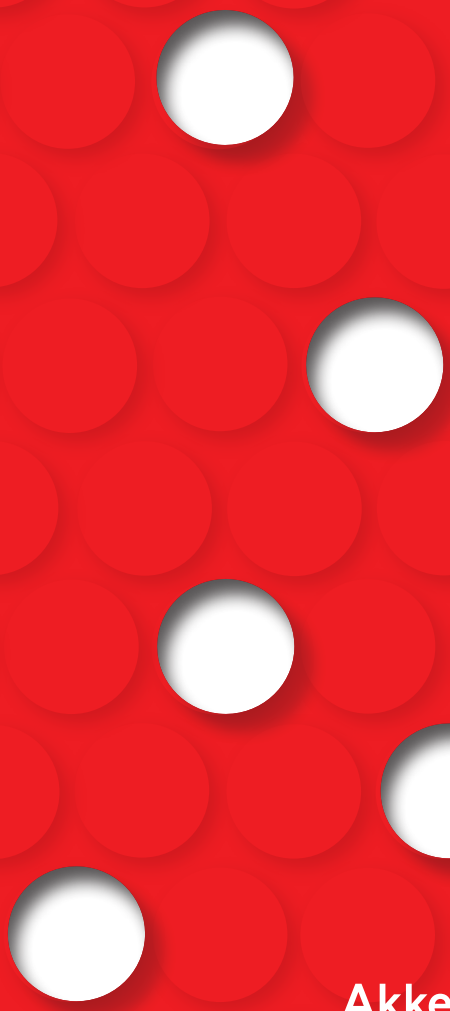
Neglected treatable traits in adult asthma



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Chapter

1

General introduction and research questions

GENERAL INTRODUCTION

Asthma is a heterogeneous airway disease with different phenotypes and variable clinical manifestations [1, 2]. It is defined by a history of respiratory symptoms, including wheeze, dyspnea, cough, chest tightness combined with confirmed variable expiratory airflow limitation and often associated with airway hyperresponsiveness and chronic airway inflammation[3]. Worldwide, the prevalence of asthma is estimated at approximately 300 million people[4]. The severity of asthma varies widely, with the majority of asthma patients being classified as mild or moderate. For years, inhaled corticosteroids (ICS), along with bronchodilators, have been the main treatment for asthma, significantly improving mild disease and making it easy to live with asthma[5, 6]. However, it has also been noted that there is a subgroup of patients in whom asthma remains difficult to control. In these patients, a lack of control remains despite high dose inhaler therapy, due to several factors, such as poor compliance, incorrect inhaler technique and untreated or undertreated comorbidities[7]. A subset of these patients might eventually be eligible for treatment with a biologic[8]. In The Netherlands, the prevalence of difficult-to-treat asthma is estimated at 17.4% of all adults with asthma[9]. A smaller subset of patients, about 4%, is classified with severe asthma[9]. These patients still experience poor asthma control even with high-intensity treatment, good compliance, proper diagnosis, well treated comorbidities and removal of possible triggers[10]. The inherent heterogeneity and complexity of asthma makes it challenging to properly manage patients with difficult-to-treat and severe asthma.

TREATABLE TRAITS IN ASTHMA

A new approach in the management of asthma

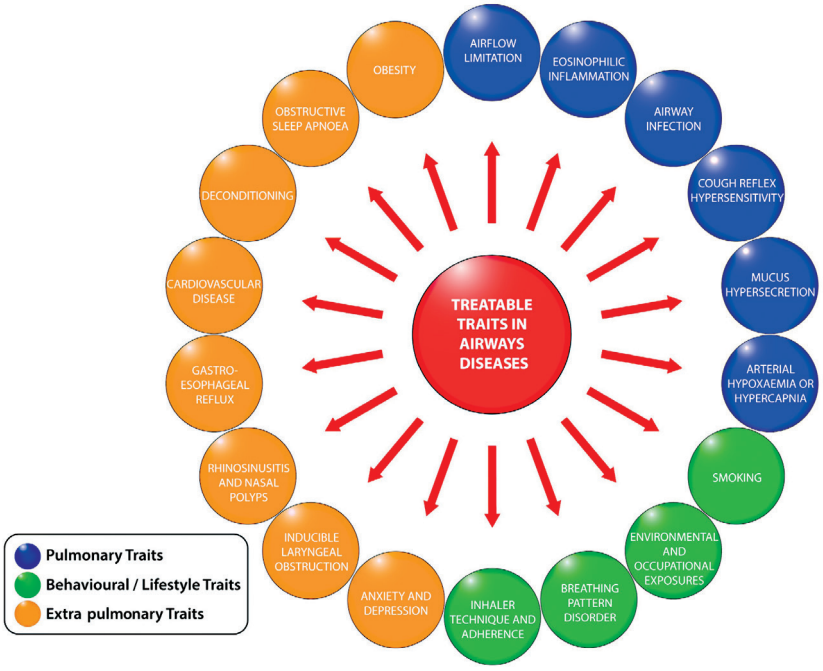
Between 2015 and 2017 there was a turnaround in the classification and management of chronic airway diseases, in particular in asthma and chronic obstructive airway disease (COPD)[11, 12]. In the 19th and 20th centuries, the diagnostic labels asthma and COPD were mainly based on physiological mechanisms[13, 14]. However, this label does not do justice to the currently known cellular and molecular mechanisms at play in asthma and COPD[2]. Moreover, extrapulmonary comorbidities, psychosocial, behavioural and environmental factors leading to morbidity and mortality in patients with chronic airway diseases were also not covered by these labels. So, a new approach to improve the management of chronic airway diseases was introduced by an international task force [11, 12]. Agusti and colleagues stated that "chronic airway diseases share biological mechanism (i.e., endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (i.e., phenotypes), which require individualised treatment". This new approach was called "a precision medicine strategy based on the presence of treatable traits". In which, precision medicine was defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations". With this, the "one size fits all" approach was abandoned[12, 15–17]. In the new paradigm of asthma management, treatable traits play a key role. They are marked as modifiable factors that impact asthma symptoms and can be targeted with treatment[11, 18, 19]. Treatable traits are, among other things, associated with impaired quality of life in asthma patients[18, 19]. Furthermore, they are significantly

related to an increased risk of exacerbations over time, subsequently leading to hospitalisations and increased healthcare costs[20]. Thus, from all perspectives it seems to be relevant to identify treatable traits in order to improve clinical outcomes in the individual asthma patient and to reduce the overall burden of uncontrolled asthma.

Common and neglected treatable traits

Agusti and colleagues were the first to present a clear overview of treatable traits in airway disease. The traits are divided into three categories; pulmonary and extra-pulmonary treatable traits and treatable behaviour/lifestyle risk factors[11]. In addition, specific diagnostic criteria and expected treatment benefits in terms of symptoms, risk of exacerbations and prognosis were outlined by trait based on the current literature[11]. As shown in Figure 1.1, there are many treatable traits and most of them have already been addressed extensively in past research[21]. For example, when it comes to asthma symptoms, a lot of research has been done on the effect of ß2-symphatomimetics on airflow limitation[22, 23]. Also, eosinophilic airway inflammation, an important biomarker in asthma, has gained a prominent place on the list of treatable traits[24, 25]. In airway bacterial colonisation and bronchiectasis, long-term macrolides, nebulised antibiotics and vaccinations are indispensable[26, 27], whereas speech pathology management and gabapentin has gained ground in the treatment of cough reflex hypersensitivity [28, 29]. Well-known extrapulmonary treatable traits that are often associated with uncontrolled asthma are deconditioning, obesity, obstructive sleep apnoea syndrome, gastro-oesophageal reflux disease, vocal cord dysfunction and psychiatric disorders[11]. The last category of traits are treatable behaviour/lifestyle risk factors. Unfortunately, poor

Figure 1.1 Identified treatable traits in asthma colored by domain



Blue, pulmonary treatable traits; orange, extra-pulmonary traits; green, behavioural/lifestyle traits. From Melhorn[21].

inhalation technique and adherence, ongoing smoking and exposure to allergens/pollution are still common in asthma[30].

As mentioned above there are many treatable traits that are well covered. Yet, at the start of our research on this topic, a number of traits emerged in patients with uncontrolled asthma that had not yet been properly addressed or were neglected. Firstly, the presence of nasal polyposis in patients with asthma. To give a clear overview of what was known about asthma and nasal polyposis at that time in 2017, we performed a literature search and wrote a review article on this topic. Secondly, it was an unanswered question whether dynamic hyperinflation, possibly due to small airway disease, played a role in moderate-to-severe asthma as was the case in COPD. In the category treatable behaviour/lifestyle risk factors, inhaler device polypharmacy and adherence to treatment are rightfully highlighted. However, medication overuse, particularly overuse of oral corticosteroids (OCS) in asthma, was missing from the list of treatable traits. Therefore, we investigated the prevalence of OCS overuse in asthma patients in the Netherlands. So, by the identification of these common and neglected treatable traits, we expected to gain essential insights, further unravelling asthma. In addition, the added value of a systematic asthma assessment, taking into account several treatable traits, was not yet known at that time. With a 1-day systematic multidisciplinary assessment in our hospital, we had an excellent opportunity to evaluate the benefit of such an asthma assessment.

SYSTEMATIC ASSESSMENT IN UNCONTROLLED ASTHMA

Patients with uncontrolled asthma report ongoing asthma symptoms, poor quality of life and extensive healthcare use. Consequently, this subgroup of patients is responsible for high healthcare costs[31]. Poorly controlled asthma can be caused by several treatable traits[32]. Therefore, an extensive assessment addressing these traits is strongly recommended. In patients with severe asthma[20, 33], new expensive biologic treatments have become available in recent years[8]. Thus, it is even more important to assess uncontrolled asthma patients properly to know whether they have true severe asthma or whether there are treatable traits that might have been overlooked[10].

Previous research has shown that by using a systematic protocol, co-morbidities could be identified in more than 30% of patients with difficult-to-treat asthma[34]. Remarkably, 74% of asthma patients were no longer difficult to treat after using such a systematic protocol[35]. Many years later, the first prospective data from a UK registry showed that management of patients with difficult-to-treat asthma at dedicated severe asthma centres resulted in improvement in asthma control and quality of life along with a decrease in healthcare utilisation and OCS use[36]. However, it remained challenging to translate a systematic multidisciplinary approach to the daily clinical practice. At the start of my research, in 2016, there were only a few assessment protocols available for patients with uncontrolled asthma[34, 37, 38]. Therefore, the development of a practical systematic asthma assessment could be helpful. To address this issue, we developed a systematic multidisciplinary assessment in a 1-day visit programme for patients with uncontrolled asthma. This assessment resulted in a personalised management plan carried out by

their own referring pulmonologists, instead of concentrating asthma care in severe asthma centres. However, the question remained whether such an approach indeed would lead to better clinical outcomes in uncontrolled asthma patients as suggested by previous research.

FOCUS ON NEGLECTED TREATABLE TRAITS IN ASTHMA

Chronic rhinosinusitis with nasal polyposis in asthma

One of the extra-pulmonary traits associated with asthma described by Agusti and colleagues is upper airway diseases, including rhinosinusitis and vocal cord dysfunction[11]. Asthma and chronic rhinosinusitis (CRS) belong to the most prevalent chronic medical conditions worldwide, with significant impact on patients' quality of life and healthcare costs[39].

Epidemiological studies have shown that CRS is common in asthma patients with a prevalence up to 60%[40, 41]. Evidence of a relation between asthma and CRS has increased since the concept of the "united airways" was introduced[42]. This concept describes the coexistence of upper and lower airway disease as a single entity, based on their similarities in pathological characteristics[43–45]. Certain histopathological data demonstrate similar remodelling and inflammatory characteristics, such as T helper (Th)-2 cell induction, interleukin (IL)-5 and IL-13 production, and eosinophilic infiltration[46, 47]. Epidemiological data have confirmed a link between asthma and CRS. Particularly, the subgroup of patients with CRS with nasal polyposis (CRSwNP) is related to asthma[48, 49]. This is recognizable from the daily practice, where we are often confronted with CRSwNP in patients with asthma[50, 51]. The prevalence of CRSwNP in asthma ranges from 10-30% in mild asthma to 70-90% in severe asthma[52, 53]. In particular, the group of patients with adult-onset non-atopic severe asthma and persistent eosinophilic airway inflammation reveal increased nasal symptoms and CRSwNP[54, 55]. In these patients the impact of CRSwNP is significant, with frequent exacerbations, reduced asthma control and poor quality of life[56, 57].

Even with increasing evidence for a relationship between certain subgroups of asthma and CRSwNP, the therapeutic implications were not yet clear at the time of the start of our research. At that time, omalizumab (a monoclonal anti-immunoglobulin E (IgE) antibody) demonstrated clinical efficacy in the treatment of nasal polyposis in patients with comorbid asthma[58]. There was also growing evidence that mepolizumab, reslizumab (both anti-IL-5), benralizumab (anti-IL-5 receptor) and dupilumab (anti-IL-4/IL-13) could be beneficial in severe asthma and nasal polyposis[59–61].

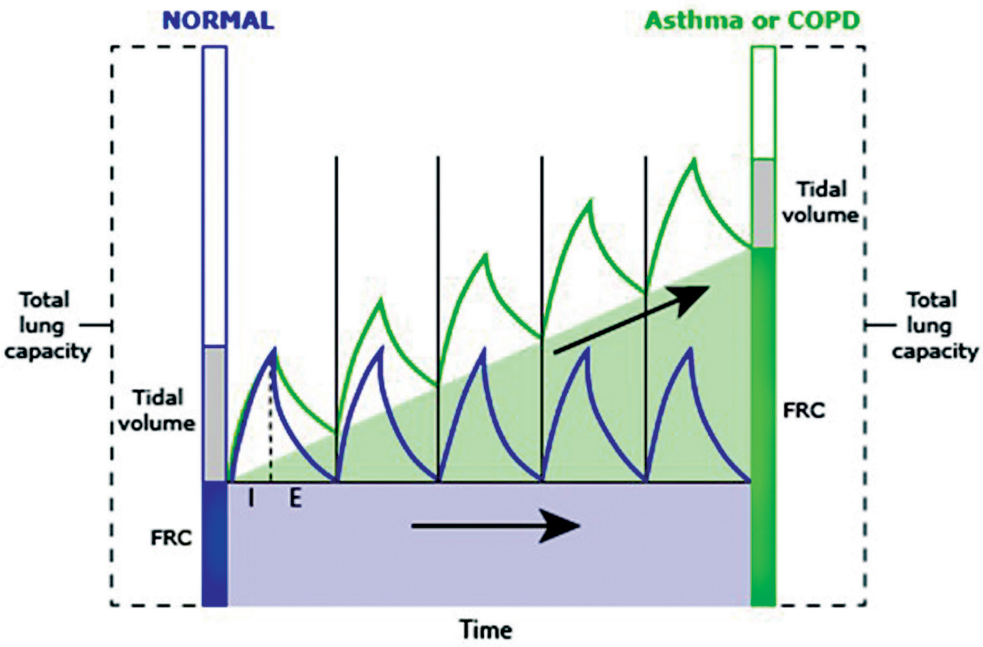
So, at the start of my research, much was still unclear about the link (and clinical relevance) between CRSwNP and asthma, both from an otorhinolaryngologist's point of view as well as from a chest physician's point of view. Therefore, there was a need for an overview of data on prevalence, pathophysiology, impact on asthma control, clinical assessment and treatment options regarding asthma and nasal polyposis from the chest physician's perspective.

Dynamic hyperinflation in asthma

A subset of asthma patients present with symptoms more familiar in COPD. They report exercise intolerance and limitations in daily life activities as the most prominent symptoms, with a major impact on their quality of life[62]. Many factors may contribute to these physical limitations in asthma, including psychological factors, respiratory muscle strength, bronchoconstriction, but dynamic hyperinflation could also play a role[63].

In normal lungs, passive exhalation will lead to a return to normal volume remaining in the lung at the end of each breath (i.e., functional residual capacity). In patients with obstructive airway disease, exhalation may not be finished by the time the next breath is initiated, which leads to trapped air at end of exhalation. This is called hyperinflation. The term dynamic hyperinflation refers to increased amounts of air trapped at the end of each exhalation under conditions of greater minute ventilation (e.g., exercise) (see Figure 1.2)[64, 65].

Figure 1.2 Dynamic hyperinflation in obstructive lung disease



Abbreviations: COPD: chronic obstructive pulmonary disease; FRC: functional residual capacity; I: inspiration; E: expiration. From 2023 UptoDate; adapted from Tuxen[64].

Dynamic hyperinflation is a well-known feature in COPD[66] and strongly related to exertional dyspnoea and diminished daily physical activity[67, 68]. The question arises if dynamic hyperinflation is present in asthma as well. Only a few small studies suggest that dynamic hyperinflation is present in asthma. Mostly provoked in experimental settings by methacholine or exercise it showed to be associated with dyspnoea and reduced

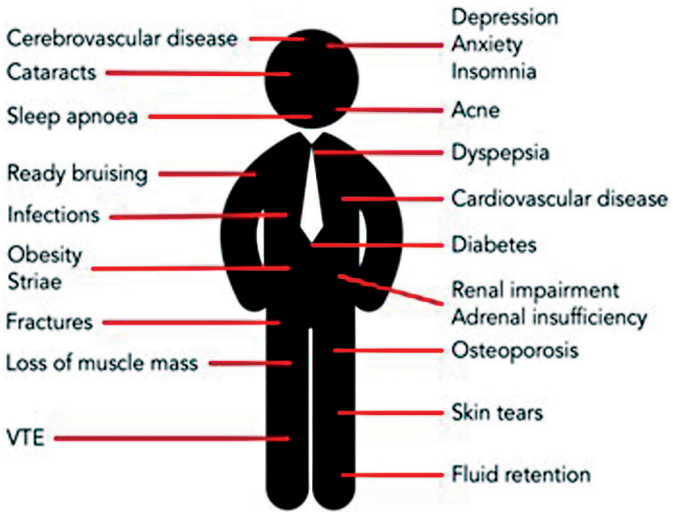
exercise capacity[69–71]. In addition, dynamic hyperinflation might be especially relevant in asthma patients with more severe disease. In patients with a history of near-fatal asthma attack the degree of dynamic hyperinflation tended to be higher as compared to patients without a near-fatal asthma attack[72]. Also, it has been shown that patients with severe asthma develop dynamic hyperinflation during exercise to the same magnitude as COPD patients[73].

In COPD, dynamic hyperinflation occurs mainly due to abnormal lung mechanics caused by decreased elastic recoil, loss of alveolar attachments and collapse of small airways [74]. In asthma, however, the mechanisms underlying dynamic hyperinflation appear to be different. Studies have shown that the degree of airtrapping was more prominent in adult-onset asthma patients with systemic eosinophilic inflammation and in severe asthma patients with higher levels of exhaled alveolar nitric oxide[75, 76]. These results suggest that airway inflammation, particularly of the small airways, may contribute to reduced airway calibre due to airway oedema, premature airway closure, air trapping and eventually dynamic hyperinflation in patients with asthma[77–79]. If ongoing airway inflammation has the potential to contribute to dynamic hyperinflation, the question rises if anti-inflammatory therapy could contribute to its reduction. Conceivably, inflammation of the small airways cannot be adequately controlled with inhaled glucocorticoids and therefore systemic anti-inflammatory therapy may be more suitable.

Oral corticosteroid overuse in asthma

Since 1949, corticosteroids have been used in the treatment of asthma with good effect on clinical outcomes [80–82]. Until 1973, OCS along with short-acting bronchodilators including beta-2-agonists and anticholinergic agents were the only treatment for patients with asthma[83]. Since then, available ICS took ground in the treatment of asthma and led to a decrease in OCS use in many patients[84, 85]. Nowadays, OCS are mainly

Figure 1.3 Side effect oral corticosteroids



Abbreviations: VTE: venous trombo-embolism. From Blakey[100].

prescribed as short OCS courses to treat acute exacerbations, as well as maintenance OCS therapy in patients with severe asthma[86–89]. OCS are known to effectively suppress airway inflammation, resulting in better asthma control, fewer exacerbations and hospitalisations in uncontrolled asthma[90]. Despite their benefits, it soon became apparent that OCS maintenance therapy[91] and even short OCS courses cause serious long-term side effects and morbidity in asthma[92–97]. These adverse outcomes include osteoporosis, cardiovascular disease, venous thromboembolism, infection, type 2 diabetes, obesity, peptic ulcers, adrenal insufficiency, ocular diseases and psychiatric disorders (see Figure 1.3)[98–100]. In addition, OCS overuse is associated with increased non-asthma-related healthcare use and costs, but above all it poses a significant burden to asthma patients causing poorer quality of life and increased mortality[101–105].

Since 2003, the treatment of asthma has dramatically changed with the introduction of the first biologic therapy for patient with severe asthma. Omalizumab (anti-IgE) showed a significant reduction in exacerbations in patients with severe allergic asthma [106], but, unfortunately, did not reduce the need for chronic maintenance treatment with OCS. Later on, other biologics targeting type 2 inflammation, characterised by cytokines IL-4, IL-5 and IL-13 and inflammatory cells such as Th-2 cells, type 2 innate lymphoid cells and eosinophilic cells, became available for the treatment of severe asthma patients[2]. In 2015 mepolizumab (anti-IL-5), followed in recent years by three other biologics; reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor) and dupilumab (anti-IL-4/IL-13) all demonstrated significant reductions in exacerbation rate and improvement in asthma control[107–112]. Interestingly, treatment with these new biologics not only resulted in fewer OCS courses due to a reduction in exacerbations, but also showed a strong OCS-sparing effect in patients on maintenance OCS therapy[113–116]. This has led the Global Initiative for Asthma (GINA) to recommend the use of OCS only as a last resort in patients with severe asthma (step 5)[3].

Nevertheless, OCS are still widely prescribed and many patients with asthma are exposed to potentially toxic cumulative doses[117–120]. However, patients are entitled to good asthma care, which includes avoiding unnecessary exposure to OCS[89, 121]. Moreover, the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) has listed unnecessary OCS use as one of its key missions[122]. This underlines the urgent need for targeted interventions to prevent OCS overuse. In order to reduce inappropriate OCS prescribing behaviour, it is important to know the prevalence of frequent OCS use in patients with asthma, the adequacy of ICS treatment in these patients and the involvement of specialists and general practitioners in OCS prescriptions.

RESEARCH QUESTIONS OF THE THESIS

As outlined above, various research questions regarding treatable traits in adult asthma remain unanswered. This thesis will focus on several key questions regarding both common and neglected treatable traits in adult asthma, namely the practical implementation and benefits of a systematic approach of treatable traits in uncontrolled asthma patients, the emerging relationship between asthma and nasal polyposis and dynamic hyperinflation and OCS overuse as a possible new target for the treatment of adult asthma.

The following research questions were formulated:

1. Does a 1-day systematic multidisciplinary assessment in a specialised severe asthma centre lead to better outcome of asthma control, quality of life and healthcare use in patients with uncontrolled asthma after 1 year? (Chapter 2)

2. What is the relationship between asthma and nasal polyposis from a chest physician's perspective? In more detail, what is the current knowledge about the epidemiology, pathophysiology, effect on asthma outcomes, clinical assessment and treatment options of nasal polyposis in asthma? (Chapter 3)

3. What is the prevalence of dynamic hyperinflation in moderate to severe asthma patients, and what is the relationship between the degree of dynamic hyperinflation and severity of respiratory symptoms and limitations in daily life activities in these patients? (Chapter 4)

4. What is the effect of the treatment with systemic glucocorticoids on the degree of dynamic hyperinflation in moderate to severe asthma patients, and what is the relationship between inflammatory markers and the change in dynamic hyperinflation? (Chapter 5)

5. What is the proportion of patients with asthma in the Netherlands who are exposed to high doses of OCS, are these patients treated with adequate doses of ICS and are they seen regularly by an asthma specialist for adjustment and optimization of their asthma therapy? (Chapter 6)

REFERENCES

1 Porsbjerg C, Melén E, Lehtimäki L, Shaw D. Asthma. *The Lancet 2023;* 401: 858–873.
2 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature Medicine 2012;* 18: 716–725.
3 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org.
4 GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respiratory Medicine 2020;* 8: 585–596.
5 Papi A, Chipps BE, Beasley R, Panettieri RA, Israel E, Cooper M, Dunsire L, Jeynes-Ellis A, Johnsson E, Rees R, Cappelletti C, Albers FC. Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. *New England Journal of Medicine 2022;* 386: 2071–2083.
6 O'Byrne PM, Reddel HK, Beasley R. The management of mild asthma. *European Respiratory Journal 2021;* 57: 2003051.
7 Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. *New England Journal of Medicine 2017;* 377: 965–976.
8 Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. *New England Journal of Medicine 2022;* 386: 157–171.
9 Hekking PPW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *Journal of Allergy and Clinical Immunology 2015;* 135: 896–902.
10 Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, Wagener AH, Wagers SS, Sterk PJ, Compton CH. Diaagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax 2011;* 66: 910–917.
11 Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: Toward precision medicine of chronic airway diseases. *European Respiratory Journal 2016;* 47: 410–419.
12 Agustí A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, Louis R, McDonald VM, Sterk PJ, Thomas M, Vogelmeier C, Pavord ID. Precision medicine in airway diseases: moving to clinical practice. *European Respiratory Journal 2017;* 50: 1701655.
13 Orie NGM, Sluiter HJ, Vries K, Tammeling GJ. Chronische aspecifieke respiratore aandoeningen. *Nederlands Tijdschrift voor Geneeskunde 1961;* 105: 2136–2139.
14 Fletcher CM, Pride NB. Definitions of emphysema, chronic bronchitis, asthma, and airflow obstruction: 25 years on from the Ciba symposium. *Thorax 1984;* 39: 81–85.
15 McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, Marks GB, Bardin PP, Beasley R, Pavord ID, Wark PAB, Gibson PG. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *European Respiratory Journal 2019;* 53: 1802058.
16 Fingleton J, Hardy J, Beasley R. Treatable traits of chronic airways disease. *Current Opinion in Pulmonary Medicine 2018;* 24: 24–31.
17 Shrimanker R, Choo XN, Pavord ID. A new approach to the classification and management of airways diseases: identification of treatable traits. *Clinical Science 2017;* 131: 1027–1043.
18 McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. *European Respiratory Journal 2020;* 55: 1901509.
19 Hiles SA, Gibson PG, Agusti A, McDonald VM. Treatable Traits That Predict Health Status and Treatment Response in Airway Disease. Journal of Allergy and Clinical Immunology in Practice 2021; 9: 1255-1264.
20 McDonald VM, Hiles SA, Godbout K, Harvey ES, Marks GB, Hew M, Peters M, Bardin PG, Reynolds PN, Upham JW, Baraket M, Bhikoo Z, Bowden J, Brockway B, Chung LP, Cochrane B, Foxley G, Garrett J, Jayaram L, Jenkins C, Katelaris C, Katsoulotos G, Koh MS, Kritikos V, Lambert M, Langton D, Lara Rivero A, Middleton PG, Nanguzgambo A, Radhakrishna N, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology 2019;* 24: 37–47.
21 Melhorn J, Howell I, Pavord ID. Should we apply a treatable traits approach to asthma care? *Annals of Allergy, Asthma & Immunology 2022;* 128: 390–397.
22 Nelson HS. β-Adrenergic Bronchodilators. *New England Journal of Medicine 1995;* 333: 499–507.
23 Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews 2014;* 0CD010314.
24 Pavord ID, Agusti A. Blood eosinophil count: a biomarker of an important treatable trait in patients with airway disease. *European Respiratory Journal 2016;* 47: 1299–1303.
25 Zhang X-Y, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Lin J-T, Gibson PG. Full blood count parameters for the detection of asthma inflammatory phenotypes. *Clinical & Experimental Allergy 2014;* 44: 1137–1145.

26 Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. *European Respiratory Journal 2015;* 45: 1446–1462.
27 Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Marks GB, Baraket M, Powell H, Taylor SL, Leong LEX, Rogers GB, Simpson JL. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *The Lancet 2017;* 390: 659–668.
28 Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. The Lancet 2012; 380: 1583–1589.
29 Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax 2006;* 61: 1065–1069.
30 Reddel HK, Bateman ED, Becker A, Boulet L-P, Cruz AA, Drazen JM, Haahtela T, Hurd SS, Inoue H, de Jongste JC, Lemanske RF, Levy ML, O'Byrne PM, Paggiaro P, Pedersen SE, Pizzichini E, Soto-Quiroz M, Szefler SJ, Wong GWK, FitzGerald JM. A summary of the new GINA strategy: a roadmap to asthma control. *European Respiratory Journal 2015;* 46: 622–639.
31 Enilari O, Sinha S. The Global Impact of Asthma in Adult Populations. *Annals of Global Health 2019;* 85: 2.
32 Janssen SMJ, van Helvoort HAC, Tjalma TA, Antons JC, Djamin RS, Simons SO, Spruit MA, van 't Hul AJ. Impact of Treatable Traits on Asthma Control and Quality of Life. *Journal of Allergy and Clinical Immunology in Practice 2023;* 11: 1823-1833.
33 Pavord ID, Barnes PJ, Lemière C, Gibson PG. Diagnosis and Assessment of the Asthmas. *Journal of Allergy and Clinical Immunology in Practice 2023;* 11: 1–8.
34 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, Gamble J. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax 2003; 58: 561–566.
35 Irwin RS, Curley FJ, French CL. Difficult-to-Control Asthma. *Chest 1993;* 103: 1662–1669.
36 Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, Bucknall CE, Menzies-Gow AN. Dedicated Severe Asthma Services Improve Health-care Use and Quality of Life. *Chest 2015;* 148: 870–876.
37 von Bülow A, Backer V, Bodtger U, Søes-Petersen NU, Vest S, Steffensen I, Porsbjerg C. Differentiation of adult severe asthma from difficult-to-treat asthma – Outcomes of a systematic assessment protocol. *Respiratory Medicine 2018;* 145: 41–47.
38 Irwin RS, Curley FJ, French CL. Difficult-to-Control Asthma. Contributing factors and outcome of a systematic management protocol. *Chest 1993;* 103: 1662–1669.
39 Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of Disease in Chronic Rhinosinusitis with Nasal Polyps. *Journal of Asthma and Allergy 2021;* 14: 127–134.
40 Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *Journal of Allergy and Clinical Immunology 1977;* 59: 17–21.
41 Larsen K. The clinical relationship of nasal polyps to asthma. *Allergy and Asthma Proceedings 1996;* 17: 243–249.
42 Bachert C, Patou J, Cauwenberge P Van. The role of sinus disease in asthma. *Current Opinion in Allergy and Clinical Immunology 2006;* 6: 29–36.
43 Brożek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision. *Journal of Allergy and Clinical Immunology 2010;* 126: 466–476.
44 Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, Adinoff AD, Bachert C, Borish L, Chinchilli VM, Danzig MR, Ferguson BJ, Fokkens WJ, Jenkins SG, Lund VJ, Mafee MF, Naclerio RM, Pawankar R, Ponikau JU, Schubert MS, Slavin RG, Stewart MG, Togias A, Wald ER, Winther B. Rhinosinusitis: Developing guidance for clinical trials. *Journal of Allergy and Clinical Immunology 2006;* 118: S17–S61.
45 Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic Rhinosinusitis with Nasal Polyps and Asthma. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 1133–1141.
46 Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, Kita H. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis. *Journal of Allergy and Clinical Immunology 2003;* 112: 877–882.
47 Håkansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, Martin-Bertelsen T, Winther O, Backer V, von Buchwald C. Airway Inflammation in Chronic Rhinosinusitis with Nasal Polyps and Asthma: The United Airways Concept Further Supported. *PLoS One 2015;* 10: e0127228.
48 Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, Gjomarkaj M, Forsberg B, Gunnbjorn-dottir M, Minov J, Brozek G, Dahlen SE, Toskala E, Kowalski ML, Olze H, Howarth P, Krämer U, Baelum J, Loureiro C, Kasper L, Bousquet PJ, Bousquet J, Bachert C, Fokkens W, Burney P. Asthma in adults and its association with chronic rhinosinusitis: The GA2LEN survey in Europe. *Allergy 2012;* 67: 91–98.

49 Håkansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A Comparative and Descriptive Study of Asthma in Chronic Rhinosinusitis with Nasal Polyps. *American Journal of Rhinology and Allergy 2014*; 28: 383–387.
50 Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. Clinical & Experimental *Allergy 2012*; 42: 650–658.
51 Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. *Journal of Internal Medicine 2016*; 279: 192–204.
52 Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, Kern RC, Schleimer RP, Peters AT. Association between Severity of Asthma and Degree of Chronic Rhinosinusitis. *American Journal of Rhinology and Allergy 2011*; 25: 205–208.
53 Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, Pandis I, Bansal AT, Bel EH, Auffray C, Compton CH, Bisgaard H, Bucchioni E, Caruso M, Chanez P, Dahlén B, Dahlen S-E, Dyson K, Frey U, Geiser T, Gerhardsson de Verdier M, Gibeon D, Guo Y, Hashimoto S, Hedlin G, Jeyasingham E, Hekking P-PW, Higenbottam T, Horváth I, Knox AJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *European Respiratory Journal 2015*; 46: 1308–1321.
54 Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, ten Brinke A, Bel EH. Severe adult-onset asthma: A distinct phenotype. *Journal of Allergy and Clinical Immunology 2013*; 132: 336–341.
55 Castillo JA, Plaza V, Rodrigo G, Julia B, Mullol J. Chronic rhinosinusitis with and without nasal polyps and rhinitis in adult asthma. Frequency distribution and relationship with asthma control and severity (the IRIS-ASMA study). *European Respiratory Journal 2013*; 42 (Suppl 57): 3448.
56 Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S, Bacharier LB, Bleecker ER, Comhair SAA, Coverstone A, DeBoer M, Erzurum SC, Fain SB, Fajt M, Fitzpatrick AM, Gaffin J, Gaston B, Hastie AT, Hawkins GA, Holguin F, Irani A-M, Israel E, Levy BD, Ly N, Meyers DA, Moore WC, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *American Journal of Respiratory Critical Care Medicine 2017*; 195: 302–313.
57 Ek A, Middelveld RJM, Bertilsson H, Bjerg A, Ekerljung L, Malinovschi A, Stjärne P, Larsson K, Dahlén S-E, Janson C. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA 2 LEN survey. *Allergy 2013*; 68: 1314–1321.
58 Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert C. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *Journal of Allergy and Clinical Immunology 2013*; 131: 110-6.
59 Gevaert P, Langloidolt D, Lackner A, Stammberger H, Staudinger H, Vanzele T, Holtappels G, Tavernier J, Vancauwenberge P, Bachert C. Nasal IL-5 levels determine the response to anti–IL-5 treatment in patients with nasal polyps. *Journal of Allergy and Clinical Immunology 2006*; 118: 1133–1141.
60 Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, De Ruyck N, Blomme K, Sousa AR, Marshall RP, Bachert C. Mepolizumab, a humanized anti–IL-5 mAb, as a treatment option for severe nasal polyposis. Journal of Allergy and Clinical Immunology 2011; 128: 989-995.
61 Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis. *Journal of American Medical Association 2016*; 315: 469-79.
62 Dockrell M, Partridge MR, Valovirta E. The limitations of severe asthma: the results of a European survey. *Allergy 2007*; 62: 134-41.
63 Weatherald J, Lougheed MD, Taillé C, Garcia G. Mechanisms, measurement and management of exertional dyspnoea in asthma. *European Respiratory Review 2017*; 26: 170015.
64 Tuxen D V. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med 1994*; 150: 870–874.
65 Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N. Simplified Detection of Dynamic Hyperinflation. *Chest 2004*; 126: 1855–1860.
66 Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *European Respiratory Journal 2012*; 40: 322–329.
67 O'Donnell DE, Travers J, Webb KA, He Z, Lam Y-M, Hamilton A, Kesten S, Maltais F, Magnussen H. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *European Respiratory Journal 2009*; 34: 866–874.
68 Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, López-Collazo E, Alvarez-Sala R. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *American Journal of Respiratory Critical Care Medicine 2009*; 180: 506–512.
69 Laveneziana P, Lotti P, Coli C, Binazzi B, Chiti L, Stendardi L, Duranti R, Scano G. Mechanisms of dyspnoea and its language in patients with asthma. *European Respiratory Journal 2006*; 27: 742–747.

70 Lougheed MD, Fisher T, O'Donnell DE. Dynamic hyperinflation during bronchoconstriction in asthma: Implications for symptom perception. *Chest 2006*; 130: 1072–1081.
71 Kosmas EN, Milic-Emili J, Polychronaki A, Dimitroulis I, Retsou S, Gaga M, Koutsoukou A, Roussos C, Koulouris NG. Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. *European Respiratory Journal 2004;* 24: 378–384.
72 Barreiro E, Gea J, Sanjuás C, Marcos R, Broquetas J, Milic-Emili J. Dyspnoea at rest and at the end of different exercises in patients with near-fatal asthma. *European Respiratory Journal 2004*; 24: 219–225.
73 Benfante A, Di Marco F, Terraneo S, Centanni S, Scichilone N. Dynamic hyperinflation during the 6-min walk test in severely asthmatic subjects. *European Respiratory Journal Open Research 2018;* 4: 00143–02017.
74 Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: Key concepts in modern respiratory physiology. *European Respiratory Journal 2005;* 25: 186–199.
75 De Groot JC, Storm H, Amelink M, De Nijs SB, Eichhorn E, Reitsma BH, Bel EHD, Brinke A Ten. Clinical profile of patients with adult-onset eosinophilic asthma. *European Respiratory Journal Open Research 2016*; 2: 1–8.
76 van Veen IH, Sterk PJ, Schot R, Gauw SA, Rabe KF, Bel EH. Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. *European Respiratory Journal 2006*; 27: 951-956.
77 Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral Lung Resistance in Normal and Asthmatic Subjects. *American Review of Respiratory Disease 1990;* 141: 584–588.
78 Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *American Journal of Respiratory Critical Care Medicine 1996*; 154: 1505–1510.
79 Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, Matsuoka H, Jinnai M, Muro S, Chin K, Mishima M. Role of small airways in asthma: Investigation using high-resolution computed tomography. *Journal of Allergy and Clinical Immunology 2006*; 118: 1019–1025.
80 Randolph TG, Rollins JP. The effect of cortisone on bronchial asthma. *Journal of Allergy 1950;* 21: 288–295.
81 Harris MS. Cortisone in treatment of bronchial asthma. *California Medicine 1951;* 75: 85–88.
82 Christie RV, Scadding JG, Boyd JT, et al. Controlled Trial of effects of cortisone acetate in chronic asthma; report to the Medical Research Council by the subcommittee on clinical trials in asthma. *The Lancet 1956;* 268: 798–803.
83 Chu EK, Drazen JM. Asthma: one hundred years of treatment and onward. *American Journal of Respiratory Critical Care Medicine 2005*; 171: 1202–1208.
84 Crompton G. A brief history of inhaled asthma therapy over the last fifty years. *Primary Care Respiratory Journal 2006;* 15: 326–331.
85 Campbell IA, Somner AR, Angel JH, et al. Inhaled Corticosteroids Compared With Oral Prednisone in Patients Starting Long-Term Corticosteroid Therapy for Asthma; a Controlled Trial By the British Thoracic and Tuberculosis Association. *The Lancet 1975;* 306: 469–473.
86 Van Staa TP, Leufkens HGM, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. *QJM 2000*; 93: 105–111.
87 Bénard-Laribière A, Pariente A, Pambrun E, Bégaud B, Fardet L, Noize P. Prevalence and prescription patterns of oral glucocorticoids in adults: A retrospective cross-sectional and cohort analysis in France. *British Medical Journal Open 2017*; 7: 1–7.
88 Pavord ID. Oral corticosteroid-dependent asthma: Current knowledge and future needs. *Current Opinion in Pulmonary Medicine 2019;* 25: 51–58.
89 Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, Cruz AA, Duijts L, Drazen JM, FitzGerald JM, Fleming LJ, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Mortimer K, Pitrez PM, Sheikh A, Yorgancioglu AA, Boulet L-P. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. *European Respiratory Journal 2022;* 59: 2102-730.
90 Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database of Systematic Reviews 2001;* CD002178.
91 Smyllie HC, Connolly CK. Incidence of serious complications of corticosteroid therapy in respiratory disease: A retrospective survey of patients in the Brompton Hospital. *Thorax 1968;* 23: 571-581.
92 Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respiratory Medicine 2009;* 103: 975–994.
93 Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, Chaudhuri R, Price D, Brightling CE, Heaney LG. Comorbidity in severe asthma requiring systemic corticosteroid therapy: Cross-sectional data from the optimum patient care research database and the british thoracic difficult asthma registry. *Thorax 2016;* 71: 339–346.

