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TREATMENT OF ATOPIC ASTHMA IN PRIMARY HEALTH CARE GUIDED BY EXHALED NITRIC OXIDE MEASUREMENT

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To my family

ABSTRACT

Aims: The overall aims of this thesis were to increase knowledge about how patients with asthma rate their health and investigate if we can improve asthma management, with focus on asthma as a chronic inflammatory disease, by use of measurement of the fraction of exhaled nitric oxide (F_ENO) in monitoring of asthma in primary health care.

Methods: Study I included data from a public health questionnaire, which was sent to 8,200 persons (age > 18 years) randomly selected from the population register in Stockholm County. After two reminders, 5,355 persons had responded (67.5 %). Study II was a longitudinal, non-controlled study. Twenty patients with physician-diagnosed atopic asthma and perennial asthma symptoms (age 18 - 50 years) were consecutively recruited from Runby primary health care centre and examined four times during eight weeks (baseline, 2, 4 and 8 weeks). Data for study III and IV were collected in a randomised, controlled study, conducted at 17 primary health care centres in the middle and south of Sweden. A total of 187 non-smoking participants with physician-diagnosed asthma, verified perennial allergy and ongoing inhaled corticosteroid (ICS) treatment (age 18 – 64 years) were randomised to F_ENO-guided treatment or usual care and were followed up for five visits during one year.

Results: Respondents with asthma in study I had approximately three times higher odds of fair/poor self-rated health (SRH) than those in the corresponding sex and age groups who did not have asthma, excepting younger women (18 – 44 years). SRH was associated at least as strong as quality of life to asthma. Study II showed a significant correlation between FENO and IgE-antibody levels against perennial allergens at baseline ($r = 0.47$, $p = 0.04$), which disappeared after a step-up in ICS treatment. Nine patients had persistently elevated F_ENO at last visit (mean 35 ppb vs. 16 ppb). This group was more frequently exposed to relevant allergens or colds (89 % vs. 27 %, $p < 0.05$) and had higher perennial IgE levels compared with the normalised group (mean 28.9 vs. 10.7 kU/l, $p < 0.05$). Results from study III showed that total and specific IgE levels decreased 10 – 36 % ($p < 0.05$ all, except for mugwort) over one year. The changes were not related to any change in allergen exposure, and specific IgG4 levels remained unaltered. The decrease in IgE against perennial allergens related to mean ICS dose ($p = 0.030$),

months on leukotriene-receptor antagonist (LTRA) ($p = 0.013$) and change in F_ENO ($p = 0.003$), and interestingly also to change in the Asthma Control Questionnaire (ACQ) score ($p = 0.012$) and Mini-Asthma Quality of Life Questionnaire (mAQLQ) score ($p = 0.009$), as well as change in SRH rating ($p = 0.041$). In study IV, the change in mAQLQ score over one year (primary endpoint) did not differ between the groups ($p = 0.197$), whereas the mAQLQ symptom domain score ($p = 0.041$) and the ACQ score ($p = 0.045$) both improved significantly more in the F_ENO-guided group. Furthermore, the moderate exacerbation rate was reduced by almost 50 % in the F_ENO-guided group ($p = 0.024$). Mean overall ICS use was similar in the two groups ($p = 0.95$).

Conclusions: In Sweden, men > 18 years and women > 45 years with asthma score SRH worse compared with people in corresponding sex and age groups without asthma, which indicates that there is a need to improve asthma management. Exposure to relevant allergens, and type and degree of sensitisation, are important factors to consider when assessing the F_ENO value. Optimised anti-inflammatory treatment with ICS and LTRA in asthma patients with ongoing treatment at baseline resulted in reduced total and specific IgE levels which were unrelated to the degree of allergen exposure. Using F_ENO to guide anti-inflammatory treatment within primary care significantly improved asthma symptom control and reduced exacerbation rate in adults with atopic asthma without increasing overall ICS use. F_ENO-guided anti-inflammatory treatment appears useful to improve the management of patients with atopic asthma.

LIST OF PUBLICATIONS

I. **Syk J**, Alving K, Undén AL. Association between asthma and self-rated health: a population-based study. Clin Respir J. 2012 Jul;6(3):150-8.

II. **Syk J**, Undén AL, Alving K. Relationship between exhaled nitric oxide and IgE sensitisation in patients with asthma: influence of steroid treatment. Clin Respir J. 2009 Jul;3(3):143-51.

III. **Syk J**, Malinovschi A, Borres MP, Undén AL, Andreasson A, Lekander M, Alving K. Parallel reductions of IgE and exhaled nitric oxide after anti-inflammatory asthma treatment. In manuscript.

IV. **Syk J**, Malinovschi A, Johansson G, Undén AL, Andreasson A, Lekander M, Alving K. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized controlled trial. J Allergy Clin Immunol Pract. 2013;1:639-48.

CONTENTS

LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
BMI	Body mass index
ECP	Eosinophil Cationic Protein
F_ENO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GQLI	Gothenburg quality of life instrument
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
LABA	Long-acting β_2-agonist
LTRA	Leukotriene receptor antagonist
mini-AQLQ	mini-Asthma Quality of Life Questionnaire
NO	Nitric oxide
ppb	parts per billion
SABA	Short-acting β_2-agonist
SRH	Self-rated health

BACKGROUND

Asthma is a chronic inflammatory airway disorder (1), which has become a major public health problem affecting people of all ages throughout the world. The prevalence of asthma has increased in Sweden and most other countries in the Western world, for unknown reasons, during the last five decades (2). More than 300 million people are estimated to be affected worldwide (3, 4), including about 800,000 people in Sweden. The majority of these people has mild to moderate asthma, which is diagnosed and treated in primary health care. Many asthma patients in primary care have insufficient asthma control (5, 6). Poorly controlled asthma may severely limit daily activities, cause reduced productivity and can sometimes be fatal. The total cost of asthma in Sweden is estimated to SEK 7.4 billion per year (7).

Short history of asthma and its treatment

Asthma is a disease that has been recognized for thousands of years. It was known in ancient Egypt and several remedies are described in hieroglyphics, for example inhalation of fumes from herbs that had been heated. The word "asthma" comes from the Greek verb aazein, to pant, and is first mentioned as a medical term in the "Corpus Hippocraticum", a collection of around 60 early ancient Greek medical works by Hippocrates (460 – 370 BC), the father of modern medicine. Inhalation of herbs containing ephedrine (a bronchodilator) has been used as treatment in China for several hundred years. Asthma was long thought of as solely a muscle spasm in Western medicine. Smoking leaves from the herb "Datura" (Datura stramonium) was introduced as a bronchodilating treatment during the 18th century and remained as a treatment in Sweden until 1975, when such cigarettes were taken off the list of registered

drugs. A strong cup of coffee could be recommended as treatment in the middle of the 19th century and theophylline derived from tea leaves was found to have a bronchodilating effect. During the 1950s, short-acting β2-receptor agonists (SABA) were introduced as a medical treatment and has been available in inhaler form since 1956. At the beginning of the 20th century, asthma was seen as a psychosomatic disease. During the 1960s, asthma was recognized as an inflammatory disease and corticosteroids started to be used. Corticosteroid treatment increased during the 1970s when it became available in inhaler form and is now basic treatment for asthma. Treatment with long-acting β2-agonists (LABA) was introduced during the 1990s and later in the same decade leukotriene receptor antagonists (LTRA) and combination therapy with corticosteroids and LABA was also introduced. Anti-IgE is part of the treatment of severe atopic asthma since the 2000s. Airway inflammation has been recognized as an important part of the disease and is since the 1990s a part of the definition of asthma.

Definition of asthma

Asthma is a multifactorial and heterogeneous disease with several different phenotypes. It is defined by its clinical, physiological and pathological characteristics. The pathogenesis is unclear and it may be recognized as a syndrome rather than as a specific disease. The most common type of asthma is atopic asthma, including more than 50 % of all asthmatics (8). The Global Initiative for Asthma (GINA) has a definition of asthma based on the consequences of airway inflammation: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness that leads to recurring episodes of wheezing, breathlessness, chest tightness, and

coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment." (9)

Diagnosis

Asthma can often be diagnosed on the basis of examination of the patient and the patient's symptoms and medical history. Typical symptoms are episodic breathlessness, wheezing, coughing and chest tightness. The most common abnormal physical finding is wheezing on auscultation. A positive family history of asthma, symptom worsening at night and by non-specific irritants, and the presence of allergies increases the probability of asthma (9). There is a 2 – 6 times higher risk of developing asthma if a person is sensitised to an allergen (10-12). Asthma in Sweden is especially associated with indoor allergens and the most important allergen is from cat. Lung function measurements, such as spirometry and peak expiratory flow (PEF), provide help to confirm the diagnosis by detecting variable airway obstruction. When lung function is normal but symptoms consistent with asthma are present, further investigation with bronchial challenge tests to detect airway hyper-responsiveness may help establish the diagnosis.

Epidemiology – prevalence, incidence and remission

The prevalence of asthma started to rise during the 60s. It increased from 1 – 2 % to 2 – 4 % in the 70s (13), to 5 – 7 % during the 80s – 90s (14, 15), and to around 7 – 10 % today (16-18). Recent studies suggest that the increase in asthma prevalence is now levelling off (19, 20). Young adults have the highest prevalence because of high incidence among children and adolescents (8 – 14 per 1000 per year) (10, 21), and the prevalence then decreases, to be lowest in

middle age. The incidence of asthma among adults is estimated to be 1 – 4 per 1000 per year (22). In children, asthma is twice as common among boys, but after puberty it becomes more prevalent among girls. In adults, asthma is regarded as a chronic disease with a low remission rate, only around 1 % per year (23). Remission of asthma is common in children and adolescents but symptoms may relapse later in life. A Swedish study reported remission in 10 % per year, but half of these relapsed within a few years (12). Results from a British birth cohort study showed that 35 % of children with asthma symptoms before seven years of age were in remission at 33 years of age (24). The mortality rate because of asthma is low in Sweden (25).

Classification of asthma severity and control

Assessment of asthma severity involves both the severity of the symptoms and responsiveness to treatment. Asthma severity is not a static feature, but may change during a patient's lifetime. Previous GINA guidelines (2005) proposed subdivision of asthma by severity into four categories in patients on medication: Intermittent, Mild persistent, Moderate persistent, and Severe persistent. The definition was based on medication, the level of symptoms, exacerbations, and lung function. The guidelines have later been modified and now focus more on asthma control. The latest consensus-based guidelines from GINA, updated 2012, propose that asthma severity should be classified on the basis of the intensity of treatment required to achieve good asthma control (9). Asthma control refers to the extent to which treatment can eliminate the manifestations of asthma for a prolonged time and minimise future risk for exacerbations, decline in lung function, and side-effects of treatment. GINA guidelines propose three levels of asthma control: "controlled", "partly controlled", and "uncontrolled". Clinical characteristics of "controlled asthma"

in GINA guidelines are: Absence of daytime symptoms (twice or less/week), no limitation of daily activities (including exercise), no nocturnal symptoms or awakening because of asthma, minimal use of rescue treatment (twice or less/week), normal or near-normal lung function, and no exacerbations. Asthma is categorized as "partly controlled" if any of these characteristics are not fulfilled and "uncontrolled" if three or more are not fulfilled.

Asthma treatment

The aim of treatment is to control the clinical manifestations of asthma for a prolonged time. An essential part of treatment is to give education and advice. Important topics to cover are: General information about asthma, purpose of medication, inhalation technique, self-management plans, smoking cessation, and allergens and other trigger factors. The recommendations on asthma treatment from the Swedish Medical Products Agency can be described in terms of steps: 1) Patients with intermittent asthma may use SABA as needed. 2) If the patient has asthma symptoms more than twice a week, inhaled corticosteroids (ICS) should be added. 3) If a patient has a medium high dose of ICS (budesonide 400 µg/day) and still has symptoms, LABA or LTRA may be added. 4) The next step is a further increase in ICS dose. 5) The last step is additional medication with oral corticosteroids or monoclonal anti-IgE antibodies.

International asthma guidelines

GINA works with health care professionals and public health officials around the world to improve the lives of people with asthma. GINA was launched in 1993, their guidelines are the most widely known and disseminated guidelines and are updated yearly on their website.

QUALITY OF LIFE AND SELF-RATED HEALTH

Quality of life

The concept quality of life (QoL) is used to evaluate the general well-being of individuals, but does not have a formal definition. It is multidimensional and reflects many different aspects of well-being, including physical, mental, emotional and social dimensions. Evaluation of asthma studies was earlier focused on biomedical parameters as outcome, especially various measures of lung function. Measurement of lung function gives important information about the status of the airways, but little information about the patient's well-being, satisfaction with health and function in everyday life. Research has shown that the relationship between lung function and QoL is weak (26, 27). Interest in measuring aspects that are important to the patient has grown during the last two decades, with an aim to get a more complete and relevant picture of a patient's status. QoL questionnaires can be classified as generic or disease-specific. Generic questionnaires can be used to compare QoL between patients suffering from different diseases or between persons with and without disease. A disease-specific questionnaire is designed to focus on symptoms and problems related to a specific disease and does not allow comparison between different diseases or with healthy persons.

Asthma-related quality of life

The Asthma Quality of Life Questionnaire (AQLQ) was developed in the 1990s by Elisabeth Juniper et al. to measure the functional problems (physical, emotional, social and occupational) that are most troublesome to adults (17 – 70 years) with asthma (28). There are 32 questions in the AQLQ within 4 domains (symptoms – 12 items, activity limitation – 11 items, emotional function – 5 items and environmental stimuli – 4 items). Respondents score

their experiences during the previous two weeks on a 7-point scale (7 = not impaired at all, 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses and the individual domain scores are the means of the items in each domain. AQLQ has shown strong measurement properties. It is thoroughly validated, has good test-retest reliability and is responsive to within-patient change over time. A change in score of 0.5 is the smallest change that can be considered clinically important and is called MCID (Minimal Clinically Important Difference).

The Mini-AQLQ (mAQLQ) is a shorter version of AQLQ with a total of 15 questions in the same domains as the original AQLQ (symptoms – 5 items, activity limitation – 4 items, emotional function – 3 items and environmental stimuli – 3 items). It is easier and quicker to use in large clinical trials. As in the AQLQ, a change in score greater than 0.5 is considered clinically important. The questionnaire is fully validated and has good reliability (29).

Generic quality of life

The Gothenburg Quality of Life Instrument (GQLI) was developed in 1973 using the WHO definition of health, including physical, mental and social well-being. Physical well-being is rated with questions about hearing, vision, memory, fitness and appetite. Mental well-being is rated with questions about mood, energy, patience, self-confidence and sleep. Social well-being is rated with questions about home and family situation, housing, work situation, economy, health and leisure. All items are rated on a Likert 7-point scale from "very poor" (1 point) to "excellent, could not be better" (7 points) (30).

Cantril's Ladder of Life is a 10-point scale where respondents rate their present, past (1 year ago), and future (1 year from now) quality of life. The highest step on the ladder represents the "best possible life for you" and the

lowest step the ” worst possible life.” The higher the score, the better (31).

