk jobs 2.6-fold.

(Eisner et al. 2006) Am J Med	465 (465)	Prospective cohort study	No	Self-report and medical record reviewed	NA	PWD: Loss of work days, changes in job duties. CWD: Leaving the job.	The prevalence of asthma-related CWD was 14% among adults with severe asthma. Among those who were currently employed, the prevalence of PWD was 38%. Job exposures and disease severity seem to be important risk factors for work disability.
(Thaon et al. 2008) Am J Ind Med	398	Longitudinal cohort study, only men	5 years	Physician diagnosed	58% childhood 42% adulthood	Self-reported sick leave, unemployment	Patients with childhood-onset asthma was more often out of work life at the beginning of their working life and current adult-onset asthmatics at the end of their working life compared non-asthmatics. Current asthmatics had higher prevalence of sick leave in previous year compared non-asthmatics (38.4% vs. 27.0%, P = 0.005). Unemployment was not higher in asthmatics.
(Toren et al. 2009) Thorax	779	Population-based	8 years	Physician diagnosed	NA	Reported job change during follow-up	Insidence rate of WD: 1.2/1000 person-years in random sample, 5.7/1000 p-y in asthma group. Occupational exposure to dust, gases or fumes predicted increased risk of respiratory WD (HR 3.5). In asthma patients, female sex was associated with an increased disability risk (HR 2.8)
(Lindström et al. 2011) Respir Med	393 (38)	Registry-based, only men	20 years	Clinically verified	onset before age 20	WAS 0-7	29% of patients with mild-moderate asthma at the age of 20, 31% of patients with severe asthma and 20% of healthy controls reported decreased WA (WAS 0-7) 20 years later. Smoking (OR 2.5), only basic education (OR 2.6), being a manual worker (OR 2.7) and current severe asthma (OR 3.8) was associated with reduced WA
(Kauppi et al. 2010) Respir Med	883	Prospective cohort study	Median 4 years	Self-reported (diagnosed by a physician)	NA	Number of sick leave days (SLD)	Mean SLD per year for patients were 17.6 days for rhinitis, 23.8 days for asthma and 24.2 days for both conditions combined. Controls without neither condition had on average 14.5 SLD.

(Hakola et al. 2011) Allergy	2 332	Register-based, prospective study	Yes	Entitled to special reimbursement for asthma medication	NA	Long-term all-cause work disability (≥90 days)/ disability pension (DP)	Asthma increased the risk of all-cause long-term WD/DP 1.8/2.1-fold compared to patients without asthma. The risk increased further with one chronic comorbidity (HR 2.2/2.6)), with two comorbidities (HR 4.5/5.5), being especially high in patients with asthma and depression (HR 3.6/6.8).
(Hansen et al. 2012) Scand J Public Health	662	Prospective population-based	5 years	Physician diagnosed	Childhood and adulthood	N of weeks receiving public transfer incomes	Asthmatics had significantly more annual weeks receiving welfare (37 vs. 21), sick leave (9 vs. 7) and disability (19 vs. 11) benefits than non-asthmatics. Adult-onset asthmatics had increased prevalence rate ratios for disability of 2.40.
(Kim et al. 2013) Am J Ind Med	1047	Multinational follow-up survey	Yes	Self-reported physician-diagnosed	Childhood and adulthood	Respiratory sickness absence	Exposure to vapours, gas, dust, or fume doubled the odds of respiratory sickness absence in patients with asthma, especially when adult-onset. Patients with higher scores in asthma symptom were more likely to have sick leave (OR1.6, expressed per point change)
(Karvala et al. 2014) Int Arch Occup Environ Health	513	Prospective survey-based study	Mean 7.8 years	Physician diagnosed	Adult-onset	Poor WAS (0-7), Early withdrawal from work	WEA and OA increased the risk of poor WAS (OR 1.8 and 2.6) compared to a reference group with upper respiratory symptoms. OA was associated with 5.7-fold and WEA 1.6-fold risk for early withdrawal from work. A perceived poor social climate at work (OR 1.5/2.3) and poor experiences with supervisory co-operation (OR 1.7/2.4) were associated with impaired WA and early withdrawal from work.
(Henneberger et al. 2015) Int J Tuberc Lung Dis	557	Cross sectional cohort study	Back to 12 months	Recorded diagnosis and use of medication	62% before age 18	Asthma exacerbation	29% of patients had severe exacerbation during the last 12 months. Exposure to several specific agents such as tobacco smoke (PR 2.5) increased aggravation of asthma symptoms at work.
(Taponen et al. 2017) J Occup Med Toxicol	2613	Population-based cross-sectional survey	No	Physician diagnosed	NA	Unemployment, WD (sickness absence, disability pension)	Asthmatics with full time work were younger, had more often nonmanual work and less symptoms, used less asthma medication and smoked less than asthmatics with WD. Severe asthma symptoms were associated with unemployment (OR 2.3) or WD (OR 4.4).

(Taponen et al. 2018) J Occup Med Toxicol.	1657	Population-based cross-sectional survey	No	Physician diagnosed	NA	Self-reported work and career changes	Career changes that were made mainly due to asthma were associated with undesirable work status, WD or unemployment 2-6-fold compared to full time work. 67% reported symptoms relieved after career changes. The authors suggested that early career changes for some asthmatics may be beneficial in maintaining sustainable career
(Taponen et al. 2019) Respir Med.	1274	Prospective survey-based study	6 years	Physician diagnosed	Childhood and adulthood	Self-reported work status	Asthma diagnosed in late adulthood (50+) was associated with higher risk for drifting out from full-time work (OR 3.6) and increased the risk of work disability (OR 10.9) compared to childhood-onset asthma.
(Klepaker et al. 2019) Respiration	626	Population-based cross-sectional survey	No	Self-reported physician-diagnosed	Not classified	WAS Sick leaves over the course of the last 12 months	Patients with asthma and obesity had not increased number of sick leaves (OR 1.2, CI 0.8-1.7) or reduced WAS (OR 1.2, CI 0.7-2.0) compared to patients with asthma and normal weight.
(de Bortoli et al. 2020) PLoS One	1110	Population-based cross-sectional survey	No	Self-reported physician-diagnosed	NA	WAS	In asthmatics, obesity (OR 1.5), former and current smoking (OR 1.4) were associated with sick leave. Low physical activity was associated with low WAS (OR 1.6). Compared to non-asthmatics, asthma modified the association between lifestyle risk factors and sick leave, but not these associations with reduced WAS.

WA=work ability, WD= work disability, NA=not available, OR=odds rate, PWD=Partial work disability, CWD=complete work disability, WAS=work ability score, HR=Hazard ratio, PR=Prevalence rate, WEA=work exacerbated asthma, OA=occupational asthma

2.3   Asthma and Smoking

Smoking increases the risk of asthma and impairs the prognosis and therapeutic outcomes of the disease (Polosa et al. 2013). Despite the negative effects of smoking, the prevalence of smoking is relatively the same in the general population and in asthma patients (Polosa et al. 2013). In Finland, 14% of adults aged 20–64 smoke daily (S. Virtanen et al. 2019), whereas the proportion of smoking among asthma patients has been reported to be 20% (Honkamäki et al. 2019). Chronic obstructive pulmonary disease (COPD) is a common tobacco-induced airway disease, but too little is known about the chronic airway diseases of smokers without spirometric evidence of COPD (FEV1/FVC >0.7). Typically, smokers have been excluded from asthma-related studies due to a possible diagnosis of COPD. However, smoking has a notable effect on the pathophysiology, clinical outcomes, and treatment of asthma. Identifying the mechanisms involved in the asthma-smoking phenotype will help us better manage smoking-related asthma in the future.

2.3.1   Smoking as a Risk Factor for Asthma

In adults, the evidence for an association between active smoking and the incidence of adult-onset asthma has been inconsistent. Several studies have found a higher incidence rate of asthma in smokers (Coogan et al. 2015; Godtfredsen et al. 2001; Rönmark et al. 1997; Vesterinen et al. 1988; Vignoud et al. 2011), whereas some studies found no link (Siroux et al. 2000). In particular, among females, the prevalence of asthma has been higher among smokers compared to non-smokers (Mcleish et al. 2010; Polosa et al. 2013; Vignoud et al. 2011). A Finnish population-based incidence case-control study found that the risk of asthma was associated with workplace environmental tobacco smoke exposure (OR 2.2) and home exposure (OR 4.8) (M. S. Jaakkola et al. 2003). Another study in this same population reported that current smoking increased asthma risk 1.3-fold and former smoking 1.5-fold (Piipari et al. 2004). A recent Finnish study showed that maternal smoking during pregnancy can affect adult-onset asthma in offspring (Toppila-Salmi et al. 2020). In asthmatic smokers, distinguishing potential COPD is challenging. A recent report summarised current evidence as suggestive but not sufficient to prove a causal relationship between smoking and adult-onset asthma (Smoking Cessation: A Report of the Surgeon General. 2020).

In children, a causal relationship between pre- and postnatal parental smoking and the development of asthma has been widely studied and accepted (Burke et al. 2012). Moreover, exposure to passive smoke in childhood has been associated with a higher asthma risk as an adult (M. L. Larsson et al. 2001; Skorge et al. 2005).

2.3.2   Pathophysiology

Cigarette smoke contains over 4500 components, including carcinogens, toxins, and oxidants, that have a direct and indirect effect on the lungs (Stämpfli et al. 2009). Similarly, asthma causes structural and inflammatory changes in the lungs, but how these two factors interact is not fully understood. Cigarette smoke alone influences the immune system, inducing both pro-inflammatory and immunosuppressive responses (Stämpfli et al. 2009). In the lungs, tobacco smoke affects epithelial cells and alveolar macrophages, causing the recruitment of inflammatory cells from microcirculation to the lungs. It also impairs innate defence mechanisms that are operated by alveolar macrophages, natural killer cells, epithelial cells, and dendritic cells (Stämpfli et al. 2009). Smokers without COPD have more inflammatory cells and cytokine staining cells, including mast cells, neutrophils, eosinophils, and macrophages, than non-smokers. Together with glandular hyperplasia, epithelial inflammation contributes to the classic symptoms of bronchitis. Also, the thickness of the laminin layer has been shown to be increased and the integrity of epithelium reduced in smokers compared with non-smokers (Amin et al. 2003). On more severe occasions, the harmful effects of smoke can lead to reduced ability of macrophages to kill viruses or bacteria, inability to remove dead cells, adverse effects on the extracellular matrix (e.g., chemical modification), and increased numbers of $CD8^+$ T cells and IL-17 secreting effector T cells. After long exposure to tobacco smoke, impaired mucosal defence results in bacterial colonisation and airway damage. The aggregation of T and B cells can lead to the production of pathogenic autoantibodies.

The structural changes in the lungs caused by smoking have also been evaluated on the basis of computed tomography (CT). Prior studies have found more emphysema, air trapping, and wall thickening in ex- and current smokers than in never-smokers (Regan et al. 2015; Tan et al. 2016). In asthma patients, emphysema is not a common finding in CT (Thomson et al. 2015). The airway wall thickness seems to be similar in smokers and never-smokers with asthma.

Sputum analysis of smokers with asthma has shown that airway inflammation is often non-eosinophilic, either neutrophilic or paucigranulocytic (Polosa et al. 2013; Thomson et al. 2009). However, some studies have not found an association between smoking and sputum inflammation type in asthma (Demarche et al. 2016). The concentration of Fe_{NO} is reduced in asthma patients who smoke, and equal in non- and ex-smokers with severe asthma (Thomson et al. 2013).

2.3.3   Clinical Outcomes

Chronic respiratory symptoms, such as wheezing and breathlessness, are more common in asthma patients who smoke compared to asthmatic non-smokers (Thomson 2017). This group of patients has an increased risk of more severe

symptoms, poorer symptom control, and decreased capacity to exercise (Kiljander et al. 2020; Polosa et al. 2013). Patients with heavier smoking histories are more symptomatic (Tommola et al. 2019). Among asthma patients, smoking is associated with disease severity, a higher prevalence rate of chronic bronchitis, and more frequent severe exacerbations during pregnancy (Thomson 2017). Moreover, the risk of life-threatening asthma attacks, hospitalisation, and unscheduled health care visits due to asthma are increased (Eisner et al. 2007; Kauppi et al. 2014; Polosa et al. 2013). The effects of smoking on clinical outcomes are similar in patients with severe asthma (Thomson et al. 2013). Recently, it has been shown that pack years have an impact on the number of hospitalisations, and a smoking history of ≥ 20 pack years was associated with respiratory-related hospitalisations (Tommola et al. 2019). In the same study, the results remained similar when the current smokers were excluded from the analysis describing the cumulative effect of smoking on health rather than current smoking only. Overall, asthma-specific quality of life, morbidity, and mortality are increased in asthma patients who smoke compared to non-smokers (Thomson et al. 2009).

2.3.4 Lung Function

Lung function is reduced and its decrease is accelerated over time in smokers with asthma compared to non-smokers with asthma (Aanerud et al. 2015; Çolak et al. 2015; J. J. K. Jaakkola et al. 2019; James et al. 2005; Tommola et al. 2016). A Finnish follow-up study with 203 asthmatics showed a significant association between smoking and an accelerated decline in FEV1, FVC, and FEV1/FVC (Tommola et al. 2016). The decline in lung function is more rapid when the patient has a smoking history of ≥10 pack-years compared to the patients who have a history <10 pack years. Interestingly, when a patient has a smoking history of over 10 years, the decline in spirometry results remains accelerated despite smoking cessation (Tommola et al. 2016). These results suggest the importance of early smoking cessation. A population-based study by Aanerud et al. (2015) observed a significantly increased risk of airway obstruction in current smokers with late-onset asthma (OR 25.6) compared to non-smokers with late-onset asthma (OR 11.2) when never-smokers with no asthma were selected as a reference group (Aanerud et al. 2015). The mean change in FEV1 in the adjusted model was -34ml/year in current smokers and -30/ml/year in never-smokers. The study included weaknesses, such as self-reported asthma diagnosis and low cut-off age (10 years) for asthma onset (Aanerud et al. 2015). A population-based study by James et al. (2005) found an association between asthma and reduced FEV1. The annual decline in FEV1 was associated with both smoking and asthma. Together these two factors had additive effects. Notably, the study used self-reported asthma diagnosis, which may lead to

misclassification of asthma. A few negative studies on the effect of cigarette smoking on lung function have been conducted (Grol et al. 1999; Jang et al. 2009), but the number of smokers with asthma was low.

2.3.5 Therapeutic Response to ICSs

ICSs are the most commonly used treatment for asthma, but one-third of asthma patients are insensitive to ICSs (P. J. Barnes 2013; Thomson 2016a). Normally, asthma is controlled with low doses of ICS, but developing resistance leads to the need for higher doses of ICS or even OCS to achieve better control. The evidence suggests that smokers with asthma are often less sensitive to short- and medium-term therapy with ICS or OCS when assessed by improvements in lung function, symptoms, and exacerbation rates compared to non-smokers with asthma (Chalmers et al. 2002; Chaudhuri et al. 2003; Thomson et al. 2009; Tomlinson et al. 2005). However, long-term treatment with corticosteroids might be beneficial for some smokers with asthma because ICSs may reduce the rate of decline in lung function (Thomson 2017). The mechanism behind corticosteroid insensitivity in smokers with asthma is not fully understood, but it might be caused by an altered type of airway inflammation towards neutrophils, increased number of glucocorticoid receptor β, and hyperactivation of proinflammatory factors (Thomson 2016b).

2.3.6 Comorbidities

In childhood, asthma often co-exists with other conditions, such as atopic eczema, allergic rhinitis, and food allergies (Spergel 2010). The common comorbidities in adults with asthma are cardiovascular diseases, gastroesophageal reflux disease, COPD, depression, anxiety disorders, type 2 diabetes, obstructive sleep apnoea, and obesity (Figure 3) (Aguiar et al. 2020; Christiansen et al. 2016; Gao et al. 2015; Kankaanranta et al. 2016; Prasad et al. 2020; Sivapalan et al. 2015). Asthma patients with comorbidities have an increased number of unscheduled health care visits, worse asthma outcomes, and decreased quality of life (Gershon et al. 2012; P. Ilmarinen et al. 2016; Wijnhoven et al. 2003). The link between asthma and comorbid conditions has been explained by several overlapping mechanisms, such as early life exposure, severe early life stress, systemic inflammation, and mitochondrial dysfunction (Kankaanranta et al. 2016; L. G. Wood et al. 2012). Asthma patients with multimorbidity have elevated rates of interleukin (IL)-6 and C-reactive protein (CRP), indicating the presence of systemic inflammation (P. Ilmarinen et al. 2016; L. G. Wood et al. 2012). Obesity is the most well-known inductor for systemic inflammation. Indeed, smoking, stress, and ageing can increase low-grade inflammation in the body (Arnson et al. 2010; Kankaanranta et al. 2016).

A population-based follow-up study by Çolak et al. showed that smokers with asthma have a higher risk of cardiovascular comorbidities and lung cancer than never smokers with asthma, suggesting that the risk is increased mainly in smokers (Çolak et al. 2015). As a limitation, the study had a short follow-up time (4.5 years), age at asthma onset was not defined, and asthma diagnosis was based on self-reports. Similarly, current smoking has been associated with a higher prevalence of mood and anxiety disorders in asthma patients (Ouellet et al. 2012). Current smoking, mood, and anxiety disorders were independently linked to poorer asthma control (Ouellet et al. 2012). A 12-year follow-up study of adult asthmatics reported a dose-dependent correlation between the number of comorbidities and pack years (rho 0.575, p <0.001) (Tommola et al. 2019).

2.3.6.1 Asthma COPD Overlap

Smoking is the most important risk factor for COPD, and asthmatic smokers can have features of COPD. Asthma COPD overlap (ACO) describes patients who have several overlapping features of these two diseases: asthma and COPD (GINA 2020). Previously, literature has also used the term "asthma-COPD overlap syndrome (ACOS)," which incorrectly refers to a single disease entity. Interestingly, the newest GOLD no longer refers to ACO; instead, it emphasizes that asthma and COPD are different diseases but may co-exist (GOLD 2020). However, according to GINA, ACO has no specific diagnostic criteria, but a history of respiratory symptoms, asthma, and smoking direct the diagnostics. Spirometric measures are also essential to confirm persistent airway obstruction (FEV1/FVC <0.7) with or without asthma-like bronchodilator reversibility (GINA 2020). A large body of evidence has shown that ACO patients experience poorer quality of life, have frequent exacerbations, have decreased lung function more rapidly, and have an increased number of health care visits and comorbidities compared to patients with COPD or asthma alone (Alshabanat et al. 2015; Gibson et al. 2009; Kauppi et al. 2011; Tommola et al. 2017). The pharmacotherapy of ACO follows asthma guidelines, and ICSs are essential in preventing severe exacerbation, morbidity, and even mortality. Usually, ACO patients also need add-on treatments, such as LABA and/or LAMA (GINA 2020).
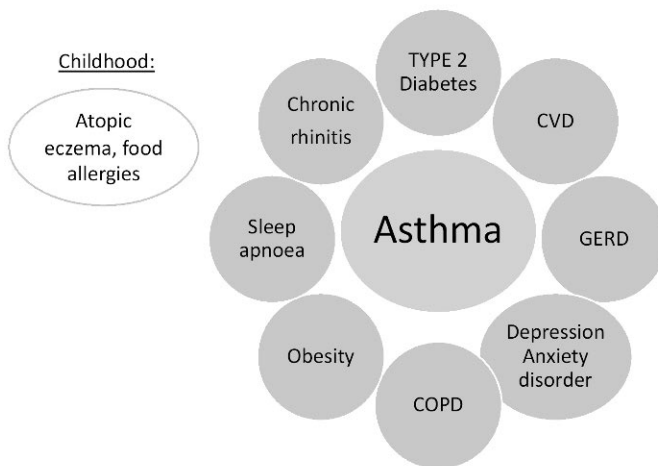
Figure 3. Common asthma related comorbidities. CVD=Cardiovascular diseases, GERD=Gastro-oesophageal reflux disease, COPD=Chronic obstructive pulmonary disease. Modified Kankaanranta 2016.

2.3.7   Smoking and Nicotine Dependence

Tobacco and nicotine dependence is a chronic disease with relapses and remissions. It is difficult to treat, which is an important reason smoking remains the leading preventable cause of death and illness in the world. Worldwide, cigarette smoking causes almost 8 million premature deaths each year (World Health Organization 2015). In Finland, there are around 4000 smoking-related deaths every year (Vähänen 2015).

Tobacco addiction involves physical, psychological, genetic, social, and environmental aspects that are maintained together with the adverse behaviour (Schwartz et al. 2010). Tobacco induces pleasure, enhances mood, and relieves withdrawal symptoms in addicted smokers (Figure 4). Behavioural conditioning has also an important role in addiction. Smokers associate cigarette smoking with specific moods, environments, and situations; they start to smoke after a meal, with friends, or when stressed. These smoking-related cues become powerful when repeated regularly (Schwartz et al. 2010).