94 Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, Albers F, Yancey S, Ortega H, Forshag M, Lin X, Dalal AA. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *Journal of Allergy and Clinical Immunology 2015*; 136: 1488–1495.

95 Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: Striking the balance between efficacy and safety. *European Respiratory Review 2020*; 29: 190151.

96 Heatley H, Tran T, Bourdin A, Menzies-Gow A, Jackson D, Maslova E, Skinner D, Carter V, Price D. Late Breaking Abstract - The burden of intermittent oral corticosteroid use in asthma. Airway pharmacology and treatment *European Respiratory Society; 2021*. p. OA1491.

97 Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegård A, Davidsen JR. Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality. *European Respiratory Journal 2022*; 60: 2103054.

98 Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Jie JLZ, Tran TN. Adverse outcomes from initiation of systemic corticosteroids for asthma: Long-term observational study. *Journal of Asthma and Allergy 2018*; 11: 193–204.

99 Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: A focused review of the impact data in the literature. *European Respiratory Journal 2018*; 52: 1800703.

100 Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, Bosnic-Anticevich S, Harrington J, Hew M, Holland AE, Hopkins T, Jayaram L, Reddel H, Upham JW, Gibson PG, Bardin P. Oral corticosteroids stewardship for asthma in adults and adolescents: A position paper from the Thoracic Society of Australia and New Zealand. *Respirology 2021*; 26: 1112–1130.

101 Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: A health economic analysis. *Respiratory Research 2017*; 18: 1–8.

102. Voorham J, Xu X, Price DB, Golam S, Davis J, Zhi Jie Ling J, Kerkhof M, Ow M, Tran TN. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy 2019*; 74: 273–283.

103 Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Quality of Life Research 2017*; 26: 1037–1058.

104 Bourdin A, Molinari N, Vachier I, Pahus L, Suehs C, Chanez P. Mortality: a neglected outcome in OCS-treated severe asthma. *European Respiratory Journal 2017*; 50: 1701486.

105 Bleecker ER, Al-Ahmad M, Bjermer L, Caminati M, Canonica GW, Kaplan A, Papadopoulos NG, Roche N, Ryan D, Tohda Y, Yáñez A, Price D. Systemic corticosteroids in asthma: A call to action from World Allergy Organization and Respiratory Effectiveness Group. *World Allergy Organization Journal 2022*; 15: 100726.

106 Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: A systematic review. *Chest 2011*; 139: 28–35.

107 Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *The Lancet 2012*; 380: 651–659.

108 Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P, MENSA Investigators. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *New England Journal of Medicine 2014*; 371: 1198–1207.

109 Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma. *Chest 2016*; 150: 799–810.

110 Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respiratory Medicine 2015*; 3: 355–366.

111 Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, Goldman M, SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; 388: 2115–2127.

112 Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. New England *Journal of Medicine 2018*; 378: 2486–2496.

113 Braunstahl G-J, Chlumský J, Peachey G, Chen C-W. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy, Asthma & Clinical Immunology 2013*; 9: 47.

114 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *New England Journal of Medicine 2014*; 371: 1189–1197.
115 Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, Barker P, Sproule S, Ponnarambil S, Goldman M. Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. *New England Journal of Medicine 2017*; 376: 2448–2458.
116 Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *New England Journal of Medicine 2018*; 378: 2475–2485.
117 Tran TN, King E, Sarkar R, Nan C, Rubino A, O'Leary C, Muzwidzwa R, Belton L, Quint JK. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *European Respiratory Journal 2020*; 55: 1902363.
118 Tran TN, MacLachlan S, Hicks W, Liu J, Chung Y, Zangrilli J, Rubino A, Ganz ML. Oral Corticosteroid Treatment Patterns of Patients in the United States with Persistent Asthma. *Journal of Allergy and Clinical Immunology: In Practice 2021*; 9: 338-346.
119 Hew M, McDonald VM, Bardin PG, Chung LP, Farah CS, Barnard A, Cooper MS, Gibson PG, Upham JW. Cumulative dispensing of high oral corticosteroid doses for treating asthma in Australia. *Medical Journal of Australia 2020*; 213: 316–320.
120 Ekström M, Nwaru Bl, Hasvold P, Wiklund F, Telg G, Janson C. Oral corticosteroid use, morbidity and mortality in asthma: A nationwide prospective cohort study in Sweden. Allergy: *European Journal of Allergy and Clinical Immunology 2019*; 74: 2181–2190.
121 Menzies-Gow A, Canonica GW, Winders TA, Correia de Sousa J, Upham JW, Fink-Wagner AH. A Charter to Improve Patient Care in Severe Asthma. Advances in Therapy 2018; 35: 1485–1496.
122 Djukanovic R, Adcock IM, Anderson G, Bel EH, Canonica GW, Cao H, Chung KF, Davies DE, Genton C, Gibson-Latimer T, Hamerlijnck D, Heuvelin E, Louis R, Korn S, Kots M, Kwon N, Naddaf R, Wagers SS. The Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) ERS Clinical Research Collaboration: a new dawn in asthma research. *European Respiratory Journal 2018*; 52: 1801671.

Chapter

2

A 1-day-visit in a severe asthma centre; effect on asthma control, quality of life and healthcare use

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ABSTRACT

Introduction
Patients with uncontrolled asthma report ongoing symptoms, poor quality-of-life and extensive healthcare use and might benefit from management by a specialised severe asthma team. It is unknown whether a one-time evaluation by asthma experts, without long-term supervision by a specialised team, provides favourable outcomes. We evaluated asthma control (ACQ), quality-of-life (AQLQ) and healthcare use (HCU) before and 1 year after a one-day-visit program in a severe asthma centre, including a multidisciplinary assessment resulting in a personalised management plan to be implemeted by patients own pulmonologists.

Methods
40 uncontrolled asthma patients completed questionnaires (ACQ, AQLQ, HCU) at baseline, and 6 and 12 months follow-up.

Results
ACQ improved from 2.6 (IQR 1.7-3.2) to 1.8 (1.2-3.2) ($p=0.003$) and AQLQ from 4.8 (4.0-5.2) to 5.3 (4.4-6.0) ($p<0.001$). We found a reduction in patients with ≥2 exacerbations (95% versus 17%, $p<0.001$), ≥1 ER visits (78% versus 37%, $p<0.001$) and ≥1 hospitalisations (47% versus 10%, $p=0.001$).

Conclusion
Evaluation of uncontrolled asthma patients in a one-day-visit program in a severe asthma centre resulted in significant improvements in asthma control, quality-of-life and healthcare use after 1 year. This one-day-visit approach seems beneficial for uncontrolled asthma patients and might reduce their dependence on expensive treatment modalities and long-term management in specialised centres.

INTRODUCTION

The majority of asthma patients can be adequately treated with inhaled corticosteroids (ICS) and bronchodilators. However, a significant subset of patients remains difficult to treat[1]. These patients report ongoing asthma symptoms, poor quality of life and extensive healthcare use (HCU) despite maximal treatment. This subgroup of patients is responsible for high direct and indirect healthcare costs and poses a major healthcare problem[2].

Poor control in these patients might be due to several factors, including incorrect diagnosis, poor adherence, undertreated asthma triggers and co-morbidities and psychosocial problems[3]. Only patients who, after an extensive assessment addressing these issues, still need high-intensity inhaled treatment or systemic corticosteroids to prevent their asthma from becoming uncontrolled or who remain uncontrolled despite this therapy should be labelled as "severe refractory" asthma patients, and are candidate for novel therapeutic approaches[3, 4]. Therefore, in patients presenting with chronic severe asthma symptoms, a systematic approach, preferably multidisciplinar[5], is recommended by all international severe asthma guidelines[6–8].

Previous studies have shown that a standardised evaluation protocol helped to identify[9] and treat comorbidities and triggering factors in patients with uncontrolled asthma and that, following such a systematic assessment, more than 50% were no longer difficult to treat[10, 11]. Recently, prospective data from a UK registry showed that management of patients with difficult asthma at dedicated severe asthma centres resulted in improvement in quality of life (QoL) and HCU[12]. So far, it is not known whether it is possible to achieve favourable results with a single extensive assessment in a specialised severe asthma centre and subsequent referral of patients to their own general pulmonologists.

In the present study, we evaluated asthma control, QoL and HCU in patients with uncontrolled asthma before and 1 year after a 1-day visit programme in a specialised severe asthma centre, which included a systematic multidisciplinary assessment resulting in a personalised management plan to be implemented by patients' own pulmonologists. In addition, we analysed whether specific characteristics could predict a better outcome.

METHODS

In 2013, in our specialised severe asthma centre, a 1-day visit programme was initiated for the evaluation of patients with uncontrolled asthma by a multidisciplinary team, including pulmonologists, physiotherapists, clinical psychologist and specialised asthma nurses. Patients were systematically evaluated with particular attention to the confirmation of asthma diagnosis and the presence of contributing factors and comorbidities. Based on clinical and inflammatory parameters, an initial determination of asthma phenotype was made. Findings were discussed in the multidisciplinary team and a personalised management plan aiming to improve asthma outcomes was provided to the patient and referring pulmonologist. All patients were referred back to their own pul-

monologist, sometimes after an optimisation period of up to 6 months. Only the small subset of patients who were eligible for treatment which was not available in their own hospital remained for follow up in our centre. Detailed information on the 1-day-visit programme as well as our report back to the referring pulmonologist (assessment and stepwise management plan) is described in the supplementary material.

In this prospective observational cohort study, we included adult non-smoking patients with uncontrolled asthma referred by pulmonologists from several hospitals in the Netherlands between June 2013 and June 2014. Six and 12 months after the assessment patients were asked to complete questionnaires on asthma control, QoL, prednisolone use and HCU. The study was approved by the hospital medical ethics committee, and all patients gave their written informed consent. The cohort was registered in The Netherlands trial register: NTR5522.

All patients underwent an extensive clinical, functional and laboratory assessment[3]. Data on demographics, medical history, smoking history, body mass index, comorbidities, psychological functioning and potential contributing factors, as well as medication use (adherence and inhalation technique) were collected. Peripheral blood cell counts were measured and expressed as absolute numbers. Atopic status was assessed by total and specific IgE to a panel of common aeroallergens. Lung function testing included spirometry before and after 400 µg inhaled salbutamol[13]. High-resolution computed tomography of the thorax, computed tomography of the sinuses and ear, nose and throat evaluation data from referring pulmonologist were used in the assessment and whenever indicated performed (again). 6-min walking distance (6MWD)[14, 15] was assessed according to American Thoracic Society criteria[16]. Airway inflammation was assessed by the level of exhaled nitric oxide (FeNO)[17] and cell differentials in induced sputum[18].

Patients completed the Asthma Quality of Life Questionnaire (AQLQ)[19], the Asthma Control Questionnaire (ACQ)[20] and a questionnaire on HCU[21] at baseline as well as at 6 and 12 months afterwards.

Patients were considered adherent if the Medication Adherence Report Scale (MARS) score was ≥4.0[22] and ICS prescription filling was ≥80%[23]. Prescription refill rates were calculated from prescription records for a 12-month time period. Exacerbations were defined as episodes with worsening of asthma symptoms, requiring prednisolone bursts or doubling oral corticosteroids (OCS) maintenance dose. Patients were phenotypically divided into non-eosinophilic, early onset atopic or late-onset eosinophilic subtypes. We labelled patients as non-eosinophilic if they had blood eosinophils $<0.3\times10^9$ cells/L and FeNO <25 ppb and, if available, sputum eosinophils <3% both at baseline assessment as well as in all measurements in the previous year. If they had blood eosinophils $\geq0.3\times10^9$ cells/L or FeNO ≥50 ppb or sputum eosinophils ≥3% they were considered eosinophilic subtypes[24]. Early onset was defined as start of asthma at age <18 years and late onset at ≥18 years. Positive atopic status was defined as a score of >0.35 kU/L for at least one of the specific IgE tested.

Statistical analysis

Baseline measurements were compared with follow-up measurements using Wilcoxon matched pairs testing or Chi-squared analyses, whenever appropriate. Spearman rank correlation coefficients were used to analyse the relationship between outcome variables and baseline variables. All analyses were performed using SPSS software, version 20 (IBM, Armonk, NY, USA).

RESULTS

In the first year of this 1-day visit programme, 47 patients with uncontrolled asthma completed the systematic assessment in which 51% classified as severe asthma and 40% as difficult-to-treat asthma[4]. In 9%, the diagnosis of asthma could not be confirmed. 40 (85%) patients had 6 and 12 months' follow up data available and were eligible for entry in this study. Based on the previously described phenotype criteria, 35% of these patients were considered as early onset atopic asthma, 45% as late-onset eosinophilic asthma, 15% as non-eosinophilic asthma and 5% could not be classified. 15 patients were considered eligible for omalizumab treatment, 10 as first step therapy, five as second step to start when still uncontrolled after optimisation of contributing factors. Three of these first 10 patients already had been treated with omalizumab by their own pulmonologist, but had discontinued it due to adverse events or lack of efficacy. After the assessment, 83% of the patients returned to their own pulmonologist provided with a personalised management plan and only seven patients remained for follow up in our centre (five anti-interleukin 5 trial, two anti-immunoglobulin E treatment).

Baseline characteristics

Patients were aged between 22 and 72 years and showed a female predominance with 52% of them being non-atopic and 63% reporting an adult onset of their asthma (table 2.1). Patients used high doses of inhaled steroids (ICS) and 28% of the patients were on daily OCS. Prescription filling analysis showed that 58.6% of the patients were adherent to their high-dose ICS with a prescription filling rate of ≥80%. An additional diagnosis potentially contributing to poor asthma control was found in the majority of patients, with chronic rhinosinusitis and dysfunctional breathing being the most prevalent. Adequate sputum samples were obtained in 58% of the patients, of which 74% showed elevated sputum eosinophils (≥3%) despite high-dose treatment.

Table 2.1 Baseline characteristics

	Total group
Patients n	40
Male sex	14 (35)
Age years	51 ± 13
BMI kg/m^{-2}	29 ± 7
Smoking history pack-years	1.0 (0-9.3)
OCS dependent	11 (28)
Fluticasone equivalent ICS dose μg	750 (500-1000)
Atopic status	19 (48)
Adult-onset asthma	25 (63)
Adherence ICS %	82 (38-104)
Inhaler technique, poor/moderate %	
Poor	5
Moderate	27
Self-management, poor/moderate %	
Poor	5
Moderate	38
Potentially contributing diagnoses	
Rhinosinusitis	24 (60)
Gastro-oesophageal reflux	13 (33)
OSAS	9 (23)
Obesity	12 (30)
Dysfunctional breathing	19 (48)
Psychological dysfunction	12 (30)
Post-bronchodilator FEV_1 % pred	80 ± 20
6-MWD m	488 ± 108
6-MWD % pred	84 ± 19
FeNO ppb	38 (17-68)
Blood eosinophils x $10^9/L^{-1}$	0.2 (0.1-0.6)
Blood neutrophils x $10^9/L^{-1}$	5.7 (3.9-6.8)
Total IgE kU/L^{-1}	129 (46-395)
Sputum eosinophils %	16 (0.8-32)
Sputum neutrophils %	45 (23-64)

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. BMI: body mass index; OCS: oral corticosteroids; ICS: inhaled corticosteroids; OSAS: obstructive sleep apnoea syndrome; FEV_1: forced expiratory volume in 1 s; % pred: percentage of predicted value; 6MWD: 6 min walking distance; FeNO: exhaled fraction of nitric oxide; ppb: parts per billion; Ig: immunoglobulin.

Effects on asthma control, QoL, OCS dose and HCU

Asthma control as assessed by ACQ score improved from 2.6 (interquartile range 1.7–3.2) at baseline to 1.9 (1.0–2.9) at 6 months and 1.8 (1.2–3.2) at 1 year. (p=0.003) (figure 2.1). 53% of patients had a clinical relevant improvement of ACQ of >0.5 point at 1 year. In addition, the Juniper AQLQ total score improved from 4.8 (4.0–5.2) at baseline to 5.4 (4.8–5.9) at 6 months and 5.3 (4.4–6.0) at 1 year. (p<0.001) (figure 2.2).

Though there were obvious changes in individual prednisolone dose (figure 2.3), for the total group, we found no differences in the dose taken at follow up compared with baseline (0 mg (0–5) versus 0 mg (0–5); p=0.7), or in the proportion of patients dependent on daily OCS (28% versus 35%; p=0.4). At 1 year follow-up, 15% of patients were treated with omalizumab whereas 13% were participating in an anti-IL5 trial.

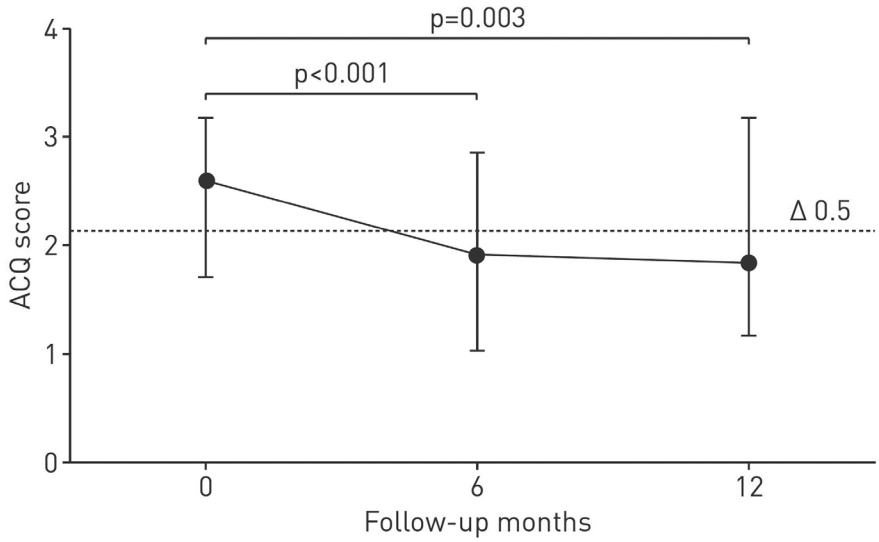
With respect to HCU, at 1 year follow up, the number of asthma-related visits and hospital admissions was significantly reduced (table 2.2). There was a significant decrease in patients who reported frequent (≥2) exacerbations (95% versus 17%; p<0.001), ≥1 emergency room visit (78% versus 37%; p<0.001), or ≥1 hospital admission in the previous year (47% versus 10%; p=0.001) compared with baseline. These 40 patients together accounted for a total number of 197 asthma exacerbations, 165 emergency room visits and 53 hospital admissions in the year preceding the 1-day visit, which had reduced to 39, 21 and 4, respectively in the year following the assessment.

Table 2.2 Healthcare use before and after a one-day-visit program in a specialised severe asthma centre

During preceding year	Baseline	1 year	p-value
Asthma related GP visits	3 (2-7)	1 (0-3)	0.001
Pulmonologist visits	4 (3-8)	3 (2-4)	0.005
Exacerbations	4.5 (2-7)	1 (0-3)	<0.001
Emergency room visits	3 (1-6)	0.5 (0-2)	<0.001
Hospital admissions	0 (0-2)	0 (0-0)	<0.001

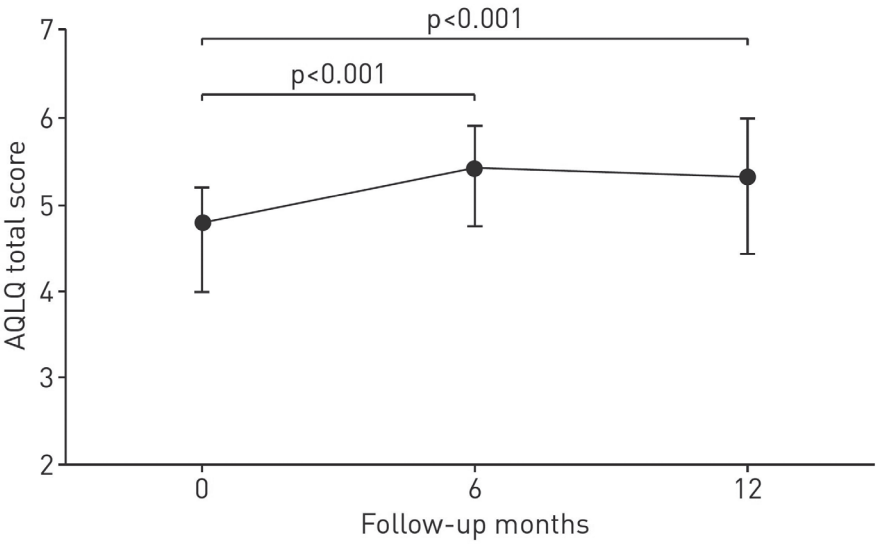
Data are presented as median (interquartile range). GP: general practitioner.

Figure 2.1. Asthma Control Questionnaire (ACQ) scores at baseline assessment (0 months) and 6 and 12 months follow-up in 40 patients with uncontrolled asthma



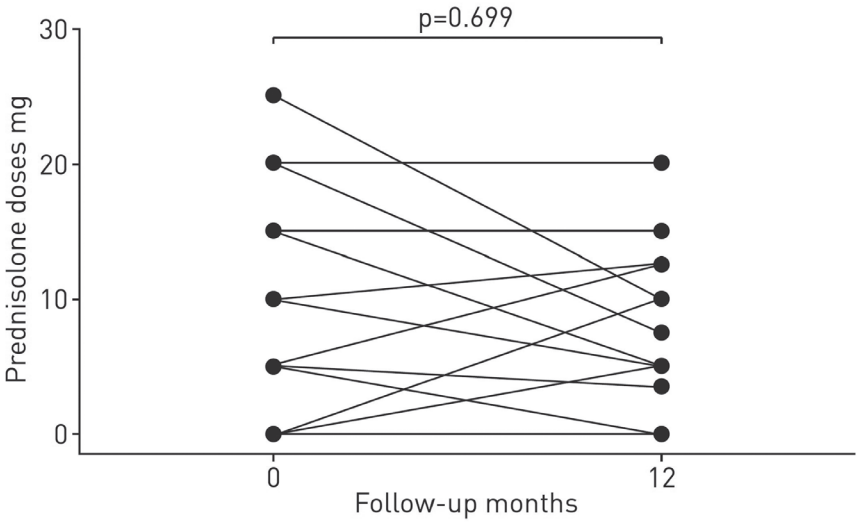
Data are presented as median (interquartile range). Δ0.5: difference of ≥0.5 indicating a clinically significant improvement in asthma control.

Figure 2.2. Asthma-related Quality of Life Questionnaire (AQLQ) scores at baseline assessment (0 months) and 6 and 12 months follow-up in 40 patients with uncontrolled asthma



Data are presented as median (interquartile range).

Figure 2.3. Changes in prednisolone dose at baseline assessment and 12 months follow-up in 40 patients with uncontrolled asthma



Predictors of asthma outcomes

Asthma outcomes (improvement in ACQ or AQLQ, reduction in numbers of exacerbations, emergency room visits or hospital admissions) were not dependent on sex, smoking history or whether patients were referred back to their own pulmonologist or not. Patients labelled as early onset atopic asthma, late-onset eosinophilic asthma and non-eosinophilic asthma all showed comparable beneficial effects after 1 year. A larger improvement in ACQ was seen in patients with higher 6MWD (r=–0.40, p=0.01), lower body mass index (r=0.34, p=0.03) and higher levels of sputum eosinophils (r=–0.41, p=0.05) at baseline. In addition, the reduction in exacerbations was related to higher baseline levels of FeNO (r=–0.34, p=0.03) and eosinophils in blood (r=–0.32, p=0.04) as well as in sputum (r=–0.43, p=0.04).

DISCUSSION

In the present study, we show that patients with uncontrolled asthma benefit from a single extensive assessment in a specialised severe asthma centre, with a significant and clinically relevant improvement in asthma control, quality of life and HCU after 1 year. In the current 1-day visit programme, patients were systematically evaluated by a multidissciplinary team, referred back to their own pulmonologists and provided with a personalised management plan. Compared with the year preceding the assessment, the number of exacerbations, emergency room visits and hospital admissions was reduced by 54%, 57% and 43%, respectively in the 12 months' follow up. Asthma outcomes were not dependent on sex, smoking history or phenotype. The greatest improvements in asthma control and exacerbation frequency were seen in the patients with higher

baseline sputum eosinophils. These results suggest that a single short-term extensive characterisation in a specialised severe asthma centre is beneficial and might be cost effective for a large group of patients with uncontrolled asthma.

In our study, we evaluated the effect of characterising patients with uncontrolled asthma by a dedicated severe asthma team and observed rather impressive improvements in asthma outcomes that persisted long after the patients were referred back to their own pulmonologists. A recent UK registry study[12] showed that management of severe asthma patients in specialised severe asthma centres was associated with improvement in asthma control, QoL and HCU, but data about how long patients visited these clinics and were managed by a specialised team were not mentioned. The present study largely confirmed their results with even more favourable effects on exacerbation and admission rates; although we found no change in daily dose of prednisolone. Our results further highlight that all phenotypes appear to benefit, with the most positive effects for patients with eosinophilic airway inflammation at baseline. The presented standardised 1-day visit approach adds a new component that hopefully contributes to a wider application of the comprehensive characterisation of patients with uncontrolled asthma by a specialised team.

The strength of this study lies in the extensive and validated description of all relevant patient characteristics, including questionnaires, allergy testing, spirometry, induced sputum and blood cell counts, psychological evaluation and 6MWD. This comprehensive systematic characterisation by a dedicated team using pre-established criteria and definitions reduces the risk of bias due to non-standardised approaches and diverse interpretations by different healthcare professionals.

We acknowledge there are several limitations in our study. Firstly, the classification of patients as difficult-to-treat or severe asthma. In our programme, we labelled 51% of the patients as severe asthma without having a 3-month follow-up period in our specialised centre, as has been recommended in guidelines[4]. This period is mainly recommended to evaluate the patients regarding appropriate diagnosis and/or treatment of confounders. In our setting, all patients were followed for several years by a pulmonologist who had already performed this evaluation to a greater or lesser extent. After our 1-day-visit programme, only the patients with confirmed asthma diagnosis, uncontrolled disease despite high doses of medication, good adherence and inhalation technique, and optimised comorbid factors/confounders were considered as severe asthma. All others were labeled as difficult asthma, for the time being, and treated for the observed potentially contributing factors. After addressing these factors we still expect some of these patients to come out as truly severe asthma patients. Secondly, the data on HCU are based on self-report, and may be influenced by recall bias. Recall of HCU data in respiratory patients is fairly reliable for hospitalisations and visits to pulmonologists[25], whereas for emergency room visits, a bias towards under-reporting has been suggested, particular at higher numbers of visits[26]. Although depending on the objective of the analysis, the chosen recall period may be more or less optimal[27], we expect a possible recall bias mainly to underestimate the dimension of the problem and not to explain the large differences in HCU we observed in the two periods. Thirdly, there are not currently widely

accepted definitions of specific asthma phenotypes. In the present study, we found no differences in asthma outcomes between the three phenotypes we defined, but we cannot rule out that adjustment of the criteria for distinct phenotypes could lead to different results. Finally, the absence of a control group is obvious. Improvements in quality of life could be attributed to the fact that patients received more attention and additional tests from different healthcare providers, but it is doubtful whether this may be responsible for the improvements after 1 year. Though we strongly believe that the given insight into their thus far uncontrollable disease contributes to patients' well-being and might have improved their adherence to therapy, we don't expect a placebo effect to explain the beneficial effects measured long after the patients were discharged from our centre.

What other reasons might explain the significant improvements in asthma control, QoL and HCU? The recommendations given in the personalised management plans encompassed various interventions, varying from optimising triggering and comorbid factors[9, 10], improving inhalation technique and adherence[28], increasing physical or psychological functioning to changes in asthma medication. Following our assessment, seven patients started omalizumab treatment and five patients participated in a placebo-controlled trial with mepolizumab, both drugs that are associated with reduction in exacerbation frequency and improvement in QoL[29, 30]. For patients who were not eligible for these biologicals, beneficial effects might further be attributed to the phenotype-specific approach, in which the presence or absence of eosinophilic inflammation played a crucial role[31]. Without evidence for eosinophilic inflammation at time of assessment or in the preceding years it was strongly advocated to taper the, in some cases very high, doses of oral and inhaled corticosteroids. Alternatively, patients with eosinophilic inflammation despite extensive treatment were encouraged to start or increase prednisolone as maintenance therapy, pending the availability of new biologicals. This approach of "giving prednisolone to the right patients" as reflected in figure 2.3, might have contributed to the better outcomes even though the mean prednisolone dose did not change. The finding that exacerbation frequency was most reduced in patients with more active eosinophilic inflammation further supports our phenotype-specific eosinophil-driven treatment.

The present findings are clinically relevant for the management of patients with uncontrolled asthma. Anticipating several novel molecular therapies we face the challenge to limit the costs of uncontrolled asthma treatment by making these expensive drugs available only for patients with truly severe asthma. We show that a comprehensive characterisation of patients with uncontrolled asthma by a specialised team is very successful in improving the condition of a majority of patients, thereby reducing the need for new expensive therapies. More important, our study showed that these favourable results were achieved by a single short-term assessment in a severe asthma centre, even though the implementation of the recommended personalised management plan was not supervised by severe asthma specialists. Assessments using a 1-day visit programme may facilitate the evaluation of uncontrolled patients by a specialised team, both by reduction of travel distances for patients, as well as by limiting time investment of severe asthma specialists. The costs of such a 1-day visit programme seem justified

in view of the anticipated reduced use of expensive asthma drugs and the observed benefits in terms of healthcare use, asthma control and quality of life.

In conclusion, in the present prospective study patients with uncontrolled asthma who were systematically evaluated by a 1-day visit programme in a specialised severe asthma centre showed a significant and clinically relevant improvement in asthma control, QoL and HCU lasting up to 12 months. These results suggest that a single visit with extensive characterisation in a dedicated severe asthma centre is beneficial and sufficient for a large group of patients with uncontrolled asthma, thereby reducing the number of patients that depend on expensive treatment modalities and continuous management in a specialised centre.

REFERENCES

1 Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med. 2004*;170(8):836-44.

2 Braman SS. The global burden of asthma. *Chest. 2006;*130(1 Suppl):4S-12S.

3 Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax. 2011*;66(10):910-7.

4 Bousquet J, Khaltaev N, Cruz A, Yorgancioglu A, Chuchalin A. International European Respiratory Society/American Thoracic Society guidelines on severe asthma. *The European respiratory journal. 2014*;44(5):1377-8.

5 McDonald VM, Vertigan AE, Gibson PG. How to set up a severe asthma service. *Respirology. 2011;* 16(6):900-11.

6 Thomson CC, Welsh CH, Carno MA, Wenzel SE, Chung F, Brozek JL et al. Severe asthma. *Annals of the American Thoracic Society. 2014*;11(6):996-7.

7 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax. 2014*;69 Suppl 1:1-92.

8 Global Initiative for Asthma (GINA) 2015. Global strategy for asthma management and prevention. http://www.ginasthma.org/. . 2015;

9 ten Brinke A, Sterk PJ, Masclee AAM, Spinhoven P, Schmidt JT, Zwinderman AH et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *The European respiratory journal. 2005*;26(5: 812-8.

10 Irwin RS, Curley FJ, French CL. Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. *Chest. 1993*;103(6):1662-9.

11 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax. 2003*;58(7):561-6.

12 Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R et al. Dedicated Severe Asthma Services Improve Health-care Use and Quality of Life. *Chest. 2015*;148(4):870-6.

13 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. [Lung volumes and forced ventilatory flows. Work Group on Standardization of Respiratory Function Tests. European Community for Coal and Steel. Official position of the European Respiratory Society]. *Rev Mal Respir. 1994*;11 Suppl 3:5-40.

14 Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed). 1982;284(6329):1607-8.

15 O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart. 1998*;80(4):377-82.

16 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med. 2002*;166(1):111-7.

17 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med. 2005*;171(8):912-30.

18 ten Brinke A, de Lange C, Zwinderman AH, Rabe KF, Sterk PJ, Bel EH. Sputum induction in severe asthma by a standardized protocol: predictors of excessive bronchoconstriction. *Am J Respir Crit Care Med. 2001*;164(5):749-53.

19 Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes. 2005*;3:58.

20 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *The European respiratory journal. 1999*;14(4):902-7.

21 ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med. 2001*;163(5):1093-6.

22 Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabó TJ et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol. 2009*;103(4):325-31.

23 McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *Am J Respir Crit Care Med. 2012*;186(11):1102-8.

24 Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet (London, England). 2012*;380(9842):651-9.

25 Ungar W. Bias--it's everywhere! A commentary on the impact of bias and the assessment of agreement in the measurement of medication use in epidemiology research. *Pharmacoepidemiol Drug Saf. 1998*;7(6):425-7.

26 Roberts RO, Bergstralh EJ, Schmidt L, Jacobsen SJ. Comparison of self-reported and medical record health care utilization measures. *J Clin Epidemiol.1996;*49(9):989-95.
27 Kjellsson G, Clarke P, Gerdtham UG. Forgetting to remember or remembering to forget: a study of the recall period length in health care survey questions. *J Health Econ. 2014;*35:34-46.
28 Kim C, Feldman Hl, Joffe M, Tenhave T, Boston R, Apter AJ. Influences of earlier adherence and symptoms on current symptoms: a marginal structural models analysis. *J Allergy Clin Immunol. 2005;* 115(4):810-4.
29. Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol. 2003*;111(2): 278-84.
30 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med. 2014;*371(13):1189-97.
31 Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet (London, England). 2002*;360(9347):1715-21.

Supplementary material

ONE-DAY-VISIT PROGRAM IN DETAIL

Information requested at referral

1. Referral letter
2. Asthma-related medical correspondence of the last five years, including ENT correspondence, CT-sinus and HRCT.
3. Lung function:
   a. All LF data of the last 3 years, including FeNO
   b. Results methacholine/histamine provocation test ever
4. Laboratory: Results on total IgE, leucocytes, cell differential, RAST or skin prick test of the last 2 years

At home completed questionnaires (1 day before visit)

1. Patients own questions and expectations
2. Asthma control questionnaire (ACQ)[1]
3. Asthma quality of life questionnaire (AQLQ)[2]
4. Healthcare use questionnaire (HCU)[3]
5. Nijmegen hyperventilation questionnaire[4]
6. 4 dimensional symptom questionnaire (4DSQ)[5]
7. Medication list

Intake specialised asthma nurse

1. Welcome and introduction
2. Check at home completed questionnaires
3. Check medication list
4. Check inhalation technique
5. Assessment of compliance (ICS prescription filling ≥ 80% in previous 12 months[6] and MARS questionnaire[7])
6. Evaluate smoking history, smoke exposure at home or work
7. Assessment level of self-management

Lung function department

1. Length and weight
2. Exhaled NO[8]
3. Spirometry before and after 400 mcg Salbutamol [9]
4. Sputum induction[10]

Laboratory

1. Leucocytes and cell differential
2. Total IgE, RAST, specific IgEs including aspergillus

Intake pulmonologist

1. Medical history, general and asthma (using referral information) and current symptoms
2. Confirm asthma diagnosis: symptoms compatible with asthma combined with at least one of the following (previously or at intake) [11]
   a. Reversibility in FEV_1 after 400 mcg salbutamol (≥12% predicted and > 200 ml)
   b. Airway hyperresponsiveness to methacholine/histamine (PC20< 9.8/8 mg/ml)
   c. Decrease of FEV_1 >12% predicted at tapering of asthma medication
3. Consider alternative or overlapping diagnoses
4. Check high intensity treatment: ≥1000 mcg/day fluticasone equivalent + LABA or other controller, with or without OCS
5. Check whether asthma is uncontrolled: ≥1 out of 2
   a. ACQ ≥ 1.5
   b. ≥ 2 exacerbations previous year

   Or asthma only controlled with maintenance systemic steroids
6. Check ongoing exposition to allergens or other triggering factors
7. Check medication potentially worsening asthma
8. Check comorbidities (rhinosinusitis/nasal polyps, GER, obesity, OSAS, vocal cord dysfunction/dysfunctional breathing) by questioning and using referral information
9. Check side effects asthma medication

Intake physiotherapist

1. Assessment of daily activity level
2. Evaluate previous programs rehabilitation / breathing technique
3. 6-minute walking test[12]
4. Likelihood of hyperventilation/dysfunctional breathing (questionnaire and obser vation)

Intake clinical psychologist

1. Psychosocial factors potentially contributing to poor control
2. Distress, depression, anxiety, somatisation (4DSQ) or other psychological factors contributing to poor control
3. Coping

Multidisciplinary team discussion

1. Truly asthma?
2. Uncontrolled despite high intensity treatment? Or controlled with daily OCS
3. Contributing factors/comorbidities
4. Initial determination of asthma phenotype (based on age at onset, atopic status and presence/absence of eosinophilic inflammation)
5. Patients own questions/expectations
6. Personalised management plan (for details see online supplementary 2)

Final extensive explanatory session with the patient (by pulmonologist), focusing on

1. Is it truly/only asthma?
2. Which factors might contribute to poor control?
   What can be done regarding these factors
3. What subtype of asthma? Explanation and specific advices for this subtype
4. Summary of advices for patient and referring doctor
5. Patients own questions/expectations answered?
6. Referral back to own pulmonologist

REFERENCES

1 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *The European respiratory journal. 1999*;14:902-7.
2 Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes. 2005*;3:58.
3 ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med. 2001*;163:1093-6.
4 van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventinlation syndrome. *J Psychosom Res. 1985*;29:199-206.
5 Terluin B, van Marwijk HWJ, Adèr HJ, de Vet HC, Penninx BW, Hermens ML, van Boeijen CA, van Balkom AJ, van der Klink JJ, Stalman WA. The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. *BMC Psychiatry 2006*;6:34.
6 McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. *American Journal of Respiratory and Critical Care Medicine, 2012*;11:1102-1108.
7 Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive Validity of a Medication Adherence Measure in an Outpatient Setting. *J Clin Hypertens 2008*;10:348-54.
8 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med. 2005*;171:912-30.
9 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. [Lung volumes and forced ventilatory flows. Work Group on Standardization of Respiratory Function Tests. European Community for Coal and Steel. Official position of the European Respiratory Society]. *Rev Mal Respir. 1994*;11 (Suppl 3):5-40.
10 ten Brinke A, de Lange C, Zwinderman, Rabe KF, Sterk PJ, Bel EH. Sputum induction in severe asthma by a standardized protocol: predictors of excessive bronchoconstriction. *Am J Respir Crit Care Med. 2001*;164:749-53.
11 Global Initiative for Asthma (GINA) 2015. Global strategy for asthma management and prevention. http://www.ginasthma.org/
12 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med. 2002*;166:111-7.

REPORT TO THE REFERRING PULMONOLOGIST IN DETAIL (ASSESSMENT AND MANAGEMENT PLAN)

General

1. Patient's own questions and expectations
2. Medical history, general and asthma, current symptoms
3. Medication use at intake
4. Confirmation asthma diagnosis
5. Level of asthma control and high intensity treatment

Contributing factors

1. Inhalation technique
2. Asthma education / self-management
3. Adherence
4. Alternative or overlapping diagnoses
5. Exposition to allergens or other triggering factors
6. Medication potentially worsening asthma
7. Comorbidities (rhinosinusitis/nasal polyps, GER, obesity, OSAS, vocal cord dysfunction/dysfunctional breathing)
8. Psychological factors

Symptoms and limitations

1. Asthma Control Questionnaire (ACQ) score
2. Asthma quality of life questionnaire (AQLQ) score
3. Healthcare use questionnaire (HCU)
4. Exercise tolerance: 6-minute walking test

Phenotype characteristics

1. Atopic status
2. Age-at-onset: early-onset, late-onset
3. Immunomodulatory medication use
4. Inflammatory pattern: blood, sputum, exhaled NO
5. Long function: airway obstruction, airtrapping, bronchial hyperreactivity

Conclusion

1. No/difficult-to-treat/severe asthma
2. Factors to optimize
3. Phenotypic characteristics (age-onset, atopic status, inflammation, airway obstruction)
4. Degree of quality of life and healthcare use

Personalised management plan

1. If applicable, specific advices on not yet optimised potentially contributing factors
2. Advice regarding optimalisation of current medication (increase/decrease doses of ICS or OCS, addition of extra controller medication)
3. When optimised and still uncontrolled, phenotype-specific advices regarding targeted therapies (ea. anti-IgE, maintenance OCS, anti-IL5 (trial or in future), macrolide, bronchial thermoplasty)

Chapter

3

Nasal polyposis and asthma: the chest physician's view

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SUMMARY

There is increasing epidemiological evidence linking asthma and chronic rhinosinusitis (CRS), with an even stronger relationship for specific phenotypes i.e. eosinophilic asthma and CRS with nasal polyps (CRSwNP). Asthma patients with concomitant nasal polyposis have more severe disease with reduced asthma control, increased airway obstruction, and more extensive eosinophilic inflammation. In asthma different pathways are presumed to lead to this eosinophilic airway inflammation, whether or not IgE-dependent. Staphylococcal Enterotoxin might be the link in underlying pathophysiology of severe adult-onset non-atopic eosinophilic asthma and nasal polyposis. Patients with uncontrolled, in particular eosinophilic, asthma should be screened for possible CRSwNP in collaboration with an Ear, Nose and Throat (ENT) specialist, since various treatment options for nasal polyposis have potential to improve asthma control. Here, we review the relationship between asthma and nasal polyposis from a chest physician's perspective. Data on epidemiology, pathophysiology, impact on asthma control and clinical assessment are discussed. Finally, treatment options and their effect on asthma outcomes are described.

