Erik-Jonas van de Griendt

Treatment of problematic severe asthma in children

THESIS

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1

General introduction

GENERAL INTRODUCTION

Before introducing the aims and chapter outline of the thesis, this chapter introduces the core definitions and challenges of childhood asthma as well as the difficulties that are encountered in treatment.

Childhood asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1] Asthma affects an estimated 300 million patients worldwide, counting for up to 15% of all children in Western countries.[2] The prevalence of asthma in children has been increasing with a slight trend towards stabilization in the new millennium.[3,4,5] Asthma in children can interfere significantly with normal daily life and that of their parents or caregivers. Asthmatic children have more missed schooldays, a lower disease specific quality of life and more scheduled and unscheduled visits to doctors or emergency care than their healthy peers.[6,7]

Asthma control and treatment

The current main focus in asthma treatment is to gain asthma symptom control.[1,8] Asthma symptom control is assessed on a combination of items, such as respiratory symptoms during the day or at night, exercise tolerance, exacerbations, need of rescue medication and can be captured in a validated checklist that assesses the level of asthma control over the past 4 weeks.[8,9,10] Based on the level of control, not severity, asthma can be well controlled, partially controlled or uncontrolled.[2] Inhalation medication (short-acting-β_2-agonists (SABA) and inhaled corticosteroids (ICS)) have been shown to be highly effective in reducing acute respiratory symptoms and airway inflammation[11,12,13] and is the cornerstone of asthma treatment.[8,14,15]

Difficulties in treatment - what if the basic approach does not work?

Pediatric asthma is a complex disease that is influenced by multiple factors.[16] A stepped approach is recommended in current asthma guidelines.[1,8,14] If asthma control is insufficient and step-up in medication from step 2 (ICS in a base dose) to 3 (doubling the dose or adding other medication) seems necessary, several factors should be assessed carefully.

Reconsider the diagnosis. Is there ever presence of the key symptom wheeze? Is this wheeze confirmed on auscultation and/or catched on pulmonary function testing? Is it reversible on administration of inhaled SABA? Other diseases might mimic asthma or asthmatic attacks.

Inhaler technique and dose deposition. A correct inhaler technique can be difficult to accomplish in young children, for example because leakage of the facemask that is attached to a spacer and crying during inhalation of the medication diminish the effective dose of inhaled medication.[17,18] Checking inhaler technique and retraining is essential to achieve optimal deposition of medication in the lungs. Instructions to do so must address both child and parents, including careful cultural and lingual adjustment.[19]

Compliance. The extent to which doctor's advices are followed is an important contribution to the management of the disease. If parents and children understand the need for regular inhalers and trust inhaled steroids, they are more likely to be motivated to take the medication regularly.[20] In these patients, compliance is usually still suboptimal due to *non-intentional factors* (simply forgetting, being busy and forgetting, having trouble incorporating medication into a daily routine, child reacting to medication and being asleep before the evening dose). Non-compliance can also be *intentional* and is influenced by symptom perception and medication beliefs.[21] Even in studies using an electronic device to measure daily medication administration, adherence is far less than 100%, i.e. 40 – 70%, with one exception of 92% due to extensive follow-up and education in the clinic.[20] In adults with mild to moderate asthma, Greaves et al showed that suboptimal compliance to medication (e.g. 50% of the dose prescribed) did not influence quality of life and did not increase the number of unscheduled doctors visits due to asthma.[22] Given that most asthma patients know the behavior of their asthma very well and know the circumstances when their symptoms will reappear this type of "well-reasoned" non-adherence could be appropriate for some patients. This observation was in contrast to the severe asthmatic group where they found that non-adherence led to a decreased quality of life and increased number of unscheduled visits.[22] So, in uncontrolled and severe asthma, non-compliance seems to be a major issue. In a group of tertiary referred children with difficult to treat asthma, compliance remained a major issue to ensure or improve.[23] Setting collective goals and achieving concordance is likely to improve (though not guarantee) compliance.[8]

Exposure. Challenging difficulties in daily management of the disease can include avoidance of allergic (see below) or aspecific and emotional triggers. Among aspecific triggers, preventing any form of smoke exposure (direct, second or third hand smoking) is important.[8]

Comorbidity. Comorbidity such as obesity (see below), allergic rhinitis (see below), dysfunctional breathing, or vocal cord dysfunction can impede the daily management of the asthma.[24,25] Gastro-oesophageal reflux as a comorbidity has been suggested and a possible association has been described[26] but its role in pediatric difficult asthma remains uncertain and treatment of gastro-oesophageal reflux to improve the asthma is seldom successful in children with persistent severe asthma.[27]

Psychosocial problems. Psychosocial problems may play an important role in asthma management. Children and adolescents with asthma have an almost 2 times higher risk at internalizing emotional and behavioral problems such as withdrawn behavior, anxiety and depressive disorders.[28] The burden of asthma can disturb normal development such as separation and individuation from parents and associated anxiety. Psychosocial factors such as acute or chronic stress may trigger asthma exacerbations.[29]

Behavioral problems may underlie poor adherence and self-management, or the other way around. Whether anxiety and depression are the cause or result of severe asthma is often not known. When both need to be addressed for proper treatment, it is even not productive to disentangle this problem.[27] Thus, behavioral and psychosocial problems are thought to influence asthma control and disease specific quality of life, but have been poorly studied. Evidence for treatment on psychological interventions for children with chronic illness such as asthma is non-conclusive, probably due to large diversity in the conditions and interventions.[30]

Problematic severe asthma

Most children respond well to treatment, however in a small portion of pediatric patients with asthma (the precise prevalence is unknown) symptoms persist despite optimal treatment and asthma is not well controlled. These children are classified to have problematic severe asthma (PSA). PSA comprises difficult-to-treat asthma (DTTA) and therapy resistant asthma (TRA) and represents the most severe group of asthmatic children.[31] 'Getting the basics right' in children with apparently problematic severe asthma makes the disease treatable again in a very substantial portion.[32,27] When systematically analyzing a group of children with PSA during treatment with i.m. triamcinolone, 85% showed a response in at least one outcome measure.[33] Only 15% of this selected group of severe instable asthmatic children did not respond to a depot of systemic corticosteroids, probably representing true (corticosteroid) treatment resistance. Thus, these results suggests that true TRA is rare in children.

Obesity and asthma

The worldwide prevalence of childhood overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010 and the number of obese children is expected to increase more.[34] Exogenous obesity is caused by a sustaining imbalance between energy intake and expenditure, resulting an accumulation of body fat (for example a longer time overshoot of only 160kCal each day for children).[35] There is evidence that adults with obesity have a higher risk to get a new doctor's diagnosis of asthma, with an overall Odds ratio of 1.51.[36] In children with high birth weight, the risk of getting asthma had an Odds ratio of 1.2, overweight in middle childhood ages had a comparable risk to adults (Odds 1.5).[37] The true contribution of obesity to asthma or asthma symptoms in children remains un-

clear.[38] In a large cohort study in The Netherlands, Body Mass Index standard deviation score (SDS-BMI) correlated with asthma symptoms as based on an online questionnaire in girls, but not in boys, which evokes questions on causality.[39] The existence of an asthma-obesity phenotype has been confirmed in other studies[40,41] and seems to fall apart in an early onset (<12 years) and a late onset asthma-obesity phenotype.[42] Children with early onset were more likely to have greater fall in obstructive lung function measures, a higher degree of bronchial hyperresponsiveness and higher immunoglobulin E (IgE) levels, and were more likely to have (severe) exacerbations, continuous chest tightness and sputum production.[42] As an explanation for the asthma-obesity link most studies assume mechanical (increased fat mass) and related systemic inflammatory changes (due to the changed body composition) that in turn can influence airway inflammation.[43,44] An overview of possible factors associated with obesity-related asthma (in the context of obesity preceding) asthma are summarized in figure 1.[45]

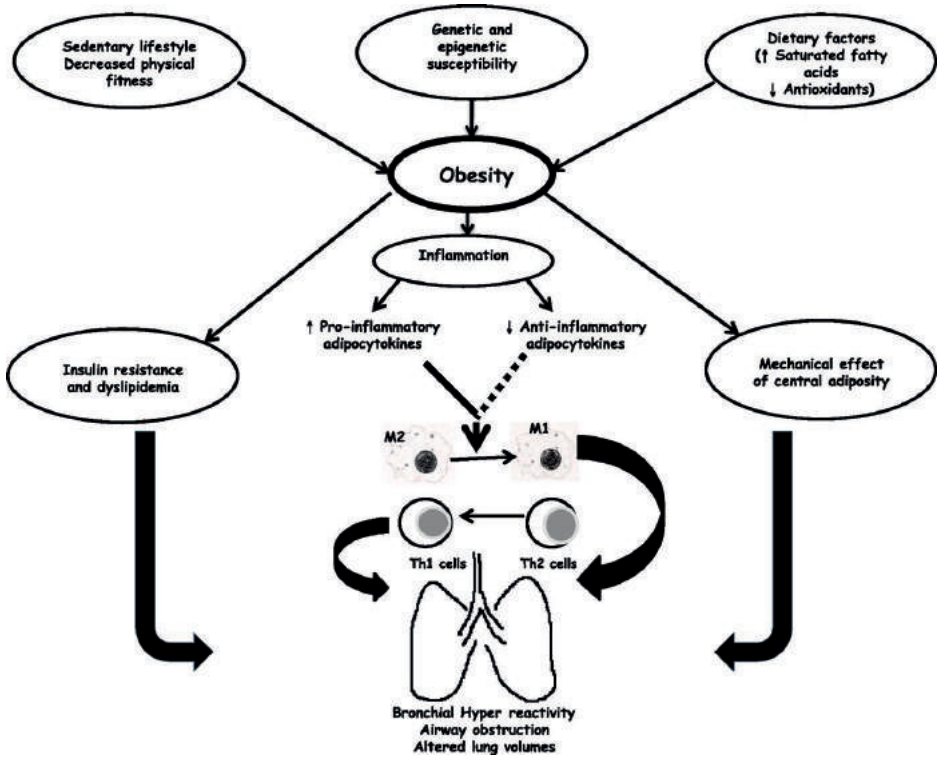

Figure 1. overview of effects of obesity on respiratory aspects (reprinted with permission).[45]

Asthma and allergic rhinitis; Immunotherapy

The most common comorbidity in allergic asthma in children is allergic rhinitis, often due to house dust mite allergy or tree / grass pollen allergy,[24] symptoms of which occur in 60-80% of asthmatic children.[25,46] In young children, being sensitized to inhalation allergens predicts a larger chance on getting asthma at the age of 6 years.[47] However, a substantial part of (young) children is sensitized to inhaled aero-allergens, without having symptoms or without having symptoms yet. Conversely, atopic adults with asthma who were exposed to high levels of dust mite or dog allergens but not sensitized to these allergens had evidence of increased airway reactivity.[48]

Allergic rhinitis shares a common pathophysiological pathway with asthma, which has been described as the *united airway concept*.[49] Manifest allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[50,51]

Treatment of allergic rhinitis is tailored according to persistent (perennial) or intermittent symptoms, and to the severity of the symptoms such as sleep disturbances, exercise intolerance, lack of concentration and depressed school results.[52] Usually, sufficient symptom control can be reached with local or systemic anti-histaminic or anti-inflammatory medication, or a combination of these.[49,53] When symptoms of allergic rhinitis cannot be controlled sufficiently with the combination of nasal corticosteroids and oral antihistamines, immunotherapy can be considered as additional treatment.[54] Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract and is available for allergens such as grass and tree pollen and house dust mite. After disappointing results of low-dose preparations in drops, effective sublingual immunotherapy (SLIT) has become available with grass pollen allergen extract in a daily sublingual tablet.[55,56] Although suggestions on prevention of asthmatic disease in children by means of subcutaneous immunotherapy have been made,[57] the effects of immunotherapy on patient relevant asthma outcomes in children remain unclear to date (*this thesis*). Immunotherapy targeting house dust mite allergy has recently become available in sublingual form and was studied in adults regarding treatment effects on allergic rhinitis and asthma.[58,59] Sublingual treatment seemed to be safe for treatment in adolescents with allergic rhinitis.[60]

Practical drawbacks and challenges; treatment options in problematic severe asthma

Guidelines treat standard patients, but the standard patient does not exist. Imagine for example a 14 year old girl with allergic asthma, obesity, decreased physical fitness and exercise intolerance, getting mood disturbances reinforced by and becoming more and

more panicked due to attacks of dyspnea of a different nature (dysfunctional breathing) than experienced before, causing her asthma rescue medication not to work.

Possible treatment options for difficult asthma or PSA can be multidisciplinary but have been poorly studied. Multidisciplinary evaluation is recommended and has the aim to decide for further invasive diagnostic steps such as bronchoscopy or CT-scanning, especially to rule out other diagnoses.[27] Besides, possible mechanisms that explain the situation and possible treatment strategies can be discussed. In most tertiary referral centers multidisciplinary evaluation is done by a pediatric pulmonologist, specialized nurse, dedicated physiotherapist and clinical psychologist, preferably with information from a home visit.[61]

Over and above multidisciplinary treatment, suggestions have been made on treatment in an (almost) allergen-free environment at high altitude. A small but controlled study in adolescents treated at high altitude showed a better outcome on hyperresponsiveness and quality of life than treatment at sea level.[62] In a larger study of severe asthmatic adults an improvement in lung function, lower (systemic) medication, better quality of life and 6-minutes walking distance was reached after multidisciplinary treatment at high altitude, both in allergic and non-allergic asthma patients.[63] However, this study was not designed for comparison with multidisciplinary treatment at sea level.

Medical treatment options in problematic severe asthma include anti-IgE injections, high dosed nebulized inhaled steroids (eventually with a breath-actuated jet nebulizer), systemic corticosteroids or other (new) anti-inflammatory drugs. Omalizumab (anti-IgE injections) is an effective add-on in children with severe allergic asthma and can diminish exacerbation rates.[64] However there are disadvantages for the patient such as time consuming injections and possible side effects and it is rather expensive, which urges for balancing the recommendation to start this therapy, especially in a non-compliant patient. Promising new anti-inflammatory drugs (biologicals) are currently investigated and are not yet imbedded in current clinical pediatric practice.

Thesis outline and aims

The aim of this thesis is to get insight into difficulties in the treatment of asthma in children both from a psychosocial (behavioral) viewpoint and from a pathophysiological point of view, as summarized above. It also aims to illuminate clues for further treatment in a deadlock situation for young patients with asthma.

This thesis starts with current insights in pediatric asthma diagnosis and treatment as presented in **chapter 2**. This chapter shows the current Dutch Guideline on Pediatric Asthma and the way it links to different synchronized initiatives on diagnosis and treatment of childhood asthma in The Netherlands.

Beyond this starting point, challenging difficulties in the treatment are being faced, specifically behavioral problems in children with problematic severe asthma and obesity and its possible link with asthma.

Chapter 3 examines behavioral problems in children and adolescents with difficult-to-treat asthma.

In **chapter 4** the association of the child's behavioral problems and asthma control and quality of life after multidisciplinary treatment in a high altitude clinic is examined.

Chapter 5 analyzes the possibility of reducing maintenance medication in severe asthmatic children in multidisciplinary treatment at a high altitude clinic. Here we try to predict which patients can be tapered from inhaled corticosteroids on the basis of asthma control, pulmonary function testing and disease specific quality of life.

A massive and growing problem in Western countries is childhood obesity, which interferes with many aspects of health and quality of life in children. In **chapter 6** we examine lung function changes related to obesity. The gain in lung function after massive weight loss in children with severe obesity without asthma is evaluated.

In **chapter 7** we describe a smaller group of children with asthma and obesity and their changes in lung function after massive weight loss. Here we try to find some clues to disentangle the asthma – obesity problem.

Chapter 8 has the viewpoint of adjuvant therapies, targeting for the common allergenic pathway in childhood asthma and its common comorbidity allergic rhinitis. In a systematic review we critically examine evidence for immunotherapy and its adjuvant value for children with asthma and allergic rhinitis using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) to rate the level of quality of studies.

The final **chapter 9** discusses the main findings of this thesis and its implications for clinical practice, offers suggestions on asthma treatment in difficult settings and problematic severe asthma and presents directions for future research.