Self-rated health

Measuring self-rated health (SRH) is based on asking individuals to rate their general health status on a four- or five-point scale. The exact wording and response options of SRH questions vary, but they represent assessment of the same phenomenon and show basically concordant results (32). The most commonly used version of the question is “How do you rate your general health status?” with five response alternatives: Very good, Quite good, Neither good nor poor (fair), Quite poor and Poor. The interest for SRH increased markedly in 1982 when a study showed that SRH was a predictor of mortality among the elderly (33). Several studies have since then shown that SRH is a powerful independent predictor of morbidity and mortality, even after controlling for different confounders including medical diagnosis, functional ability and psychosocial factors (34-37). SRH can also predict hospitalisation and frequent examinations in out-patient clinics (38-40). Improvement in SRH is associated with reduced risk of mortality (41). Little is known about the biological mechanisms connecting poor SRH with higher morbidity and mortality. Two recent studies have shown an association between poor SRH and elevated levels of circulating inflammatory cytokines (42, 43). Inflammatory cytokines can affect both the immune system and the brain and give rise to a sickness response that includes symptoms such as depression, tiredness and loss of interest in one’s environment (44, 45). Although there is a strong correlation between SRH and QoL, they may reflect and include different aspects of well-being (46).

ASTHMA CONTROL

The Asthma Control Questionnaire (ACQ) was developed in the 1990s by Elisabeth Juniper et al. to measure the adequacy of asthma control and change in asthma control in adults. The ACQ has seven questions covering night-time symptoms, morning symptoms, limitation of daily activities, shortness of breath, wheezing, FEV1% predicted (pre-bronchodilator) and daily rescue bronchodilator use. Patients score their experience during the previous week on a 7-point scale (0 = no impairment, 6 = maximum impairment), FEV1 is measured and FEV1% predicted is estimated. The ACQ score is the mean of seven questions. Shortened versions of the ACQ, where FEV1 or bronchodilator use has been omitted, have also shown good measurement properties for large clinical trials and epidemiological studies (47). The ACQ has strong measurement properties and has been fully validated. Well-controlled asthma has a score below 1.0. A change in score of 0.5 is the smallest change that can be considered clinically important (28, 48).

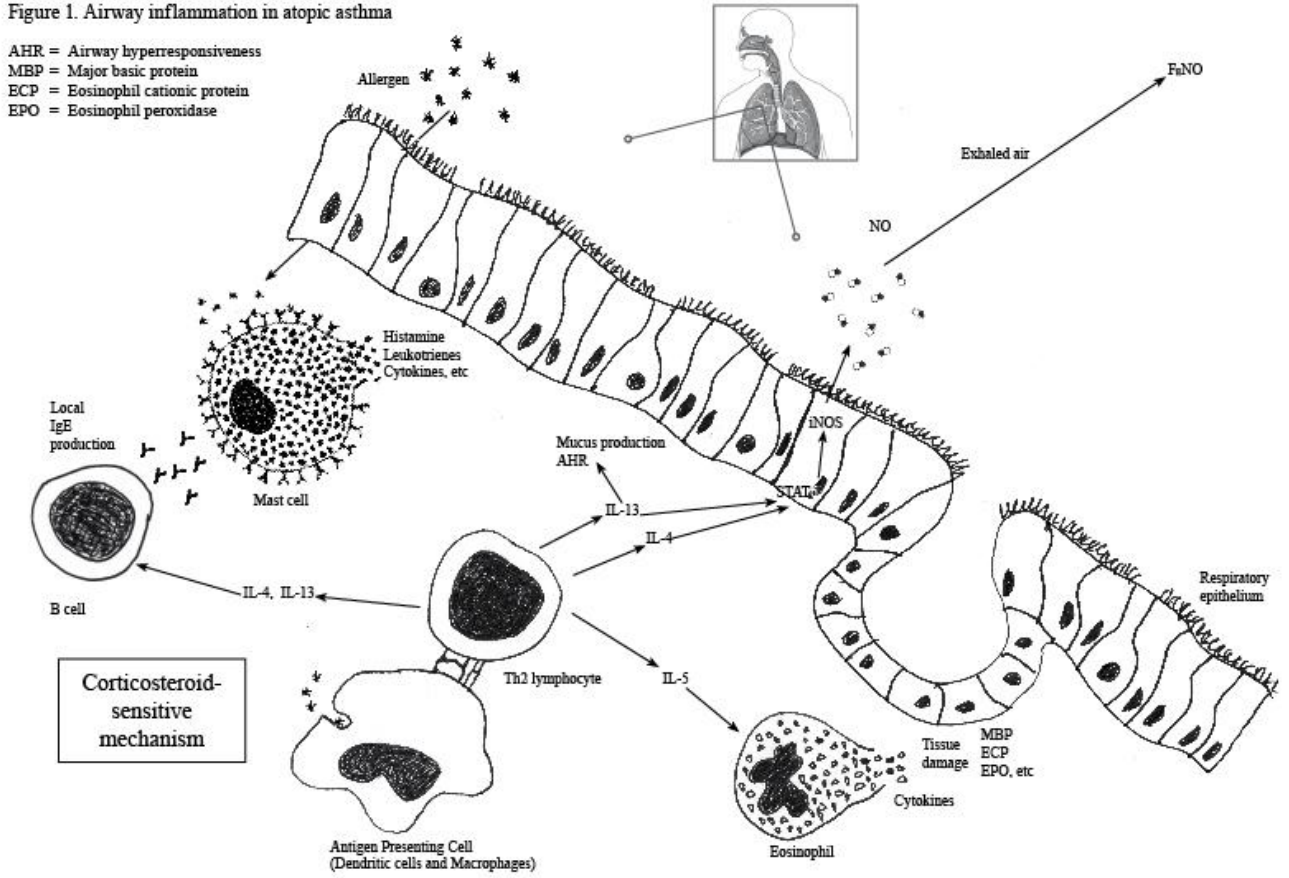
AIRWAY INFLAMMATION IN ASTHMA

Inflammatory mechanisms in atopic asthma

Asthma is by definition a chronic inflammatory disorder of the airways. The inflammation is recognized as Th2 lymphocyte-driven and is characterized by an increased number of inflammatory cells in the airway mucosa (especially eosinophils and mast cells) (1), mucous oedema, hypertrophy of smooth muscles and glands, increased mucus secretion, and basement membrane thickening (Figure 1). The inflammation may lead to permanent structural changes in the airways, so called airway remodelling (8, 50). The Th2 cells are activated through presentation of allergens by antigen presenting cells (APC), for example

dendritic cells or macrophages. The cells then modulate the inflammation by producing several cytokines, which activate and recruit other inflammatory cells and promote immunoglobulin E (IgE) production (51). The dominant cytokines are interleukins IL-4, IL-5 and IL-13. IL-4 is crucial in the primary sensitisation process, IL-13 seems to be important in the development and manifestation of airway changes typical to asthma and IL-5 seems to be the main cytokine involved in maturation, differentiation, and activation of eosinophils, and also recruits eosinophils to the airways. Further, IL-4 and IL-13 can induce the expression of the enzyme inducible nitric oxide synthase (iNOS), which forms nitric oxide (NO) in the airway epithelium, resulting in higher concentration of NO in exhaled air (52). The predominant mechanism for the development of asthma is sensitisation to allergens resulting in the formation of IgE antibodies, most commonly initiated in childhood by sensitisation to airborne allergens (8). IgE is an important mediator in atopic asthma, especially in the acute response to allergens and in the propagation of airway inflammation. Indoor and outdoor allergens are common and important triggers of asthma in the majority of patients. ICS represents the most effective maintenance therapy for this group of patients. IgE levels are considered to be relatively inert if allergen exposure is constant, and the effect of ordinary anti-inflammatory asthma treatment on IgE levels has been little studied

Figure 1. Airway inflammation in atopic asthma



Nitric oxide

NO has long been known as an atmospheric pollutant present in, for example, vehicle exhaust emissions and cigarette smoke, and it came as a surprise in the 1980s when NO was found to have a biological function as a vasodilator. The discovery triggered intense research activity and was awarded the Nobel Prize in 1998. In the beginning of the 1990s, Gustafsson *et al.* found that healthy humans have NO in exhaled air in low concentrations, measured in parts per billion (ppb) (53). Continuous and high production of NO takes place in the nasal cavity, especially in the paranasal sinuses (54, 55). NO is mainly formed by iNOS in the apical part of the respiratory and squamous epithelium in the airways and oropharyngeal tract, and can diffuse out into the airway lumen (56-58). iNOS produces NO in nanomolar concentrations in a continuous manner and is primarily regulated at the transcriptional level. There are low levels of NO in the alveolar tract because NO binds rapidly to haemoglobin in the blood. NO can also be formed non-enzymatically in the pharynx and mouth from nitrate in saliva by nitrate reductases in anaerobic bacteria (59). Nitrate is present in many vegetables, particularly in green leafy vegetables and is actively taken up by the salivary glands from plasma. Rhinovirus infections and air pollution increase exhaled NO levels, but bacterial respiratory tract infections do not seem to cause an elevation (60-62). Current cigarette smoking is associated with a 40 – 60 % decrease in exhaled NO levels (63). Assumed contributions of NO in exhaled air from different parts of the airways in normal individuals are: pharyngo-oral tract (40 %), hypopharynx-upper trachea (15 %), lower trachea-bronchi (35 %), bronchioli (5 – 10 %) and alveoli (2 – 3 %) (52).

Nitric oxide and asthma

The measurement of exhaled NO has been standardized for clinical use and ATS/ERS guidelines are the current standard with regard to methodological aspects and clinical interpretation (64, 65). Measurement is done after inhalation to total lung capacity followed by immediate exhalation into a NO analyser for 10 seconds at a flow rate of 50 ml/s. Exhaled NO can easily be measured in primary health care with a safe, simple, accurate and reproducible method. The result is expressed as the fraction of exhaled nitric oxide (F_ENO) in ppb. F_ENO has been shown to be elevated primarily in atopic asthma, whereas non-atopic asthma shows normal or near normal F_ENO levels (66-69). iNOS is markedly up-regulated in atopic asthma by Th2 cell-driven inflammation via IL-4 and IL-13 secretion. In line with this, F_ENO correlates with the degree of IgE sensitisation, as indicated both by IgE-antibody titres and by the number of positive skin-prick tests (70-73). F_ENO is elevated by relevant allergen exposure and conversely reduced by allergen avoidance (74, 75). Several studies have shown correlation between eosinophil counts (blood, induced sputum and bronchial biopsies) and F_ENO (76, 77). However, eosinophilia and F_ENO can be discordant, especially in severe asthma, and F_ENO should be regarded as a biomarker for mucosal Th2 cell-driven inflammation, regardless of eosinophil counts. Increasing F_ENO levels can predict deterioration in asthma control and forthcoming asthma exacerbations (78). Treatment with anti-inflammatory drugs, especially corticosteroids but also LTRA, reduces F_ENO levels (79-82). Use of F_ENO creates for example possibilities to diagnose corticosteroid-responsive disease, identify poor adherence and improve ICS dosing, which in turn can give better asthma control, improved quality of life and fewer relapses. F_ENO may be used as a complementary tool to traditional ways of assessing asthma (medical history, physical examination, and lung function test).

AIMS

The aims of the thesis were:

- To investigate how adult people with asthma rate their health and learn more about the association between asthma, a chronic inflammatory disease with a recognised systemic component, and self-rated health (SRH), by comparing SRH ratings in participants with and without asthma, and by comparing SRH with other generic quality-of-life instruments within each group.
- To investigate if F_ENO could be normalised by inhaled corticosteroid (ICS) treatment, following a stepwise algorithm based on the F_ENO value, and to learn more about the relationship between IgE sensitisation and F_ENO.
- To investigate if a year of optimised anti-inflammatory treatment could affect IgE levels in adult patients with ongoing ICS treatment and if a change in IgE levels was related to change in local (F_ENO) and/or systemic (serum ECP) inflammatory biomarkers, anti-inflammatory treatment, exposure to relevant allergens, asthma control, general and asthma-related quality of life, or self-rated health.
- To investigate if F_ENO-guided anti-inflammatory treatment could improve asthma-related quality of life (primary outcome), asthma symptom control, exacerbation rate, lung function and overall medication use in patients with atopic asthma over a study period of one year.

MATERIAL AND METHODS

Paper I

Data collection and study group

A total of 8,200 persons aged ≥ 18 years was randomly selected from the population register of two health care regions in Stockholm County: the north-western health care region and the Södertälje health care region. All data were collected from the answers to a public health questionnaire posted to the selected subjects in the spring of 1995. The original purpose of the questionnaire was to investigate health, quality of life, and health care use in the population. After two reminders, 5,355 persons (67.5 %) had responded. Persons reported dead, no longer living at an address or temporarily absent from an address were excluded (271 persons). Respondents were divided into those with and those without asthma (see definition below). Both groups were further divided by sex and age (18 – 44 and ≥ 45 years) (Figure 2). The cut-off point between the age groups was chosen to make the groups approximately equal in size and to minimise the risk of including persons with chronic obstructive pulmonary disease (COPD) in the younger age group.

Health variables

Asthma: Respondents were categorised as having asthma (i.e. current asthma) if they answered yes to both of two questions: "Do you have or have you had asthma?" and "Do you use any asthma medicine?" All others were included in the group of respondents who did not have asthma.

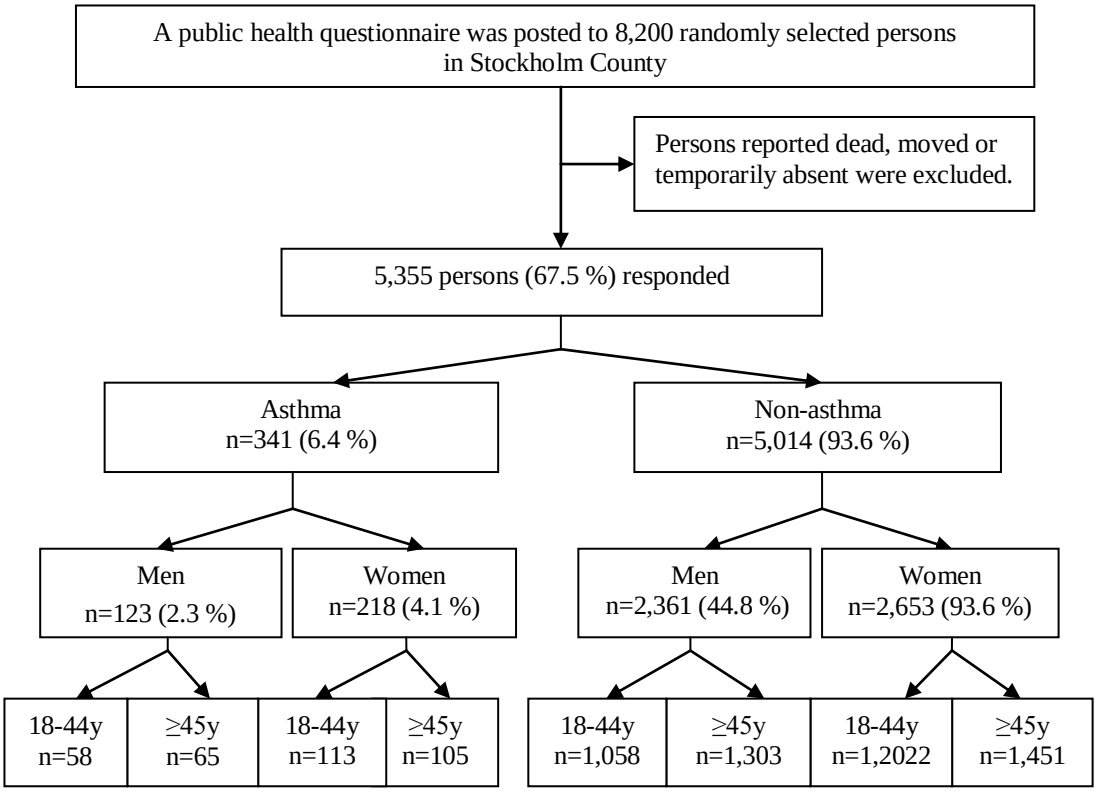
Self-rated health: Information on SRH was gathered using the question "How do you rate your general health status?" with five response alternatives (see

background for more information) In the text, the health of those who chose the alternative "neither good nor poor" is referred to as "fair".