INTRODUCTION

Asthma and CRS belong to the most prevalent chronic medical conditions worldwide, with a significant impact on patients' quality of life (QoL) and healthcare costs[1, 2]. Since the concept of the "united airways" was introduced mounting evidence has supported a link between asthma and CRS[3]. Epidemiological studies have shown that asthma and CRS frequently coexist[4], and histopathological data demonstrate similar inflammatory and remodelling characteristics[5].

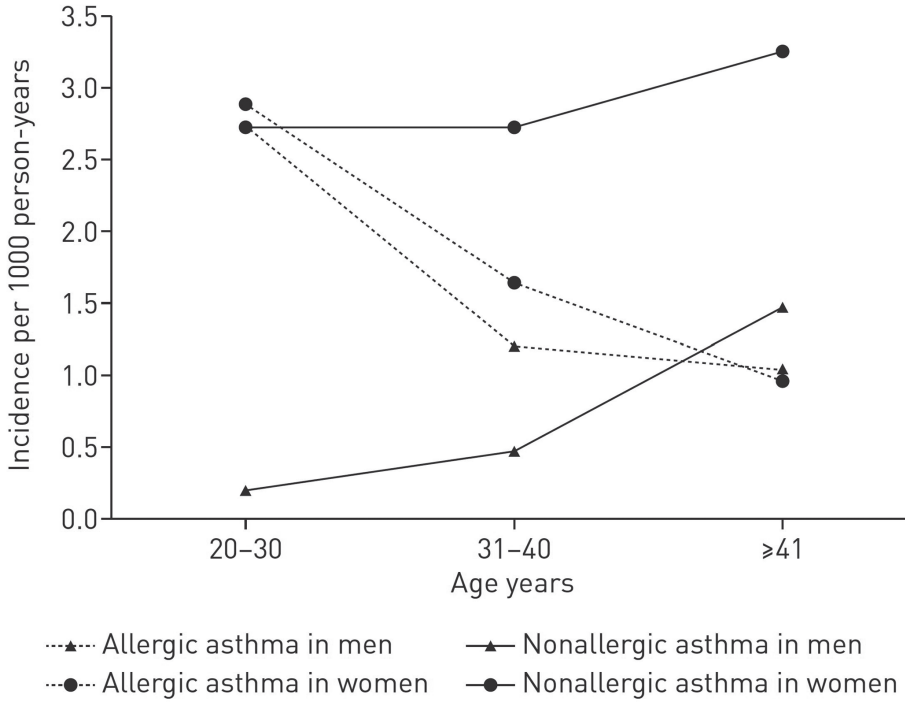
Asthma is a disease with a variety of clinical presentations[6] and, within this heterogeneous condition, specific subtypes (phenotypes) seem to be associated with CRS[7, 8]. Subgroups within CRS can also be identified and, in particular, CRS with nasal polyps (CRSwNP) is related to asthma[9, 10]. Even though there is increasing support for a relationship between certain subgroups of asthma and CRS, the underlying pathophysiological mechanisms and therapeutic implications are not yet clear. This chapter summarises data on prevalence, pathophysiology, impact on asthma control, clinical assessment and treatment options regarding asthma and nasal polyposis from the chest physician's perspective. Fokkens and Hellings[11] discuss nasal polyposis and asthma from the otorhinolaryngologist's perspective elsewhere in the *ERS Monograph*.

EPIDEMIOLOGY

Asthma is a disease characterised by chronic airway inflammation and respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, combined with variable expiratory airflow limitation[6]. It is a serious global health problem affecting an estimated 300 million individuals worldwide, with rising treatment costs, and is becoming an economic burden for patients and the community[12]. Asthma prevalence varies substantially between countries, ranging from 1% to 18% of the

population, and is increasing in many developing countries[9, 13]. The development of asthma might be associated with genetic[14] or perinatal factors, atopy[15], obesity [16], and environmental factors including indoor and outdoor allergens[17], viral and bacterial infections[18, 19], cigarette smoke[20], air pollution[21], and occupational exposure[22]. Most of these factors are also implicated as potential triggers for asthma exacerbations, whereby subgroups of asthma patients might be more sensitive to specific triggers (e.g. allergens or aspirin). Asthma affects all ages, with a prevalence showing a sex shift during puberty, changing from a higher risk in boys to a higher risk in women after adolescence[9]. Although exposure to environmental irritants might be involved, exposure to allergens is unlikely to account for the higher incidence of asthma in women. Indeed, in a recent large population-based cohort, no sex difference was observed for allergic asthma, whereas the incidence of nonatopic asthma was found to be more than three times higher in women than in men (figure 3.1)[23]. The high incidence of adult-onset nonatopic asthma in this cohort emphasises the need for more attention to this still poorly recognised subtype of asthma. This might apply especially when considering the relationship between asthma and CRS.

Figure 3.1 Sex- and age-specific incidence rates for allergic and nonallergic asthma



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CRS is defined as the presence of at least two symptoms persisting for a period of >12 weeks, wherein radiological or endoscopic documentation of inflammation is required [24]. Symptoms of rhinosinusitis include nasal blockage, purulent nasal discharge, facial pain/

pressure and reduction or loss of smell. CRS can be described as infectious or allergic, seasonal or perennial, acute or chronic and with (CRSwNP) or without (CRSsNP) nasal polyps, wherein nasal polyps are described as inflammatory lesions that project into the nasal airway, are typically bilateral and originate from the ethmoid sinus[25]. CRS is present in 5–15% of the adult population[9, 26], and has an impact on QoL comparable to diseases such as chronic obstructive pulmonary disease and congestive heart failure[27]. The prevalence of CRSwNP is 2-4%, with a higher prevalence in men than women[28]. Nasal polyposis is rare under the age of 20 years and increases with age, with a mean onset between the ages of 40 and 50 years across all ethnic groups. The aetiology of nasal polyposis is still unknown and is considered multifactorial, with several potentially contributing factors such as atopy[29], bacterial or fungal infections[30], or environmental factors, including cigarette smoke and occupational exposure[31]. Nasal polyps are frequently found in aspirin-sensitive patients and are an obligatory comorbidity in aspirin-exacerbated respiratory disease (AERD), a distinct asthma subtype characterised by acute upper and lower respiratory tract reactions to ingestion of aspirin and other cyclooxygenase-1-inhibiting NSAIDs[32, 33].

In addition to asthma and AERD, CRSwNP is often associated with other comorbid respiratory conditions such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD) and idiopathic bronchiectasis[34]. These associations are the focus of other chapters elsewhere in the *ERS Monograph*[35].

Asthma and CRS(wNP) frequently occur in the same patient. Compared with the general population, CRS is more prevalent in patients with asthma[36] and asthma is more frequently diagnosed in patients with CRS[37]. There is a wide variation in the prevalence of asthma observed in patients with CRS, ranging from 20% to 60%[28, 38]. Likewise, the presence of CRS in patients with asthma varies in studies from 40% to 75%[4, 39]. With regard to AERD, the actual prevalence remains uncertain, with numbers ranging from 2% to 25% in asthma and 1% to 22% in CRS, depending on the populations surveyed[40, 41]. These large variations can be attributed to several causes, including changing diagnostic definitions and criteria. Moreover, several of these studies rely on subjective self-reported asthma, AERD or CRS, instead of confirmation by objective measures. Furthermore, asthma and CRS are both heterogeneous diseases with distinct subtypes in which different prevalences may be found.

Initially the asthma–CRS association was mostly described among the allergic population[42], but more recently this was confirmed in the nonatopic subgroup, questioning the role of atopy in this complex relationship[43]. The Global Allergy and Asthma Network of Excellence (GA^{2}LEN) conducted a large multicentre European survey in young, middle-aged and older adults to assess the presence of asthma and CRS defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)[24]. In all centres, there was a strong association of asthma with CRS (adjusted odds ratio (OR) 3.47, 95% CI 3.20–3.76) independent of age, sex and smoking status[9]. The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted OR 11.85, 95% CI 10.57–13.17). In the nonatopic population, CRS was associated positively with adult-onset asthma (relative risk ratio 3.09, 95% CI 2.51–3.81) and negatively with childhood-onset asthma (relative risk ratio 0.45, 95% CI 0.35–0.57).

Data on the association of asthma with subtypes of CRS are rare and primarily concern CRSwNP. In prospective studies, asthma was found in patients with CRSwNP far more often (26%) than in those without polyps (6%) (OR 5.9, 95% CI 1.79–19.65)[28], independent of atopic status[10]. In a general asthma population, 7–17% of patients also suffer from CRSwNP[44, 45]. The prevalence of CRSwNP is higher in severe asthma, where CT-confirmed CRS could be shown in 24% of patients and was associated with a later onset of asthma[46]. When focusing on the subgroup of patients with severe adult-onset asthma, endoscopically confirmed nasal polyps were present in as many as 54% of the cases, the vast majority of them being nonatopic[47]. In another severe asthma cohort, a similar subphenotype was identified by cluster analysis including patients with later-onset, mostly severe asthma with nasal polyps and eosinophilia[48].

These data suggest that for CRSsNP the association with asthma is most evident in allergic patients, whereas in CRSwNP patients the relationship is strongest with nonatopic adult-onset asthma.

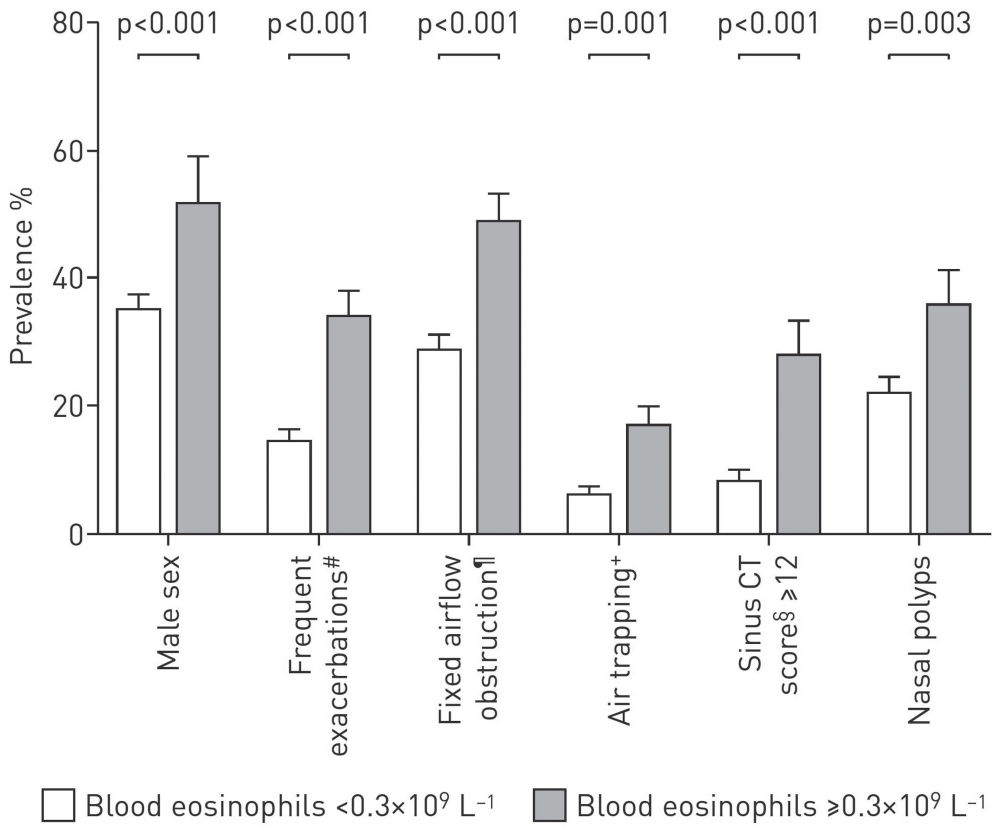
PATHOPHYSIOLOGY AND TRIGGERING FACTORS

Asthma and CRSwNP are both heterogeneous disorders with a complex pathophysiology. They share a number of histological and immunological characteristics, including airway remodelling, T helper (Th)-2 cell induction, interleukin (IL)-5 and IL-13 production, and eosinophilic infiltration[49]. In addition, direct relationships between inflammation in the lower airways and nasal mucosa have been observed[46, 50]. These similarities and associations suggest comparable pathological processes and have contributed to the concept of "united airways disease"[51, 52]. However, despite growing evidence for the link between upper and lower airway diseases, the underlying mechanism is still not clear. This might be partly attributed to the fact that most research up to now has been done in general asthma and/ or CRS populations, without taking specific subgroups into account.

The relevance of defining subtypes in asthma has been increasingly recognised, and multiple phenotypes of asthma have been identified based on the inflammatory cell profile, presence of allergy and age at onset of disease[53–55]. In addition to the up-to-now poorly differentiated mixed group of patients without eosinophilic inflammation, distinct asthma phenotypes are distinguished in which eosinophilic airway inflammation plays an important role. In particular, the strongest association with CRS and nasal polyps is found in these eosinophilic subtypes of asthma (figure 3.2)[47, 56–58]. Eosinophilic inflammation in asthma occurs in allergic as well as nonallergic patients, for which a different underlying pathobiology is presumed. In allergic eosinophilic asthma, allergen-specific induced Th2 cells produce cytokines such as IL-4, IL-5 and IL-13, leading to immunoglobulin E (IgE) switching in B-cells and airway eosinophilia[59]. In nonallergic eosinophilic asthma, eosinophilic airway inflammation is considered to be the result of air pollutants, microbes and glycolipids inducing cytokines such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which activate type 2 innate lymphoid cells (ILC2) in an allergen-independent way to produce high amounts of IL-5 and IL-13, leading to eosinophilia (figure 3.3)[60]. TSLP, an upstream cytokine, may play a central role in eosinophilic in-

flammation, in allergen-induced as well as allergen-independent asthma[61]. Additionally, TSLP is suggested to be involved in the pathogenesis of nasal polyposis[62] and AERD[63]. Eosinophilia is a characteristic feature of AERD, with increased levels of eosinophils in bronchial mucosa, nasal polyps and peripheral blood[58, 64]. Although the pathophysiology of AERD is not yet fully understood, there appears to be a dysregulation of arachidonic acid metabolism, particularly with an overproduction of leukotrienes, exacerbated by aspirin intake. Together with the increased leukotrienes and reduced prostaglandin levels, an increase in mast cells and several Th2 cytokines is observed. Thus, different pathways may lead to eosinophilic airway inflammation in asthma, which might also be involved in the pathogenesis of CRSwNP.

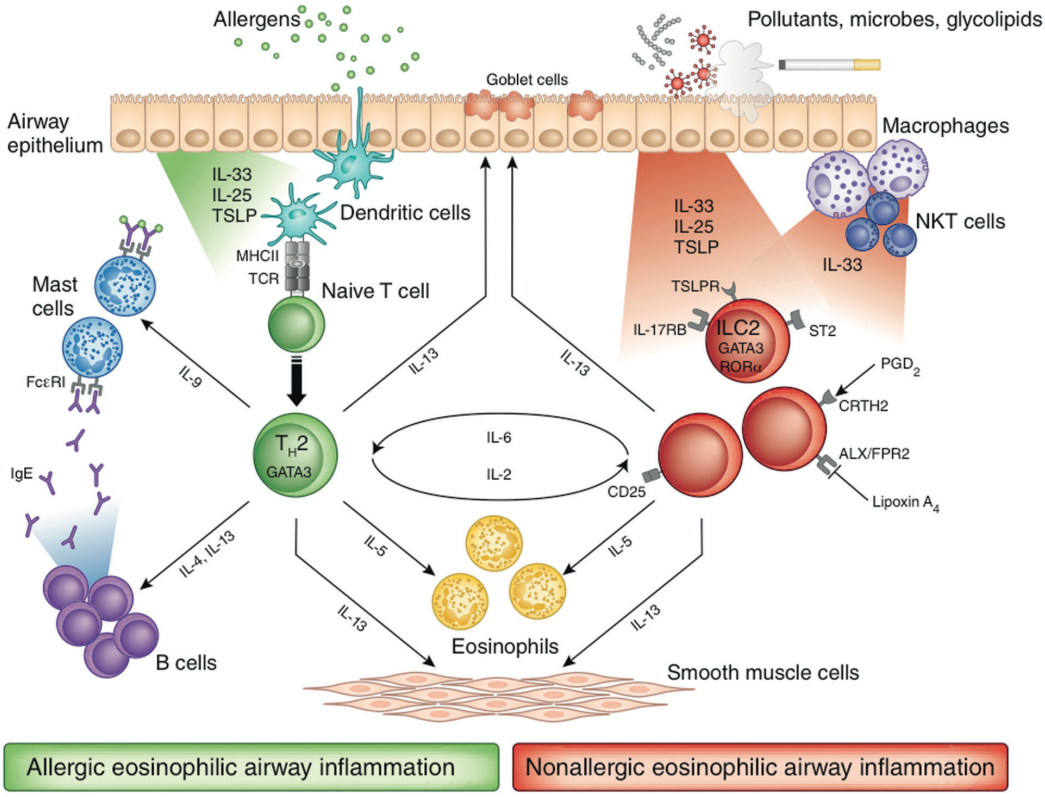
Figure 3.2 The characteristic profile of adult-onset eosinophilic asthma



Prevalence of distinct characteristics is shown for eosinophilic and noneosinophilic adult-onset asthma patients. #: patients with two or more exacerbations per year; ¶: patients with post-bronchodilator FEV_1/forced vital capacity <70%; +: patients with residual volume/total lung capacity ≥120% pred; §: according to the Lund–Mackay scoring system. Reproduced and modified from [56] with permission from the publisher.

In recent years it has been shown that CRSwNP and CRSsNP have different inflammatory patterns in the Western world. CRSwNP is characterised by higher eosinophilia, IgE and IL-5 compared with CRSsNP[65]. Novel evidence indicates that there is considerable heterogeneity also within the CRSwNP subgroup. In Europe, the vast majority of nasal polyps are Th2-driven and eosinophilic, in sharp contrast to the Chinese population in which nasal polyps are mostly neutrophilic showing a Th1 profile[66, 67]. It is still unclear whether genetic or environmental factors drive these differences as different inflammatory profiles can be found even within a single ethnic group[6]. From a chest physician's perspective the subgroup of patients with IL-5-positive nasal polyps is of special interest because the most severe eosinophilic inflammation and comorbid asthma is found in this subgroup[66, 67]. Underlining this, a recent cluster analysis based solely on immune markers assessed in patients with CRS revealed several IL-5-negative clusters without nasal polyps or increased asthma prevalence and distinct IL-5-positive clusters clearly associated with asthma[68]. The group with the highest IL-5 levels consisted of an almost exclusive nasal polyps phenotype with strongly increased asthma prevalence. In this high IL-5 group, two clusters were identified with the highest IgE levels and asthma prevalence, in which all nasal polyps expressed *Staphylococcus aureus* enterotoxin-specific IgE (SE-IgE)[68]. *S. aureus* is a known coloniser of the nasal cavities in Caucasian subjects and is found in the majority of patients with CRSwNP. Eosinophilic inflammation might be intensified by *S. aureus* enterotoxins acting both as antigens stimulating specific IgE responses (SE-IgE) and as superantigens promoting a polyclonal IgE response reflected by an increased total IgE level[29]. Thus, in CRSwNP, but also in asthma, staphylococcal enterotoxin might be involved in the eosinophilic inflammatory process. This concept is confirmed by several studies that have linked high SE-IgE serum levels with an increased risk of not only asthma[69, 70], but also severe asthma[70–72], and have associated its presence with increased levels of total IgE[70]. The level of serum SE-IgE in patients with severe asthma in a Polish cohort was three times higher compared with patients with nonsevere asthma[71]. Aspirin hypersensitivity was highly prevalent in this cohort, particularly in the severe asthma patients, and without exception concomitant with SE-IgE positivity. In another European study the likelihood of having severe asthma was about 11 times higher for SE-IgE-positive versus SE-IgE-negative patients. In the subset of nonatopic SE-IgE-positive patients, oral steroid use and hospitalisations were significantly increased and SE-IgE was associated with a lower forced expiratory volume in 1 s (FEV_1)[72]. A recent Korean elderly asthma cohort study showed that high serum levels of SE-IgE were associated with more severe asthma, more sputum eosinophilia and more CRSwNP compared with those with lower SE-IgE levels[73]. Interestingly, SE-IgE was associated with the presence of asthma independent of sensitisation to other allergens. High levels of SE-IgE were found in 20–30% of patients who tested negative to the regular aeroallergens[71, 72], i.e. patients that would be considered nonatopic and up to now formally excluded from treatment with omalizumab. Thus, growing evidence supports the concept that staphylococcal enterotoxin might underlie the pathophysiology of severe asthma, especially the phenotype of adult-onset nonatopic asthma associated with CRS (with or without nasal polyps), high levels of blood and sputum eosinophils, and high serum total IgE [74]. This association is also discussed in more detail by Bachert et al.[75] elsewhere in the *ERS Monograph*.

Figure 3.3 Two different pathways lead to eosinophilic airway inflammation in asthma



In allergic asthma, dendritic cells present allergens to CD4+ T-cells, inducing Th2 cells, which produce IL-4, IL-5 and IL-13, leading to IgE switching in B-cells, airway eosinophilia and mucous hypersecretion. In nonallergic eosinophilic asthma, air pollutants, microbes and glycolipids induce the release of epithelium-derived cytokines, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which activate ILC2 cells in an antigen-independent manner via their respective receptors (IL-17RB, ST2 and TSLPR). Activated ILC2 cells produce high amounts of IL-5 and IL-13, leading to eosinophilia, mucous hypersecretion and airway hyperreactivity. CRTH2: chemoattractant receptor-homologous molecule expressed on Th2 cells; ALX/FPR2: receptor for lipoxin A4; FcεRI: high-affinity receptor for IgE; GATA3: GATA-binding protein 3; PGD2: prostaglandin D2; RORα: retinoic acid receptor-related orphan receptor-α; MHC: major histocompatibility complex; TCR: T-cell receptor. Reproduced and modified from [60] with permission from the publisher.

IMPACT ON ASTHMA CONTROL

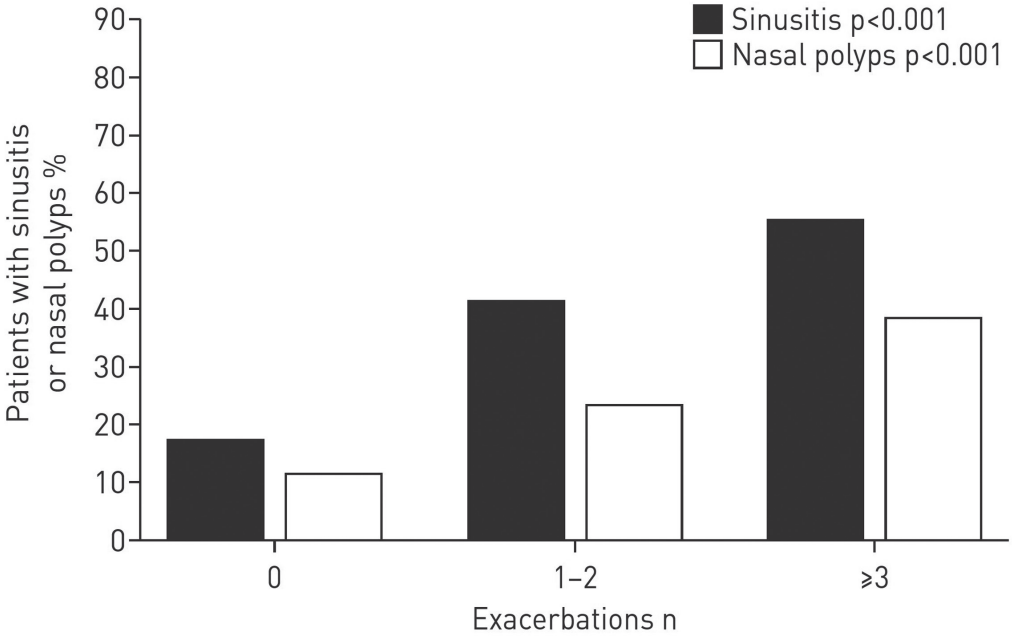
How much impact does the presence and severity of CRSwNP have on asthma severity and control? Several studies have demonstrated a relationship between severity of asthma and the presence of nasal polyps[47, 76]. Amelink et al.[47] reported associations between severe adult-onset asthma and nasal polyposis, sputum eosinophil count, exhaled nitric oxide, blood neutrophil count and absence of atopy. van Veen et al.[77] also reported difficult-to-treat asthma characterised by persistent sputum eosinophilia, nonatopy and extensive sinus disease.

A French group showed that among patients with asthma, those with nasal polyps had reduced asthma control, increased airway obstruction and more extensive eosinophilic inflammation compared with those without nasal polyps[78]. In addition, AERD is also associated with severe asthma. In AERD, asthma is usually preceded by the nasal problems evolving from persistent rhinitis, to refractory CRS, anosmia and recurrent nasal polyps. As the disease worsens, asthma develops and often becomes severe, with reduced lung function, poor asthma control despite extensive treatment and a risk of life-threatening asthma attacks[79].

A subset of patients with asthma is prone to frequent exacerbations, and thus requires special monitoring and treatment. CRS and nasal polyps have both been identified as independent risk factors for frequent exacerbations in several studies around the world, with ORs varying from 1.4 to 5.5 (figure 3.4)[80–82]. In a recent study identifying clinical features of exacerbation-prone asthma (Severe Asthma Research Program (SARP)-3), chronic sinusitis was again found to be one of the factors associated with exacerbation frequency even after adjustment for multiple factors[82]. Remarkably, African-American patients with CRS more often had nasal polyps than Caucasian patients with CRS, with the increased polyposis being associated with more hospitalisations for asthma[83]. Recently, we reported on risk factors of frequent severe exacerbations in the subgroup of patients with late-onset, eosinophilic asthma, and identified air trapping and high sinus CT scores as independent predictors, suggesting that in these patients inflammations of the distal airways and paranasal sinuses are important predisposing factors for the development of exacerbations[57]. Indeed, there is some evidence that treatment of CRS and nasal polyps might prevent asthma exacerbations. In a management programme including patients with frequent exacerbations, reduction of healthcare utilisation was strongly associated with gastro-oesophageal reflux disease and sinusitis therapy[84]. Outpatient asthma clinic visits were reduced by 50% in the follow-up after sino-nasal surgery[85]. In addition, several studies suggest improved asthma outcomes (including exacerbations) when upper airway inflammation is controlled with medications[39, 86] or treated surgically[87], although the lack of well-controlled studies limits the strength of the conclusions.

Data on the impact of coexisting nasal polyps on lung function in asthma patients are scarce. A French longitudinal study showed that subjects with severe nasal polyps requiring nasal surgery exhibited a significant decline in FEV_1 over a 4-year period, unrelated to the presence of nonspecific bronchial hyperresponsiveness or asthma at baseline, or the appearance of asthma symptoms during follow-up[88]. More studies revealed a relationship between the extent of nasal sinus inflammation and lower airway function. In severe asthma, sinus CT scores were positively related to functional residual capacity, a measure of small airway function, particularly in patients with adult-onset asthma[46], suggesting that in this subtype of asthma an inflammatory process involves the whole respiratory tract, from the paranasal sinuses to the very distal airways.

Figure 3.4 Sinusitis and nasal polyps were significantly associated with exacerbation frequency in a large cohort study identifying clinical features of patients with exacerbation-prone asthma



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Asthma and CRS have both been linked with an impaired QoL, and comorbid CRS has been identified as a negative predictor of QoL in asthma[89]. Data on asthma and nasal polyps having an accumulative negative impact on QoL are inconsistent, but patients with combined asthma and nasal polyps showed the largest QoL benefit after sinus surgery[90]. Olfactory dysfunctioning is a known symptom in patients with nasal polyps, with a significant impact on QoL. Asthma associated with nasal polyps has an additional impact on the sense of taste and smell, and loss of smell has been proposed as a clinical tool to predict nasal polyposis in patients with asthma[91]. It is noteworthy that some patients with severe asthma, when asked, report significant hearing loss, seriously threatening their QoL. This might be related to a relatively recently recognised middle ear disease, i.e. eosinophilic otitis media, characterised by a highly viscous, eosinophil-predominant middle ear effusion causing progressive deterioration of hearing[92]. This otitis is associated with asthma and nasal polyps, is most prevalent in nonatopic subjects, and might be due to mucosal inflammation extending from the lower airways even to the middle ears or be related to local sensitisation to foreign agents (e.g. *S. aureus*)[93]. Hearing loss with recurrent refractory otitis can prompt the physician to consider severe eosinophilic asthma.

MANAGEMENT OF ASTHMA PATIENTS WITH NASAL POLYPOSIS AND CLINICAL ASSESSMENT

In clinical practice, early recognition of concomitant CRS and nasal polyposis in patients with asthma is important, thereby identifying patients at risk of more severe disease, which has clear implications for asthma management. Various items in the history may be of help. If a patient has a history of previous CRSwNP or nasal sinus surgery, recurrence of nasal polyposis might be more likely[94]. In addition, in patients with known aspirin sensitivity or those reporting symptoms of nasal congestion and bronchoconstriction 1-4 h after ingestion of aspirin or NSAIDs, the presence of AERD including nasal polyposis might be considered. However, many AERD patients are unaware of aspirin sensitivity unless provoked[95]. Definitive diagnosis of AERD strictly requires aspirin challenge, although this is not often performed as expensive precautions with respect to safety limit its availability.

The identification of patients with CRSwNP in daily asthma practice may be rather difficult without the help of an ENT specialist and imaging. The characteristic presentation of CRSwNP is gradually worsening nasal congestion/obstruction, fatigue, sinus fullness and pressure, posterior nasal drainage, and hyposmia or anosmia, sometimes with loss of taste. In contrast, fever and severe facial pain are uncommon. Although these symptoms are not specific for CRSwNP, the impaired sense of smell seems a rather predictive symptom in this context and might alert the chest physician to the possibility of nasal polyps[90]. CRS patients may report a variety of other symptoms, such as malaise, cough, sleep disturbance, ear pain or pressure, dizziness, dental pain, dysphonia, or nasal or throat irritation, but all of these lack specificity and are not clinically helpful in diagnosis. Specifically asking for hearing loss and recurrent otitis may prompt the physician to consider eosinophilic otitis media, in particular in adult-onset eosinophilic asthma.

Several questionnaires have been developed to evaluate sino-nasal symptoms, e.g. the Sino-Nasal Outcome Test, which are sensitive to changes in symptom severity; however, their usefulness in identifying CRS or nasal polyposis in individual patients in day-to-day practice is limited[96, 97].

Unfortunately, symptoms correlate poorly with objective findings upon imaging or endoscopy, and also physical examination is not of great help to an asthma doctor. Large polyps may be visible with anterior rhinoscopy using a nasal speculum or otoscope (in the hands of a trained clinician), but smaller polyps certainly require nasal endoscopy or imaging. Thus, diagnosis of CRSwNP requires the expertise of an ENT specialist[24].

Clinical evaluation of patients suspected of CRSwNP by an ENT specialist involves routine otolaryngological examination and a detailed endoscopy of the sino-nasal cavity. Inspection of the ears may demonstrate extranasal manifestations, such as eosinophilic otitis media, with important management consequences. Nasal endoscopy can directly visualise the nasal cavities and identify polyps, but also assess the patency of the major ostia and check on purulent drainage from the ostia. Nasal polyps generally begin to form around the ostiomeatal complex, although they may eventually be found throughout the nasal cavities and sinuses, and should be bilateral. Nasal polyps are translucent, yellow-

ish-grey to white, glistening masses filled with gelatinous inflammatory material, the grey-white colour being due to the relatively avascular nature of the polyp tissue.

Noncontrast CT with fine cuts through the paranasal sinuses with bony windowing is the standard protocol for CRSwNP evaluation. A bilateral thickened mucosa is typically observed on sinus CT, in which polyps can be differentiated from nonpolypoid mucosal thickening by their shape and contours. Polyps often protrude as rounded mucosal swellings into the nasal or sinus cavities.

Since CRSwNP is most common in patients with eosinophilic asthma with an adult onset of disease (figure 3.2) and/or aspirin sensitivity, these patients in particular should be checked for the presence of nasal polyposis. Elevated markers of eosinophilic airway inflammation, including peripheral blood eosinophils and exhaled nitric oxide fraction, may point towards eosinophilic asthma and hint at the possibility of sino-nasal involvement[46]. Therefore, a patient with adult-onset eosinophilic asthma preferably should be referred to an ENT clinic to prove or rule out sino-nasal involvement. In addition, all patients with difficult-to-control asthma should be assessed for the possibility of CRS being the reason for poor asthma control, even in case of absent or only subtle sinonasal symptoms.

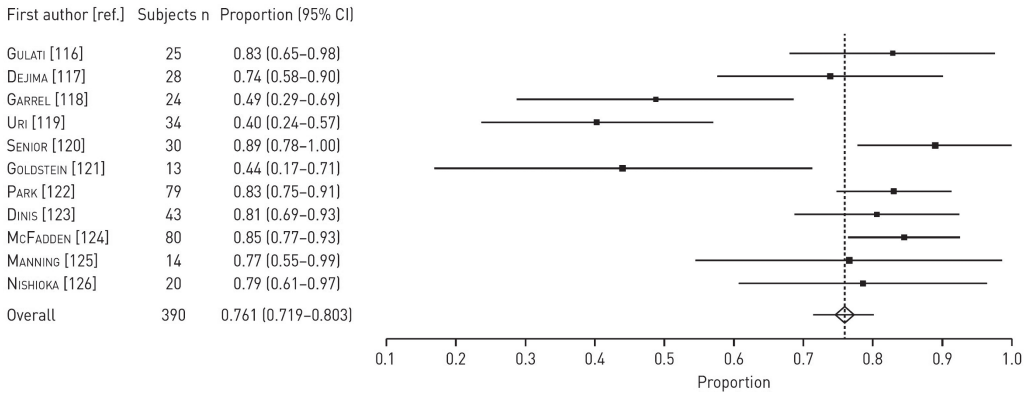
TREATMENT OPTIONS

The most recent EPOS revision (EPOS2012) provides a guideline for the treatment of CRS, making a stricter division between CRSwNP and CRSsNP management[24]. This specific treatment guideline applies to CRSwNP patients with or without asthma. It is advised to start the treatment of CRSwNP with intranasal corticosteroids in conjunction with nasal saline irrigation. Intranasal corticosteroids have proven effectiveness on nasal symptoms and nasal polyp size[98]. Patients need to be advised about proper inhalation techniques in order to reduce the risk of local side-effects, i.e. nasal irritation and epistaxis. Based on the severity of symptoms, impairment of QoL and extent of mucosal disease, subsequent therapies can be considered on top of topical nasal corticosteroid spray, such as increasing the dose, using nasal drops, or adding antibiotics or oral corticosteroids [24]. Nasal drops might be more effective than sprays due to better distribution within the nasal cavities, in particular after surgery. Regarding antibiotics, a recent Cochrane Systematic Review found very little evidence of their effectiveness in patients with CRS in general, with a slight indication of a modest improvement in QoL in patients with CRSsNP[99]. However, the use of doxycycline is provided as an option in EPOS2012[24], possibly based on a randomised controlled trial in patients with CRSwNP showing that 100 mg of doxycycline for 3 weeks had a moderate effect on the size of nasal polyps and nasal symptoms[100]. Macrolides have been specifically identified as potentially useful in CRS as well as in asthma due to their anti-inflammatory effects rather than for their antibacterial action [101, 102]. In a heterogeneous CRS group, erythromycin improved all nasal outcome parameters comparable to surgical intervention[103]. Moreover, in a 1-year follow-up of 43 patients with CRS and coexisting asthma, a 12-week course of low-dose erythromycin combined with nasal lavage and fluticasone drops resulted in improvement in asthma symptoms, bronchodilator use, hospitalisations, FEV_1 and levels of exhaled nitric oxide[104]. In the same study, patients randomised to surgery showed similar improvements in asthma outcomes,

but erythromycin was found superior to surgery in the subgroup of patients with nasal polyposis. These data suggest that subsets of patients with CRS and/or asthma might benefit from macrolide treatment[102, 105], although possibly not the eosinophilic subgroups, but more research is needed for proper identification. The effect of leukotriene antagonist treatment on clinical outcome measures of CRSwNP was systematically reviewed and showed significant improvements in CRSwNP symptoms over placebo; results that were similar to those found in the nasal corticosteroid treatment arms[106]. There are only two studies in which treatment with the leukotriene receptor antagonist montelukast was studied in CRSwNP with asthma, showing significant improvements in nasal and pulmonary symptoms, asthma medication intake, and sino-nasal inflammation, but no relevant effects on lung function parameters[107, 108]. The beneficial effects appeared independent of aspirin sensitivity, yet leukotriene-modifying agents are administered in most patients with AERD[109]. In these AERD patients, treatment can be very challenging, with polyposis and asthma often being refractory to medical as well as surgical therapy. Oral aspirin desensitisation followed by daily aspirin administration may improve upper and, to a lesser extent, lower respiratory tract symptoms in selected cases[41]. As in asthma, oral corticosteroids have a beneficial effect on clinical outcomes in patients with nasal polyposis; however, there is some debate on the maintenance of the effect and long-term oral corticosteroid treatment is discouraged in view of the high risk of significant side-effects. Thus, a variety of medical treatments is available, and the challenge is to determine the most beneficial strategy and patient population for the use of the different therapies.

When these medical strategies fail, functional endoscopic sinus surgery (ESS) might be indicated. If so, it is very important that patients are properly informed about the fact that CRS is a chronic condition and have reasonable expectations for treatment[110]. Surgical treatment rarely results in permanent cure and, in particular, in CRSwNP recurrence rates are reported to be as high as 80%[104], with the need for revision surgery being highest in patients with increased eosinophil counts and IL-5 and IgE levels in nasal tissue[111]. Therefore, surgery must be accompanied by medical therapy, since topical steroids slow the recurrence of polypoid inflammation[112]. Together, surgical and medical treatments aim to relieve symptoms and minimise the impact on QoL. In the case of asthma patients it is likewise important to know if improvement in asthma outcomes is to be expected by treatment of CRSwNP. Previously, several authors concluded that available evidence suggested a beneficial effect of both medical and surgical treatment[113, 114], and concerns with respect to possible worse post-operative endoscopic outcomes in asthma patients are no longer shared[115]. Further evidence for the beneficial effects of surgical treatment in patients suffering from both CRS and asthma is given in a recent systematic review [87]. Although reasonable concern regarding quality of the studies was reported, functional ESS for CRS in patients who failed maximal medical therapy appeared to improve clinical asthma outcome measures (figure 3.5)[87, 116–126]. In general, patients reported improved overall asthma symptoms, decreased use of asthma-specific medications, and fewer hospital admissions and emergency room visits due to asthma exacerbations. Moreover, the cost-effectiveness of functional ESS in severely asthmatic patients with CRS was demonstrated prospectively, with a reduction in outpatient asthma clinic visits of 50%[85]. Thus, both medical and surgical treatments for CRS with concomitant asthma improve asthma status, with a possible slight advantage for the medical treatment in cases with nasal polyposis.