Nicotine is the drug in the tobacco plant that causes addiction (Nicotine - The Health Consequences of Smoking—50 Years of Progress - NCBI Bookshelf 2014). It is absorbed quickly into the bloodstream and binds to the nicotine acetylcholine receptors (nAChRs), which are located in the brain and muscles. In the brain, nAChRs release neurotransmitters, including dopamine, which is associated with a sense of pleasure and rewarding. Repeated exposure to nicotine results in the development of tolerance (neuroadaptation) to many of the effects of nicotine. The

symptoms of withdrawal and craving begin when the level of nicotine in the body decreases, which is believed to be related to the desensitisation of receptors (Nicotine - The Health Consequences of Smoking—50 Years of Progress - NCBI Bookshelf 2014). Tobacco and nicotine dependence is a substance abuse disorder, and the determinants of their addiction have been described as to other drugs, such as heroine. The treatment of nicotine dependence is based on the assessment of the degree of the dependence. The most common measurements are the Fagerström test for nicotine dependence (FTND) (Heatherton et al. 1991), or its shorter version called the heaviness of smoking index (HSI) (Heatherton et al. 1989).
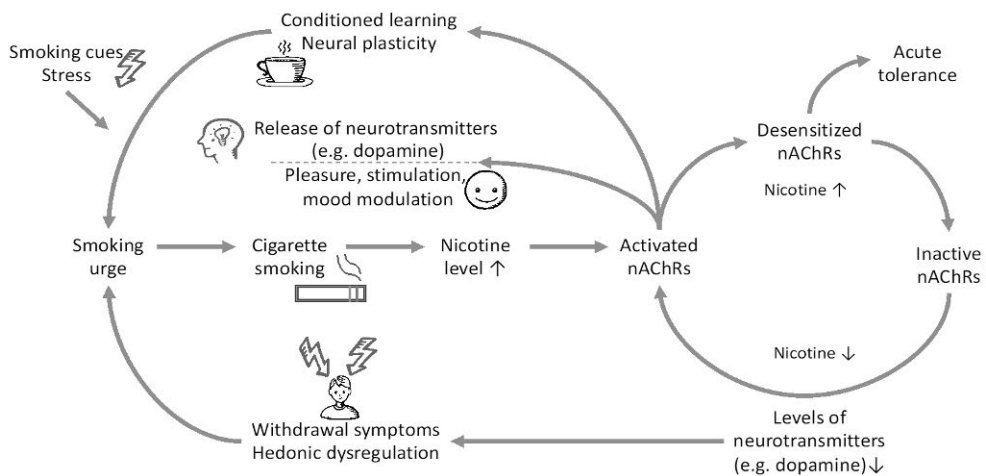
Figure 4. The mechanism of nicotine addiction. Modified from Schwartz and Benowitz (2010).

2.3.8   Smoking Cessation

Smoking cessation is one of the main goals in the management of obstructive pulmonary diseases. It is the only evidence-based treatment that improves the prognosis of COPD (Smoking Cessation: A Report of the Surgeon General. 2020). Smoking cessation also has many beneficial effects on symptoms and the effectiveness of treatment in asthma patients (Smoking Cessation: A Report of the Surgeon General. 2020). Nevertheless, the smoking cessation rates are poor both in asthma and COPD patients (Thomson 2017; van Eerd et al. 2016). Even though they are well aware of the adverse health effects of tobacco smoking, asthmatics are no more likely to receive smoking cessation assistance from a physician or smoking cessation pharmacotherapy compared to the general smoking population (Vozoris et al. 2011).

In general, a large body of evidence has established that smoking cessation has both immediate and long-term health benefits, including improved quality of life,

reduced risk for smoking-related diseases, and improved treatment outcomes in many diseases (Smoking Cessation: A Report of the Surgeon General. 2020). Around 54–68% of smokers reportedly want to quit, but only one-third of the patients get help from a physician (Babb et al. 2017; Helldán et al. 2015; Smeds et al. 2017). The first step is always to ask about smoking. A Finnish questionnaire-based study reported that 65% of physicians nearly always ask about smoking. However, only 58% of physicians documented their smoking status in electronic health records (EHR) (Keto et al. 2015). Prior studies have reported that 44–95% of patients with asthma or COPD have a smoking status documented in primary care EHR (Bailey et al. 2020; Heinmüller et al. 2020; Kaufmann et al. 2015; Lange et al. 2007). Studies in secondary health care are scarce. It is known that a brief intervention from healthcare professionals increases the quitting rates (Stead et al. 2008; West et al. 2015). The national guidelines recommend using a 5A approach in smoking cessation intervention, which includes the following steps (Figure 5) (Tobacco and Nicotine Dependency, Prevention and Treatment. Current Care Guidelines 2018):

1) Ask: Ask and record the current and previous smoking status of every patient at least once a year, as well as the type and amount of smoking. Asking about smoking signals to smokers that their smoking is important and increases the rates of clinician intervention and quitting.

2) Advice: Advice the importance of smoking cessation in a way that is clear, supportive, unambiguous, and non-confrontational. The advice is good for linking to individual health concerns.

3) Assess: Assess a smoker's readiness to quit. For smokers who have considered quitting, the assessment of the level of nicotine dependence is important to provide suitable pharmacotherapy. It can be assessed by FTND or HIS.

4) Assist: Assist the patient in planning cessation and thinking about how to reach abstinence. Consider the necessary pharmacotherapy, schedule, and support. Concrete tips are effective.

5) Arrange: Arrange follow-up, either appointment or phone call after one week, one month, and three months. Organising follow-up encourages patients in their quitting attempts and helps them cope with adversities.

Smoking affects almost every part of the body; therefore, it is important for health professionals to integrate some elements of 5A into their routine care. The most effective way is to combine pharmacotherapy with behavioural support (Stead et al. 2015). First-line pharmacotherapies for smoking cessation are nicotine replacement therapy, varenicline, and bupropion (Tobacco and Nicotine Dependency, Prevention and Treatment. Current Care Guidelines 2018). Varenicline has been shown to be

the most effective drug therapy compared to single forms of NRT and bupropion, but it is equally effective as a combination NRT (Greenhalgh et al. 2020). There are several opportunities to deliver smoking cessation interventions, such as a visit to the cessation specialist, group quit courses, telephone quit line, printed, or internet-based self-help materials, and individual counsellors. Interventions delivered by more than one type of health professional increase readiness to quit and quitting rates (An et al. 2008). In future appointments, healthcare professionals should compliment patients who successfully quit and encourage smokers who have relapsed. For individuals who are not ready for cessation, the issue of tobacco smoking should be raised regularly.

Despite the 5As procedure being included in the national guidelines for tobacco and nicotine dependency in Finland and some other countries, physicians do not always implement it in practice (Fiore et al. 2008; Keto et al. 2015; Tobacco and Nicotine Dependency, Prevention and Treatment. Current Care Guidelines 2018). The first step is most commonly conducted, but physicians are less likely to offer practical advice to quit (Meijer et al. 2019). Barriers cited by physicians include lack of time, lack of training, knowledge, attitudes, and interest (Keto et al. 2015; Meijer et al. 2019). In Finland, the majority of smoking cessation services are located in primary health care, where smoking cessation interventions are also delivered more actively than secondary health care (Keto et al. 2015). However, specialists play an important role in promoting smoking cessation when a patient is diagnosed with a chronic disease or is receiving demanding therapy.

A limited number of studies have examined the effects of smoking cessation on the clinical outcomes of asthma (Chaudhuri et al. 2006; Jang et al. 2010; Tommola et al. 2016; Tønnesen et al. 2005; Westergaard et al. 2014). Most of these studies have several limitations, such as a small sample size, short duration, and self-reported asthma diagnosis. The evidence is suggestive but not sufficient to infer that quitting reduces respiratory symptoms and improves the effectiveness of treatment and respiratory-specific quality of life among asthmatic smokers (Smoking Cessation: A Report of the Surgeon General. 2020; Westergaard et al. 2014). However, asthma patients might experience prolonged withdrawal symptoms and cravings compared to patients without asthma (McLeish et al. 2016). The count of sputum neutrophils has been reported to be higher among asthmatic smokers compared to asthma patients who do not smoke. After successful smoking cessation, sputum neutrophils have been shown to decrease (Chaudhuri et al. 2006; Westergaard et al. 2014). There is also little evidence that smoking cessation improves lung function, but most studies have included a small number of participants (Chaudhuri et al. 2006; Jang et al. 2010). Alternatively, a Finnish study with 203 asthma patients showed that after 10 pack years of smoking, the rate of lung function decline remains accelerated even when a patient quits smoking

(Tommola et al. 2016). This study further underlines the importance of early-phase smoking cessation interventions for patients with asthma.
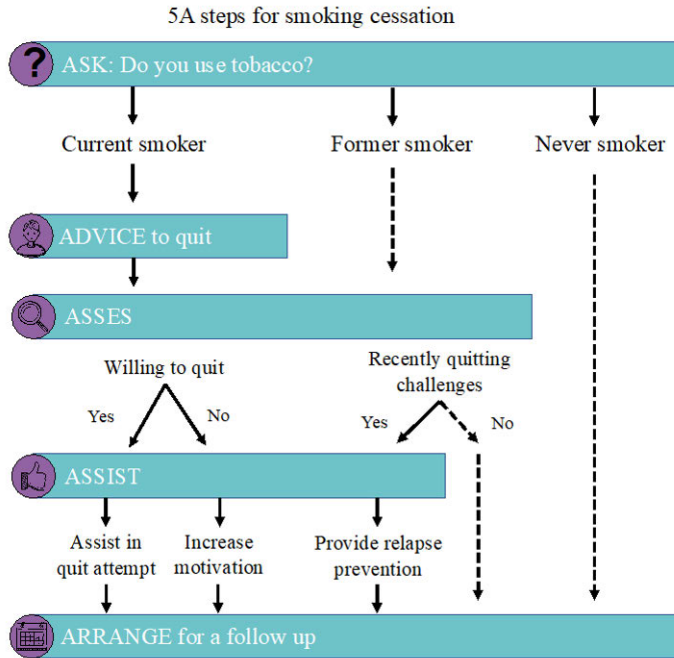
Figure 5. 5A steps for smoking cessation intervention. Modified from Ohio Smoke Free Families 2021.

2.3.9   Reliability of self-reported smoking data

The reliability of a patient's smoking history is important when evaluating smoking-related health risks and the efficacy of treatments both in research and in clinical work. Currently, the only way to collect historical data on smoking is by using self-reported questionnaires or a structured interview (Axelsson et al. 2016). Biological indicators, such as serum, plasma, and urine levels of nicotine, cotinine (Binnie et al. 2004), carbon monoxide (Pearce et al. 2005), thiocyanate (Morabia et al. 2001), and other smoke toxicants (Blank et al. 2016; Joseph et al. 2005) have been used to confirm the self-reported data, but these indicators only detect the current use of tobacco and other nicotine products (Dolcini et al. 2003).

In cross-sectional studies, the accuracy of current self-reported smoking status has been consistent with the biomarker ratings in the general population both in Finland (E Vartiainen et al. 2002) and other countries (Gorber et al. 2009; Patrick et al. 1994; West et al. 2007; Wong et al. 2012). However, more unreliability has been reported in patient populations in which smoking is considered a significant risk

factor, such as among ischaemic heart disease (From Attebring et al. 2001) and lung cancer patients (Studts et al. 2006). Also, underrated results have been observed in situations where patients experience their smoking as socially inappropriate, such as during pregnancy (Boyd et al. 1998; Campbell et al. 2001), or after receiving medical disapproval from health care providers (Patrick et al. 1994; Studts et al. 2006).

Previous longitudinal studies using self-reported smoking data have assessed the consistency and stability of responses over repeated, standardised questionnaires using 'test–retest reliability' assessment (Bernaards et al. 2001; Brigham et al. 2008; Huerta et al. 2005; Johnson et al. 2001; Soulakova et al. 2012). This indicates that the identical questions are repeated on two or more occasions. In prior studies, the test–retest interval has usually been between a few weeks and 1 to 3 months. Studies where the test–retest interval spans years are scarce (Brigham et al. 2008; Hudmon et al. 2005). To the best of our knowledge, only cross-sectional studies have been conducted in asthma and COPD.

2.3.10   Pharmacological Treatments

Beyond smoking cessation, current asthma guidelines regarding drug therapy do not differ between asthmatics who smoke and non-smokers with asthma (GINA 2020; Asthma. Current Care Guidelines 2012). In the majority of clinical asthma studies, smokers have been excluded from the analysis, and no clear evidence of effective pharmacological treatment exists. A substantial body of research has reported reduced sensitivity of ICS in smokers with asthma (Chalmers et al. 2002; Chaudhuri et al. 2003; Thomson et al. 2009; Tomlinson et al. 2005). It is known that minor exposure to cigarette smoke can induce inflammation in the small airway. The use of extra-fine-particle ICS, which deposit better into the small airways, may positively impact the efficacy and safety of inhaled corticosteroids compared to large particle ICS. Observational studies have suggested using extra-fine particle ICS, which may achieve better symptom control with lower prescribed doses (Roche et al. 2015). The addition of LABA has been proven to be beneficial for smokers with asthma and is probably a more preferable option than increasing the dose of ICS (Polosa et al. 2013). One controlled trial in smokers with asthma studied the effectiveness of fluticasone propionate and Montelukast over six months. Patients with a smoking history of ≤ 11 pack-years tended to show better symptom control with fluticasone, whereas patients with a smoking history >11 pack-years tended to have more benefit with montelukast (Price et al. 2013). In 2015, the Global Initiative for Asthma guidelines included the long-acting muscarinic antagonist tiotropium as an alternative add-on therapy for patients with a history of exacerbations. Tiotropium has a good and sustained bronchodilator effect in non-eosinophilic asthma and could be effective in the treatment of smokers with asthma (Cheng et al. 2018). However,

current smokers and ex-smokers with a smoking history of more than 10 pack years were excluded from all clinical trials of tiotropium, which makes it difficult to apply these results to the therapy of smokers with asthma. There is little evidence for the effectiveness of tiotropium in two real-life studies in which current smokers and ex-smokers with asthma were included (Cheng et al. 2018; Price et al. 2015).

2.3.11 Non-Pharmacological Treatments

Non-pharmacological therapies are an important part of the treatment in asthma patients. The common non-pharmacological treatments in addition to smoking cessation include physical activity, breathing exercises, healthy diet, weight reduction in obese patients, avoidance of medication that may worsen asthma, such as non-steroidal anti-inflammatory drugs, and avoidance of exposures, indoor allergens, and air pollution (GINA 2020).

Complementary and alternative medicine (CAM) is a diverse group of practices, interventions, and products that are not considered part of the usual care. These therapies usually address lifestyle issues and aim to reduce withdrawal symptoms, develop a balance between mind and body, and relieve stress. Alternative therapies for smoking cessation include acupuncture, hypnotherapy, exercise, aversive conditioning, and transcranial magnetic stimulation.

Acupuncture and related therapies, including acupressure, laser therapy, and electrical stimulation, aim to stimulate acupuncture points on the body with or without needles. A Cochrane review from 2014 concluded that, although there is some evidence for short-term effects, there is no consistent and bias-free evidence that acupuncture, laser therapy, or acupressure are effective with regard to long-term smoking cessation (White et al. 2014). The review also concluded that electrostimulation was not effective for smoking cessation. The authors suggested building more robust studies since these types of interventions are popular, although when used alone they are less effective than evidence-based strategies. Similar findings were found in a recent systematic review and meta-analysis of 24 randomised controlled trials (J. H. Wang et al. 2019). The authors concluded that acupuncture as monotherapy was less effective than acupuncture combined with an educational smoking cessation programme, counselling, or moxibustion for long-term smoking cessation. They also underlined the need for high-quality trials.

Hypnotherapy is often promoted as a good method to quit smoking. It aims to weaken smokers' desire to smoke, strengthen their will to stop, and, overall, help people to concentrate on a cessation program. A 2019 Cochrane review concluded that evidence is insufficient to determine whether hypnotherapy has a greater effect on decreased quit rates than other behavioural interventions or no treatment (J. Barnes et al. 2019). Additionally, the current evidence suggests that the possible

benefit is rather small. Studies concerning the adverse effects of hypnotherapy are rare, and no disadvantages have been found (Dickson-Spillmann et al. 2013).

Regular exercise has been suggested to help smokers quit tobacco smoking. In particular, exercise appears to reduce smoking withdrawal symptoms and cravings while controlling weight gain. Despite this assumption, a 2019 Cochrane review of exercise interventions for smoking cessation found no evidence that exercise combined with smoking cessation support improved abstinence compared to cessation support alone (Ussher et al. 2019). However, the authors report that evidence is insufficient to evaluate whether a modest benefit exists.

Yoga includes physical, mental, and spiritual practices that aim to create a balance between the human mind and body. A growing body of evidence supports the idea that yoga is beneficial for both physical and mental health (Gothe et al. 2019; O'Neill et al. 2020). A review of yoga interventions for smoking cessation found that yoga seems to be a promising method for smoking cessation (Dai et al. 2014). In most of the studies, yoga was found to increase quit rates, but the authors underlined the need for high-quality research (Dai et al. 2014).

Aversive conditioning is a method in which an unwanted behaviour is paired with an unpleasant stimulus. There are many reported aversion methods for smoking cessation, such as rapid smoking (smokers take a puff every few seconds to make smoking unpleasant), covert sensitisation (smoking while imagining unpleasant associations), and pairing smoking or urges to smoke with other unpleasant methods or products. A 2004 Cochrane review concluded that evidence is insufficient to determine the efficacy of rapid smoking, and that other versions of aversive smoking are not effective (Hajek et al. 2001).

Repetitive transcranial magnetic stimulation (rTMS) has recently been proposed as a potential therapy for tobacco addiction (Abdelrahman et al. 2021). It is believed to reset the reorganisation of brain circuits caused by the long-term use of nicotine (Thickbroom 2007). The target area is often the dorsolateral prefrontal cortical region (DLPFC). The left DLPFC (L-DLPFC) is known as a critical area in the process of cigarette craving, and based on magnetic resonance imaging, active smokers have reported hypoactivation in the same area (McBride et al. 2006; Nestor et al. 2011). In particular, high-frequency rTMS has been shown to be effective in the treatment of smoking addiction by decreasing craving and relieving withdrawal symptoms during abstinence of smoking (Abdelrahman et al. 2021; Dinur-Klein et al. 2014; Li et al. 2017).

2.4 Novel Text Mining Methods for Building the Foundation for Evidence-Based Medicine

Text mining, also known as text data mining, is the process by which high-quality information is derived from textual data (Hearst 1999). In the field of medicine, text mining creates an opportunity to derive previously unknown and valuable insights from medical data for the foundation of evidence-based medicine. Nowadays, electronic health records (EHR) contain an increasing amount of medical information in a digital format that can be used to advance research, support clinical decision-making, and measure the quality of systems. However, the majority of the clinical data are documented as free text to medical narratives, causing challenges for data analysis (Jensen et al. 2017). Historically, unstructured data have been extracted manually and transformed into a structured format, but it is rather time-consuming and expensive. The development of natural language processing (NLP) methods has improved these processes (Collobert et al. 2011). NLP is a field of artificial intelligence (AI) that allows machines to read, understand, and interpret human language. Simplified, NLP can extract clinical text and automatically transform it into clean and structured data for machine learning algorithms. It can also be used to support traditional research methods, for example, by extracting blood pressure values, medications, and spirometry results from texts. The use of NLP in the clinical domain is increasing, and many successful applications have been reported, such as predicting the onset of gestational diabetes from EHR (Artzi et al. 2020; Sheikhalishahi et al. 2019). In Finland, simple methods using structured data have been used in the clinical domain, such as the Evidence-Based Medicine Electronic Decision Support (EBMEDS) system, which was developed by Duodecim (Evidence-Based Medicine Electronic Decision Support, EBMeDS. EBMeDS White Paper 2020). EBMEDS can be integrated into EHRs to support clinical decision making. EBMEDS receives patient data from EHRs and returns reminders, therapeutic suggestions, and diagnosis-specific links to guidelines. At the moment, EBMEDS is based on simple rules. By contrast, NLP tools can read and interpret free text, and could potentially provide structured input data for decision support systems, such as for EBMEDS. However, the development of NLP systems is challenging because the Finnish language is unique, and international models cannot be utilised in text mining in the same way as in pathology and radiology. Overall, the ultimate goal of text mining is to discover NLP applications that can guide clinical decision making, offer a better understanding of patient clinical trajectories, and even prevent disease onset.

2.4.1 Machine Learning and Deep Learning

Machine learning is a subset of artificial intelligence in which machines are trained to learn for themselves (Murphy 2012). They learn from experience, which is developed through the given data. Notably, machine learning can obtain new insights from given data without the need to specify them a priori. However, in contrast to deep learning, traditional machine learning algorithms require human effort in feature engineering (Figure 6).
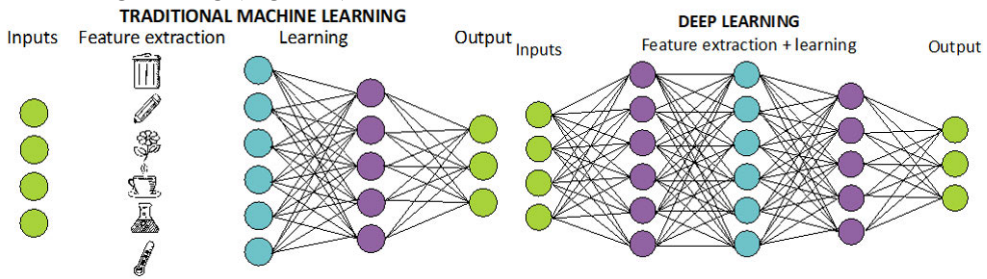

Figure 6. Comparison of traditional machine learning, and deep learning. In traditional machine learning, feature extraction needs human effort, whereas in deep learning it is done automatically through a neural network. Deep learning requires a large body of data to eliminate fluctuation and to perform properly. Deep learning consists of multiple layers of artificial neural networks that are complex and can be compared to the human brain.

In medical text processing tasks, machine learning algorithms can be used, for example, to extract valuable information from EHR. In general, machine learning techniques are based on five steps: pre-processing (e.g., segmentation, tokenisation, stemming), feature extraction, training, evaluation, and performance improvement. In pre-processing, unstructured input data are cleaned, integrated from different sources, reduced to gain a smaller dataset size, and transformed into a united form (Sun et al. 2018). The pre-processing is conducted with NLP techniques such as tokenization, lemmatization, and stemming. Tokenization refers to a process of separating the text into smaller units called tokens, lemmatization means converting words to their base forms, and stemming is a process of reducing words to their word stems by removing suffixes. Simplified, pre-processing results in cleaned text that can be described as numbers and analysed by algorithms.

Machine learning approaches have garnered a lot of interest due to their effectiveness and success in many tasks (Wang et al. 2018). Most machine learning algorithms can be divided into two main categories: supervised or predictive, and unsupervised or descriptive models (Murphy 2012). There is also a third type of machine learning—reinforcement learning—which is used less commonly. In supervised learning, the target is known, and the model is used to predict the future result. The input data includes information and answers; therefore, the model has clear instruction on what to learn. In the field of medicine, supervised learning is

used, for example, in cancer classification (Gao et al. 2015). In unsupervised learning, the target is unknown, and the model is used to find useful information hidden in the data. Traditionally supervised learning has further subdivided into regression and classification problems according to the type of predicted variable (continuous or categorical). Similarly, unsupervised learning can also be subdivided into cluster analysis, density estimation, and dimension reduction (Murphy 2012).