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Dutch Guideline on pediatric asthma

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EJG chaired the guideline working group, defined clinically relevant outcome measures, performed AGREE comparison, analyzed literature outcome, wrote and revised the guideline, and approved the final version. MKT was methodologist of the guideline working group, provided methodological input (provided literature search, selection, critical appraisal, GRADE evidence profiles), wrote and revised the guideline, and approved the final version. NB and JvE advised the working group, guided the guideline process. NB analyzed literature outcome. JvE made revisions to the final version of the guideline.
Working group members judged conclusions from the selected literature, discussed recommendations and provided practical and clinical input. All authors revised and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Richtlijn astma bij kinderen

Nederlandse Vereniging voor Kindergeneeskunde
Status: GEAUTORISEERD, 2013

INHOUD:

Inleiding en verantwoording

De richtlijn 'astma bij kinderen' is een initiatief van de Nederlandse Vereniging voor Kindergeneeskunde (NVK). Deze richtlijn is een herziening van de richtlijn van de NVK uit 2008. Deze nieuwe richtlijn is grotendeels gebaseerd op de multidisciplinaire richtlijn van de British Thoracic Society (BTS, juni 2012), aangevuld met de uitwerking van onderwerpen waarover discussie is voor de Nederlandse situatie. Hiervoor zijn evidence reviews met behulp van GRADE opgesteld.

Bij deze richtlijn hoort een website. Hierop is in het achtergronddocument de verantwoording van de ontwikkeling van deze richtlijn en de volledige evidence-based uitwerking van de vastgestelde uitgangsvragen opgenomen.

Verklaring symbolen:

- Kwaliteit van het bewijs GRADE-methodiek:
  - ⊕⊕⊕⊕: Hoge kwaliteit: Het is onwaarschijnlijk dat nieuw onderzoek het vertrouwen in het geschatte effect verandert
  - ⊕⊕⊕⊖: Matige kwaliteit: Het is waarschijnlijk dat nieuw onderzoek een belangrijke impact heeft op het vertrouwen in het geschatte effect. Nieuw onderzoek kan deze schatting veranderen.
  - ⊕⊕⊖⊖: Lage kwaliteit: Het is zeer waarschijnlijk dat nieuw onderzoek een belangrijke impact heeft op het vertrouwen in het geschatte effect. Waarschijnlijk verandert deze schatting hierdoor.
  - ⊕⊖⊖⊖: Zeer lage kwaliteit: De schatting van het effect is erg onzeker
- Kwaliteit van het bewijs BTS-richtlijn:
  - A: At least one meta-analysis, or RCT rated as 1^{++}, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
  - B: A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^{+}
  - C: A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2^{++}
  - D: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^{+}
  - ☑: Good clinical practice point
- Daar waar afgeweken wordt van of aangevuld wordt op de BTS Guideline is dit aangegeven met
- Bij onvoldoende bewijs is geen symbool in de kantlijn vermeld.

Gebruikte afkortingen:

- ACT: astma controle test
- ACQ: asthma Control Questionnaire
- AQLQ: Asthma Quality of Life Questionnaire
- BTS: British Thoracic Society
- c-ACT: childhood ACT
- DPI: droogpoederinhalator
- FeNO: fractie stikstofmonoxide (NO) in de uitgeademde lucht
- FEV_1: forced expiratory volume in 1 second
- ICS: inhalatiecorticosteroïden
- LABA: langwerkende β_2-agonisten
- LTRA: leukotrieenreceptorantagonisten
- pMDI: pressurized metered dose inhaler (dosisaerosol)
- SABA: kortwerkende β_2-agonisten
- SCIT: subcutane immuuntherapie
- SLIT: sublinguale immuuntherapie
- VCD: vocal cord dysfunction (stembanddisfunctie)
- WHO: World Health Organization
- QOL: Quality of Life (kwaliteit van leven)

Diagnose astma bij kinderen

Bij kinderen met verdenking op astma is de diagnostiek gericht op:

- De aanwezigheid van klinische verschijnselen in anamnese en lichamelijk onderzoek. Daarbij wordt enerzijds onderscheid gemaakt in klinische verschijnselen die de diagnose astma waarschijnlijker maken en anderzijds onwaarschijnlijker (zie onderstaande tabel)
- Zorgvuldige overweging van alternatieve diagnoses

B

Zie voor meer informatie over episodisch viraal piepen en piepen op meerdere prikkels deze link

Waarschijnlijkheid diagnose astma

Klinische verschijnselen die de diagnose astma waarschijnlijker maken	• Meer dan een van de volgende symptomen: piepen [kernsymptoom], hoesten, kortademigheid of benauwdheid, vooral als deze symptomen: – Vaak voorkomen en terugkeren – Het ergst zijn 's nachts – Optreden in reactie op inspanning of andere prikkels zoals blootstelling aan allergenen, sigarettenrook, koude of vochtige lucht, of bij emoties of slappe lach • Voorgeschiedenis met atopische aandoening • Familie anamnese van atopische aandoening en/of astma • Piepend verlengd expirium bij auscultatie • Anamnese van duidelijke verbetering van symptomen of longfunctie in reactie op adequate therapie
Klinische verschijnselen die de diagnose astma minder waarschijnlijk maken	• Alleen symptomen ten tijde van verkoudheid/bovenste luchtweginfectie • Alleen hoesten; piepen of kortademigheid afwezig • Langer durende productieve hoest in de anamnese • Klachten van duizeligheid, lichtheid in het hoofd, tintelingen in handen of voeten en rond de mond • Bij herhaling normaal lichamelijk onderzoek ten tijde van symptomen • Normale longfunctie ten tijde van symptomen • Geen respons op proefbehandeling • Klinische verschijnselen die passen bij een andere diagnose

Na anamnese en lichamelijk onderzoek kan een patiënt meestal worden ingedeeld in een van de onderstaande groepen:

1. Hoge waarschijnlijkheid: diagnose astma aannemelijk
2. Intermediaire waarschijnlijkheid: diagnose onzeker
3. Lage waarschijnlijkheid: waarschijnlijk andere diagnose dan astma

Deze driedeling leidt dan tot de volgende vervolgacties:

Leg longfunctie met reversibiliteit vast als uitgangswaarde voor het vervolg

<u>Hoge waarschijnlijkheid (diagnose astma aannemelijk):</u>

- Start proefbehandeling (zonodig SABA of dagelijks ICS met zonodig SABA), afhankelijk van ernst en symptoomfrequentie)
- Evalueer het effect (het kan nodig zijn de proefbehandeling hiervoor te onderbreken)
- Bewaar verdere diagnostiek voor kinderen met een niet overtuigende respons

Overweeg onderzoek naar sensibilisatie voor allergenen als 'circumstantial evidence'

<u>Lage waarschijnlijkheid (waarschijnlijk andere diagnose dan astma):</u>

- Overweeg nader onderzoek, eventueel verwijzing kinderlongarts

<u>Intermediaire waarschijnlijkheid (diagnose astma onzeker):</u>

- Bij kinderen die in staat zijn tot longfunctieonderzoek: evalueer reversibiliteit van FEV_1 na luchtwegverwijder en de respons op proefbehandeling
  - Bij significante reversibiliteit (≥12%) (zie document standaardisatie longfunctieonderzoek pag. 36-59) of gunstig effect van proefbehandeling wordt de diagnose astma waarschijnlijker. Behandel als astma, probeer de minimaal effectieve dosis te vinden. Probeer de dosering ICS te reduceren of te staken op een later tijdstip
  - Als er geen significante reversibiliteit is, én gunstig effect van proefbehandeling ontbreekt; stop medicatie en overweeg nader onderzoek naar andere diagnose
- Bij kinderen die niet in staat zijn tot spirometrie: start proefbehandeling.
  - Bij gunstig effect: behandel als astma, evalueer later opnieuw
  - Bij geen effect: stop astmabehandeling en overweeg nadere diagnostiek voor alternatieve diagnose of verwijzing kinderlongarts
- Bij kinderen bij wie de diagnose astma onzeker is: als er geen significante reversibiliteit is, overweeg onderzoek naar sensibilisatie voor inhalatieallergenen en indien mogelijk bronchiale hyperreactiviteit m.b.v. metacholine, histamine of inspanningsprovocatie

Duur ICS: 6-12 weken

C

Bij kinderen, vooral jonger dan 6 jaar, die (nog) onvoldoende verschijnselen hebben op grond waarvan een duidelijke diagnose astma kan worden gesteld (en bij wie kenmerken die een alternatieve diagnose suggereren ontbreken) zijn verschillende strategieën mogelijk, zoals

- Afwachten en terug laten komen bij klachten
- Proefbehandeling
- Spirometrie met reversibiliteit (te proberen vanaf 4 jaar)

Longfunctieonderzoek is het meest informatief ten tijde van klachten. Normale spirometrie sluit astma niet uit. Herhaalde spirometrie kan nodig zijn.

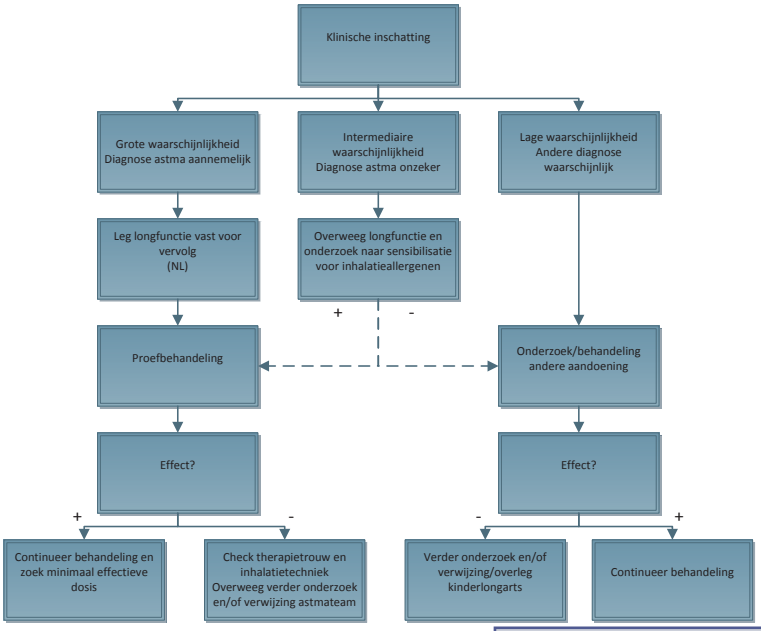
- FeNO heeft bij kinderen met astma vooralsnog geen toegevoegde waarde in aanvulling op of in de plaats van de standaard diagnostiek (gestructureerde anamnese, lichamelijk onderzoek tijdens klachten, spirometrie en provocatietesten)
- Titreren (afbouwen van inhalatiecorticosteroïden) van de behandeling op geleide van FeNO-metingen leidt niet tot een betere uitkomst en wordt niet aangeraden

⊕⊕⊖⊖

De diagnose astma is een klinische diagnose, gesteld op herkenning van een karakteristiek patroon van terugkerende symptomen, in afwezigheid van een andere verklaring.

Een positieve provocatietest is geen gouden standaard, maar *ondersteunt* de diagnose astma

Het hierboven besproken stappenplan is onderstaand schematisch weergegeven in een flowdiagram:



Alle hieronder genoemde uitspraken hebben expliciet betrekking op primaire preventie (voorkomen van de ziekte)
Zie ook JGZ-richtlijn astma

Primaire preventie

Interventie	Conclusies	Aanbeveling	
Vermijding allergenen	Er is geen eenduidig bewijs voor het nut van het vermijden van inhalatieallergenen in huis	Onvoldoende bewijs voor een aanbeveling	
Borstvoeding	Borstvoeding lijkt mogelijk te beschermen tegen het ontstaan van astma	Borstvoeding heeft een potentieel beschermend effect en wordt daarom aanbevolen	C
Hypoallergene zuigelingen-voeding	Tot nu toe verrichte onderzoeken hebben te korte follow-up om vast te stellen of er invloed is op astma	Onvoldoende bewijs voor een aanbeveling	
Voedingssup-plementen tijdens zwangerschap	Er is beperkt bewijs van wisselende kwaliteit studies; mogelijk beschermend effect van visolie, selenium en vitamine E tijdens zwangerschap	Onvoldoende bewijs voor een aanbeveling	
Immuuntherapie	Er zijn geen onafhankelijk uitgevoerde onderzoeken waarin het effect van immuuntherapie als primaire preventie is aangetoond	Onvoldoende bewijs voor een aanbeveling	
Probiotica	Er is geen onderzoek waaruit een gunstig effect van probiotica op astma blijkt.	Onvoldoende bewijs voor een aanbeveling	
Vermijden van sigarettenrook	Er is een sterke associatie tussen roken tijdens de zwangerschap door de moeder en/of rookblootstelling op zuigelingenleeftijd en een toegenomen risico op astma bij de zuigeling	Ontraad alle vormen van rookblootstelling	B

Niet-medicamenteuze behandeling van astma

Het bewijs voor het effect van niet-medicamenteuze beïnvloeding van astma is beperkt en studies op dit gebied zijn lastig uit te voeren.

Interventie	Conclusies	Aanbeveling	
Visolie en vetzuren	Onderzoeksresultaten zijn inconsistent en verder onderzoek is nodig	Onvoldoende bewijs voor een aanbeveling	
Elektrolyten	De onderzoeksresultaten van enkele interventieonderzoeken suggereren een verwaarloosbaar of minimaal effect	Onvoldoende bewijs voor een aanbeveling	
Gewichtsreductie	Onderzoeksresultaten wijzen op een verband tussen toegenomen body mass index en astmasymptomen	Stimuleer obese patiënten met astma het gewicht te reduceren om de algehele gezondheid en de astmacontrole te verbeteren	C
Luchtverontreiniging	Er lijkt een associatie tussen luchtverontreiniging en verergering van bestaand astma, maar verder onderzoek is nodig om de rol van luchtverontreiniging *binnenshuis* in relatie tot astma op te helderen	Onvoldoende bewijs voor een aanbeveling	
Huisstofmijt	Maatregelen om huisstofmijt te reduceren verminderen het aantal huisstofmijten, maar hebben geen duidelijk effect op de ernst van het astma	Onvoldoende bewijs voor een aanbeveling	
		Bij aangetoonde sensibilisatie kan een pakket van maatregelen om huisstofmijtexpositie te verminderen helpen	☑
Huisdieren	Dierlijk allergeen kan astmasymptomen uitlokken bij kinderen met astma. Maar er zijn geen gecontroleerde studies naar de voordelen van het verwijderen van huisdieren uit huis.	Onvoldoende bewijs voor een aanbeveling	
		Laat de patiënt bij een duidelijke reactie op expositie aan dierlijk allergeen of bij moeilijk behandelbaar astma blootstelling zo veel mogelijk vermijden	
Roken	Directe of passieve blootstelling aan sigarettenrook heeft een negatief effect op de ziektespecifieke kwaliteit van leven, longfunctie, noodzaak voor noodmedicatie en lange termijn controle met inhalatiecorticosteroïden (ICS)	Probeer patiënten alle vormen van rookblootstelling te laten vermijden. Ouders en kinderen krijgen voorlichting over schadelijke effecten van roken	C
Acupunctuur	Er is geen klinisch relevant effect aantoonbaar en geen significante verbetering van de longfunctie	Onvoldoende bewijs voor een aanbeveling	
Buteyko ademhalingstechniek	Deze therapie focust op verlaging van de ademhalingsfrequentie. Er is mogelijk voordeel in de vorm van symptoomreductie en minder gebruik van noodmedicatie, maar geen effect op steroïdgebruik of longfunctie [evidence bij volwassenen]	Onvoldoende bewijs voor een aanbeveling	
Gezins-/ systeemtherapie	Zie evidence review family therapy	Gezinstherapie is geen standaard aanvulling op medicamenteuze behandeling van kinderen met astma, maar kan in individuele gevallen (met name bij kinderen met problematisch ernstig astma / moeilijk behandelbaar astma) bijdragen aan het verminderen van psychosociale gevolgen van astma	
(Chinese) kruiden	Onderzoeksresultaten tonen wisselende effecten	Onvoldoende bewijs voor een aanbeveling	