Quality of life: The Gothenburg Quality of Life Instrument and Cantril's Ladder of Life were used to measure generic quality of life (see background for more information).

Physical health: We used the question "Are you suffering from any of the following chronic diseases? (yes or no)" as a measure of physical health. The chronic diseases listed included cardiovascular disease, diabetes, hypertension, joint/musculoskeletal disease, and chronic pain. The total number of positive responses (0 – 5) constituted the variable of physical health.

Figure 2. Trial profile study I



Socio-demographic factors

Educational status was divided into three levels: Compulsory schooling only, secondary schooling, and university education. The questionnaire included six response alternatives for occupational status: “working,” “studying,” “unemployed,” “on sick leave,” “retired,” and “other.” Respondents were divided into two categories on the basis of whether they were married or cohabiting (the first category) or not married or cohabiting (the second category). Physical activity during leisure time in the past year was also reported. There were four response alternatives: “inactive”, “moderate physical activity”, “moderate regular physical activity”, and “regular physical activity and exercise.” The two groups with most frequent exercise were merged into one group for the purpose of logistic regression analysis. Respondents were categorised into smokers and non-smokers on the basis of their response to the question “Do you smoke?”.

Paper II

Study group

Altogether, 20 patients (6 males) with physician-diagnosed allergic asthma and perennial asthma symptoms, between 18 – 50 years of age (mean 33.4 years), were consecutively recruited from Runby primary health care centre (PHC) in Upplands Väsby, a northern part of Stockholm County, during September – December 2003. All patients were non-smokers since at least six months and had not smoked for more than five years in total. Patients using LABA and/or LTRA had to change therapy or were excluded. Six patients using combined inhalation therapy with corticosteroids and LABA, changed therapy to ICS only (budesonide or fluticasone) and SABA (salbutamol or terbutaline) when needed, at least one week before inclusion in the study.

Study design

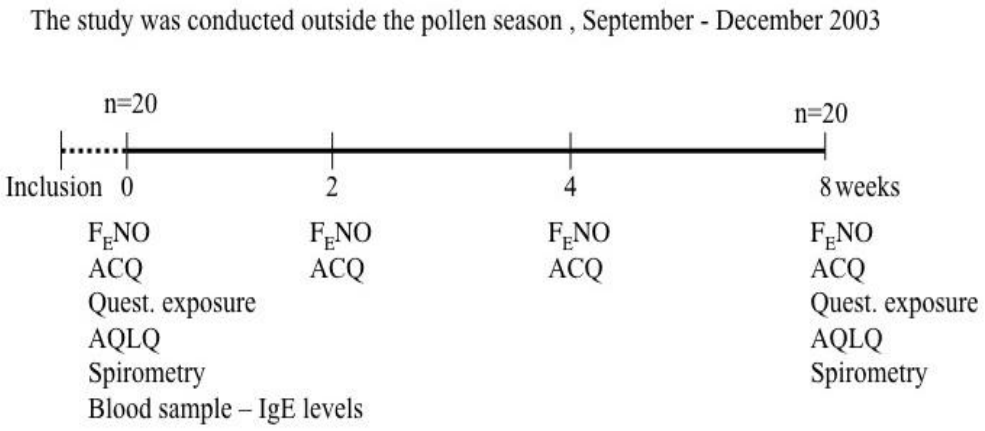
Participants were examined four times during eight weeks (baseline, 2, 4 and 8 weeks). The study was conducted outside the Swedish pollen season. At every visit, F_ENO was measured (mean value out of three measurements at an exhalation flow rate of 50 ml/s according to ATS/ERS guidelines with the NIOX® [Aerocrine AB, Stockholm, Sweden]) (64). ACQ and a questionnaire about environmental exposure* (allergen, cigarette smoke) were completed at every visit. Spirometry (Vitalograph, Spirotrac IV, Buckingham, England) with β_2-agonist reversibility test was performed (FVC, FEV_1, FEV%) and AQLQ was completed at baseline and the last visit. Asthma-related events including respiratory infections were registered at every visit. The patients were asked to keep diaries of daily medication intake (Figure 3). Allergy was confirmed with quantitative analyses of serum levels of IgE antibodies to cat, horse, dog, cladosporium and mite (perennial allergens), and timothy, birch and mugwort (seasonal allergens) (ImmunoCAP™, Phadia AB, Uppsala, Sweden). Sensitivity was confirmed toward at least one perennial allergen in all study subjects. The ICS dose was adjusted based on the F_ENO value using a stepwise algorithm (Table 1).

Table 1. Treatment algorithm guided by F_ENO

Treatment step	**1**	**2**	**3**	**4**	**5**
Budesonide, µg daily	0	200	400	800	1600
Fluticasone, µg daily	0	100	250	500	1000

A FE_{NO} value ≥ 22 ppb indicates a step-up and < 22 ppb a step-down of treatment. A step-down resulting in an increased NO value (≥ 22 ppb) was only allowed once during the study. Corticosteroid therapy was not withdrawn if the patient had used ICS at inclusion of the study.

Figure 3. Trial profile study II



F_ENO = Fraction of exhaled nitric oxide, ACQ = Asthma Control Questionnaire
Quest. exposure = Questionnaire about exposure to allergens, AQLQ =Asthma Quality of Life Questionnaire

*Environmental exposure was assessed with the following questions:
1. Do you regularly get exposed to smoke from cigarettes (almost daily since at least one month), at home, at work or anywhere else? – if yes, how many hours per day on average?
2. Do you have any pet animal at home? – if yes, what sort of animal?
3. Do you regularly (at least once a week since at least one month) get exposed to furred animals outside your home? – if yes, what sort of animal?
4. Do you get window pane condensation at home during the winter?

Relevant allergen exposure was defined as "yes" to questions no. 2 and/or 3.

Paper III

Study design and study group

All data in this study were collected from the study described in paper IV. Both treatment groups in paper IV were merged for this post-hoc analysis. Even though the treatment was adjusted on different grounds in these groups, both groups were focused on improving treatment by optimising the anti-

inflammatory treatment and used the same treatment steps. Mean ICS use did not change significantly within or between treatment groups during the study, but there was a significant redistribution of treatment steps in both groups (Figure 9). Thus, participants with high F_ENO or more symptoms, depending on group belonging, received more treatment, and participants with low F_ENO or few symptoms received less treatment. Thus, the anti-inflammatory treatment changed in both groups. After merging of the two original groups, it was confirmed that in patients with elevated F_ENO at baseline (women ≥ 24 ppb and men ≥ 26 ppb), the proportion of participants with LTRA increased from 2.5 to 22.2 % ($p < 0.001$). We also saw that mean ICS use increased with 180 µg/day ($p < 0.001$), resulting in a reduction in mean F_ENO levels with 13.5 ppb ($p < 0.001$) in this subpopulation. Furthermore, there was no significant difference in the change of IgE levels between the two original groups. Based on this, we merged the two original groups in paper IV to examine relationships between changes over time for the variables being studied in this post-hoc analysis.

Venous blood was sampled for analysis of specific IgE, total IgE and serum ECP at the start and end of the study. The titres of individual IgE antibody levels were grouped by summing the IgE titres. The groups were: perennial IgE (cat, dog, horse, mite x 2, and mould), seasonal IgE (birch, timothy and mugwort), food IgE (fx5= cow's milk protein, egg white, peanut, soy, wheat and fish) and all specific IgE (perennial, seasonal and food). Total IgE and specific IgE antibodies were analysed in a Phadia® 100 system with ImmunoCAP® reagents (Thermo Fisher Scientific, Immunodiagnostics, Uppsala, Sweden). Serum samples were initially stored at -20 °C (< 6 months) and then at -80 °C. Patient samples from the start and end of the study were analysed side by side for all serum measurements. Pollen count data were collected during 2006 – 2009 from three

stations: Stockholm, Forshaga and Malmö, which were as close to the participating primary health care centres as possible.

Paper IV

Study design and study group

This multicentre, open-label, parallel-group, randomised controlled study was conducted at 17 primary health care centres in the middle and south of Sweden from November 2006 to March 2010. A total of 187 participants were randomised to F_ENO-guided treatment or usual care. Eligible participants had a physician's diagnosis of asthma, had been on prescribed ICS treatment for at least six months, and had confirmed IgE sensitisation to at least one major airborne perennial allergen (dog, cat or mite). In addition, they were 18 to 64 years old, non-smokers since at least one year, and with a smoking history of < 10 pack-years. Exclusion criteria were: Ongoing pregnancy or breastfeeding, participation in another study, medical treatment solely with LTRA or in combination with an ICS in a budesonide equivalent dose of 0 – 400 µg (dose steps 1 – 3 in the study), and unstable asthma defined as ≥ 4 oral corticosteroid courses during the past year or hospitalization in the past six months.

Procedures

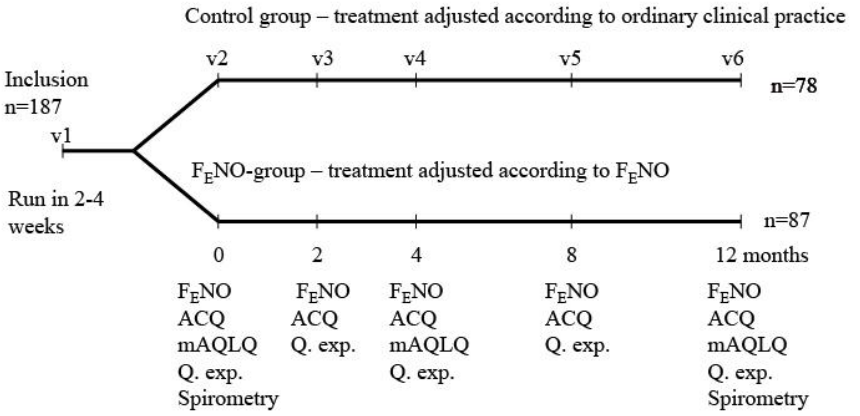
At visit 1 (screening) eligibility was confirmed and informed consent collected. Capillary blood was sampled to confirm perennial allergy using ImmunoCAP Rapid Wheeze/Rhinitis Child (Phadia AB, Uppsala, Sweden). All patients currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler and withdraw the LABA component. All patients switched SABA to a salbutamol inhaler (Buventol Easyhaler; Orion Corp, Espoo, Finland), with an

incorporated dose counter. Randomization was done by lottery. The examination *at visit 2* (2 – 4 weeks later) included F_ENO measurement (NIOX MINO; Aerocrine AB, Solna, Sweden), spirometry with reversibility test, mAQLQ, GQLI, SRH, ACQ, and a questionnaire on allergen exposure. Venous blood was sampled for serum IgE and ECP analyses. In the F_ENO-guided group, the anti-inflammatory treatment (ICS and LTRA) was adjusted according to an algorithm based on F_ENO levels (Table 2) and six fixed treatment steps (Table 3). In the control group, F_ENO measurement was done, but blinded to both operator and patient, and treatment was adjusted according to usual care, i.e. based on patient-reported symptoms, SABA use, physical examination and results of pulmonary function tests. Only the treatment steps described in Table 3 were allowed, but changes in treatment steps were entirely at the discretion of the treating physician and immediate changes over several steps were allowed. Permissible treatment steps basically followed the prevailing national guidelines at the time of study start, issued in 2002 by the Swedish Medical Product Agency, with the exception that only LTRA was used as add-on treatment. The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patient should be free from symptoms, maintain normal activity levels including physical exercise, maintain pulmonary function as close to normal as possible, avoid adverse effects of asthma medication, and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations. *At visit 3* (2 months), ACQ, SRH and questions about allergen exposure were reported. F_ENO was measured and treatment adjusted as described above. *Visit 4* (4 months), as visit 3 and also included mAQLQ. *Visit 5* (8 months) was identical to visit 3. *Visit 6* (12 months) was identical to visit 2. All participants received a logbook to bring home, in which they noted contacts with health

care, changes in drug therapy, sick leave or other problems between scheduled visits. Figure 4 shows a summary of the study design.

Cut-off levels for F_ENO were based on data showing that most healthy subjects have F_ENO levels below 20 ppb and on the suggestion that levels above approximately 25 ppb are associated with eosinophilic inflammation (83, 84). Also, the cut-off levels took into consideration the fact that men have slightly higher values than women, and a grey zone of 5 ppb was applied to avoid frequent dose changes. Exacerbations met the ATS/ERS Task Force criteria (85), and we defined moderate exacerbations as deterioration in symptoms with the need to step up controller treatment for at least two days, with or without a concomitant clinic visit or contact. Prophylactic increase in controller treatment before the pollen season was disregarded. Severe exacerbations were defined as worsenings in asthma that necessitated a course of oral corticosteroids.

Figure 4. Trial profile study IV



Exacerbations, SABA and ICS use were registered at every visit.

F_ENO = Fraction of exhaled nitric oxide, ACQ = Asthma Control Questionnaire,
mAQLQ = Asthma Quality of Life Questionnaire, Q. exp.= Questionnaire about exposure to allergens

Table 2. Algorithm guided by F_ENO

FENO, ppb		Change of treatment step
Women	**Men**	
<19	<21	↓ 1 step
19-23	21-25	No change
≥24	≥26	↑ 1 step*
≥30	≥32	↑ 2 steps**

*no change of treatment step if on step 4 or 5 and using ≤ 2 inhalations of short-acting β2-agonist per week. **only if on treatment step 1.

Table 3. Treatment steps

µg/daily	1	2	3	4	5	6
Budesonide	0	200	400	800	800 + LTRA	1600 + LTRA
Fluticasone	0	100	250	500	500 + LTRA	1000 + LTRA
Mometasone	0	100	200	400	400 + LTRA	800 + LTRA

LTRA = leukotriene-receptor antagonist (montelukast 10 mg daily)

ETHICAL APPROVAL

Studies I and II was approved by the local ethics committee at Karolinska Hospital, Stockholm, Sweden (Dnr: 94-289 and 03-246). Studies III and IV were approved as a multicentre study by the regional ethics committee in Stockholm, Sweden (Dnr: 2006/185-31).

STATISTICS PAPERS I-IV:

Common for all studies: Analyses of changes within and between groups were done with Wilcoxon signed-rank test and Mann-Whitney U-test, or the corresponding Student's t-tests when applicable. Categorical data were analysed using a chi-squared test, or Fisher's exact test when applicable. Spearman's rank test and Pearson's test were used for bivariate analysis. Two-sided tests with p-values less than 0.05 were considered significant.