All machine learning algorithms need to be trained before performing optimally (Murphy 2012). In the training process, the machine learns data properties from the training data and improves the model until it reaches its best performance. Testing data are used to apply the learned properties to new data and to compare the results with the known answers. In the latter phase, the model no longer changes; only its performance is tested. If it works as desired, the model is ready for real application.
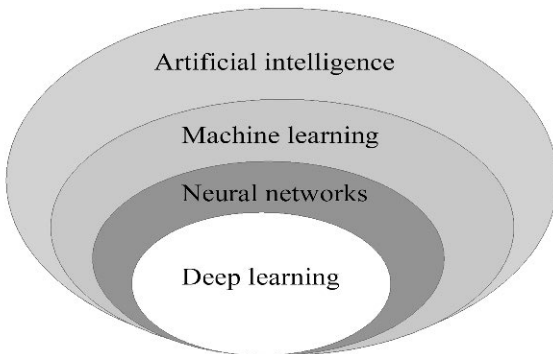
Figure 7. The relation between artificial intelligence, machine learning, neural networks, and deep learning.

Deep learning is a subfield of machine learning, and it is based on artificial neural networks (ANN) with feature learning or representation learning (Figure 7) (Lecun et al. 2015). Compared to a traditional ANN that contains 2–3 hidden layers, deep learning consists of multiple processing layers in a neural network (Goodfellow et al. 2016). Each of these levels learns to transform the input data into a more composite and abstract representation for the next layer. Deep neural networks also have the capability to learn the deeper structure of the data, and the learned representations are generalisable. One important advantage is also scalability. The performance of deep learning models typically continues to increase as more data are used for training. This is usually different from older machine learning algorithms, which yield a plateau in their performances. At the moment, deep learning is a state-of-the-art method for several applications.

Deep learning involves a variety of types of algorithms that use different techniques and are suitable for different tasks. The most popular techniques are convolutional neural networks, recurrent neural networks, and transformers (Fu et al. 2019). The differences are based on interlayer connections and neuronal function. Altogether, in many problems, a combination of different algorithms, such as deep

learning algorithms and traditional machine learning models, leads to the best results. Machine learning algorithms can be combined with rule-based algorithms, which are known as a hybrid approach (Fu et al. 2019).

All deep learning algorithms also need training before performing optimally. Training can start from scratch, which requires the design of network architecture and the collection of a large labelled dataset. This approach can be used for new applications, but it usually takes days or weeks to train. Nowadays, a more common way is to use transfer learning, which can take only minutes or hours to train the model (Pan et al. 2010).

2.4.2   Transfer Learning

Transfer learning refers to a method in which a model developed to solve one task is reused on the basis of solving a second, somehow similar task (Pan et al. 2010). In traditional machine learning, the task and the domain of the training and testing set are the same and are not generalisable (Figure 8). These models need a large labelled dataset for training and perform well only on unseen data from the same domain. In traditional machine learning, it is not possible to transfer knowledge from one model to another model, whereas in transfer learning, the task and domain used for training and testing can be different (Ruder 2017). The knowledge learned from one model is stored and applied to a different, but somehow similar task. For example, a model trained for language modelling (predicting the next word in a sentence) on Wikipedia can be used on the basis of text classification in EHR. Transfer learning is also widely used in other medical domains than text processing, such as in medical imaging (Chan et al. 2020). Overall, transfer learning consists of two main training stages: pre-training, where the network is generally trained on a large dataset including a wide range of categories, and fine-tuning, where a pre-trained model is further trained on the target task of interest with labelled data (Ruder et al. 2019).
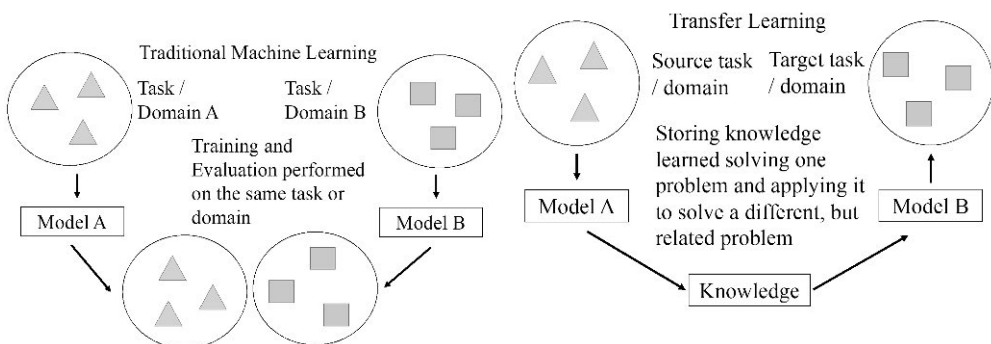

Figure 8.   The difference between traditional machine learning and transfer learning. Modified from Ruder 2017.

Transfer learning is not a new phenomenon in NLP, but in the form of pre-trained language models, it has become revolutionary. Today, the most commonly used types of transfer learning in NLP can be roughly classified based on differences in tasks, domains, and learning styles (Figure 9).
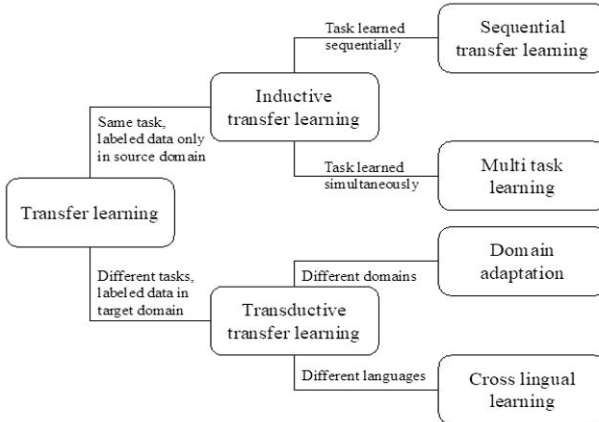
Figure 9. The most commonly used type of transfer learning. Modified from Ruder 2019.

The sequential transfer learning technique has led to the greatest results so far (Ruder et al. 2019). The general procedure includes pretraining and adaptation, where representations are first pre-trained using a large, unlabelled training set and then adapted to a supervised target setting using labelled data (Ruder et al. 2019). One of the most considerable advantages of pretraining is that the need for labelled data reduces. Moreover, the pre-trained representations can be improved by simply increasing the volume of the pre-trained data and the number of parameters used in the model (Ruder et al. 2019). The adaptation of a pre-trained model to a target task can be performed in different directions, such as architectural modification and optimisation schemes. In an architectural modification, the internals of a pre-trained model can be kept unchanged, or they can be modified. In an optimisation scheme, the scientist can decide which weights to update, when, and how to update those weights. Representations can be directly encoded with the model, or the model can be fine-tuned on the target task (Ruder et al. 2019).

2.4.3 ULMFiT

Universal language model fine-tuning (ULMFiT) is a transfer learning method developed by Jeremy Howard and Sebastian Ruder in 2018 (Howard et al. 2018). It can be used in various NLP tasks, but it is mostly used for text classification. ULMFiT is trained on a large amount of unlabelled data in the target language. This knowledge is then used to build a classification model using a typically much smaller labelled dataset in the target language. In the medical field, ULMFiT has been used, for example, to classify the severity of radiation oncology incident reports (Syed et

al. 2020) and to identify metastatic cancer patients from clinical notes (Swaminathan et al. 2020).

Since ULMFiT, various other models have been developed, such as BERT (Devlin et al. 2018), GPT-2 (Radford et al. 2019) and GPT-3 (Brown et al. 2020), ELMo (M. E. Peters et al. 2018), XLM (Lample et al. 2019) and ELECTRA (Clark et al. 2020). Currently, top models typically use transformer blocks, which are specific kinds of neural nets especially suitable for text processing (Ruder et al. 2019).

The area of deep learning is growing fast. For example, after BERT was released in 2018, several models based on BERT were developed, such as RoBERTa created by Facebook (Liu et al. 2019), ALBERT created by Google (Lan et al. 2019) and the Finnish version FinBERT (A. Virtanen et al. 2019). In 2019, a biomedical language representation model, BioBERT, was developed for biomedical text mining tasks (Lee et al. 2020). It was trained from scratch using PubMed and PubMed Central articles. One of the most recent models, GPT-3, was released in July 2020 (Brown et al. 2020). It has been built on 175 billion parameters and is the most complex and biggest language model ever trained. GPT-3 does not need fine-tuning on specific data and can understand the desired task with only a small number of initial examples. GPT-3 has already been tested in many tasks in healthcare, but at the moment, it is not ready yet. However, in the future, GPT-3-like approaches could significantly help healthcare in several tasks, such as in more complicated chatbots, automatic consulting, diagnostic, summarising complicated texts, and advancing research.

3 Aims

The specific aims of the study were as follows:

1. To investigate the consistency of the responses of asthma and COPD patients to repeated questions concerning their smoking history. The standardised questions regarding the present smoking status, starting, and quitting year, and the amount of tobacco consumed were enquired six times over a period of ten years. (Study I)

2. To study the development of work ability score (WAS) among asthma patients in a longitudinal setting to find asthma and other health-related risk factors for poor development of WAS. (Study II)

3. To understand the relationship between WAS and health-related quality of life instruments 15D and AQ20. (Study II)

4. To examine whether the documentation of smoking status, as well as the guidance to smoking cessation, has improved in asthma and COPD patients over a nine-year period at Turku University Hospital. (Study III)

5. To study the performance of an ULMFiT-based smoking algorithm in classifying patients' smoking status of current, ex- and never smokers. (Study III)

4 Materials and Methods

4.1 Study Subjects

4.1.1 Studies I and II

The study population of the Studies I and II represent subpopulations of the Finnish Chronic Obstructive Airway Disease (CAD) cohort. This two-centre, mainly survey-based, 10-year follow-up study was conducted between 2005 and 2017. The CAD cohort originally comprised 2390 asthma and COPD patients who enrolled in the study through the Pulmonary Clinics of the Helsinki (N = 2054) and Turku University Hospitals (N = 336) during the years 2005-2007. The patients were extracted from the hospital discharge registers using ICD10 code J44.8 or J45. All patients aged 18 to 75 years were invited to participate in the study through a two-phase mailing campaign.

At the beginning of the study, all participants visited the research nurse once. They donated their blood samples for DNA extraction and gave their informed consent for the study. Thereafter, the participants were followed by a mailed questionnaire in years 1, 2, 4, 6, 8, and 10.
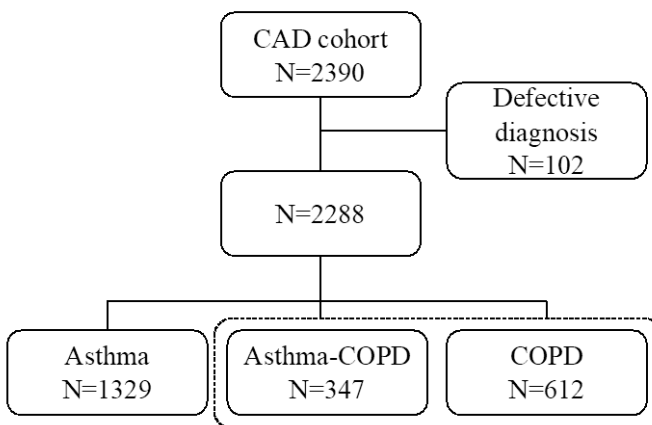
Figure 10. Flow chart of the study population in Study I. Asthma-COPD overlap and COPD groups were combined for analysis.

A recruitment diagnosis of all patients was reassessed by a pulmonologist: asthma, COPD, or asthma-COPD overlap showing the features of both diseases (GINA 2020; GOLD 2020; Laitinen et al. 2009). In Study I, 102 patients were excluded due to defective or poorly documented diagnosis; thus, the study population comprised of 2,288 subjects (Figure 10). COPD and asthma-COPD overlap groups were combined, since there was no significant difference between the groups. In Study II, our aim was to study work ability among asthma patients. First, we excluded 102 patients with defective diagnoses and 959 patients with COPD (Figure 11). The average age of COPD patients was higher, and the majority of patients were retired at baseline or retired during the first years of follow-up. Next, we evaluated the patients' work ability scores (WAS) over the follow-up. All the patients who had reported their WAS in at least three of the six questionnaires while being actively employed (N = 529) were included in Study II.
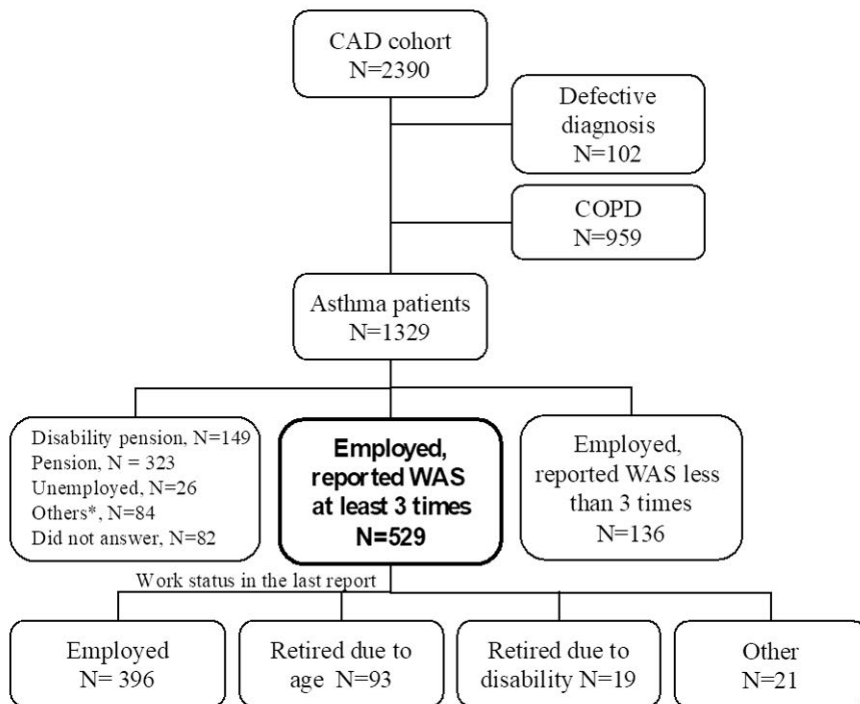
*Other: student, maternity leave, paternity leave, unemployed

Figure 11. Flow chart of the study population in Study II.

4.1.2   Study III

Study III was a register-based follow-up study based on the Turku University hospital discharge register. We selected all narrative reports of the patients who were over 18 years of age and diagnosed with asthma (ICD10 codes J45–46), chronic obstructive pulmonary disease (COPD, J44), type 1 diabetes (E10), type 2 diabetes (E11), sleep apnoea (G47), ischemic heart diseases (IHD I20-25), or cerebral infarction (I63) between 2010 and 2016 (Figure 12). The study subjects were either diagnosed for the first time with the disease or referred to a specialist for the treatment optimisation. The medical narratives of the patients were then followed for two years. All patients with more than one of the above-mentioned diagnoses were included only in the group defined by the diagnosis that appeared first.
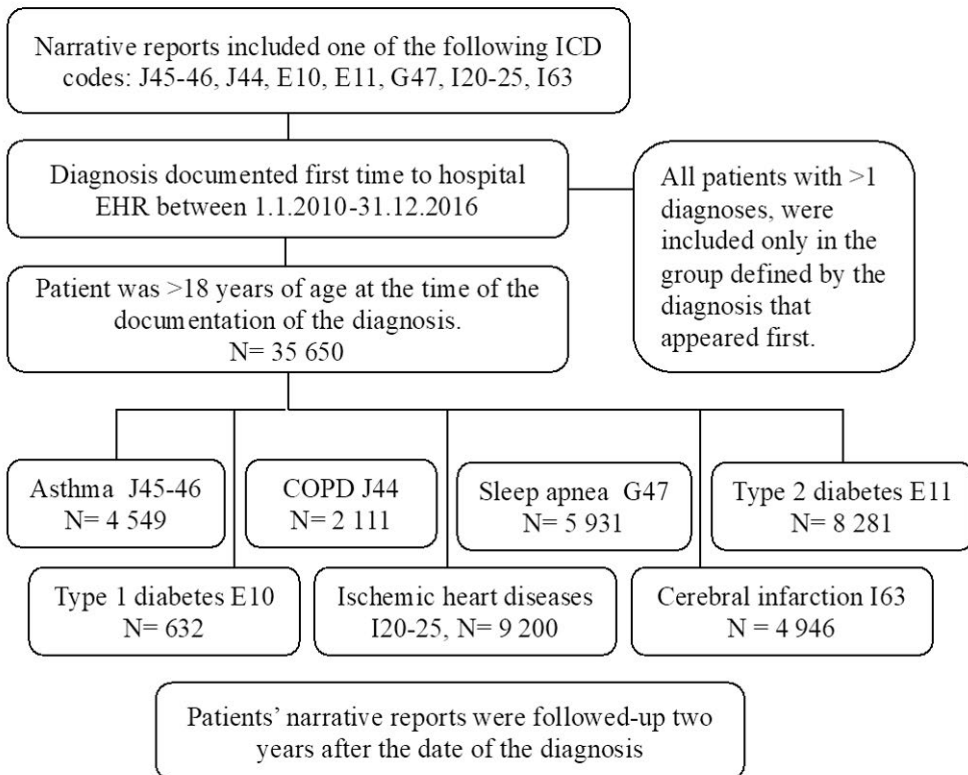

Figure 12. Flow chart of the study population in Study III.

4.2 Methods

4.2.1 Studies I and II

4.2.1.1 Patient Characteristics

At the baseline, lung function tests, age at onset of the disease, and BMI were retrospectively evaluated based on the patients' medical records from all health care providers (hospitals, health care centres, outpatient clinics) that had treated the patient in the past 5 years. Similarly, 10 common comorbidities were retrospectively assessed: hypertension, hyperlipidaemia, cardiovascular disease (CVD; including coronary, cerebrovascular, and peripheral arterial disease), diabetes type 1 and 2, alcohol abuse, psychiatric conditions, cancer, hypothyroidism, atrial fibrillation, and gastroesophageal reflux disease (GERD) (Koskela et al. 2014). The comorbidity was considered only when the patient used regular medication at the baseline (except cancer and alcohol abuse). The number of these diseases was summed up to describe a rough estimate of the extent of comorbidities. Finnish reference values of Viljanen et al. (1982) were used for FEV1 and FVC. Adult onset asthma was defined as onset at older than 20 years of age.

4.2.1.2 Questionnaire

A follow-up questionnaire was mailed to the study subjects 1, 2, 4, 6, 8, and 10 years after recruitment, always at the same time of the year for each patient (+/- 1 month) (Appendices 1). Postal addresses were updated every year using the population register, and one reminder was sent if a patient did not answer within four weeks. The participants could withdraw from the study at any time. Deaths were followed from the population registry.

The questionnaire always included two validated HRQoL instruments, the 15D (Sintonen 2001) and the Airway Questionnaire 20 (AQ20) (Barley et al. 1998), as well as questions about smoking and work ability. These sections were identical each year. A section of current medication was added in the fourth follow-up year and a standard pattern of chronic bronchitis-related questions was added in the eighth follow-up year. Fageström's test for nicotine dependence (Heatherton et al. 1991) was required once, as well as a separate questionnaire on exercise habits and physical activity among patients in the COPD or Asthma-COPD overlap cohort.

4.2.1.3   Health-Related Quality of Life (HRQoL)

The questionnaire included two HRQoL instrument, 15D, and AQ20, which measured general and disease-specific health-related quality of life (HRQoL), respectively. The 15D score summed up the 15-dimensional description of patient health status and was scaled from 0 (being dead) to 1 (no problem with any dimension, full HRQoL). The minimum clinically important change/difference in the 15D scores has been estimated to be 0.015 (Alanne et al. 2015). The AQ20 instrument contained 20 items, and a summary score ranged from 0 (no airway symptoms) to 20 (multiple airway symptoms). The participants completed both HRQoL instruments the first time they were enrolled (year 0).

4.2.1.4   Work Ability

The work section of the questionnaire included five questions. First, the patients chose their current work status from the list: full-time work, part-time work, disability pension, retired due to age, student, unemployed, maternity/paternity leave, and other (open question). The rest of the questions in this section were addressed only for patients working full or part time. Work type was classified as physical, mental, or a combination of both. The patients reported their current work ability compared to their lifetime best. We used a validated instrument called the work ability score (WAS), which is scaled from 0 (completely unable to work) to 10 (work ability at its best) (Tuomi et al. 1998). The sick leaves during the last 12 months were categorised as: not at all, 1–9 days, 10–24 days, 25–99 days, or 100–365 days.

4.2.1.5   Smoking

In the smoking section, participants were investigated regarding their current smoking status, whether they had never been regular smokers, were current regular smokers, or were former regular smokers. Thereafter, smokers reported their starting and potential stopping year, as well as the type (cigarettes, cigars, pipes, hand-rolled cigarettes) and amount of tobacco products they smoked or had smoked. Based on the data from the first questionnaire, pack years were calculated to measure lifetime exposure to tobacco (D. M. Wood et al. 2005). One pack year equalled 20 cigarettes smoked per day for one year. The other tobacco products were transformed into cigarettes as follows: one cigar was equal to four cigarettes; one cigarillo was equal to two cigarettes; and one gram of loose tobacco was equal to two cigarettes (D. M. Wood et al. 2005). A heavy smoker was defined as a person who smoked a pack or more per day. Similar question patterns have been used in several Finnish epidemiological studies (Laatikainen et al. 2003). A complete smoking-related data

set, including the starting (and quitting) year as well as the number of cigarettes, was available for 1128 patients out of the 1360 former or current smokers in the first follow-up year.

To analyse the consistency of the reported smoking statuses over the follow-up period, we chose all the patients who had answered the smoking-related questions at least three times during the follow-up, regardless of which survey year. In total, 1154 asthma patients and 698 COPD patients fulfilled the criteria. By selecting this subgroup for the analysis, we were able to better distinguish the different trends and thus improve the reliability of the results. Next, we divided the participants into four groups:

- (1) A stable group that consistently reported the same status throughout the follow-up
- (2) Unstable type 1 group that changed the status once
- (3) Unstable type 2 group that changed the status more than once
- (4) Unreliable group that reported first being a current or a former smoker but later claiming to be a never-smoker

To evaluate the changes in smoking behaviour during the follow-up, we used this same subgroup for the analyses; that is, we excluded all the patients who had reported their smoking statuses only once (the analyses of changes not possible) or twice (the responses gave mainly in the first and second follow-up year). This enabled us to obtain more reliable results covering the overall follow-up period.