Hypnose en ontspannings-therapieën	Er is geen bewijs van effect. Spierrelaxatie kan mogelijk een effect hebben op de longfunctie	Onvoldoende bewijs voor een aanbeveling	
Homeopathie	Er is geen bewijs voor het effect van (geïndividualiseerde) homeopathie	Onvoldoende bewijs voor een aanbeveling	
Luchtreiniger/ ionisator	Er is geen effect op het reduceren van symptomen	Luchtreinigers/ionisatoren zijn niet aan te raden voor de behandeling van astma	A
Lichaams-beweging	Onderzoeksresultaten tonen effect op conditie, maar niet op astmasymptomen	Geen bewijs voor specifiek positief effect	
Influenza-vaccinatie	Influenza vaccinatie verergert het astma niet; het heeft mogelijk een klein gunstig effect op QOL.	Tegenstrijdig bewijs, geen plaats voor routinematige influenza vaccinatie bij alle kinderen met astma	

Medicamenteuze behandeling van astma

Doel van de behandeling

Doel van de behandeling is optimale controle over de ziekte
Volledige ziektecontrole wordt gedefinieerd als:

- Geen symptomen overdag
- Niet ontwaken door astma 's nachts
- Geen noodzaak voor 'zo nodig' medicatie (SABA)
- Geen exacerbaties
- Geen beperking in activiteiten, inclusief inspanning
- Normale longfunctie (in de praktijk FEV_1 >80% van voorspeld of van 'personal best')
- Minimale bijwerkingen van medicatie

De zorgstandaard astma bij kinderen van de Longalliantie Nederland (LAN) definieert als goede controle max. 2 keer per week noodzaak voor 'zonodig medicatie' en baseert zich daarbij op Global Initiative for Asthma (GINA), 2011

Stapsgewijze aanpak

1. Start behandeling in de stap die het meest past bij de klinische inschatting van de ernst
2. Streef naar spoedige ziektecontrole
3. Behoudt ziektecontrole door:
   - ↑ Step-up als het nodig is
   - ↓ Step-down als het mogelijk is

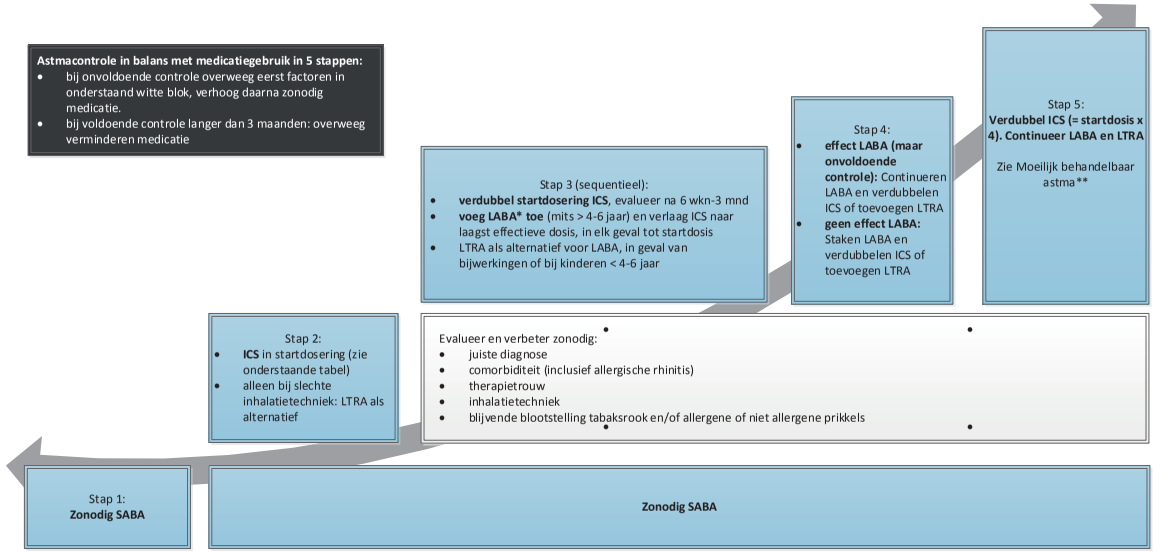
Controleer voor het starten van een nieuw medicament of verhogen van dosering: therapietrouw, inhalatietechniek en elimineer uitlokkende factoren ☑

Afbouwen van de medicamenteuze behandeling

- Bij afbouwen van de medicatie is regelmatige controle door een behandelaar belangrijk. Bij het bepalen van het afbouwbeleid is het van belang rekening te houden met de ernst van de astma, mate van ziektecontrole, bijwerkingen van medicatie, duur van de behandeling, behandelresultaat en patiëntenvoorkeuren.
  - Het doel is patiënten een goede controle te laten behouden met een zo laag mogelijke onderhoudsdosering ICS. Het afbouwen van de dosis gebeurt langzaam omdat de astmacontrole bij verschillende doseringen langzaam kan verslechteren. Het afbouwen wordt elke 3 maanden heroverwogen, waarbij de dosis telkens stapsgewijs (bijv. 25-50%) wordt verminderd.

☑

Medicatieschema (zie ook evidence reviews leukotrieenreceptorantagonisten, fijne deeltjes ICS en ICS met klachten)



* LABA altijd in een combinatiepreparaat met ICS, salmeterolcomponent: 2 dd 25-50µg of formoterolcomponent 2 dd 6-12 µg (geregistreerd vanaf 4 respectievelijk 6 jaar)
** : Het voorschrijven van omalizumab wordt voorbehouden aan een astma-expert.
noot **comorbiditeit** (allergische rhinitis):de werkgroep wijst op de samenhang van allergische neusklachten en bronchiale hyperreactiviteit (common airway concept); zie voor de internationale richtlijn http://www.whiar.org/docs/ARIAReport_2010.pdf

ICS Startdoseringen (zie voor toedieningswijze: Inhalatoren en voorzetkamers)

ICS*	Dosering (µg)†
Beclomethason	2 dd 200
Beclomethason extra fijn	2 dd 100
Budesonide	2 dd 200
Fluticason	2 dd 100-125
Ciclesonide	1 dd 160

* Raadpleeg voor registratieleeftijden en label het Kinderformularium. De selectie van een inhalator wordt allereerst bepaald door de keuze voor de werkzame stof en de gebruikersvriendelijkheid/bruikbaarheid voor de patiënt. Daarnaast dient ook de kostenoverweging een rol te spelen (zie www.medicijnkosten.nl).
† Bij de keuze van een individueel geschikte inhalator en een goede techniek is de startdosering van hetzelfde preparaat in dosisaerosol met voorzetkamer, ademgestuurd aerosol of droog poeder inhalator gelijk.

SCIT/SLIT

Interventie	Conclusies	Aanbeveling	
SCIT/SLIT	Zie evidence review SCIT/SLIT	Subcutane en sublinguale immuuntherapie zijn niet aan te bevelen voor de behandeling van kinderen en adolescenten met astma, vanwege een gebrek aan bewijs voor de effectiviteit van de interventies op astma-uitkomsten, en vanwege de nadelen die met de behandeling gepaard gaan	⊕⊕⊖⊖

Inspanningsastma

Inspanningsastma is meestal een uiting van onvoldoende ziektecontrole bij patiënten met astma. In dat geval wordt de onderhoudsbehandeling met inhalatiesteroïden gecontroleerd en zonodig bijgesteld.	☑
Als inspanning een specifieke uitlokker is, geef dan een SABA kort vóór inspanning.	A
Bij patiënten die inhalatiesteroïden gebruiken en inspanningsgebonden klachten hebben met verder een goede ziektecontrole hebben, overweeg dan: • Langwerkende β_2-agonist • Leukotrieenreceptorantagonist	A C

Inhalatoren en voorzetkamers

Schrijf alleen inhalatoren voor nadat patiënten instructie hebben gehad voor gebruik en hebben laten zien de techniek voldoende te beheersen.	☑

Overzicht inhalatoren en voorzetkamers

Zie voor een korte inhalatieinstructie voorzetkamer en droogpoederinhalator deze link

Leeftijd	Toedieningswijze
0 t/m 3 jaar	Voorzetkamer met masker + pMDI (evt. vernevelaar indien ineffectief)
4 t/m 6 jaar	Voorzetkamer met mondstuk + pMDI
7 jaar en ouder	Voorzetkamer met mondstuk + pMDI of DPI of ademgestuurde inhalator

Inhalatoren en voorzetkamers voor β_2-agonisten

Acuut astma Kinderen (en volwassenen) met milde tot matig ernstige exacerbaties worden behandeld met een dosisaerosol (pMDI) met voorzetkamer (zie acuut astma)	A/B
Stabiel astma Voor kinderen vanaf 6 jaar is een dosisaerosol met voorzetkamer even effectief als een droogpoederinhalator (DPI), maar patiënten kunnen een voorkeur hebben voor een bepaald type inhalator	A

Inhalatoren en voorzetkamers voor inhalatiecorticosteroïden

Stabiel astma Voor kinderen vanaf 6 jaar met stabiel astma is een dosisaerosol met voorzetkamer even effectief als een droogpoederinhalator (DPI).	A

Bij de keuze voor een toedieningsvorm wordt een afweging gemaakt op basis van gebruiksgemak en individuele effectiviteit; bij middelen met gelijke geschiktheid kiezen voor goedkoopste variant

Voorzetkamers

• De keuze van voorzetkamer kan worden bepaald door de keuze van het medicament • Als de patiënt de voorzetkamer niet goed kan gebruiken, wordt een alternatief gezocht • De patiënt moet het gebruik van de voorzetkamer aan de behandelaar kunnen demonstreren • Evalueer en controleer de inhalatietechniek bij het voorschrijven van een nieuwe inhalator, de eerstvolgende controle en daarna minimaal jaarlijks ☑

Acuut astma

Zie richtlijn acuut astma (NVK geautoriseerd april 2012)

Samenvatting praktische handelingen bij acuut astma

- Saturatie ≤ 94% → geef zuurstof
- Saturatie > 94 % → bronchusverwijding met voorzetkamer (juiste voorzetkamer/techniek)

Salbutamol:	Ipratropiumbromide (min. 2 x geven i.c.m. salbutamol):
4 - 8 inhalaties à 100 µg	4 inhalaties à 20 µg

- Saturatie ≤ 94 % → bronchusverwijding met een vernevelaar met O_2 8 L/min (juiste techniek, zie NVK richtlijn acuut astma, bijlage 3)

Salbutamol:	**Ipratropiumbromide***
≤ 4 jr: 2,5 mg/dosis	≤ 4 jr: 0,25 mg/dosis
> 5 jr: 5,0 mg/dosis	> 5 jr: 0,5 mg/dosis

*minimaal 2 x geven i.c.m. salbutamol

- Een (ernstig) benauwd kind wordt zo vaak als nodig tot continu behandeld met een vernevelaar met salbutamol en (minimaal) tweemaal ipratropiumbromide bij de eerste inhalaties
- Na 1 à 2 maal inhaleren en onvoldoende effect: start laagdrempelig prednisolon (bij voorkeur drank voor kleine kinderen) 1-2 mg/kg in 2 dd gedurende 3-5 dagen (max. 40-60 mg/dag)
- Bij verdenking anafylaxie: geef adrenaline i.m. 0,01 mg/kg/dosis (tot 30 kg) max 0,3 mg
- Overweeg magnesiumsulfaat i.v. na onvoldoende effect van 3 vernevelingen 40 mg/kg, in 15 minuten i.v. (max. 2 gram)
- Bij levensbedreigend astma / onvoldoende verbetering: start salbutamol continu i.v.

Tekenen van ernstig/levensbedreigend astma

Tekenen van ernstig astma	Tekenen van levensbedreigend astma
Te kortademig om te eten of te spreken	Verminderd bewustzijn/ geagiteerd gedrag
Intrekkingen en gebruik van hulpademhalingsspieren	(Dreigende) uitputting
Ademfrequentie >50/min (2-5 jaar), >30/min (>5 jaar)	Sterk verminderde ademarbeid, gasping
Polsfrequentie > 140/min	Zuurstofsaturatie < 88% in lucht of zichtbare cyanose
Stille thorax	

Astma bij adolescenten

Adolescenten zijn door de World Health Organisation (WHO) gedefinieerd als jonge mensen van 10-19 jaar.

Sleutelelementen om effectief met adolescenten te werken in de transitie naar volwassenheid zijn:

- Zie kinderen vanaf 12 jaar geleidelijk aan ook zonder ouders, gedurende een deel van het consult
- Bespreek vertrouwelijkheid en de grenzen daaraan

Prevalentie

Astma komt veel voor bij adolescenten maar de diagnose wordt frequent gemist ten gevolge van onderrapportage van symptomen.

Behandelaars die adolescenten zien met cardiorespiratoire symptomen behoren te vragen naar symptomen van astma.

Diagnose en behandeling

Aanwijzingen voor en symptomen van astma zijn bij adolescenten niet anders dan bij een andere leeftijdsgroep. Inspanningsgebonden piepen en benauwdheid zijn vaak voorkomende astmasymptomen bij adolescenten maar slechts een minderheid heeft aanwijzingen voor inspanningsgeïnduceerde bronchoconstrictie. Andere oorzaken van (inspannings)gebonden benauwdheid zoals ademdisregulatie, vocal cord dysfunction (stembanddisfunctie) of slechte conditie kunnen meestal worden gediagnosticeerd middels zorgvuldige anamnese.

Hulpmiddelen bij diagnostiek van astma bij adolescenten

Parameter	Conclusies	Aanbeveling	
Astmacontrole	De astma controle test (ACT) is gevalideerd voor kinderen vanaf 12 jaar	Het gebruik van de gevalideerde vragenlijsten kan een hulpmiddel zijn	
Kwaliteit van leven	Kwaliteit-van-levenvragenlijsten kunnen worden gebruikt (zoals de AQLQ 12+)	Het gebruik van kwaliteit- van-levenvragenlijsten kan behulpzaam zijn	
Longfunctie	Meting van longfunctie met reversibiliteit en bronchiale hyperreactiviteit kan de diagnose astma ondersteunen maar de meeste adolescenten met astma hebben een normale longfunctie	Op indicatie	
Bronchiale hyperreactiviteit	Een negatieve inspanningsprovocatietest kan helpen in het uitsluiten van astma bij klachten van benauwdheid bij inspanning	Laat bij onbegrepen inspanningsbenauwdheid een inspanningsprovocatietest uitvoeren	
Angst en depressie	Depressie, paniekaanvallen en angststoornissen komen vaker voor bij adolescenten met astma en kunnen symptomen van astma meer prominent maken	Gebruik screenende vragenlijsten bij verdenking op angst en depressie	

Leg longfunctie met reversibiliteit vast als uitgangswaarde voor het vervolg

Wees alert op angst om te stikken, ook bij jongere kinderen, en stel zonodig gerust

Disfunctionele ademhaling

	Conclusies	Aanbeveling	
Disfunctionele ademhaling	Zie evidence review dysfunctional breathing	Overweeg in de differentiële diagnose van astma de diagnose disfunctionele ademhaling bij kinderen en adolescenten met aanvallen van benauwdheid die vergezeld gaan van specifieke symptomen (kortademigheid, druk op de borst, duizeligheid, tremoren en paresthesieën) en die niet goed reageren op luchtwegverwijding (consensus; expert opinion). Stel de diagnose disfunctionele ademhaling op anamnese en de afwezigheid van positieve tests die een andere diagnose suggereren. Een hyperventilatieprovocatietest met capnogram wordt niet aanbevolen. Het gebruik van een (voor volwassenen gevalideerde) vragenlijst kan behulpzaam zijn. Bij (vermoeden van) disfunctionele ademhaling valt behandeling door een ervaren oefentherapeut te overwegen. Probeer, afhankelijk van de lokale situatie, in individuele gevallen logopedie of ontspanningsoefeningen d.m.v. yoga uit. Bij (een vermoeden van) gelijktijdige of voorafgaande bronchusobstructie is luchtwegverwijding aangewezen.	☑
Vocal cord dysfunction (stemband-disfunctie)	Zie evidence review vocal cord dysfunction	Overweeg flexibele laryngoscopie tijdens een benauwdheidsaanval die verdacht lijkt voor VCD. Spirometrie met aandacht voor de inspiratoire curve is aangewezen bij een benauwdheidsaanval verdacht voor VCD.	