Study I: For investigation of influence of confounding factors, we performed a multivariate analysis with fair/poor SRH as a dependent variable and education, physical activity, smoking, and marital status as independent variables (Table 5).

SRH was dichotomised into "good health" (response alternatives "very good" and "quite good") and "fair/poor health" (response alternatives "neither good nor poor," "quite poor," and "very poor"). We estimated two logistical models, one age-adjusted and one full model by sex and age group. Results are shown with odds ratios (OR) and 95 % confidence intervals (CI). The fit of the models was assessed and considered acceptable ($p > 0.05$) using the Hosmer-Lemeshow goodness-of-fit test. Analysis was also performed with occupational status and physical health as independent variables; this did not affect the association between fair/poor SRH and asthma (data not shown). Statistical analyses were performed with SPSS version 15 and Stata/IC 10.0.

Study II: For repeated measures (four visits), the change from baseline was tested using the Friedman test with Dunn's Multiple Comparison Test, or repeated measures ANOVA with Tukey's Multiple Comparison Test when appropriate. F_ENO values were transformed into the corresponding logarithm before statistical evaluation. Analysis of IgE sensitisation was evaluated by using the sum of IgE-antibody titres (kU/l) for either all eight allergens tested or subsets of allergens. Statistical analyses were performed with Graph Pad Prism (version 4.0c).

Study III: The titres of individual IgE-antibody levels were grouped by summing the IgE titres. IgE data were converted to the log base 10 scale and analysed with a paired t-test. Statistical analyses were performed with Stata/IC11 version 2.14.1.

Study IV: Sample size was calculated with a two-sided 5 % significance level and a power of 80 %. A total of 64 participants per group was needed to detect a mean difference of 0.5 in mAQLQ between groups, assuming a standard deviation of 0.7 (based on data from study II). Data were analysed on an intention-to-treat basis. The primary endpoint and most of the secondary

endpoints were analysed by comparing changes between visit 2 and visit 6 according to the objectives of the study. Exacerbation rates were analysed using Poisson regression with group as an independent variable and time as offset. Time to first exacerbation was analysed using log-rank test and graphically presented in Kaplan-Meier plots. In addition, the hazard ratios were estimated using a Cox proportional hazards model adjusted for LABA use before study entry, age, gender and BMI. Statistical analyses were performed with Stata/IC11 version 2.14.1.

RESULTS AND COMMENTS

Paper I

Characteristics of the study group

The study group consisted of 5,355 people (54 % women), 18 to 100 years of age. A total of 341 of the participants (6.4 %) reported that they had current asthma, including 123 men (2.3 %) and 218 women (4.1 %). With regard to basic characteristics, the only difference between asthma and no asthma groups was a significant difference in age and occupational status for men ≥ 45 years. Men with asthma were older (mean age 62.2 years *vs.* 59.2 years; $p < 0.05$), fewer of them were employed (36.9 % *vs.* 56.6 %; $p < 0.01$) and more of them were retired (56.9 % *vs.* 34.5 %; $p < 0.01$), compared with men without asthma.

Association between asthma and self-rated health

There was a significant difference in SRH between those with and those without asthma. Respondents with asthma rated their health worse, and this association was more marked in respondents ≥ 45 years. The most common response to the SRH question in each group was “quite good” and few answered “very poor”. However, respondents with asthma rated their general health as less than good

approximately twice as often as respondents without asthma, excepting women aged 18 – 44 years. Approximately half of the respondents with asthma who were ≥ 45 years rated their health as less than good. Over 20 % in this group rated their health as poor – twice as many as those ≥ 45 years without asthma (Table 4).

Table 4. Comparison of self-rated health in men and women by age and self-report of asthma or no asthma

	Men							
	18-44 years				**≥ 45 years**			
	Asthma n=58	**No asthma** n=1,058			**Asthma** n=65	**No asthma** n=1,303		
	%	%	χ^2	p	%	%	χ^2	p
			19.8	<0.01			34.8	<0.001
Very good	13.8	34.4			7.7	20.5		
Quite good	50.0	48.7			43.1	54.5		
Neither good nor poor	27.6	13.2			26.2	17.9		
Quite poor	8.6	3.3			23.1	6.2		
Very poor	0	0.4			0	0.9		
	Women							
	n=113	n=1,202			n=105	n=1,451		
			18.7	<0.01			30.6	<0.001
Very good	18.6	28.7			5.9	21.1		
Quite good	59.3	51.9			41.6	50.0		
Neither good nor poor	8.8	13.6			30.7	18.6		
Quite poor	10.6	5.3			18.8	9.0		
Very poor	2.7	0.5			3.0	1.3		

Statistics: chi-squared test

Association between asthma and quality of life

The analysis of the answers to the questions on the GQLI showed no difference between men with and without asthma in the 18 – 44 year age group. However, quality of life was significantly lower for all three categories of well-being

(social; $p < 0.05$, physical; $p < 0.05$, and mental; $p < 0.001$) in men ≥ 45 years with asthma as compared with in men in the same age group without asthma. Women with asthma showed lower rates of social well-being in both age groups compared with women in corresponding age groups without asthma (18 – 44 y, $p < 0.05$ and ≥ 45 y, $p < 0.01$).

The analysis of the answers to the Ladder of Life showed no difference between respondents with and without asthma in the 18 – 44 year age group. Both male and female respondents with asthma who were ≥ 45 years had significantly lower quality of life scores than respondents in the corresponding age group without asthma, excepting women predicting their future quality of life (men: present and past QoL, $p < 0.05$, future QoL, $p < 0.01$; women: present and past QoL, $p < 0.05$).

Multiple regression analyses

Further analysis with multiple regression to exclude confounding factors in the relation between SRH and asthma showed a significant association between asthma and fair/poor SRH in all groups excepting women 18 – 44 years. Women ≥ 45 years who had asthma and all men who had asthma had approximately three times higher odds of fair/poor SRH than those in the corresponding sex and age groups who did not have asthma (Table 5).

Separate analyses comparing the prevalence of fair/poor SRH in respondents with and without asthma in different age groups (18 – 29, 30 – 44, 45 – 64, and ≥ 65) showed that differences in prevalence were greatest among men ≥ 65 years (data not shown).

Table 5. Results of logistic regression analysis, showing associations between fair/poor self-rated health in men and women by socio-demographic characteristics in a full model and an age-adjusted model

	Men				
	18-44 years			**≥ 45 years**	
	Age-adjusted model OR (95% CI)	Full model OR (95% CI)		Age-adjusted model OR (95% CI)	Full model OR (95% CI)
18-29 y	1	1	45-64 y	1	1
30-44 y	1.16 (0.85-1.59)	0.77 (0.53-1.14)	≥65 y	1.41 (1.09-1.83)	1.36 (1.01-1.83)
No asthma	1	1		1	1
Asthma	2.85 (1.62-5.00)	2.77 (1.46-5.26)		2.83 (1.71-4.69)	3.05 (1.74-5.34)
Education					
Compulsory		1			1
Secondary		0.73 (0.48-1.11)			0.98 (0.67-1.45)
University		0.39 (0.21-0.72)			0.70 (0.47-1.02)
Physical activity					
High		1			1
Medium		2.60 (1.70-4.00)			2.17 (1.49-3.16)
Low		4.54 (2.81-7.38)			4.92 (3.20-7.59)
Smoking					
No		1			1
Yes		1.50 (1.00-2.25)			1.45 (1.06-1.99)
Married/Cohab.					
Yes		1			1
No		1.54 (1.08-2.22)			1.90 (1.38-2.60)
	Women				
18-29 y	1	1	45-64 y	1	1
30-44 y	1.23 (0.93-1.64)	1.13 (0.82-1.56)	≥65 y	1.51 (1.21-1.91)	1.01 (0.76-1.33)
No asthma	1	1		1	1
Asthma	1.19 (0.75-1.90)	1.18 (0.72-1.95)		2.71 (1.80-4.08)	2.78 (1.78-4.36)
Education					
Compulsory		1			1
Secondary		0.75 (0.52-1.08)			0.99 (0.68-1.44)
University		0.58 (0.37-0.91)			0.76 (0.52-1.11)
Physical activity					
High		1			1
Medium		1.52 (1.07-2.16)			1.89 (1.33-2.69)
Low		2.62 (1.71-4.01)			5.07 (3.39-7.59)
Smoking					
No		1			1
Yes		1.40 (1.02-1.94)			1.07 (0.80-1.44)
Married/Cohabi.					
Yes		1			1
No		1.52 (1.11-2.08)			1.34 (1.03-1.74)

CI=confidence interval, OR=odds ratio, y=years.

Paper II

One patient made an unscheduled visit during the study because of an upper respiratory tract infection, but no change in asthma therapy was needed. No other asthma-related events were registered during the study.

Relation between F_ENO and specific IgE

All patients were sensitised against at least one perennial allergen. Cat was the dominant perennial allergen with 95 % sensitised (n/N; 19/20), followed by dog (15/20 [75 %]) and horse (10/20 [50 %]). Birch (13/20 [65 %]) and timothy (12/20 [60 %]) were the most common seasonal allergens. There was a large scatter of IgE-antibody titres for these allergens. Few subjects were sensitised to mugwort (2/20 [10 %]) and cladosporium (2/20 [10 %]). We found a significant correlation between the sum of IgE-antibody titres for all allergens as well as perennial allergens versus F_ENO at baseline, but no correlation between F_ENO and the sum of IgE-antibody titres for seasonal allergens. All significant correlations between F_ENO and IgE titres seen at baseline had disappeared at the 8-week follow-up (Table 6).

Table 6. Correlations between sum of IgE titres and F_ENO at baseline and last visit

	Baseline		**Last visit**	
	rho	p	rho	p
Perennial IgE (5)	0.47	**0.04**	0.38	0.10
Seasonal IgE (3)	0.32	0.17	-0.07	0.77
All IgE (8)	0.48	**0.03**	0.22	0.36

Statistics: Pearson's correlation test. No. of allergens given in brackets.

Effect of F_ENO-guided steroid treatment

At baseline, 8 subjects (40 %) were not taking ICS and none used the highest dose. Seventeen out of twenty patients (85 %) had elevated exhaled NO values ($\geq$ 22 ppb) at baseline. F_ENO changed significantly at visits 3 and 4 compared

with baseline on the group level. The average F_ENO level decreased by from 40.1 ppb to 24.8 ppb (38 %) between baseline and last visit. At the last visit, all subjects had ICS therapy and 8 were treated with the highest allowed dose. Three patients decreased the corticosteroid dose, two patients stayed at the same dose and fifteen patients increased the dose of ICS. The mean daily dose of ICS increased by 147 % (from 340 µg to 840 µg). The mean ACQ score decreased significantly from 1.0 at baseline to 0.7 at the second visit ($p < 0.05$). The mean score was still numerically reduced at visits 3 and 4 compared with baseline, but the decrease was no longer statistically significant. Total mean score for AQLQ and all separate domains did not change significantly. Four questions out of 32 showed significantly increased positive responses ($p < 0.05$), all from the symptom domain. Seven subjects showed a clinically relevant change (≥ 0.5 units) in total AQLQ score. None of the spirometry measures, including β_2-agonist reversibility, changed significantly during the study.

Characterization of patients with persistently elevated F_ENO at last visit

Nine patients (45 %) still had a clearly elevated F_ENO value at the last visit, whereas the rest showed normal NO values (< 22 ppb) (Table 7). There was no difference in the mean ICS use between these subgroups at the first visit, but there was a significant rise of the corticosteroid dose between the first and last visits in the group with persistently elevated F_ENO, and the change in ICS dose during the study was significantly higher compared with the normalised group. The average F_ENO value decreased significantly in the normalised subgroup but not in the non-normalised group. There was no difference between the groups with regard to gender (three men in each group) and self-reported adherence to ICS treatment (95 % and 96 % in the normalised and non-normalised group, respectively). The subgroup with persistently elevated F_ENO levels was

characterised by significantly higher titres of IgE antibodies against perennial allergens, and a significantly higher proportion of subjects were sensitised against horse (89 % *vs.* 18 %). Also, significantly more patients in this group were recently or regularly exposed to relevant allergens (primarily pet allergens) and one patient had symptoms of a respiratory infection at this time point. However, if this patient was omitted from the statistical evaluation, the difference in the proportion of exposed subjects between the subgroups was still significant ($p < 0.05$). Furthermore, the non-normalised subgroup had significantly higher F_ENO values at baseline. There was a statistical trend toward an increase in the AQLQ total mean score in the group with normalised F_ENO, whereas such a trend was lacking in the non-normalised subgroup (Table 7). Mean ACQ score and results from spirometry, including β_2-agonist reversibility, did not show any significant differences between subgroups.

Table 7. Characteristics for the subgroups that were normalised and not normalised with regard to F_ENO

	Visit no.	**Normalised (n=11)**	**Non-normalised (n=9)**
Sum of IgE (kU/l)			
Perennial (5)		10.7 (3.9)	28.9 (7.0)*
Seasonal (3)		5.5 (2.2)	14.4 (6.9)
All (8)		16.1 (4.1)	43.3 (11.9)*
Exposure (no)	v. 4	3/11 (27)	8/9 (89)**
F_ENO	v. 1	26.3 (3.3)	57.1 (12.6)*
	v. 4	16.5 (1.1)	35.0 (3.4)***
	Δ	-9.8 (2.9)$^{\#\#}$	-22.1 (11.6)$^{(\#)}$
ICS use	v. 1	382 (109)	289 (111)
	v. 4	636 (188)	1089 (209)
	Δ	+255 (83)	+800 (180)$^{\#\#(*)}$
AQLQ	v. 1	5.6 (0.3)	5.7 (0.2)
	v. 4	6.1 (0.2)	5.9 (0.3)
	Δ	+0.5 (0.2)$^{(\#)}$	+0.2 (0.2)
LABA use before study start		4/11 (36)	2/9 (22)

Data are mean (SD) or n/N (%). $^{(*)}P < 0.10$, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with normalised group (Fisher, Mann-Whitney or unpaired t-test), $^{(\#)}P < 0.10$, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ for change between visit 1 and visit 4 (Wilcoxon or paired t-test). Positive = IgE > 0.35 kU/l.

Paper III

Characteristics of the study group

In all, 181 participants (48 % women) came to the baseline visit and 165 completed the study. Those who had left blood samples both at baseline and the last visit of the study, 158 participants, were included in this post-hoc analysis. The study group consists of adult multi-sensitised asthmatics from primary health care, with ongoing ICS treatment and fairly well-controlled asthma at baseline. Baseline characteristics and efficacy results for the study group are described in Table 8.