4.2.1.6   Medication

A structured section regarding the participant's current asthma and allergy medication was added to the questionnaire from the fourth year onwards. Other regular medication-related questions were asked an open question. All asthma products and drug strengths in the Finnish market were shown in a complete list (Appendices 1). New products were added each follow-up year.

For the comparison of different inhaled corticosteroids (ICS), all products were transformed into fluticasone propionate dose equivalents using the following transformation: 1ug fluticasone propionate (dry powder inhaler (DPI), hydrofluoroalkane (HFA)) equals to 0.18 µg fluticasone furoate (DPI), to 0.64 µg ciclesonide (HFA), to 0.8 µg mometasone furoate, to 0.8 µg beclomethasone dipropionate (HFA), to 1.28 µg budesonide, to 1.60 µg budesonide (DPI), and to 1.60 µg beclomethasone, respectively (GINA 2020).

The use of oral corticosteroids (OCS), short-acting beta agonist (SABA), and allergy medication were enquired with the multiple-choice questions. The courses of

OCS used for exacerbation of asthma were classified into five categories: not at all, once, twice, three, and five or more times during the last year. The use of SABA when needed was classified into six categories: not at all, once a week or less, 2–4 times per week, every day, at least two times per day, or acute symptoms treated by long-acting beta-agonists alone; use of antihistamines into three categories: not at all, one packet/10-12 pills, two or more packets during the last year; and the use of nasal corticosteroids into three categories: not at all, one dispenser, two or more dispensers during the last year.

The definition of severe asthma was based on medication: a high dose of ICS and with at least one second controller, such as a leukotriene receptor antagonist, theophylline, cromones, OCS, or biological drug in use (Chung et al. 2014). According to the International ERS/ATS guideline, high dose of ICS (µg) is defined as follows (Chung et al. 2014):

- Beclomethasone dipropionate ≥2000 (DPI or chlorofluorocarbon metered-dose inhaler (MDI)) or ≥1000 (HFA MDI) or,

- Budesonide ≥1600 (MDI or DPI) or,

- Ciclesonide ≥320 (HFA MDI) or,

- Fluticasone propionate ≥1000 (HFA MDI or DPI) or,

- Mometasone furoate ≥800 (DPI)

4.2.1.7 Dyspnoea and Chronic Bronchitis

Three questions about dyspnoea and chronic bronchitis were included in the questionnaire from the eighth year onwards. The participants were asked how often they had shortness of breath: only under very heavy exertion; only when rushing or uphill; I have to walk slower than my age and stop sometimes when walking on a flat ground; I can only walk about 100 m or a few minutes before I have to stop or daily during normal activities.

A standard pattern of chronic bronchitis-related questions was used to evaluate chronic cough. The patients were asked if they have had a cough in which they brought up sputum/phlegm almost daily for at least 3 months in a year, and how long it lasted.

4.2.2   Study III

4.2.2.1   Identification of the Smoking Status

All smoking-related phrases that were documented within two years of the date of the diagnosis were extracted from the medical narratives using a rule-based algorithm 1 (Table 5). The algorithm also recognised the Finnish word for e-cigarette. Then, these sentences were classified with an ULMFiT-based algorithm into three classes: current smoker, ex-smoker, or never smoker. The ULMFiT-based algorithm was pre-trained using Finnish Wikipedia 2019 and then fine-tuned using 5,000 manually annotated smoking-related phrases (Figure 13). To validate the performance of the algorithm in the particular disease groups studied here, a total of 240 random patients, 40 from each of the six disease groups, were classified in a similar way by one physician (EH). If the smoking status of the patients changed over time, the most frequently occurring status was included in the study.
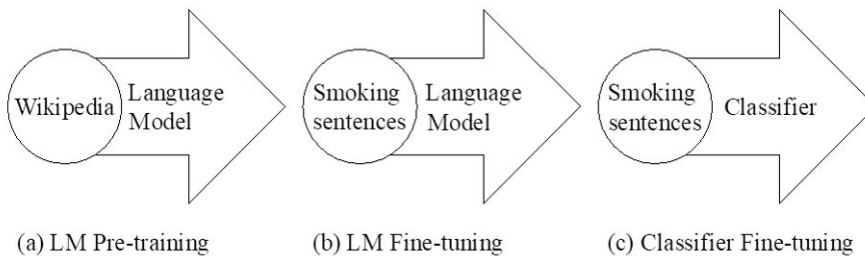
Figure 13. Training of the ULMFIT-based smoking algorithm involved three major stages. (a) First, the language model (LM) was pre-trained using Finnish Wikipedia to learn the structure and general features of the Finnish language. (b) Second, the model was fine-tuned using the smoking related sentences to specialise the model into the domain specific language. (c) Third, the classifier was built on the top of the fine-tuned LM using a 5000 manually annotated smoking related phrases. Modified from nlp.fast.ai.

4.2.2.2   Smoking Cessation Intervention

To identify patients who were encouraged to quit smoking, we extracted all corresponding sentences from the medical narratives using a rule-based algorithm 2. The rules were produced ad hoc from Finnish terms describing discussion/encouragement to quit smoking. The algorithm was manually validated using a random sample of 50 patients classified as current smokers and having an intervention sentence in EHR and 50 patients classified as current smokers but no intervention sentence. Furthermore, the number of visits to the nurse-managed smoking cessation programme of Turku University Hospital was evaluated based on the patients' medical records.

Table 5.   Functions of the three algorithms used in Study III

Algorithm	Function
Rule-based algorithm 1	Identification of smoking-related sentences from EHR
ULMFiT-based algorithm	Classification of sentences including smoking status: current smoker, former smoker, never smoker
Rule-based algorithm 2	Identification of sentences where patient was encouraged to quit smoking

4.3   Statistics

In all studies, continuous variables were presented as means and standard deviation (SD) for normally distributed variables or medians, and interquartile range (IQR) for non-normally distributed. Categorial variables are shown as frequencies and percentages (%). Statistical comparisons between groups were made by using a Chi-squared test for categorical variables, and either a t-test, a one-way ANOVA, or a Kruskal-Wallis test for continuous variables. A Mann–Whitney U test was used for pairwise comparison if a significant difference was observed in the Kruskal–Wallis test with Bonferroni correction. Statistical significance was considered as a *p* value <0.05. Analysis was performed using IBM SPSS Statistics for Mac, version 24.0 (SPSS Inc., Chicago, IL), Excel for Windows (2013), Excel for Mac (2018), and the R-package kmlShape version 0.9.5 (Genolini, Ecochard, et al. 2016; Genolini, Guichard 2016).

4.3.1   Study I

An intraclass correlation coefficient (ICC) was used to estimate consistency between the reported starting and stopping years, as well as the number of reported cigarettes smoked by a person per a day. All ICC values and their 95% confidence intervals were calculated using SPSS based on a single-rating, absolute-agreement, 2-way mixed-effects model. The interpretation of ICC values was done according to the guidelines: values ≥0.90 were defined as excellent; 0.75 to 0.89 were defined as good; 0.50 to 0.74 were defined as moderate; and values less than 0.50 were defined as poor (Koo et al. 2016).

4.3.2   Study II

The development of WAS over time was analysed by computing the discrete Fréchet distance, which describes the similarity between the shapes of WAS curves (Fréchet

1906). The clustering was conducted using different choices for the number of clusters. The average WAS curves inside the clusters were manually inspected, and a suitable number of clusters was chosen to be four. Compared to some other approaches, Fréchet distance leads to more conservative results, but it is not affected by missing values (Gong et al. 2019).

The risk factors for the poor development of WAS were assessed using logistic regression. We chose several baseline clinical characteristics as predictors and conducted both univariate and gender- and age-adjusted multivariate, logistic regression analyses. In univariate models, only one predictor was included to each model. The multivariate models always included age, gender, and one of the clinical characteristics. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI).

Trends in 15D and AQ20 scores were analysed separately using a hierarchical linear mixed model, where time (fixed effects) and cluster were factors in the model. Cluster x time interaction was also included in the model to examine whether the mean change over time was different between four clusters. Compound symmetry covariance structure was used for repeated measures. Data included some missing values, but they were assumed to be completely at random. The correlations between WAS, 15D, and AQ20 were calculated using Spearman's correlation coefficient.

4.3.3   Study III

To evaluate the performance of the three algorithms used in study III, we built a 2 × 2 confusion matrix with labels true positive (TP), true negative (TN), false positive (FP), and false negative (FN) (Figure 14). We compared the physician's classification (actual values) to the algorithm's results to calculate accuracy, precision, recall, and *F1* score.

Figure 14. Confusion matrix

Accuracy (Equation 1) defines the fraction of correctly classified sentences (TP + TN) about the total number of sentences.

$$(Equation\ 1)\ \frac{TP + TN}{TP + TN + FP + FN}$$

Precision (Equation 2) describes the accuracy for positive example predictions; for example, how many of the sentences that the algorithm classified as positive were actual positive.

$$(Equation\ 2)\frac{TP}{TP + FP}$$

Recall (Equation 3) is the proportion of correctly predicted true values of all true values; for example, how many of the positive examples did the algorithm get right.

$$(Equation\ 3)\frac{TP}{TP + FN}$$

The F score or $F1$ score (Equation 4) combines the properties of precision and recall into a single value. It is commonly used to describe the performance of machine learning algorithms.

$$(Equation\ 4)\ F = \frac{2}{1/recall + 1/precision}$$

The performance of the ULMFiT classifier was studied separately for current, ex- and non-smokers.

4.1　　Ethics

The protocol of studies I and II was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District, with permission to conduct this research granted by the Helsinki and Turku University Hospitals. All participants gave their written informed consent for the study, including permission to collect, merge, and analyse their comprehensive medical records for the past 5–10 years and ten forthcoming years.

The approach of Study III was registered and approved by the administration of Turku University Hospital. The data were stored in a secured server within the hospital firewall, and only personnel of the study team had access to the data through the personal login and password of the hospital network. All studies were performed in accordance with the Declaration of Helsinki (2008).

4.4 CAD Cohort (Studies I and II)

4.4.1 Characteristics of the Participants

Clinical characteristics of the CAD cohort (Study I) are presented in Table 6. The cohort consisted of 1,329 asthma and 959 COPD patients who lived in South-Western Finland. The majority of asthma patients were women (74%), while a large proportion of COPD patients were men (61%). At baseline, the average age of the asthma patients was 55 years, whereas the COPD patients were almost 10 years older (mean 64).

The study population of Study II represented a subpopulation of CAD cohort. To analyse the development of the WAS over time, we included in the study only participants who had reported their WAS in at least three out of six questionnaires while being actively employed (N = 529) (Figure 11). Out of all patients, 82 patients reported WAS 3 times, 99 patients 4 times, 142 patients 5 times, and 206 patients 6 times. In total, 310 patients reported WAS in the first and 10th follow-up year.

The patient characteristics of Study II are shown in Table 7. The majority of patients in this subpopulation were also women (77%), but the average age was lower (46 years). Of all responders, 86.4% had adult onset asthma. On average, the participants were mildly overweight (mean BMI 26.3 kg/m^2), and their lung functions were within the normal range (mean FEV1 91.4% of predicted). Majority of the patients had either mental work (53%) or a combination of mental and physical work (33%), while only 5% of patients had physical work. Over half of the participants (55.6%) had at least one of the studied comorbidities, most commonly psychiatric conditions (24.4%), GERD (17.4%), and hypertension (17.4%) (Figure 15).

Table 6. Patient characteristics and smoking statuses at baseline, including follow-up data from deaths and withdrawals (Study I). Modified from original Publication I.

	ALL N=2288	Asthma N = 1329	COPD[1] N = 959	p value
Women	1357 (59.3)	982 (73.9)	375 (39.1)	<0.001
Men	931 (40.1)	347 (26.1)	584 (60.9)	
Mean age (SD)	58.9 (11.6)	54.9 (12.5)	64.4 (7.0)	<0.001
Smoking status[2]				<0.001
Current smoker	480 (19.2)	134 (10.1)	346 (36.1)	
Former smoker	880 (38.5)	427 (32.1)	453 (47.2)	
Never smoker	704 (30.8)	672 (50.6)	32 (3.3)	
Did not answer	47 (2.1)	21 (1.6)	26 (2.7)	
Questionnaire was not returned	142 (7.7)	70 (5.3)	72 (7.5)	
Deaths	35 (1.5)	5 (0.4)	30 (3.1)	
Mean pack years[2,3] (SD)	32.3 (25.9)	15.1 (17.1)	43.5 (24.3)	<0.001
<10	239/1128 (21.2)	213/446 (47.8)	26/682 (3.8)	
10–19.9	164/1128 (14.5)	94/446 (21.1)	70/682 (10.3)	
20–39.9	363/1128 (32.2)	109/446 (24.4)	254/682 (37.2)	
40–59.9	223/1128 (19.8)	19/446 (4.2)	204/682 (29.9)	
>60	139/1128 (12.3)	11/446 (2.5)	128/682 (18.8)	
Withdraws during the follow-up	72 (3.1)	48 (3.6)	24 (2.5)	0.13
Deaths during the follow-up	463 (20.2)	82 (6.2)	381 (39.7)	<0.001
N of omitted smoking related questions[4]				
Once	192/2185 (8.8)	109/1295 (8.4)	83/890 (9.3)	
Two times	32/2059 (1.6)	15/1246 (1.2)	17/813 (2.1)	
Three or more times	10/1890 (0.5)	7/1098 (0.6)	3/720 (0.3)	

Data are presented as *N* (%) unless otherwise stated. SD=standard deviation. [1] Chronic obstructive pulmonary disease. [2] Data based on the first follow up (one year after enrolment). [3] Pack years calculated for all the current and the former smokers who had answered their starting and potential quitting year as well as the average number of smoked cigarettes per day. [4] Compared to the number of patients who returned the questionnaire (withdrawals, deaths and non-responders excluded each year). *p* value is given for the chi-square test or t-test.

Table 7. Patient characteristics and smoking statuses at baseline (Study II). Modified from original Publication II.

Variable	Patients in total N = 529	Patient clusters according to their work ability				p value	Missing values
		Cluster 1 Excellent N = 168	Cluster 2 Good N = 194	Cluster 3 Moderate N = 126	Cluster 4 Poor N = 41		
Women	408 (77.1)	125 (74.4)	152 (78.4)	96 (76.2)	35 (85.4)		
Men	121 (22.9)	43 (25.6)	42 (21.6)	30 (23.8)	6 (14.6)	0.47	0 (0)
Age, mean (SD)	45.8 (9.5)	42.4 (9.7)	46.3 (9.3)	49.2 (9.1)	47.3 (6.4)	<0.001	0 (0)
20–39	124 (23.4)	59 (35.1)	44 (22.7)	18 (14.3)	3 (7.3)		
40–49	201 (38.0)	69 (41.2)	69 (35.6)	41 (32.5)	22 (53.7)		
50–59	176 (33.3)	35 (20.8)	71 (36.6)	54 (42.9)	16 (39.0)		
≥60	28 (5.3)	5 (3.0)	10 (5.2)	13 (10.3)	0 (0)		
BMI, mean (SD)	26.3 (5.4)	24.7 (4.9)	26.0 (4.8)	27.6 (5.9)	29.3 (6.5)	<0.001	73 (13.8)
FEV1% of predicted, mean (SD)	91.4 (14.2)	92.5 (14.7)	91.4 (16.8)	89.7 (12.9)	91.7 (12.0)	0.49	67 (12.7)
Diagnosis age of asthma, mean (SD)	35.7 (13.9)	30.7 (14.4)	37.1 (12.7)	39.1 (14.0)	39.6 (11.1)	<0.001	5 (0.9)
<20	67 (12.7)	36 (21.4)	17 (8.8)	12 (9.5)	2 (4.9)	<0.001	
≥20	457 (86.4)	130 (77.4)	174 (89.7)	114 (90.5)	39 (95.1)		
Smoking							
Never smoker	285 (53.9)	98 (58.3)	105 (54.1)	57 (45.2)	25 (61.0)	0.21	14 (2.6)
Former smoker	156 (29.5)	41 (24.4)	59 (30.4)	47 (37.3)	9 (22.0)		
Current smoker	74 (14.0)	25 (14.9)	24 (12.4)	18 (14.3)	7 (17.1)		
Pack years, mean (SD)							
Current smokers	16.9 (18.0)	15.7 (13.0)	12.2 (7.6)	26.0 (31.0)	15.0 (11.9)	0.33	7 (9.5)
Former smokers	12.3 (14.8)	9.8 (8.1)	11.1 (15.4)	16.6 (20.3)	11.9 (10.8)	0.27	23 (14.7)
N of deaths	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (2.4)		0 (0)

N of comorbidities per patient, mean (SD)	0.95 (1.09)	0.51 (0.85)	0.96 (1.00)	1.34 (1.21)	1.46 (1.27)	<0.001	0 (0)
Work type							
Mental	280 (52.9)	93 (55.4)	111 (57.2)	60 (47.6)	16 (39.0)	0.03	46 (8.7)
Physical	28 (5.3)	5 (3.0)	7 (3.6)	12 (10.6)	4 (9.8)		
Combination	175 (33.1)	53 (31.5)	62 (32.0)	41 (36.3)	19 (46.3)		

Data is presented as N (%) unless otherwise stated. SD=Standard Deviation; BMI=Body mass index; FEV1=Forced expiratory volume in 1 second; P value shows statistical significance for differences found in comparisons between all four identified clusters. p value is given for the chi-square test, a one-way ANOVA, or a Kruskal-Wallis test.
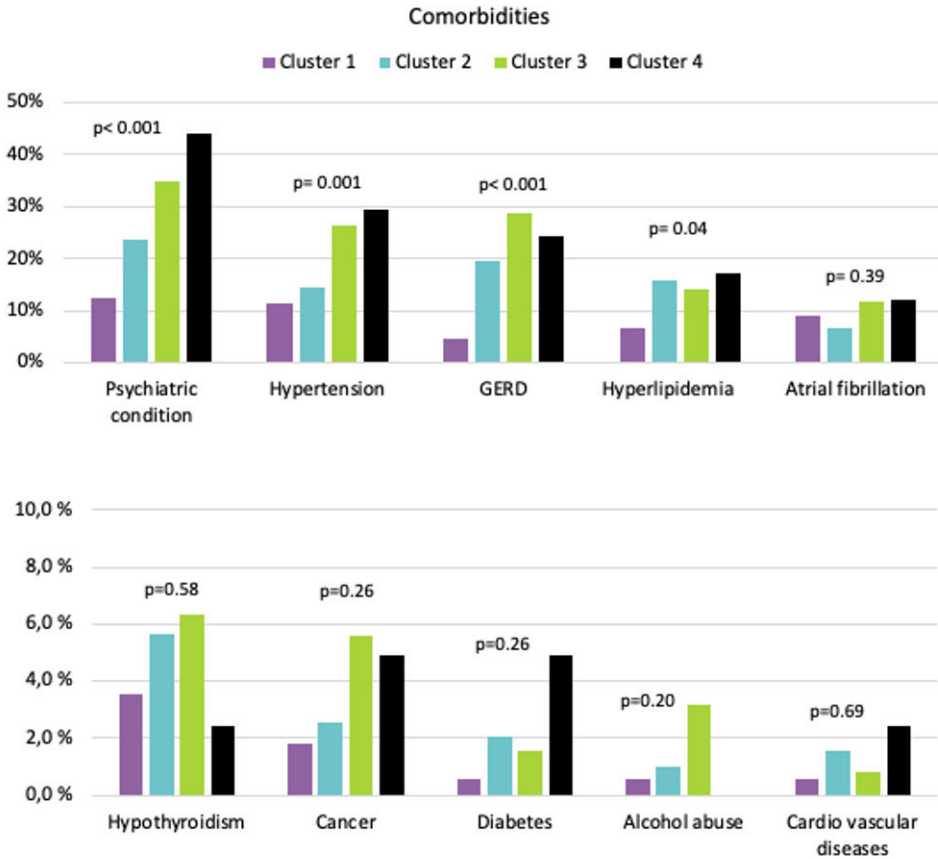
Figure 15. Percentages of patients with different comorbidities according to work ability clusters. *P* value is marked if a statistically significant difference was observed in the comparison of all four identified clusters. Note the differences in y-axis scaling. GERD=gastroesophageal reflux disease. *p* value is given for the chi-square test.

4.4.2 Response Rates, Deaths, and Withdrawals During the Study

In the CAD cohort (Study I), the response rates were excellent (95–98%) in the first follow-up year, decreasing gradually over time to 67–70% in both patient groups (Figure 16). The response rates of asthma patients were always slightly higher than among the COPD patients. The follow-up times from the first to the last questionnaire or from the first questionnaire to death/withdrawal were good in both groups. The median follow-up times among asthma and COPD patients were 9.3 (SD 2.4) years and 8.2 (SD 2.9) years, respectively. Throughout the follow-up period, the mortality rate was significantly higher in the COPD group (381/959 = 39.7%), compared to that among the asthma patients (82/1329 = 6.2%, p <0.001) (Table 6).

Withdrawing was, however, even in both COPD and asthma groups (24/959 = 2.5% vs. 48/1329 = 3.6%, p = 0.1).