Figure 3.5 Forest plot of studies examining patient-reported improvement in overall asthma assessment following endoscopic sinus surgery



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Despite all these medical and surgical therapeutic measures, a subset of patients is not adequately controlled, both in terms of asthma as well as in sino-nasal aspects. In particular, patients with severe eosinophilic asthma benefit from novel immunomodulatory therapies, such as anti-IgE, anti-IL-5 and anti-IL-4/IL-13, targeting specific pathological processes. Omalizumab (anti-IgE) proved efficacy in reducing asthma exacerbations and improving QoL in patients with severe allergic asthma, an indication for which it is registered[127]. However, there is some evidence that omalizumab may also have a therapeutic role in nonatopic asthma[128]. In line with this, omalizumab demonstrated clinical efficacy in the treatment of nasal polyps in patients with comorbid asthma, irrespective of the presence of allergy, which the investigators suggested was related to local IgE formation in the upper airways[129]. Several anti-IL-5 therapies have been developed or are currently under investigation for patients with poorly controlled eosinophilic asthma. Many studies have shown that in a select group of asthma patients with severe eosinophilic asthma, inhibition of IL-5 results in clinically important benefits, with significant reductions in steroid dose and a reduced exacerbation rate[130, 131]. There is growing evidence that IL-5 inhibition is, likewise, a potential novel therapeutic approach in patients with severe eosinophilic nasal polyposis. In a randomised controlled trial, 12 out of 20 patients with severe nasal polyposis refractory to corticosteroid therapy who received two single intravenous injections of mepolizumab (anti-IL-5) showed a significant reduction in nasal polyp size and sinus CT score[132]. Remarkably, not all patients with nasal polyps responded to mepolizumab, suggesting IL-5-independent pathways may be involved. This fits in with the clinical observation that some patients with severe eosinophilic asthma and comorbid CRS demonstrate complete recovery of asthma symptoms during mepolizumab treatment, whereas their sino-nasal symptoms persist. Whether anti-IgE treatment would be more successful in these patients remains to be investigated. Several compounds aiming to target IL-4 and IL-13 are now being evaluated and have shown beneficial effects on asthma outcomes[133, 134], as well as also on nasal polyp size in selected patients[135]. Thus, several studies, from the perspective of both asthma and CRSwNP, have shown the promising effects of biologicals in severe airway disease and might be used to avoid daily oral corticosteroid use or repeated sinus surgery in patients.

CONCLUSIONS

The goal of this chapter was to explore the relationship between asthma and CRS with nasal polyposis from a chest physician's perspective. Epidemiological data have already confirmed a link between asthma and CRS, but the recent awareness of subphenotypes of both disease reveals new insights into this association. In particular, for patients with adult-onset nonatopic eosinophilic asthma the presence of CRSwNP seems not to be a comorbidity, but a broadening of the spectrum of the disease. These patients share pathophysiology, severity of disease and poor responses to regular treatment. Several studies have shown promising effects of biological agents in severe eosinophilic upper and lower airway disease. These findings further support the connection between eosinophilic asthma and CRSwNP, and encourage chest physicians and ENT specialists [11] to join forces and work together to find underlying common mechanisms and best treatment options for these severely disabled patients. A major challenge will be to find easily accessible biomarkers to select the patients who have the best chance of a positive therapeutic response to innovative approaches.

REFERENCES

1 Braman SS. The global burden of asthma. *Chest 2006*; 130: 1 Suppl., 4S–12S.
2 Beule A. Epidemiology of chronic rhinosinusitis, selected risk factors, comorbidities, and economic burden. *GMS Curr Top Otorhinolaryngol Head Neck Surg 2015*; 14: Doc11.
3 Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol 2010*; 126: 466–476.
4 Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *J Allergy Clin Immunol 1977*; 59: 17–21.
5 Ponikau JU, Sherris DA, Kephart GM, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol 2003*; 112: 877–882.
6 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2017. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ Date last accessed: March 30, 2017.
7 Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy 2012*; 42: 650–658.
8 Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. *J Intern Med 2016*; 279: 192–204.
9 Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy 2012*; 67: 91–98.
10 Håkansson K, Thomsen SF, Konge L, et al. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy 2014*; 28: 383–387.
11 Fokkens WJ, Hellings PW. Nasal polyposis and asthma: the otorhinolaryngologist's view. In: Bachert C, Bourdin A, Chanez P, eds. The Nose and Sinuses in Respiratory Disorders (ERS Monograph). Sheffield, *European Respiratory Society, 2017*; pp. 87–104.
12 Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med 2009*; 9: 24.
13 Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy 2004*; 59: 469–478.
14 Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature 2002*; 418: 426–430.
15 Weinmayr G, Weiland SK, Björkstén B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med 2007*; 176: 565–574.
16 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med 2007*; 175: 661–666.
17 Brussee J, Smit H, Vanstrien R, et al. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. *J Allergy Clin Immunol 2005*; 115: 946–952.
18 Holt PG, Sly PD. Viral infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. *Nat Med 2012*; 18: 726–735.
19 Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med 2016*; 375: 411–421.
20 Coogan PF, Castro-Webb N, Yu J, et al. Active and passive smoking and the incidence of asthma in the Black Women's Health Study. *Am J Respir Crit Care Med 2015*; 191: 168–176.
21 American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. *Am J Respir Crit Care Med 2000*; 161: 665–673.
22 Kogevinas M, Zock J-P, Jarvis D, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet 2007*; 370: 336-341.
23 Leynaert B, Sunyer J, Garcia-Esteban R, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax 2012*; 67: 625-631.
24 Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinology 2012*; 50: Suppl. 23, 1–298.
25 Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy 2008*; 38: 260–275.
26 Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA2LEN study. *Allergy 2011*; 66: 1216–1223.
27 Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg 1995*; 113: 104–109.
28 Klossek JM, Neukirch F, Pribil C, et al. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. *Allergy 2005*; 60: 233–237.
29 Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol 2001*; 107: 607–614.

30 Schlosser RJ, London SD, Gwaltney JM, et al. Microbiology of chronic frontal sinusitis. *Laryngoscope 2001;* 111: 1330–1332.
31 Hox V, Delrue S, Scheers H, et al. Negative impact of occupational exposure on surgical outcome in patients with rhinosinusitis. *Allergy 2012;* 67: 560–565.
32 Samter M, Beers RF. Concerning the nature of intolerance to aspirin. *J Allergy 1967*; 40: 281–293.
33 Szczeklik A, Sanak M. The role of COX-1 and COX-2 in asthma pathogenesis and its significance in the use of selective inhibitors. *Clin Exp Allergy 2002;* 32: 339–342.
34 Guilemany JM, Angrill J, Alobid I, et al. United airways: the impact of chronic rhinosinusitis and nasal polyps in bronchiectasic patient's quality of life. *Allergy 2009*; 64: 1524–1529.
35 Bachert C, Bourdin A, Chanez P, eds. The Nose and Sinuses in Respiratory Disorders (ERS Monograph). Sheffield, *European Respiratory Society, 2017*.
36 Thorstensen WM, Bugten V, Sue-Chu M, et al. Sino-nasal characteristics in asthmatic patients. *Otolaryngol Head Neck Surg 2012;* 147: 950–957.
37 Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. *Ear Nose Throat J 2007*; 86: 409–411.
38 Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. *Am J Rhinol 2004*; 18: 15–21.
39 Langdon C, Mullol J. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. *J Asthma Allergy 2016*; 9: 45–53.
40 Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. *J Allergy Clin Immunol Pract 2014;* 2: 653–657.
41 Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *Am J Rhinol Allergy 2013*; 27: 473–478.
42 Newman LJ, Platts-Mills TA, Phillips CD, et al. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA 1994*; 271: 363–367.
43 Pakdaman MN, Luong A. The links between chronic rhinosinusitis and asthma. *Curr Opin Otolaryngol Head Neck Surg 2011;* 19: 218–223.
44 Larsen K. The clinical relationship of nasal polyps to asthma. *Allergy Asthma Proc 1996*; 17:243–249.
45 Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol 1999*; 28: 717–722.
46 ten Brinke A, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol 2002*; 109: 621–626.
47 Amelink M, de Groot JC, de Nijs SB, et al. Severe adult-onset asthma: a distinct phenotype. *J Allergy Clin Immunol 2013*; 132: 336–341.
48 Wu W, Bleecker E, Moore W, et al. Unsupervised phenotyping of Severe Asthma Research Program participants using expanded lung data. *J Allergy Clin Immunol 2014*; 133: 1280–1288.
49 Håkansson K, Bachert C, Konge L, et al. Airway inflammation in chronic rhinosinusitis with nasal polyps and asthma: the united airways concept further supported. *PLoS One 2015*; 10: e0127228.
50 Braunstahl GJ, Overbeek SE, Fokkens WJ, et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med 200*1; 164: 858–865.
51 Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol 1997*; 99: S781–S786.
52 Braunstahl G-J, Hellings PW. Allergic rhinitis and asthma: the link further unraveled. *Curr Opin Pulm Med 2003;* 9: 46–51.
53 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med 2012;* 18: 716–725.
54 de Groot JC, ten Brinke A, Bel EHD. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res 2015;* 1: 00024-2015.
55 Hekking P-PW, Bel EH. Developing and emerging clinical asthma phenotypes. *J Allergy Clin Immunol Pract 2014*; 2: 671–680.
56 de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res 2016*; 2: 00100-2015.
57 de Groot JC, Amelink M, de Nijs SB, et al. Risk factors for frequent severe exacerbations in late-onset eosinophilic asthma. *Am J Respir Crit Care Med 2015;* 192: 899–902.
58 Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol 2003*; 111: 913–921.
59 Lambrecht BN, Hammad H. The role of dendritic and epithelial cells as master regulators of allergic airway inflammation. *Lancet 2010;* 376: 835–843.
60 Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: eosinophilic airway inflammation in nonallergic asthma. *Nat Med 2013;* 19: 977–979.
61. Gauvreau GM, O'Byrne PM, Boulet L-P, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med 2014;* 370: 2102–2110.

62 Nagarkar DR, Poposki JA, Tan BK, et al. Thymic stromal lymphopoietin activity is increased in nasal polyps of patients with chronic rhinosinusitis. *J Allergy Clin Immunol 2013;* 132: 593–600.
63 Buchheit KM, Cahill KN, Katz HR, et al. Thymic stromal lymphopoietin controls prostaglandin D2 generation in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol 2016*; 137: 1566–1576.
64 Choi JH, Kim MA, Park HS. An update on the pathogenesis of the upper airways in aspirin-exacerbated respiratory disease. *Curr Opin Allergy Clin Immunol 2014*; 14: 1–6.
65 Kato A. Immunopathology of chronic rhinosinusitis. *Allergol Int 2015*; 64: 121–130.
66 Bachert C, Zhang N, Holtappels G, et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. *J Allergy Clin Immunol 2010*; 126: 962–968.
67 Zhang N, Van Zele T, Perez-Novo C, et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol 2008*; 122: 961–968.
68 Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol 2016*; 137: 1449–1456.
69 Bachert C, Gevaert P, Howarth P, et al. IgE to Staphylococcus aureus enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol 2003;* 111: 1131–1132.
70 Tomassen P, Jarvis D, Newson R, et al. Staphylococcus aureus enterotoxin-specific IgE is associated with asthma in the general population: a GA2LEN study. *Allergy 2013*; 68: 1289–1297.
71 Kowalski ML, Cieślak M, Pérez-Novo CA, et al. Clinical and immunological determinants of severe/refractory asthma (SRA): association with staphylococcal superantigen-specific IgE antibodies. *Allergy 2011*; 66: 32–38.
72 Bachert C, van Steen K, Zhang N, et al. Specific IgE against Staphylococcus aureus enterotoxins: an independent risk factor for asthma. *J Allergy Clin Immunol 2012;* 130: 376–381.
73 Song W-J, Sintobin I, Sohn K-H, et al. Staphylococcal enterotoxin IgE sensitization in late-onset severe eosinophilic asthma in the elderly. *Clin Exp Allergy 2016;* 46: 411–421.
74 Chung KF. Staphylococcal enterotoxin-specific IgE: a biomarker for a distinct phenotype of severe asthma? *Clin Exp Allergy 2016;* 46: 387–389.
75 Bachert C, Zhang N, Krysko O, et al. Nasal polyposis and asthma: a mechanistic paradigm focusing on Staphylococcus aureus. In: Bachert C, Bourdin A, Chanez P, eds. The Nose and Sinuses in Respiratory Disorders (ERS Monograph). Sheffield, *European Respiratory Society, 2017*; pp. 122-137.
76 Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J 2015;* 46: 1308–1321.
77 van Veen IH, ten Brinke A, Gauw SA, et al. Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. *J Allergy Clin Immunol 2009;* 124: 615–617.
78 Bilodeau L, Boulay M-E, Prince P, et al. Comparative clinical and airway inflammatory features of asthmatics with or without polyps. *Rhinology 2010;* 48: 420–425.
79 Mascia K, Haselkorn T, Deniz YM, et al. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol 2005*; 116: 970–975.
80 ten Brinke A, Sterk PJ, Masclee AAM, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J 2005*; 26: 812–818.
81 Loymans RJB, Honkoop PJ, Termeer EH, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model. *Thorax 2016*; 71: 838–846.
82 Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and co-morbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med 2017*; 195: 302–313.
83 Mahdavinia M, Fox SR, Smith BM, et al. Racial differences in food allergy phenotype and health care utilization among US children. *J Allergy Clin Immunol Pract 2017*; 5: 352–357.
84 Jain VV, Allison R, Beck SJ, et al. Impact of an integrated disease management program in reducing exacerbations in patients with severe asthma and COPD. Respir Med 2014; 108: 1794–1800.
85 Al Badaai Y, Valdés CJ, Samaha M. Outcomes and cost benefits of functional endoscopic sinus surgery in severely asthmatic patients with chronic rhinosinusitis. *J Laryngol Otol 2014;* 128: 512-517.
86 Senior BA, Kennedy DW, Tanabodee J, et al. Long-term impact of functional endoscopic sinus surgery on asthma. *Otolaryngol Head Neck Surg 1999;* 121: 66–68.
87 Vashishta R, Soler ZM, Nguyen SA, et al. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol 2013*; 3: 788–794.
88 Lamblin C, Brichet A, Perez T, et al. Long-term follow-up of pulmonary function in patients with nasal polyposis. *Am J Respir Crit Care Med 2000*; 161: 406–413.
89 Ek A, Middelveld RJM, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA2LEN survey. *Allergy 2013*; 68: 1314–1321.
90 Zhang Z, Adappa ND, Doghramji LJ, et al. Quality of life improvement from sinus surgery in chronic rhinosinusitis patients with asthma and nasal polyps. *Int Forum Allergy Rhinol 2014;* 4: 885–892.

91 Alobid I, Cardelus S, Benítez P, et al. Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. *Rhinology 2011*; 49: 519–524.
92 Iino Y, Tomioka-Matsutani S, Matsubara A, et al. Diagnostic criteria of eosinophilic otitis media, a newly recognized middle ear disease. *Auris Nasus Larynx 2011*; 38: 456–461.
93 Kanazawa H, Yoshida N, Iino Y. New insights into eosinophilic otitis media. *Curr Allergy Asthma Rep 2015*; 15: 76.
94 Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. *J Allergy Clin Immunol 2015*; 136: 1431–1440.
95 Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J 2000*; 16: 432–436.
96 Thamboo A, Santos RCD, Naidoo L, et al. Use of the SNOT-22 and UPSIT to appropriately select pediatric patients with cystic fibrosis who should be referred to an otolaryngologist. JAMA Otolaryngol Neck Surg 2014; 140: 934.
97 Lachanas VA, Woodard TD, Antisdel JL, et al. Sino-nasal outcome test tool assessment in patients with chronic rhinosinusitis and obstructive sleep apnea. *ORL J Otorhinolaryngol Relat Spec 2012*; 74: 286–289.
98 Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol 2014*; 113: 347–385.
99 Head K, Chong LY, Piromchai P, et al. Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database Syst Rev 2016*; 4: CD011994.
100 Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. J Allergy Clin Immunol 2010; 125: 1069–1076.
101 Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med 2004; 117*: Suppl. 9A, 5S–11S.
102 Brusselle GG, Joos G. Is there a role for macrolides in severe asthma? *Curr Opin Pulm Med 2014*; 20: 95–102. 103. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope 2004*; 114: 923–930.
104 Ragab S, Scadding GK, Lund VJ, et al. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J 2006*; 28: 68–74.
105 Brusselle GG, VanderStichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax 2013*; 68: 322–329.
106 Wentzel JL, Soler ZM, DeYoung K, et al. Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review. *Am J Rhinol Allergy 2013*; 27: 482–489.
107 Ragab S, Parikh A, Darby YC, et al. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. *Clin Exp Allergy 2001*; 31: 1385–1391.
108 Schäper C, Noga O, Koch B, et al. Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. *J Investig Allergol Clin Immunol 2011*; 21: 51–58.
109 Dahlén S-E, Malmström K, Nizankowska E, et al. Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med 2002*; 165: 9–14.
110 McCoul ED, Tabaee A. A practical approach to refractory chronic rhinosinusitis. *Otolaryngol Clin North Am 2016*; 50: 183–198.
111 Van Zele T, Holtappels G, Gevaert P, et al. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy 2014*; 28: 192–198.
112 Kalish L, Snidvongs K, Sivasubramaniam R, et al. Topical steroids for nasal polyps. *Cochrane Database Syst Rev 2012*; 12: CD006549.
113 Lund VJ. The effect of sinonasal surgery on asthma. *Allergy 1999*; 54: Suppl. 57, 141–145.
114 Scadding G. The effect of medical treatment of sinusitis upon concomitant asthma. *Allergy 1999*; 54: Suppl. 57, 136–140.
115 Marks SC, Shamsa F. Evaluation of prognostic factors in endoscopic sinus surgery. *Am J Rhinol 1997*; 11: 187–191.
116 Gulati SP, Chaudhry D, Kalra V, et al. The role of functional endoscopic sinus surgery (FESS) in patients with asthma and chronic sinusitis. *Indian J Otolaryngol Head Neck Surg 2008*; 60: 152-155.
117 Dejima K, Hama T, Miyazaki M, et al. A clinical study of endoscopic sinus surgery for sinusitis in patients with bronchial asthma. *Int Arch Allergy Immunol 2005*; 138: 97–104.
118 Garrel R, Gardiner Q, Khudjadze M, et al. Endoscopic surgical treatment of sinonasal polyposis – medium term outcomes (mean follow-up of 5 years). *Rhinology 2003*; 41: 91–96.
119 Uri N, Cohen-Kerem R, Barzilai G, et al. Functional endoscopic sinus surgery in the treatment of massive polyposis in asthmatic patients. *J Laryngol Otol 2002*; 116: 185–189.
120. Senior BA, Kennedy DW, Tanabodee J, et al. Long-term impact of functional endoscopic sinus surgery on asthma. *Otolaryngol Head Neck Surg 1999*; 121: 66–68.

121 Goldstein MF, Grundfast SK, Dunsky EH, et al. Effect of functional endoscopic sinus surgery on bronchial asthma outcomes. *Arch Otolaryngol Head Neck Surg 1999*; 125: 314–319.
122 Park AH, Lau J, Stankiewicz J, et al. The role of functional endoscopic sinus surgery in asthmatic patients. *J Otolaryngol 1998*; 27: 275–280.
123 Dinis PB, Gomes A. Sinusitis and asthma: how do they interrelate in sinus surgery? *Am J Rhinol 1997*; 11: 421–428.
124 McFadden EA, Woodson BT, Fink JN, et al. Surgical treatment of aspirin triad sinusitis. *Am J Rhinol 1997*; 11: 263–270.
125 Manning SC, Wasserman RL, Silver R, et al. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. *Arch Otolaryngol Head Neck Surg 1994*; 120: 1142–1145.
126 Nishioka GJ, Cook PR, Davis WE, et al. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. *Otolaryngol Head Neck Surg 1994*; 110: 494–500.
127 Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev 2014*; 1: CD003559.
128 Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. *Chest 2013*; 144: 411–419.
129 Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol 2013*; 131: 110–116.
130 Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med 2009*; 360: 973–984.
131 Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med 2014*; 371: 1189–1197.
132 Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti–IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol 2011*; 128: 989–995.
133 Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 2011; 365: 1088–1098.
134 Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet 2016*; 388: 31–44.
135 Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA 2016*; 315: 469–479.

Chapter

4

Dynamic hyperinflation impairs daily life activity in asthma

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ABSTRACT

Introduction
Dynamic hyperinflation has been documented in asthma, yet its impact on overall health and daily life activities is unclear. We assessed the prevalence of dynamic hyperinflation in moderate to severe asthma and its relationship with the scores of a set of specific and general respiratory health questionnaires.

Methods
77 non-smoking asthma patients (GINA step 4-5) were consecutively recruited and completed 5 questionnaires: Asthma Control Questionnaire, Clinical COPD Questionnaire , St. George's Respiratory Questionnaire, London Chest Activity of Daily Living scale (LCADL), Shortness of Breath with Daily Activities (SOBDA). Dynamic hyperinflation was defined as ≥10% reduction in inspiratory capacity induced by standardized metronome-paced tachypnea. Associations between level of dynamic hyperinflation and questionnaire scores were assessed and adjusted for asthma severity.

Results
81 percent (95% CI 71.7-89.4%) of patients showed dynamic hyperinflation. Higher levels of dynamic hyperinflation were related to poorer scores on all questionnaires ($r=0.228$-0.385, $p<0.05$). After adjustment for asthma severity, dynamic hyperinflation remained associated with poorer scores on LCADL ($p=0.027$) and SOBDA ($p=0.031$).

Conclusion
Dynamic hyperinflation is associated with poorer overall health and impaired daily life activities, independent of asthma severity. Because of its major impact on everyday life activities, dynamic hyperinflation is an important target for treatment in asthma.

INTRODUCTION

Asthma is a heterogeneous condition of the airways with many clinical and inflammatory sub-phenotypes[1]. In day-to-day practice these different subtypes may present with different asthma symptoms. A subset of asthma patients report exercise intolerance and limitations in daily life activities as the most prominent symptoms, rather than the classical wheezy attacks, with a major impact on their quality of life[2]. Many factors may contribute to these exercise and activity limitations in asthma, including psychological factors, respiratory muscle strength, bronchoconstriction and dynamic hyperinflation[3].

Dynamic hyperinflation, described as an increase in end-expiratory lung volume under conditions of greater minute ventilation (e.g. exercise), is a well-known feature in chronic obstructive pulmonary disease (COPD) resulting from reduced expiratory airflow[4]. It is strongly related to exertional dyspnoea and diminished daily physical activity in COPD patients[5, 6]. Interestingly, dynamic hyperinflation is not exclusive to COPD, and a few small studies suggest it to be present in asthma as well. Dynamic hyperinflation has been reported in patients with stable asthma following methacholine provocation[7, 8] or exercise testing[9], probably reflecting induced bronchoconstriction. Recently, it was suggested that dynamic hyperinflation is particularly important in patients with more severe asthma. These patients have been shown to develop dynamic hyperinflation during exercise to the same magnitude as COPD patients with similar degrees of airway obstruction[10]. Unlike COPD, it has been suggested that in asthma ongoing inflammation may impair small airway function[11]. In patients with late-onset asthma, air trapping was markedly present, and associated with systemic eosinophilic inflammation and severe exacerbations[12]. Moreover, in a small unblinded study in 10 patients with moderate to severe allergic asthma, the extent of dynamic hyperinflation decreased with omalizumab treatment, which corresponded to an improvement in symptoms and exercise capacity [13]. So, ongoing small airway inflammation might promote the development of dynamic hyperinflation and play a role in daily exercise limitations in subsets of asthma patients. Importantly, dynamic hyperinflation is found to be greater in obese versus nonobese asthma patients, whether or not related to reduced chest wall compliance, and therefore obesity has to be taken into account when evaluating dynamic hyperinflation in asthma[14]. Whatever the underlying mechanism, so far little is known about the prevalence of dynamic hyperinflation in moderate to severe asthma and in particular its impact on asthma symptoms, activities of daily life and perceived wellbeing.

Although asthma symptoms, limitations in daily life activities and reduced quality of life are all important outcomes from the patient's perspective, not all are taken into account equally well in asthma management. Asthma symptoms are generally scored using the Asthma Control Questionnaire (ACQ) or Asthma Control Test, focusing on classical symptoms of variable dyspnoea and wheezing and with only little emphasis on symptoms of exercise intolerance and limitations in daily life activity. The latter symptoms might better be detected by questionnaires used for COPD patients. This is supported by observations in recent studies on the effects of mepolizumab in severe eosinophilic asthma patients, showing greater improvements in the St George's Respiratory Questionnaire (SGRQ) score than in the ACQ score[15, 16].

These observations stress the need to investigate the role of dynamic hyperinflation in asthma symptoms and limitations in daily activities, in particular in patients with more severe disease. If dynamic hyperinflation indeed explains important patient-related outcomes this could become an important target for treatment of asthma. Therefore, in the present study we primarily investigated the prevalence of dynamic hyperinflation in moderate to severe asthma. As a secondary objective, we assessed the relationship between the degree of dynamic hyperinflation and severity of respiratory symptoms and limitations of daily life activities derived from different specific and general respiratory health questionnaires.

METHODS

Patients

Patients with moderate to severe asthma (age ≥18 years) were recruited from a nonacademic pulmonary outpatient department in the Netherlands (Medical Centre Leeuwarden) between June 2016 and January 2018. 77 patients were consecutively included in the present study, which is part of an extensive research programme aimed at exploring the clinical relevance of dynamic hyperinflation in asthma. All patients were on regular treatment with medium to high doses of inhaled corticosteroids (ICS) (≥500 µg/day fluticasone or equivalent) with or without daily oral corticosteroids, combined with long-acting β-agonists or other controller for ≥6 months, according to the Global Initiative for Asthma steps 4–5[17]. All patients had stable asthma without exacerbations during the 4 weeks before inclusion, were nonsmokers (smoking history ≤10 pack-years), had a body mass index (BMI) ≤30 kg/m2, and airway obstruction with a forced expiratory volume in 1s (FEV_1)/forced vital capacity ≤80% predicted. Patients with concurrent respiratory disease, major unrelated comorbidities and pregnancy were excluded. The study was approved by the local medical ethics committee and all patients gave their written informed consent. The trial is registered at the Netherlands Trial Register (identification number NTR5873).

Methods and design

For the present study all measurements were performed during one visit. First, data on all relevant patient characteristics, medication use and asthma related healthcare use in the previous year were collected by the investigator. Then, the patients completed a set of five specific and general respiratory health questionnaires. Finally, they performed lung function tests and had blood drawn for cell differential counts and total immunoglobulin E levels.

Questionnaires

All subjects completed a set of five respiratory health questionnaires: ACQ-6 (range 0–6), focusing on asthma control[18]; the Clinical COPD Questionnaire (CCQ) (range 0–6), focusing on COPD control[19]; SGRQ (range 0–100)[20], focusing on respiratory symptoms, quality of life and limitations in daily life activities; and the London Chest Activity of Daily Living (LCADL) questionnaire (range 0–75)[21], and the Shortness of Breath with Daily Activities (SOBDA) questionnaire (range 1–4)[22], both focusing on limitations in daily life activities. The ACQ is validated in asthma patients; the other questionnaires used in this study are validated in COPD patients.

Lung function
Pulmonary function tests included exhaled nitric oxide fraction measurement[23], spirometry and body plethysmography[24]. Bronchodilators were withheld before pulmonary function tests for ≥6 and ≥12 h for the short-acting and long-acting β2-agonists, respectively.

Dynamic hyperinflation
To test for dynamic hyperinflation, all subjects underwent metronome-paced tachypnoea measurement (MPT)[25]. Subjects were seated, breathing through a mouthpiece connected to the spirometer (MasterScreen-PFT; Jaeger, Mettawa, IL, USA) and were instructed on the performance of the inspiratory capacity manoeuvres. At the start of this test the baseline inspiratory capacity was measured as the mean of three acceptable inspiratory capacity manoeuvres while the patient was at rest. Subjects were then asked to breathe at a metronome-paced frequency of twice the resting breathing rate for 20 s, and immediately afterwards an inspiratory capacity manoeuvre was performed[26]. The procedure was repeated after subjects had returned to their resting breathing level. Subjects were encouraged to maintain a stable tidal volume. Dynamic hyperinflation was calculated as the difference between the inspiratory capacity measured during increased pacing and the inspiratory capacity at rest. A decrease of ≥10% in the inspiratory capacity was considered as dynamic hyperinflation[26].

Statistical analyses
Differences between subjects with and without dynamic hyperinflation were analysed using unpaired t-tests, Mann–Whitney U-tests or Chi-squared tests, wherever appropriate. Subsequently, linear associations between the MPT-induced degree of dynamic hyperinflation and the questionnaire scores were assessed using Spearman rank correlations. Finally, we assessed whether univariate associations remained when adjusting for asthma severity parameters (ACQ score, fluticasone equivalent dose and FEV_1 % pred) using multivariable linear regression models. All analyses were performed using SPSS software (version 20; IBM, Armonk, NY, USA). Two-sided p-values <0.05 were considered to be statistically significant.

RESULTS

Patient characteristics and dynamic hyperinflation

77 patients with moderate to severe asthma participated in the study. Patient characteristics are shown in table 4.1. The majority of patients was male and had adult-onset asthma. Only 31% of patients had smoked previously. Despite the limited cigarette exposure in the past (median (range) 0 (0–10) pack-years), the degree of airway obstruction varied with FEV_1 values ranging from 26% pred to 104% pred.

In the whole group of 77 patients, the median (range) of MPT-induced reduction in inspiratory capacity was 0.47 (–0.42–1.57) L or 17.8 (–14.1–47.2)% from baseline. According to the predefined cut-off level, 62 out of 77 patients (80.5%, 95% CI 71.7–89.4%) showed dynamic hyperinflation, with a median (range) MPT-induced reduction in inspiratory capacity of 0.55 (0.19–1.57) L or 19.5 (10.2–47.2)% change from base-

line inspiratory capacity. The other 15 patients showed no dynamic hyperinflation with a median (range) reduction in inspiratory capacity of only 0.16 (–0.42–0.35) L (4.8 (–14.1–9.0)%). When comparing the two groups, patients with dynamic hyperinflation reported significantly more visits to the pulmonologist in the preceding year (p=0.031) and tended to use higher daily doses of inhaled and oral corticosteroids. There was no difference between the groups in smoking history or atopic status, nor was there a difference in blood eosinophil counts. At baseline, patients with dynamic hyperinflation had lower levels of FEV_1 and showed more severe air trapping and static hyperinflation.

Table 4.1 Characteristics of moderate to severe asthma patients with and without dynamic hyperinflation

	All	No dynamic hyperinflation	Dynamic hyperinflation	p-value
Subjects	77	15 (19)	62 (81)	
Male	45 (58)	11 (73)	34 (55)	0.192
Age years	62 (49–67)	54 (48–64)	62 (51–70)	0.142
Adult-onset (age >18 years) asthma	42 (55)	6 (40)	36 (58)	0.207
Atopy	36 (47)	9 (60)	27 (44)	0.252
BMI kg·m^{-2}	25±3	26±3	25±3	0.398
Pack-years	0 (0–2)	0 (0–0)	0 (0–2.5)	0.351
Fluticasone equivalent mg	500 (500–1000)	500 (500–500)	500 (500–1000)	0.058
OCS-dependent	10 (13)	0 (0)	10 (16)	0.095
OCS dose mg	0 (0–10)	0 (0–0)	0 (0–10)	0.099
Pulmonologist visits in preceding year	2 (1–3)	2 (1–3)	2 (2–4)	0.031
⩾1 ER visit in preceding year	11 (14.3)	3 (20)	8 (12.9)	0.484
⩾1 admission in preceding year	8 (10.4)	1 (6.7)	7 (11.3)	0.601
Blood eosinophils ×10^9·L^{-1}	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.974
Blood neutrophils ×10^9·L^{-1}	4.4 (3.5–5.7)	4.3 (3.2–5.2)	4.5 (3.6–6.0)	0.210
Total IgE, kU·L^{-1}	110 (35–287)	118 (20–491)	105 (39–285)	0.657
F_{eNO} ppb	27 (19–54)	24 (19–53)	27 (20–55)	0.699
FEV_1 % pred	68 (56–80)	78 (73–86)	66 (56–79)	0.017
FVC % pred	102±19	108±19	100±18	0.156
FEV_1/FVC % pred	70 (63–76)	72 (64–79)	69 (63–76)	0.241
TLC % pred	110±14	110±16	109±14	0.855
RV/TLC % pred	113±25	99±20	117±25	0.010
FRC/TLC % pred	113±16	101±18	115±14	0.001
IC baseline L	2.86 (2.25–3.77)	3.32 (2.99–3.90)	2.79 (2.13–3.77)	0.045
ΔIC L	0.47 (0.31–0.68)	0.16 (–0.01–0.26)	0.55 (0.37–0.71)	<0.001
ΔIC %	17.8 (12–25)	4.8 (–0.51–7.65)	19.5 (14.3–25.9)	<0.001

Data are presented as n, n (%), median (interquartile range) or mean±SD, unless otherwise stated. BMI: body mass index; OCS: oral corticosteroids; ER: emergency room; Ig: immunoglobulin; FeNO: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: function residual capacity; IC: inspiratory capacity; ΔIC: reduction in inspiratory capacity (=dynamic hyperinflation) measured as the difference between IC at baseline and IC following metronome-paced tachypnoea.

Dynamic hyperinflation and symptom scores

All patients completed the five questionnaires. The scores in ACQ and CCQ were not significantly different between patients with and without dynamic hyperinflation (table 4.2). In the group with dynamic hyperinflation 42% of the patients had an ACQ score of ≥1.5 versus 27% of the patients in the group without dynamic hyperinflation (p=0.179). The patients with dynamic hyperinflation showed a poorer score on the LCADL (p=0.0031) and a trend towards a poorer score on the SGRQ (p=0.070) and SOBDA (p=0.094).

When analysed linearly, the scores of all the questionnaires were significantly related to the MPT-induced degree of dynamic hyperinflation, as shown in figure 4.1. Higher levels of dynamic hyperinflation corresponded with poorer scores on all five question-

Table 4.2 Respiratory symptom scores in asthma patients with and without dynamic hyperinflation

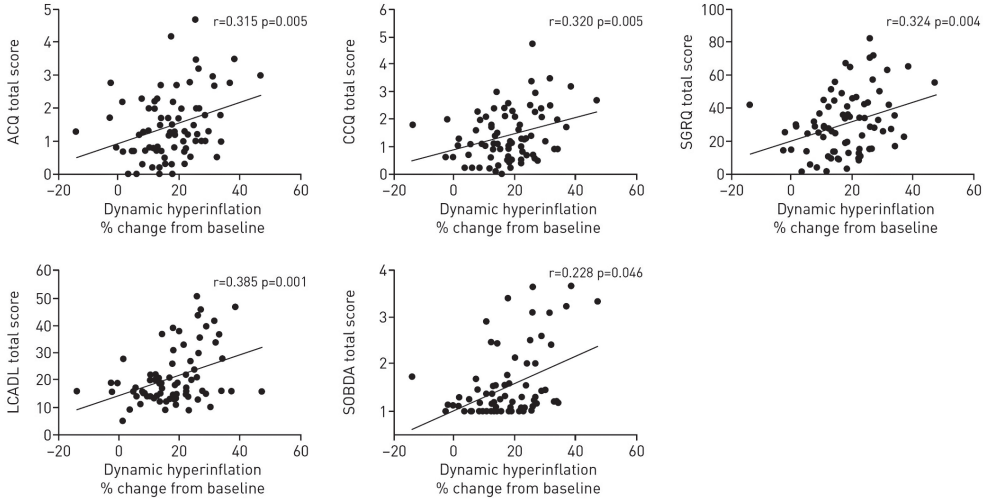
	No dynamic hyperinflation	Dynamic hyperinflation	p-value
Subjects	15 (19)	62 (81)	
ACQ#	0.8 (0.7–1.7)	1.3 (0.8–2.0)	0.144
CCQ#	1.1 (0.6–1.8)	1.2 (0.7–2.1)	0.234
SGRQ#	25.3 (13.6–30.1)	28.8 (15.9–45.3)	0.070
LCADL#	16 (14–17)	19 (15–28)	0.031
SOBDA#	1.1 (1.0–1.3)	1.2 (1.0–2.0)	0.094

Data are presented as n (%) or median (interquartile range), unless otherwise stated. ACQ: Asthma Control Questionnaire; CCQ: Clinical COPD (chronic obstructive pulmonary disease) Questionnaire; SGRQ: St George's Respiratory Questionnaire; LCADL: London Chest Activity of Daily Living questionnaire; SOBDA: Shortness of Breath with Daily Activities questionnaire. #: total score.

naires. Information on the association between dynamic hyperinflation and the subdomains of the questionnaires is presented in supplementary table S4.1. For FEV_1 % pred, there was no significant correlation with any of the questionnaire scores (p≥0.13). Nor were parameters of static hyperinflation associated with questionnaire scores, except for the SOBDA questionnaire (supplementary table S4.2).

After adjustment for parameters of asthma severity (ACQ score, FEV_1% pred, ICS dose), dynamic hyperinflation remained associated with poorer scores on LCADL (β=0.198, p=0.044) and SOBDA (β=0.016, p=0.009), but not with the other questionnaires (table 4.3).

Figure 4.1 Relation dynamic hyperinflation and questionnaires



r: correlation coefficient, with corresponding p-value. ACQ: Asthma Control Questionnaire; CCQ: Clinical COPD (chronic obstructive pulmonary disease) Questionnaire; SGRQ: St George's Respiratory Questionnaire; LCADL: London Chest Activity of Daily Living questionnaire; SOBDA: Shortness of Breath with Daily Activities questionnaire.

Table 4.3 The association between degree of dynamic hyperinflation (ΔIC) and the different questionnaire scores

	β (ΔIC) % (95% CI)	p-value
CCQ#	0.010 (−0.004–0.024)	0.155
SGRQ#	0.139 (−0.135–0.414)	0.315
LCADL#	0.198 (0.005–0.391)	0.044
SOBDA#	0.016 (0.004–0.028)	0.009

Linear regression analyses adjusted for asthma severity parameters (inhaled corticosteroid dose, percentage of predicted forced expiratory volume in 1 s and Asthma Control Questionnaire score).
ΔIC: reduction in inspiratory capacity (=dynamic hyperinflation) measured as the difference between IC at baseline and IC following metronome-paced tachypnoea; CCQ: Clinical COPD (chronic obstructive pulmonary disease) Questionnaire; SGRQ: St George's Respiratory Questionnaire; LCADL: London Chest Activity of Daily Living questionnaire; SOBDA: Shortness of Breath with Daily Activities questionnaire.
#: total score.

DISCUSSION

In the present study, we showed that dynamic hyperinflation is a relevant feature in moderate to severe asthma. The proportion of patients with dynamic hyperinflation was high. The severity of dynamic hyperinflation was related to lower scores on five different respiratory health questionnaires and significantly associated with impaired daily life activities. These results suggest that dynamic hyperinflation may be an important target for treatment in moderate to severe asthma.

In this study we explored the occurrence of dynamic hyperinflation in moderate to severe asthma and investigated its relationship with respiratory symptoms and limitations in daily life activities. Although most studies on dynamic hyperinflation are performed in the COPD population, a few studies reported the presence of dynamic hyperinflation in asthma, mostly provoked by methacholine or exercise testing. These studies showed that dynamic hyperinflation was associated with reduced exercise capacity[9, 27] and inconsistent levels of dyspnoea during testing[8, 28, 29]. Interestingly, dynamic hyperinflation might be especially relevant in asthma patients with more severe disease. In a study comparing asthma patients with and without a near-fatal asthma attack, the degree of dynamic hyperinflation during exercise tended to be higher in the patients with near-fatal asthma[30]. It has been shown that severe asthma patients develop dynamic hyperinflation during exercise comparable to COPD patients, a phenomenon that according to the authors might add some insight into the mechanism of daily exercise limitations in this population[10]. Moreover, in a small group of severe asthma patients, dynamic hyperinflation was shown to be treatable as it decreased after omalizumab therapy[13]. Unfortunately, in these studies no data were provided on the relationship of dynamic hyperinflation with respiratory symptoms and limitations of daily life activities. Our results confirm and extend previous studies by showing that dynamic hyperinflation is highly prevalent in moderate to severe asthma and related to important patient-related outcomes in daily life.

In the current study we found a high proportion of patients showing MPT-induced dynamic hyperinflation, which might be explained by several factors. Firstly, we purposely

chose to include only nonobese asthma patients with documented airway obstruction, and without overt smoking-related COPD. However, we cannot exclude that in other subgroups of asthma, e.g. those without airway obstruction or those with obesity, the proportion of patients showing dynamic hyperinflation and the clinical relevance of dynamic hyperinflation might be different. Secondly, we used MPT to measure dynamic hyperinflation. In COPD dynamic hyperinflation is commonly assessed by measuring changes in inspiratory capacity during cardiopulmonary exercise testing (CPET)[31], a complex and laborious test. MPT, a far simpler and less strenuous surrogate of CPET, has been shown in COPD patients to have a good overall accuracy to identify subjects who are susceptible to developing dynamic hyperinflation during CPET and during activities in daily life[32, 33]. In asthma, there are no studies on the role of dynamic hyperinflation in daily life activities and on the superiority of CPET or MPT to measure it. Our study showed a good coherence between MPT-induced dynamic hyperinflation and asthma symptoms during daily activities. This suggests that a simple MPT measurement might be useful to predict the clinical effects of dynamic hyperinflation in daily practice.