Table 8. Patient characteristics at baseline and efficacy results over 1-year study period

Demographic characteristics	**Baseline**	Δ	p
Gender (male)	82/158 (51.9)		
Age	41.2 (12.4)		
Asthma and atopy characteristics			
Years since asthma diagnosis (rank 1-5)	4 [3-5]		
Number of positive aeroallergens (max 9)	4 [3-5]		
Sensitised to a seasonal allergen	120/158 (76)		
F_ENO (ppb; Geometric mean [CI])	22.1 (20.0-24.5)	-1.84 (22.7)	.286
S-ECP	12.8 [7.30-19.7]	0.43 [-3.18-3.25]	.461
Budesonide equivalent ICS dose (µg/day)	400 [400-800]	0 [-200-200]	.431
Patients on LTRA	4/158 (2.5)	35/158 (22)	**<.001**
ACQ	0.83 [0.33-1.33]	-0.16 [-0.66-0.16]	**.015**
mAQLQ	5.94 [5.19-6.51]	0.20 [-0.17-0.77]	**<.001**
GQLI	5.39 [4.94-5.83]	0 [-0.33-0.33]	.674
SRH	4 [4-4]	0 [0-0]	.247
FEV_1 (% predicted)	83.8 (13.3)	-0.72 (7.19)	.292

Data are median [IQR], mean (SD) or n/N (%), unless otherwise indicated. n=158.
Years since asthma diagnosis (rank 1-5): 0-2 years = 1, 3-5 y = 2, 6-10 y = 3, 11-20 y = 4, > 20 y = 5, Analysed allergens = cat, dog, birch, timothy, horse, mite (two), mugwort and cladosporium, S-ECP = Serum Eosinophil Cationic Protein, ACQ = asthma control questionnaire, mAQLQ = mini asthma quality of life questionnaire, SRH = self-rated health, FEV_1=forced expiratory volume in 1 second.

Change of IgE and IgG4

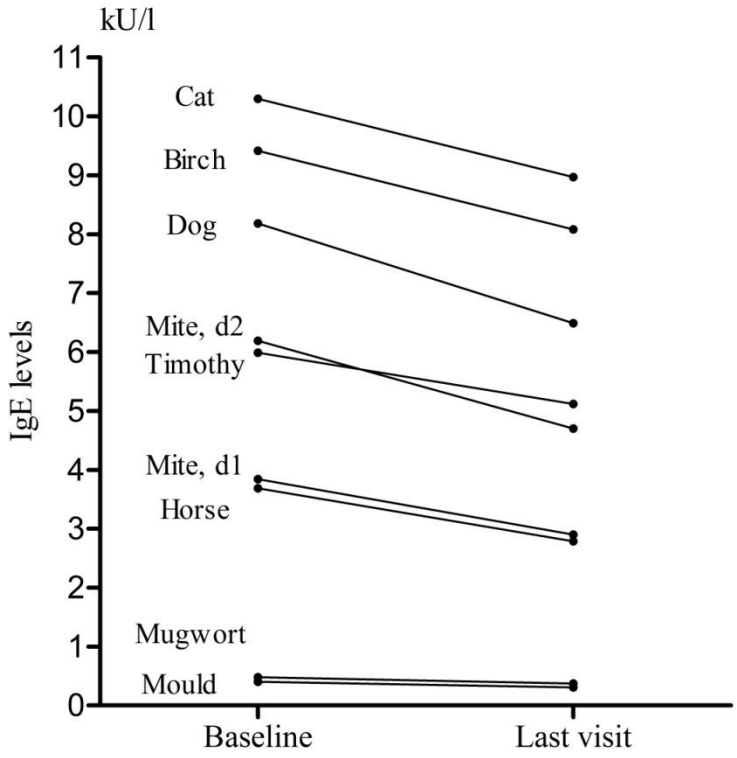
Mean levels for all types of specific IgE and total IgE decreased significantly between baseline and the 1-year follow-up. The median for relative decrease of IgE levels was 7.8 – 36.4 % with the vast majority between 10 – 20 % (Table 9, Figure 5). There was a significant negative correlation between age and IgE levels at both baseline and end of study for perennial and all specific IgE, and a trend toward correlation with seasonal IgE. Relative change of food IgE showed a significant positive correlation with age. Thus, the reduction in food IgE was larger for younger subjects, and a trend toward a similar relationship was seen for total IgE. No significant difference between genders was found for changes in IgE levels. IgG4-antibody levels against cat and timothy did not show any significant changes during the study.

Table 9. Change of IgE levels at 1-year follow-up

Variables (kU/l)	n	Baseline	1-year follow-up	Median relative change (%)	p
Mite, d1	158/158	3.84 (11.8)	2.90 (9.04)	-12.1	**.008**
Mite, d2	156/157	6.19 (21.3)	4.70 (15.6)	-14.3	**.020**
Cat, e1	157/155	10.3 (19.3)	8.97 (18.3)	-16.2	**.008**
Horse, e3	157/156	3.69 (8.42)	2.79 (6.12)	-13.3	**.006**
Dog, e5	158/158	8.18 (29.5)	6.49 (18.6)	-14.2	**.033**
Timothy, g6	149/146	5.99 (16.8)	5.12 (15.2)	-20.8	**<.001**
Birch, t3	158/157	9.42 (17.9)	8.08 (14.8)	-17.7	**<.001**
Mould, m2	131/115	0.40 (2.34)	0.31 (1.88)	-36.4	**<.001**
Mugwort, w6	156/158	0.48 (1.45)	0.37 (0.98)	-10.8	.079
Perennial IgE	158/158	32.6 (58.1)	26.2 (44.2)	-16.0	**<.001**
Seasonal IgE	158/158	15.9 (28.5)	13.6 (24.8)	-17.4	**<.001**
Food IgE (fx5)	158/158	2.07 (10.5)	1.64 (9.61)	-7.80	**.004**
All specific IgE	158/158	50.5 (74.3)	41.4 (59.5)	-15.7	**<.001**
Total IgE	158/158	263 (464)	236 (425)	-10.2	**<.001**

Perennial = cat, dog, horse, mite (two), and cladosporium. Seasonal = birch, timothy and mugwort. Food = cow's milk protein, egg white, peanut, soy, wheat and fish. All specific IgE = sum of perennial, seasonal, and fx5. Data are shown as mean (SD). Statistics: Data were converted to the log base 10 scale and analysed using a paired t-test.

Figure 5. Change of IgE levels at 1-year follow-up



F_ENO

F_ENO at baseline showed a significant correlation with perennial IgE, all specific IgE and total IgE, which had disappeared at the last visit, excepting the correlation with perennial IgE (corresponds to the results in Study II). There was a positive correlation between change in F_ENO and relative change in IgE levels for perennial IgE, all specific IgE and total IgE, and a trend for seasonal IgE (Figure 6). Change in serum ECP showed a positive correlation only with change of perennial IgE (Table 10). Another comparison with study II shows the same results concerning association between persistently elevated F_ENO and high IgE-

levels. Those with elevated F_ENO (≥ 22 ppb) at last visit had significantly higher IgE levels of perennial (p = 0.001), all specific (p = 0.02) and total IgE (p = 0.02), but not seasonal IgE (p = 0.82), compared with those with normal F_ENO (< 22 ppb).

Table 10. Correlation analysis between relative change (%) of IgE levels and change of F_ENO, serum ECP and treatment variables at 1-year follow-up

	Δ Perennial IgE		**Δ Seasonal IgE**		**Δ Food IgE**		**Δ Total IgE**		**Δ All specific IgE**	
	rho	p	rho	p	rho	p	rho	p	rho	p
Δ F_ENO	0.23	**.003**	0.15	.058	0.09	.250	0.27	**<.001**	0.25	**.002**
Δ ECP	0.20	**.014**	0.02	.786	0.07	.376	0.08	.319	0.07	.377
Mean ICS dose	-0.17	**.030**	-0.02	.789	-0.13	.103	-0.10	.194	-0.16	**.044**
Months on LTRA	-0.20	**.013**	-0.001	.903	-0.21	**.009**	-0.16	**.044**	-0.17	**.036**

Months LTRA use = number of months with leukotriene receptor antagonist treatment.
Statistics: Spearman rank correlation test

There was a significant difference in the distribution of F_ENO (≤ 20 ppb or > 20 ppb) at baseline between those who showed an unchanged or increased F_ENO (F_ENO-up group) and those who showed a decrease in F_ENO (F_ENO-down group) during the study (p < 0.001). A majority of the F_ENO-up group had a normal F_ENO at baseline with only a small increase in F_ENO during the study, while a majority in the F_ENO-down group had an elevated F_ENO at baseline with a significant reduction in F_ENO at the follow-up. Patients with an elevated F_ENO at baseline increased LTRA use significantly during the study in both the F_ENO-up and F_ENO-down groups, whereas mean ICS use increased in the F_ENO-down group only. Those with normal F_ENO at baseline showed a clear decrease of ICS use and use of LTRA was low and did not change (Table 11).

Table 11. Change of treatment and F_ENO in F_ENO-up/down groups based on F_ENO at baseline

	F_ENO-up			**F_ENO-down**		
F_ENO ≤20 at baseline	Baseline	Last visit	p	Baseline	Last visit	p
LTRA use, n	2/54 (4)	5/54 (9)	.437	0/22 (0)	1/22 (4)	1.00
Mean ICS use, µg	615 ± 382	425 ± 358	**<.001**	657 ± 330	394 ± 292	**.003**
F_ENO, ppb, median	13 [10.5-13.5]	19.5 [15-27]	**<.001**	13.5 [10.5-18]	9.75 [7-13.5]	**<.001**
F_ENO >20 at baseline						
LTRA use, n	2/21 (10)	10/21 (48)	**.015**	0/59 (0)	19/59 (32)	**<.001**
Mean ICS use, µg	619 ± 424	616 (354)	.394	533 ± 317	705 ± 385	**<.001**
F_ENO, ppb, median	29 [24.5-46.5]	42.5 [35.5-71]	**<.001**	31.5 [25.5-49]	20 [15-28]	**<.001**

Data are shown as median [IQR], mean ±SD, or no./N (%), unless otherwise indicated.
Statistics: Fischer`s exact test and Wilcoxon signed-rank test

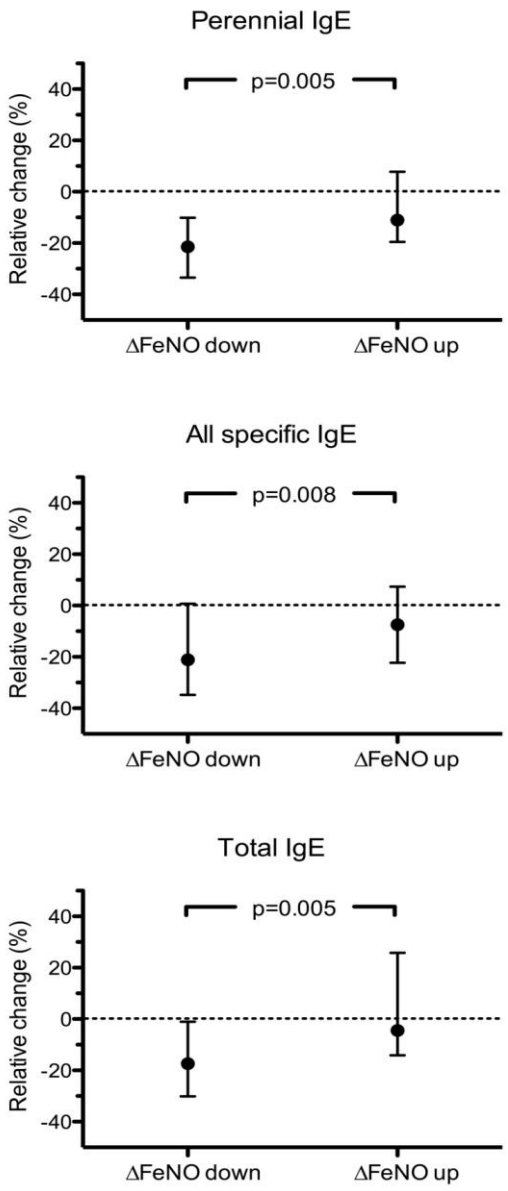
Anti-inflammatory treatment

Mean ICS use was 559 µg/day during the study and did not change significantly between baseline and last visit ($p = 0.43$), but there was a significant increase in the number of LTRA users, from four to 35 participants ($p < 0.001$). There was a significant change in the distribution of treatment steps between baseline and last visit, with more patients receiving the two highest doses of treatment or no treatment, and fewer patients at intermediate doses (Figure 8). Months on LTRA showed significant negative correlation with the relative change of all groups of IgE except seasonal IgE (Table 10). Mean ICS dose showed a negative correlation with relative change in perennial IgE and all specific IgE.

Asthma control, asthma-related quality of life and self-rated health

There was a significant correlation between improvements in the ACQ and mAQLQ scores and the relative reduction in perennial IgE, all specific IgE, and total IgE levels (Table 12). There was also a significant correlation between change in ACQ and change in F_ENO, and between change in SRH and relative change in perennial IgE. No significant correlations with change in the GQLI score were seen.

Figure 6. Correlation of change in F_ENO with change in IgE



ΔF_ENO down = decrease of $F_ENO \geq 5$ ppb, ΔF_ENO up = increase of $F_ENO \geq 5$ ppb

Table 12. Correlation analysis between relative change (%) of IgE levels and F_ENO, and change of ACQ, mAQLQ, SRH and GQLI at 1-year follow-up

	Δ F_ENO		**Δ Perennial**		**Δ Seasonal**		**Δ Food**		**Δ Total**		**Δ All specific**	
	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Δ ACQ	16	**.046**	0.21	**.012**	0.15	.069	0.12	.159	0.24	**.004**	0.19	**.019**
Δ mAQLQ	-0.12	.148	-0.21	**.009**	-0.10	.228	-0.12	.142	-0.17	**.034**	-0.16	**.042**
ΔSRH	-0.08	.296	-0.16	**.041**	0.10	.189	0.05	.520	-0.12	.123	-0.09	.279
ΔGQLI	-0.03	.662	-0.01	.942	0.03	.698	-0.03	.707	-0.02	.796	-0.01	.946

ACQ=asthma control questionnaire, mAQLQ=mini asthma quality of life questionnaire, SRH=self-rated health, GQLI=Gothenburg quality of life instrument.
Statistics: Spearman rank correlation test

Allergen exposure

Thirty-one participants were exposed daily to relevant pets (cat and dog), while 84 reported that they never had contact with pets during the study. At the study start, 28 participants reported a pet at home and six of them removed their pet during the study. Two participants acquired a pet during the study. The proportion of participants with a pet at home compared with those who reported no contact with pets did not change significantly ($p = 0.443$) during the study. Levels of IgE against pets were significantly higher at start and end of the study for those who had daily contact with pets compared with those who never had contact. Both groups significantly lowered their IgE levels for pets during the study, with no significant difference between the groups.

There was no major difference in reported pollen levels during the years when the study was conducted, except for very high levels of birch pollen in 2006. Fifteen participants were included during the year after the birch pollen season 2006. These participants did not have higher IgE levels for birch at inclusion compared with those who were included after birch pollen season 2007 and onwards, but they had a significantly larger reduction of IgE against birch although both groups showed a significant reduction in birch IgE levels.

However, there was no significant difference for change of other types of IgE between these two groups.