Number of questionnaires returned

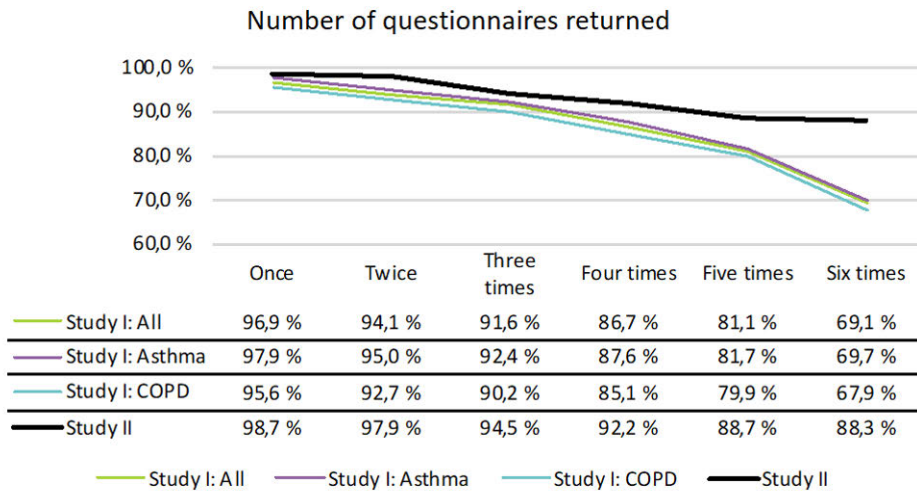|	Once	Twice	Three times	Four times	Five times	Six times
Study I: All	96,9 %	94,1 %	91,6 %	86,7 %	81,1 %	69,1 %
Study I: Asthma	97,9 %	95,0 %	92,4 %	87,6 %	81,7 %	69,7 %
Study I: COPD	95,6 %	92,7 %	90,2 %	85,1 %	79,9 %	67,9 %
Study II	98,7 %	97,9 %	94,5 %	92,2 %	88,7 %	88,3 %

Figure 16. Response rates in Study I and II. The number of responders was compared to the number of patients who could have replied to the questionnaire (withdrawals and deaths excluded each year).

In study II, the response rates were high throughout the study period, decreasing gradually from 98.7% to 88.3% (Figure 16). The average follow-up time from enrolment to the last questionnaire or to death/withdrawal was 9.7 years (SD 1.2) (Table 8). One person died during the follow-up period.

Table 8. Follow-up times according to work ability clusters (Study II).

	All patients	Cluster 1 Excellent	Cluster 2 Good	Cluster 3 Moderate	Cluster 4 Poor
Overall follow-up time	9.7 (1.2)	9.6 (1.2)	9.7 (1.4)	10.0 (0.9)	9.9 (0.5)
Follow-up time of work questions[1]	8.9 (2.0)	8.6 (2.1)	8.9 (2.0)	9.3 (1.7)	8.7 (2.1)

[1]Follow-up ended when patient was out of work life.

4.4.3 Consistency and Reliability of Smoking-Related Variables (Study I)

Smoking statuses were evaluated for the first time one year after enrolment. At that point, half of the asthma patients (50.6%) were never smokers and only 10.1% smoked actively, whereas 3.3% of COPD patients had never smoked and 36.1% were current smokers (Table 6). A heavy smoking history of COPD patients was observed when the consumption of cigarettes and pack years were compared between the patient groups (Figure 17). Among current smokers, the proportion of heavy smokers was significantly higher in the COPD group (178/346, 51.4%) than among the asthma patients (33/134 = 24.6%, $p < 0.001$). A similar trend was seen among ex-smokers, with 68% (309/453) of COPD patients and 30% (127/427) of asthma patients being heavy smokers ($p < 0.001$).
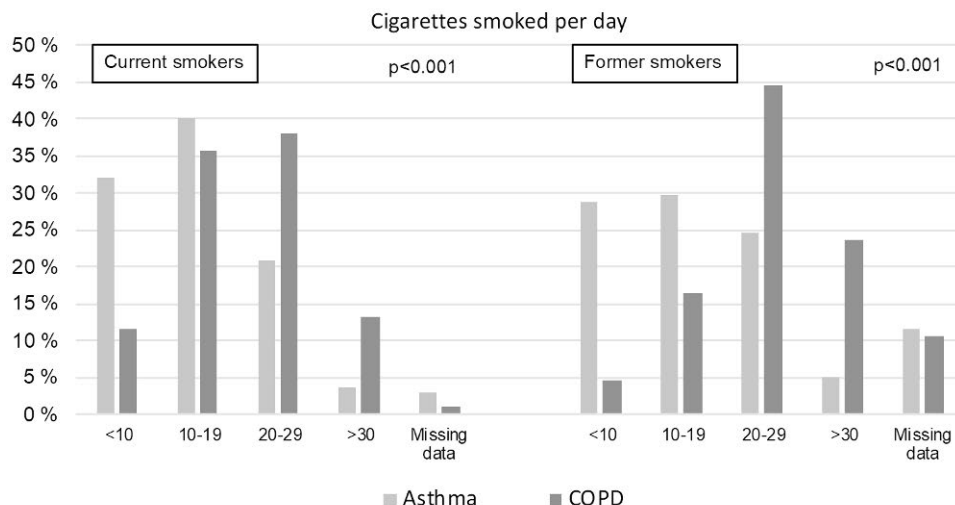
Figure 17. Self-reported consumption of cigarettes among current (left) and former (right) smokers with asthma and COPD. Data based on first follow-up questionnaire. p value is given for the chi-square test.

A few participants left the smoking section of the questionnaire unanswered, even though they had returned the questionnaire (Table 6). Of all patients, 8.8% (192/2185) failed to complete the section once, 1.6% (32/2059) twice and 0.5% (10/1890) three or more times. Based on the given answers, almost 75% of the patients, with incomplete smoking information, had stable smoking status. Furthermore, we studied whether the smoking statuses of the withdrawals differed between the disease groups, but no significant difference was observed.

4.4.3.1   Smoking Behaviour and Cessation Rates

To study the potential changes in the participants' smoking habits and the reliability of reported outcomes, we chose all patients who had answered the smoking-related questions at least three times (N = 1,852). The patients were classified based on changes in their smoking status. Almost 80% of the study subjects (N = 1454) reported an identical smoking status throughout the study (Table 9). More variation, that is, changes from former smokers to current smokers and vice versa, were seen in the COPD group. Overall, only 4.5% of the participants gave an unreliable pattern of responses. The proportion of subjects with unreliable responses was significantly higher among asthma patients (5.8%) than in the COPD group (2.3%, p < 0.001).

The success rates of smoking cessation were assessed by comparing participants' first and last given smoking status in this same subgroup (N = 1,852). Based on the first reported smoking status, 420 COPD and 1,030 asthma patients were smoke free. Of all current smokers, 33.9% (42/124) of the asthma and 44.6% (124/278) of the COPD patients succeeded in quitting smoking (smoke-free in their last report) during the follow-up. In the end of the follow-up, 91.5% of the asthma patients and 73.1% of the COPD patients were smoke-free. Based on the latest report, 49 of 105 smokers who struggled with relapses (Unstable 2 group, changing status between current and former smokers) were smoke-free.

Table 9. Comparison of the changes in smoking status between asthma and COPD patients over the 10-year follow-up. Modified from original Publication I.

	All N = 1852[1]	Asthma N = 1154[1]	COPD[2] N = 698[1]	p value
Stable	1454 (78.5)	985 (85.4)	469 (67.2)	<0.001
Smoking	*185 (12.7)*	*63 (6.4)*	*122 (26.0)*	
Non-smoking	*1269 (87.3)*	*922 (93.6)*	*347 (74.0)*	
Unstable, changing once	210 (11.3)	60 (5.2)	150 (21.5)	<0.001
Smoking [3]	*42 (20.0)*	*10 (16.7)*	*32 (21.3)*	
Non-smoking [3]	*168 (80.0)*	*50 (83.3)*	*118 (78.7)*	
Unstable, changing more than once	105 (5.7)	42 (3.6)	63 (9.0)	<0.001
Smoking [3]	*56 (53.3)*	*23 (54.8)*	*33 (52.4)*	
Non-smoking [3]	*49 (46.7)*	*19 (45.2)*	*30 (47.6)*	
Unreliable	83 (4.5)	67 (5.8)	16 (2.3)	<0.001

Data is presented as N (%) unless otherwise stated. [1] including all the patients who had answered at least three times to the smoking-related questions during the 10-year follow-up. [2] COPD=Chronic obstructive pulmonary disease. [3] in their last report. *p* value is given for the chi-square test.

4.4.3.2   Reliability of Smoking Variables

To evaluate the reliability of the reported starting and stopping years, we studied the variances and ICCs between patients' answers during the follow-up. These analyses were also done for the patients who had answered the smoking-related questions at least three times (N = 1,852). A high degree of reliability was found between the starting years in all groups (ICCs 0.78–0.91). The reliability of stopping years was excellent in the stable (ICC 0.94, CI 0.93–0.94) and the Unreliable groups (ICC 0.98, CI 0.97–0.99). Moreover, the same analysis was conducted between the disease and smoking groups. The reported starting years were more reliable among asthmatics (ICC 0.90, CI 0.88–0.91) than among COPD patients (ICC 0.83, CI 0.81–0.85). A comparison of ICC values between different smoking groups revealed a good reliability of starting years among former smokers (ICC 0.83, CI 0.80–0.85) and excellent reliability among current smokers (ICC 0.91, CI 0.88–0.93).

4.4.4   Work Ability Among Asthmatics (Study II)

The development of self-reported work ability was studied in a longitudinal setting using the Fréchet distance (Fréchet 1906). The clustering was conducted using different choices for the number of clusters. The average WAS curves inside the clusters were manually inspected, and a suitable number of clusters were chosen to be four. In three clusters, the WAS trajectories were stable throughout the follow-up period with either excellent, good, or moderate WAS level. In the fourth cluster,
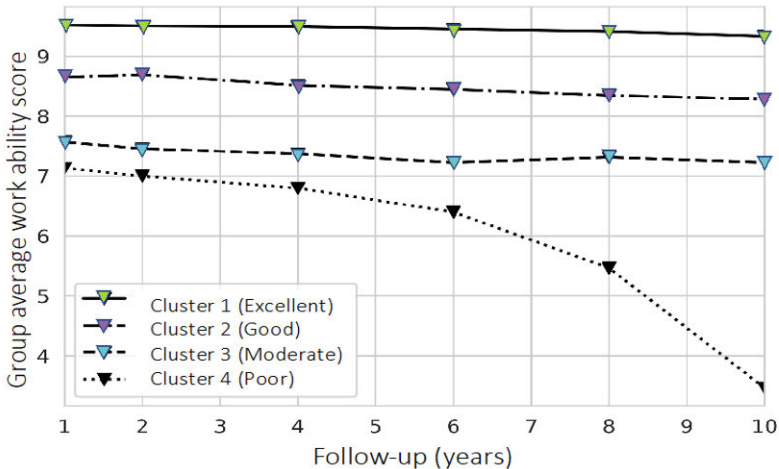

Figure 18. Development of asthma patients' work ability during 10-year follow-up. Four clusters were identified based on patients' longitudinal work ability scores. Modified from original Publication II.

work ability was already poor at the beginning and decreased even more during the follow-up (Figure 18, Table 7). There was no difference in the number of missing values between the clusters.

The characteristics of the poorest cluster (Cluster 4) differed from those of the other clusters. They most frequently had adult onset asthma, the poorest HRQoL (Figures 19 and 20), the highest BMI, and more co-morbidities (especially psychiatric disorders). However, no significant differences in smoking habits were seen when compared to the other groups. The mean changes in the 15D scores from baseline to 10 years were statistically significantly different between the clusters (p <0.001), while no statistically significant difference was seen in the mean changes in the AQ20 scores (p = 0.69).
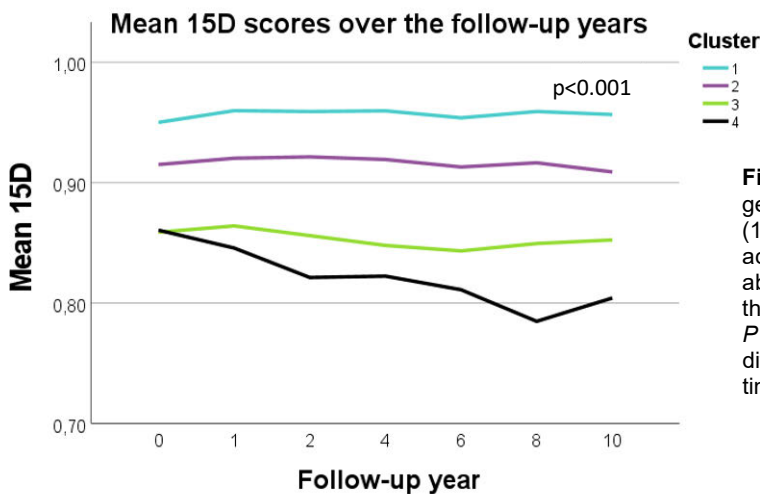

Figure 19. Trends in general HRQoL (15D) scores according to the work ability clusters over the 10-year follow-up. *P* value shows difference between time and clusters.
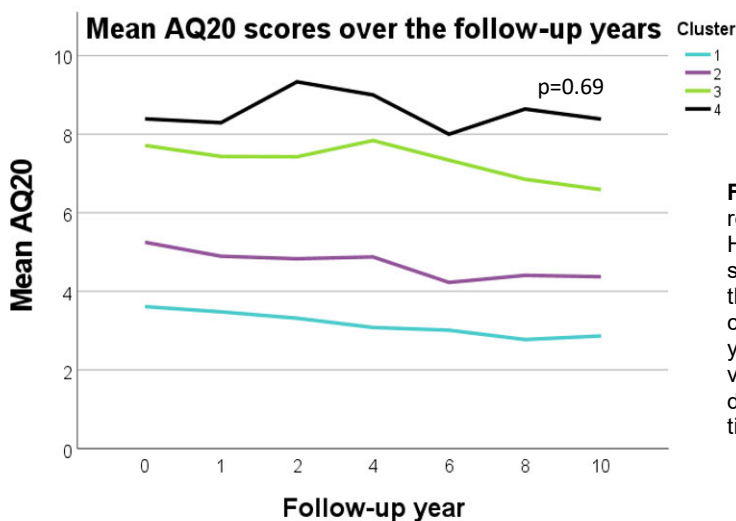

Figure 20. Trends in respiratory specific HRQoL (20AQ) scores according to the work ability clusters over the 10-year follow-up. P value shows difference between time and clusters.

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4.4.4.1 Medication and Severity of Asthma

The use of asthma and allergy medication was included in the questionnaire from the fourth follow-up year onwards. A comparison of the use of allergy and asthma medication between the groups in the fourth follow-up year is presented in Table 10 and Figures 21–23. In total, 81.4% (407/500) of the participants used ICS in the fourth follow-up year. The use of ICS (90.6% vs. 80.1%, p = 0.003), LABA (62.3% vs. 42.8%, p <0.001) and OCS (44.0% vs. 22.3%, p <0.001) were more common in Clusters 3 and 4 when compared to Clusters 1 and 2. There was no difference in the use of nasal corticosteroids and antihistamines between the clusters. Based on medication, the criteria for severe asthma were fulfilled in 7.6% (38/500) of all patients. The use of reported asthma and allergy medicines was also evaluated in the sixth, eighth, and tenth years, but no significant changes were observed in comparison to those reported in year 4 (data not shown).
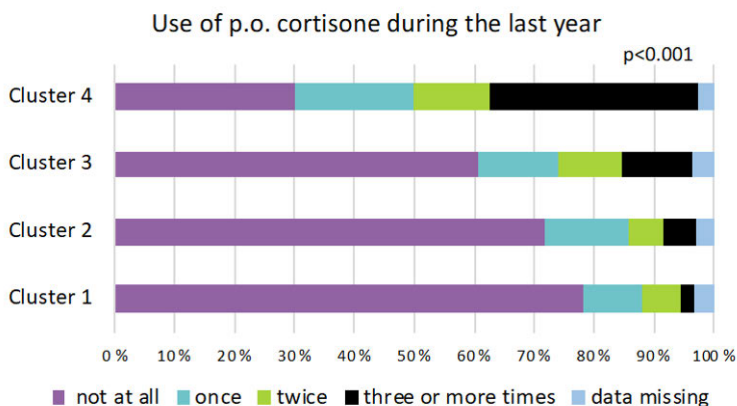
Figure 21. Use of per os (p.o.) corticosteroids at the fourth follow-up year when medication was required first time. The results are presented according to the work ability clusters. *p* value is given for the chi-square test.
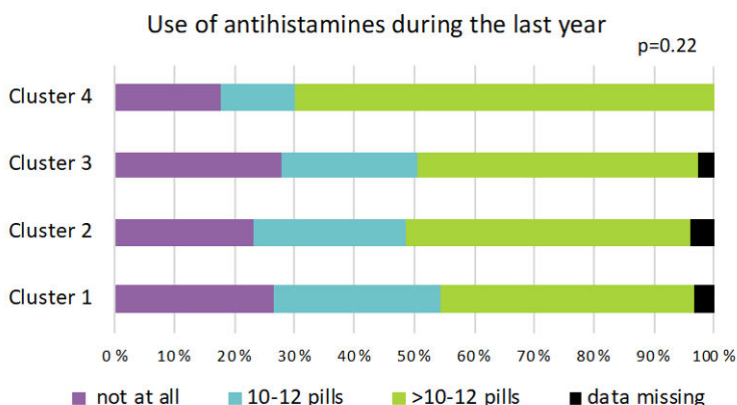
Figure 22. Use of antihistamines at the fourth follow-up year when medication was required first time. The results are presented according to the work ability clusters. *p* value is given for the chi-square test.
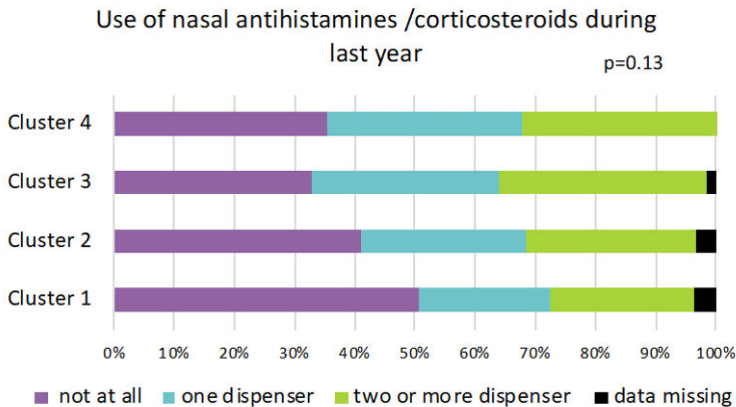
Figure 23. Use of nasal antihistamines /corticosteroids at the fourth follow-up year when medication was required first time. The results are presented according to the work ability clusters.

4.4.4.2 Risk Factors for Poorly Developing WAS

To evaluate the possible risk factors for poorly developing WAS, a logistic regression analysis was performed. First, the poorest performing Cluster 4 was compared to the better performing Clusters 1, 2, and 3. Then, the two poorest performing clusters, 3 and 4, were compared to the two best performing clusters, 1 and 2. In both models, multiple baseline clinical characteristics were used as predictors. We calculated univariate and age- and gender-adjusted multivariate analyses for each characteristic (Table 11 and Table 12).

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Table 10. Use of the asthma and allergy medication at the fourth follow-up year when medication was required first time. In total 500 participants returned the questionnaire this follow-up year.

Variable	Patients in total N = 500	Patient clusters according to their work ability				p value
		Cluster 1 Excellent N = 160	Cluster 2 Good N = 181	Cluster 3 Moderate N = 119	Cluster 4 Poor N = 40	
Users of inhaled corticosteroids (ICS)						0.006
yes	407 (81.4)	117 (73.1)	146 (80.7)	105 (88.2)	39 (97.5)	
no	91 (18.2)	42 (26.3)	34 (18.8)	14 (11.8)	1 (2.5)	
unknown	2 (0.4)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	
Mean used dose of ICS[1] (µg) (SD)	570 (355)	475 (254)	532 (319)	641 (370)	785 (522)	<0.001
Users of LABA	245 (49.0)	59 (36.9)	87 (48.1)	68 (57.1)	31 (77.5)	<0.001
Users of LAMA	6 (1.2)	0 (0)	1 (0.6)	4 (3.4)	1 (2.5)	0.05
Users of other controllers[2]	120 (24.0)	20 (12.5)	46 (25.4)	33 (27.7)	21 (52.5)	<0.001
Classified as having severe asthma based on medication[3]	38 (7.6)	3 (1.9)	11 (6.1)	14 (11.8)	10 (25.0)	<0.001
Use of SABA						
not at all	149 (29.8)	60 (37.5)	52 (28.7)	30 (25.2)	7 (17.5)	0.06
once a week	215 (43.0)	64 (40.0)	86 (47.5)	50 (42.0)	15 (37.5)	
2-4 times per week	45 (9.0)	16 (10.0)	10 (5.5)	13 (10.9)	6 (15.0)	
at least once a day	42 (8.5)	10 (6.3)	11 (6.1)	15 (12.6)	6 (15.0)	
acute symptoms treated by long-acting asthma medicine	26 (5.2)	6 (3.8)	10 (5.5)	6 (5.0)	4 (10.0)	
data missing	23 (4.6)	4 (2.5)	12 (6.6)	5 (4.2)	2 (5.0)	

Data is presented as N (%) unless otherwise stated. [1] ICS dose reported as Fluticasone Propionate equivalents. [2] Leukotriene receptor antagonists, theophyllines, cromones, OCS and/or biological drugs. [3] High dose of ICS and second controller in use. LABA= long-acting β2-agonist, LAMA=long acting muscarinic antagonist. SABA=short-acting β2 -agonist.

Table 11. The association of clinical characteristics and poor work ability among asthma patients during 10 year follow -up. Odds Ratios (OR) and 95% CI of the clinical characteristics explaining decreased WAS. Modified from original Publication II.