The relationship between limitations in daily life activities and dynamic hyperinflation, irrespective of level of airway obstruction, suggests a role for small-airway dysfunction. In asthma, inflammation and remodelling have been demonstrated in central as well as peripheral airways and there is growing evidence that small airway pathology is more extensive and clinically relevant in patients with severe disease[34–36]. Small-airway abnormalities, whether due to remodelling, transient obstruction or ongoing inflammation contribute to increased airflow limitation and may lead to premature airway closure, air trapping and eventually dynamic hyperinflation[37, 38]. Several studies have shown small-airway dysfunction to be associated with poorly controlled asthma and asthma exacerbations[39, 40]. Our results further contribute to the clinical relevance of small-airway dysfunction by showing the relationship between dynamic hyperinflation and limitations in daily life activities.

Interestingly, in severe asthma, the level of exhaled alveolar nitric oxide is closely related to air trapping and airway closure[11], supporting the theory that peripheral airway inflammation and functional abnormalities are interrelated. Ongoing eosinophilic inflammation in the small airways might underlie the demonstrated dynamic hyperinflation in our patients, for which treatment with inhaled corticosteroids might be insufficient. In line with this, a recent pilot study evaluating the usefulness of CPET in verifying and quantifying symptomatic changes following omalizumab treatment showed significant improvements in dynamic hyperinflation as well as exercise capacity[13]. Previous and current results suggest that the identification of small airways disease is not merely speculative, but carries pathophysiological and therapeutic implications[36].

Our results may have important implications for research as well as asthma management in daily practice. The present study provides evidence that dynamic hyperinflation is one of the factors contributing to asthma symptoms and impaired daily life activity. Importantly, FEV_1 was not related to questionnaire scores, in line with previous findings that FEV_1 cannot be used to predict exertional symptoms in asthma [29]. These findings encourage the development of questionnaires capturing a broader panel of airway

symptoms and the monitoring of dynamic hyperinflation in asthma management. We showed that a relatively simple measurement of MPT-induced dynamic hyperinflation may be used as an objective parameter significantly linked to patients' subjective reporting of activity limitation. So, MPT testing may provide an additional and useful tool to assess and verify the individual clinical response to treatment, in daily practice as well as in clinical studies. It remains intriguing what mechanisms underlie the development of dynamic hyperinflation in subsets of patients with asthma. Whether the demonstrated dynamic hyperinflation and related asthma symptoms are the consequence of ongoing inflammation in the peripheral airways and might be reversed by systemic anti-inflammatory treatment needs to be investigated.

In conclusion, in the present prospective study we have shown that in moderate to severe asthma the proportion of patients showing dynamic hyperinflation is high. Dynamic hyperinflation is associated with poorer overall health, lower wellbeing and impaired activities of daily life. Therefore, dynamic hyperinflation is an important target for treatment in moderate to severe asthma.

REFERENCES

1 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med 2012;* 18: 716–725.
2 Foster JM, McDonald VM, Guo M, *et al*. "I have lost in every facet of my life": The hidden burden of severe asthma. *Eur Respir J* 2017; 50.
3 Weatherald J, Lougheed MD, Taillé C, *et al*. Mechanisms, measurement and management of exertional dyspnoea in asthma. *Eur Respir Rev* 2017; 26.
4 Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur Respir J* 2012; 40: 322–329.
5 O'Donnell DE, Travers J, Webb KA, *et al*. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *Eur Respir J* 2009; 34: 866–874.
6 Garcia-Rio F, Lores V, Mediano O, *et al*. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *Am J Respir Crit Care Med* 2009; 180: 506–512.
7 Laveneziana P, Lotti P, Coli C, *et al*. Mechanisms of dyspnoea and its language in patients with asthma. *Eur Respir J* 2006; 27: 742–747.
8 Lougheed MD, Fisher T, O'Donnell DE. Dynamic hyperinflation during bronchoconstriction in asthma: Implications for symptom perception. *Chest* 2006; 130: 1072–1081.
9 Kosmas EN, Milic-Emili J, Polychronaki A, *et al*. Exercise-induced flow limitation, dynamic hyperiflation and exercise capacity in patients with bronchial asthma. *Eur Respir J* 2004; 24: 378–384.
10 Benfante A, Di Marco F, Terraneo S, *et al*. Dynamic hyperinflation during the 6-min walk test in severely asthmatic subjects. *ERJ Open Res* 2018; 4: 00143-2017.
11 van Veen IH, Sterk PJ, Schot R, *et al*. Alveolar nitric oxide *versus* measures of peripheral airway dysfunction in severe asthma. *Eur Respir J* 2006; 27: 951–956.
12 de Groot JC, Storm H, Amelink M, *et al*. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res* 2016; 2: 00100-2015.
13 Schäper C, Gläser S, Felix SB, *et al*. Omalizumab treatment and exercise capacity in severe asthmatics-Results from a pilot study. *Respir Med* 2011; 105: 3–7.
14. Ferreira PG, Freitas PD, Silva AG, *et al*. Dynamic hyperinflation and exercise limitations in obese asthmatic women. *J Appl Physiol* 2017; 123: 585–593.
15 Ortega HG, Liu MC, Pavord ID, *et al*. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *N Engl J Med* 2014; 371: 1198–1207.
16 Chupp GL, Bradford ES, Albers FC, *et al*. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017; 5: 390–400.
17 Global Initiative for Asthma, GINA. Global Strategy for Asthma Management and Prevention. 2015.
18 Juniper EF, O'Byrne PM, Guyatt GH, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14: 902–907.
19 van der Molen T, Willemse BWM, Schokker S, *et al*. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003; 1: 13.
20 Jones PW, Quirk FH, Baveystock CM, *et al*. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321-1327.
21 Garrod R, Bestall JC, Paul EA, *et al*. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: The London chest activity of daily living scale (LCADL). *Respir Med* 2000; 94: 589–596.
22 Watkins ML, Wilcox TK, Tabberer M, *et al*. Shortness of Breath with Daily Activities questionnaire: validation and responder thresholds in patients with chronic obstructive pulmonary disease. *BMJ Open* 2013; 3: e003048.
23 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171: 912–930.
24 Miller MR, Hankinson J, Brusasco V, *et al*. ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
25 Gelb AF, Gutierrez CA, Weisman IM, *et al*. Simplified Detection of Dynamic Hyperinflation. *Chest* 2004; 126: 1855–1860.
26 Lahaije AJMC, Willems LM, van Hees HWH, *et al*. Diagnostic accuracy of metronome-paced tachpnea to detect dynamic hyperinflation. *Clin Physiol Funct Imaging* 2013; 33: 62–69.
27 Murariu C, Ghezzo H, Milic-Emili J, *et al*. Exercise limitation in obstructive lung disease. *Chest* The American College of Chest Physicians; 1998; 114: 965–968.

28 van der Wiel E, Postma DS, van der Molen T, *et al*. Effects of small airway dysfunction on the clinical expression of asthma: a focus on asthma symptoms and bronchial hyper-responsiveness. *Allergy* 2014; 69: 1681–1688.
29 Vermeulen F, Garcia G, Ninane V, *et al*. Activity limitation and exertional dyspnea in adult asthmatic patients: What do we know? *Respir Med* 2016; 117: 122–130.
30 Barreiro E, Gea J, Sanjuás C, *et al*. Dyspnoea at rest and at the end of different exercises in patients with near-fatal asthma. *Eur Respir J* 2004; 24: 219–225.
31 O'Donnell DE, Revill SM, Webb KA. Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
32 Lahaije A, van Helvoort H, Dekhuijzen R, *et al*. Can COPD Patients Who Hyperinflate During Daily Life Activities Be Identified by Laboratory Tests? *Respiration* 2013; 86: 237–242.
33 Lahaije AJMC, van Helvoort HAC, Dekhuijzen PNR, *et al*. Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV_1. *Respir Med* 2013; 107: 834–840.
34 Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. *Eur Respir J* 2002; 20: 254–259.
35 Berry M, Hargadon B, Morgan A, *et al*. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. *Eur Respir J* 2005; 25: 986–991.
36 Contoli M, Santus P, Papi A. Small airway disease in asthma. *Curr Opin Pulm Med* 2015; 21: 68–73.
37 Wagner EM, Liu MC, Weinmann GG, *et al*. Peripheral Lung Resistance in Normal and Asthmatic Subjects. *Am Rev Respir Dis* American Lung Association; 1990; 141: 584–588.
38 Ueda T, Niimi A, Matsumoto H, *et al*. Role of small airways in asthma: Investigation using high-resolution computed tomography. *J Allergy Clin Immunol* 2006; 118: 1019–1025.
39 Bourdin A, Paganin F, Préfaut C, Kieseler D, *et al*. Nitrogen washout slope in poorly controlled asthma. *Allergy* 2005; 61: 85–89.
40 Pisi R, Tzani P, Aiello M, *et al*. Small airway dysfunction by impulse oscillometry in asthmatic patients with normal forced expiratory volume in the 1st second values. *Allergy Asthma Proc*. 2013; 34: 14–20.

Supplementary material

Table S4.1 Relationship of degree of dynamic hyperinflation with questionnaire scores - total and subdomains

ACQ	r= 0.315 p=0.005
CCQ	r= 0.320 p=0.005
SGRQ	r= 0.324 p=0.004
LCADL	r= 0.385 p=0.001
SOBDA	r= 0.228 p=0.046
CCQ, subdomains	
Symptoms	r= 0.245 p= 0.032
Functional state	r= 0.194 p= 0.091
Mental state	r= 0.381 p= 0.001
SGRQ, subdomains	
Symptoms	r= 0.287 p= 0.011
Activities	r= 0.347 p= 0.002
Impact	r= 0.241 p= 0.034
LCADL, subdomains	
Self care	r= 0.362 p= 0.001
Domestic	r= 0.284 p= 0.012
Physical	r= 0.193 p= 0.093
Leisure	r= 0.315 p= 0.005

r: correlation coefficient by Spearman rank, with corresponding p-value. Definitions of abbreviations: ACQ = Asthma Control Questionnaire, CCQ = Clinical COPD Questionnaire, SGRQ = St. George Respiratory Questionnaire, LCADL = London Chest Activity of Daily Living questionnaire, SOBDA = Shortness of Breath with Daily Activities questionnaire.

Table S4.2 Relationship of FEV_1 and static hyperinflation with questionnaire scores

	FEV_1 %pred	RV/TLC %pred	FRC/TLC %pred
ACQ	r= 0.158 p= 0.169	r= 0.099 p= 0.393	r= 0.146 p= 0.204
CCQ	r= 0.055 p= 0.633	r= 0.039 p= 0.735	r= 0.041 p= 0.726
SGRQ	r= 0.142 p= 0.219	r= 0.200 p= 0.081	r= 0.185 p= 0.107
LCADL	r= 0.175 p= 0.128	r= 0.189 p= 0.104	r= 0.167 p= 0.148
SOBDA	r= 0.156 p= 0.142	r=0.254 p= 0.026	r= 0.284 p= 0.0012

r: correlation coefficient by Spearman rank, with corresponding p-value. Definitions of abbreviations: ACQ = Asthma Control Questionnaire, total score, CCQ = Clinical COPD Questionnaire, total score, SGRQ = St. George Respiratory Questionnaire, total score, LCADL = London Chest Activity of Daily Living questionnaire, total score, SOBDA = Shortness of Breath with Daily Activities questionnaire, total score, FEV_1 = forced expiratory volume in one second, FRC = function residual capacity, % pred = percentage of predicted value, RV = residual volume, TLC = total lung capacity.

Chapter

5

Targeting dynamic hyperinflation in moderate-to-severe asthma

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ABSTRACT

Background
Dynamic hyperinflation (DH) is highly prevalent in moderate to severe asthma, which may significantly impede activities of daily life. We hypothesized that DH in asthma is due to inflammation of large and small airways and can be reduced by systemic anti-inflammatory treatment. Therefore, we investigated the effect of systemic glucocorticoids on DH in moderate to severe asthma patients and explored the relationships between inflammatory markers and changes in DH.

Methods
In this randomized placebo-controlled trial we included 32 asthma patients on inhaled glucocorticoid therapy showing DH, defined by a ≥10% reduction in inspiratory capacity measured by standardized metronome-paced tachypnea test. Patients received either triamcinolone (80mg) or placebo intramuscularly. Before and 2 weeks after treatment, patients completed respiratory health questionnaires, had blood eosinophils and exhaled nitric oxide levels measured and underwent lung function and DH testing.

Results
After adjustment for potential confounders, DH was significantly reduced by 28.1% in the triamcinolone group, and increased by 9.4% in the placebo group (p=0.027).
In the triamcinolone-treated patients, the reduction in DH was greater in patients with higher blood eosinophils at baseline (r=-0.592, p=0.020) and tended to be associated with a reduction in blood eosinophils (r=0.412, p=0.127) and exhaled nitric oxide (r=0.442, p=0.099).

Conclusions
This exploratory study suggests that dynamic hyperinflation in asthma can be reduced by systemic anti-inflammatory treatment, particularly in patients with elevated blood eosinophils. This supports the hypothesis that dynamic hyperinflation in asthma is due to airway inflammation and should be considered an important target for treatment.

INTRODUCTION

Asthma is a heterogeneous airway disease affecting the large and small airways exhibiting a variety in clinical, functional and inflammatory characteristics[1, 2]. Recently, we have shown that dynamic hyperinflation is highly prevalent in moderate-to-severe asthma and is associated with poorer overall health and impaired daily life activity[3]. Because of this impact on important patient-related outcomes, dynamic hyperinflation might be a new target for treatment in moderate-to-severe asthma.

Dynamic hyperinflation is a well-known feature in COPD, but its importance in asthma has only recently been appreciated[4]. In COPD, dynamic hyperinflation is mainly due to abnormal lung mechanics caused by decreased elastic recoil, loss of alveolar attachments and collapse of small airways[5]. In asthma, however, the mechanisms underlying dynamic hyperinflation appear to be different. Studies have shown that asthma patients with systemic eosinophilic inflammation were more likely to show air trapping as compared to their non-eosinophilic controls[6], and in patients with severe asthma the degree of air trapping was shown to be significantly related to the level of exhaled alveolar nitric oxide[7]. These and other findings suggest that airway inflammation, particularly of the peripheral airways, may be the major contributor to reduced airway calibre, premature airway closure, air trapping and eventually dynamic hyperinflation in patients with asthma [8–10]. Conceivably, inflammation of the peripheral airways cannot be adequately controlled with inhaled glucocorticoids and therefore systemic anti-inflammatory therapy may be more suitable.

In the present study we hypothesise that in asthma patients dynamic hyperinflation is mainly caused by peripheral airway inflammation and can be reduced by systemic anti-inflammatory treatment. To that end, we investigated the effect of a single high dose of intramuscular triamcinolone on the degree of dynamic hyperinflation as measured by metronome-paced tachypnea (MPT) test in moderate-to-severe asthma patients on GINA step 4–5 treatment[11]. In addition, we explored the relationship between inflammatory markers (blood eosinophils and exhaled nitric oxide) and the change in dynamic hyperinflation.

METHODS

Study participants

Patients (age ≥18 years) with moderate-to-severe asthma, using GINA step 4–5 treatment (inhaled corticosteroids/long-acting β agonists and/or muscarinic antagonists) [11] for at least 6 months, were consecutively recruited from an outpatient clinic of a large teaching hospital in the Netherlands (Medical Centre Leeuwarden) between June 2016 and January 2018. All patients were nonsmokers or ex-smokers with ≤10 pack-years, had a body mass index (BMI) ≤30, had airway obstruction with a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ≤80% of predicted, and had stable respiratory disease prior to inclusion. A patient was considered to be atopic when showing allergen-specific IgE level of ≥0.35 IU/mL to any of the tested common respiratory allergens. Patients with concurrent respiratory disease, major comorbidities and preg-

nancy were excluded. The study was approved by the local medical ethics committee and all patients gave their written informed consent. The trial is registered at the Netherlands Trail Register under number NTR5873.

Study design

This study is part of a research programme on the role of dynamic hyperinflation in asthma.For the current randomised, double-blind placebo-controlled intervention study, patients were included only if the degree of dynamic hyperinflation measured by MPT was >10% and confirmed by a cardiopulmonary exercise test[3, 12–15]. At baseline patient characteristics were collected (table 5.1). Patients were then randomised 1:1 to one of the two treatment arms using a randomisation list with a block size of 6, with stratification for level of baseline blood eosinophils (threshold at 0.4×10^9 cells/L). Two weeks after the administration of the study medication, the effect on the degree of dynamic hyperinflation was measured by MPT test[16]. Before and 2 weeks after the administration of study medication patients completed a set of respiratory health questionnaires, had blood drawn and underwent lung function tests.

The administered study medication consisted of one single intramuscular injection of either 2 mL (40 mg/mL) triamcinolone acetonide (Kenacort-A® "40", Bristol-Myers Squibb, Utrecht, The Netherlands) or matched placebo (2 mL NaCL 0.9%). Study medication was prepared and blinded at the hospital pharmacy by an independent member of the pharmacy and administered to the patients by an independent nurse. Therefore participants, care providers and those assessing outcomes remained blinded till the study ended. During the study patients continued their own medication.

Study measurements

MPT-induced dynamic hyperinflation

The degree of dynamic hyperinflation was assessed after bronchodilation with 400 µg inhaled salbutamol[12, 14]. For detailed explanation of the MPT testing procedure, see the online supplementary material. The degree of dynamic hyperinflation was calculated as the difference between the post-MPT inspiratory capacity and baseline inspiratory capacity at rest.

Lung function and questionnaires

Spirometry and body plethysmography testing were performed after inhalation of 400 µg salbutamol[17, 18]. This was followed by an exhaled nitric oxide fraction (FeNO) measurement wherein subjects performed a slow expiratory vital capacity manoeuvre with a constant expiratory flow of 50 mL/s. Levels of FeNO were expressed as parts per billion (ppb)[19]. Symptoms were assessed using specific and general respiratory health questionnaires (table 5.2)[3].

Statistical analysis

Sample size

A sample size of 16 subjects per group was calculated to have 80% power (with α=0.05) to detect a difference in change in dynamic hyperinflation of 50% from pre- to post-intervention between the two groups[20].

Analysis
First, between-group differences at baseline were investigated by independent t-tests, Mann–Whitney U-tests or Fisher's Exact test.

Primary outcome: The primary outcome was the change in postbronchodilator MPT-induced dynamic hyperinflation from baseline to post-treatment measured as the difference between dynamic hyperinflation 2 weeks after study medication minus dynamic hyperinflation at baseline as percentage of dynamic hyperinflation at baseline. The difference in change in dynamic hyperinflation between the placebo and triamcinolone group was assessed by independent t-test, followed by linear regression analyses to adjust for potential confounders, i.e. variables with baseline differences ($p<0.1$) between the two groups (FeNO, BMI, FEV_1/FVC and functional residual capacity (FRC)/total lung capacity (TLC)).

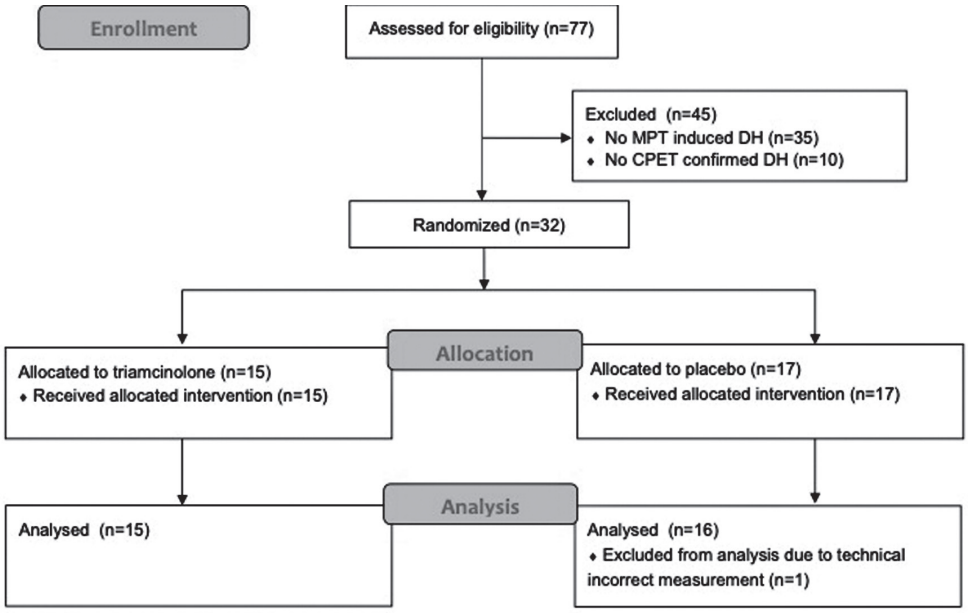
Secondary outcomes: As secondary outcome, we evaluated the treatment-induced effects on symptoms, lung function and inflammatory parameters for which we used paired t-tests or Wilcoxon rank tests (within-group differences) and independent t-tests or Mann–Whitney U-tests (between-group differences). Finally, the relationship between (change in) dynamic hyperinflation and (change in) inflammatory markers was assessed by Spearman rank correlation coefficients. All analyses were performed using SPSS software, version 24 (SPSS Inc., Armonk, NY, USA).

RESULTS

Randomisation

Seventy-seven patients were assessed for eligibility of whom 32 patients met the inclusion criteria and were enrolled in this study (see flowchart figure 5.1). 17 patients were randomised to placebo and 15 to triamcinolone treatment. Owing to a technically incorrect measurement, one patient randomised to placebo was excluded prior to the analyses.

Figure 5.1 Flowchart study eligibility



DH: dynamic hyperinflation, reduction in inspiratory capacity measured as the difference between inspiratory capacity at rest and inspiratory capacity following metronome-paced tachypnea; MPT: metronome-paced tachypnea; CPET: cardiopulmonary exercise testing.

Baseline characteristics

There were no significant differences between the two groups in sex, age or smoking history, but BMI tended to be slightly higher in the triamcinolone-treated patients compared to placebo (table 5.1). We found no difference in blood eosinophil levels, as expected after stratification; however, baseline FeNO was significantly lower in the triamcinolone group as compared to the placebo group (median (IQR)=21 (13–26) ppb versus 35 (22–92) ppb, p=0.036). There were no significant between-group differences in baseline lung function parameters, though we observed a trend towards higher FEV_1/FVC and lower FRC/TLC values in the triamcinolone- versus placebo-treated patients.

Effects of triamcinolone treatment

Effect on dynamic hyperinflation

At baseline, there was no significant difference in the degree of postbronchodilator MPT-induced dynamic hyperinflation between the groups (median (IQR)=600 mL (370–860 mL) versus 520 mL (330–730 mL) for triamcinolone versus placebo group, respectively, p=0.527). Two weeks after administration of the study medication, there was a reduction in the degree of dynamic hyperinflation of 23.2% (95% CI −46.6 to 0.25) compared to baseline in the triamcinolone group versus an increase of 4.8% (95% CI −17.9 to 27.5) in the placebo group (between-group difference p=0.087) (figure 5.2).

Table 5.1 Baseline characteristics

	Placebo	Triamcinolone	p-value
Subjects, n	16	15	
Sex, male, n (%)	9 (56)	9 (60)	1.000
Age, years#	65 (55-74)	63 (51-67)	0.452
Adult-onset (>18 yrs) asthma, n (%)	11 (69)	8 (53)	0.473
Atopic, n (%)	7 (44)	5 (33)	0.716
BMI, kg/m^2¶	25.2 ± 2.3	26.8 ± 2.8	0.080
Pack years#	0 (0-1.5)	0 (0-5)	0.830
Fluticasone equivalent, mg#	500 (500-1000)	500 (500-1000)	0.578
OCS dependent, n (%)	3 (19)	2 (13)	1.000
Exacerbations, preceding year#	2 (0-3)	2 (1-5)	0.493
Blood eosinophils, x 10^9/L^{-1}#	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.951
FeNO, ppb#	35 (22-92)	21 (13-26)	0.036
Pb FEV_1, % pred¶	66 ± 16	77 ± 17	0.235
Pb FEV_1/FVC, % pred¶	65 ± 12	72 ± 8	0.060
FRC/TLC, % pred¶	119 ± 14	111 ± 15	0.097
ACQ, total score#	1.5 (1.0-2.4)	1.3 (0.8-2.8)	0.874

BMI: body mass index; OCS: oral corticosteroids; FeNO: exhaled nitric oxide fraction; Pb: post-bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity; ACQ: asthma control questionnaire; IQR: interquartile range.
#: median (IQR); ¶: mean±SD

After adjustment for differences in baseline FeNO, one of the potential confounding factors, it appeared that the effect of triamcinolone treatment on dynamic hyperinflation was even stronger, with a reduction of 28.1% (95% CI −51.1 to −5.1) in dynamic hyperinflation in the group treated with triamcinolone and an increase of 9.4% (95% CI −12.9 to 31.6) in the placebo group (between-group difference p=0.027) (figure 5.3). Adjustment for other potential confounders at baseline (BMI, FEV_1/FVC and FRC/TLC) did not change this result (see figure S5.1 in the supplementary material).

Effect on inflammatory parameters, lung function and questionnaire scores
Blood eosinophil levels decreased and neutrophil levels increased after triamcinolone treatment, whereas these levels were unaffected by placebo (between-group differences for blood eosinophils p=0.011 and neutrophils p=0.006) (table 5.2).

With respect to lung function, treatment with triamcinolone significantly improved FEV_1 and FVC (between-group differences p≤0.004), but parameters of static hyperinflation and air trapping did not change in both treatment arms (between-group differences for FRC/TLC and residual volume (RV)/TLC p≥0.175).

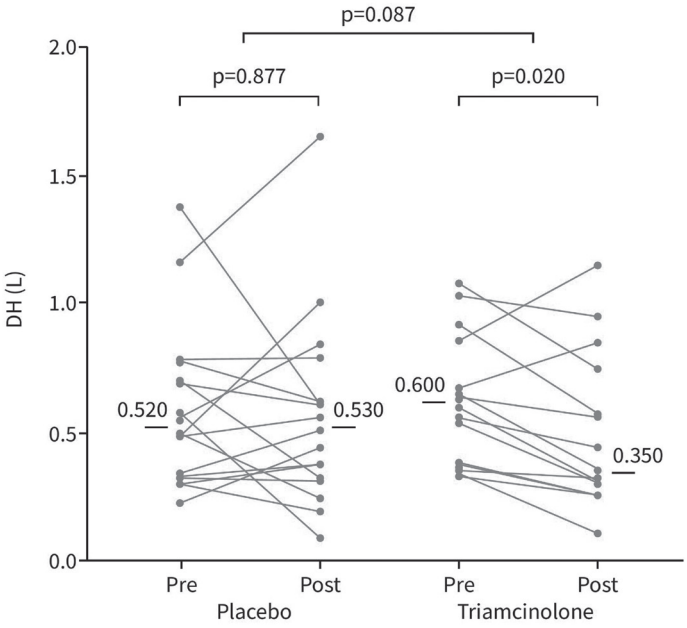
All questionnaires showed an improvement in total scores after triamcinolone as well as placebo treatment (table 5.2). There was a significantly larger improvement in the Clinical COPD Questionnaire score in the triamcinolone group as compared to placebo (p=0.030).

Table 5.2 Differences between triamcinolone and placebo treatment

	Triamcinolone (n=15)			Placebo (n=16)			
	Baseline	Post treatment	Within-group p-value *	Baseline	Post treatment	Within-group p-value *	Between-group p-value **
Blood eosinophils, x $10^9/L^{-1}$#	0.2 (0.1-0.3)	0.1 (0.1-0.2)	0.010	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.392	0.011
Blood neutrophils, x $10^9/L^{-1}$#	4.9 (3.4-6.1)	6.6 (5.7-8.6)	0.001	4.8 (4.1-6.1)	5.1 (4.5-6.3)	0.133	0.006
FeNO, ppb#	21 (13-26)	15 (12-22)	0.090	35 (22-92)	34 (20-70)	0.088	0.470
Pb FEV_1, % pred¶	77 ± 17	87 ± 20	0.001	66 ± 16	69 ± 19	0.333	0.004
Pb FVC, % pred¶	109 ± 19	116 ± 17	<0.001	106 ± 19	103 ± 17	0.215	<0.001
Pb FEV_1/FVC, % pred¶	72 ± 8	77 ± 11	0.010	65 ± 12	69 ± 14	0.017	0.654
TLC, % pred¶	114 ± 17	115 ± 17	0.100	110 ± 13	112 ± 16	0.199	0.379
RV, % pred¶	141 ± 41	132 ± 37	0.268	148 ± 32	152 ± 41	0.552	0.078
RV/TLC, % pred¶	113 ± 23	105 ± 22	0.233	124 ± 20	125 ± 22	0.796	0.175
FRC, % pred¶	138 ± 30	138 ± 28	0.932	142 ± 23	147 ± 32	0.242	0.423
FRC/TLC, % pred¶	111 ± 15	114 ± 14	0.730	119 ± 14	120 ± 16	0.609	0.800
ACQ, total score#	1.3 (0.8-2.8)	1.2 (0.5-1.8)	0.172	1.5 (1.0-2.4)	1.2 (0.5-2.2)	0.033	0.654
CCQ, total score#	1.5 (0.8-2.0)	0.8 (0.6-1.6)	0.018	2.0 (0.7-2.3)	1.6 (0.6-2.5)	0.876	0.030
SGRQ, total score#	28.9 (10.8-47.4)	19.9 (8.1-51.2)	0.078	38.3 (20.1-53.5)	31.8 (18.9-53.5)	0.918	0.281
LCADL, total score#	16 (15-30)	16 (14-24)	0.207	22 (15-35)	17 (15-28)	0.074	0.654
SOBDA, total score#	1.2 (1.0-3.1)	1.3 (1.0-1.8)	0.657	1.3 (1.1-2.1)	1.3 (1.0-1.6)	0.311	0.626

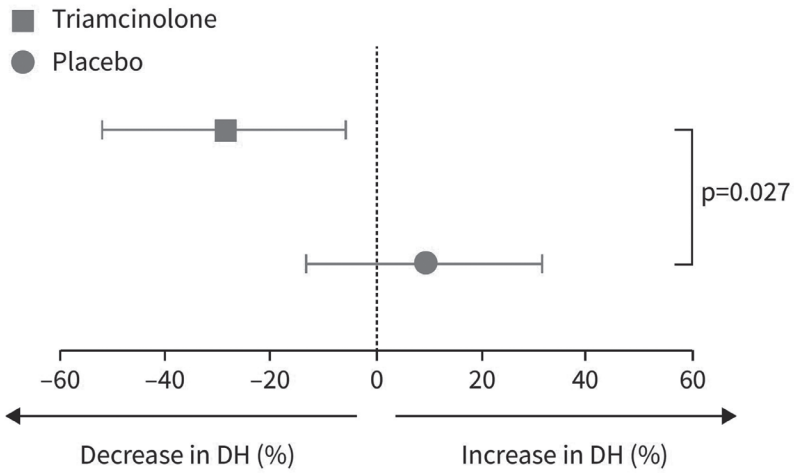
FeNO: exhaled nitric oxide fraction; Pb: post-bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; ACQ: Asthma Control Questionnaire, total score; CCQ: Clinical COPD Questionnaire, total score; SGRQ: St. George's Respiratory Questionnaire, total score; LCADL: London Chest Activity of Daily Living questionnaire, total score; SOBDA: Shortness of Breath with Daily Activities questionnaire, total score; IQR: interquartile range. *: within-group p-value: difference between baseline and post-treatment values of symptoms, lung function and inflammatory parameters measured separately for the triamcinolone group and placebo group; **: between group p-value: difference between the triamcinolone and placebo-induced changes in symptoms, lung function and inflammatory parameters. #: median (IQR); ¶: mean±SD.

Figure 5.2 Effect of treatment with intramuscular placebo or triamcinolone on dynamic hyperinflation



DH: dynamic hyperinflation, reduction in inspiratory capacity measured as the difference between inspiratory capacity at rest and inspiratory capacity following metronome-paced tachypnoea. Data are presented as median (interquartile ranges).

Figure 5.3 Change from baseline in dynamic hyperinflation (DH) after triamcinolone or placebo



The change measured as the difference between dynamic hyperinflation post-treatment minus dynamic hyperinflation at baseline as a percentage of dynamic hyperinflation at baseline and adjusted for differences in baseline exhaled nitric oxide fraction (FeNO). Data are presented as the adjusted mean and 95% confidence interval estimated from the regression model conditional on the mean value for the level of FeNO at baseline.

Dynamic hyperinflation and inflammation
At baseline, in the group as a whole, a higher degree of dynamic hyperinflation was related to higher baseline levels of blood eosinophils (r=0.446, p=0.012) and to higher FeNO (r=0.278, p=0.131). In addition, higher levels of blood eosinophils at baseline were associated with greater reductions in dynamic hyperinflation following treatment with triamcinolone (r=−0.592, p=0.020). In the triamcinolone-treated patients, the reduction in dynamic hyperinflation tended to be related to the reduction in blood eosinophils (r=0.412, p=0.127) and reduction in FeNO (r=0.442, p=0.099). Furthermore, in these patients the improvement in FEV_1 was shown to be associated with the reduction in dynamic hyperinflation (r=−0.603, p=0.017).

DISCUSSION

This study shows that the degree of dynamic hyperinflation in patients with moderate-to-severe asthma was significantly reduced by systemic anti-inflammatory treatment such as intramuscular glucocorticoids. This was independent of the degree of airway obstruction. Moreover, the decrease in dynamic hyperinflation was greater in patients with higher baseline blood eosinophils and tended to be related to a decrease in blood eosinophils and FeNO. These results support the hypothesis that dynamic hyperinflation is largely caused by airway inflammation and is therefore an important treatable trait, especially in patients with eosinophilic asthma.

Our study expands previous findings on the importance of dynamic hyperinflation in asthma and provides evidence that this disabling symptom is most prevalent in patients with elevated blood eosinophils and, unlike in patients with COPD, can be ameliorated by systemic anti-inflammatory treatment. We selected patients with dynamic hyperinflation and observed a higher age in this group as compared to regular asthma populations. In addition, the majority of our included patients with dynamic hyperinflation were male patients with an adult-onset non-atopic asthma and elevated blood eosinophils, suggesting that dynamic hyperinflation might be more prominent in the so-called "late onset eosinophilic asthma" phenotype. A few previous studies have investigated therapeutic interventions on dynamic hyperinflation in asthma. One unblinded study in 10 patients with moderate-to-severe allergic asthma showed that the degree of dynamic hyperinflation decreased with omalizumab treatment[21], whereas another study showed improvements in hyperinflation indices in a subgroup of severe asthma patients treated with benralizumab[22]. More recently, the degree of MPT-induced dynamic hyperinflation was found to be related to serum periostin levels in mild to severe asthma patients[23], again suggesting a role for inflammation in the development of dynamic hyperinflation in asthma. While the mechanisms underlying the development of dynamic hyperinflation in asthma merit further research, these and our results suggest that systemic anti-inflammatory treatments, including monoclonal antibodies, may have the potential to reduce impairments in daily life activities and improve exercise capacity by decreasing dynamic hyperinflation, at least in a subset of asthma patients.

The strengths of our study are the prospective randomised controlled design of the study, the selection of patients with exercise-test-confirmed dynamic hyperinflation, the inclusion of inflammatory parameters and the use of a solid systemic anti-inflam-

matory intervention. In this way, it was possible to demonstrate a clear relationship between dynamic hyperinflation and airway inflammation, as well as to provide a potential treatment option.

Our study has limitations as well. First, there appeared to be a suboptimal balance between the groups in asthma severity (lower FeNO and better lung function in the triamcinolone-treated group). This might create a risk of underestimation of the effects of triamcinolone, and therefore we adjusted for these variables. Second, the current study was not primarily designed to investigate the effect on symptoms or quality of life. Two weeks after trial medication we found a small improvement in favour of triamcinolone treatment for one symptom score (Clinical COPD Questionnaire), whereas the other symptom questionnaires improved equally in both treatment arms. A longer follow-up period will be necessary to evaluate whether reduction of dynamic hyperinflation indeed leads to an improvement in asthma symptoms and quality of life in the long term.

The mitigating effect of triamcinolone on dynamic hyperinflation supports a causal role for airway inflammation in the development of this phenomenon in asthma. Since the patients in our study were already treated with inhaled anti-inflammatory drugs, our findings suggest residual inflammation in the bronchial tree, which may occur in the central airways but certainly also in the peripheral airways, especially because the peripheral airways are known to be suboptimally reached by inhaled medications[24, 25]. Residual inflammation in the peripheral airways causing dynamic hyperinflation may also explain why many patients with severe eosinophilic asthma require systemic glucocorticoids or steroid-sparing biologics in addition to inhaled medication to control their disease. This is supported by studies showing that the anti-IL-5 monoclonal antibody mepolizumab improves indices of peripheral airway function[26] and computational modelling studies that confirm the impact of anti-inflammatory type 2 biologics on small airway calibre [27].

Our findings have clinical implications. The current study provides evidence that dynamic hyperinflation in asthma, a major contributing factor to asthma symptoms and impairment of daily life activities, can be treated with systemic anti-inflammatory treatments in addition to inhaled glucocorticoids and β-2 agonists. This differs from COPD, where dynamic hyperinflation is usually difficult to treat because it mostly results from irreversible narrowing and collapsibility of the small airways. Now that we know that in patients with Type 2 asthma dynamic hyperinflation can be reversed with systemic anti-inflammatory treatments, the long-term benefits on asthma control and quality of life have to be confirmed to further support that dynamic hyperinflation deserves a prominent place on the list of "treatable traits"[28].

In conclusion, this study shows that dynamic hyperinflation, a common and underestimated disability in patients with asthma, improves after treatment with systemic glucocorticoids. This suggests that in asthma, unlike in COPD, dynamic hyperinflation is at least partly caused by steroid-sensitive inflammatory processes in the airways. The improvement in dynamic hyperinflation was found to be most pronounced in patients with elevated blood eosinophils, suggesting that these patients will benefit most from systemic anti-inflammatory therapies like the novel anti-eosinophil biologics.

REFERENCES

1 Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, Chu HW. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am. J. Respir. Crit. Care Med. 1999*; 160: 1001–1008.

2 Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am. J. Respir. Crit. Care Med. 2008*; 178: 218–224.

3 van der Meer AN, de Jong K, Hoekstra-Kuik A, Bel EH, Ten Brinke A. Dynamic hyperinflation impairs daily life activity in asthma. *Eur. Respir. J. 2019*; 53: 1–8.

4 Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, López-Collazo E, Alvarez-Sala R. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *Am. J. Respir. Crit. Care Med. 2009*; 180: 506–512.

5 Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: Key concepts in modern respiratory physiology. Eur. Respir. J. 2005; 25: 186–199.

6 De Groot JC, Storm H, Amelink M, De Nijs SB, Eichhorn E, Reitsma BH, Bel EHD, Brinke A Ten. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res. 2016*; 2: 1–8.

7 van Veen IH, Sterk PJ, Schot R, Gauw SA, Rabe KF, Bel EH. Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. *Eur. Respir. J. 2006*; 27: 951–956.

8 Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral Lung Resistance in Normal and Asthmatic Subjects. *Am. Rev. Respir. Dis. American Lung Association; 1990*; 141: 584–588.

9 Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am. J. Respir. Crit. Care Med. American Public Health Association; 1996*; 154: 1505–1510.

10. Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, Matsuoka H, Jinnai M, Muro S, Chin K, Mishima M. Role of small airways in asthma: Investigation using high-resolution computed tomography. *J. Allergy Clin. Immunol. 2006*; 118: 1019–1025.

11 Global Initiative for Asthma, GINA. Global Strategy for Asthma Management and Prevention. 2015.

12 Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N. Simplified Detection of Dynamic Hyperinflation. *Chest 2004*; 126: 1855–1860.

13 Lahaije AJMC, Willems LM, van Hees HWH, Dekhuijzen PNR, van Helvoort HAC, Heijdra YF. Diagnostic accuracy of metronome-paced tachypnea to detect dynamic hyperinflation. Clin. Physiol. Funct. Imaging 2013; 33: 62–69.