Paper IV

Characteristics of the study group

In all, 187 participants were included at 17 primary health care centres. Six participants withdrew before randomization. Thus, 181 participants (48 % women) came to the baseline visit (visit 2) and 165 of them completed the study (Figure 4). A total of 54 participants stopped LABA treatment at study entry. Participants who withdrew before the end of the study had significantly worse asthma control (ACQ median [IQR], 1.58 [1.33 – 2.0] *vs.* 0.83 [0.33 – 1.33], p = 0.005) and lower scores in the activity domain of the mAQLQ (median [IQR], 5.50 [5.00 – 6.25] *vs.* 6.50 [5.75 – 6.75], p = 0.015) than those who completed the study. Those who stopped using LABA did not withdraw more than those who did not use LABA before study entry (p = 1.00). There was no significant difference between study groups in terms of participants who withdrew from the study. At baseline, mean age was 41 years (SD 12.4), median daily ICS dose 400 µg/day (IQR 400 – 800) budesonide equivalents, mean FEV_1 84.0 % predicted (SD 13.3), geometric mean F_ENO value 20.4 ppb (CI 18.5 – 22.5), median mAQLQ score 5.93 (IQR 5.20 – 6.47), and median ACQ score 0.83 (IQR 0.33 – 1.50) (Table 13). The mean study treatment period was 387 days (SD 48.4) in the F_ENO-guided group and 377 days (SD 36.7) in the control group (p = 0.13). Adherence to the F_ENO algorithm was 85 – 88 % in the F_ENO-guided group, whereas the treatment decisions in the control group mimicked the F_ENO algorithm in less than 30 % of the decision points, with a trend toward lower congruence at the end of the study. The most common reason not to follow the

algorithm in the F_ENO-guided group was declining to use a lower treatment step because of an upcoming pollen season.

Table 13. Patient characteristics at baseline

	Control (N=88)	**F_ENO-guided (N=93)**
Demographic characteristics		
Gender (male)	46/88 (52.3)	48/93 (51.6)
Age	41.1 (12.9)	40.9 (11.8)
Height (cm)	173.6 (9.8)	172.9 (10.4)
BMI (kg/m^2)	26.1 (4.79)	27.0 (5.08)
Asthma and atopy characteristics		
Years since diagnosis (rank 1-5)	4 [3-5]	5 [3-5]
Number of positive allergens (max 9)	4 [3-6]	4[3-5]
Sensitised to a seasonal allergen	65/87 (75)	67/92 (73)
Total IgE (kU/l)	102 [54-260]	135 [63-307]
Sum of IgE – perennial allergens (kU/l)	11 [3.4-26]	12 [3.7-44]
F_ENO (ppb; Geometric mean [CI])	21.6 (18.7-25.0)	22.0 (19.3-25.2)
Budesonide equivalent ICS dose (µg/day)	400 [400-800]	400 [400-800]
LABA use before study entry	30/88 (34.1)	24/93 (25.8)
ACQ	0.83 [0.33-1.5]	0.83 [0.5-1.5]
Quality of life		
mAQLQ	5.93 [5.07-6.53]	5.93 [5.27-6.73]
GQLI	5.31 [4.89-5.83]	5.44 [4.83-5.80]
Spirometry results		
FEV_1 (% predicted)	83.7 (12.5)	84.3 (14.1)
FVC (% predicted)	87.4 (11.3)	88.7 (12.5)
FEV_1/FVC	0.79 (0.08)	0.78 (0.08)
Reversibility (ml)	203 (178)	221 (192)
Significant reversibility	14/86 (16.3)	21/92 (23.0)

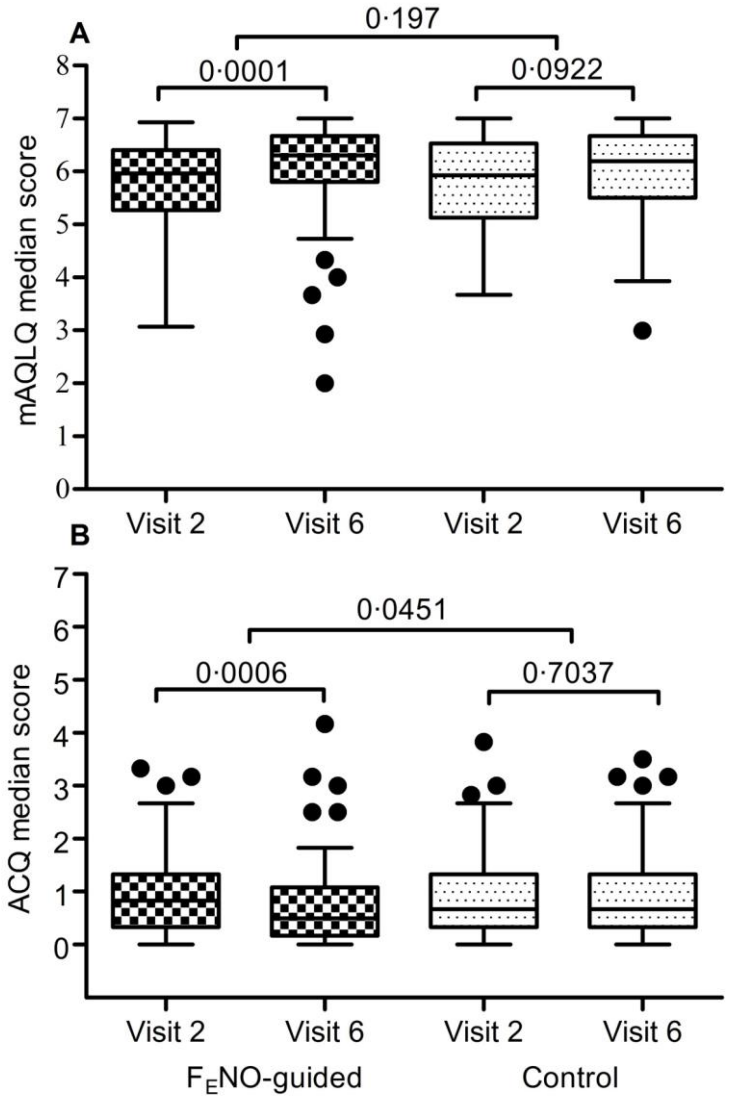
Data are median [IQR], mean (SD) or n/N (%), unless otherwise indicated. All p-values > 0.10. Years since diagnosis rank: 0-2 years = 1, 3-5 y = 2, 6-10 y = 3, 11-20 y = 4, > 20 y=5. Analysed allergens=cat, dog, birch, timothy, horse, mite (two different), mugwort and cladosporium. Perennial allergens=cat, dog, horse, mite and cladosporium. Significant reversibility= ≥ 12 % improvement of FEV_1 and ≥ 200 ml.
Statistics: Student's t test, Mann-Whitney U-test, and chi-squared test.

Asthma-related quality of life

Median overall mAQLQ score changed significantly within the F_ENO-guided group (p = 0.0001), but the change was not significantly larger than that in the

control group (p = 0.197) (Figure 7A). However, analysis of the domains of the mAQLQ revealed that improvement of the symptom domain was significantly larger in the F_ENO-guided group than in the control group (p = 0.041).

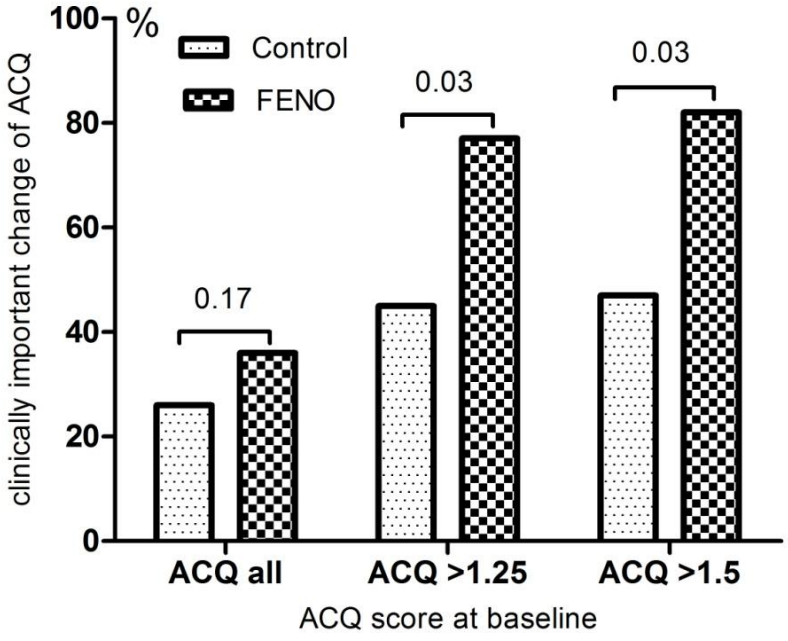
Figure 7. Comparison of mAQLQ and ACQ scores between and within groups.



Asthma control

Asthma control rated with ACQ showed that patients were generally well-controlled at study start (Table 13). A significantly larger improvement of the ACQ score was noted in the F_ENO-guided group compared with the control group ($p = 0.045$) (Figure 7B). The effect on ACQ and the symptom domain of mAQLQ was only significant when changes over the whole study period were compared. In an analysis of the proportion of patients that showed a clinically significant improvement of the ACQ score (≥ 0.5), a higher proportion was noted in the F_ENO-guided group, but this difference was not significant. However, in a subgroup analysis in patients with inadequately controlled asthma at baseline (ACQ score > 1.25 or > 1.5), this proportion was significantly larger in the F_ENO-guided group (Figure 8).

Figure 8. Proportion of patients with clinically important change in ACQ score.



The use of SABA did not differ significantly between the groups at any time point and did not change over time within any group. Furthermore, the groups did not differ significantly in terms of mean F_ENO or measures of lung function (FEV_1, FVC, FEV_1/FVC and reversibility) during the study (Table 14). Generic quality of life was measured with GQLI but no significant differences between the groups were noted.

Table 14. Efficacy results over 1-year study period

	Control	**n**	**F_ENO-guided**	**n**	**p**
Quality of life					
mAQLQ	0.07 [-0.20-0.80]	77	0.23 [0.07-0.73]	80	0.197
GQLI	0 [-0.39-0.39]	78	0.06 [-0.22-0.28]	85	0.666
Exacerbations					
Moderate (≥1 event)	20/88 (22.7%)	88	8/93 (8.6%)	93	**0.009**
Severe (≥1 event)	6/88 (6.8%)	88	8/93 (8.6%)	93	0.654
Any (≥1 event)	25/88 (28.4%)	88	15/93 (16.1%)	93	**0.047**
No. of exacerbations/patient/year	0.41 (0.29-0.58)	88	0.22 (0.14-0.34)	93	**0.024**
Asthma control					
ACQ	0 [-0.33-0.50]	74	-0.17 [-0.67-0.17]	81	**0.04**
F_ENO (ppb; Arithmetic mean)	-1.46 (23.86)	76	-2.57 (20.94)	87	0.75
Lung function					
FEV_1 (l)	-0.006 (0.28)	78	-0.034 (0.28)	88	0.648
FVC (l)	-0.019 (0.29)	78	-0.084 (0.35)	88	0.185
FEV_1/FVC	0.002 (0.054)	78	0.009 (0.057)	88	0.396
Reversibility (ml)	1.54 (178)	78	18.3 (186)	88	0.652
Treatment					
Budesonide equivalent ICS dose (µg/day)	0 [-200-200]	78	0[-400-400]	86	0.945
Participants with LTRA	19/85 (22.4)	85	33/92 (35.9)	92	0.069
Months on LTRA	1.81 (3.89)	85	2.87 (4.42)	92	0.094

Values presented in the table represent change between visits 2 and 6 unless otherwise indicated. Data are shown as median [IQR]or mean (SD) or n/N (%). Statistics: Mann-Whitney U test, Student's t test and Fisher's exact test

Exacerbations

We recorded a total of 52 exacerbations (35 moderate and 17 severe), and they were distributed as follows: January – March: 14, April – June: 12, July – September: 8, and October – December: 18. A significantly lower cumulative incidence of exacerbations was found in the F_ENO-guided group *vs.* the control group (p = 0.029). This was dependent on the fact that moderate exacerbations were reduced in the F_ENO-guided group (p = 0.006): 9 exacerbations in 8 participants compared with 26 exacerbations in 20 participants in the control group. The proportion of patients experiencing at least one exacerbation was significantly lower in the active group (p = 0.047) (Table 13). In a Cox proportional hazards model adjusted for confounding factors, the hazard ratio for having a moderate exacerbation still showed a significant difference between the study groups (0.349 [0.152 – 0.798]; p = 0.013). The number needed to treat (NNT) was 9. We found no significant difference in the number of severe exacerbations between the groups.

Treatment

A change in treatment step was more common in the F_ENO-guided group than in the control group at visits 2 – 4, but this difference had disappeared by visit 5 due to a gradual decline in the proportion of patients changing treatment steps in the active group. The number of changes between treatment steps was generally lower in the control group and remained relatively stable throughout the study (Table 15).

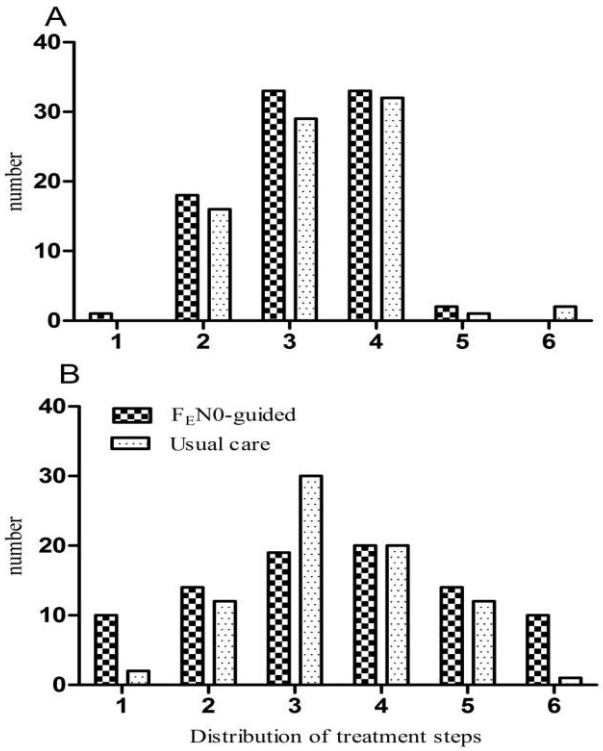
Table 15. Comparison of change in treatment step between groups

Visit	**2**	**3**	**4**	**5**
F_ENO-guided	65/85 (76%)	53/90 (59%)	41/87 (47%)	31/86 (36%)
Control	27/78 (35%) ***	15/81 (18%) ***	18/79 (23%) ***	21/78 (27%)

Proportion of participants who took a treatment step up or down.
Statistical analysis between groups: Fisher's exact test. ***p = 0.001

The mean ICS dose did not differ between groups. However, clear differences developed between the groups over time concerning the distribution of treatment steps. This distribution changed significantly between visits 2 and 6 in both the F_ENO-guided ($p < 0.001$) and the control group ($p = 0.024$). There was no difference between the groups in the distribution of treatment steps at visit 2 ($p = 0.83$), but the difference was significant at visit 6 ($p = 0.035$), owing mainly to more patients ending up at the lowest or highest treatment steps in the F_ENO-guided group (Figure 9). These changes in treatment resulted in slightly higher LTRA use in the F_ENO-guided group, but the difference was not statistically significant (Table 13).

Figure 9. Distribution of treatment steps at visit 2 (A) and visit 6 (B).