VCD kan waarschijnlijk het best worden behandeld met behulp van ademhalings-/ontspanningsoefeningen door logopedist of fysiotherapeut

Niet-medicamenteuze astmabehandeling adolescenten

Interventie	Conclusies	Aanbeveling	
Roken en passief roken	Passief en actief roken zijn significante risicofactoren voor astma en piepen bij adolescenten	Ontraad rookblootstelling – zowel passief als actief – aan adolescenten met astma én hun ouders/verzorgers. Geef voorlichting over risico's. Geef dringend advies om niet te starten met roken.	
Alternatieve en complementaire geneeskunde	Adolescenten lijken veel gebruik te maken van alternatieve geneeskunde. Dit kan een indicator zijn voor non-adherentie	Behandelaren zijn zich bewust van mogelijke alternatieve therapieën en informeren daarnaar	

Medicamenteuze astmabehandeling adolescenten

Specifieke evidence over de medicamenteuze behandeling van adolescenten met astma is beperkt en wordt doorgaans geëxtrapoleerd uit resultaten bij kinderen of volwassenen. Datzelfde geldt voor evidence over inhalatoren.

Interventie	Conclusies	Aanbeveling	
Inhalatoren	Adolescenten kunnen goed in staat zijn om inhalatoren te gebruiken, maar hun therapietrouw kan beïnvloed worden door factoren zoals voorkeur	Besteed aandacht aan de eigen voorkeur van de adolescent. Naast controleren van de inhalatietechniek is het ook belangrijk te informeren naar real-life factoren die medicatie-inname beïnvloeden, zoals gebruik op school. Overweeg een meer draagbare inhalator voor te schrijven voor gebruik buitenshuis als alternatief voor een dosisaerosol met voorzetkamer.	☑

Er kan schaamte bestaan voor gebruik van een inhalator in het openbaar

Langetermijnperspectief en eerste werkervaring

Interventie	Conclusies	Aanbeveling	
Bespreken werk- en carrièrekeuze	Veel jongvolwassenen met astma hebben slecht inzicht in welk soort werk astma kan verergeren (bijv. aanwezigheid van stof, dampen, fysieke inspanning en temperatuursverandering)	Bespreek de werk- en carrièrekeuzes met adolescenten met astma en geef aan wanneer werkomstandigheden ongunstig zijn.	☑

Transitie naar volwassen zorg

Een goede transitie is belangrijk voor alle adolescenten met astma, onafhankelijk van de ernst van het astma. Transitie wordt ter sprake gebracht als proces, en niet pas vlak voor de overdracht naar volwassen zorg. Transitie begint vroeg, wordt gepland en betrekt de jongere. Transitie moet aansluiten bij kalender- en ontwikkelingsleeftijd.
De ouders worden gestimuleerd geleidelijk de verantwoordelijkheid over te dragen aan hun kind.
Effectieve transitie betekent dat de adolescent zelf verantwoordelijk gemaakt wordt voor haar/zijn eigen astmamanagement. Behandelaren leren adolescenten hun ziektecontrole zelf ter hand te nemen.

Spreek af wie in de toekomst de centrale zorgverlener wordt (huisarts/longarts)

Therapietrouw

Interventie	Conclusies	Aanbeveling	
Therapietrouw	Bij navraag geven adolescenten met astma vaak toe dat hun therapietrouw en het vermijden van prikkels vaak matig is	Gebruik strategieën om therapietrouw te vergroten: focus op het individu en zijn/haar levensstijl, gebruik geïndividualiseerde astma actieplannen en persoonlijke doelstellingen.	

Een medicament met een eenmaal daags voorschrift kan om redenen van therapietrouw worden overwogen.

Moeilijk behandelbaar astma

Moeilijk behandelbaar astma ('problematisch ernstig astma') wordt gedefinieerd als persisterende symptomen en/of frequente exacerbaties ondanks behandeling in stap 4 of 5.

Aanpak

Patiënten met moeilijk behandelbaar astma worden systematisch geëvalueerd, inclusief:

- Bevestiging van de diagnose astma (en identificeren van comorbiditeit (zoals disfunctionele ademhaling, allergische rhinitis en eczeem, obesitas, bronchomalacie, gastro-oesofageale reflux, VCD)
- Identificatie van het mechanisme achter de persisterende symptomen (inclusief blootstelling aan prikkels)
- Evaluatie van therapietrouw

Deze evaluatie wordt uitgevoerd of ondersteund door een gespecialiseerd astmateam dat is toegerust voor de evaluatie en aanpak van moeilijk behandelbaar astma

D

het opsporen en zo nodig behandelen van allergische rhinitis kan een bijdrage leveren aan de stabiliteit van de onderste luchtweg (common airway concept). Zie ook een overzicht van diagnostiek en behandeling van allergische rhinitis

de gestructureerde aanpak van moeilijk behandelbaar astma is gefaseerd: in fase 1 worden factoren gezocht die het astma weer behandelbaar maken; multidisciplinaire aanpak in een astmacentrum kan daarbij helpen; alleen bij persisterende symptomen volgt daarna fase 2: therapieresistent astma; overleg met astma-expert

Factoren die bijdragen aan moeilijk behandelbaar astma

Factor	Conclusies	Aanbeveling	
Slechte therapietrouw	Slechte therapietrouw kan een mogelijk mechanisme zijn voor moeilijk behandelbaar astma	Tip: vraag een apotheekhistorie van het afgelopen jaar op	C
Psychosociale factoren	Moeilijk behandelbaar astma is vaak geassocieerd met bijkomende psychologische problematiek	Evalueer co-existente psychologische morbiditeit – bij kinderen kan dit een psychologisch onderzoek inhouden	D
Monitoring van ontsteking		Onvoldoende bewijs voor het nut van monitoring met behulp van sputum eosinofielen bij kinderen met moeilijk behandelbaar astma	

Organisatie van zorg

Hiervoor wordt verwezen naar de zorgstandaard astma kinderen & jongeren en de landelijke transmurale afspraken (LTA).

Monitoring

De mate van astmacontrole staat centraal bij de monitoring van astma bij kinderen

Minstens op jaarlijkse basis wordt vastgelegd*:

- Aantal exacerbaties, orale corticosteroïdkuren, antibioticumkuren en gemiste tijd op school of dagverblijf
- Longfunctie met reversibiliteit
- Inhalatietechniek
- Astma symptoom score (bijv. c-ACT, ACT of ACQ)
- Therapietrouw
- Gebruik van geschreven of gepersonaliseerd actieplan
- Blootstelling aan sigarettenrook
- Groei (lengte en gewicht)

☑

* Op basis van ziekte-ernst wordt de frequentie en inhoud van de monitoring bepaald

• Regelmatige monitoring met behulp van bronchoprovocatietesten leidt niet tot betere astmacontrole.	☑
• Het monitoren van astma (titreren van ICS) bij kinderen met behulp van FeNO metingen kan op dit moment niet worden aanbevolen in de huisarts- en de kindergeneeskundige praktijk. FeNO-monitoring met als doel betere astmacontrole zou dan ook alleen moeten plaatsvinden in het kader van onderzoek (zie ook evidence review titreren behandeling o.b.v. FeNO)	⊕⊕⊖⊖

Zelfmanagement

Interventie	Conclusies	Aanbeveling	
Zelf-management	Zie evidence review self management	Neem bij kinderen met onvoldoende astmacontrole maatregelen ter verbetering van longfunctie en ziektecontrole. Pas bij kinderen met frequente exacerbaties ook interventies toe op gebied van zelfmanagement en educatie. Verstrek een geschreven actieplan , zeker aan kinderen met instabiel astma.	⊕⊕⊖⊖

Astma-educatie en zelfmanagement

• Een ongeplande (acute) afspraak geeft de mogelijkheid om te zien welke actie (van het geschreven actieplan) al is ondernomen om met de exacerbatie om te gaan. • Geef korte, eenvoudige educatie die aansluit bij de behandeldoelen.	☑
• Zelfmanagement-educatie moet worden aangeboden met focus op individuele wensen en ondersteuning door een geschreven actieplan. • Voor ontslag moet een opgenomen patiënt een geschreven actieplan krijgen uit handen van een behandelaar met expertise op het gebied van astmamanagement.	A
• Door astma-educatie wordt het actieplan meer 'eigen'/ gepersonaliseerd.	B

Therapietrouw en overeenstemming in behandeldoelen

• Verstrek simpele, mondelinge en geschreven instructie en informatie over de medicamenteuze behandeling voor de patiënt en zijn/haar verzorgers. • Herhaalrecepten via een elektronisch voorschrijfsysteem geven een aardige indruk van therapietrouw – vraag zo nodig een apotheekhistorie op.	☑

Praktische tips voor het vergroten van therapietrouw

• Stel vragen met een open einde zoals 'als we één ding beter zouden kunnen maken voor je astma, wat zou dat dan moeten zijn?'. Dit kan helpen voor een meer patiënt-gecentreerde agenda • Luister actief en reageer op zorgen en doelen van de patiënt • Overweeg herinneringsstrategieën of geheugensteuntjes • Roep patiënten op die afspraken missen

Tips voor het bereiken van concordantie:
- Motivational interviewing kan behulpzaam zijn
- Maak een lijstje met voor- en nadelen voor het gebruik van ICS, vooral als ouders of de patiënt veel vragen hebben over bijwerkingen ("pro-/con lijst")

3

Behavioral problems in children and adolescents with difficult-to-treat asthma

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ABSTRACT

Background: The aim of this study was to quantify behavioral problems in clinically treated children and adolescents with asthma and to examine the association of these problems and quality of life with difficult-to-treat asthma.

Methods: Clinical patients with difficult-to-treat asthma (*n* = 31) and patients with asthma who were not classified as difficult-to-treat asthma (*n* = 52) completed the Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)]. Their parents completed the Child Behavior Checklist (CBCL) to assess behavioral problems. Behavioral problem scores were compared to norms of population reference groups and both behavioral problems and quality of life were compared between children and adolescents with and without difficult-to-treat asthma.

Results: Especially internalizing behavioral problems such as being withdrawn/depressed and somatic complaints were more severe in the asthmatic groups compared to the healthy reference groups. The behavioral problems "somatic complaints" and "thought problems" as well as a lower quality of life were more severe in children and adolescents with difficult-to-treat asthma than in asthma patients who did not fulfill the criteria of difficult-to-treat asthma.

Conclusion: Behavioral problems and a lower quality of life are suggested to be more pronounced in clinically treated children and adolescents with difficult-to-treat asthma than in asthma patients who are not classified as difficult-to-treat asthma. With respect to practical implications, our data suggest that health-care professionals should –especially in children and adolescents with difficult-to-treat asthma- assess and, if necessary, treat behavioral problems.

INTRODUCTION

Asthma, the most common chronic disease in children, is a respiratory disease characterized by airway obstruction, airway inflammation, and bronchial hyperresponsiveness[1] with negative consequences for quality of life.[2] In adults, some 5 % of patients with asthma have difficult-to-treat asthma as defined by the European Respiratory Society.[3] In difficult-to-treat asthma, the clinical manifestations of disease are insufficiently reduced despite optimal treatment.[4] Difficult-to-treat-asthma has been less well studied in children and adolescents than in adults. It is unclear why these patients are difficult-to-treat, to what extent the quality of life of children and adolescents with difficult-to-treat asthma is disturbed and which specific behavioral problems most severely deviate from normal.[5, 6]

Selected children and adolescents with asthma may have a higher than normal risk of internalizing behavioral and emotional problems such as anxiety and depressive symptoms.[7, 8] There are multiple, complementary explanations for the association between asthma and behavioral problems. The burden of disease may lead to behavioral problems such as difficulties in separation and individuation from parents and associated anxiety,[8] and psychosocial factors may trigger the expression of asthma through neuro-endocrine and immune mechanisms.[9] Behavioral problems may underlie poor adherence, poor asthma management, and poor functional health status.[10] As such, behavioral problems play a key role in difficult-to-treat asthma. Both the symptoms of asthma and the associated emotional and behavioral problems threaten the quality of life of children and adolescents with asthma.[6]

In contrast to previous studies in children and adolescents with asthma, the focus of our study is on difficult-to-treat asthma. First, our aim was to quantify behavioral problems in a selected group of children and adolescents with asthma from specialized clinics. Second, we examined the association of these problems and quality of life with being or not being classified as difficult-to-treat asthma. We hypothesized that children with difficult-to-treat asthma have more behavioral problems and a lower quality of life than children with asthma who are not classified as difficult-to-treat asthma.

METHODS

Design

A cross sectional study examined children and adolescents with asthma before the start of inpatient treatment in the *Dutch Asthma Center Davos* (hosting Dutch patients) and the *Hochgebirgsklinik Davos* (high-altitude clinic Davos, hosting German patients), Switzerland, two high-altitude asthma clinics with a hypoallergenic environment due to a lower concentration of pollen and almost complete absence of house dust mite.[11]

Study population

All children aged 7-17 years with a confirmed diagnosis of asthma were included. The diagnosis of asthma and criteria of difficult-to-treat asthma including (history of) compliance were approved or rejected by one selected pediatrician per clinic, on the day of arrival. From January to December, 2008, the patients were invited to participate in the study.

The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. The parents of all children and adolescents provided written informed consent.

Procedure

Patients were diagnosed and treated for asthma in their respective countries. Two weeks before the start of clinical treatment in one of the high altitude clinics, all patients and parents received questionnaires at their homes. On arrival of the patients at the clinic, medical history was taken including atopic symptoms, exercise intolerance, medication, reliever therapy, and adherence. Pulmonary function testing was performed. History and physical examination were performed on the day of arrival by one selected pediatrician per clinic.

Asthma diagnosis

The diagnosis of asthma was approved or rejected on the basis of history, examination, and confirmed bronchoconstriction with (partial) reversibility in history.

Difficult-to-treat asthma was defined using criteria of the Dutch Pediatric Respiratory Society,[12] which are based on task forces of the American Thoracic Society and European Respiratory Society, and ENFUMOSA study (Table 1).[13-16] A positive score on difficult-to-treat asthma denotes persistent or severe asthma and lack of adequate control of asthma symptoms (such as exercise intolerance, two or more times per week in need of extra reliever therapy, symptoms at night) despite high dose of maintenance therapy, adequate use of spacers and devices, confirmed diagnosis, and good compliance. Difficult-to-treat asthma according to these criteria was established on the day of arrival by one pediatrician per clinic during a structured interview with the patients and their parents, and using data from the referring clinician about compliance history and pulmonary function testing at the time of diagnosis. Good compliance implicated no missing doses on 6 or 7 days per week. In case of doubt or an anamnestic compliance less than 6 days a week, compliance was regarded as "poor" and thus criteria on difficult-to-treat asthma were not met. Intake of medication was supervised during the stay in the clinic.

Table 1. Criteria of difficult–to-treat asthma[12]

1.	Age ≥ 6 years.
2.	≥ 6 months treatment on the following treatment regime (doses are adapted to the Dutch situation): daily use of ≥ 800 μg budesonide/beclometasone dipropionate or equivalent (≥ 500 μg fluticasone of ≥ 400 μg beclometasone dipropionate extra-fine or ≥ μg 320 ciclesonide), and long acting β_2-agonist, and a (history of) treatment on a leukotriene receptor antagonist.
3.	With respect to the medication mentioned above, at least one of the following criteria should apply: decreased exercise tolerance and/or symptoms at night and/or, use of reliever therapy ≥ 2 times weekly, frequent exacerbations with need for oral prednisolone (≥ 2 per year), exacerbation(s) requiring ICU treatment in history, persistent airway obstruction (FEV_1 < 80 % post reliever).
4.	At least 6 months treatment in pediatric practice.
5.	History of good compliance.
6.	Checked inhalation technique.
7.	Asthma diagnosis, confirmed at that time by pulmonary function testing, defined as obstructive flow volume curve with (partial) reversibility of forced expiratory volume in 1 second (FEV_1) on β_2-agonists.
8.	Medication as mentioned above may be prescribed temporarily and built down because of lack of effect.