14 O'Donnel DE, Revill SM, Webb KA. Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med. 2001*; 164: 770–777.

15 Lahaije AJMC, van Helvoort HAC, Dekhuijzen PNR, Vercoulen JH, Heijdra YF. Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV_1. *Respir. Med. 2013*; 107: 834–840.

16 Brinke A Ten, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: Effect of parenteral corticosteroids. *Am. J. Respir. Crit. Care Med. 2004*; 170: 601–605.

17 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. *Eur. Respir. J. 2005*; 26: 319–338.

18 Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W, Mitfessel H, Rasche K, Rolke M, Worth H, Jörres RA. Body plethysmography - Its principles and clinical use. *Respir. Med. 2011*; 105: 959–971.

19 Measurement O. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am. J. Respir. Crit. Care Med. 2005*; 171: 912–930.

20 Jones SR, Carley S, Harrison M. An introduction to power and sample size estimation The importance of power and sample size estimation for study design and analysis. *Emerg Med J 2003*; 20: 453–458.

21 Schäper C, Noga O, Koch B, Ewert R, Felix SB, Gläser S, Kunkel G, Gustavus B. Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. *J. Investig. Allergol. Clin. Immunol. 2011*; 21: 51–58.

22 Panettieri RA, Welte T, Shenoy K V., Korn S, Jandl M, Kerwin EM, Feijoo R, Barker P, Olsson RF, Martin UJ. Onset of effect, changes in airflow obstruction and lung volume, and health-related quality of life improvements with benralizumab for patients with severe eosinophilic asthma: Phase iiib randomized, controlled trial (SOLANA). J. Asthma Allergy 2020; 13: 115–126.

23 Asano T, Ohbayashi H, Ariga M, Furuta O, Kudo S, Ono J, Izuhara K. Serum periostin reflects dyna-

mic hyperinflation in patients with asthma. *ERJ Open Res. 2020;* 6: 00347–02019.
24 Tunon-de-Lara JM, Laurent F, Giraud V, Perez T, Aguilaniu B, Meziane H, Basset-Merle A, Chanez P. Air trapping in mild and moderate asthma: Effect of inhaled corticosteroids. *J. Allergy Clin. Immunol. 2007;* 119: 583–590.
25 Berry M, Hargadon B, Morgan A, Shelley M, Richter J, Shaw D, Green RH, Brightling C, Wardlaw AJ, Pavord ID. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. *Eur. Respir. J. 2005*; 25: 986–991.
26 Farah CS, Badal T, Reed N, Rogers PG, King GG, Thamrin C, Peters MJ, Seccombe LM. Mepolizumab improves small airway function in severe eosinophilic asthma. *Respir. Med. Elsevier; 2019*; 148: 49–53.
27 Foy BH, Soares M, Bordas R, Richardson M, Bell A, Singapuri A, Hargadon B, Brightling C, Burrowes K, Kay D, Owers-Bradley J, Siddiqui S. Lung computational models and the role of the small airways in asthma. *Am. J. Respir. Crit. Care Med. 2019;* 200: 982–991.
28 Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: Toward precision medicine of chronic airway diseases. *Eur. Respir. J. 2016;* 47: 410–419.

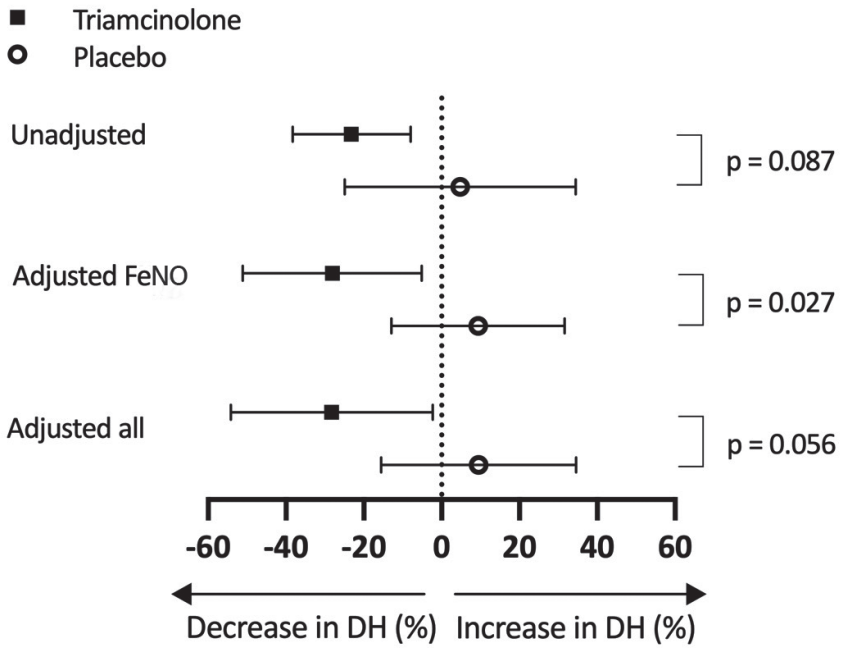
Supplementary material

PROCEDURE TO ASSESS DYNAMIC HYPERINFLATION

The presence and degree of dynamic hyperinflation (DH) persisting after maximal bronchodilatation was assessed by metronome-paced tachypnea test[1]. The test was performed after inhalation of 400 mcg Salbutamol.

Performing metronome-paced tachypnea test, subjects were seated, breathing through a mouthpiece connected to the spirometer (MasterScreen-PFT, Jaeger) and were instructed how to perform the inspiratory capacity (IC) manoeuvres. At the start of this test the baseline IC was measured as the mean of three acceptable IC manoeuvres while the patient was at rest. Subjects were then asked to breathe at a metronome-paced frequency of twice the resting breathing rate for 20 seconds and immediately afterwards an IC manoeuvre was performed[2]. The procedure was repeated after subjects had returned to their resting breathing level. Subjects were encouraged to maintain a stable tidal volume. DH was calculated as the difference between the IC measured during increased pacing and the IC at rest. A decrease in IC of ≥10% was considered as DH[2, 3].

Figure S5.1 Change from baseline in dynamic hyperinflation after triamcinolone or placebo



The change measured as the difference between DH post-treatment minus DH at baseline as a percentage of DH at baseline and adjusted for differences in baseline FeNO, BMI, FEV_1/FVC and FRC/TLC. Data are presented as the adjusted means and 95% confidence intervals estimated from the regression model and conditional on the potential confounders being centered around their mean values.

REFERENCES

1 Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N. Simplified Detection of Dynamic Hyperinflation. *Chest 2004*;126:1855–1860.
2 Lahaije AJMC, Willems LM, van Hees HWH, Dekhuijzen PNR, van Helvoort HAC, Heijdra YF. Diagnostic accuracy of metronome-paced tachypnea to detect dynamic hyperinflation. *Clin Physiol Funct Imaging 2013*;33:62–69.
3 Lahaije A, van Helvoort H, Dekhuijzen R, Heijdra Y. Can COPD Patients Who Hyperinflate During Daily Life Activities Be Identified by Laboratory Tests? *Respiration 2013*;86:237–242.

Chapter

6

Overuse of oral corticosteroids in asthma is often underdiagnosed and inadequately addressed

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ABSTRACT

Background
Overuse of oral corticosteroids (OCS) is associated with serious adverse effects. It is currently unknown what proportion of asthma patients regularly use these drugs, nor whether they are optimally treated by specialists to minimize their use.

Objective
To investigate 1) the prevalence of patients requiring ≥2 courses or maintenance use of OCS (i.e. frequent users), 2) their use of inhaled corticosteroids, 3) and who prescribed their asthma medications.

Methods
We analysed OCS prescription data (Dutch IQVIA Prescription Database) focusing on adult patients receiving asthma medication between March 2017 and March 2018 (focus year). An OCS course was defined as ≥20mg prednisolone equivalent for 3 to 28 days; maintenance OCS as 2.5 to17.5 mg/day for >28 days. Prescribers were classified as specialist or general practitioners.

Results
Of 182,849 adults taking asthma medications, 77.8% had not received a prescription for OCS and 7.2 % of patients were frequent OCS users: 2.6% received ≥2 OCS courses and 4.6% were on maintenance OCS. Of the frequent OCS users 45.8% received only low or medium doses (<500 µg/day) of inhaled corticosteroids. Within the preceding 3 years (2014-2017), 51.1% and 34.3% of patients prescribed ≥2 OCS courses or maintenance OCS, respectively, had received prescriptions from a general practitioner without medication adjustments by a specialist.

Conclusion
This prescription-fill study shows that 7.2% of Dutch asthma patients were overexposed to OCS, of which only about half used adequate doses of inhaled corticosteroids, and 40.3% had not received specialist intervention within the previous 3 years. This suggests that OCS overuse is often underdiagnosed and inadequately addressed.

INTRODUCTION

Oral corticosteroids (OCS) are powerful anti-inflammatory drugs and 25-40% of all OCS prescriptions are attributable to respiratory conditions, especially airway diseases [1–3]. For asthma this includes short OCS courses to treat acute exacerbations, as well as maintenance OCS therapy in severe asthma patients[4]. Despite their benefits, OCS have well-known long-term side effects[5–8]. While recognizing the potential side effects of OCS in high-risk patients, many health care providers seem to assume that short courses of OCS are innocuous[9]. However, there is growing evidence that the risk of side effects is related to the cumulative lifetime OCS exposure[10,11] and that not only maintenance OCS treatment, but also repeated short OCS courses have significant impact on steroid-induced morbidity in asthma[12]. The latter is associated with increases in non-asthma related healthcare use and costs, but above all it poses a significant burden to patients [13,14].

Patients are entitled to good asthma care, which includes avoiding unnecessary exposure to OCS [4,15]. This is increasingly achievable through the development of new monoclonal antibodies targeting type 2 inflammation 16 which have strong corticosteroid-sparing properties, and have hugely improved outcomes for many patients with severe asthma [17–21]. Nevertheless, OCS are widely prescribed [22,23] and many asthma patients are exposed to potentially toxic cumulative doses[24,25], underlining the need for strategies to prevent avoidable harm.

To develop a model of "corticosteroid stewardship" with targeted interventions aimed at reducing inappropriate OCS prescribing behaviour 9, it is important to know the proportion of patients who are exposed to high doses of OCS, whether these patients are treated with adequate doses of inhaled corticosteroids (ICS), and whether they are seen regularly by an asthma specialist for adjustment and optimization of asthma therapy.

To that end, we analysed Dutch dispensing data to investigate the prevalence of OCS users in asthma patients, as well as the involvement of specialists and general practitioners (GPs) in the prescription of OCS in patients with asthma of different levels of severity. In addition, we estimated the contribution of OCS course prescriptions versus maintenance OCS use prescriptions to cumulative OCS exposure in these patients.

METHODS

Data source

This national retrospective cohort study included data obtained from IQVIA's Real-World Data Longitudinal Prescription database (LRx, Amsterdam, The Netherlands) from March 2017 to March 2018 (focus year). The database provided a coverage of approximately 75% of all prescriptions dispensed in the Netherlands, represented by retail pharmacies, hospital pharmacies and dispensing GPs (n=1430). This database is generally representative for the Netherlands and contains coded patient prescription pick up data from pharmacy records, including patient (e.g., sex, age), dispensing (e.g., pharmacy, pres-

cription date), medication (e.g., name, dose, strength, therapy duration), and prescriber information[26]. For this study, records (e.g., patients) with dispensed prescriptions of appropriate asthma medication were selected (see next section).

Patient selection
First, the records of the total pharmacy database were restricted to appropriate R03 medications for airways diseases (inhaled corticosteroids (ICS), long-acting β-agonists (LABA), muscarinic antagonists (LAMA), ICS/LABA, LABA/LAMA), (Anatomical Therapeutic Chemical (ATC) codes R03; system of alphanumeric codes developed by the World Health Organisation for the classification of drugs, subgroup R03 is part of the anatomical group R Respiratory system). Secondly, patients ≥18 years, who received ≥2 prescriptions of ICS (e.g., single ICS or ICS/LABA) for at least 4 months of therapy duration were selected. This 4-month period could have started before the focus year. Patients with single LABA, LAMA or LABA/LAMA use and patients >50 years using ICS without having prescriptions for biologics or allergy medication were excluded to limit the potential influence of COPD on OCS prescriptions. In addition, an average prednisolone equivalent dose of ≥30mg for ≥28 days was considered as medication use for other chronic diseases (for example, sarcoidosis, vasculitis, other interstitial lung diseases) and patients receiving these were therefore excluded. In this context, patients with the co-medication methotrexate were also excluded. Patients who met the above inclusion criteria were defined as asthma patients on ICS (Figure 6.1).

Inhaled and oral corticosteroids use
The dose strengths for all ICS molecules were converted to fluticasone equivalent. The average daily dose was calculated for each 90-day period for up to 1 year (focus year) using moving averages. Subsequently, patients were classified into low, medium and high dose ICS users based on the GINA treatment steps [27].

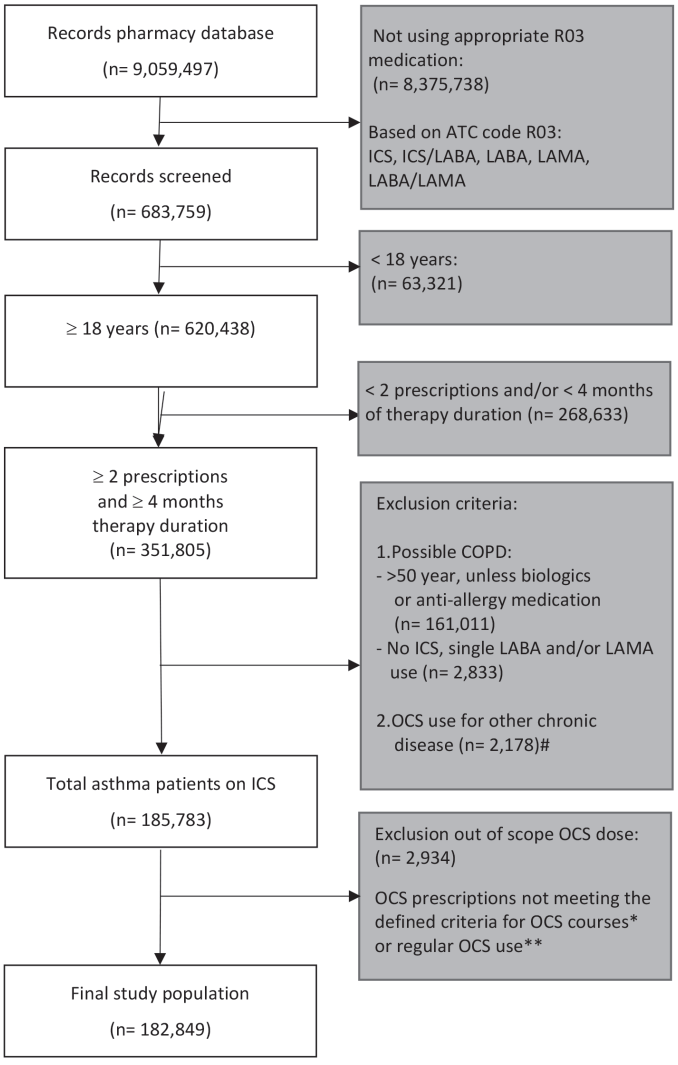
The use of OCS was determined by the drug name on the prescription records and the average daily dose per prescription was calculated as an average of all OCS prescription in the focus year. Subsequently, patients were classified as non-users, course-only patients and those on maintenance use. OCS courses were defined as a prescription of ≤28 days and average daily dose ≥20mg prednisolone equivalent. Maintenance OCS therapy was defined as a prescription of >28 days (with a minimum of 2 prescriptions) and an average daily dose of ≥2.5mg to ≤17.5mg prednisolone equivalent. Treating patients with an OCS dose of ≥20mg for ≥28 days is uncommon in asthma treatment in the Netherlands. Based on the number of prescription days and the average daily dose per prescription, all remaining combinations of OCS dose and duration were considered as out of scope and were excluded (Figure 6.1).

Finally, for each patient the cumulative OCS dose in the focus year was calculated by multiplying the number of prescription days with the average daily dose per prescription day. To assess the relative contribution of the patients on courses versus those on maintenance therapy to the total OCS exposure, we calculated the total OCS dose in the focus year for this population as the sum of the yearly cumulative doses of all patients included.

Prescriber information

For each patient we classified which prescriber made the prescription of asthma medication. In the focus year, if any prescription (i.e. ICS, OCS or other asthma medication) was found from a pulmonologist, Ear-Nose-Throat (ENT) specialist or allergist, the prescriber was set to specialist. Otherwise, the prescriber was set to whatever other physician was

Figure 6.1 Patient flowchart



ATC, Anatomical therapeutic chemical; code R03, drug claim for obstructive lung disease; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonists; OCS, oral corticosteroids. #OCS use for other chronic disease defined as a prednisolone equivalent dose of ≥30 mg for >28 days or comedication methotrexate. *OCS course defined as a prescription of ≤28 days and daily dose ≥20 mg prednisolone equivalent. **Maintenance OCS use defined as a prescription of >28 days (with a minimum of 2 prescriptions) and a daily dose of ≥2.5 mg to ≤17.5 mg prednisolone equivalent.

found, which in all cases was the GP. Likewise, this was extended up to 1, 2 and 3 years prior to the focus year.

Dutch healthcare system
In the Netherlands the healthcare system is managed by the government and supplemented by private insurance companies, with residents required to take out health insurance coverage to access healthcare services. To visit a specialist the patient needs a referral from a GP. In addition, the prescription of biologics in the treatment of severe asthma is only performed by asthma specialists, who in the vast majority of cases will be pulmonologists and in a few cases allergists or ENT specialists.

Statistical analyses
The data were evaluated descriptively. First, we calculated the proportion of patients with ≥2 OCS courses or maintenance OCS (i.e. frequent users) and analysed the proportion of patients using low, medium and high dose ICS [27]. Then we investigated the contribution of specialists and GPs in the prescribing of asthma medications, in the focus year and up to 1, 2 and 3 years before the focus year. We also described the median cumulative OCS dose (with interquartile range) among patients receiving OCS courses or maintenance OCS therapy in the focus year, and subsequently calculated the relative contribution of these patient groups to the total OCS exposure on population level. All data selection and validation steps were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and descriptive analyses performed using Microsoft Excel 2003 and SPSS version 24 (IBM, Armonk, NY).

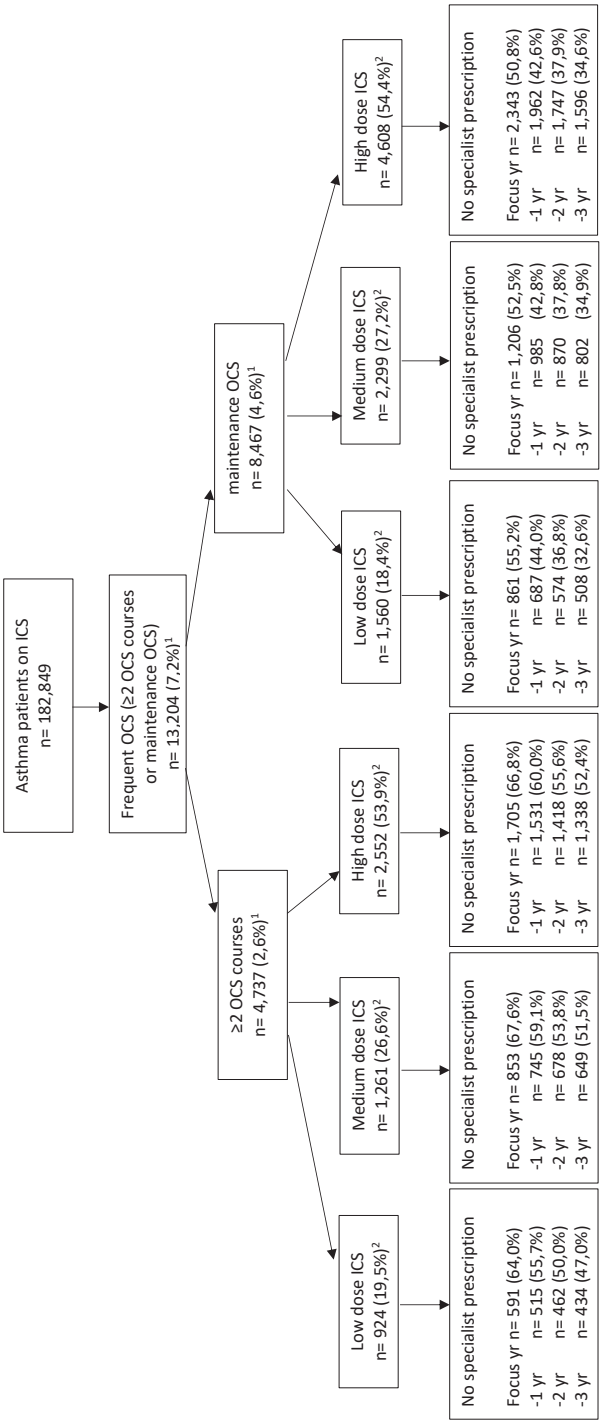
RESULTS

Study population
Figure 6.1 shows patients' inclusion flowchart. From a total of 9,059,497 records in the IQVIA prescription database, we selected 185,783 patients on asthma medication (≥18 year and ≥2 prescriptions of ICS for at least 4 months of therapy duration). Of this group, 2,934 patients were excluded due to out-of-scope OCS doses, i.e. OCS prescriptions that did not meet the defined criteria for OCS courses or maintenance OCS use.

The final study population consisted of 182,849 adult patients on asthma medication. The median age was 51 years (inter quartile range (IQR) 39-66), 59.4% were female and the majority (75.6%) were treated with medium to high dose ICS[27].

Of the 182,849 enrolled patients, 40,679 (22.2%) had received at least one OCS prescription in the focus year. Of these, 8,467 (4.6%) patients were classified as maintenance OCS users, with a median daily dose of 10mg prednisolone equivalent (IQR 7.3-12.9mg). The remaining 32,212 (17.6%) patients were labelled as course-only patients, who received a median of 1 OCS course (range 1-7) in the focus year.

Figure 6.2 ICS use and specialist involvement in the management of frequent OCS users



ICS, Inhaled corticosteroid; low, 100-250 mcg fluticasone equivalent; medium, >250-500 mcg fluticasone equivalent; *high*, >500 mcg fluticasone equivalent; OCS, oral corticosteroid. [1]Proportion of all patients with asthma on ICS (n = 182,849). [2]Proportion within ≥2 OCS courses and maintenance OCS.

In the focus year, 83.9% of patients did not receive any prescription of a specialist. Of 16.1% who did, 94.1% was attributable to pulmonologists, 4.8% to ENT physicians and 1.2% to allergists.

Proportion of patients with ≥2 OCS courses or maintenance OCS use
Figure 6.2 shows ICS use and specialist involvement in the management of frequent OCS users. We found that 13,204 (7.2%) of the total group of asthma patients had either received ≥2 courses of OCS (2.6%) or maintenance OCS therapy (4.6%) in the focus year. Of the 4,737 patients with ≥2 courses of OCS, only 53.9% had used high ICS doses in the focus year, and 51.1% had not received any prescription for asthma medications from an asthma specialist up to 3 years before the focus year. Of the 8,467 patients on maintenance OCS therapy 54.4% used high doses of inhaled corticosteroids, and still 34.3% had not received a prescription from a specialist over the previous 3-year period.

Contribution of OCS courses versus maintenance OCS to (high) OCS exposure
The cumulative dose of OCS in the focus year was the highest in the group treated with maintenance OCS therapy (median 760 mg prednisolone equivalent/person, IQR 450-1680 mg/person) as compared to the group with ≥2 OCS courses (median 400mg/person, IQR 300-449 mg/person) and group with 1 course (median 210, IQR 150-210). These cumulative doses did not substantially differ between the ICS low, medium and high dose groups (data not shown).

Although the group of patients using maintenance OCS therapy was relatively small (i.e., 4.6% of all patients included in the study, and 20.8% of all patients who had used any OCS during the focus year), this group contributed most (i.e., 56.8%) to the total OCS exposure on a population level. Patients receiving one or ≥2 OCS courses contributed 32.6% and 10.6%, respectively, to the total OCS exposure on a population level in the focus year.

DISCUSSION

The present study using pharmacy dispensing data from 182,849 adult asthma patients in the Netherlands, shows that 22.2% of patients received at least one prescription for OCS during the focus year; 2.6% of patients were exposed to ≥2 OCS courses and 4.6% to maintenance OCS therapy. The majority (≥57%) of patients with frequent OCS use had their OCS prescribed by a GP in the focus year. About half of patients with frequent OCS courses and one third of patients on maintenance OCS had not been prescribed any asthma medication by a specialist up to 3 years before the focus year, suggesting that these patients were treated in primary care, without specialist supervision. Maintenance OCS therapy contributed most to the cumulative OCS dose, both at patient and population level. However, OCS dose attributable to courses still accounted for about 40% of total OCS exposure and this pattern did not substantially differ between different levels of asthma severity.

Consistent with previous studies, we found that frequent OCS use in asthma patients is common, although there are differences in reported prevalence varying from 3.6 to 62% [25,28]. We distinguished between frequent OCS courses and maintenance therapy. This showed that while OCS maintenance therapy contributed most to the cumulative OCS dose, the contribution of frequent courses to OCS exposure was also significant. The harmful effects of maintenance OCS are widely recognised, but previous studies have made it clear that even short courses for the treatment of asthma exacerbation are not without harm [9,12,24]. Our data substantiates the impact of these frequent courses and highlights the need to pay extra attention to exacerbation management. Our study also showed that a large proportion of asthma patients received prescriptions for asthma medications including OCS exclusively from their GP. This is in line with the findings of other studies conducted in Europe and Australia [24,25,29]. In Australia 76% of OCS prescriptions were provided by GPs[24], which is not surprising given the better geographic availability of the GP in case of acute asthma exacerbations. Our results confirm and extend previous findings not only by providing a clearer insight into the involvement of specialists and GPs in the prescription of OCS, but also into the contribution of frequent courses and maintenance OCS to the total OCS exposure.

The strength of this study lies in the use of the IQVIA's Real-World Data Longitudinal Prescription database. This database has a coverage of 75% of all prescriptions dispensed in the Netherlands, which makes the results of this study highly representative at a national level for asthma patients. However, it remains challenging to include only patients with OCS use related to asthma. For this reason, we used a reserved approach towards the inclusion of patients with the risk of underreporting of the actual number of the asthma population. We excluded all patients not using ICS. It may be possible that OCS overuse in these asthmatics is even higher. Furthermore, we excluded patients >50 years who otherwise met our inclusion criteria if they were not taking a biologic or anti-allergy medication in addition to their ICS. This was done in an attempt to exclude the potential influence of COPD on OCS prescriptions. In doing so, we may have unfairly excluded older non-allergic asthma patients. Another limitation of this study might be the difficulty to distinct between OCS courses for acute situations and maintenance OCS use. We have proposed certain definitions of OCS use, but we are also well aware that this might be arbitrary. With these definitions, the patients with maintenance OCS therapy contributed most to the OCS cumulative dose (56.8%) as compared to the group with OCS courses (43.2%). However, the contribution of OCS courses could potentially be underestimated by missing the temporally increased maintenance OCS dose in an acute exacerbation or extra OCS courses on top of the maintenance OCS therapy.

Remarkably, our Dutch dispensing data showed that even up to 3 years before the focus year both patients with frequent OCS courses and maintenance OCS had not been prescribed any asthma medication by a specialist. This suggests that there has been no specialist intervention in these patients for a long period of time, potentially inadequate assessment of asthma control, adherence to ICS, and adjustment of ICS dose while high-risk OCS doses were frequently prescribed. Apparently, there are many patients with uncontrolled asthma who are not seen by an asthma specialist. This is supported by previous studies in other countries in which a substantial part of more severe asthma

patients is managed without asthma specialist involvement [24,25,29,30]. It is important to identify these uncontrolled asthma patients regardless of where they are being managed, as they are at risk for OCS toxicity and deserve to be treated with adequate doses of ICS and, if indicated, with add-on biologics according to current guideline recommendations.

Our study provides a clear insight into the high prevalence of OCS prescriptions in asthma patients. Both GPs and specialists seem to prescribe these drugs too often and too easily. This may be due to unnoticed repeat prescriptions of OCS, ignorance of the toxicity of short OCS courses, and lack of awareness of novel treatment options by both physicians and patients [31]. Yet, this is not surprising. For many years OCS was the main treatment for uncontrolled asthma by effectively suppressing airway inflammation leading to better asthma control and reduction of exacerbations and hospitalisations [32]. However, we can no longer take for granted the serious side-effects and co-morbidities associated with long-term and even short-term OCS [11,33,34]. New biologics effectively target type 2 inflammation resulting in a significant reduction of exacerbations, fewer OCS courses, and an eminent OCS sparing effect in patients on maintenance OCS therapy [17–21]. It is also important to identify patients with uncontrolled asthma without proven type 2 airway inflammation. While these patients may not benefit from OCS, this may go unnoticed if there is an inappropriate assessment of medication response and asthma control. Unfortunately, still a substantial proportion of these patients receive frequent OCS courses or even maintenance OCS therapy without any effect on their symptoms. Such inappropriate prescribing of OCS is also reflected in our findings, that half of the patients who were frequently exposed to OCS courses and even to maintenance OCS therapy used only low doses of ICS.

Global guidelines recommend only a short course of OCS for severe asthma exacerbations while low dose maintenance OCS should now only be given as a last resort in uncontrolled asthma patients who have failed treatment with biologics [4]. So, we have to rethink our approach towards prescription of maintenance OCS use and frequent OCS courses in asthma exacerbation management. To address this issue, it is essential to create awareness and understanding about the OCS burden among GPs and specialists to make a major difference in patient outcomes and healthcare costs. And even more importantly to educate, involve and empower patients in the treatment of their asthma. Based on our findings we strongly encourage the implementation of new protocols and tools, such as alert systems flagging OCS overuse or asthma attack risk scales, that can be used in daily practice for physicians and patients to reduce the OCS burden in asthma patients [35,36].

In conclusion, our study shows that a substantial proportion of asthma patients in the Netherlands were exposed to frequent OCS courses or maintenance OCS therapy. Half of the patients did not use ICS in sufficient doses and 40.3% had not undergone intervention of an asthma specialist for years. This suggests that OCS are often incorrectly prescribed, both by specialists and GPs. Exposure of asthma patients to OCS could be drastically reduced if work-up and therapy adjustment protocols are implemented and better education is provided about new targeted treatments. These measures will ultimately minimize the dreaded long-term side effects of OCS therapy.

REFERENCES

1 Van Staa TP, Leufkens HGM, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. *QJM - Mon J Assoc Physicians*. 2000;93:105–11.
2 Bénard-Laribière A, Pariente A, Pambrun E, Bégaud B, Fardet L, Noize P. Prevalence and prescription patterns of oral glucocorticoids in adults: A retrospective cross-sectional and cohort analysis in France. *BMJ Open*. *2017*;7:1–7.
3 Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: A cross sectional study. *Br Med J*. *1996;*313:344–6.
4. Reddel HK, Bacharier LB, Bateman ED, Boulet L-P, Brightling C, Brusselle G, et al. *Global Initiative For Asthma*. *2021*. p. 1–217.
5 Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med*. *2009*;103:975–94.
6 Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: Cross-sectional data from the optimum patient care research database and the british thoracic difficult asthma registry. *Thorax*. *2016*;71: 339–46.
7 Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. *2015*; 136:1488–95.
8 Zazzali JL, Broder MS, Omachi TA, Chang E, Sun GH, Raimundo K. Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use. *Allergy Asthma Proc*. *2015*;36: 268–74.
9 Wallace BI, Waljee AK. Burst Case Scenario: Why Shorter May Not Be Any Better When It Comes to Corticosteroids. *Ann Intern Med*. *2020*;173:390–1.
10 Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Jie JLZ, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: Long-term observational study. *J Asthma Allergy*. *2018*;11:193–204.
11 Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. *2018*;141:110-116.e7.
12 Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: Striking the balance between efficacy and safety. *Eur Respir Rev*. *2020*;29.
13 Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: A health economic analysis. Respir Res. 2017;18:1–8.
14 Voorham J, Xu X, Price DB, Golam S, Davis J, Zhi Jie Ling J, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy Eur J Allergy Clin Immunol*. *2019*;74:273–83.
15 Menzies-Gow A, Canonica GW, Winders TA, Correia de Sousa J, Upham JW, Fink-Wagner AH. A Charter to Improve Patient Care in Severe Asthma. Adv Ther. 2018;35:1485–96.
16 Fahy J V. Type 2 inflammation in asthma-present in most, absent in many. *Nat Rev Immunol*. *2015*; 15:57–65.
17 Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: A systematic review. *Chest*. *2011*;139:28–35.
18 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *N Engl J Med*. *2014*;371:1189–97.
19 Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. *2015*;3: 355–66.
20 Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med*. *2017*;376:2448–58.
21 Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Engl J Med*. *2018*;378:2475–85.
22 Tran TN, King E, Sarkar R, Nan C, Rubino A, O'Leary C, et al. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *Eur Respir J*. *2020*;55.
23 Tran TN, MacLachlan S, Hicks W, Liu J, Chung Y, Zangrilli J, et al. Oral Corticosteroid Treatment Patterns of Patients in the United States with Persistent Asthma. *J Allergy Clin Immunol Pract*. *2021*; 9:338-346.e3.
24 Hew M, McDonald VM, Bardin PG, Chung LP, Farah CS, Barnard A, et al. Cumulative dispensing of high oral corticosteroid doses for treating asthma in Australia. *Med J Aust*. *2020*;213:316–20.
25 Ekström M, Nwaru BI, Hasvold P, Wiklund F, Telg G, Janson C. Oral corticosteroid use, morbidity and mortality in asthma: A nationwide prospective cohort study in Sweden. *Allergy Eur J Allergy Clin Immunol*. *2019*;74:2181–90.

26 Janssen CA, Oude Voshaar MAH, Vonkeman HE, Krol M, van de Laar MAFJ. A retrospective analysis of medication prescription records for determining the levels of compliance and persistence to urate-lowering therapy for the treatment of gout and hyperuricemia in The Netherlands. *Clin Rheumatol. 2018*;37:2291–6.
27 Global Initiative. GLOBAL STRATEGY FOR Global Strategy for Asthma Management and Prevention. *Glob Initiat Asthma. 2019*;
28 Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med. 2020*; 201:276–93.
29 Lommatzsch M, Sauerbeck IS, Wilmer C, Taube C. Oral corticosteroid prescription for asthma by general practitioners: A three-year analysis in Germany. *Respir Med. 2021*;176:106242.
30 Hidden in UK Primary Care. *J Allergy Clin Immunol Pract. 2021*;9:1612-1623.e9.
31 Song W-J, Won H-K, Lee SY, Park H-K, Cho YS, Chung KF, et al. Patients' experiences of asthma exacerbation and management: a qualitative study of severe asthma. *ERJ Open Res. 2021*;7:00528–2020.
32 Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev. 2001*;
33 Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Tran TN. Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma. J Allergy Clin Immunol Pract. 2017*;5:1050-1060.e9*.
34 Taube C, Bramlage P, *Hofer* A, Anderson D. Prevalence of oral corticosteroid use in the German severe asthma population. ERJ Open Res. 2019;5:1–10.
35 Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax. 2021;1–4.
36 Murphy KR, Chipps B, Beuther DA, Wise RA, McCann W, Gilbert I, et al. Development of the Asthma Impairment and Risk Questionnaire (AIRQ): A Composite Control Measure. *J Allergy Clin Immunol Pract. 2020*;8:2263-2274.e5.

Chapter

7

General discussion

AIM OF THE THESIS

The overarching aim of this thesis was to focus on several key questions related to common and neglected treatable traits in adult asthma. First, we evaluated the possible benefits of a systematic multidisciplinary patient assessment, taking into account several treatable traits, in a specialised severe asthma centre. Further, we provided an overview on the emerging relationship between asthma and nasal polyposis, one of the most important traits, to gain insight in the epidemiology, pathophysiology, impact on asthma control and clinical assessment as well as the treatment options. Next, we evaluated the role and treatment of a possible new high impact treatable trait in asthma. Namely, dynamic hyperinflation in moderate-to-severe asthma. Lastly, we explored the overuse of oral corticosteroids (OCS) as an important treatable trait. We estimated the prevalence of OCS overuse in asthma patients in the Netherlands, and investigated whether these patients were treated with adequate doses of inhaled corticosteroids (ICS) and whether they regularly visited an asthma specialist to minimize excessive OCS use.

MAIN FINDINGS AND THEIR RELATION TO PREVIOUS LITERATURE

A systematic multidisciplinary approach is indispensable

In patients with difficult-to-treat asthma, a wide range of contributing factors may play a role, such as incorrect diagnosis, under- or untreated comorbidities, poor compliance and continuous exposure to triggers, leading to uncontrolled asthma despite high intensity asthma treatment[1]. Because of this complexity, it is often too time-consuming for clinicians to accurately assess these patients during a short routine consultation. However, a thorough assessment is very important, not only to prevent patients from being treated unnecessarily with OCS but also to assess whether they suffer from truly severe asthma and are therefore eligible for treatment with expensive biologics[2]. As a consequence, a systematic approach, preferably multidisciplinary[3], is recommended by all international severe asthma guidelines[4–7]. The importance of such an asthma assessment is commonly recognized, but the implementation in daily practice remains challenging.

In **chapter 2**, we prospectively evaluated the possible benefits of a 1-day systematic multidisciplinary assessment, resulting in a personalised management plan carried out by the referring pulmonologist, in patients with uncontrolled asthma despite standard asthma therapy in a specialised severe asthma centre. This assessment included an evaluation by an asthma specialist, physiotherapist, clinical psychologist and specialised asthma nurse. The effect of a personalised management plan on asthma control, quality of life and healthcare use was evaluated after 1 year in 40 patients. Compared to the year preceding the assessment both asthma control and quality of life significantly improved in the 12 months' follow up. Regarding healthcare use, the number of exacerbations, emergency room visits and hospital admissions were reduced by 54%, 57% and 43% after 1 year. These results suggest that a 1-day systematic multidisciplinary assessment is beneficial in uncontrolled asthma patients.

Following the publication of our work[8], several systematic asthma assessment models have been developed and published that prove their added value in asthma care[9]. Hew and colleagues conducted a review comparing various models of patient selection, service configuration, and assessment protocols for difficult-to-treat asthma [8, 10–12]. This review also included our extensive 1-day assessment. The other models in which a systematic assessment was delivered ranged from a "total care" model with an initial assessment ending in ongoing treatment in a specialised asthma centre to a model with an initial assessment ending in time-limited treatment in a specialised asthma centre. Although the design of the other three systematic asthma assessments differed, they all showed comparable results with fewer exacerbations, improved asthma control and quality of life, and reduced healthcare use.

The limitation of all these studies is the lack of comparison with standard care in a randomized controlled trial (RCT). Interestingly, in 2020 an RCT was published in which usual care was compared to targeted management of treatable traits after a multidimensional assessment of all patients in a specialised severe asthma centre[13]. The intervention group showed a significant improvement in health-related quality of life and, asthma control, and less asthma exacerbations as compared to the group with usual care.

The abovementioned studies were conducted during the time when relatively few biologics were prescribed and OCS maintenance therapy was the last resort in patients with severe asthma. In our study 28% of the uncontrolled asthma patients were on OCS maintenance therapy at presentation. Although not statistically significant for the overall group of patients, there was marked reduction in individual OCS maintenance dose 1 year after the assessment and personalized treatment. The trend we observed in OCS use, has since been confirmed by a more recent study performed in Australia. The authors demonstrated that a systematic assessment followed by management of factors that result in difficult-to-treat-asthma can lead to a more than 50% reduction in OCS use, which is comparable to the effect of biologic therapy[14]. These results show that a systematic approach can also contribute to reducing the OCS burden in uncontrolled asthma patients. Recently, the benefits of a systematic asthma assessment in the current era of biologic therapy have been evaluated in centres for severe asthma in UK, Scotland and Northern Ireland[15]. This large study with 1,140 patients with severe asthma again showed improvement in asthma control, reduced healthcare utilisation and reduction in maintenance OCS use, irrespective of the use of biologic therapy.

In recent years, it has become clear that a multidisciplinary systematic assessment leads to better outcomes in patients with uncontrolled asthma. The results of chapter 2 highlight the need for such an approach. Furthermore, chapter 2 shows that favourable outcomes can be achieved with a single extensive 1-day assessment at a specialised severe asthma centre resulting in a personalised management plan carried out by the referring pulmonologist instead of continuous management in a specialised centre. Given the challenges in embedding a systematic asthma assessment into everyday practice, our study yields important and clinically relevant results, providing a model of care that can be implemented in other asthma centres.