DISCUSSION

General aspects

Most people with mild or moderate asthma are managed in primary health care and should be able to live a normal life with the right treatment. Despite the introduction of new treatment options (LABA, ICS and LABA combined and LTRA) in the late 1990s, asthma control seems not to have improved in a significant way in the population. A Swedish study, comparing two surveys performed 2001 and 2005, showed that many patients with asthma treated in primary care do not achieve asthma control and there was no improvement between the two surveys (5). The introduction of treatment with monoclonal anti-IgE antibodies during the 2000s has improved asthma control and quality of life among patients with severe atopic asthma (86), but this is not a treatment alternative for patients in primary health care. Thus, there is a need for further improvement in management of patients with asthma in primary care.
The overall aims of this thesis were to investigate how patients with asthma rate their general health, and investigate if we can improve asthma management, with focus on asthma as a chronic inflammatory disease, by use of F_ENO measurements in monitoring of asthma treatment in primary health care.

Quality of life

Self-rated health

Quality of life, measured with various questionnaires (28, 29, 87, 88), is being used in a growing number of clinical studies to evaluate asthma treatment and can also be used to evaluate asthma treatment in routine daily care. As poor SRH has shown association to elevated levels of circulating inflammatory cytokines it

is interesting to look at the association between SRH and asthma, a chronic inflammatory disease with a recognised systemic component (89).

Results from study I, analysed with multiple regression analysis, present how asthmatics are affected by their disease. They show that adults (> 18 years) with asthma in Sweden scored worse in SRH and had approximately three times higher odds of fair/poor SRH than those in the corresponding sex and age groups who did not have asthma, excepting women 18 – 44 years of age. The difference may be due to several things, for example, lower well-being due to uncontrolled asthma, awareness of suffering from a chronic disease, fear and anxiety about getting worse or losing control of their asthma, the influence of circulating inflammatory cytokines, or a combination of these alternatives. The lower rating of SRH predicts higher morbidity and health care use (40) among asthmatics, which reinforces the view that there is a need for improvement of asthma management. Three previous studies in elderly persons have had results similar to the results in study I (90-92), but little is known about the relationship between asthma and SRH in younger adults. Our study showed that young men with asthma rated their health worse than their peers in the general population, but the same was not true for younger women. One possible explanation is that asthma affects physical fitness, which may be more important to men than women in this age group. This hypothesis is supported by a Finnish study that investigated the variables that affected the way men rated SRH (93). The researchers compared three age groups: 31 – 35, 51 – 55, and 71 – 75 years. They found that in the youngest age group, SRH was best explained by the symptoms the men felt and by the men's physical fitness; in the middle-aged group, by symptoms and well-being; and in the older group, by chronic diseases (95). Other explanations could be that women more often seek help in health

care and therefore have better treatment or perhaps have easier to adapt to and accept their physical performance.

General well-being was measured in three ways in study I: with the GQLI, the Ladder of Life, and SRH. SRH was more strongly and consistently associated with asthma than the two quality-of-life instruments. Moreover, GQLI and the Ladder of Life showed no significant difference in quality of life between young men with and without asthma. Thus, although there is a strong correlation between SRH and quality of life (46), it seems that they may reflect and include different things. The SRH question is focused on health and is a more comprehensive and inclusive measure than the GQLI, and may cover dimensions of health that cannot be covered by more detailed or guided questions. One possible explanation is that poorly controlled asthma may be due to elevated levels of circulating inflammatory cytokines, which may create symptoms that can be sensed and incorporated in the self-assessment process.

Study I has some limitations; the data were self-reported and did not include total tobacco exposure, type of asthma, or asthma duration. Additionally, there is a risk that people with COPD were included in the study population. Patients with asthma, but not with COPD, received medicines free of charge until the early 1990s. Because of that, some patients with COPD may have been classified as having asthma. However, it is unlikely that this has influenced the association between SRH and asthma since adjusting for smoking in multivariate analysis did not affect the association between SRH and asthma in the older age group and the proportion of respondents with asthma in this study was close to the reported prevalence of asthma in Sweden at the time (16, 17, 94). The strengths of the study include the large population-based sample and the wide age range of respondents (18 – 100 years).

Study IV did not show any significant change in SRH and GQLI at the 1-year follow-up in 158 patients with atopic asthma. However, interestingly, there was a correlation between the relative decrease of perennial IgE levels, the IgE group with most impact on airway inflammation, and improvement in SRH during the study. GQLI did not show any such association, which reinforces that they measure partly different things, consistent with the results from study I.

Asthma-related quality of life

In study II, total AQLQ score improved non-significantly in both normalised and non-normalised groups (with regard to FENO), with a trend toward greater improvement in the normalised group. This was a quite good result given that the number of participants was rather small and that the study was relatively short. The score would probably have improved more if the study had continued for a longer period.

One interesting observation in study II was that participants that used LABA before inclusion in the study rated total AQLQ and AQLQ symptom domains ($p = 0.04$ both) lower at baseline compared with those that did not have to cease LABA treatment. It was observed that some patients experienced that the airways became more unstable some weeks after withdrawal of LABA and the interval between inclusion and baseline was just one week in this study. However, there was no difference between these groups concerning AQLQ and ACQ at the last visit. This was an important observation for the planning of the study IV, where patients were without LABA for at least four weeks before the study start.

In study IV, mAQLQ was primary endpoint. Median overall mAQLQ score improved in both groups, but this was significant only in the F_ENO-guided group. However, the change was not significantly larger than in the control

group. Analysis of the domains of mAQLQ revealed that improvement of the symptom domain was significantly larger in the F_ENO-guided group than in the control group.

There was little room for improvement of the mAQLQ score (ceiling effect) for several different reasons, which made it difficult to generate a difference between the groups. Firstly, the participants had mild to moderate asthma. Secondly, they had to have ongoing ICS treatment at inclusion. Thirdly, they were well-treated at study entry, with rather high quality of life and asthma control scorings already at baseline. The scorings were higher than those of the general asthma population managed in primary health care in Sweden (5). One reason for this is probably an effect of the participating investigators being experienced general practitioners with a special interest in asthma. Another reason may be suboptimal recruitment of participants. Around 50 % were recruited consecutively at regular visits at the health care centre, whereas 50 % were recruited through information about the study in newspaper ads, posters in the waiting room, information from other participants and letters, thus demanding initiative from the patients for participation. Those who were included through such own initiatives may have been healthier, more interested in their disease and its treatment, and more treatment-adherent compared with the average asthma patient. This is also reflected by a rather low drop-out rate (12 %) from the study, despite its length. Fourthly, both study groups improved their rating. The control group gained benefit from participating in a study with more attention from health care, which may increase motivation to use their maintenance medicine as they should. This is reflected by a marked improvement in the control group in the beginning which then levels off (study IV). The mAQLQ domain ratings seem to vary in how fast they are influenced by changes in anti-inflammatory treatment. The symptom domain contains

questions about wheezing, chest tightness, coughing etc., symptoms that may change in days or weeks with better anti-inflammatory treatment. The environmental domain contains questions about reactions to irritants such as dust and cigarette smoke etc., symptoms related to airway hyper-responsiveness (AHR). AHR is known to change slowly, over periods of months, even with the right treatment. The emotional domain contains questions about anxiety and fear about asthma, which probably, in most cases, will also take a slightly longer time to change. The activity domain contains questions about limitations of activities because of asthma. Patients who have had asthma for several years (median around 20 years in study IV) will adapt their lives to minimise their problems and avoid doing things that make them feel worse. Therefore, it may take time before they recognise that they can be active in a way that they were formerly unable.

Adjustment to optimal ICS dose took longer time in the F_ENO group than in the control group and often required multiple visits. A follow-up visit at 18 months could have enabled better outcome for the F_ENO-guided group. Interestingly, improvement in asthma-related quality of life correlated with reductions in perennial IgE, all specific IgE and total IgE, but not with changes in F_ENO. This may be due to the fact that reductions in IgE, but not F_ENO, tended to correlate with improvements in the environmental and emotional domains of the mAQLQ instrument which may relate to, for example, airway hyper-responsiveness (study III).

F_ENO and IgE

In many patients whose asthma is considered to be clinically controlled, airway inflammation may persist and put them at higher risk for future exacerbations and lung function decline (95). Study II, where patients were recruited

consecutively, showed that 17 out of 20 participants had elevated F_ENO values at baseline, which indicates that many patients with perennial allergic asthma have an ongoing inflammation in the airways and need better management. Some authors have proposed that increased F_ENO is more a marker of atopy than a marker of airway inflammation (96, 97). This theory is contradicted by the finding in study II showing a significant positive correlation between F_ENO and perennial IgE (the IgE group with most impact on airway inflammation), and all specific IgE, but not seasonal IgE. This correlation disappeared after intensified anti-inflammatory treatment, supporting the view that F_ENO is a marker of inflammation and not a marker of atopy *per se*. As confirmation, the same type of significant correlations between F_ENO and levels of IgE that disappeared after intensified anti-inflammatory treatment were also seen in study IV. In the latter study, this was shown also for total IgE.

We did not succeed in lowering F_ENO below our treatment algorithm's cut-off level (< 22 ppb) in 9 out of 20 participants in study II, despite a considerable increase of ICS doses. This group increased mean ICS use significantly more than the normalised group and ended up at a 70 % higher mean daily dose of ICS. Neither poor adherence to ICS treatment (reported generally good) nor inadequate inhalation technique (checked in connection with spirometry) could explain the difference, and only one patient had signs of an ongoing upper respiratory infection. We found that the non-normalised group had significantly higher levels of perennial IgE and all specific IgE, but not seasonal IgE, compared with the normalised group. They also reported exposure (8 patients of 9) to allergens that they were sensitised to before the last visit. A comparison with study IV confirms the same results; those with $F_ENO \geq 22$ ppb at the last visit had significantly higher IgE levels of perennial, sum of all and total IgE than those with $F_ENO < 22$ ppb, though this was not the case for seasonal IgE.

A high level of specific-IgE antibodies against an aeroallergen in combination with exposure to this allergen seems to make it difficult or even impossible to lower F_ENO to a normal level with ICS treatment. Thus, exposure to relevant allergens, and type and degree of sensitisation, are important factors to take into account when interpreting F_ENO and in conjunction with ICS therapy monitoring using F_ENO. The data also suggest that allergen avoidance regimens may be more effective than further increasing the ICS dose in some patients. IgE plays a pivotal role in the propagation of airway inflammation in atopic asthma and a direct correlation between total IgE and prevalence of asthma exists, regardless of proven allergy (98, 99). The effect of corticosteroid treatment on IgE levels in patients with atopic asthma is equivocal and long-term effects are unclear. There are consistent reports of an initial transient increase of IgE during the first 1 – 2 weeks of treatment with systemic corticosteroids, followed by a decrease to baseline or below (100-102). Two more recent, although relatively small studies on steroid-naïve patients with atopic asthma indicate that the introduction, for 3 – 6 months, of anti-inflammatory treatment with at least medium doses of ICS as well as LTRA reduce IgE levels (103, 104). A 12 week long study in children could not show any significant change in IgE levels with low-dose ICS treatment (105). Few long-term data are available, but Kerstjens *et al.* did a retrospective analysis of data from a completed multicentre study with data on 134 adults with obstructive airways disease, mainly asthma (73 % were atopic) but also COPD, who were followed for 2.5 years. All patients used a β_2-agonist with either a medium dose of beclomethasone, ipratropium, or placebo, but IgE levels were similar in the three groups after the study and did not change during the study (106). A study on children with food allergy showed significantly lower levels of total IgE for participants treated with LTRA for 1 year (107).

Interestingly, study III showed a substantial and significant decrease in all IgE levels over one year, with relative reductions mainly between 10 – 20 %. IgE against perennial allergens was reduced by 16 %, IgE against seasonal allergens by 17 %, and IgE against food allergens by 8 %, and total IgE was reduced by 10 %. The reason for the reduction in IgE most probably relates to an optimisation of the anti-inflammatory treatment. A larger proportion of participants ended up in treatment steps with the highest or the lowest level of anti-inflammatory treatment compared with baseline. Thus, those with low F_ENO or less asthma symptoms received less treatment and those with high F_ENO or more symptoms increased their use of ICS and LTRA. Participants in both groups with a high baseline F_ENO increased their LTRA and ICS use, and F_ENO decreased significantly with no significant difference between the two original study groups. No major changes in pet or pollen exposure could be seen during the study, except for high levels of birch pollen 2006. Participants who were included during the year after the birch pollen season 2006 (15 of 158) decreased birch pollen IgE significantly more during the study than those who were included after birch pollen season 2007 and onwards, but this difference was not seen for other types of IgE. Unaltered levels of IgG4 antibodies to cat and timothy support the view that a change in allergen exposure does not explain the reduction in IgE (108).

It is reasonable to believe that anti-inflammatory treatment with ICS and LTRA can reduce IgE synthesis. Both agents inhibit Th2 cells, the main conductors of allergic airway inflammation, with reduced production of IL-4, IL-13 and/or IL-5 as a result (52, 109-112). IL-4 and IL-13 are particularly essential for IgE synthesis. Interestingly, we could see a significant correlation between the change in F_ENO and the relative change of perennial IgE, all specific IgE and total IgE. Serum ECP, which signals systemic eosinophilic Th2 cell-driven

inflammation only correlated with the relative change of perennial IgE. Blood eosinophil count may be a better marker for IgE-mediated systemic Th2-driven inflammation (113, 114), whereas ECP levels are also influenced by virus exposure (115, 116). The correlation between change in F_ENO and relative changes in IgE levels seemed to be stronger than that between anti-inflammatory drug use and changes in IgE. This is logical since the actual anti-inflammatory effect (reduction in F_ENO) should be more important for effects on IgE levels than the amount of drug given.

A majority of participants with unchanged or increased F_ENO during the study (FENO-up group), showed a decrease in IgE levels. However, a large majority of them (72 %) had normal F_ENO at baseline and F_ENO showed just a small increase in this group during the study, resulting in a median $F_ENO < 20$ ppb at last visit. Additionally, those in the FENO-up group with elevated F_ENO levels at baseline (28 %) substantially increased their LTRA use, but not their mean ICS dose. LTRA can affect IgE production systemically (104, 107), but does not affect F_ENO (local inflammation) as much as ICS does.

Thus, results from study III strengthen the assumption that IgE levels can be reduced in adult asthmatics with ongoing ICS treatment by intensified and optimised anti-inflammatory treatment (ICS and LTRA). It can only be speculated how much IgE levels can be reduced through intensified anti-inflammatory treatment, but combination with allergen avoidance would probably strengthen the effect (117). An early study by Kumar *et al.* showed that children who were expected to have elevated IgE levels had normal IgE levels after long-term oral corticosteroid treatment (118). Maybe allergen avoidance in combination with effective anti-inflammatory treatment, as early as possible after diagnosis, would be beneficial in the long-term perspective for atopic asthmatics.

F_ENO, asthma control and exacerbations

Current asthma guidelines recommend that anti-inflammatory treatment should be based on the patient's symptoms, need for short-acting β2-agonists, and results from lung function tests. However, studies have pointed out that asthma control in the population remains suboptimal (5, 6) and there is also evidence for overtreatment of asthma with ICS (119, 120), with unnecessary risk of side-effects. Studies have shown that asthma treatment can be improved when it is guided by markers of inflammation such as airway hyper-responsiveness and sputum eosinophil count (121, 122). However, both tests are too expensive and time-consuming to use in routine clinical practice. F_ENO, a marker of Th2-driven inflammation, is an appealing alternative to these two methods, as it is readily measured, gives reproducible results and is responsive to changes in ICS doses.