Pulmonary function testing

Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Hoechberg, Germany). A standardized protocol was used and at least three technically correct maneuvers were performed. Short- or long-acting β_2-adrenergic agonists were stopped at least 12 hours before PFT. Lung function parameters that were obtained and evaluated were forced expiratory volume in 1 second (FEV_1) and maximal expiratory flow at 50% of forced vital capacity (MEF_{50}). Airway inflammation was measured using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS and ERS guidelines.[17, 18] The Niox Flex (Aerocrine, Solna, Sweden) was used according to the manufacturer's instructions.

Instruments

Parental report: The Child Behavior Checklist. The Child Behavior Checklist (CBCL) is a standardized questionnaire for assessing emotional and behavioral problems of children and adolescents by parent or caregiver ratings.[19] Parents of the Dutch and German children and adolescents filled out the Dutch 2001 version of the CBCL (6-18 years) or the 1998 German version of the CBCL (4-18 years).[20, 21]

Results of the CBCL are expressed in a global score and in scores for internalizing and externalizing behavior problems. Internalizing behavior problems include the syndrome domains anxious/depressed, withdrawn/depressed, and somatic complaints. Externalizing problems include rule-breaking behavior and aggressive behavior. Three other syndrome domains are not part of the global scores: social problems, thought problems, and attention problems. The raw scores of the CBCL were used in analysis.

Children's self-report: Quality of life. The Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)] is a widely used disease-specific health-related quality of life self-report measure for children and adolescents aged 7-17 years.[22] The Dutch PAQLQ(S) has adequate psychometric properties and excellent responsiveness, which supports longitudinal and cross-sectional construct validity.[23] It has three domains: symptoms (10 items), activity limitations (5 items), and emotional function (8 items). The item range 1 - 7 is reported per domain and for the whole instrument. Higher scores indicate better quality of life.[22]

Statistical analysis

The score distributions were checked for outliers and normality. Outliers ($z > 3.29$) were detected for the following CBCL scales: total problem score (1 outlier), the broad band scales internalizing (1 outlier) and externalizing problems (2 outliers); and the domain scales anxious/depressed (2), withdrawn/depressed (1), thought problems (1), attention problems (1), rule-breaking behavior (2), and aggressive behavior (2). These outlying variables were assigned a score that was one unit larger than the next most extreme score of the score distribution.[24]

Statistical analyses were done with SPSS 16.0. The values of $\alpha < .05$ (two-sided) were considered statistically significant. Differences between groups were examined with independent samples *t*-tests and with a nonparametric test for lung function (Mann-Whitney *U* test). Cohen's effect size estimates (*d*) were calculated: $0.2 \leq d < 0.5$ indicates a small effect, $0.5 \leq d < 0.8$ a medium effect, and $d \geq 0.8$ a large effect.[25]

RESULTS

Patient characteristics

Thirty-three of 38 (87 %) Dutch clinical patients were included; 2 patients did not provide informed consent, the parents of 2 patients did not complete the CBCL, and in 1 patient the diagnosis of asthma was withdrawn. Out of 63 German clinical patients, 50 were included (79 %); 3 patients did not provide informed consent, 8 did not complete the CBCL questionnaire, and in 2 the diagnosis of asthma was withdrawn.

Table 2 shows the characteristics of 83 patients with a complete data set and a certified diagnosis of asthma. The children and adolescents in the difficult-to-treat asthma ($n = 31$) and non-difficult-to-treat asthma ($n = 52$) groups did not differ with respect to percentage girls and mean age. Most of the children and adolescents with difficult-to-treat asthma were Dutch. There was no relevant difference in lung function between the two groups. The FEV_1 score in the difficult-to-treat asthma group was significantly better. The scores of both groups were in the normal range.

Table 2. Characteristics of the 83 asthma patients who did and did not fulfill the criteria of difficult-to-treat asthma

	Difficult-to-treat asthma	Non-difficult-to-treat asthma	*p*
Total group *n* (%)	31 (37 %)	52 (63 %)	
Dutch sample	27	6	<.001[a]
German sample	4	46	
Female total group (%)	17 (55 %)	23 (44 %)	.35[a]
Dutch sample	16	3	
German sample	1	20	
Mean age (*SD*) yrs	12.7 (2.6)	13.0 (3.0)	.59[b]
Dutch sample (*SD*)	12.5 (2.4)	13.3 (2.0)	
German sample (*SD*)	13.8 (3.3)	13.0 (3.1)	
Mean FEV_1 (*SD*)[c]	106.7 (14.6)	99.8 (14.4)	.04[d]
Dutch sample (*SD*)	107.3 (14.2)	101.5 (12.9)	
German sample (*SD*)	102.8 (18.5)	99.4 (14.8)	
Mean MEF_{50} (*SD*)[c]	97.0 (25.9)	87.6 (23.9)	.06[d]
Dutch sample (*SD*)	97.1 (23.3)	89.0 (27.4)	
German sample (*SD*)	96.4 (41.7)	87.3 (23.6)	
Mean FeNO (*SD*)[e]	39.5 (30.0)	33.8 (31.6)	.21[d]
Dutch sample (*SD*)	38.8 (27.5)	35.7 (19.6)	
German sample (*SD*)	45.9 (55.5)	33.4 (33.9)	

Note. FEV_1 (forced expiratory volume in 1 second) and MEF_{50} (maximal expiratory flow at 50 % of forced vital capacity) are expressed as percent of predicted. Values are geometric (FeNO; fractional concentration of exhaled nitric oxide) or arithmetic means (FEV_1 and MEF_{50}).
[a] Chi^2 test for gender and country; [b] Independent samples *t*-test; [c] % pred, percentage predicted; [d] Mann-Whitney *U* test; [e] ppb, parts per billion.

Quality of life

Table 3 shows the quality of life scores [PAQLQ(S)] of children and adolescents with and without difficult-to-treat asthma. Patients with difficult-to-treat asthma experienced a poorer overall quality of life than patients without difficult-to-treat asthma (large effect size, $d > 0.8$). They reported more symptoms (large effect size, $d = 0.8$) and were more hampered in their activities (large effect size, $d = 0.8$) than patients without difficult-to-treat asthma. The group difference in emotional problems was just not significant (small effect size, $d = 0.4$).

Behavioral problems

Table 4 shows the parental ratings of behavioral problems as measured by the CBCL in children with difficult-to-treat asthma and those who did not fulfill the criteria of difficult-to-treat asthma. The scores (*d)* reflect deviations in standard deviation units from healthy norm groups, and thus are effect sizes.

Table 3. Quality of life of patients with difficult-to-treat asthma ($n = 31$) versus non-difficult-to-treat asthma ($n = 52$)

	Quality of life (range 1-7)[a]			
	Difficult-to-treat asthma ($n = 31$)	**Non-difficult-to-treat asthma ($n = 52$)**	*t*	*p*
Overall, mean ± *SD* (range)	4.5 ± 1.4 (1.4-6.8)	5.4 ± 1.2 (2.8-7.0)	-3.31	<.001
Symptoms, mean ± *SD*	4.2 ± 1.5 (1.0-6.7)	5.3 ± 1.3 (2.7-7.0)	-3.52	<.001
Activities, mean ± *SD*	4.1 ± 1.5 (1.4-6.5)	5.2 ± 1.2 (2.0-7.0)	-3.48	<.001
Emotions, mean ± *SD*	5.1 ± 1.5 (1.8-7.0)	5.7 ± 1.2 (2.3-7.0)	-1.95	.06

[a] A higher score on the quality of life scales reflects a better quality of life.

The deviation from healthy norm groups on parents' reported behavioral problems of patients with difficult-to-treat asthma was significant on the total problem score (medium effect size) and internalizing problems (large effect size), and on the domains anxious/depressed (medium effect size), withdrawn/depressed (large effect size), somatic complaints (large effect size), and thought problems (large effect size). Within this group of patients with difficult-to-treat asthma, 7 (22 %) patients scored in the clinical range with respect to the total problem score (CBCL *T*-score ≥ 63; 90th percentile).

The patients who did not meet the criteria of difficult-to-treat asthma showed deviations from healthy norm groups on the CBCL domains internalizing problems (medium effect size), anxious/depressed (small effect size), withdrawn/depressed (medium effect size), and somatic complaints (large effect size).

Patients with difficult-to-treat asthma showed significantly higher scores than patients who did not fulfill the criteria of difficult-to-treat asthma on the domains somatic complaints ($t = 3.1$, $p = .003$) and thought problems ($t = 2.2$, $p = .03$).

The mean scores reflect the magnitude of deviations from the normative population in standard deviation units (*d*-scores). A positive score indicates that the children with asthma are judged to have more problems than the healthy norm group. The *d*-values have the following common effect sizes: a value smaller than 0.2 reflects no deviation from the norm, whereas values between 0.2 and 0.5, between 0.5 and 0.8, and greater than 0.8 reflects small, medium, and large deviations, respectively.

One sample *t*-tests examined whether norm deviation scores deviated from zero (the norm) and independent sample *t*-tests examined whether the scores of the two groups were different.

Table 4. Behavioral problems of patients with difficult-to-treat asthma and non-difficult-to-treat asthma. The mean scores reflect deviations from healthy CBCL norms

Group	Difficult-to-treat asthma *n* = 31			Non-difficult-to-treat asthma *n* = 52			Comparison between groups	
CBCL[a]	Mean ± *SD*	*t*	*p*	Mean ± *SD*	*t*	*p*	*t*	*p*
Total problems	0.69 ± 1.33	2.87	.007	0.27 ± 1.17	1.69	.10	1.48	.14
Internalizing	1.37 ± 1.43	5.33	<.001	0.77 ± 1.36	4.07	<.001	1.91	.06
Externalizing	0.04 ± 1.26	0.16	.88	-0.01 ± 1.11	-0.05	.96	0.16	.87
Anxious/depressed	0.63 ± 1.60	2.20	.04	0.38 ± 1.33	2.09	.04	0.76	.45
Withdrawn/depressed	0.83 ± 1.05	4.41	<.001	0.63 ± 1.52	3.02	.004	0.63	.53
Somatic complaints	2.41 ± 2.26	5.94	<.001	1.11 ± 1.61	5.00	<.001	3.05	.003
Social problems	0.37 ± 1.43	1.44	.16	0.21 ± 1.24	1.20	.24	0.55	.58
Thought problems	0.96 ± 1.44	3.69	.001	0.29 ± 1.26	1.63	.11	2.23	.03
Attention problems	0.37 ± 1.05	1.96	.06	-0.04 ± 0.95	-0.31	.76	1.83	.07
Rule-breaking behavior	-0.04 ± 1.01	-0.22	.83	-0.13 ± 1.08	-0.87	.39	0.38	.71
Aggressive behavior	0.14 ± 1.47	0.55	.59	0.15 ± 1.24	0.86	.39	-0.01	.99

[a] Mean scores, standard deviations (SD) and *t-test (*and *p*-values) examining whether the scores deviate from the norm (healthy CBCL groups) as well as *t*- and *p*-values of the comparison between the two asthma groups.

DISCUSSION

The behavioral problems of the clinically treated children and adolescents with asthma in our study were more severe compared to the healthy reference groups, especially internalizing problems such as being withdrawn/depressed, and somatic complaints. The main analysis in our study showed that the behavioral problems "somatic complaints" and "thought problems" as well as a lower quality of life were more pronounced in children and adolescents with difficult-to-treat asthma than in asthma patients who did not fulfill the criteria of difficult-to-treat asthma.

Our finding of more severe internalizing problems in children and adolescents with asthma is in agreement with previous studies[6,7,8]. In our study, one out of every five children (22 %) with difficult-to-treat asthma scored in the clinical range of the total behavioral problem score of the CBCL. This high frequency was mainly due to somatic and thought problems. "Somatic complaints" include items such as "nightmares," "dizzy," "tired," "(head)aches," "nausea," and "stomach problems." "Thought problems" comprise items such as "hears things," "sleep problems," and "strange behavior." Thus, the severity of behavioral problems - especially in children with difficult-to-treat asthma - mainly included somatic and thought problems that are not exemplary asthma manifestations.

The higher severity of behavioral problems in children and adolescents with asthma can theoretically be due to the disease, to medication related to the asthma, or to psy-

chosocial effects such as being treated differently due to the disease by parents. Adverse effects of asthma medications are rare.[26] Adverse effects of inhaled corticosteroids (ICS) are mild and sporadic[27] and ICS should not be avoided for that reason.[28] More severe internal behavioral problems may intensify the severity of asthma through poor adherence or neuro-endocrine mechanisms.[9, 10] The higher prevalence of somatic problems in our sample of children with difficult-to-treat asthma may also suggest that more severe asthma is a risk factor for more internalizing problems instead of the other way around. Correlation is necessary to verify an association, but it does not prove the causal direction of the association. Our data also confirmed the hypothesis that difficult-to-treat asthma coincides with a lower quality of life. Mostly large differences in physical and mental aspects of quality of life were observed between patients with difficult-to-treat asthma and patients with non-difficult-to-treat asthma. At a descriptive level, our study clearly indicates that especially the children and adolescents with difficult-to-treat asthma have behavioral problems and a low quality of life.

Difficult-to-treat asthma denotes lack of adequate control of asthma symptoms. We did not find relevant differences in pulmonary function testing between children with and without difficult-to-treat asthma. Pulmonary function testing even indicated a better FEV_1 score in the difficult-to-treat asthma group, which suggests that the more pronounced behavioral problems and lower quality of life of the children with difficult-to-treat asthma as compared to the children without difficult-to-treat asthma are unlikely to be explained by current differences in lung function. Poor disease control has been observed to be associated with a poor quality of life.[29] Although asthma severity appears as a risk factor for a poorer quality of life and a better control of asthma symptoms may probably improve quality of life, the association between asthma severity and quality of life is far from a one-to-one correlation.[6, 30] To the extent that disease control is difficult, to improve quality of life, treatment should be aimed at improving the coping with symptoms and emotions and at increasing activities.

Our study design has strengths and limitations. Children have the tendency to be more positive about their functioning. They notice fewer problems than parents or teachers.[31] Strength of our choice to use parental ratings to assess behavioral problems is that parents are more objective observers, but a limitation is that parental worries about the behavioral functioning of their children may still color the ratings. We chose to compare the behavioral problem ratings to established norms (i.e., normality). However, because the norm group excluded children who received professional help for mental health problems or who attended special education,[20] our analysis may have overestimated the actual behavioral dysfunctioning. The children and adolescents of our study represent a population that was referred to a specialized asthma clinic, which limits the generalizability of our results to a general asthma population. The observed differences between difficult-to-treat asthma and non-difficult-to-treat asthma in the two clinical

centers may be due to possible differences between selection criteria and treatment in these centers. From the moment of arrival, the administration of medication was supervised on a twice daily basis. Before arrival in the clinic, compliance was taken into account as reported by the patients and their parents. We did not use electronic devices (like a Smartinhaler®) to detect irregularities in compliance. However, using the data of the referring clinician and adding a structured interview on the day of arrival with the patients and their parents, made the best consideration clinically possible. Still, this might implicate that compliance on the moment of arrival was lower than assumed and therefore overestimates the number of patients in the difficult-to-treat asthma group.

The inclusion of both Dutch and German patients will not have influenced the behavioral problem scores to a large extent. In a cross-cultural comparison of parental CBCL ratings of healthy children and adolescents in Germany,[21] in the Netherlands and in the United States, relatively minor differences were observed between the three groups.[32] The discriminant validity of the German version of the CBCL is comparable to the English 2001 version.[33] Studies employing the 2001 version of the CBCL demonstrated a somewhat lower rate of behavioral problems in Germany than in the Netherlands and United States.[19, 34]

Our cross-sectional observation of groups does not give a full account of all extraneous variables that might have an effect on both behavioral problems and the diagnosis difficult-to-treat-asthma, such as time since diagnosis, age at which asthma was diagnosed, and the history of hospitalization. Considering the factors that hamper the unconfounded comparison between the difficult-to-treat asthma and non-difficult-to-treat asthma samples in our study, our conclusions need substantiation in future studies in other groups of children and adolescents with asthma. Our quantitative specification of behavioral problems in the difficult-to-treat asthma sample indicates the usefulness of future studies that offer a more in-depth account of factors of the child and family that play a role in the persistence of behavioral problems. In a systems approach that also focuses on the role of the parents or other caregivers, therapeutic strategies should aim at these behavioral problems and focus on self-management and compliance.