A new era in the treatment of chronic rhinosinusitis with nasal polyposis

At the start of the work described in this thesis, the link between asthma and chronic sinusitis (CRS) was well known, but the importance of chronic rhinosinusitis with nasal polyposis (CRSwNP) was only recognized by a few asthma specialists. In **chapter 3**, we reviewed the relationship between asthma and nasal polyposis from the chest physician's view. We found that asthma patients with concomitant nasal polyposis experienced more severe disease with impaired asthma control, increased airway obstruction and eosinophilic airway inflammation. We concluded that screening for and treatment of nasal polyposis in uncontrolled asthma patients is important, as is collaboration with otorhinolaryngologists in order to improve asthma control. These observations perfectly fitted within the concept of united airway disease[16].

Over the past 6 years, there have been significant advances in the treatment of asthma with comorbid CRSwNP. Already at the time of writing our review article, chest physicians gained experience with the new immunomodulatory therapies for patients with severe eosinophilic asthma, which were not yet available for patients with CRSwNP. In light of the concept of "united airways disease", similar pathological processes underlying asthma and CRSwNP were hypothesized and therefore the same beneficial effects of biologic agents on both upper and lower respiratory tract disease were expected. Indeed, omalizumab (anti-immunoglobulin E (IgE)) was the first to show such positive effects on both asthma and nasal polyposis[17, 18]. Furthermore, there was growing evidence that anti-interleukin (IL)-5 therapy, in addition to its beneficial effect on severe asthma, was also effective in comorbid nasal polyposis[19, 20]. Dupilumab (anti-IL-4/IL-13) was still under investigation at that time, but also showed tentative positive effects on both severe asthma and nasal polyposis[21, 22]. Yet, several years later it turns out that biologic treatment of severe asthma with comorbid CRSwNP is more complicated than we initially thought. We now have experience that several patients with severe eosinophilic asthma and comorbid CRSwNP show complete recovery of asthma symptoms during biologic therapy, while their sinonasal symptoms persist. Although nasal polyposis emerged as a predictor of better asthma outcomes for anti-IL-5 biologics[23], the same nasal polyposis does not always respond, suggesting that IL-5 independent pathways may be involved. Thus, despite the obvious relationship between asthma and CRSwNP, the divergent response to biologic therapy warrants further research.

In recent years, the treatment of CRSwNP with biologics has undergone impressive further developments[24–26]. Currently, three biologics (omalizumab, mepolizumab and dupilumab) have received approval from the United States Food and Drug Administration (FDA) specifically for the treatment of nasal polyposis in patients with and without comorbid asthma[27, 28]. In patients with CRSwNP omalizumab significantly improves nasal polyps score, nasal congestion, sense of smell, postnasal drip and reduced the need for surgery[29, 30]. Moreover, the improvements in asthma outcomes were greater in severe asthma patients with CRSwNP as compared to those without CRSwNP[31, 32]. Both mepolizumab and dupilumab showed similar results in improvement of sinonasal symptoms and asthma outcomes, with more improvement in patients with nasal polyposis[33–37]. Interestingly, some recent reviews have been published that indirectly compared the effect of omalizumab, mepolizumab and dupilumab in patients with CRSwNP.

All of these studies show that dupilumab is most effective in improving sinonasal symptoms, reducing disease severity and the need for surgery, while omalizumab and mepolizumab alternately rank second in efficacy[38–40]. Benralizumab and reslizumab, two other asthma biologics, did not (yet) receive approval from the FDA for the treatment of nasal polyposis in patients with or without comorbid asthma. Nevertheless, favourable outcomes of these therapies have been described in studies in patients with severe asthma which also included the effects on comorbid CRSwNP [41, 42].

Thus, with **chapter 3**, we contributed to the emerging knowledge about the link between asthma and nasal polyposis, which now has become a key topic. Taking into consideration the available evidence, it is now clear that the presence of chronic rhinosinusitis especially with nasal polyposis plays a crucial role in asthma control. Remarkably, nasal polyposis or the combination of CRSwNP was not mentioned on the list with treatable traits[43]. However, nasal polyposis cannot longer be denied and should be added to this list.

Discovery of a new treatable trait

Dynamic hyperinflation is a well-known feature in chronic obstructive pulmonary disease[44] and strongly related to exertional dyspnoea and diminished daily life activity[45, 46]. Since a subset of asthma patients present with similar complaints[47] the question arises whether dynamic hyperinflation could play a role and could become a target for treatment in these patients as well. At the start of our research only a few small studies suggested that dynamic hyperinflation was present in asthma[48–50].

In **chapter 4**, we prospectively evaluated the prevalence of dynamic hyperinflation in moderate-to-severe asthma patients. In addition, we assessed the relationship between the degree of dynamic hyperinflation and severity of respiratory symptoms and limitations of daily life activities derived from five different respiratory health questionnaires. We found that 81% of patients with moderate-to-severe asthma showed dynamic hyperinflation. Also, higher levels of dynamic hyperinflation were related to poorer overall health and impaired daily life activities, independent of asthma severity.

Our results were confirmed by a recent study in which a substantial proportion of asthma patients showed hyperinflation[51]. Moreover, patients with active asthma, and more severe and uncontrolled disease showed a higher degree of hyperinflation. In another, smaller study, 60% of asthma patients presented with dynamic hyperinflation[52]. And again, patients with more severe disease, defined by GINA treatment step 4-5, showed higher levels of dynamic hyperinflation. These results suggest that there should be a greater awareness of dynamic hyperinflation in asthma patients in daily practice.

In COPD, abnormal lung mechanics caused by reduced elastic recoil, loss of alveolar attachments and airway collapse are invoked to explain the occurrence of dynamic hyperinflation[53]. In asthma, it is believed that airway inflammation, particularly of the small airways, contributes to the pathogenesis of dynamic hyperinflation. Both airway oedema and increased mucus production due to inflammation has the potential to

limit airflow and lead to premature airway closure, air trapping and eventually dynamic hyperinflation in patients with asthma[54–56]. On the other hand, dynamic hyperinflation itself can enhance inflammation through cellular stretching and tissue damag[57]. Moreover, air trapping was more prominent in patients with adult-onset (severe) asthma with systemic eosinophilic inflammation or higher levels of exhaled alveolar nitric oxide[58–60]. The fact that inflammation is associated with dynamic hyperinflation, was also demonstrated in a study in which periostin, an inflammatory marker in asthma, was related to a higher degree of dynamic hyperinflation[52].

Considering the impact of dynamic hyperinflation on relevant patient related outcomes and its relation with small airway inflammation, it could be seen as a target for treatment. Therefore, in **chapter 5**, we assessed in an RCT the effect of systemic glucocorticoids (a single high dose of intramuscular triamcinolone) on the degree of dynamic hyperinflation in moderate-to-severe asthma. The degree of dynamic hyperinflation was significantly reduced in the group treated with triamcinolone as compared to the placebo group. Furthermore, we evaluated the relationship between inflammatory markers and the change in dynamic hyperinflation. In the triamcinolone-treated group, the reduction in dynamic hyperinflation was greater in patients with elevated blood eosinophils ($\geq 0.3 \times 10^9$/L) and tended to be related to a reduction in blood eosinophils and exhaled nitric oxide.

The role of small airway disease (SAD) has been understudied in asthma, although it contributes significantly to airflow limitation which can lead to dynamic hyperinflation as mentioned above. The ATLANTIS study, the first large multinational study on this topic, emphasized the important role of SAD by showing its presence in the majority of asthma patients[61]. More recent studies have shown that the prevalence of SAD increases with disease severity and is associated with poorer asthma control and more exacerbations[62]. SAD has also been linked to diminished physical activity[63]. Thus, SAD is increasingly recognized as a relevant target for asthma treatment. A recent review suggests that biologics can favourably improve the function of small airways[64]. Although direct comparisons are lacking between the five available asthma biologics, in this review mepolizumab and benralizumab appeared to be of greater impact on SAD as compared to other biologic agents. With regard to dynamic hyperinflation as a SAD parameter, apart from our study, there are no other RCTs investigating its modifiability by biologics. Only a small unblinded study showed that the extent of dynamic hyperinflation decreased with systemic omalizumab treatment, which also corresponded to an improvement in symptoms and exercise capacity[65]. Other studies showed improvements in (static) hyperinflation indices in a subgroup of severe asthma patients treated with benralizumab, omalizumab or dupilumab[66–68].

Thus, with **chapter 4** and **chapter 5**, we have contributed to a better understanding of SAD in asthma, in particular regarding dynamic hyperinflation. As mentioned above, dynamic hyperinflation seems to be associated with important patient related outcomes, such as asthma symptoms and limitations in daily life activities, in a subset of asthma patients. And with the metronome-paced tachypnoea test, it is simple and less strenuous to measure dynamic hyperinflation as compared to cardiopulmonary exercise tes-

ting in daily practice. Furthermore, there is evidence that systemic anti-inflammatory therapy affects the degree of dynamic hyperinflation. Therefore, we consider dynamic hyperinflation is an important treatable trait and we believe that it should no longer be neglected in asthma. However, only airway smooth muscle contraction, loss of elastic recoil (emphysema) and airway mucosal oedema are mentioned under the heading of airflow limitation in the list of treatable traits[43]. Perhaps dynamic hyperinflation should be on that list too.

OCS overuse is far too often neglected

OCS are widely prescribed by physicians and many patients with asthma are exposed to potentially toxic cumulative doses[69–72]. In order to reduce inappropriate OCS prescribing behaviour, more information is needed about the proportion of patients using high doses of OCS, the adequacy of ICS treatment, and the involvement of a specialist.

Therefore, in **chapter 6**, we assessed the prevalence of frequent OCS use in patients with asthma in the Netherlands. In addition, we evaluated whether these patients were treated with adequate doses of ICS, and whether they were seen regularly by an asthma specialist. In this study we analysed pharmacy dispensing data from 182,849 adult patients with asthma (≥18 years of age, receiving 2 prescriptions of ICS (e.g., single ICS or ICS/long-acting β-agonists (LABA)) for ≥4 months), focusing on prescriptions of low-, medium- and high-dose ICS in frequent OCS users. Between March 2017 and March 2018 (focus year), 22.2% of asthma patients received at least 1 prescription for OCS; 2.6% were exposed to 2 or more OCS courses and 4.6% to OCS maintenance therapy. Moreover, half of the patients with asthma who received frequent OCS courses or maintenance OCS used low and possibly inadequate ICS doses, and 40.3% had not received specialist intervention in 3 years. These results suggest that OCS overuse is present in many patients and that asthma management should be intensified in order to reduce inappropriate OCS use.

In recent years, several studies have confirmed a high incidence of OCS overuse among asthma patients in different countries[72–74]. It is increasingly known that not only maintenance OCS treatment but also repeated short OCS courses have a significant impact on steroid-induced morbidity[75, 76]. There is also growing evidence that the risk of OCS-induced morbidities is dose dependent and related to the cumulative lifetime OCS exposure[77–79]. The risk of many OCS-induced morbidities, e.g. type 2 diabetes, cardiovascular disease and osteoporosis, starts at cumulative exposures of 500-1000 mg prednisolone-equivalent. This corresponds to only two to four short OCS courses for treating an acute asthma exacerbation[77, 80]. Therefore, a lifetime cumulative dose of 500 mg prednisolone-equivalent is quickly reached, with all the concomitant disadvantages. Remarkably, the international GINA guideline still states that low-dose OCS is an accepted treatment option in patients with severe asthma, although it is explicitly qualified as a last resort treatment in case biologic therapies are not available[7s]. It is true that OCS are highly effective and inexpensive compared to biologics, but the side effects of OCS undoubtedly outweigh the beneficial effects in the end.

Calls for action to reduce the burden of OCS in asthma patients are growing. For example, limitation of unnecessary OCS use is one of the key missions listed by the Severe Heterogeneous Asthma Registry Patient-centred (SHARP)[81]. To address this issue, it is essential to create awareness under physicians about the OCS burden to make a major difference in patient outcomes and health care costs. And probably even more important is it to educate, involve, and empower patients in the treatment of their asthma. This approach is also known as OCS Stewardship; defined as "a collaborative systematic effort to protect patients and reduce the harm from inappropriate or cumulative OCS use"[82]. The first key step in achieving good OCS Stewardship is primary prevention of exacerbations and improving asthma control[83]. This can be reached by optimizing asthma treatment and addressing treatable traits, in particular therapy adherence and inhaler technique[84]. As shown in chapter 6, high-risk OCS doses were frequently prescribed in patients on low dose ICS suggesting there has been no adequate assessment of asthma control, level of adherence to ICS, or adjustment of ICS dose. The second key step is to identify uncontrolled asthma patients in primary care, to timely refer them to an asthma specialist and when necessary to a specialised asthma centre for a systematic multidisciplinary assessment in order to reduce OCS use and consider OCS-sparing biologics when appropriate[85]. Unfortunately, referral rates to specialist asthma care are low. In primary care in the UK less than 20% of asthma patients with 3 or more OCS courses per year were referred to specialist care[86]. In a recent study in the USA, only 8% of asthma patients managed in primary care were referred to a specialist within 2 years after initial diagnosis, despite 43% having uncontrolled asthma and one third receiving frequent OCS courses[87]. This corresponds with the results of chapter 6, in which about half of patients with frequent OCS courses and one-third of patients on maintenance OCS had not been prescribed any asthma medication by a specialist for up to 3 years, suggesting that these patients were treated in primary care, without specialist supervision.

As mentioned above, OCS overuse has emerged as a major issue in asthma and we were one of the first to address this issue[83]. The results of the study described in chapter 6 contributes to our knowledge of inappropriate OCS use by our patients, and highlights the need for timely referral to an asthma specialist in order to optimise asthma management. Thus, OCS overuse, and even more generally, medication overuse, should not be neglected due to its enormous burden in patients, specifically in asthma. Therefore, OCS overuse deserves a prominent position in the list of treatable traits alongside the more general terms "side-effects of other treatments" and "inhaler device polypharmacy"[43].

CLINICAL IMPLICATIONS

The findings of this thesis have led to several implications for clinical practice. First, the results from chapter 2 emphasize the need for a multidisciplinary systematic assessment in uncontrolled asthma patients. This is in line with the recommendations of national and international severe asthma guidelines[4–7, 88]. However, it is conceivable that clinicians struggle to implement such an assessment in daily practice. The provided practical model of care in our study however, can serve as an example to deliver appropri-

ate asthma care. With this approach, it is not needed to concentrate asthma care in severe asthma centres. An extensive 1-day-visit programme or a more pared-down version can result in a personalised management plan implemented by the referring pulmonologist and is sufficient in a subset of patients to improve asthma outcomes.

Second, chapter 3 emphasizes that patients with uncontrolled, in particular eosinophilic, asthma should be screened for possible CRSwNP in collaboration with an otorhinolaryngologist, since various treatment options for nasal polyposis have the potential to improve asthma control. This has become even more relevant since the treatment with biologics has evolved tremendously over the last few years for patients with nasal polyposis and comorbid asthma[24–26]. In severe asthma, there is already plenty of clinical experience with the use of biologics, whereas in the field of nasal polyposis it is still growing. Therefore, it may be advisable to initiate a multidisciplinary consultation between the pulmonologist and otorhinolaryngologist to exchange knowledge and discuss complex casuistry, in which biologics are not effective in both asthma and CRSwNP, in order to improve patient outcomes. This might also provide a more personalised management approach in the individual patient with asthma and comorbid CRSwNP.

Third, chapter 4 provides evidence that dynamic hyperinflation is a relevant treatable trait in moderate to severe asthma. It contributes to asthma symptoms and impairment of daily life activities. In addition, chapter 5, demonstrates that dynamic hyperinflation in asthma can be reduced with systemic anti-inflammatory treatments in addition to inhaled corticosteroids and β-2 agonists. These findings encourage the monitoring of dynamic hyperinflation in daily practice. Dynamic hyperinflation is commonly assessed by measuring changes in inspiratory capacity during cardiopulmonary exercise testing, which is a complex and laborious test[89]. We showed that the metronome-paced tachypnoea test, a far simpler and less strenuous surrogate of cardiopulmonary exercise testing, can be used instead to measure dynamic hyperinflation[90, 91]. This provides a useful tool to assess and verify the individual clinical response to treatment, in daily practice as well as in clinical studies.

Finally, the results of chapter 6 contribute to the awareness of the burden of OCS in asthma. Some important lessons for daily practice can be drawn from the OCS overuse data. It is essential to create awareness and understanding about the OCS burden among general practitioners and specialists to make a major difference in patient outcomes and health care costs, and even more importantly to educate, involve, and empower patients in the treatment of their asthma. In addition, it cannot be highlighted enough, not only OCS maintenance therapy, but also frequent OCS courses have a significant impact on steroid-induced morbidity[75, 76]. Therefore, asthma treatment should by all means be optimized in order to prevent exacerbations and improve asthma control[83]. Furthermore, when OCS maintenance therapy is used as a last resort in the treatment of severe asthma, it is advisable to strive for the lowest possible dose [92]. The longer a patient is exposed to OCS, the less likely the patient will be able to completely discontinue this therapy[93]. Therefore, it is important to monitor OCS use and its side effects closely.

GENERAL CONCLUSION AND FUTURE PERSPECTIVES

This thesis has contributed to answering a number of key questions regarding common and neglected treatable traits in adult asthma. Looking at the research questions of this thesis, several conclusions can be made.

First, this thesis has shown that a 1-day systematic multidisciplinary assessment in a specialised severe asthma centre leads to better asthma control, quality of life and reduced healthcare use in patients with uncontrolled asthma after 1 year.

Second, it was shown that chronic rhinosinusitis with nasal polyposis in asthma patients was related to a more severe disease with less asthma control, increased airway obstruction and eosinophilic inflammation; and is therefore an important treatable trait in asthma.

Third, in this thesis we have shown that the proportion of patients with dynamic hyperinflation is high in moderate to severe asthma; and that dynamic hyperinflation is associated with poorer overall health, lower wellbeing and impaired activities in daily life.

Fourth, it was shown that the degree of dynamic hyperinflation in patients with moderate to severe asthma could significantly be reduced by systemic anti-inflammatory treatment; and that the decrease in dynamic hyperinflation was found to be most pronounced in patients with elevated blood eosinophils.

And lastly, this thesis showed that a substantial proportion of patients with asthma in the Netherlands was exposed to OCS overuse, including frequent OCS courses or maintenance OCS therapy; that half of the patients use low and possibly inadequate ICS doses; and that 40% had not undergone intervention of an asthma specialist for years.

Future perspectives regarding a systematic multidisciplinary approach

While it is clear that a systematic multidisciplinary assessment is crucial in treating patients with uncontrolled asthma, it is time to take appropriate action by implementing it into daily practice. Several examples on how (severe) asthma care should be organized have been described[94, 95]. Regional networks have emerged accordingly, resulting in better identification of treatable traits and asthma endotyping for appropriate biologic treatment by the local pulmonologist[95]. By embracing a "right care in the right place" approach, asthma patients are treated properly and rising healthcare costs can be suppressed[96]. In addition, structural monitoring of difficult-to-treat and severe asthma patients is also useful for national and international registries and future research.

An important question is what the role of primary care is in these regional networks. The current asthma guidelines provide straightforward recommendations on when to request a referral to a specialist for patients with difficult-to-treat asthma[4, 7]. In addition, timely referral to a specialist leads to better asthma control and less health care utilisation [15, 97]. However, as the results of our study suggested, studies in the USA and UK have shown that patients with severe or uncontrolled asthma are not always referred

to a specialist. A review of asthma management in the USA showed that a substantial proportion of patients were uncontrolled and only 22% of patients visited a specialist for asthma care. Remarkably, 50% of patients had never been referred to a specialist at all[98]. In a more recent study in the UK, it was found that a large number of patients were eligible for referral to a specialist according the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guideline recommendations, but only 4% were actually referred and with a long duration until referral[97]. These data support the important unmet need in the management of asthma in primary care.
Therefore, more attention should be paid to the knowledge and implementation of the guideline recommendations and the referral process in order to improve the clinical outcomes in asthma patients[99, 100].

As mentioned above, providing good asthma care can be both challenging and time-consuming. With the outbreak of the Covid-19 pandemic, standard patient care changed drastically. And with it, so did asthma care. Remote care became the new standard in some cases. With this in mind, the question arises as to what extent it is possible to deliver asthma care partly digitally. Both as a means to improve healthcare, while keeping the growing demand for care manageable. Telemedicine is one of the tools that seems to enable the physician to deliver efficacious and innovative asthma care [101].
There is evidence that telemedicine appears beneficial in improving asthma control and quality of life in general asthma[102, 103]. Although more RCT's are needed to compare telemedicine with standard asthma care, personalised asthma management in the home environment will likely be the next step in the development of future asthma management.

Future perspectives regarding chronic sinusitis with nasal polyposis
With the emergence of biologics indicated for both severe asthma and CRSwNP, new research questions arise. In the overall study population biologics are proven to be effective in improving clinical and patient related outcomes. However, variability in the response to biologics have been observed. For example, some patients respond incredibly well on anti-IL-5 treatment with regards to asthma, but experience no or little effect on CRSwNP. These observations stress the need to identify responders and non-responders to biologic treatment. Also, the question arises as to what could explain this heterogeneity in severe asthma with comorbid CRSwNP. Is there not a united airway disease after all or only in a subset of asthma patients? Are there other types of inflammation at play or are nasal polyposis not properly reached by each biologic[104]? Also, we do not know whether severe asthma patients with mild, instead of severe, nasal polyposis respond similarly to biologic therapy regarding asthma control and sinonasal symptoms. Unfortunately, data are scarce due to the fact that upper and lower airways diseases are still considered as two separate entities in daily practice [26].
Only indirect evidence on the effect of different biologic therapies in both severe asthma and CRSwNP has been provided by review articles[25, 27, 28]. Therefore, head-to-head RCT's are needed to compare the efficacy between these different biologics. These studies may also contribute to the identification of clinical characteristics and/or biomarkers associated with the response to biologics.

Meanwhile, there is evidence that a dual biologic therapy approach might be effective in patients with suboptimal response to one biologic[105]. This may provide an opportunity in patients with improved asthma control under biologic therapy, but who experience persistent sinonasal symptoms. Unfortunately, most of the evidence is based on case reports[106, 107]. Yet, despite the potential benefits, the high costs associated with dual biologic therapy should also be taken into account. Thus, future research is crucial to adequately address the unmet needs in patients with severe asthma and comorbid CRSwNP as abovementioned.

Future perspectives regarding dynamic hyperinflation

There are unresolved research questions regarding dynamic hyperinflation in patients with asthma. Given the important clinical impact of dynamic hyperinflation on overall health and daily life activities, it is important to be aware of dynamic hyperinflation in moderate to severe asthma patients who present with exertional dyspnoea and diminished daily physical activity. In line with this, asthma questionnaires with consideration of a broader panel of airway symptoms (i.e. daily life activities) should be developed to use in daily practice. Dynamic hyperinflation, as a consequence of SAD, may represent type 2 inflammation that significantly improves after systemic anti-inflammatory therapy in asthma patients (e.g. glucocorticoids and biologics). Therefore, dynamic hyperinflation might be useful in identifying patients suitable for biologic therapy, among other type 2 inflammatory biomarkers. Moreover, there is a gap of knowledge on how best to define biologic treatment outcomes[108, 109]. In fact, treatment response in the large clinical trials with biologics are often based on exacerbation rate and the reduction in OCS use and asthma control. However, these outcomes might not fully reflect the response in the individual asthma patient. Improvement in quality of life, overall health and daily life activity are also of great importance. As mentioned earlier, dynamic hyperinflation is related to these outcomes. Perhaps dynamic hyperinflation might be a new biomarker that reflects these outcomes. Therefore, future clinical trials are needed to confirm the added value of dynamic hyperinflation as a new biomarker that can be used in patient identification and prediction of biologic treatment outcomes in asthma patients.

Future perspectives regarding OCS overuse

The most important research question regarding OCS overuse is how to reduce OCS exposure to the greatest possible extent. The first step is to be very cautious with prescribing OCS in asthma patients without proven type 2 airway inflammation. This seems obvious, but a substantial proportion of patients without type 2 airway inflammation receive frequent OCS courses or even maintenance OCS therapy without any effect on their symptoms. Therefore, awareness of assessment of medication response and phenotyping is crucial. Our data shows that both general practitioners and specialists seem to prescribe OCS too often and too easily. This may be due to several causes. First, unnoticed repeated prescriptions of OCS. The development of alert systems flagging OCS overuse could be helpful in this. To our knowledge, these systems are not yet available, making us dependent on the readiness of a pharmacist or requested pharmacy records in daily practice. Secondly, ignorance of the toxicity of short OCS courses. Implementation of new tools, such as asthma attack risk scales and question-

naires can be beneficial in preventing asthma exacerbations and additional OCS use[110, 111]. Moreover, a method for measuring the toxicity of OCS in individual patients may be insightful. An example of such a method is the Glucocorticoid Toxicity Index, which is validated with both real-world experience and clinical trials across multiple diseases including asthma[112, 113]. However, it has not yet been embedded into daily practice. Lastly, the lack of awareness of the risks of OCS overuse and novel treatment options, such as biologics, by both physicians and patients. In addition, many patients rely on OCS because of the impact they experience on asthma control and well-being. Several medical education initiatives have been developed, including patient association video lectures, media campaigns, the publication of a charter to improve care for severe asthma and consensus on the biologic OCS-sparing effect in severe asthma, to raise awareness among physicians and patients[85, 114, 115]. Whether these initiatives will actually help, is something future research will have to address.

With the emerging data on OCS overuse, awareness of the negative consequences of OCS overuse is growing. As described previously, there are many adverse outcomes associated with the use of OCS[116]. Treatment with biologics has led to a substantial OCS sparing effect in patients with severe asthma[117–120]. And although tapering or completely eliminating maintenance OCS therapy is a positive thing, adrenal insufficiency became increasingly apparent. Symptoms due to adrenal insufficiency are often non-specific. However, during stressful events (e.g. severe infections) it can even be fatal. Adrenal insufficiency due to OCS can disappear 1 week after stopping OCS in some patients. Unfortunately, in the majority of patients adrenal insufficiency persists for months or OCS cannot be stopped[121]. Therefore, guidance in safely tapering OCS and screening for adrenal insufficiency is needed. The PONENTE study is the first trial that provided a personalised OCS tapering schedule, based on baseline maintenance OCS dosage in severe asthma patients treated with benralizumab[122]. Also, advice was given about when and how to screen for adrenal insufficiency. The future step is to incorporate this model into the current guidelines and implement a local protocol in daily practice in patients with severe asthma.

In conclusion, with this thesis we aimed to contribute to the concept of treatable traits in asthma patients. The concept of treatable traits was a major breakthrough in the management of asthma. This thesis underlines the need for a systematic multidisciplinary approach of treatable traits in the management of patients with uncontrolled asthma. In the concept of treatable traits all kinds of traits are covered. However, the list of treatable traits is not yet complete. The presented studies are of great value by adding new treatable traits (nasal polyposis, dynamic hyperinflation and OCS overuse) to that list. Finally, this thesis encourages further research on new and existing treatable traits.

REFERENCES

1 Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, Wagener AH, Wagers SS, Sterk PJ, statement from the Innovative Medicine Initiative (IMI). *Thorax 2011;* 66: 910–917.
2 König IR, Fuchs O, Hansen G, von Mutius E, Kopp M V. What is precision medicine? *European Respiratory Journal 2017*; 50: 1700391.
3 McDonald V, Vertigan A, Gibson P. How to set up a severe asthma service. *Respirology 2011;* 16: 900–911.
4 BTS/SIGN British Guideline on the Management of Asthma, 2019. Available from: www.brit-thoracic.org.uk.
5 Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S, McDonald VM, Morgan RL, Ortega VE, Rigau D, Subbarao P, Tonia T, Adcock IM, Bleecker ER, Brightling C, Boulet L-P, Cabana M, Castro M, Chanez P, Custovic A, Djukanovic R, Frey U, Frankemölle B, Gibson P, Hamerlijnck D, Jarjour N, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *European Respiratory Journal 2020;* 55: 1900588.
6 NICE guideline. Asthma: diagnosis, monitoring and chronic asthma management, 2021. Available from: www.nice.org.uk.
7 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org.
8 van der Meer A-N, Pasma H, Kempenaar-Okkema W, Pelinck J-A, Schutten M, Storm H, ten Brinke A. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *European Respiratory Journal 2016*; 48: 726–733.
9 Hew M, Menzies-Gow A, Hull JH, Fleming L, Porsbjerg C, Brinke A Ten, Allen D, Gore R, Tay TR. Systematic Assessment of Difficult-to-Treat Asthma: Principles and Perspectives. *Journal of Allergy and Clinical Immunology in Practice 2020*; 8: 2222–2233.
10 Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, Bucknall CE, Mezies-Gow AN. Dedicated Severe Asthma Services Improve Health-care Use and Quality of Life. *Chest 2015;* 148: 870–876.
11 Tay TR, Lee J, Radhakrishna N, Hore-Lacy F, Stirling R, Hoy R, Dabscheck E, O'Hehir R, Hew M. A Structured Approach to Specialist-referred Difficult Asthma Patients Improves Control of Comorbidities and Enhances Asthma Outcomes. *Journal of Allergy and Clinical Immunology in Practice 2017*; 5: 956-964.
12 National Health Service. Specialised respiratory services (adult)—severe asthma, 2019. Available from: www.england.nhs.uk/publication/specialisedrespiratory-services-adult-severe-asthma.
13. McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. European Respiratory Journal 2020; 55: 1901509.
14 Denton E, Lee J, Tay T, Radhakrishna N, Hore-Lacy F, Mackay A, Hoy R, Dabscheck E, O'Hehir RE, Hew M. Systematic Assessment for Difficult and Severe Asthma Improves Outcomes and Halves Oral Corticosteroid Burden Independent of Monoclonal Biologic Use. *Journal of Allergy and Clinical Immunology in Practice 2020*; 8: 1616–1624.
15 Redmond C, Heaney LG, Chaudhuri R, Jackson DJ, Menzies-Gow A, Pfeffer P, Busby J. Benefits of specialist severe asthma management: demographic and geographic disparities. *European Respiratory Journal 2022;* 60: 2200660.
16 Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic Rhinosinusitis with Nasal Polyps and Asthma. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 1133–1141.
17 Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. In: Walker S, editor. *Cochrane Database of Systematic Reviews 2014*; CD003559.
18 Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, Hellings P, Brusselle G, De Bacquer D, van Cauwenberge P, Bachert C. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. Journal of Allergy and Clinical Immunology 2013; 131: 110-6.
19 Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. *New England Journal of Medicine 2009*; 360: 973–984.
20 Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, De Ruyck N, Blomme K, Sousa AR, Marshall RP, Bachert C. Mepolizumab, a humanized anti–IL-5 mAb, as a treatment option for severe nasal polyposis. *Journal of Allergy and Clinical Immunology 2011;* 128: 989-995.
21 Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NMH, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting 2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *The Lancet 2016*; 388: 31–44.

22 Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis. *Journal of American Medical Association 2016;* 315: 469.

23 Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, Goldman M, Newbold P, Zangrilli JG. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *European Respiratory Journal 2018;* 52: 1800936.

24 Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, Canonica GW, Deneyer L, Desrosiers M, Diamant Z, Han J, Heffler E, Hopkins C, Jankowski R, Joos G, Knill A, Lee J, Lee SE, Mariën G, Pugin B, Senior B, Seys SF, Hellings PW. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy 2019;* 74: 2312–2319.

25 Bakakos P. Asthma: From Phenotypes to Personalized Medicine. *Journal of Personalized Medicine 2022;* 12: 1853.

26 Mullol J, Azar A, Buchheit KM, Hopkins C, Bernstein JA. Chronic Rhinosinusitis With Nasal Polyps: Quality of Life in the Biologics Era. *Journal of Allergy and Clinical Immunology in Practice 2022;* 10: 1434-1453.

27 Morse JC, Miller C, Senior B. Management of Chronic Rhinosinusitis with Nasal Polyposis in the Era of Biologics. *Journal of Asthma and Allergy 2021;* 14: 873–882.

28 Hellings PW, Verhoeven E, Fokkens WJ. State-of-the-art overview on biological treatment for CRSwNP. *Rhinology Journal 2021;* 59:151-163.

29 Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, Kaufman D, Ligueros-Saylan M, Howard M, Zhu R, Owen R, Wong K, Islam L, Bachert C. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *Journal of Allergy and Clinical Immunology 2020;* 146: 595–605.

30 Gevaert P, Saenz R, Corren J, Han JK, Mullol J, Lee SE, Ow RA, Zhao R, Howard M, Wong K, Islam L, Ligueros-Saylan M, Omachi TA, Bachert C. Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study. *Journal of Allergy and Clinical Immunology 2022;* 149: 957-965.

31 Heffler E, Saccheri F, Bartezaghi M, Canonica GW. Effectiveness of omalizumab in patients with severe allergic asthma with and without chronic rhinosinusitis with nasal polyps: a PROXIMA study post hoc analysis. *Clinical and Translational Allergy 2020;* 10: 25.

32 Tiotiu A, Oster J, Roux P, Nguyen Thi P, Peiffer G, Bonniaud P, Dalphin J, de Blay F. Effectiveness of Omalizumab in Severe Allergic Asthma and Nasal Polyposis: A Real-Life Study. *Journal of Investigational Allergology and Clinical Immunology 2020;* 30: 49–57.

33 Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, Smith SG, Martin N, Mayer B, Yancey SW, Sousa AR, Chan R, Hopkins C, Ahlström Emanuelsson C, Ardusso L, Armstrong M, Bardin P, Barnes S, Bergna M, Betz C, Beule A, Blotter J, Bronescu V, Brown M, Carrie S, Chaker A, Cho H-J, Corriveau M-N, Courville T, Cuevas M, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respiratory Medicine 2021;* 9: 1141–1153.

34 Howarth P, Chupp G, Nelsen LM, Bradford ES, Bratton DJ, Smith SG, Albers FC, Brusselle G, Bachert C. Severe eosinophilic asthma with nasal polyposis: A phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy. *Journal of Allergy and Clinical Immunology 2020;* 145: 1713–1715.

35 Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME, Kariyawasam HH, Gilbert J, Austin D, Maxwell AC, Marshall RP, Fokkens WJ. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *Journal of Allergy and Clinical Immunology 2017;* 140: 1024-1031.

36 Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, Mullol J, Greos LS, Bosso J V, Laidlaw TM, Cervin AU, Maspero JF, Hopkins C, Olze H, Canonica GW, Paggiaro P, Cho SH, Fokkens WJ, Fujieda S, Zhang M, Lu X, Fan C, Draikiwicz S, Kamat SA, Khan A, Pirozzi G, Patel N, Graham NMH, Ruddy M, Staudinger H, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *The Lancet 2019;* 394: 1638–1650.

37 Laidlaw TM, Bachert C, Amin N, Desrosiers M, Hellings PW, Mullol J, Maspero JF, Gevaert P, Zhang M, Mao X, Khan AH, Kamat S, Patel N, Graham NMH, Ruddy M, Staudinger H, Mannent LP. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. *Annals of Allergy, Asthma & Immunology 2021;* 126: 584-592.

38 Wu Q, Zhang Y, Kong W, Wang X, Yuan L, Zheng R, Qiu H, Huang X, Yang Q. Which Is the Best Biologic for Nasal Polyps: Dupilumab, Omalizumab, or Mepolizumab? A Network Meta-Analysis. *International Archives of Allergy and Immunology 2022;* 183: 279–288.

39 Chong L-Y, Piromchai P, Sharp S, Snidvongs K, Webster KE, Philpott C, Hopkins C, Burton MJ. Biologics for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews 2021;* 3: CD013513.

40 Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, Xu Y, Chuang C-C, Neupane B, Msihid J, Mannent LP, Guyot P, Kamat S. Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 2461-2471.
41 Canonica GW, Harrison TW, Chanez P, Menzella F, Louis R, Cosio BG, Lugogo NL, Mohan A, Burden A, Garcia Gil E. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. *Allergy 2022*; 77: 150–161.
42 Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG, Lugogo NL, Mohan A, Burden A, McDermott L, Garcia Gil E, Zangrilli JG, Pohl W, Voves R, Deschampheleire M, Louis R, Martinot J-B, Peché R, Chapman K, Cheema A, Dorscheid D, FitzGerald JM, Gagnon R, Killorn WP, Olivenstein R, Philteos G, Ramsey C, Rolf JD, Walker B, Hilberg O, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respiratory Medicine 2021*; 9: 260–274.
43 Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: Toward precision medicine of chronic airway diseases. *European Respiratory Journal 2016*; 47: 410–419.
44 Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? European Respiratory Journal 2012; 40: 322–329.
45 O'Donnell DE, Travers J, Webb KA, He Z, Lam Y-M, Hamilton A, Kesten S, Maltais F, Magnussen H. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *European Respiratory Journal 2009*; 34: 866–874.
46 Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, López-Collazo E, Alvarez-Sala R. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *American Journal of Respiratory Critical Care Medicine 2009*; 180: 506–512.
47 Vermeulen F, Garcia G, Ninane V, Laveneziana P. Activity limitation and exertional dyspnea in adult asthmatic patients: What do we know? *Respiratory Medicine 2016*; 117: 122–130.
48 Laveneziana P, Lotti P, Coli C, Binazzi B, Chiti L, Stendardi L, Duranti R, Scano G. Mechanisms of dyspnoea and its language in patients with asthma. *European Respiratory Journal 2006*; 27: 742–747.
49 Lougheed MD, Fisher T, O'Donnell DE. Dynamic hyperinflation during bronchoconstriction in asthma: Implications for symptom perception. *Chest 2006*; 130: 1072–1081.
50 Kosmas EN, Milic-Emili J, Polychronaki A, Dimitroulis I, Retsou S, Gaga M, Koutsoukou A, Roussos C, Koulouris NG. Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. *European Respiratory Journal 2004*; 24: 378–384.
51 Schultz CUB, Tupper OD, Ulrik CS. Static lung volumes and diffusion capacity in adults 30 years after being diagnosed with asthma. *Asthma Research and Practice 2022*; 8: 4.
52 Asano T, Ohbayashi H, Ariga M, Furuta O, Kudo S, Ono J, Izuhara K. Serum periostin reflects dynamic hyperinflation in patients with asthma. *European Respiratory Journal Open Research 2020*; 6: 00347–02019.
53 Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: Key concepts in modern respiratory physiology. *European Respiratory Journal 2005;* 25: 186–199.
54 Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral Lung Resistance in Normal and Asthmatic Subjects. *American Review of Respiratory Disease 1990;* 141: 584–588.
55 Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *American Journal of Respiratory Critical Care Medicine 1996*; 154: 1505–1510.
56 Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, Matsuoka H, Jinnai M, Muro S, Chin K, Mishima M. Role of small airways in asthma: Investigation using high-resolution computed tomography. *Journal of Allergy and Clinical Immunology 2006*; 118: 1019–1025.
57 Agusti A, Soriano JB. Dynamic hyperinflation and pulmonary inflammation: a potentially relevant relationship? *European Respiratory Review 2006*; 15: 68–71.
58 De Groot JC, Storm H, Amelink M, De Nijs SB, Eichhorn E, Reitsma BH, Bel EHD, Brinke A Ten. Clinical profile of patients with adult-onset eosinophilic asthma. *European Respiratory Journal Open Research 2016*; 2: 1–8.
59 van Veen IH, Sterk PJ, Schot R, Gauw SA, Rabe KF, Bel EH. Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. *European Respiratory Journal 2006*; 27: 951-956.
60 in 't Veen J, Beekman A, Bel E, Sterk P. Recurrent Exacerbations in Severe Asthma Are Associated with Enhanced Airway Closure During Stable Episodes. *American Journal of Respiratory Critical Care Medicine 2000*; 161: 1902–1906.
61 Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, Papi A, Van der Molen T, Rabe KF, Siddiqui S, Singh D, Nicolini G, Kraft M, Pizzichini E, Cukier A, Stelmach R, Olivenstein R, Zhang Q, Badorrek P, Gessner C, Scichilone N, Chetta A, Paggiaro P, Milleri S, D'Amato M, Spanevello A, Foschino MP, Boersma WG, Broeders M, Vroegop JS, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. *Lancet Respiratory Medicine 2019*; 7: 402–416.