	Risk of having poor work ability (Cluster 4 vs. Clusters 1, 2 and 3)			
	Crude model		Adjusted model[1]	
	OR (95% CI)	p	OR (95% CI)	p
Baseline age	1.02 (0.98–1.05)	0.31		
Men gender	0.56 (0.23–1.36)	0.20		
Baseline BMI (kg/m²)	**1.10 (1.04–1.16)**	**<0.001**	**1.09 (1.04–1.15)**	**0.001**
Asthma onset				
Childhood	1.00		1.00	
Adulthood	3.03 (0.71–12.8)	0.13	2.66 (0.60–11.72)	0.20
FEV1% of predicted	1.00 (0.98–1.02)	0.88	1.00 (0.98–1.03)	0.76
Smoking				
Pack years	0.98 (0.94–1.02)	0.33	0.98 (0.94–1.02)	0.31
Never smoker	1.00		1.00	
Current smoker	1.09 (0.45–2.62)	0.85	1.10 (0.46–2.66)	0.83
Former smoker	0.64 (0.29–1.40)	0.26	0.63 (0.28–1.40)	0.26
Co–morbidities				
Comorbidities per patient	**1.50 (1.16–1.93)**	**0.002**	**1.46 (1.11–1.91)**	**0.01**
Psychiatric conditions	**2.62 (1.37–5.04)**	**0.004**	**2.42 (1.24–4.70)**	**0.01**
Hypertension	**2.10 (1.03–4.29)**	**0.04**	1.93 (0.91–4.08)	0.09
GERD	1.60 (0.75–3.39)	0.22	1.51 (0.71–3.24)	0.29
Atrial fibrillation	1.44 (0.54–3.85)	0.47	1.35 (0.50–3.62)	0.56
CVD	2.42 (0.28–21.18)	0.43	2.00 (0.23–17.66)	0.54
Hypothyroidism	0.46 (0.06–3.49)	0.45	0.39 (0.05–2.95)	0.36
Diabetes	3.08 (0.63–14.99)	0.16	2.92 (0.59–14.43)	0.19
Cancer	1.66 (0.36–7.52)	0.51	1.50 (0.32–6.94)	0.60
Work type				
Mental	1.00		1.00	
Physical	2.75 (0.85–8.88)	0.09	2.87 (0.88–9.36)	0.08
Combination	**2.01 (1.00–4.02)**	**0.049**	1.76 (0.87–3.56)	0.12

[1] regression model was adjusted for age and gender. CI=confidence intervals; BMI=Body mass index; FEV1=Forced expiratory volume in 1 second; GERD=Gastro Oesophageal Reflux Disease; CVD=Cardio Vascular Diseases

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Table 12. The association of clinical characteristics and poor or moderate work ability among asthma patients during 10 year follow -up. Odds ratios (OR) and 95% CI of the clinical characteristics explaining decreased WAS. Modified from original Publication II.

	Risk of having either poor or moderate work ability (Clusters 3 and 4 vs. Clusters 1 and 2)			
	Crude model		Adjusted model[1]	
	OR (95% CI)	p	OR (95% CI)	p
Baseline age	1.05 (1.03–1.07)	<0.001		
Men gender	0.90 (0.58–1.39)	0.62		
Baseline BMI (kg/m²)	**1.09 (1.05–1.13)**	**<0.001**	**1.08 (1.04–1.12)**	**<0.001**
Asthma onset				
Childhood	1.00		1.00	
Adulthood	**1.91 (1.03–3.54)**	**0.04**	1.23 (0.64–2.38)	0.54
FEV1% of predicted	0.99 (0.98–1.01)	0.27	1.00 (0.98–1.01)	0.62
Smoking				
Pack years	**1.02 (1.01–1.04)**	**0.01**	1.02 (1.00–1.03)	0.06
Never smoker	1.00		1.00	
Current smoker	1.26 (0.73–2.18)	0.40	1.30 (0.75–2.28)	0.35
Former smoker	1.39 (0.92–2.10)	0.12	1.24 (0.81–1.91)	0.32
Co–morbidities				
Comorbidities per patient	**1.67 (1.41–1.99)**	**<0.001**	**1.54 (1.28–1.84)**	**<0.001**
Psychiatric conditions	**2.59 (1.72–3.91)**	**<0.001**	**2.37 (1.55–3.12)**	**<0.001**
Hypertension	**2.46 (1.55–3.89)**	**<0.001**	**1.90 (1.18–3.06)**	**0.01**
GERD	**2.61 (1.65–4.13)**	**<0.001**	**2.34 (1.46–3.75)**	**<0.001**
Atrial fibrillation	1.62 (0.89–2.97)	0.12	1.55 (0.83–2.88)	0.17
CVD	1.09 (0.20–5.98)		0.85 (0.15–4.76)	0.85
Hypothyroidism	1.15 (0.50–2.64)	0.74	0.99 (0.42–2.32)	0.98
Diabetes	1.46 (0.41–5.23)	0.57	1.65 (0.45–6.13)	0.45
Cancer	2.54 (0.96–6.70)	0.06	1.82 (0.68–4.90)	0.24
Work type				
Mental	1.00		1.00	
Physical	**3.58 (1.62–7.91)**	**0.002**	**3.62 (1.61–8.64)**	**0.002**
Combination	1.40 (0.93–2.11)	0.11	1.25 (0.82–1.90)	0.31

[1] regression model was adjusted for age and gender. CI=confidence intervals; BMI=Body mass index; FEV1=Forced expiratory volume in 1 second; GERD=Gastro oesophageal reflux disease; CVD=cardio vascular diseases

4.4.4.3 Association Between WAS and HRQoL Instruments

At baseline, general HRQoL (15D) was lower in the Groups 3 and 4 (mean 0.86) than in Groups 1 and 2 (mean 0.93, p <0.001). A similar trend was seen in respiratory-specific HRQoL analysis with AQ20 scores of 7.9 and 4.5, respectively (p <0.001).

The association between WAS and HRQoL instruments (15D and AQ20) is shown in Table 13. A significant but rather weak association was observed between WAS and both HRQoL instruments. However, the correlations were stronger between WAS and 15D (Spearman's r = 0.61 to 0.65) than between WAS and AQ20 (Spearman's r = -0.43 to -0.51).

Table 13. Correlation between work ability score (WAS) and health-related quality of life (HRQoL) instruments during the follow-up years.

	Spearman's correlation coefficient	p	Missing (%)
WAS – AQ20			
Follow-up 1	-0,43	<0.001	51 (9.6)
Follow-up 2	-0.47	<0.001	44 (8.3)
Follow-up 4	-0.51	<0.001	68 (12.9)
Follow-up 6	-0.48	<0.001	102 (19.3)
Follow-up 8	-0.44	<0.001	145 (27.4)
Follow-up 10	-0.46	<0.001	205 (38.8)
WAS – 15D			
Follow-up 1	0.61	<0.001	78 (14.8)
Follow-up 2	0.65	<0.001	73 (13.8)
Follow-up 4	0.64	<0.001	70 (13.2)
Follow-up 6	0.63	<0.001	126 (23.8)
Follow-up 8	0.64	<0.001	165 (31.2)
Follow-up 10	0.60	<0.001	204 (38.6)
15D – AQ20			
Follow-up 1	-0.57	<0.001	43 (8.1)
Follow-up 2	-0.62	<0.001	47 (8.9)
Follow-up 4	-0.61	<0.001	36 (6.8)
Follow-up 6	-0.59	<0.001	65 (12.3)
Follow-up 8	-0.59	<0.001	83 (15.7)
Follow-up 10	-0.59	<0.001	83 (15.7)

WAS=Work Ability Score; 15D=15 dimensional, general HRQoL instrument; AQ20=Airway Questionnaire 20, disease specific HRQoL instrument.

4.4.4.4 Work History, Retirement Age, and Sick Days in Relation to Work Ability

At baseline, the majority of patients had full-time jobs in all clusters (76–88%). However, the participants in the two poorest clusters worked more often part-time (12.6% vs. 5.6%, p <0.01). During the follow-up, almost a fifth of the patients in Cluster 4 retired due to disability, which was a significantly higher portion than in the three other clusters (6.1%, p <0.001). Also, sick days were more common in Cluster 3 and especially in Cluster 4. In total, 56.1% of the patients in Cluster 4 and 20.6% of the patients in Cluster 3 had an average of over 24 sick days per year, which was a significantly higher proportion than in clusters 1 and 2 (5.0%, p <0.001). Overall, the unemployment rates were low in all clusters, and only 6% reported unemployment at some point during the follow-up.

4.5 Study III

4.5.1 Characteristics

Based on our study approach, we identified 35,650 patients with adult asthma (N = 4,549), COPD (N = 2,111), sleep apnoea (5,931), IHD (9,200), cerebral infarction (4,946), type 1 diabetes (N = 632), or type 2 diabetes (8,281) (Table 14). There were significantly more women in the asthma group compared to the other patient groups (68% vs. 44%, p <0.001). The mean age of the asthma patients was 51 years. The median length of asthma patients' 2-year medical narrative after the given diagnosis ranged from 6 to 28 events. Majority of these events were either inpatient or outpatient visits.

4.5.2 Smoking Status and Changes Over Time

Using the rule-based algorithm 1, we were able to find at least one smoking-related phrase for 61% of asthma patients in their two-year medical narrative. Compared to the asthma group, smoking statuses were documented significantly more frequently among COPD patients (61.0% vs. 86.2%, p <0.001) and sleep apnoea patients (61.0% vs. 83.4 %, p <0.001). We analysed the differences in documentation between the years 2010–2012 and 2016–2018, and observed 11% improvement in documentation among asthma patients (57.4% vs. 67.7%, p <0.001, respectively), while in patients with cerebral infarction, the documentation rate increased by 18% (49.5% and 67.2%, p <0.001, respectively) (Figure 24). During the follow-up, health professionals had documented smoking statuses generally more often for ex- and current smokers than for never-smokers (Figure 25).

Table 14. Characteristics and smoking statuses of the patient groups studied based on the two-year follow-up.

	All patients N 35,650	Asthma N 4,549	COPD[1] N 2,111	Sleep Apnoea N 5,931	IHD[2] N 9,200	Cerebral infraction N 4,946	Type 1 diabetes N 632	Type 2 diabetes N 8,281
Women	16 653 (46.7)	3 094 (68.0)	714 (33.8)	1 986 (33.5)	3 954 (43.0)	2 594 (52.4)	297 (47.0)	4 014 (48.5)
Men	18 997 (53.3)	1 455 (32.0)	1 397 (66.2)	3 945 (66.5)	5 246 (57.0)	2 352 (47.6)	335 (53.0)	4 267 (51.5)
Mean age (SD)	63.5 (16.4)	50.7 (19.0)	66.3 (10.8)	53.5 (12.7)	71.2 (13.0)	70.8 (14.2)	40.6 (18.3)	65.9 (13.4)
Smoking related sentence(s) found in the EHR during the follow-up[3]	21,372 (59.9)	2,775 (61.0)	1,820 (86.1)	4,949 (83.4)	5,005 (54.4)	2,858 (57.8)	331 (52.4)	3,634 (43.9)
Smoking status[4]								
Current smoker	7 105 (19.9)	813 (17.9)	1 268 (60.1)	1 243 (21.0)	1 586 (17.2)	942 (19.0)	118 (18.7)	1135 (13.7)
Ex-smoker	4 852 (13.6)	599 (13.2)	501 (23.7)	1 384 (23.3)	1 114 (12.1)	396 (8.0)	38 (6.0)	820 (9.9)
Never smoker	9 415 (26.4)	1363 (30.0)	51 (2.4)	2 322 (39.2)	2 305 (25.1)	1520 (30.7)	175 (27.7)	1 679 (20.3)
Missing data	14 278 (40.1)	1774 (39.0)	291 (13.8)	982 (16.6)	4195 (45.6)	2088 (42.2)	301 (47.6)	4647 (56.1)
N of sentences per patient regarding their smoking, mean (SD)	2.0 (3.2)	1.7 (2.7)	5.3 (5.8)	1.8 (2.3)	1.8 (2.9)	2.4 (3.6)	1.5 (3.3)	1.3 (2.7)
N of events per patient during the follow-up, median (IQR)	18 (9-34)	14 (6-28)	22 (10-43)	12 (7-22)	19 (11-34)	28(17-45)	18 (8-31)	17 (8-35)

Data are presented as n (%) unless otherwise stated. SD=Standard Deviation. IQR=Inter quartile range.[1] Chronic obstructive pulmonary diseases. [2]Ischemic heart diseases. [3] Electronic health records. [4] percentages have been calculated from the patients whose EHR contained at least one smoking-related sentence.
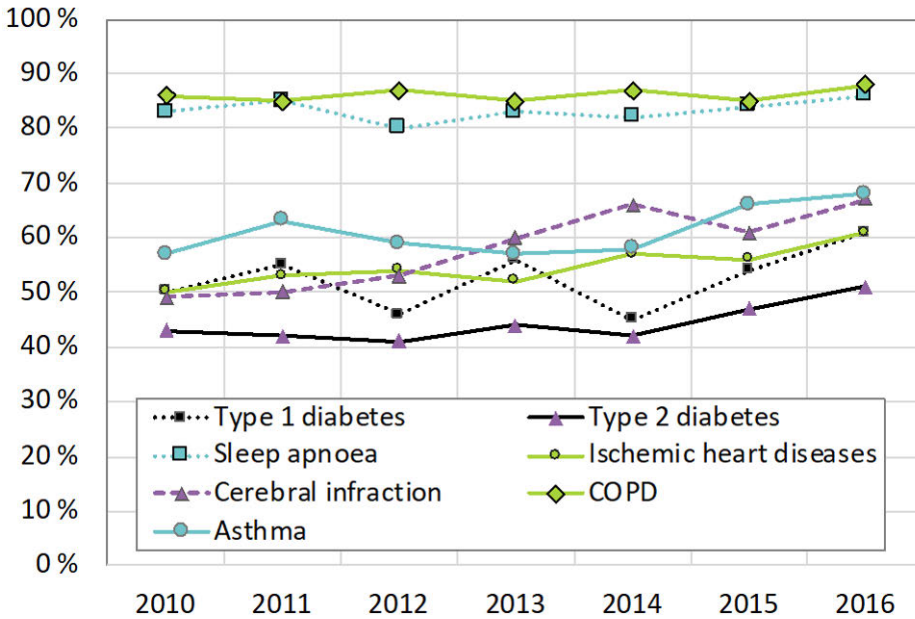
Figure 24. Proportion of patients with at least one documented smoking status during two-year follow-up according to disease groups. In asthma patients, the documentation rate increased 11% during the study period. COPD=chronic obstructive pulmonary disease. Modified from original Publication III.
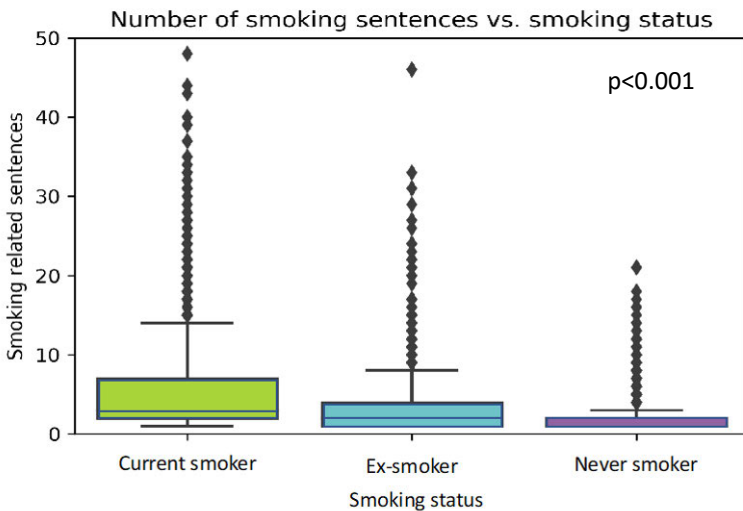

Figure 25. Number of smoking related sentences per patient according to the patients' smoking status.

Table 15. Smoking statuses in different disease groups over the study years. Percentages calculated within the disease group and study year.

Year	Smoking Status	Asthma	COPD[1]	Sleep Apnoea	IHD[2]	Cerebral infraction	Type 1 diabetes	Type 2 diabetes
2010	Never	165 (27)	6 (2)	254 (34)	341 (23)	158 (23)	20 (22)	243 (20)
	Current	96 (16)	160 (58)	189 (25)	250 (17)	132 (19)	21 (23)	165 (13)
	Former	84 (14)	70 (25)	175 (23)	166 (11)	54 (8)	5 (5)	121 (10)
	Missing	256 (43)	40 (14)	131 (17)	748 (50)	351 (51)	46 (50)	711 (57)
2011	Never	220 (31)	9 (3)	300 (40)	343 (25)	194 (27)	27 (28)	234 (18)
	Current	134 (19)	169 (61)	165 (22)	240 (17)	121 (17)	22 (22)	179 (14)
	Former	91 (13)	59 (21)	169 (23)	146 (11)	47 (6)	5 (5)	136 (10)
	Missing	259 (37)	41 (15)	109 (15)	651 (47)	367 (50)	44 (45)	768 (58)
2012	Never	213 (29)	12 (3)	255 (36)	317 (25)	206 (28)	21 (21)	244 (19)
	Current	126 (17)	224 (63)	159 (22)	215 (17)	129 (17)	16 (16)	180 (14)
	Former	97 (13)	75 (21)	158 (22)	153 (12)	58 (8)	8 (8)	98 (8)
	Missing	304 (41)	47 (13)	139 (20)	595 (46)	350 (47)	53 (54)	744 (59)
2013	Never	175 (28)	3 (1)	313 (39)	295 (23)	222 (30)	32 (33)	211 (19)
	Current	122 (20)	192 (61)	159 (20)	223 (17)	175 (24)	18 (18)	164 (15)
	Former	58 (9)	75 (24)	187 (23)	153 (12)	49 (7)	5 (5)	115 (10)
	Missing	267 (43)	47 (15)	139 (17)	622 (48)	295 (40)	43 (44)	618 (56)
2014	Never	206 (30)	9 (3)	382 (42)	357 (27)	243 (37)	24 (30)	262 (20)
	Current	117 (17)	189 (62)	170 (19)	232 (17)	128 (20)	7 (9)	155 (12)
	Former	79 (11)	66 (22)	190 (21)	162 (12)	57 (9)	5 (6)	126 (10)
	Missing	292 (42)	39 (13)	168 (18)	576 (43)	223 (34)	44 (55)	758 (58)
2015	Never	183 (32)	6 (2)	406 (39)	314 (26)	244 (34)	28 (34)	235 (22)
	Current	109 (19)	155 (54)	215 (21)	198 (17)	127 (18)	10 (12)	149 (14)
	Former	83 (15)	82 (29)	249 (24)	154 (13)	61 (9)	6 (7)	114 (11)
	Missing	197 (34)	43 (15)	162 (16)	522 (44)	281 (39)	38 (46)	564 (53)
2016	Never	201 (33)	6 (2)	412 (42)	338 (28)	253 (38)	23 (27)	250 (25)
	Current	109 (18)	179 (61)	186 (19)	228 (19)	130 (19)	24 (29)	143 (14)
	Former	107 (17)	74 (25)	256 (26)	180 (15)	70 (10)	4 (5)	110 (11)
	Missing	199 (32)	34 (12)	134 (14)	481 (39)	221 (33)	33 (39)	484 (49)

Data are presented as N (%). [1] Chronic obstructive pulmonary disease. [2] Ischemic heart diseases

Half of the asthma patients (49%) had never smoked, and 30% smoked daily (Table 14). The other groups showed a similar distribution, except the COPD group, where the majority of patients (70%) were classified as current smokers. Overall, the proportions of current smokers decreased in all disease groups over the 9-year observation period (Table 15). We compared the proportion of current smokers among asthma patients in the years 2010–2011 (230/790, 29%) and 2015–2016 (218/792, 28%) and found a 2% decline in active smoking (p = 0.48). When the comparison was done across the patient groups, the average decline in active smoking was 4% between 2010–2011 (N = 2 043/5 885, 35%) and 2015–2016 (N = 1 962/6 411, 31%).

4.5.3 Smoking Cessation Intervention

The possible smoking cessation interventions delivered by healthcare professionals were analysed among current smokers. A little more than half of the currently smoking asthma patients (55%) and 60% of COPD patients had discussed smoking cessation with their physician. We compared the ratio of patients who received tobacco intervention between different disease groups. When asthma patients were selected as a control group, patients with type 1 diabetes discussed 11% and COPD patients 9% more frequently of smoking cessation with the physician (Figure 26). Patients with asthma had the highest proportion of visits (9%) to the nurse managed cessation programme, which was significantly more compared to the patients with sleep apnoea (5%, p <0.001) while no significant differences were seen between asthma and COPD patients (7%, p = 0.08).
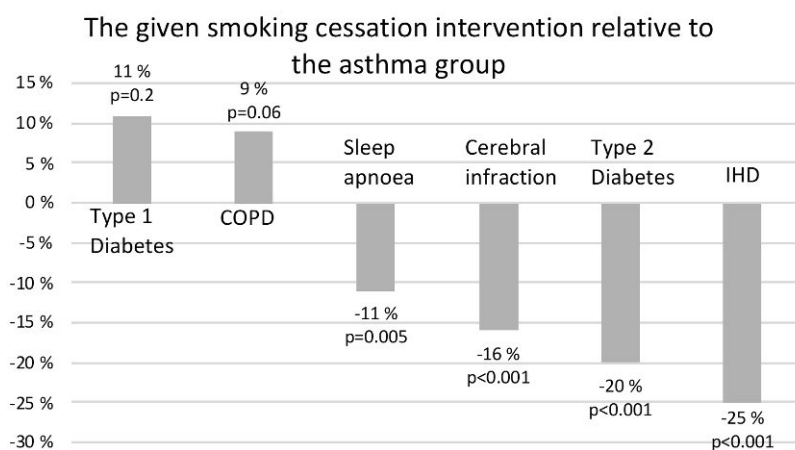

Figure 26. Relative proportion of patients who had been encouraged smoking cessation by the clinician. The differences between the subgroups are presented relative to the asthma group. *p* value is given for the logistic regression (asthma group=control group). COPD=chronic obstructive pulmonary disease. IHD=ischemic heart disease.

4.5.4   Validation of the Algorithms

The performance of the algorithms used in the study is summarised to Table 16. The rule-based algorithm 1 had excellent performance in finding any smoking-related sentence (F1-score 96.1). The performance of the ULMFiT-based classifier was excellent for never smokers with an *F1* score of 91.9, and good for ex-smokers and current smokers with *F1* scores of 80.4 and 78.5, respectively. The errors observed in the function of the ULMFiT-based algorithm were linked to (1) the distinguishing between current and former smokers, (2) ambiguous expressions such as "occasional smoker" and "long smoking history," (3) exposure to passive smoking, and (4) the content of separate documents. The rule-based algorithm 2 had excellent performance in identifying sentences related to smoking cessation intervention (F1-score 87.9).

Table 16. Performance of the algorithms. Modified from original Publication III.