In conclusion, our study indicates that behavioral problems (somatic complaints and thought problems) and a lower quality of life are more severe in clinically treated children and adolescents with difficult-to-treat asthma than in asthma patients who are not classified as difficult-to-treat asthma. With respect to practical implications, our data suggest that health-care professionals should -especially in children and adolescents with difficult-to-treat asthma- assess and, if necessary, treat behavioral problems.

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4

The prospective association between behavioral problems and asthma outcome in young asthma patients

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MV and RG designed the study; MV and EJG collected the data, MV processed the data; MV, AAK, RG, EJG, LVZ and ED analyzed and interpreted the data. MV wrote the paper, EJG, AAK, RG, LVZ and ED made substantial revisions to the manuscript. All authors revised and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

ABSTRACT

Aim: The aim of this prospective study was to examine the association between behavioral problems and medical and psychological outcomes in clinically treated children and adolescents with asthma.

Methods: Patients (n = 134) were recruited from two high altitude asthma clinics in Switzerland and one asthma clinic in the Netherlands. Outcome measures were Asthma Control Test (ACT), Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)], forced expiratory volume in 1 second (FEV_1) and fractional concentration of exhaled nitric oxide (FeNO). Parents completed the Child Behavior Check List (CBCL) (predictor variable). Data were collected at the start and end of treatment. Multiple regression analysis was used while adjusting for demographic variables, clinic, and length of stay.

Results: More severe internalizing behavioral problems were associated with less improvement of total quality of life (t = -2.26, p = .03) and the domains symptoms (t = -2.04, p = .04), and emotions (t = -2.3, p = .02) after clinical treatment. Behavioral problems were not associated with a change of lung function measurements (FEV_1 and FeNO) and asthma control (ACT) during treatment.

Conclusion: A focus of health-care professionals on the treatment of internalizing behavioral problems may optimize the quality of life in clinically treated youth with asthma.

INTRODUCTION

Although many children and adolescents with asthma function well, selected children and adolescents with asthma may have behavioral problems; especially internalizing problems such as being withdrawn and depressed.[1] These behavioral problems possibly affect the outcome of asthma treatment through multiple, complementary pathways. Behavioral problems and patients' beliefs about their illness may cause poor adherence, poor asthma management, poor functional health status,[2, 3] and delay in seeking medical help.[4] Furthermore, psychosocial stressors may trigger the expression of asthma, e.g. through neuro-endocrine and immune mechanisms.[5] Conversely, the burden of disease may lead to behavioral problems such as difficulty in separation and individuation from parents and associated anxiety.[6]

Over the past decade, the emphasis in asthma management has shifted from treatment decided by level of asthma severity to therapy aimed at achieving full control of asthma.[7] Full control comprises a combination of little or no asthma symptoms (day and night), little or no use of reliever medication, no restriction of activities, no exacerbations, and normal lung function.[8] Behavioral factors such as illness perceptions, the cognitive-emotional representation of asthma symptoms and management have been observed to influence asthma outcome.[3] This suggests that complementary to medical care, targeting behavioral problems could possibly help patients with a psychological risk profile to better manage the disease.

Although in cross-sectional studies psychological variables have been shown to be associated with clinical asthma outcome, studies of the *prospective* association between behavioral problems and asthma outcome are scarce and show equivocal results. Family routines predicted asthma outcome[9] and parental stress and depression at baseline were associated with subsequent increases in children's inflammatory profiles over a six-month period.[10] It is not known whether behavioral problems in children and adolescents are prospectively associated with asthma outcome during clinical treatment.

The aim of our study was to examine the association between behavioral problems and the subsequent biomedical (lung function) and perceived (control of asthma and quality of life) outcome in a longitudinal design. We expected to find less improvement of asthma control, quality of life, and lung function during treatment in children and adolescents with more severe behavioral problems at the start. Our prospective study was conducted in a heterogeneous sample of children and adolescents clinically treated at high altitude or sea level.

METHODS

Study population

Patients were children and adolescents with asthma who were admitted for clinical treatment in one of three clinics: two high altitude asthma clinics with a hypo-allergenic environment in Switzerland, the *Netherlands Asthma Center Davos* (Dutch asthma clinic, hosting Dutch patients) and the *High Altitude Clinic Davos* (German asthma clinic, hosting German patients), and one clinic at sea level in the Netherlands, the *Asthma Center Heideheuvel* (hosting Dutch patients). From 2008-2010 all children aged 7-18 years with a confirmed diagnosis of asthma were invited to participate in the study.

Treatment

The participating clinics provide care for children with difficult-to-treat asthma with allergy for one or more inhaled allergens, bronchial hyperresponsiveness and eczema, or other presentations of the atopic syndrome commonly being present.[11] The reason for referral to one of the centers by the local or academic pediatrician or pediatric pulmonologist is often the co-existence of multiple asthma-related problems and the need for an extensive multidisciplinary approach.

The three clinics provide integrated multidisciplinary treatment programs of 1 to 3 months. A standard diagnostic program is performed with both somatic and psychosocial investigations. The children participate in a group psycho-educational asthma program that aims to increase knowledge, technical skills (inhalation technique), and coping strategies. Besides, they have individual therapeutic contacts with a pediatric pulmonologist or pediatrician, pulmonary nurse, physical and sports therapist, pedagogical worker, psychologist, and social worker. If possible, the parents participate in an educational program.

Several factors are unique to the treatment in Davos, Switzerland. In contrast to children treated at sea level in Hilversum, the Netherlands, the children in Davos temporarily live in a hypo-allergenic environment due to a lower concentration of pollen and almost complete absence of house dust mite.[12] The German high altitude clinic has a more exclusive focus on medical pulmonary treatment. The patients in Switzerland live separated from their family and their own social network. They all remain there for the whole treatment period (including the weekends). In contrast, the children in Asthma Center Heideheuvel are at home every weekend.

Procedure

The medical ethics committee of the Academic Medical Center (AMC), Amsterdam, the Netherlands, approved the study. The children ≥ 12 years of age and the parents of all children provided written informed consent.

Two weeks before the start of treatment in one of the three clinics, patients with asthma and their parents received paper-and-pencil questionnaires at their homes. On arrival of the patients at the clinic, medical history was taken including atopic symptoms, exercise intolerance, medication, reliever therapy, and adherence. Lung function testing (spirometry) and inflammometry (FeNO) were performed. History and physical examination were performed by one selected pediatrician per clinic. The diagnosis of asthma was approved or rejected on the basis of history, examination, and confirmed bronchoconstriction with (partial) reversibility in history.

At discharge, the self-report questionnaires (self-administered) of patients and lung function and airway inflammation measurements were repeated.

Instruments

Predictor variable

Parental report: Emotional and behavioral problems. The Child Behavior Checklist (CBCL) is a standardized questionnaire for assessing emotional and behavioral problems of children by parents or caregivers.[13] Parents of the children and adolescents filled out the Dutch 2001 version of the CBCL (6-18 years) or the 1998 German version of the CBCL (4-18 years).[14] The CBCL consists of 120 questions, range 0-2 per item. Results of the CBCL are expressed in a global score (120 questions, range 0-240) and in scores for internalizing (32 questions, range 0-64) and externalizing (35 questions, range 0-70) behavioral problems. We used the raw scores of the CBCL in our analyses. Higher scores indicate more behavioral problems.

Outcome variables

Children's self-report: Quality of life. The Pediatric Asthma Quality of Life Questionnaire, PAQLQ(S), is a widely used disease-specific health-related quality of life self-report measure for children and adolescents aged 7-17 years.[15] The Dutch PAQLQ(S) has adequate psychometric properties and excellent responsiveness, which supports longitudinal and cross-sectional construct validity.[16] The PAQLQ(S) is responsive to change of asthma control and has strong measurement properties.[17] The questionnaire assesses three domains: symptoms (10 items), activity limitations (5 items), and emotional function (8 items). The item range of 1 - 7 is reported per domain and for the whole instrument. Higher scores indicate better quality of life.[15]

Children's self-report: Asthma control. The Childhood Asthma Control Test (C-ACT)[18] is a 7-item checklist, with a maximum score of 27 points. This questionnaire shows the control of asthma at the moment of measurement, reported by the child (4 questions) and their caregivers. Only the raw scores of the 4 child questions (self-report) with a range from 0-12 were assessed at the start of treatment and at discharge.

Lung function. Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Germany). A standardized protocol with at least 3 technically correct manoeuvres was performed. Short or long acting β_2-adrenergic agonists were stopped 12 hours before PFT. The lung function parameter that was obtained and evaluated was forced expiratory volume in 1 second (FEV_1).

Airway inflammation was measured with the Niox Flex (Aerocrine, Sweden) using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS and ERS guidelines.[19]

Statistical analysis

Statistical analyses were done with SPSS 17.0. P-values < .05 (2-sided) were considered statistically significant.

The score distributions were checked for outliers and normality. Outliers (z > 3.29) were detected for the CBCL scales "total" (2 outliers), "internalizing" (1 outlier) and "externalizing" (4 outliers) problems at the start of treatment, and the PAQLQ(S) scale "emotions" (2 outliers) at discharge. These outlying variables were assigned a score that was one unit larger than the next most extreme score of the score distribution.[20]

The characteristics of the three treatment groups were compared using univariate analysis of variance with pair-wise Bonferroni comparisons in case of significant group differences. The gender distribution of groups was compared using a Chi-square test.

Paired samples *t*-test and univariate analysis of variance were used to examine the pre-to-post treatment change in outcome variables. Because the outcome of asthma treatment at high altitude and sea level may differ,[21, 22] we adjusted analyses for clinics. Also patient characteristics that were correlated with the outcome were defined as a covariate.

Linear regression analysis was used to predict the treatment outcome as a function of behavioral problems (CBCL), while controlling for treatment clinic. Clinics were dummy coded using codes for the Netherlands Asthma Center Davos (1 = Yes, 0 = No) and for the High Altitude Clinic Davos (1 = Yes, 0 = No). Thus, patients of the Asthma Center Heideheuvel obtained a value of zero on these variables. Control variables that were significantly related to at least a single outcome variable were entered in the analyses. In the first block of the regressions, the baseline score of the outcome variables was entered; as a consequence in the next blocks, the baseline adjusted change score at the outcome variable was predicted. In the second block, the patient characteristics were entered. In the third block, the clinic was entered, and in the fourth block, the length of stay in the clinic. In the final block, the behavioral problems were entered. The prediction variables "total," "internalizing" and "externalizing" behavioral problems were entered in separate regression analyses.

RESULTS

Patient characteristics

Fifty-one of 62 (82 %) Dutch clinical patients of the Netherlands Asthma Center Davos were included; 4 patients did not provide informed consent, the parents of 6 patients did not complete the Child Behavior Check List (CBCL) questionnaire, and in one patient the diagnosis asthma was withdrawn. Out of 63 German clinical patients of the High Altitude Clinic Davos, 48 were included (76 %); 3 patients did not provide informed consent, 10 did not complete the CBCL, and in 2 the diagnosis asthma was withdrawn. Thirty-five of 40 (88 %) Dutch clinical patients of Asthma Center Heideheuvel participated in our study; 2 did not provide informed consent, 2 did not respond, and one did not complete the CBCL.

Table 1 shows the characteristics of 134 patients with a complete data set and a certified diagnosis of asthma at the start of treatment in one of the three asthma clinics. The mean age of the total group was 12.9 (*SD* 2.7, range 7-18) years, with 52 % girls.

The children and adolescents in the three groups did not significantly differ with respect to percentage girls (Chi^2 = .53, p = .77) and mean age (F = .54, p = .59). The mean length of stay was longer in the Dutch (Netherlands Asthma Center Davos and Asthma Center Heideheuvel) patients as compared to the German (High Altitude Clinic Davos) patients (F = 33, p < .001). Behavioral problems did not differ significantly at the start of treatment between the three groups (total score, F = .63, p = .54; internalizing problems, F = .39, p = .69; externalizing problems, F = .24, p = .79). FEV_1 measurements projected in the normal range but showed significant differences between clinics (F = 3.38, p = .04). FeNO did not differ (F = 1.79, p = .17). Control of asthma (ACT) differed (F = 18.51, p <.001) between clinics. Quality of life [PAQLQ(S)] did not significantly differ with respect to the total score (F = 1.83, p = .16) and the domain "emotions" (F = 1.11, p = .33), but the domains "symptoms" (F = 3.14, p = .05) and "activity" (F = 3.63, p = .03) differed significantly.

Treatment effect

Table 2 shows the lung function measurements (FEV_1 and FeNO), control of asthma (ACT) and quality of life [PAQLQ(S)] scores at the start and end of treatment per clinic. Table 3 shows the standardized baseline adjusted pre-to-post therapy change scores.

FEV_1 did not significantly change in any group. FeNO improved significantly in all groups (Table 2); the differences between clinics were not significant (Table 3).

Control of asthma improved significantly in the populations of the Netherlands Asthma Center Davos and the Asthma Center Heideheuvel (Table 2) and improved significantly more in the Netherlands Asthma Center Davos than in the other clinics (Table 3). All domains of quality of life improved significantly in all groups (Table 2). The patients of

the Netherlands Asthma Center Davos improved significantly more than the patients of the High Altitude Clinic Davos on total quality of life (Table 3).

Table 1. Characteristics of the 134 asthma patients at the start of treatment

	Netherlands Asthma Center Davos		High Altitude Clinic Davos		Asthma Center Heideheuvel	
	n = 51		*n* = 48		*n* = 35	
Female, number (%)	26	(51 %)	21	(44 %)	17	(49 %)
Age, mean (SD) yrs	12.7	(2.6)	13.2	(3.0)	12.8	(2.5)
Length of stay, mean (SD), range (days)	68	(3), 14-123	33	(9), 7-56	62	(23), 7-115
[1] Behavioral problems (CBCL)						
Total score, mean (SD)	31	(20)	28	(19)	33	(24)
Internalizing, mean (SD)	12	(7)	10	(7)	12	(9)
Externalizing, mean (SD)	6	(8)	7	(6)	7	(6)
Lung function						
[4] FEV_1 in % pred[2] (SD)	105.8	(3.4)	99.4	(14.0)	100.2	(14.8)
[5] FeNO in ppb[3] (SD)	33.9	(26.5)	33.4	(33.4)	22.1	(22.4)
[6] Control of asthma (ACT)						
Total child score	6.6	(2.0)	9.1	(2.1)	6.0	(2.4)
[7] Quality of life [PAQLQ(S)]						
Total	4.8	(1.1)	5.3	(1.4)	5.1	(1.1)
Symptoms	4.5	(1.4)	5.2	(1.5)	4.7	(1.4)
Activities	4.3	(1.5)	5.1	(1.4)	4.6	(1.2)
Emotions	5.6	(1.1)	5.5	(1.5)	6.0	(1.1)

[1] CBCL= Child Behavior Checklist (total score range 0-240; internalizing 0-64, externalizing 0-70. Higher scores reflect more problems)

[2] % pred = percentage predicted

[3] ppb = parts per billion

[4] FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted

Values are geometric ([5] FeNO: fractional concentration of exhaled nitric oxide) or arithmetic means (FEV_1, ACT and PAQLQ(S))

[6] ACT = Childhood Asthma Control Test (range 0-12; a higher score reflects better control)

[7] PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (range 1-7; a higher score reflects better quality of life)

Table 2. Mean scores (*SD*) and *p*- values at the start and end of treatment per clinic: Lung function measurements FEV_1 and FeNO, control of asthma (ACT) and quality of life [PAQLQ(S)]