Study IV (the NOAK study) is the first randomised controlled trial that has assessed the value of using F_ENO to guide asthma treatment in a primary health care setting. Our ambition was to conduct a close to real-life study with high generalisability for the primary care sector. The patient sample had only minor limitations and the control group was treated as close to routine clinical practice (according to Swedish guidelines) as possible. We used "physician's diagnosis" as criterion for asthma diagnosis and avoided using strict objective criteria based on for example spirometry, which would greatly reduce the external validity of the study since reversibility is seen in only a fraction of treated asthma patients (123). In this way, our study resembles many previous studies in the field (124-126). Smokers were excluded from the study, but only about 10 % of asthmatics in Sweden smoke regularly (5). LABA was not allowed because of the risk of masking symptoms due to airway inflammation. There were no difference in drop-outs from the study between those who used LABA before the study and

those who did not. The rationale for using F_ENO as a marker of asthmatic inflammation is that it indicates bronchial Th2 cytokine-driven inflammation, and by only selecting subjects with atopic asthma we ensured that increased disease activity could be reflected by F_ENO. In contrast to most other studies on F_ENO guidance, the algorithm in the NOAK study was completely focused on the F_ENO value as a guide to change the anti-inflammatory treatment and had no element of change in treatment based on symptoms. This was with one small exception: participants on treatment step 5 with SABA use of less than 3 doses/week should not increase to treatment step 6. It may be regarded as a weakness that only patients with atopic asthma were included in the study, but we must consider that asthma is a heterogeneous disease with several different phenotypes which may need different kinds of treatment and the majority of asthma patients in our country have atopic asthma. We did not use a structured algorithm for the control group, which might have increased the risk of bias. However, asthma control increased slightly in the control group too and we could not find any evidence of mismanagement.

The use of F_ENO as a complement to conventional monitoring of asthma has been studied in ten randomised controlled trials so far, with equivocal results (124-133). However, these studies have been identified as having possible limitations in the design and methodology (134).

Furthermore, previous studies have not been performed within primary health care, where the majority of asthma patients are managed, and six of them were carried out in children. It is difficult to compare these ten studies because they are different in several ways. For example, they have differences with regard to: Outcomes and definition of outcome measures, cut-off levels for F_ENO, treatment algorithms, type of asthma included, length of the study and asthma treatment at start. Six of them are rather small (in total between 47 and 103

participants completed the study) and may not have had enough power. Seven of them show a lower rate of exacerbations in the F_ENO-guided group, but only two of the studies were statistically significant. Interestingly, a meta-analysis on three studies with adult participants (124-126) published before study IV showed a significantly lower exacerbation rate in favour of F_ENO-based management (135). Various reasons can be recognised that may have contributed to the failure of some of the studies.

1) *The study type*: This type of study is called an ASTRAL (ASthma TReatment ALgorithm) study. It differs from the typical placebo-controlled drug trial in that both study arms have active treatment. The possibility to change active treatment in both study arms makes it more difficult to differentiate between the two arms.

2) *Treatment adherence:* Just participating in a study usually improves adherence to treatment. This is reinforced by frequent visits in the studies, far more than during ordinary care, and often the studies have a run-in period in order to optimize treatment. Both study arms will improve and there is less room for further improvement. For example, in the study by de Jongste *et al.*, participants had contact with the investigators every three weeks (127).

3) *ICS treatment:* Almost all studies only included patients with ongoing steroid treatment from the start, which leads to less room for improvement. For example, in the study in children by Pike *et al.*, the median budesonide dose was 750 µg per day already from the start (132).

4) *The F_ENO algorithm:* The algorithm that guided the treatment of the F_ENO group also included symptoms as a guide in 7 out of 10 studies. Because of this, the algorithms used did not allow the F_ENO value to have full impact on treatment decisions in the active group and F_ENO could not have enough influence. For example, in the study by Szefler *et al.*, the F_ENO value could only

increase the anti-inflammatory treatment and affected a decision to modify treatment in only 26 % of the study visits (130).

5) *Type of asthma:* F_ENO can detect changes in disease activity in atopic asthma, not in non-atopic (non-Th2-driven) asthma. Five studies have included both types of asthma and in one study only 35 % of participants were atopic (132).

6) *LABA use:* Eight of the studies included LABA as part of asthma treatment. The use of LABA makes it more difficult to detect a difference between groups, because it reduces asthma-related symptoms (symptom-free days constitute primary endpoint in three of the studies) and the need to use SABA (often included as part of the algorithms that guide treatment of the control group), without reducing inflammation.

The main finding in study IV was that the F_ENO-guided group had improved asthma symptom control, as shown by improved scores for both the ACQ and the mAQLQ symptom domain, compared with the usual care group. Interestingly, in subpopulations with inadequately controlled asthma at baseline (elevated ACQ score) the proportion of patients showing a clinically important improvement was significantly larger in the F_ENO-guided group.

It is noteworthy that these results were achieved solely by optimising anti-inflammatory treatment, without increased use of bronchodilators. Another noteworthy observation was that the change in the ACQ score was incremental over the study period in the F_ENO-guided group, probably due to a gradual fine-tuning of the optimal anti-inflammatory dose, whereas the control group showed a transient effect on that outcome. The transient effect in the control group was probably an effect of participating in a study, with more frequent visits and increased attention, as described at point 2 above. Analyses using mixed linear models were not optimal because of this non-linear effect and strongly skewed distribution, and such analyses turned out non-significant, as would be expected.

A shorter titration phase with more frequent visits to find optimal anti-inflammatory dose guided by F_ENO or a follow-up for a longer period than one year might have been even better to show a clinical effect of F_ENO guidance. We could see a significant reduction in exacerbations in the F_ENO-guided group, as a consequence of improved asthma control. The effect was due to a reduction in moderate exacerbations. The number of severe exacerbations was low in both groups and there was no significant difference between the groups. Severe exacerbations may primarily be caused by rhinovirus infections (136, 137) and a stepping up in ICS treatment has little effect on virus-induced exacerbations (138). Four previous randomised controlled trials on F_ENO guidance had exacerbations (124-126) or treatment failure (133) as the primary endpoint, but only the study by Powell *et al.* (124) showed a significant effect. Two studies were smaller than the study by Powell *et al.* and ours, and probably did not have sufficient power. The fourth study included only well-controlled asthma patients on low doses of ICS, with little room for improvement in the F_ENO-guided arm. Absence of data on exacerbations in the prior year was a limitation of our study.

A plausible explanation for the reduction of moderate exacerbations in the F_ENO-guided group may be that moderate exacerbations often are linked to increased airway inflammation due to allergen exposure, which is reflected early on by the F_ENO value (74, 139). Optimised treatment using F_ENO guidance lead to intensified anti-inflammatory treatment, both with ICS and LTRA, for those with elevated F_ENO, with lower risk for moderate exacerbations as a result. Mean ICS use during the study did not differ significantly between the groups, but the groups came to differ in the distribution of treatment steps. The distribution of treatment steps did not differ significantly between the groups at baseline, but a change in treatment step was more common in the F_ENO-guided

group at visits 2 – 4, with a gradual decline toward the end of the study. The number of treatment step changes in the control group was generally lower and remained relatively stable during the study. The distribution of treatment steps changed significantly in both groups, but more strongly in the F_ENO-guided group, which resulted in a significant difference in the distribution of treatment steps between the groups at last visit. The redistribution of treatment steps in the F_ENO-guided group resulted in more participants ending up at the lowest or highest treatment steps, while more participants stayed at intermediate treatment steps in the control group. As more participants ended up at higher treatment steps in the F_ENO-guided group, the proportion of patients using LTRA was 60 % higher (non-significant) in this group, and this could have added to the effect on both exacerbations and symptom control (140, 141). However, the addition of LTRA to treatment with intermediate to high doses of ICS only caused a minor further reduction in F_ENO in patients with asthma (142). This is consistent with F_ENO being similar in the two groups in our study.

CONCLUSIONS

- Adults with asthma in Sweden scored self-rated health worse and had approximately three times higher odds of fair/poor SRH than those in the corresponding sex and age groups who did not have asthma, excepting women aged 18 – 44 years. SRH was associated at least as strong as quality of life to asthma.
- F_ENO is positively correlated with perennial and total IgE levels and the correlation disappeared after a period of intensified anti-inflammatory treatment, supporting the view that F_ENO is a marker of inflammation and not a marker of atopy *per se*. Exposure to relevant allergens, and type and degree of sensitisation are factors with high impact on F_ENO, and are important to take into account when interpreting F_ENO.
- Optimised ICS and LTRA treatment in adult patients with atopic asthma resulted in a significant decrease in IgE levels with no significant change in allergen exposure. The decrease in IgE levels correlated with reductions in F_ENO as well as improvements in asthma control, asthma-related quality of life and SRH. The results suggest long-term beneficial effects of keeping F_ENO as low as possible and that IgE levels may be used as a long-term marker of successful anti-inflammatory treatment.
- The NOAK study is the first randomised controlled study on F_ENO-guided asthma management within primary care. It shows, with high external validity and without increasing overall ICS use, that anti-inflammatory asthma therapy guided by F_ENO measurement significantly improved asthma symptom control and reduced exacerbation rate in patients with atopic asthma compared with usual care. F_ENO-guided anti-inflammatory treatment appears potentially useful in long-term management of patients with atopic asthma.

SVENSK SAMMANFATTNING

Bakgrund: Vid astma föreligger en kronisk inflammation i luftrören. Det finns flera olika typer av astma, den vanligaste är den allergiska typen, som finns hos över hälften av alla astmatiker i Sverige. Förekomsten av astma har ökat i Sverige och många andra länder under de senaste årtiondena och ligger nu på ca 8 – 10 % av befolkningen. Majoriteten har en lindrig till medelsvår astma som följs upp i primärvården. Grundbehandlingen för att dämpa inflammationen utgörs av kortison i inhalationsform. Studier har visat att astmakontrollen hos många patienter är dålig trots dyr läkemedelsbehandling. I början av 1990-talet upptäckte forskare på Karolinska Institutet att människan utsöndrar låga halter av kväveoxid (NO) i utandningsluften. NO-halten ökar vid allergisk astma och avspeglar graden av inflammation i luftrören. Behandling med kortison minskar NO-nivåerna. Utandad NO (F_ENO) kan numera mätas med en enkel och standardiserad metod i primärvården.

Syfte: Avhandlingens syften var att undersöka hur astmatiker skattar sin hälsa och att undersöka om vi kan förbättra omhändertagandet av astmatiker, med fokus på astma som en inflammatorisk luftvägssjukdom, genom att använda mätning av utandad NO i primärvården för att styra den antiinflammatoriska behandlingen.

Metod: Resultaten i studie I baseras på svaren från en folkhälsoenkät som skickades ut under 1995 till 8 200 slumpvis utvalda personer boende i Stockholms län. Sammanlagt 5 355 personer (67,5 %) svarade på enkäten. I studie II inkluderades konsekutivt 20 icke-rökande personer (18 – 50 år) från Runby vårdcentral med läkardiagnosticerad allergisk astma med perenna (året-runt) besvär. Studien utfördes utanför pollensäsongen. Vid varje besök (0, 2, 4, 8 veckor) mättes F_ENO och deltagarna fick svara på ett frågeformulär om exponering mot allergener. Dosen av inhalerat kortison styrdes utifrån F_ENO

värdet. Blodprover togs för analys av IgE-antikroppar vid baslinjen. Data till studie III hämtades från studie IV efter mätning av IgE i blodprover. Studie IV var en randomiserad kontrollerad multicenterstudie som utfördes på 17 vårdcentraler i mellersta och södra Sverige. Sammanlagt 187 personer inkluderades och 165 fullföljde studien. Deltagarna randomiserades till två grupper, en kontrollgrupp där den antiinflammatoriska behandlingen styrdes enligt gällande riktlinjer och en där den antiinflammatoriska behandlingen styrdes utifrån NO-värdet. Efter ett initialt screeningbesök följdes deltagarna vid fem besök under ett år. F_ENO mättes vid varje besök och frågeformulär om astmakontroll, livskvalitet och allergenexponering m.m. fylldes i. Deltagarna hade en loggbok och rapporterade vid varje besök försämringsperioder samt förbrukning av läkemedel. Spirometri och blodprov togs vid studiens start och avslut.

Resultat: Svar från studie I visade att vuxna personer med astma skattade sin hälsa som signifikant sämre jämfört med vuxna personer utan astma, med undantag för kvinnor i 18 – 44 års ålder. Studie II visade att det fanns en signifikant koppling mellan halten av perenna IgE antikroppar och F_ENO vid baslinjen. Denna koppling försvann efter intensifierad kortisonbehandling. Nio deltagare hade en kvarstående förhöjd halt av F_ENO vid studiens slut trots ökad antiinflammatorisk behandling. Denna grupp var mer exponerad mot ämnen som de var allergiska mot och hade högre sammanlagda nivåer av IgE-antikroppar i blodet jämfört med de som normaliserade sitt F_ENO. Resultaten från studie III visade att nivåerna av nästan alla sorter av IgE-antikroppar minskade med 10 – 20 % under det år som studien varade utan att någon förändring av exponering mot allergen kunde påvisas. Förändringen av perenna IgE-antikroppar visade en signifikant koppling till förändring av F_ENO samt förändring av den antiinflammatoriska behandlingen och intressant nog också en koppling till

förändring av astmakontroll, astmarelaterad livskvalitet och självskattad hälsa. I studie IV förbättrades den astmarelaterade livskvaliteten i den F_ENO-styrda gruppen, men utan signifikant skillnad gentemot kontrollgruppen. Däremot påvisades en signifikant förbättrad astmakontroll uppmätt med två skilda frågeformulär i den F_ENO-styrda gruppen. Ett minskat antal försämringsperioder kunde också uppmätas i den F_ENO-styrda gruppen. Förbättringen kunde uppnås genom en optimering av den antiinflammatoriska behandlingen, utan att den genomsnittliga förbrukningen av inhalerat kortison ökade.

Konklusion: Män > 18 år och kvinnor > 45 år skattar sin hälsa som sämre jämfört med motsvarande köns- och åldersgrupper som inte har astma, vilket visar att det finns behov av ett förbättrat omhändertagandet av astmatiker i Sverige. Exponering mot allergen, samt typ och grad av sensibilisering, är viktiga faktorer att ta hänsyn till när man tolkar F_ENO-värdet. Optimerad antiinflammatorisk behandling ledde till minskning av alla typer av IgE-antikroppar utan att förändrad exponering mot allergen kunde påvisas. Genom att använda F_ENO i primärvården för att styra den antiinflammatoriska behandlingen hos vuxna personer med allergisk astma kunde antalet försämringsperioder minskas signifikant och astmakontrollen signifikant förbättras utan att totalförbrukningen av inhalerat kortison ökade. F_ENO-styrd antiinflammatorisk behandling verkar användbart för att förbättra omhändertagandet av patienter med allergisk astma.

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