Algorithm	Performance of the algorithm in	F1 score	Accuracy	Precision	Recall
Rule-based 1	Identifying smoking related sentences	96.1	94.3	99.0	93.3
Rule-based 2	Identifying sentences related to smoking cessation interventions	87.9	87.0	94.0	82.5
ULMFiT-based language model	Classifying smoking statuses				
	current smoker	78.5	85.9	66.2	96.2
	ex-smoker	80.4	89.9	97.6	68.3
	never smoker	91.9	93.4	94.9	89.2

5   Discussion

The objectives of this study were to assess smoking and work ability in patients with asthma using both a prospective and a retrospective study approach. The purpose was to understand how reliably patients report their smoking habits and whether smoking behaviours have changed over the years. The retrospective study approach was used to evaluate the documentation of the discussions between the physician and the patient about smoking and smoking cessation. Subsequently, the performance of the ULMFiT-based smoking algorithm in classifying patients' smoking status was investigated. The development of work ability was studied in a longitudinal setting to determine asthma and other health-related risk factors for poor development of work ability.

In the longitudinal analysis, self-reported smoking data were reliable, but pack years could be considered only as a rough estimate of the comprehensive consumption of tobacco products over time. According to the register-based study, 61% of asthma and 86% of COPD patients had a smoking status documented in the EHR, and the documentation rates improved over the years. However, only 55% of currently smoking asthma and 60% of currently smoking COPD patients were encouraged by the clinician to quit smoking.

The longitudinal analysis of asthmatics' work ability showed that the majority of asthma patients had stable work ability, but 8% of patients had a poor outcome. The risk of poor and moderate work ability was associated with the severity of the disease, high BMI, physically strenuous work, and comorbidities.

5.1   Smoking

Smoking has several adverse effects on the body, which are related to the onset and progression of the disease as well as long-term treatment outcomes. Smoking has been suggested to increase the onset of asthma (Polosa et al. 2013) and to worsen the outcome of the disease, as evidenced by an accelerated decrease in lung function (Aanerud et al. 2015; J. J. K. Jaakkola et al. 2019; Tommola et al. 2016), corticosteroid insensitivity (Chalmers et al. 2002; Tomlinson et al. 2005), and increased severity of asthma (Eisner et al. 2007; Polosa et al. 2011; Westerhof et al. 2014). Nevertheless, the prevalence of smoking has been shown to be similar in

asthma patients and healthy study populations (Cerveri et al. 2012; Polosa et al. 2013). In COPD, smoking cessation is the only evidence-based treatment that improves the prognosis of the disease (Smoking Cessation: A Report of the Surgeon General. 2020).

In Study I and II, the proportion of currently smoking asthma patients was 10.1% and 14.0%, respectively. Among COPD patients, 36% smoked daily. According to a Finnish tobacco statistics 2018 report, 14% of adults aged 20–64 smoked daily in 2018 (S. Virtanen et al. 2019). The average age of the asthma patients in Study I (55 years) was 10 years higher than the subpopulation in Study II (46 years), which can explain the difference. By contrast, the proportion of currently smoking asthma patients in Study III was 18%, which was exactly the same proportion found in the Finnish Seinäjoki Adult Asthma Study (SAAS) cohort (Tommola et al. 2016). However, almost 39% of asthma patients in Study III had no documentation of smoking status in EHR; therefore, the real proportion is probably higher. When the results were calculated from the patients whose EHR contained at least one smoking-related sentence, the proportion of currently smoking asthma patients increased to 29%, indicating that the real proportion was somewhere between 18% and 29%.

During the last 15 years, smoking has decreased in Finland (S. Virtanen et al. 2019). In 2004, 28% of men and 19% of women aged 20–64 smoked daily, whereas the corresponding proportions in 2018 were 15% and 13%, respectively. However, in adults, the declining trend seems to have stopped in 2018 (S. Virtanen et al. 2019). In Study I, the majority of asthma patients (85%) had stable smoking status during the 10-year follow-up, but 8.5% of the patients struggled with smoking cessation. More fluctuation was seen in the COPD group, where less than 70% of the patients had stable smoking status over the study years. Smoking is a highly addictive habit that typically requires three to four attempts before a smoker can quit smoking (Curry et al. 1994). In the present study, 34% of asthma patients and 45% of COPD patients who were active smokers at the beginning of the study succeeded in quitting (smoke-free in their last report). At the end of the follow-up, 92% of asthma and 73% of COPD patients were smoke-free. The previous study in this same cohort showed that smoking cessation is linked to the severity of airway obstruction, older age, and a greater history of pack years in COPD patients (Kupiainen et al. 2012). In the same study, patients had, on average, moderate smoking dependence (mean FNDT score 4.3), but the FNDT score did not significantly associate with FEV1 of predicted values. Smoking also accelerates the decline in lung function in asthma patients, which can increase symptoms of asthma and force the patient to quit smoking in a manner similar to that of COPD.

The trends in smoking were also analysed in the register-based study (Study III). In asthma patients, active smoking decreased only 2% when the two first study years were compared to the two last study years among those whose EHR contained at

least one smoking-related sentence. It is possible that documentation of smoking is most commonly missing when the patient does not smoke; therefore, these results should be interpreted with caution.

5.1.1 Consistency and Reliability of Smoking-Related Variables

The prevalence of smoking is commonly based on the self-reports of the patients. Previous studies have shown that the prevalence of smoking is often underestimated when it is based on self-reports (Gorber et al. 2009). The reliability of self-reported smoking data has been studied in cross-sectional settings among asthma patients (Lores Obradors et al. 1999; Pinheiro et al. 2018; Sato et al. 2003; Stelmach et al. 2015). All the studies used biochemical validation for the analysis of current smoking status. A Brazilian study of 51 asthma patients compared self-reported smoking statuses with levels of exhaled carbon monoxide and urinary cotinine (Stelmach et al. 2015). The misreporting rate among asthma patients was 29%. Another Brazilian study of 915 asthma patients found that misreporting was associated with the severity of the disease (Pinheiro et al. 2018). Among patients who reported being former smokers, the levels of urinary cotinine were higher in patients with severe asthma than in patients with mild-to-moderate asthma or no asthma diagnosis. The authors suggested that patients with severe asthma should be better screened for smoking. By contrast, a study conducted in Japan reported that only 2 of the 161 asthma patients claimed to be non-smokers, although biological validation indicated smoking (a serum cotinine level > 50 ng/mL) (Sato et al. 2003). However, the study subjects were aware of biological validation, which may have influenced the self-reports. Similar studies on COPD patients have shown that misreporting rates are higher in smoking cessation studies compared to epidemiological studies where no expectations of succeeding in smoking cessation have been announced (Hilberink et al. 2011; Monninkhof et al. 2004; Murray et al. 1993). Overall, cultural factors and external expectations seemed to affect the results.

In the present study (Study I), the consistency and reliability of self-reported smoking history were analysed in a longitudinal setting using the test–retest method. The questions used were similar to those used previously in several Finnish epidemiological studies. Test–retest reliability assessment is a common way to analyse the consistency and stability of responses over repeated, standardised questionnaires. Several previous longitudinal studies using self-reported smoking data have investigated the reliability of responses by repeating identical question patterns at two or more time points (Bernaards et al. 2001; Brigham et al. 2008, 2009; Huerta et al. 2005; Johnson et al. 2001; Soulakova et al. 2012). However, no longitudinal studies have been performed in patients with asthma or COPD in the

past. Smoking-related data play an important role in the treatment of patients with asthma or COPD. Both patient groups could potentially misreport their smoking habits because the relationship between smoking and lung diseases is usually known among patients. In the 10-year follow-up study (Study I), the patients' self-reported smoking statuses were examined between the follow-up years. Only 5.8% of asthma patients reported an unreliable path of responses. The corresponding rate was 2.3% among COPD patients. The results may suggest that patients with asthma experience more social pressure that is traced by the rising disapproval towards tobacco smoking. Previous population-based studies in the USA and Israel have reported misreporting rates of 11% and 8%, respectively (Huerta et al. 2005; Soulakova et al. 2012). Overall, our results showed that patients with asthma or COPD reported their smoking status truthfully.

The consistency of other smoking-related variables, such as the number of cigarettes, starting, and stopping years, were analysed by computing intraindividual variation between questionnaires (ICC values). ICC values were moderate for cigarette consumption, good for the starting year, and excellent for stopping year. Obviously, participants remembered the quitting year better than the starting year, since it was closer to the time of the study. However, starting years were remembered correctly even in cases where the individuals had been ex-smokers for several years (mean variation 2.1-4.1 years). Similar findings have been reported in earlier studies where the test–retest method has been used. A study by Soulakova et al. (2012) found good reliability for stopping (ICC 0.86) and starting years (ICC 0.78) (Soulakova et al. 2012). In other studies, ICC values for starting years have varied between 0.73-0.83 (Huerta et al. 2005; Johnson et al. 2001). In the present study, more variation was observed in cigarette consumption, probably due to misremembering or real fluctuation. A population-based study by Soulakova et al. (2012) reported ICC values of 0.77 for cigarette consumption, which was almost the same as that found in asthma and COPD patients in our study (ICC 0.74). These days, smoking may not be as stable a habit as it used to be, especially in study populations that are actively reminded of the dangers of smoking. The set of smoking-related questions used in the study was quite simple. The short questions might increase the response rates, but unfortunately, these questions did not optimally consider the dynamic changes in participants' smoking habits, such as gaps in smoking. Therefore, pack years can be considered only as a rough estimate of the comprehensive consumption of tobacco products over time. Some of the study subjects realised the problem and described their complete smoking history in free text next to the questions.

5.1.2   Smoking Intervention

All clinical guidelines encourage physicians to ask patients about smoking and advise smokers to quit (GINA 2020; Asthma. Current Care Guidelines 2012). In the register-based study (Study III), 61% of asthma patients had smoking status documented in the narrative reports of EHR. The analyses were conducted using a combination of rule-based and deep learning-based algorithms to extract and classify smoking statuses from the natural language of EHR. Compared to the asthma group, smoking status was documented more frequently in patients with COPD (86%) and sleep apnoea (83%). The trends over time showed that physicians documented patients' smoking status more frequently in 2016–2018 than in 2010–2012. The trends improved, especially in asthma and other disease groups, with the lowest documentation rate at the beginning of the study period. At the end of the study, the documented rates were highest in asthma, COPD, and sleep apnoea patients. In the study hospital, these patient groups were treated by pulmonologists, but this did not explain the differences alone. Compared to other specialties, a pulmonologist may ask patients more systematically about their smoking. Additionally, the introduction of preliminary information forms a few years ago likely increased documentation activity. A recent study by Meijer et al. found that pulmonologists often experience fewer barriers, such as lack of time and training, than other specialists and healthcare professionals (Meijer et al. 2019). Most previous studies examining the documentation rate of smoking status in patients with asthma or COPD have been conducted in primary care. The documentation rates in COPD patients vary between countries. A recent German study reported that 44% of COPD patients had a smoking status documented in primary care (Heinmüller et al. 2020). In a Danish study, the documentation rate was 92.1% in primary care (Lange et al. 2007) and a Swiss study reported a rate of 95% (Kaufmann et al. 2015). A study conducted in primary care clinics in the USA found that 94% of asthma patients had their smoking status recorded (Bailey et al. 2020).

Earlier studies have shown that although clinicians ask about smoking, they are less likely to advise smokers to quit (Gräsbeck et al. 2020; Keto et al. 2015; Meijer et al. 2019). In a Finnish questionnaire-based study, 65% of the physicians reported nearly always asking how much the patient smoked, and 58% of the physicians marked smoking status in the EHR (Keto et al. 2015). However, only 4% of the physicians reported nearly always prescribing withdrawal medication, and 10% nearly always recommended nicotine replacement therapy. Primary care physicians were about 2–10% more active than secondary care physicians in most individual consultation activities (Keto et al. 2015). However, the study was based on self-reports, and the results need to be interpreted with caution. Another Finnish study by Gräsbeck et al. studied smoking cessation interventions before surgery (Gräsbeck et al. 2020). This register-based study examined how smoking status is documented in

primary care referrals and outpatient clinic records before surgery, and the initiation of preoperative smoking cessation in current smokers. Based on hospital EHR, 14% of the primary care referrals and 18% of the outpatient clinic records included smoking status. Out of all current smokers, 2% had received smoking cessation intervention in primary health care and 15% in secondary health care unit (Gräsbeck et al. 2020). The initiation of smoking cessation interventions in primary health care was based on referrals, and it is possible that the intervention activity is higher than documented in the referrals. In the present work (Study III), 49% of currently smoking patients discussed smoking cessation with the clinician. In the asthma patients, the corresponding rate was 55%, and in the COPD patients 60%. However, it is possible that physicians discussed smoking and smoking cessation with the patients more often than what was written in the EHR.

Compared to the asthma group, the proportion of patients who were currently smoking and were encouraged to quit smoking by the clinician was 11% higher in patients with type 1 diabetes and 9% higher in patients with COPD. The average age of the patients with type 1 diabetes was lowest, which may affect the clinician's ability to implement smoking cessation care. Interestingly, the same analysis between asthma and sleep apnoea patients showed that sleep apnoea patients received 11% less encouragement from the physician, despite more frequent documentation of smoking status. The reason for this observation is unclear. One explanation may be that physicians do not consider smoking as harmful in sleep apnoea patients as in asthma patients. Another could speculate that sleep apnoea patients are less motivated to quit smoking due to the fear of gaining more weight after smoking cessation. Overall, it seemed that the specialists still missed the opportunity to discuss the effects of quitting on long-term treatment outcomes. Past studies have reported that attitudes, guideline familiarity, interest, skills, lack of time, and confidence are the common explanations for not implementing smoking cessation care more effectively (Keto et al. 2015; Meijer et al. 2019). In summary, clinicians working in secondary health care should use their authoritative role in supporting cessation.

Nurse-managed smoking cessation programmes are usually run both in primary and secondary health care, but physicians often underuse these services (Meijer et al. 2019). In the present study, patients treated in the pulmonary clinic were referred to the cessation nurse more often than in the other patient groups, and similar findings have been reported in a recent study (Meijer et al. 2019). Overall, the proportions were rather small in all groups, which are mostly due to the organisational factors. In Finland, primary health care has the main responsibility of counselling and managing smoking cessation programs. Smokers' interest, clinicians' unawareness of available services, and disregard for shared responsibility could also expound the discrepancy in the findings.

5.2   Work Ability

Asthma is a common disease in working-aged people and may have a negative impact on an individual's work ability and productivity (Blanc et al. 2001; Jousilahti et al. 2016; Lundbäck et al. 2016). In the present longitudinal study (Study II), the development of WAS trends was followed in a cohort of 529 asthma patients. Using Fréchet distance clustering, we identified the four clusters of patients with differently developing WAS. Almost 70% of the patients had a stable WAS trend with either excellent or good work ability. In one-fourth of the patients, WAS remained moderate but stable, while eight percent of patients had poor WAS already at the beginning of the study, and it decreased even more during follow-up. To find asthma-related and other health-related risk factors for the poor development of WAS, we built logistic regression models in which baseline characteristics were used as predictors. As a result, moderate or poor development of work ability was associated significantly with the number of pack years, high BMI, adult onset of asthma, physically strenuous work, and number of comorbidities, especially in psychiatric conditions, GERD, and hypertension. After adjusting for age and gender, pack years and adulthood onset of asthma lost their significance.

Previous studies have suggested that the severity of asthma is associated with decreased work ability, and similar findings have been seen in this study (Eisner et al. 2006; Gonzalez Barcala et al. 2011; Lindström et al. 2011). Based on patient-reported medication, there were significantly more patients with severe asthma (the use of a high dose of ICS with a second controller) in the poor and moderate groups compared to the groups with good to excellent WAS. Overall, work disabilities have been shown to be common among asthma patients. For example, sick leaves are reported to be more common in asthma patients than in healthy controls (Hansen et al. 2012; Kauppi et al. 2010). During the 10-year study period, 3.4% of patients retired due to disability, and 6% reported being unemployed at some point in the study. In Finland, asthma, as such, is an unusual cause of disability pension (Nyman 2018). A small number of prior studies have compared unemployment rates in asthma patients and controls, but no significant difference has been found (Eisner et al. 2002; Hansen et al. 2012; Sauni et al. 2001). However, there is some evidence that patients with severe asthma, severe respiratory symptoms, or a lower level of education are more often unemployed than asthmatics with good disease control (Eisner et al. 2007; J. Peters et al. 2007; Taponen et al. 2017). In the current study, the unemployment rate was low over the follow-up years, varying between 1% and 2%, which was less than the general unemployment rate among middle-aged Finns (6%) (Labour Force Survey 2018).

Work type has an important effect on work ability, especially when a patient has a chronic disease. In asthma patients, a high physical workload was associated with decreased work ability, and similar findings were seen in this study (Van Den Berg

et al. 2009). The risk of moderate-poor work ability increased 3.5-fold when a patient had physical work. However, the risk was not significant when the poor work ability group alone was compared to the other groups. The reason is probably lower statistical power (Cluster 4 included only 41 patients) and a similar trend for physical work in the two poorest clusters. Altogether, patients with asthma might experience respiratory symptoms more easily during physical work, which can further lead to a decrease in work ability.

Age at asthma onset is an important factor in the phenotypic expression of the disease (P. Ilmarinen et al. 2015). In the cohort (Study II), the majority of the participants (86%) had adult-onset asthma, which is often nonatopic, more severe, and leads generally to poorer prognosis. By contrast, childhood-onset asthma is usually characterised by atopy and corticosteroid sensitivity, and it usually has a good prognosis (Bisgaard et al. 2010; Paaso et al. 2014). Previous studies have associated adult-onset asthma with obesity, female sex, smoking, occupational exposures, stressful life events, chronic rhinosinusitis, and respiratory infections (Amelink et al. 2013; P. Ilmarinen et al. 2015; Wenzel 2012). According to a recent study, patients with adult-onset asthma have a higher risk of work disability than patients with childhood-onset asthma, with the risk increasing later the asthma is diagnosed (Taponen et al. 2019). In the current study, some evidence of increased risk was found, but the effect was not statistically significant in the adjusted model. The reason for inconsistency is probably different adjustment. In a study by Taponen et al. (2019), the model was adjusted for gender and smoking status, while in our study the model was adjusted for age and gender. Consistently, in our study, the mean age of the study population was low, and therefore, the diagnosis ages of asthma were overall lower. In the study by Taponen et al. (2019), age at asthma diagnosis was not related to risk of work disability under 50 years of age. In the 50+ age group, the risk of work disability was raised (OR 3.6, 95% CI 1.4–9.1) when asthma was diagnosed at the age of 50 years or more compared to patients with asthma diagnosed at the age of 0–17.

Smoking could potentially have an influence on asthmatics' work ability, but previous studies have reported inconsistent results. Many studies have found no association between smoking and work ability or disability (Blanc et al. 2003; de Bortoli et al. 2020; Hakola et al. 2011). By contrast, current cigarette smoking, past smoking, and environmental tobacco smoke have been shown to be associated with respiratory symptoms at work (Blanc et al. 2003). There is some evidence that tobacco smoking could also have a negative impact on work ability (Eisner et al. 2006; Lindström et al. 2011; Taponen et al. 2017) and increase sick leaves (de Bortoli et al. 2020). In the present study, the number of smokers was small, and no association was observed between smoking status and WAS. Similarly, the pack years showed no clear effect on decreased work ability. In the univariate model, the

number of pack years was a significant risk factor for moderate to poor work ability. However, the significance was lost in the adjusted model, most probably due to the higher mean age of Cluster 3.

Asthma patients with comorbid conditions have been shown to have decreased quality of life and worse asthma control (Gershon et al. 2012; P. Ilmarinen et al. 2016; Wijnhoven et al. 2003). Comorbidities also affect asthma patients' work ability, increasing, for example, the risk of long-term work disability (Hakola et al. 2011). At the present study, many of the comorbidities that had a negative influence on the development of WAS, were overweight-related. Prior studies have reported that being overweight is an important risk factor for asthma (Sivapalan et al. 2015). In addition, obesity-related asthma has been suggested to be a distinct asthma phenotype (Sivapalan et al. 2015; Wenzel 2012). It is known that obese and overweight asthma patients have reduced HRQoL, more respiratory symptoms, and worse asthma control, and they are less sensitive to asthma therapy, especially for ICS (Klepaker et al. 2019; Sivapalan et al. 2015). In general, BMI has been reported to link negatively with work ability in the healthy population, and the same association was seen among asthma patients in this study. However, in our study, type 2 diabetes did not affect the poor development of WAS in any of the tested models.

Psychosocial factors, such as depression and perceived stress, have been shown to increase the risk of adult-onset asthma, but the direction of causality between asthma and psychosocial factors remains unclear (P. Ilmarinen et al. 2015). There is also evidence that patients with worse asthma control have an increased risk of depression (Katz et al. 2010). The mechanisms behind the co-occurrence of asthma and depressive disorder have been suggested to be explained by several common pathophysiological mechanisms, such as high levels of inflammatory mediators (Gao et al. 2015; P. Ilmarinen et al. 2015). The literature also suggests that the presence of depression and asthma together increases the risk of work disability (Ehteshami-Afshar, FitzGerald, Carlsten, et al. 2016; Hakola et al. 2011). In the present study, all psychiatric conditions requiring medication were combined for analysis. As a result, we found that psychiatric diseases were an independent risk factor for moderate and poor WAS trends in asthma patients.

At the beginning of the study (Study II), the patient-reported HRQoL scores (15D and AQ20) were significantly worse in the two poorest clusters than in clusters 1 and 2. The same trend was observed in the later follow-up years. WAS correlated better with the general HRQoL instrument than with the respiratory-specific HRQoL scores. This further suggests that asthma-related comorbidities play an important role in the development of symptoms experienced by a patient. Comorbidities play a significant role in severe asthma and thus affect patients' work ability. Therefore, the diagnosis of existing diseases and patients' comprehensive treatment are

essential to maintaining the patients' work ability until the end of their work career (Padilla-Galo et al. 2019). Overall, healthcare professionals should identify those asthma patients who have risk factors for decreased work ability based on clinical examination and anamnesis. These patients need regular controls in occupational healthcare units, where their work ability can be supported.