	Netherlands Asthma Center Davos *n* = 51					High Altitude Clinic Davos *n* = 48					Asthma Center Heideheuvel *n* = 35				
Mean (SD)	**Start**		**End**		***p****	**Start**		**End**		***p****	**Start**		**End**		***p****
Lung function															
FEV_1 (% pred)	105.8	(3.4)	106.1	(13.7)	.76	99.4	(14.0)	99.7	(15.5)	.92	100.2	(14.8)	103.5	(14.4)	.05
FeNO (ppb)	33.9	(26.5)	16.0	(8.9)	<.001	33.4	(34.4)	14.2	(7.6)	<.001	22.1	(22.4)	12.7	(7.1)	.03
Control of asthma (ACT)															
Total	6.6	(2.0)	9.6	(1.7)	<.001	9.1	(2.1)	8.9	(2.3)	.55	6.0	(2.4)	7.7	(1.9)	.002
Quality of life [PAQLQ(S)]															
Total	4.8	(1.1)	6.1	(.81)	<.001	5.3	(1.4)	5.7	(1.1)	.008	5.1	(1.1)	5.8	(.93)	.009
Symptoms	4.5	(1.4)	5.9	(.93)	<.001	5.2	(1.5)	5.6	(1.3)	.04	4.7	(1.4)	5.3	(1.4)	.04
Activity	4.3	(1.5)	5.9	(1.1)	<.001	5.1	(1.4)	5.6	(1.0)	.007	4.6	(1.2)	5.4	(1.4)	.02
Emotions	5.6	(1.1)	6.5	(.73)	<.001	5.5	(1.5)	6.1	(1.0)	.003	6.0	(1.1)	6.6	(.43)	.007

*Paired samples t-test
% pred = percentage predicted
ppb = parts per billion
FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted
Values are geometric (FeNO: fractional concentration of exhaled nitric oxide) or arithmetic means (FEV_1, ACT and PAQLQ(S))
ACT = Childhood Asthma Control Test (range 0-12; a higher score reflects better control)
PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (range 1-7; a higher score reflects better quality of life)

Table 3. Standardized baseline adjusted pre-to-post therapy change scores per clinic: Mean (standard error) and *p*-values of lung function, control of asthma and quality of life scores

	Netherlands Asthma Center Davos (NAC)		High Altitude Clinic Davos (HAC)		Asthma Center Heideheuvel (ACH)		Comparison between clinics		
Mean (*SE*)	***n* = 51**		***n* = 48**		***n* = 35**		***F***	***p****	**Posthoc**
Lung function									
FEV_1 (% pred)	.14	(1.4)	-1.4	(1.5)	1.7	(1.7)	.94	.40	NAC = HAC = ACH
FeNO (ppb)	1.5	(1.1)	-1.8	(1.4)	-.93	(1.6)	1.99	.14	NAC = HAC = ACH
Control of asthma (ACT)									
Total child Score	.94	(.28)	-.59	(.31)	-.74	(.37)	9.50	<.001	NAC > HAC= ACH
Quality of life [PAQLQ(S)]									
Total	.26	(.13)	-.20	(.13)	-.15	(.18)	3.76	.03	NAC > HAC NAC=ACH HAC = ACH
Symptoms	.33	(.16)	-.18	(.17)	-.32	(.23)	3.53	.03	NAC = HAC = ACH
Activity	.30	(.15)	-.15	(.16)	-.31	(.21)	3.49	.03	NAC = HAC = ACH
Emotions	.13	(.11)	-.23	(.11)	.16	(.15)	3.50	.03	NAC = HAC = ACH

* Univariate Analysis of Variance with age as covariate
FEV_1 = forced expiratory volume in 1 second; % pred = percentage predicted
FeNO = fractional concentration of exhaled nitric oxide; ppb = parts per billion
ACT = Childhood Asthma Control Test
PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (Self-Report)
NAC = Netherlands Asthma Center Davos
HAC = High Altitude Clinic Davos
ACH = Asthma Center Heideheuvel

Prospective associations

Asthma control. Table 4 shows the results of linear regression analyses predicting asthma outcome (lung function, and control of asthma) from age, clinic, length of stay, and behavioral problems. In the first block, baseline scores were shown to be associated with post-treatment scores at a high significance. Having controlled for baseline scores, in the subsequent blocks, the baseline-adjusted change at the outcome variable was predicted. In block 2, a higher age was just not significantly associated with less improvement of lung function (decreased $FEV_{1,}$ t = -1.93, p =. 06 and increased FeNO, t = 1.90, p = .06). In block 3, being treated at the Netherlands Asthma Center Davos was associated with more increase of control of asthma (t = 3.54, p = .001), and in block 4, a longer length of stay was associated with increased control of asthma (t = 3.20, p = .002). In block 5, more severe externalizing problems were not significantly associated with decreased FeNO (t = -1.67, p = .098).

Table 4. Results of regression analyses predicting asthma outcome (lung function and control of asthma) from baseline scores (block 1), person characteristics (block 2), clinic (block 3), length of stay (block 4), and behavioral problems (block 5)

	Lung function				**Control of asthma**	
	FEV1 (% pred)		**FeNO** (ppb)		**ACT**	
Predictor variable	***B***	**Adj R^2**	***B***	**Adj R^2**	***B***	**Adj R^2**
Block 1		**.55*** **		**.13*** **		**.15*** **
Baseline	.74***		.38***		.40***	
Block 2		**.56†**		**.16†**		**.15**
Baseline	.73***		.36***		.41***	
Age	-.11 †		.17†		-.07	
Block 3		**.56**		**.17**		**.29*** **
Baseline	.73***		.37***		.52***	
Age	-.11 †		.21*		-.03	
Clinics						
NAD	-.05		.15		.39**	
HAC	-.10		-.04		-.03	
Block 4		**.56**		**.17**		**.36** **
Baseline	.73***		.37***		.53***	
Age	-.11 †		.21*		-.04	
Clinics						
NAD	-.06		.13		.36**	
HAC	-.08		-.01		.14	
Length of stay	.04		.09		.33**	
Block 5[1]						
Baseline	.74***		.37***		.53***	
Age	-.11 †		.21*		-.04	

Table 4. Results of regression analyses predicting asthma outcome (lung function and control of asthma) from baseline scores (block 1), person characteristics (block 2), clinic (block 3), length of stay (block 4), and behavioral problems (block 5) (*continued*)

	Lung function				**Control of asthma**	
	FEV_1 (% pred)		**FeNO** (ppb)		**ACT**	
Clinics						
NAD	-.06		.13		.36**	
HAC	-.08		-.02		.14	
Length of stay	.03		.10		.33	
Behavioral problems						
Total	.08	**.56**	-.09	**.17**	.004	**.35**
Internalizing	.05	**.55**	-.003	**.16**	-.09	**.36**
Externalizing	.09	**.56**	-.15†	**.18**†	.03	**.35**

† p < .10, * p < .05, ** p < .01, *** p < .001

[1]Note: the variables total and internalizing and externalizing behavioral problems were entered in separate regression analyses.

FEV_1 = forced expiratory volume in 1 second; % pred = percentage predicted

FeNO = fractional concentration of exhaled nitric oxide; ppb = parts per billion

ACT = Childhood Asthma Control Test

NAC = Netherlands Asthma Center Davos

HAC = High Altitude Clinic Davos

Quality of life. Table 5 shows the longitudinal associations of age, clinics, length of stay, and behavioral problems with quality of life.

In block 2, a younger age was significantly associated with more increase of total quality of life (t = -2.00, p = .05), and more improvement on the domains symptoms (t = -2.29, p = .02) and activity (t = -2.04, p = .04). In block 3, being treated at the Netherlands Asthma Center Davos was associated with better scores on quality of life improvement: total quality of life (just not significant: t = 1.93, p = .06), and the domains symptoms (t = 2.32, p = .02) and activity (t = 2.37, p = .02). Being treated at the High Altitude Clinic Davos, Switzerland was associated with more improvement on the domain emotions (t = -2.13, p = .04). Duration of treatment (block 4) was not significantly associated with more improvement of quality of life. In block 5, more severe internalizing behavioral problems were associated with less improvement of total quality of life (t = -2.26, p = .03) and the domains symptoms (t = -2.04, p = .04), and emotions (t = -2.33, p = .02).

Table 5. Results of regression analyses predicting quality of life from baseline scores (block 1), person characteristics (block 2), clinic (block 3), length of stay (block 4), and behavioral problems (block 5)

	Quality of life [PAQLQ(S)]							
	Total		Symptoms		Activity		Emotions	
Predictor variable	***B***	**Adj R^2**	***B***	**Adj R^2**	***B***	**Adj R^2**	***B***	**Adj R^2**
Block 1		**.14*** **		**.11*** **		**.12*** **		**.25*** **
Baseline	.39***		.34***		.36***		.50***	
Block 2		**.17***		**.14***		**.15***		**.24**
Baseline	.39***		.33***		.37***		.51***	
Age	-.18*		-.20*		-.18*		-.06	
Block 3		**.21***		**.18***		**.19***		**.28***
Baseline	.43***		.38***		.41***		.48***	
Age	-.15†		-.18*		-.16†		-.05	
Clinics								
NAD	.22†		.27*		.27*		-.02	
HAC	-.03		.05		.06		-.23*	
Block 4		**.21**		**.18**		**.20**		**.28**
Baseline	.44***		.38***		.43***		.48***	
Age	-.15†		-.18*		-.16†		-.05	
Clinics								
NAD	.20†		.25*		.25*		-.04	
HAC	.04		.10		.14		-.19	
Length of stay	.14		.11		.17		.09	
Block 5[1]								
Baseline	.42***		.37***		.43***		.46***	
Age	-.16†		-.18*		-.16†		-.05	
Clinics								
NAD	.20†		.25*		.25*		-.04	
HAC	.04		.10		.14		-.19	
Length of stay	.15		.11		.17		.10	
Behavioral problems								
Total	-.09	**.22**	-.90	**.18**	-.03	**.21**	-.12	**.28**
Internalizing	-.20*	**.24***	-.18*	**.20***	-.14	**.21**	-.20*	**.30***
Externalizing	-.07	**.21**	-.07	**.18**	-.003	**.19**	-.11	**.28**

† p < .10, * p < .05, ** p < .01, *** p < .001

[1]Note: the variables total and internalizing and externalizing behavioral problems were entered in separate regression analyses.

PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (Self-Report)

NAC = Netherlands Asthma Center Davos

HAC = High Altitude Clinic Davos

DISCUSSION

This prospective study examined the association between behavioral problems in children and adolescents with asthma at the start of clinical treatment and the outcome of asthma after treatment. The main analysis of our study showed that more severe internalizing behavioral problems were associated with less increase of quality of life after clinical treatment; asthma improvement was not associated with behavioral problems. Younger age was associated with improvement of quality of life. Longer length of stay was associated with increased control of asthma.

Outcomes were analyzed in patients treated at high altitude and in patients treated at sea level. FeNO improved, control of asthma improved in two clinics, and quality of life improved in all clinics. We did not find an improvement in FEV_1; measurements at the start of treatment were already in the normal range. While improvement in airway inflammation during a stay at high altitude might occur independent of pharmacological treatment or severity of the disease,[21] in the current study airway inflammation (FeNO) improved in the whole sample, without a significant difference between the clinics.

On average, asthmatic children have a significantly poorer quality of life than children from the general population,[15] especially children with problematic severe asthma.[1, 23] Asthma control test scores are also lower in problematic severe asthma compared to controlled asthma.[23] In our study, control of asthma and the total quality of life improved most in the patients treated in the Netherlands Asthma Center Davos. A previous study also suggested that quality of life improved more during clinical treatment in a hypoallergenic environment than at sea level.[22] Our present study replicates this finding for the Dutch but not for the German high altitude clinic. This may suggest that the improvement in quality of life is not due to treatment at high altitude per se. However, also the short length of stay may have played a role here. Furthermore, the more positive effects on asthma control and quality of life in the Dutch compared to the German high altitude clinic could be due to the more exclusive focus on integrative medical and psychological treatment in the Dutch high altitude clinic. The current study, however, was not designed to compare the clinics. Perhaps the combination of high altitude treatment and treatment by a multidisciplinary team are especially effective to improve quality of life.

Age was not significantly associated with improvement of lung function. However, a younger age was associated with an increase of total quality of life and an improvement in the domains symptoms and activity. Longer treatment duration was associated with a larger increase of asthma control. Although this observation might reflect that a longer stay is better to achieve asthma control, it is also possible that the medical specialist correctly appraised which patients could better stay longer because benefit in terms of asthma control was still possible. It is also possible that the child experiences increased

asthma control as a justification for a longer stay in the clinic (cognitive dissonance theory).

Because treatment allocation was not random, we cannot conclude that this reflects that a treatment program of relatively long duration is necessary to improve asthma control.

More severe internalizing behavioral problems predicted less increase of total quality of life after treatment, specifically a less positive change in the domains symptoms and emotions. This was the core question of our study. Behavioral problems might have an effect on asthma through multiple, complementary mechanisms, such as neuro-endocrine stress responses affecting immune processes that influence asthma,[2] poor asthma management such as poor adherence to asthma medication, and poor functional health status such as having a sedentary life-style.[24] In our previous cross-sectional study, we observed that behavioral problems were associated with more severe asthma, suggesting that a focus on behavioral problems might be beneficial for asthma control.[1] Our current study showed that behavioral problems did not obstruct the outcome of asthma. Thus, our results suggest that treatment of behavioral problems might be useful to improve quality of life while no effects on the outcome of asthma are to be expected.

Our study has strengths and limitations. The children and adolescents of our study represent a population that was referred to specialized asthma clinics, which limits the generalizability of our results to a general asthma population. Moreover, with respect to comparison of clinics, our study was descriptive. The three specialized clinics differ regarding the educational program, the location at high altitude or sea level, and the duration of treatment. In regression analysis involving outcome prediction from behavioral problems, we adjusted for these differences between clinics. However, random allocation to clinics would have been needed to make a true comparison of treatment effects between clinics. Earlier research suggested that the inclusion of both Dutch and German patients will not have influenced the behavioral problem scores to a large extent.[25, 26] Strength of our choice to use parental ratings to assess behavioral problems is that parents are more objective observers than children.[27] A major strength of our study is the prospective design and the adjustment for covariates in regression analysis.

Our study indicates that more severe internalizing behavioral problems are associated with less improvement of quality of life during clinical treatment. In children with chronic diseases including asthma, there is evidence of effectiveness for interventions incorporating cognitive behavioral techniques on variables such as self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation, social competence, and days absent from school.[28] Cognitive behavioral interventions are the more indicated in the selected group of children and adolescents with behavioral problems.

In conclusion, the findings of the present study in a clinically treated population with asthma indicate that health-care professionals should focus on the treatment of internalizing behavioral problems in order to optimize the quality of life of children and adolescents with asthma.

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5

Problematic severe asthma in children treated at high altitude: tapering the dose while improving control

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ABSTRACT

Background: Multidisciplinary treatment at high altitude is a possible treatment option for problematic severe asthma (PSA) in children. This management can result in the tapering of inhaled corticosteroids.

Aim: Our aim was to analyze the effect of multidisciplinary treatment at high altitude, notably the ability to taper corticosteroids. To get an insight into possible factors influencing tapering, we examined whether demographic variables, disease control and quality of life at treatment entrance could predict the tapering of corticosteroids.

Methods: This prospective open-phase cohort study analyzed the data of 43 children aged 8-17 years referred to a specialized high altitude treatment center. Lung function ($FEV_{1,}$ FEV_1/VC), inflammation (FeNO), medication level, asthma control (ACT), and quality of life [PAQLQ(S)] were evaluated on admission and at discharge.

Results: Thirty-two (74 %) children fulfilled PSA criteria. Three (7 %) children used daily oral steroids. After 72 ± 30 (mean ± SD) days of treatment, the mean dosage of inhaled corticosteroids (ICS) could be significantly reduced from 1315 µg ± 666 budesonide equivalent to 1132 µg ± 514. Oral steroid maintenance therapy could be stopped in all patients. FeNO, asthma control and quality of life improved ($p < .001$) from admission to discharge; FEV_1 was in the normal range on both occasions. Apart from ICS levels at entrance, multiple regression analyses did not show any associated factor predicting the reduction of ICS dosage during treatment.

Conclusion: The results indicate that high altitude treatment may be a treatment option for children with PSA, but it is not possible to predict ICS tapering off from health status variables at treatment entrance.