62 Kraft M, Richardson M, Hallmark B, Billheimer D, Van den Berge M, Fabbri LM, Van der Molen T, Nicolini G, Papi A, Rabe KF, Singh D, Brightling C, Siddiqui S, Pizzichini E, Cukier A, Stelmach R, Olivenstein R, Zhang Q, Badorrek P, Gessner C, Scichilone N, Chetta A, Paggiaro P, Milleri S, D'Amato M, Spanevello A, Foschino MP, Boersma WG, Broeders M, Vroegop JS, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respiratory Medicine 2022; 10: 661–668.
63 Abdo M, Trinkmann F, Kirsten A-M, Pedersen F, Herzmann C, von Mutius E, Kopp M V., Hansen G, Waschki B, Rabe KF, Watz H, Bahmer T. Small Airway Dysfunction Links Asthma Severity with Physical Activity and Symptom Control. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 3359-3368.
64 Lombardi C, Cottini M, Berti A, Comberiati P. Monoclonal antibodies targeting small airways: a new perspective for biological therapies in severe asthma. *Asthma Research and Practice 2022;* 8: 6.
65 Schäper C, Gläser S, Felix SB, Gogolka A, Koch B, Krüll M, Ewert R, Noga O. Omalizumab treatment and exercise capacity in severe asthmatics - Results from a pilot study. *Respiratory Medicine 2011;* 105: 3–7.
66 Panettieri RA, Welte T, Shenoy K V., Korn S, Jandl M, Kerwin EM, Feijoo R, Barker P, Olsson RF, Martin UJ. Onset of effect, changes in airflow obstruction and lung volume, and health-related quality of life improvements with benralizumab for patients with severe eosinophilic asthma: Phase IIIb randomized, controlled trial (SOLANA). *Journal of Asthma and Allergy 2020*; 13: 115–126.
67 Paganin F, Mangiapan G, Proust A, Prudhomme A, Attia J, Marchand-Adam S, Pellet F, Milhe F, Melloni B, Bernady A, Raspaud C, Nocent C, Berger P, Guilleminault L. Lung function parameters in omalizumab responder patients: An interesting tool? *Allergy 2017;* 72: 1953–1961.
68 Pelaia C, Lombardo N, Busceti MT, Piazzetta G, Crimi C, Calabrese C, Vatrella A, Pelaia G. Short-Term Evaluation of Dupilumab Effects in Patients with Severe Asthma and Nasal Polyposis. *Journal of Asthma and Allergy 2021;* Volume 14: 1165–1172.
69 Tran TN, King E, Sarkar R, Nan C, Rubino A, O'Leary C, Muzwidzwa R, Belton L, Quint JK. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *European Respiratory Journal 2020*; 55: 1902363.
70 Tran TN, MacLachlan S, Hicks W, Liu J, Chung Y, Zangrilli J, Rubino A, Ganz ML. Oral Corticosteroid Treatment Patterns of Patients in the United States with Persistent Asthma. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 338-346.
71 Hew M, McDonald VM, Bardin PG, Chung LP, Farah CS, Barnard A, Cooper MS, Gibson PG, Upham JW. Cumulative dispensing of high oral corticosteroid doses for treating asthma in Australia. *Medical Journal of Australia 2020*; 213: 316–320.
72. Ekström M, Nwaru BI, Hasvold P, Wiklund F, Telg G, Janson C. Oral corticosteroid use, morbidity and mortality in asthma: A nationwide prospective cohort study in Sweden. *Allergy 2019;* 74: 2181–2190.
73 Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, Alacqua M, Tran TN. Systematic literature review of systemic corticosteroid use for asthma management. *American Journal of Respiratory Critical Care Medicine 2020*; 201: 276–293.
74 Taube C, Bramlage P, Hofer A, Anderson D. Prevalence of oral corticosteroid use in the German severe asthma population. *European Respiratory Journal Open Research 2019;* 5: 1–10.
75 Wallace BI, Waljee AK. Burst Case Scenario: Why Shorter May Not Be Any Better When It Comes to Corticosteroids. *Annals of Internal Med 2020*; 173: 390–391.
76 Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: Striking the balance between efficacy and safety. *European Respiratory Review 2020;* 29: 190151.
77 Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Jie JLZ, Tran TN. Adverse outcomes from initiation of systemic corticosteroids for asthma: Long-term observational study. *Journal of Asthma and Allergy 2018*; 11: 193–204.
78 Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. Journal of Allergy and Clinical Immunology 2018; 141: 110-116. .
79 Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegård A, Davidsen JR. Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality. *European Respiratory Journal 2022*; 60: 2103054.
80 Bloechliger M, Reinau D, Spoendlin J, Chang S-C, Kuhlbusch K, Heaney LG, Jick SS, Meier CR. Adverse events profile of oral corticosteroids among asthma patients in the UK: cohort study with a nested case-control analysis. *Respiratory Research 2018*; 19: 75.
81 Djukanovic R, Adcock IM, Anderson G, Bel EH, Canonica GW, Cao H, Chung KF, Davies DE, Genton C, Gibson-Latimer T, Hamerlijnck D, Heuvelin E, Louis R, Korn S, Kots M, Kwon N, Naddaf R, Wagers SS. The Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) ERS Clinical Research Collaboration: a new dawn in asthma research. *European Respiratory Journal 2018*; 52: 1801671.
82 AAFA. Oral corticosteroid stewardship statement, 2018. Available from: www.aafa.org.

83 Bleecker ER, Al-Ahmad M, Bjermer L, Caminati M, Canonica GW, Kaplan A, Papadopoulos NG, Roche N, Ryan D, Tohda Y, Yáñez A, Price D. Systemic corticosteroids in asthma: A call to action from World Allergy Organization and Respiratory Effectiveness Group. *World Allergy Organization Journal 2022*; 15: 100726.

84 Eger K, Amelink M, Hashimoto S, Hekking PP, Longo C, Bel EH. Overuse of Oral Corticosteroids, Underuse of Inhaled Corticosteroids, and Implications for Biologic Therapy in Asthma. *Respiration 2021*; 101: 116-121.

85 Price D, Bourdin A. Proactive Risk Management: A Novel Approach to Embedding Oral Corticosteroid Stewardship into Asthma Care. *EMJ Respiratory 2022*; 10[Suppl 2]:2-10.

86 Bloom CI, Walker S, Quint JK. Inadequate specialist care referrals for high-risk asthma patients in the UK: an adult population-based cohort 2006–2017. *Journal of Asthma 2021*; 58: 19–25.

87 Ortega H, Bharmal N, Khatri S. Primary care referral patterns for patients with asthma: analysis of real-world data. *Journal of Asthma 2023*; 60: 609–615.

88 NVALT. Diagnostiek en behandeling van ernstig astma, 2022. Available from: www.richtlijnendatabase.nl.

89 O'Donnell D, Revill S, Webb K. Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory Critical Care Medicine 2001*; 164: 770–777.

90 Lahaije A, van Helvoort H, Dekhuijzen R, Heijdra Y. Can COPD Patients Who Hyperinflate During Daily Life Activities Be Identified by Laboratory Tests? *Respiration 2013*; 86: 237–242.

91 Lahaije AJMC, van Helvoort HAC, Dekhuijzen PNR, Vercoulen JH, Heijdra YF. Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV_1. *Respiratory Medicine 2013*; 107: 834–840.

92 Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: A focused review of the impact data in the literature. *European Respiratory Journal 2018*; 52: 1800703.

93 Kroes JA, Zielhuis SWJ, De Jong K, Hashimoto S, Sont JK, Zielhuis SW, Van Roon EN, Bel EH, Ten Brinke A. Cumulative corticosteroid-sparing effect of anti-interleukin-5/5Ra in eosinophilic asthma. *European Respiratory Journal 2022*; 60: 2102983.

94 Porsbjerg C, Ulrik C, Skjold T, Backer V, Laerum B, Lehman S, Janson C, Sandstrøm T, Bjermer L, Dahlen B, Lundbäck B, Ludviksdottir D, Björnsdóttir U, Altraja A, Lehtimäki L, Kauppi P, Karjalainen J, Kankaanranta H. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. *European Clinical Respiratory Journal 2018*; 5: 1440868.

95 Valk JPM, Kappen JH, Campen JSJA, Epping G, Retera JMAM, Bondt D, Suwandy F, Tolboom M, in 't Veen JCCM, Braunstahl GJ. Roadmap to improve regional care for patients with severe asthma. *Clinical Translational Allergy 2021*; 11: e12080.

96 Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *American Journal of Respiratory Critical Care Medicine 2019*; 200: 1102–1112.

97 Blakey JD, Gayle A, Slater MG, Jones GH, Baldwin M. Observational cohort study to investigate the unmet need and time waiting for referral for specialist opinion in adult asthma in England (UNTWIST asthma). *British Medical Journal Open 2019*; 9: e031740.

98 Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: Results of the 2009 Asthma Insight and Management survey. *Allergy Asthma Proceedings 2012*; 33: 54–64.

99 Price D, Bjermer L, Bergin DA, Martinez R. Asthma referrals: A key component of asthma management that needs to be addressed. *Journal of Asthma and Allergy 2017*; 10: 209–223.

100 Levy ML, Bacharier LB, Bateman E, Boulet L-P, Brightling C, Buhl R, Brusselle G, Cruz AA, Drazen JM, Duijts L, Fleming L, Inoue H, Ko FWS, Krishnan JA, Mortimer K, Pitrez PM, Sheikh A, Yorgancıoğlu A, Reddel HK. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. *NPJ Primary Care Respiratory Medicine 2023*; 33: 7.

101 Hashimoto S, Brinke AT, Roldaan AC, van Veen IH, Moller GM, Sont JK, Weersink EJM, van der Zee JS, Braunstahl G-J, Zwinderman AH, Sterk PJ, Bel EH. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. *Thorax 2011*; 66: 514–520.

102 Chongmelaxme B, Lee S, Dhippayom T, Saokaew S, Chaiyakunapruk N, Dilokthornsakul P. The Effects of Telemedicine on Asthma Control and Patients' Quality of Life in Adults: A Systematic Review and Meta-analysis. *Journal of Allergy and Clinical Immunology in Practice 2019*; 7: 199-216.

103 Persaud YK. Using Telemedicine to Care for the Asthma Patient. *Current Allergy Asthma Reports 2022*; 22: 43–52.

104 Yang SK, Cho S-H, Kim DW. Interpretation of Clinical Efficacy of Biologics in Chronic Rhinosinustis With Nasal Polyps via Understanding the Local and Systemic Pathomechanisms. *Allergy, Asthma &Immunology Research 2022*; 14: 465.

105 Serajeddini H, Venegas Garrido C, Bhalla A, Kjarsgaard M, Huang C, LaVigne N, Radford K, Zhang K, Ho T, Svenningsen S, Mukherjee M, Nair P. A case series of dual biologics therapy for severe asthma. *Journal of Allergy and Clinical Immunology in Practice 2023*; 11: 335-340.

106 Chikumoto A, Oishi K, Hamada K, Hirano T, Kakugawa T, Kanesada K, Matsunaga K. Sequential Biotherapy Targeting IL-5 and IL-4/13 in Patients with Eosinophilic Asthma with Sinusitis and Otitis Media. *Biomolecules 2022;* 12: 522.

107 Baccelli A, Koćwin M, Parazzini EM, Rinaldo RF, Centanni S. Long-term outcomes of combination biologic therapy in uncontrolled severe asthma: a case study. *Journal of Asthma 2023;* 60: 1050–1053.

108 Kroes JA, Zielhuis SW, van Roon EN, ten Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochemical Pharmacology 2020;* 179: 113978.

109 Pérez de Llano L, Dávila I, Martínez-Moragón E, Domínguez-Ortega J, Almonacid C, Colás C, García-Rivero JL, Carmona L, García de Yébenes MJ, Cosío BG, Torrego A, Mena AH, Viña AL, Arrondo AP, Crespo A, Santana AH, Cisneros C, Picado C, Domingo C, Antolin D, Álvarez F, Soto G, Ercoreca IA, Ojanguren Í, Bobolea I, Urrutia I, Moguel IG, Dominguez JS, Rivera JMO, Chicote JMV, et al. Development of a Tool to Measure the Clinical Response to Biologic Therapy in Uncontrolled Severe Asthma: The FEV_1, Exacerbations, Oral Corticosteroids, Symptoms Score. *Journal of Allergy and Clinical Immunology in Practice 2021;* 9: 2725–2731.

110 Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, Pavord I. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax 2022;* 77: 199-202.

111 Murphy KR, Chipps B, Beuther DA, Wise RA, McCann W, Gilbert I, Eudicone JM, Gandhi HN, Harding G, Coyne KS, Zeiger RS, Kobernick AK, Mohammad A, Cherry AT, Fein A, Gaines A, Allison Ramsey, Michaud AL, Palmer A, Kim AS, Smith AM, White AA, Ricci AR, Kettelhut B V., Modena BD, Stone B, Rolston BS, Schnapf BM, Krajicek B, Kraft C, et al. Development of the Asthma Impairment and Risk Questionnaire (AIRQ): A Composite Control Measure. Journal of Allergy and Clinical Immunology In Practice 2020*; 8: 2263-2274.*

112 Stone JH, McDowell PJ, Jayne DRW, Merkel PA, Robson J, Patel NJ, Zhang Y, Yue H, Bekker P, Heaney LG. The glucocorticoid toxicity index: Measuring change in glucocorticoid toxicity over time. Seminars in Arthritis and Rheumatism 2022; 55: 152010.

113 McDowell PJ, Stone JH, Zhang Y, Honeyford K, Dunn L, Logan RJ, McGarvey LPA, Butler CA, Heaney LG. Glucocorticoid toxicity reduction with mepolizumab using the Glucocorticoid Toxicity Index. *European Respiratory Journal 2022*; 59: 2100160.

114 Menzies-Gow A, Jackson DJ, Al-Ahmad M, Bleecker ER, Cosio Piqueras F de BG, Brunton S, Canonica GW, Chan CKN, Haughney J, Holmes S, Kocks J, Winders T. A Renewed Charter: Key Principles to Improve Patient Care in Severe Asthma. *Advances in Therapy 2022;* 39: 5307–5326.

115 Canonica GW, Blasi F, Paggiaro P, Senna G, Passalacqua G, Spanevello A, Aliberti S, Bagnasco D, Bonavia M, Bonini M, Brussino L, Bucca C, Caiaffa MF, Calabrese C, Camiciottoli G, Caminati M, Carpagnano GE, Caruso C, Centanni S, Conte ME, Corsico AG, Cosmi L, Costantino MT, Crimi N, D'Alò S, D'Amato M, Del Giacco S, Farsi A, Favero E, Foschino Barbaro MP, et al. Oral Cortico-Steroid sparing with biologics in severe asthma: A remark of the Severe Asthma Network in Italy (SANI). *World Allergy Organization Journal 2020;* 13: 100464.

116 Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, Bosnic-Anticevich S, Harrington J, Hew M, Holland AE, Hopkins T, Jayaram L, Reddel H, Upham JW, Gibson PG, Bardin P. Oral corticosteroids stewardship for asthma in adults and adolescents: A position paper from the Thoracic Society of Australia and New Zealand. *Respirology 2021;* 26: 1112–1130.

117 Braunstahl G-J, Chlumský J, Peachey G, Chen C-W. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy, Asthma & Clinical Immunology 2013;* 9: 47.

118 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID, SIRIUS Investigators. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *New England Journal of Medicine 2014;* 371: 1189–1197.

119 Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, Barker P, Sproule S, Ponnarambil S, Goldman M. Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma. *New England Journal of Medicine 2017;* 376: 2448–2458.

120 Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *New England Journal of Medicine 2018*; 378: 2475–2485.

121 Dinsen S, Baslund B, Klose M, Rasmussen AK, Friis-Hansen L, Hilsted L, Feldt-Rasmussen U. Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. *European Journal of Internal Medicine 2013;* 24: 714–720.

122 Menzies-Gow A, Corren J, Bel EH, Maspero J, Heaney LG, Gurnell M, Wessman P, Martin UJ, Siddiqui S, Garcia Gil E. Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. *European Respiratory Journal Open Research 2019;* 5: 00009–02019.

Chapter

8

Summary

SUMMARY

Since 2016 the classification and management of chronic airway diseases has changed tremendously. A new management approach in asthma was introduced in order to improve clinical outcomes in the individual asthma patient. This new approach is based on a precision medicine strategy, in which treatable traits play a key role. Treatable traits have a significant impact on asthma control, quality of life, healthcare use and healthcare costs. There are many treatable traits identified that can be targeted with treatment, hence the name, treatable traits. However, a number of treatable traits in patients with uncontrolled asthma remain improperly addressed or neglected. This thesis focused on several key questions related to common and neglected treatable traits in adult asthma.

Chapter 2 describes a 1-day systematic multidisciplinary assessment of uncontrolled asthma patients in a specialised severe asthma centre. This assessment included an evaluation by an asthma specialist, physiotherapist, clinical psychologist and specialised asthma nurse and resulted in a personalised management plan carried out by the referring pulmonologist. Asthma control, quality of life and healthcare use were evaluated 1 year before and 1 year after the 1-day visit program. The study showed that patients with uncontrolled asthma benefit from a single extensive assessment, with a relevant improvement in asthma control, quality of life and healthcare use after 1 year. Compared with the year preceding the assessment, the number of exacerbations, emergency room visits and hospital admissions was reduced by 54%, 57% and 43%, respectively in the 12 months' follow up. These results suggest that a single short-term extensive characterisation in a specialised severe asthma centre is beneficial and might be cost effective for a large group of patients with uncontrolled asthma.

Chapter 3 provides an overview of nasal polyposis and asthma. From a chest physician's perspective, this review describes the relation between asthma and nasal polyposis, data on epidemiology, pathophysiology, impact on asthma control and clinical assessment as well as the treatment options and their effect on asthma outcomes.

Chapter 4 describes dynamic hyperinflation in patients with moderate to severe asthma. In patients with obstructive airway disease, exhalation may not be fully finished by the time the next breath is initiated, which leads to trapped air at end of exhalation. This is called hyperinflation. The term dynamic hyperinflation refers to increased amounts of air trapped at the end of each exhalation under conditions of a faster breathing rate (e.g., exercise). This may cause exertional dyspnea and diminished physical activity.
In this study we assessed the prevalence of dynamic hyperinflation in moderate to severe asthma. Secondly, we investigated the relationship between the degree of dynamic hyperinflation and severity of respiratory symptoms and limitations of daily life activities derived from different specific and general respiratory health questionnaires. 81% of patients with moderate to severe asthma showed dynamic hyperinflation. The severity of dynamic hyperinflation was related to lower scores on five different respiratory health questionnaires and significantly associated with impaired daily life activities. These results suggest that dynamic hyperinflation may be an important target for treatment in moderate to severe asthma.

Chapter 5 describes a trial that evaluates the effect of systemic glucocorticoids (a single injection with a high dose of triamcinolone) on the degree of dynamic hyperinflation in patients with moderate to severe asthma. The study showed that the degree of dynamic hyperinflation was significantly reduced in the group treated with triamcinolone as compared to the placebo group. The improvement in dynamic hyperinflation was found to be most pronounced in patients with elevated blood eosinophils and tended to be related to a decrease in blood eosinophils and fractionated exhaled nitric oxide. This suggest that dynamic hyperinflation is largely caused by airway inflammation and is therefore an important treatable trait, especially in patients with eosinophilic asthma.

In **chapter 6**, we analysed Dutch dispensing data from 182,849 adult patients with asthma between March 2017 and March 2018 (focus year). The aim of this study was to investigate the prevalence of patients requiring 2 or more courses or maintenance use of oral corticosteroids (OCS) (i.e. frequent users), their use of inhaled corticosteroids (ICS), and who prescribed their asthma medications (specialist or general practitioner). In addition, we estimated the contribution of OCS course prescriptions versus maintenance OCS use prescriptions to the cumulative OCS exposure in these patients. The study showed that 7.2% of Dutch patients with asthma were overexposed to OCS. 2.6% of patients received 2 or more OCS courses and 4.6% were on maintenance OCS therapy, of whom only about half used adequate doses of ICS. The majority (57%) of patients with frequent OCS use had their OCS prescribed by a general practitioner in the focus year. About half of patients with frequent OCS courses and one-third of patients on maintenance OCS had not been prescribed any asthma medication by a specialist up to 3 years before the focus year. This suggests that these patients were treated in primary care, without specialist supervision. Furthermore, maintenance OCS therapy contributed most to the cumulative OCS dose. However, the OCS dose attributable to courses still accounted for approximately 40% of total OCS exposure, and this pattern did not substantially differ between different levels of asthma severity. The results of this study suggest that OCS overuse is often underdiagnosed and inadequately addressed.

In conclusion, with this thesis we aimed to contribute to the concept of treatable traits in asthma patients. We emphasized the need for systematic multidisciplinary assessment of patients with uncontrolled asthma and showed that asthma control, quality of life and healthcare use can be improved with a single extensive assessment in a specialised severe asthma centre. Furthermore, we focused on three new treatable traits, namely nasal polyposis, dynamic hyperinflation and OCS overuse. By highlighting these treatable traits, we have attempted to further unravel the complexity of asthma.

Chapter

9

Samenvatting

SAMENVATTING

Sinds 2016 is de manier waarop chronische longziekten worden ingedeeld en behandeld enorm veranderd. De astmabehandeling werd op een andere manier benaderd om beter aan te sluiten op de klachten die individuele patiënten met astma ervaren. Deze nieuwe aanpak wordt 'precision medicine' genoemd. Hierbij wordt gezocht naar specifieke kenmerken die astma kunnen verergeren en behandelbaar zijn. We noemen dit 'treatable traits'. Deze kenmerken hebben aanzienlijke invloed op astmacontrole, kwaliteit van leven, het gebruik van gezondheidszorg en de bijbehorende kosten. Helaas worden veel van deze 'treatable traits' bij patiënten nog altijd onvoldoende behandeld of miskend. Dit proefschrift richt zich op verschillende belangrijke vragen over veelvoorkomende en miskende 'treatable traits' bij volwassenen met astma.

Hoofdstuk 2 beschrijft een gestructureerde 1-daagse beoordeling van patiënten met ongecontroleerd astma door verschillende medische disciplines in een gespecialiseerd ernstig astmacentrum. Deze beoordeling bestond uit een evaluatie door een astma-specialist, fysiotherapeut, klinisch psycholoog en gespecialiseerde astmaverpleegkundige. Dit resulteerde in een persoonlijk behandelplan voor de patiënt met ongecontroleerd astma, welke vervolgens werd uitgevoerd door de verwijzend longarts. Astmacontrole, kwaliteit van leven en zorggebruik werden 1 jaar voor en 1 jaar na het 1-daagse programma geëvalueerd. De studie toonde aan dat patiënten met ongecontroleerd astma baat hebben bij deze eenmalige uitgebreide beoordeling. Er was sprake van een relevante verbetering van de astmacontrole, kwaliteit van leven en zorggebruik na 1 jaar. Vergeleken met het voorafgaande jaar was het aantal longaanvallen, spoedeisende hulp bezoeken en ziekenhuisopnames met respectievelijk 54%, 57% en 43% gedaald. Deze resultaten suggereren dat een eenmalige uitgebreide beoordeling in een gespecialiseerd ernstig astmacentrum een positieve invloed heeft op de astma controle en kwaliteit van leven. Ook zou het kosteneffectief kunnen zijn door afname van zorggebruik voor een grote groep patiënten met ongecontroleerd astma.

Hoofdstuk 3 betreft een overzicht over neuspoliepen en astma. In dit overzichtsartikel wordt de relatie tussen astma en neuspoliepen beschreven vanuit het oogpunt van de longarts. Er wordt informatie gegeven over hoe vaak deze aandoeningen gezamenlijk voorkomen (epidemiologie) en hoe ze ontstaan en werken (pathofysiologie). Daarnaast wordt de invloed van neuspoliepen op astmacontrole besproken. Ook de beoordeling door de arts en de behandelmogelijkheden en hun effect op astma uitkomsten.

Hoofdstuk 4 gaat over dynamische hyperinflatie bij patiënten met matig tot ernstig astma. Bij een snellere ademhaling, zoals bij inspanning, is er minder tijd om volledig uit te ademen voordat de volgende inademing begint. Bij astma- en COPD-patiënten met vernauwde luchtwegen kan hierdoor extra lucht in de longen achterblijven. Dit fenomeen wordt 'dynamische hyperinflatie' genoemd. Het kan een gevoel van kortademigheid en beperking bij inspanning geven. In deze studie evalueerden wij het voorkomen van dynamische hyperinflatie bij patiënten met matig tot ernstig astma. Daarnaast onderzochten wij het verband tussen dynamische hyperinflatie, de ernst van astmasymptomen en de beperkingen bij inspanning. Deze uitkomsten baseerden we op scores van verschillende vragenlijsten over longziekten. Bij 81% van de patiënten met matig tot ernstig astma was er sprake van dynamische hyperinflatie. De ernst van dynamische hyper-

inflatie was gerelateerd aan lagere scores op de verschillende vragenlijsten met betrekking tot astmasymptomen en beperking bij inspanning. Deze resultaten suggereren dat dynamische hyperinflatie een belangrijk doel kan zijn in de behandeling van patiënten met matig tot ernstig astma.

Hoofdstuk 5 beschrijft een onderzoek waarin gekeken wordt naar het effect van ontstekingsremmers (eenmalige injectie met een hoge dosis triamcinolon) op de mate van dynamische hyperinflatie bij patiënten met matig tot ernstig astma. Uit deze studie bleek dat dynamische hyperinflatie was afgenomen in de groep die werd behandeld met triamcinolon in vergelijking met de placebogroep. De verbetering van de dynamische hyperinflatie was het meest uitgesproken bij patiënten met een verhoogd aantal ontstekingscellen (eosinofiele cellen) in het bloed. De verbetering van dynamische hyperinflatie ging ook samen met een afname van de eosinofiele cellen in het bloed en de hoeveelheid stikstofmonoxide in de uitgeademde lucht (maat voor ontsteking in de luchtwegen). Dit suggereert dat dynamische hyperinflatie grotendeels wordt veroorzaakt door ontsteking van de luchtwegen en is daarom een belangrijke 'treatable trait', vooral bij patiënten met astma waarbij eosinofiele cellen een belangrijke rol spelen.

In **hoofdstuk 6** analyseerden wij de uitgifte van orale corticosteroïden (OCS) door de apotheek aan 182,849 volwassen patiënten met astma tussen maart 2017 en maart 2018 in Nederland. Het doel van deze studie was om inzicht te krijgen in het aantal patiënten dat twee of meer OCS stootkuren of OCS onderhoudsbehandeling nodig hadden. Ook werd gekeken naar het gebruik van inhalatiemedicatie en of dit was voorgeschreven door de huisarts of de specialist. Daarnaast werd de bijdrage van OCS stootkuren en OCS onderhoudsbehandeling aan de totale OCS blootstelling bij deze patiënten berekend. Uit de studie bleek dat 7,2% van de Nederlandse patiënten met astma werden blootgesteld aan OCS. 2,6% van de patiënten kreeg twee of meer OCS stootkuren en 4,6% kreeg een OCS onderhoudsbehandeling, waarvan slechts ongeveer de helft een goede dosis inhalatiemedicatie gebruikte. De meerderheid (57%) van de patiënten die vaak OCS gebruikten kreeg dit voorgeschreven door de huisarts. Ongeveer de helft van de patiënten die vaak een OCS stootkuur kregen en een derde van de patiënten met OCS onderhoudsbehandeling hadden tot drie jaar van te voren geen astmamedicatie voorgeschreven gekregen door een specialist. Dit suggereert dat deze patiënten in de eerstelijnszorg worden behandeld, zonder een beoordeling door een specialist. Daarnaast droeg onderhoudsbehandeling met OCS het meest bij aan de totale OCS blootstelling. Maar ook stootkuren droegen voor ongeveer 40% hieraan bij. De resultaten van deze studie suggereren dat overmatig OCS gebruik vaak wordt miskend en onvoldoende wordt aangepakt.

Concluderend, met dit proefschrift hebben wij een bijdrage geleverd aan het 'treatable traits' concept bij astmapatiënten. Zo hebben we het belang van een gestructureerde 1-daagse beoordeling van patiënten met ongecontroleerd astma door verschillende medische disciplines benadrukt. Ook toonden we aan dat astma controle, kwaliteit van leven en zorggebruik kunnen worden verbeterd met een eenmalige uitgebreide beoordeling in een gespecialiseerd ernstig astma centrum. Verder hebben wij ons op drie nieuwe 'treatable traits' gericht, namelijk neuspoliepen, dynamische hyperinflatie en overmatig OCS gebruik. Met het belichten van deze 'treatable traits' hebben wij geprobeerd de complexiteit van astma verder te ontrafelen.

Appendices

Curriculum Vitae

PhD portfolio

List of publications

List of abbreviations

Contributions of authors

Dankwoord

CURRICULUM VITAE

Akke-Nynke van der Meer werd op 26 april 1985 geboren te Smallingerland. In 2003 rondde zij het gymnasium op het Lauwers College te Buitenpost af en startte in datzelfde jaar met de studie Geneeskunde aan de Rijks Universiteit Groningen.
Na het behalen van het artsexamen in 2009 ging zij werken als ANIOS op de Spoedeisende Hulp van de Tjongerschans te Heerenveen. Na een klein jaar besloot zij te gaan werken als ANIOS Longziekten op de longafdeling in het Medisch Centrum Leeuwarden, waarna zij aldaar in 2011 startte met de opleiding tot longarts. Na een afsluitende stage bij de Allergologie in het Universitair Medisch Centrum Groningen rondde zij in 2017 de opleiding tot longarts af. Vanaf 2016 startte zij met haar promotietraject onder begeleiding van prof. dr. E.H.D. Bel (Amsterdam Universitair Medische Centra) en dr. A. ten Brinke (Medisch Centrum Leeuwarden). Sinds 2017 is Akke-Nynke als longarts werkzaam in de Maatschap Friese Longartsen in het Medisch Centrum Leeuwarden. Hier beoefent zij het longartsen vak in de volle breedte, maar heeft zich gespecialiseerd in ernstig astma en allergologie.

Akke-Nynke is verloofd met Sebastiaan Lommelaars en samen hebben zij een zoon (Levi 2021). Zij wonen momenteel in Groningen, maar hopen over niet al te lange tijd in Leeuwarden te gaan wonen.

PhD PORTFOLIO

PhD Training	Year	ECTS
General courses		
Basic course regulations and organization for clinical investigators (BROK)	2017	1.0
AMC World of Science	2020	0.7
Talents in PhD	2020	0.2
Specific courses		
Evidence based richtlijn ontwikkeling (EBRO) webinars (3)	2020	0.3
Seminars, workshops and master classes		
Op de Hoogte van Astma, Davos	2015, 2019 2021, 2023	4.0
Netherlands Respiratory Society (NRS), Young Investigator Symposium	2017	0.4
ERS Masterclass in airway disease	2019	0.6
Presentations		
Op de Hoogte van Astma, Davos, Bijwerkingen van corticosteroïden bij astma (workshop)	2015	0.3
Regionale refereeravond, Leeuwarden, The one stop asthma shop	2015	0.2
OOR-onderwijs AIOS Longziekten, Leeuwarden, Ernstig Astma Expertise Centrum-Eendaagse beoordeling	2018	0.2
Op de Hoogte van Astma, Davos, Treatable traits in asthma, longartsen (workshop)	2019, 2021	0.6
Asthma on Top symposium, Davos, Treatable traits in asthma, longverpleegkundigen (workshop)	2019	0.3
MediaMed, Amsterdam, OCS afbouwen in de praktijk, hoe pak je dat evidence based aan? (webinar)	2021	0.2
CAHAG Klankbordbijeenkomst, Utrecht, "Doet u mij nog maar een prednison kuur!"	2023	0.2
(Inter)national conferences		
American Thoracic Society (ATS)	2014-2019	
- ATS 2014, San Diego, The walking bike as a tool to improve exercise capacity: comparison between COPD and heart failure patients (poster discussion)		3.5
- ATS 2016, San Francisco, A 1-day visit in a severe asthma centre; effect on asthma control, QOL and healthcare use (poster)		3.0
- ATS 2018, San Diego		2.0
- ATS 2019, Dallas, Dynamic hyperinflation: a treatable trait in asthma (poster discussion)		3.5

European Respiratory Society (ERS)	2017-2020	
- ERS 2017, Milan, Dynamic hyperinflation: an important target for treatment in asthma (poster)		3.0
- ERS 2018, Paris, Dynamic hyperinflation predicts impaired daily life activity in asthma (poster)		3.0
- ERS 2019, Madrid		2.0
- ERS 2020, online, Oral corticosteroids for asthma usually prescribed by non-specialists (poster)		3.0
European Academy of Allergy and Clinical Immunology (EAACI)	2015	
- EAACI 2015, Barcelona, Evaluation of patients with uncontrolled asthma in a specialized severe asthma centre; the effect on asthma control, quality of life and healthcare utilization (poster discussion)		3.5
Longdagen	2017	
- AIOS-symposium 2017, Ermelo, Ernstig Astma Expertise Centrum - betere astma controle na eendaagse beoordeling		0.2
Medisch Centrum Leeuwarden research symposium	2016-2019	
- 2016, A one-day-visit program in a specialized severe asthma center; The effect on asthma control, quality of life and healthcare utilization (oral)		0.2
- 2018, Dynamic hyperinflation, an important target for treatment in asthma (powertalk)		0.2
- 2019, Dynamic hyperinflation, a treatable trait in asthma (oral)		0.2

Other activities

Chair thematic poster session ERS	2017	0.5
Meet the Evidence, research meeting Medisch Centrum Leeuwarden	2018-2023	1.8

Teaching	Year	ECTS
Lecturing		
Longdagen, Ermelo, Vitamine D goed voor alles, ook voor astma?	2016	0.2
Longdagen, Ermelo, (niet) Medicamenteuze behandeling ernstig astma	2018	0.3
Longfonds, patiëntenvereniging, Alles over astma	2018	0.2
ALK, Kopenhagen, ''State of the art'' astma en allergie	2018	0.3
Longdagen, Ermelo, Clinical year in review; ontwikkelingen astma/COPD zorg	2019	0.2
Asthma on Top symposium, Davos, Organisatie astma zorg	2019	0.2
Bronkhorst, Antwerpen, De longarts in consult: Astma en zwangerschap wat nu?	2019	0.3
Het Astma Spreekuur, Leeuwarden	2019-2021	0.6
MedNet Live webcast, Hilversum, Astma zorg anno 2021	2021	0.2

Supervising

Consultant Respiratory Medicine, Medisch Centrum Leeuwarden	2017 - present
Supervising residents, physicians and students	2017 - present

Other activities	Year
Online moderator webinar ''Behandeling van ernstig astma, Medicamenteus en niet medicamenteus''	2018
Dagelijks bestuur Stichting Rotterdam Leeuwarden Expertise (RoLeX) Obstructieve Longziekten	2019 - present
Online moderator webinar "Nieuwe richtlijn ernstig astma''	2020
Programmacommissie Op de Hoogte van Astma	2020 - present
Co-auteur Richtlijn Astma en Zwangerschap	2020 - 2023
Programmacommissie Allergie aan Zee	2021 - present

Parameters of esteem	Year
Autletius prijs research symposium Medisch Centrum Leeuwarden	2019

LIST OF PUBLICATIONS

Chapters of this thesis

A.N. van der Meer, H. Pasma, W. Kempenaar-Okkema, J.A. Pelinck, M. Schutten, H. Storm, A. ten Brinke. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. *European Respiratory Journal 2016; 48: 726-733*.

A.N. van der Meer, A. ten Brinke. *Nasal polyposis and asthma: the chest physician's view. In: Bachert C, Bourdin A, Chanez P, eds. The Nose and Sinuses in Respiratory Disorders (ERS Monograph). Sheffield, European Respiratory Society, 2017; pp. 105-121*.

A.N. van der Meer, K. de Jong, A. Hoekstra-Kuik, E.H. Bel, A. ten Brinke. Dynamic hyperinflation impairs daily life activity in asthma. *European Respiratory Journal 2019; 53: 1-8*.

A.N. van der Meer, K. de Jong, A. Hoekstra-Kuik, E.H. Bel, A. ten Brinke. Targetting dynamic hyperinflation in moderate to severe asthma – a randomised controlled trial. *European Respiratory Journal 2021; 7: 00738-2020*.

A.N. van der Meer, K. de Jong, M. Ferns, M. Krol, C. Widrich, A. ten Brinke. Overuse of oral corticosteroids is often underdiagnosed and inadequately adressed. *The Journal of Allergy and Clinical Immunology: In Practice 2022; 10: 2093-2098*.

Other publications

J.A. Kroes, S.W. Zielhuis, **A.N. van der Meer**, K. de Jong, E.N. van Roon, A. ten Brinke. Optimizing omalizumab dosing in severe asthma – the exploration of therapeutic drug monitoring. *The Journal of Allergy and Clinical Immunology: In Practice 2021; 9: 1408-1410*.

J.A. Kroes, S.W. Zielhuis, **A.N. van der Meer**, K. de Jong, A. ten Brinke, E.N. van Roon. Patient-reported outcome measures after 8 weeks of mepolizumab treatment and long-term outcomes in patients with severe asthma: an observational study. *International Journal of Clinical Pharmacy 2022; 44: 570-574*.

J.A. Kroes, L.H.G. van Hal, L. van Dijk, S.W. Zielhuis, **A.N. van der Meer**, E.N. van Roon, A .ten Brinke. "The last week is drama" - The perceived waning of biologics in severe asthma. *Submitted*

Z. Tempels-Pavlica, M.C.J. Aarts, P.M.J. Welsing, **A.N. van der Meer**, L.P. van der Zwan, E. Uss, A.C. Knulst. House dust mite sublingual allergen immunotherapy tablet is safe and well-tolerated in Dutch clinical practice. *Submitted*

S.A. van Nederveen-Berdien, M. de Kruif, **A.N. van der Meer**, A.H. Feitsma, C. van Hoolwerff, K. Koehorst-ter Huurne, A. Kuiterman, A. Wittkampf, M. Poulissen-Erinkveld, A. Brons. *Multidisciplinaire richtlijn Astma en Zwangerschap. NVALT 2023*.

LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
ACT	Asthma Control Test
AERD	Aspirin Exacerbated Respiratory Disease
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BMI	Body Mass Index
BTS	British Thoracic Society
CCQ	Clinical COPD Questionnaire
CF	Cystic Fibrosis
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardio Pulmonary Exercise Testing
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyposis
CRSwNP	Chronic Rhinosinusitis with Nasal Polyposis
CT	Computer Tomography
DH	Dynamic Hyperinflation
4DSQ	4 Dimensional Symptom Questionnaire
E	Expiration
ENT	Ear, Nose, and Throat
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ER	Emergency Room
ESS	Endoscopic Sinus Surgery
FDA	Food and Drug Administration
FeNO	Exhaled Fraction of Nitric Oxide
FEV_1	Force Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GA^2LEN	Global Allergy and Asthma Network of Excellence
GER	Gastroesophageal Reflux
GP	General Practitioner
GINA	Global Initiative for Asthma
HCU	Healthcare Use
HRCT	High Resolution Computer Tomography
I	Inspiration
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
ILC2	Type 2 Innate Lymphoid Cells
IQR	Interquartile Range
kU	Kilo Units
Kg	Kilogram

L	Litre
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Antagonists
LCADL	London Chest Activity of Daily Living scale
MARS	Medication Adherence Report Scale
MPT	Metronome-Paced Tachypnoea
µg	Microgram
Mg	Milligram
Ml	Millilitre
6-MWD	Six-Minute Walking Distance
NSAID	Non-Steroidal Anti-Inflammatory Drug
NY	New York
OCS	Oral Corticosteroids
OR	Odds Ratio
OSAS	Obstructive Sleep Apnoea Syndrome
PCD	Primary Ciliary Dyskinesia
Ppb	Parts per billion
QoL	Quality of Life
RAST	Radio Allergo Sorbent Test
RCT	Randomized Controlled Trial
RV	Residual Volume
SAD	Small Airway Disease
SARP	Severe Asthma Research Program
SE	Staphylococcus aureus Enterotoxin
SGRQ	St. George's Respiratory Questionnaire
SHARP	Severe Heterogeneous Asthma Research collaboration, Patient-centred
SIGN	Scottish Intercollegiate Guidelines Network
SOBDA	Shortness of Breath with Daily Activity
Th	T helper
TLC	Total Lung Capacity
TSLP	Thymic Stromal Lymphopoietin
UK	United Kingdom
USA	United States of America

CONTRIBUTIONS OF AUTHORS

Chapter 2
Conception and design: A.N. van der Meer (AM), A. ten Brinke (AB)
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Design of tables and figures: AM, AB
Drafting of manuscript: AM, AB
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Chapter 3
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Chapter 4
Conception and design: A.N. van der Meer (AM), A. ten Brinke (AB), E.H. Bel (EB)
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Data collection: AM
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Chapter 5
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Chapter 6
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