5.3   Text Mining Methods

The implementation of EHR has led to the explosive growth of digital health data. This creates an opportunity to derive valuable insights from patient data for the foundation of evidence-based medicine. In Finland, EHRs comprise both structured and unstructured elements in which smoking statuses are usually documented in an unstructured manner. In general, structured data is easier to analyse, while unstructured data requires natural language processing tools before it is usable for analyses. In the current study (Study III), patients' smoking statuses and the conversations between the patient and the physician about smoking cessation were studied using a combination of rule-based and deep learning-based algorithms. Both rule-based algorithms had excellent performance, but algorithm 1 (identifying smoking-related sentences) performed better than algorithm 2 (identifying sentences related to smoking cessation intervention), since the desired task was simpler. However, important disadvantages of these types of algorithms are that the rules need to be constructed manually and they work only in a specific dataset. In Finland, simple methods using structured data have been used in clinical setting. For example, the Finnish Evidence-Based Medicine Electronic Decision Support (EBMEDS) system, developed by Duodecim, is based on rules and has been used to support clinical decision making (Evidence-Based Medicine Electronic Decision Support, EBMeDS. EBMeDS White Paper 2020). EBMEDS can be integrated into EHRs, and it provides reminders, therapeutic suggestions, and diagnosis-specific links to guidelines. More complex models have been studied and developed, but many of them are not yet in clinical use yet. In future, NLP tools such as ULMFiT could interpret free text and create structured data for decision support systems.

Clinicians often believe that point-and-click EHR templates could limit their ability to describe a patient's clinical story and to thoroughly document the medical decision-making process that is always unique to each patient encounter (Barry 2010). Further, hospitals need to build the foundation for evidence-based medicine and clinical decision-making, which can become a challenge without validated language models and classifiers that work in multiple languages. In the present study, the deep learning-based ULMFiT algorithm classified patients' smoking statuses from Finnish narrative reports with good performance. The algorithm learned the structure and general features of the Finnish language from Finnish Wikipedia. Then

the language model was fine-tuned with the narrative reports of EHR. Lastly, a classifier was built on top of the fine-tuned language model using annotated smoking-related sentences. One important advantage of using this type of language model is that once the model has been fine-tuned to Finnish narrative reports, it can be further used as the basis for new classifiers needed in other studies. In general, the ULMFiT and other deep learning-based approaches used in NLP tasks are based on pre-trained language models. These models have been shown to be promising tools for the standardisation of the language used in narrative reports, including acronyms, abbreviations, eponyms, and jargon words (Swaminathan et al. 2020; Syed et al. 2020). A study by Karlsson et al. (2021) used this same algorithm to examine the effect of smoking cessation in cancer patients and validated it with 1014 patients (Karlsson et al. 2021). The performance of the algorithm was similar to that of our patient cohort. To the best of our knowledge, no other previous study has used the ULMFiT-based approach in Finland. Overall, deep-learning-based models will play an important role in the future when building tools to support clinical decision-making and research.

5.4 Strengths and Limitations

The major strengths of the study are the longitudinal study design with many patients, especially in Study III. Using an algorithmic approach, we were able to study in total 35 650 patients in Study III. Study I and II had both prospective (patient-reported outcomes) and retrospective (medical history) elements. The participants did not undergo a clinical examination, but their health status was retrospectively reviewed from the medical records at the baseline. The asthma diagnosis, as well as all the other diagnoses, was physician-diagnosed; no self-reported diagnoses were used. In addition, a pulmonologist verified asthma and COPD diagnosis in Study I and II.

The study was also strengthened by the long test–retest interval that was used in Study I. 'Test–retest reliability' assessment measures the consistency and stability of the responses over repeated, standardised questionnaires. Several studies using self-reported smoking data have evaluated the reliability of responses by repeating identical sets of questions on two or more occasions (Bernaards et al. 2001; Brigham et al. 2008, 2009; Huerta et al. 2005; Johnson et al. 2001; Soulakova et al. 2012). In these studies, the test–retest interval varied commonly between a few weeks and two to three months. Studies, where test–retest intervals spanned years were scarce (Brigham et al. 2008; Hudmon et al. 2005). To the best of our knowledge, Study I was the first longitudinal study in asthma and COPD patients concerning the reliability of their smoking habits. The previous cross-sectional studies have verified patients' answers with a biological indicator, such as measuring the cotinine level

(Hilberink et al. 2011; Lores Obradors et al. 1999; Monninkhof et al. 2004; Murray et al. 1993; Sato et al. 2003; Stelmach et al. 2015). In general, biological indicators are considered the most reliable methods for confirming patients' self-reported smoking. However, self-reported questionnaires and structured interviews are currently the only way to collect historical data on smoking (Axelsson et al. 2016).

One important strength of the CAD cohort (Study I and II) was the high response rates across the study years. In Study I, the response rates decreased gradually from 97% to the level of 69%. As expected, the mortality rate among asthma patients was significantly lower compared to that in the COPD group (39.7% vs. 6.2%, P <0.001). Despite the long follow-up period, only 72 (3.1%) of the study subjects withdrew from the study. The characteristics of withdrawals were studied, but no differences were observed in their smoking habits. Therefore, no significant response bias occurred in the results. As a limitation, the participants had left the smoking-related questions rather often unanswered. Nearly 9% of all respondents who returned the questionnaire omitted the smoking section once or more. The reason for this observation might be frustration with answering the repeated questions, especially if the smoking status remained unchanged. Further analysis showed that 75% of these patients had stable smoking status. The response rates in the subpopulation of the CAD cohort (Study II) were even better throughout the study period, decreasing gradually from 99% to 88%. There were no withdrawals, and only one patient died.

One of the strongest elements of the study was the use of validated questionnaires that were well suited for epidemiological studies. Both HRQoL instruments, 15D and AQ20, have been validated and widely used in medical studies. Each follow-up year, the questions in each section were identical, but the sections involved varied slightly. The medication section was updated in each follow-up year, and new products on the market were added to the list. There were also some limitations regarding the questionnaire. The smoking section was simple and did not consider the dynamic changes in patient's smoking habits, such as gaps in smoking and changes in the number and type of tobacco products over time. The evaluation of patients' work abilities was also simple. The multidimensional WAI instrument is often used in occupational health care to assess the work ability of employees (Tuomi et al. 1998), but due to our study design, we were not able to use it. However, previous studies have shown that WAS, which is a single item of WAI, predicts future work disability almost as accurately (Jääskeläinen et al. 2016; Kinnunen et al. 2018; Lundin et al. 2017). As an additional limitation, sick leave and quality of work were based on patient-reported data.

An obvious limitation of the study was that the assessment of asthma severity was based on medication only. We did not evaluate whether asthma was controlled or not. According to ERS/ATS guidelines, control is defined by symptoms, exacerbations, and degree of obstruction (Chung et al. 2014). All the patients did not

have spirometry results and asthma test was not included in the questionnaire, which led to an inability to assess asthma control. Therefore, the results need to be interpreted with caution. The study also had weaknesses related to the type of asthma. First, occupational asthma could not be assessed because potential work-related exposures were not recorded. Second, the evaluation of allergy was based on self-reported medication, and no data from allergy testing were available (e.g., prick test, IgE test).

One of the major limitations of Study III is that the results were based on an algorithmic approach, and in reality, the conversations between a patient and a clinician are probably more active. Furthermore, only behavioural support for smoking cessation was evaluated, even though pharmacological treatment has also been shown to increase success rates (Fant et al. 2009). In Finland, first-line pharmacotherapies for smoking cessation are nicotine replacement therapy (NRT), varenicline, and bupropion. Since NRT is based on over-the-counter products, it was impossible to monitor treatment through the hospital's EHR. Study III also had weaknesses related to the patient classification. Some patients had more than one of the studied diagnoses, but they were classified into only one disease group based on the diagnosis that appeared first. This choice was made on the basis of making the patient group definitions and follow-up time definitions unique and simple. A more refined approach could be used in future studies.

5.5   Future Aspects

Over the past 10 years, the smoking rate in the adult population has generally decreased, but the trend of decline seems to have stopped in 2018 (S. Virtanen et al. 2019). Finland has a goal to be a smoke-free country by 2030; specifically, less than 5% of the working-age population is expected to smoke and use other non-medical nicotine products (*Savuton Suomi 2030*). Overall, smoke-free legislation has been shown to be effective in Finland and other countries (Joossens et al. 2020). The Finnish Tobacco Act has led to many societal changes that prevent people from taking up smoking, support smokers in quitting, and protect individuals from being exposed to tobacco smoke. However, the increasing use of e-cigarettes and snus has created new challenges. Health care has an important role in counselling and delivering smoking cessation interventions, but smoking cessation care is often not systematic (Meijer et al. 2019). It is known that two-thirds of smokers want to quit, but only one-third of them get support from a physician (Babb et al. 2017; Helldán et al. 2015). We found that smoking status was documented in 60% of patients with chronic disease and that the physician had discussed smoking cessation in 49% of patients who were current smokers. Overall, it is obvious that the treatment of

tobacco and nicotine addiction should be better integrated into the comprehensive treatment of every patient.

The common barriers to inadequate implementation of smoking cessation care are lack of time, lack of knowledge, lack of interest, and lack of confidence (Keto et al. 2015; Meijer et al. 2019). To improve smoking cessation care, it is necessary to invest in the training of health care professionals. It could be useful to understand the mechanisms behind addiction, to learn the basics of motivational interviewing, and to be more familiar with the clinical guidelines. In general, the treatment of tobacco and nicotine addiction is not simple, and repeated relapses may also frustrate the physician. However, it is good to keep in mind that smoking cessation requires three to four attempts before a smoker is able to quit; therefore, relapse does not necessarily suggest treatment failure (Curry et al. 1994). Understandably, tight schedules do not allow cessation interventions to be carried out properly. In these cases, it is important that all healthcare units have a treatment protocol for smoking cessation. This could be built around the classical 5A approach. Every healthcare professional should know where a smoker can be referred if there is not enough time and knowledge to deliver cessation care themselves. These options may include smoking cessation nurses, telephone helplines, group, and individual cessation programmes, and self-help materials. Altogether, it is useful to always construct these protocols within healthcare units or areas to maximise their usability in clinical work.

The negative effects of smoking on the progression of several diseases and long-term treatment outcomes are undeniable. As shown in the present study, clinicians still do not systematically document patient's smoking status. Therefore, it may be possible that they also do not take smoking into account when monitoring treatment outcomes. The importance of documentation has also increased with the introduction of e-health services. The Finnish online health service Kanta gives patients the opportunity to browse their own health records and prescriptions. A lack of mention of smoking or the importance of quitting may be a signal to the patients that their smoking is not considered as harmful for the health. In some countries, smoking is a mandatory element in EHR, which means that physicians cannot save records before marking a patient's smoking status. This type of system is more likely to increase physicians' activity in providing smoking cessation assistance, but how many mandatory elements can we include in the EHR without further complicating physicians' work?

The holistic treatment of asthma and co-existing comorbidities is essential to maintaining patients' work ability. In addition to pharmacological treatments, it is important to integrate the guidance of nonpharmacological therapies into routine care. This includes avoidance of exposures (smoking, occupational exposures, indoor/outdoor allergens/air pollution), avoidance of medications that worsen

asthma (e.g., NSAID), weight management, support for psychological and socioeconomic problems, a healthy diet, and encouraging regular physical activity. It is also good to remind you how to prevent exercise-induced bronchoconstriction (warm-up and SABA before exercise).

Artificial intelligence will significantly change healthcare systems over the next 10 years. This will also be reflected in how we can leverage EHRs. EHRs are already huge databases, but there is a need for effective and automated tools to exploit them. The synergy of various methods, such as text mining, NLP, and ML, can help to build cognitive systems that support healthcare professionals in complex tasks, such as early disease diagnosis, individualised treatment planning, and risk prediction. Such smoking algorithms could help healthcare professionals consider patients who do not have smoking status documented in EHRs or who have had years of previous documentation. This would create the possibility of implementing smoking cessation interventions at an earlier stage. It could also help clinicians consider the possibility of COPD in patients who have had smoking data for several decades. Artificial intelligence will also advance research and enable large-scale studies to be carried out. For example, using different text mining techniques, researchers can derive valuable insights from textual data. This creates an opportunity to develop novel and improved therapies, identify relationships between symptoms, diseases, and treatments, and discover new hypotheses and hidden knowledge. Currently, deep learning-based approaches are state-of-the-art in many text mining applications (Lecun et al. 2015). They are built on language models that aim to standardise the language used in narrative reports. However, the Finnish language creates an additional challenge in building functional language models. In the future, the development of these models and their open sharing will certainly improve the quality of Finnish healthcare systems.

6   Conclusions

Based on the aims of the study, the main results were as follows:

1. Self-reported smoking data is reliable and consistent among elderly asthma and COPD patients over a 10-year follow-up. Pack years can be considered only as a rough estimate of the comprehensive consumption of tobacco products over time. About 20 % of the patients can have some fluctuation in their smoking habits, or the responses may include uncertainties to some extent. (Study I)

2. Over 90% of asthma patients' WAS remained stable throughout the ten-year follow-up period. However, 8% of the patients who had either more severe asthma, high BMI, or multiple comorbidities showed significantly poorer outcomes. (Study II)

3. The general HRQoL instrument correlated stronger with WAS than respiratory-specific HRQoL, further supporting the importance of the comprehensive treatment of asthma and co-existing chronic diseases. (Study II)

4. Based on the hospital EHR, smoking status was documented in 61% of asthma patients, and clinicians discussed smoking cessation with 55% of asthmatics who were current smokers. Corresponding rates among COPD patients were 86% and 60%, respectively. Overall, the trends in documentation improved over a 9-year study period. (Study III)

5. The ULMFiT-based classifier showed good performance in classifying smoking statuses from Finnish narrative reports and allowed us to efficiently examine a large amount of patient data. (Study III)

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Appendices

Appendix 1. Questionnaire used in Study I and II (translated from Finnish to English)

1.QUALITY OF LIFE QUESTIONNAIRE (15D©)(Sintonen 2001)
Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).

2 ( ) I hear normal speech with a little difficulty.

3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.

4 ( ) I hear even loud voices poorly; I am almost deaf.

5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.

2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.

3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.

4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.

5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.

2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.

3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.

4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.

5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.

2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).

3 ( ) I need some help from another person in eating.

4 ( ) I am unable to eat by myself at all, so I must be fed by another person.

5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.

2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.

3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.

4 ( ) Most people have great difficulty understanding my speech.

5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.

2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.

3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.

4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.

5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free- time activities) without difficulty.

2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.

3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.

4 ( ) I can only manage a small proportion of my previously usual activities.

5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( )I am able to think clearly and logically, and my memory functions well

2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.

3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.

4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.

5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity. 4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

2.Medication (Note! All new products on the market are added each year)

2.1 My regular lung medicines at the moment. *Please circle the right strength and write your daily dose (inhalation/tablets per day).*

1. Inhaled long acting bronchodilators

Product	Strength		Inhalations per day
1. Serevent	25	50	
2. Oxis	6	12	
3. Foradil	12		
4. Formoterol	12		
5. Spiriva	2,5	18	
6. Cycloterol	12		
7. Fomeda	12		
8. Formaxa	12		
9. Onbrez	150	300	
10. Striverdi	2.5		
11. Eklira	322		
12. Seebri	44		

2. Inhaled corticosteroids

Product	Strength					Inhalations per day
1. Pulmicort	100	200	250	400		
2.Novopulmon	200	400				
3. Aerobec	50	100				
4. Beclomet	200	400				
5. Flixotide	100	125	200	250	500	
6. Alvesco	80	160				
7. Asmanex	200	400				
8. Budesonid	100	200	400			
9. Budesonide	250					
10. Flutide	250					

3. Inhaled combination therapy

Product	Strength						Inh. per day
1. Seretide	25/50	25/125	25/250	50/100	50/250	50/500	
2.Symbicort turbuhaler	xx						
3.Symbicort turbuhaler Forte	xx						
4.Symbicort turbuhaler Mite	xx						
5. Innovair	100/6						
6. Bufomix	160/4,5	320/9					
7. Relvar	92/22	184/22					
8. Flutiform	50/5	125/5	250/10				
9. Ultibro	85/43						

4. Leukotriene receptor antagonist

Product	Strength	Tablet(s) per day
1. Singulair/Montelukast/Astecon	10 mg	
2. Accolate	20mg	

5. Theophylline

Product	Strength			Tablet(s) per day
1. Retafyllin	200mg	300mg		
2. Nuelin Depot	175mg	250mg	350mg	
3. Aminocont	225mg			
4. Daxas	500mg			

5.Cromons

Product	Strength	Inhalations per day
1. Tilade	2mg	
2. Lomudal	5mg	

7. My other regular medicines (write freely) _____

2.2 When required (PRN) medicines, treatment of exacerbations and support medicines for asthma.

1. **Have you used short acting bronchodilators <u>during the last year</u>?**
   (products like: Airomir®, Atrodual®, Atrovent®, Atrovent Comp®, Bricanyl®, Buventol®, Ipramol®, Ipraxa®, Ipratropiumbromid®, Salbuvent®, Salipra®,Ventilastin®, Ventoline®)
   - ( ) not at all
   - ( ) on average once a week or less
   - ( ) on average 2-4 times per week
   - ( ) on average once a day
   - ( ) on average at least two times per day
   - ( ) I treat acute symptoms by using long acting beta agonist or combination medication (like products: Serevent®, Seretide®,Foradil®, Formoterol®, Oxis®, Symbicort®)

2. **Have you used oral corticosteroids for the worsening of asthma or COPD <u>during the last year</u>?** (products like: Medrol®, Prednisolon®, Prednison®)
   - ( ) not at all
   - ( ) once
   - ( ) twice
   - ( )more than two times

3. **Have you used antihistamines <u>during the last year</u>?** (products like Aerius®, Alzyr®, Benadryl®, Cetimax®, Cetirizin®, Clarityn®, Gardex®, Geklimon®, Heinix®, Histanova®, Histec®, Histadin®, Kestine®, Kestox®, Levazyr®, Loratadin®, Revitelle®, Senirex®, Siterin®, Telfast®, Tuulix®, Xyzal®, Zyrtec®, Aerinaze®, Cirrus®, Clarinase®, Duact®)
   - ( ) not at all
   - ( ) yes, one packet (10-12 pills)
   - ( ) yes, two or more packets

4. **Have you used nasal cortisone sprays, powders or drops for the treatment of rhinitis <u>during the last year</u>?** (products like Avamys®, Beclonasal®, Beconase®, Flixonase®, Nasacort®, Nasofan®, Nasonex®, Rhinocort®)
   - ( ) not at all
   - ( ) yes, one dispenser
   - ( ) yes, two or more dispensers

5. **Have you used nasal cromones/antihistamines for the treatment of rhinitis <u>during the last year</u>?** (products like Glinor®, Lastin®, Livostin®, Lomudal®)
   - ( ) not at all
   - ( ) yes, one dispenser ( ) yes, two or more dispenser

3. Health related work ability

3.1 I am currently
( ) employed full time
( ) employed part time
( ) on a disability pension (go to question 4)
( ) an old-age pension (go to question 4)
( ) a full time student (go to question 4)
( ) unemployed (go to question 4)
( ) on maternity leave (go to question 4)
( ) having child care leave (go to question 4)
( ) other, what_____(go to question 4)

3.2 Occupation or working duty _____

3.3 Are your main job requirements?
( ) mental
( ) physical
( ) combination of mental and physical

3.4 How is your current work ability compared with your life time best?
Assuming your work ability has got 10 points at its best, circle the score that you give for your current work ability.

_____

0   1   2   3   4   5   6   7   8   9   10

_____

0 = unable to work   10 = work ability at its best

3.5 Sick leave days from gainful employment?
How many full days have you been away from work due to your health status (treatment and examination of any disease) in the last year (12 months)?
( ) not at all
( ) maximum 9 days
( ) 10-24 days
( ) 25-99 days
( ) 100-365 days

How many months have you been gainfully employed during the past 12 months?
( ) not at all
( ) 1-3 months
( ) 3-6 months
( ) 6-12 months

4.Smoking

4.1 Have you ever smoked regularly?
    ( ) never (go to question 5)
    ( ) I quit smoking
            starting year _____
            stopping year _____
    ( ) I still smoke
            starting year_____

4.2 What and how much on average do you smoke or have you smoked?
( ) cigarettes   ___pcs/day
( ) cigar   ___pcs/day
( ) pipe   ___gr/week
( ) loose tobacco   ___gr/week

5.Shortness of breath

5.1 Which of the following statements describe best your current health?
  ( ) Shortness of breath occurs only under very heavy exertion
  ( ) Shortness of breath occurs only when rushing or uphill
  ( ) Because of shortness of breath, I have to walk slower than my age and stop sometimes when walking on a flat ground.
  ( ) Because of shortness of breath, I can only walk about 100m or few minutes before I have to stop.
  ( ) I have shortness of breath daily during normal activities, for example when I get dressed; I can't go out due to shortness of breath.

Chronic bronchitis
Have you had a cough where you bring up sputum/phlegm almost daily for at least 3 months a year?
( ) no
( ) yes

How long does the cough last?
( ) never as long as two consecutive years
( ) at least two consecutive years or more

6.The following questions refer to the effect of asthma or COPD in your daily life <u>during the last month.</u> (Barley et al. 1998)
Please, answer Yes or No or Does not apply for each item.

	yes	no	not apply
1. Do you cough often during the day?	☐	☐	☐
2. Does your chest trouble often make you feel restless?	☐	☐	☐
3. Does gardening make you breathless?	☐	☐	☐
4. Do you worry when going to a friend's house that there might be something there that will upset your chest?	☐	☐	☐
5. Do you get chest problems when you come into contact with strong smells, exhaust fumes, cigarette smoke, perfume etc?	☐	☐	☐
6. Does your partner find your chest trouble upsetting?	☐	☐	☐
7. Do you feel breathless when trying to sleep?	☐	☐	☐
8. Do you worry about the long term effects of the drugs you take for your chest trouble?	☐	☐	☐
9. Does getting emotionally upset make your chest trouble worse?	☐	☐	☐
10. Are there times when you have difficulty getting around the house because of your chest trouble?	☐	☐	☐
11. Does your chest problem make you breathlessness when you do things at work? (paid employment).	☐	☐	☐
12. Does walking upstairs make you breathless?			
13. Do you get breathless doing housework?	☐	☐	☐
14. Does your chest trouble make you go home sooner than others after a night out?	☐	☐	☐
15. Do you suffer from breathlessness when you laugh?	☐	☐	☐
16. Does your chest trouble often make you feel impatient?	☐	☐	☐
17. Do you think the fullness of your life is limited by your chest trouble?	☐	☐	☐
18. Do you feel drained after a cold because of your chest trouble?	☐	☐	☐
19. Do you have a feeling of chest heaviness?	☐	☐	☐
20. Do you worry a lot about your chest trouble?	☐	☐	☐

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