INTRODUCTION

Asthma is a common chronic respiratory disease in childhood characterized by airway obstruction, airway inflammation, and bronchial hyperresponsiveness (BHR). The reported prevalence of asthma in childhood and adolescence ranges from 5 % to 15 %.[1] A small portion (the precise prevalence is unknown) of pediatric asthma patients can be classified as having problematic severe asthma (PSA), defined as asthma that is not under control despite optimal treatment.[2, 3] PSA is characterized by longer periods of unstable asthma, lower forced expiratory flow in 1 s (FEV_1), higher dose of inhaled steroids, and more severe airway obstruction at the time of referral to a specialist.[4] Despite the low prevalence, PSA is of major interest as these patients have more morbidity, a larger disease burden, higher treatment costs[5, 6] and a poorer overall quality of life.[7] Insight into the prevalence and characterization of pediatric PSA as well as the response to treatment and long term effects of treatment on quality of life is needed. High doses of inhaled corticosteroids (ICS) or oral steroids may be needed to stabilize PSA in children, which may result in a reduction in growth velocity or bone density. In such a scenario, it is desirable to use the lowest possible level of (inhaled) steroids.

High altitude treatment is one of the possible treatment options to reduce the dosage of ICS in children with PSA.[8] Climatologic advantages, the absence of house dust mite allergen and the removal of the child from his daily surroundings may be responsible for stabilization of the disease in the high altitude environment.[9] Whether high altitude treatment can result in successful tapering of ICS remains unknown, however. Moreover, the role of other determinants (such as asthma control, lung function, and disease-specific quality of life (QOL)) in successful reduction of ICS is unknown. Asthma control correlates with the need for change in pharmacotherapy as indicated by the specialist's rating of asthma control.[10] However, we were unable to find studies in children with asthma that show a better quality of life preceding reduced medication use.

Our aim was to investigate the effect of multidisciplinary high altitude treatment on the (minimum) dose of inhaled corticosteroid required to keep the asthma under control. In order to gain insight in possible factors influencing the tapering, we examined whether the reduction in inhaled corticosteroid requirement after high altitude treatment could be predicted by demographic (gender and age), clinical (asthma control or quality of life) or lung function variables at entrance. We hypothesized that a lower dose of ICS could be used at the end of high altitude treatment while gaining stability. We had no clear expectations whether QOL or ACT could be predictors for tapering ICS.

METHODS

Patients

From January 2008 till March 2009, patients aged 8 – 17 years with a confirmed diagnosis of asthma, who were admitted to the Netherlands Asthma Center in Davos, Switzerland, were invited to participate in this prospective cohort study. This center, specialized in the treatment of difficult asthma, is situated in the Swiss Alps at an altitude of 1690 M above sea level, and treats patients aged 8 years and older with unstable or uncontrolled asthma. The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. The children ≥ 12 years of age and the parents of all children provided written informed consent.

The diagnosis of asthma was made or dismissed on the basis of history, physical examination, confirmed bronchoconstriction with (partial) reversibility (≥ 12 % FEV_1 predicted). Problematic severe asthma (PSA) was defined using criteria of the Dutch Pediatric Respiratory Society,[11] which are based on task forces of the American Thoracic Society and European Respiratory Society, and ENFUMOSA study (Table 1).[2, 12, 13] A positive score on PSA denotes persistent or severe asthma and lack of adequate control of asthma symptoms (such as exercise intolerance, two or more times per week in need of extra reliever therapy and night time symptoms) despite high doses of controller

Table 1. Criteria of problematic severe asthma

1.	Age ≥ 6 years.
2.	≥ 6 months treatment on the following treatment regime (doses are adapted to the Dutch situation):
	- daily use of ≥ 800 μg budesonide/beclometasone dipropionate or equivalent (≥ 500 μg fluticasone of ≥ 400 μg beclometasone dipropionate extra-fine or ≥ μg 320 ciclesonide),
	- and long acting β_2-agonist,
	- and a (history of) treatment on a leukotriene receptor antagonist
3.	With respect to the medication mentioned above, at least one of the following criteria should apply:
	- decreased exercise intolerance and/or symptoms at night and/or, use of reliever therapy ≥ 2 times weekly,
	- frequent exacerbations with need for oral prednisolone (≥ 2 per year),
	- exacerbation(s) requiring ICU treatment in history,
	- persistent airway obstruction (FEV_1 < 80 % post reliever).
4.	At least 6 months treatment in pediatric practice.
5.	History of good compliance.
6.	Checked inhalation technique.
7.	Confirmation of diagnosis asthma on pulmonary function testing defined as obstructive flow volume curve with (partial) reversibility of forced expiratory volume in 1 second (FEV_1) on β_2-agonists).
8.	Medication as mentioned above may be prescribed temporarily and build down because of lack of effect.

FEV_1 forced expiratory volume in one second, LABA long acting ß$_2$-agonist, LTRA leukotriene receptor agonist, ICU intensive care unit

therapy, adequate use of spacers and devices, confirmed diagnosis, and good compliance. Intake of medication was supervised during the stay in the clinic. Compliance was regarded as "poor" in cases of doubt *or* suspected lack of compliance on more than one day per week based on the history, and thus the criteria for problematic severe asthma were not met.

Design and treatment protocol

The prospective, uncontrolled design comprised pre- and post-treatment measurements. Two weeks before the start of clinical treatment in the high altitude clinic, all patients and parents received questionnaires at their homes. On the day of arrival, a medical history was taken in a structured interview including atopic symptoms, exercise intolerance, medication and reliever therapy. Pulmonary function testing was performed. The diagnosis of asthma and criteria of PSA including (history of) compliance were approved or rejected by one selected pediatrician. A structured day program consisted of school, health education, physical exercise, and multidisciplinary treatment. The treatment duration was scheduled for 10 weeks. Adherence to medication was assured before treatment in the clinic and reassured during the period of stay due to daily supervision of nurses while using medication. On the basis of weekly physical examination and the absence of exacerbations, the dosage of (oral prednisolone and) ICS was changed at intervals of 4 weeks. Dose reduction of ICS was based on pre-designed steps of 50 % per time. Montelukast was not changed. At discharge, pulmonary function testing was repeated and the children completed questionnaires on asthma control and quality of life again.

Pulmonary function testing

Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Germany). A standardized protocol was used and at least 3 technically correct maneuvers were performed. Short or long acting β_2-agonists were stopped ar least 12 h before PFT. Lung function parameters that were obtained and evaluated were forced expiratory volume in 1 s (FEV_1), vital capacity (VC) and Tiffeneau-index (FEV_1/VC). Airway inflammation was measured using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS and ERS guidelines.[14] The NIOX Flex (Aerocrine, Sweden) was used according to the manufacturer's instructions.

Instruments

Asthma control test

The childhood asthma control test (ACT) is a seven-item checklist. This questionnaire assesses the control of asthma at the time of measurement, as reported by the child (four

questions) and their caregivers. The childhood ACT has been validated in children from the age of 4 with relatively mild, controlled asthma.[10] A cut-off point of ≤ 19 indicates uncontrolled asthma with a sensitivity of 74 % and a specificity of 68 %. An association has been observed between ACT scores and specialist-assessed change in child's therapy ($F = 20.07$, $p < .001$) and specialist assessment of asthma control ($F = 36.89$, $p < .001$). Validation and cut-off points for children with more severe disease or less control have been described.[15] Since parents were absent during treatment, raw scores of the four child questions (self- report; range 0-12) at the start of treatment and at discharge were compared.

Children's self-report: Quality of life

The Pediatric Asthma Quality of Life Questionnaire, PAQLQ(S), is a widely used disease-specific health-related quality of life self-report measure for children and adolescents aged 7-17 years.[16] It has three domains: symptoms (10 items), activity limitations (5 items), and emotional function (8 items). The item range 1 - 7 is reported per domain and for the whole instrument. Higher scores indicate better quality of life. The Dutch PAQLQ has adequate psychometric properties and excellent responsiveness.[17]

Statistical analysis

Statistical analyses were done with SPSS 18.0. *P*-values < .05 (two-sided) were considered statistically significant. Pre- to post-treatment differences were examined with paired-samples *t*-tests and with a non-parametric test for lung function (Mann-Whitney *U* test). Hierarchical linear regression analysis was used to predict the budesonide dose at discharge while controlling for the baseline dose, age, and gender. In the first block, the baseline dose of budesonide was entered; consequently in the next blocks, the pre- to post-therapy change of budesonide was predicted. In block 2, age and gender were entered as control variables. In block 3, lung function (FEV_1 and FeNO), ACT and PAQLQ were entered.

RESULTS

Forty-four patients were eligible for inclusion. One was excluded due to a different diagnosis (dysfunctional breathing). Thus, 43 patients with a diagnosis of asthma were asked to participate in the study and all gave informed consent. Patient characteristics and baseline features are shown in Table 2; all had moderate persistent to severe asthma, and kept having symptoms despite a higher (step 3-4) of highest (step 5) dose of ICS and a (trial) of montelukast. Moreover, 74 % of the patients fulfilled PSA criteria, whereas 26 % did not due to either lack of (trial of) treatment with LTRA or suspected lack of

compliance. The mean dose of inhaled controller medication was high: daily 1315 µg (SD 666) budesonide equivalent. Three patients were on a continuous administration of oral corticosteroids (dose 5-20 mg daily). Mean ACT on admission was 14.3 (range 5-24), four patients (10 %) had a score higher than 19 (denoting "good control"). Nine (23 %) had a score of 12 or less ("very poorly controlled"). Data on ACT of four patients were missing due to reporting later than the first week of treatment.

Table 3 shows a detailed description of lung function parameters, inhaled steroid use and ACT and PAQLQ(S) on admission and discharge. Lung function (FEV_1, FEV_1/VC) did not change significantly and still projected in the (higher) normal range. FeNO improved significantly ($p < .001$) as did asthma control and quality of life ($p < .001$).

The inhaled steroid dose could significantly be decreased ($p = .02$). The effect size (d) of the difference was 0.31. Daily ICS doses were stable in 29 patients, decreased (400-800 µg/day) in 12 patients, decreased (1200 µg/day) in 1 patient, and increased in 1 patient. Oral steroids could be stopped completely in all three patients.

The results of multiple regression analysis are shown in Table 4. In the first block, baseline values of budesonide equivalents highly significantly correlated with budesonide values at discharge. Of the biographic variables, female sex was almost significantly associated with budesonide suggesting that after correction for baseline values, reducing ICS might be somewhat more likely in the boys than the girls. Separate regression analyses for boys and girls did not yield significant predictors other than budesonide at baseline. FEV_1, FeNO, ACT or PAQLQ(S) at admission did not correlate with the possibility to reduce the dose of daily inhaled steroids.

Table 2. Characteristics of the 43 patients

	Statistics	
Female, number (%)	24	(58)
Problematic severe asthma, number (%)	32	(74)
Age, mean (SD) yrs	13.0	(2.4)
Length of stay, mean (SD) days	72	(30)
Daily inhaled Budesonide, mean (SD) µg	1315	(666)
Used medication: LTRAs, number (%)	24	(59)
LTRAs[a] in the recent past, number	8	
Oral corticosteroids daily, number	3	
FEV_1 [b], mean (SD)	105.3	(14.5)
FEV_1 / VC [b], mean (SD)	114.8	(16.1)
FeNO, ppb, mean (SD)	39.8	(26.0)

[a] LTRAs: leukotriene receptor agonists

[b] % pred, percentage predicted

FEV_1, forced expiratory volume in 1 s; FeNO, fractional concentration of exhaled nitric oxide; ppb, parts per billion

Table 3. Mean scores (SD) on admission and at discharge and *t*- and *p*-values:
Lung function measurements, control of asthma (ACT) and quality of life [PAQLQ(S)]

	N	Admission mean (SD)	Discharge mean (SD)	*t*	*p*[d]
FEV1[a]	41	105.1 (14.7)	108.1 (13.9)	-1.5	.14
FEV1 / VC[a]	39	115.3 (16.4)	111.5 (12.1)	1.7	.10
FeNO[b]	42	39.8 (26.4)	15.2 (7.6)	6.3	< .001
Eq Budesonide[c]	41	1315 (666)	1132 (514)	2.5	.02
ACT total child	32	6.5 (1.7)	9.7 (1.7)	-8.5	< .001
PAQLQ(S) total	37	4.8 (1.2)	6.2 (.76)	-7.3	< .001

FEV_1, forced expiratory volume in 1 s; VC, vital capacity; FeNO, fractional concentration of exhaled nitric oxide; Eq, Equivalent; ACT, childhood asthma control test; PAQLQ(S), pediatric asthma quality of life questionnaire (self-report)

[a] % pred, percentage predicted

[b] ppb, parts per billion

[c] µg

[d] Paired samples *t*-test

Table 4. Results of regression analyses predicting budesonide at discharge from the baseline dose (Block 1), person characteristics (Block 2), and in separate regression analyses FEV_1 FeNO, ACT, and PAQLQ (Block 3)

	FEV1 (*n* = 41)		FeNO (*n* = 41)		ACT (*n* = 34)		PAQLQ(S) (*n* = 35)	
	β	Adj R^2	*β*	Adj R^2	*β*	Adj R^2	*B*	Adj R^2
Block 1		.49***		.49***		.72***		.72***
baseline budesonide	.71***		.71***		.85***		.86***	
Block 2		.51		.51		.71		.73
female sexe	-.20†		-.20†		-.08		-.14	
age	.01		.01		.04		.02	
Block 3		.50		.50		.71		.72
FEV_1	-.05							
FeNO			-.02					
ACT					.08			
PAQLQ(S)							.01	

† p < .10, *p < .05, **p < .01, ***p < .001

FEV_1, forced expiratory volume in 1 s; FeNO, fractional concentration of exhaled nitric oxide; ACT, childhood asthma control test; PAQLQ(S), pediatric asthma quality of life questionnaire (self-report)

DISCUSSION

We described a referral population of children with asthma being treated in a high altitude clinic where the majority had PSA. At the end of treatment, we found a stable lung function that projected in the normal range, and we found an improvement in FeNO level, asthma control and quality of life while ICS levels were reduced. All oral steroids could be stopped. There were no associations found between the level of disease control at baseline and other clinical parameters measured at baseline and the likelihood of reducing steroids.

Beneficial reduction in FeNO levels during high altitude treatment without intensifying the medication regime, have been shown before in allergic and non-allergic patients.[18, 19] The most obvious mechanism is that reduction in allergen exposure and reduction in other environmental inflammatory triggers reduces the degree of inflammation and thus the level of FeNO, but the exact mechanism behind this is still to be elucidated. No randomized controlled trials comparing treatment modules at high altitude and sea level have been performed as yet. The possible importance of vitamin D has recently been suggested.[20, 21] One parallel group study compared atopic adolescents with mild to moderate asthma in high altitude treatment and at sea level.[8] This small study of 18 adolescents showed better improvement in BHR and urinary levels of eosinophil protein X and leukotriene E4 in the group that was treated at high altitude l. Moreover, 6 weeks after renewed allergen exposure at sea level these improvements were maintained.

The lack of associations between self-reports of asthma control and quality of life with clinical parameters is in line with the results of a recent study in a group of adolescents with partly uncontrolled asthma showing no significant correlations between asthma control and lung function parameters or psychosocial problems.[22] The lack of an association between disease-specific factors like lung function, asthma control or quality of life is not easy to understand. Perhaps the heterogeneity of the population of children with PSA plays a role.[3] Another explanation might be that the study is done in adolescents, who commonly want to be as "normal" as possible and also want to be part of a peer group. When these patients are admitted together, their self-reported quality of life and asthma control can be exaggerated, which may explain the lack of correlation between lung function measures. The absence of correlations suggests that lung function parameters, disease-specific quality of life and asthma control are independent domains of health status. This supports the idea that a "total" approach or multidisciplinary treatment is needed in order to interact with all domains of PSA in children and adolescents.

There are several study limitations. The power of the study is low with this small sample size. As the selected children mainly classified for PSA, the sample is not representative for all childhood asthma in general. We did neither assess reversibility of FEV_1 in all children at entrance, nor atopy or smoking at home, so we were not able to examine the

possible relevance of these variables in multiple regression analysis. This prospective study lacks a follow-up measurement due to geographical problems (the children went home) and differences in lung function measurement at high altitude and sea level. Follow-up of asthma control and quality of life scores of our study group and association with behavioral problems have been reported previously.[7, 23] The current study was not designed as a randomized controlled trial which would have given better insight into possible causal relationships. Theoretically, randomization into a multidisciplinary treatment clinic at high altitude or sea level is possible, but the referral system and insurance policy in the Netherlands hamper such a study design. Adherence to medication was already assured before treatment in the clinic and reassured during the period of stay due to daily supervision. However, it might have changed during the treatment period. We did not use a smart tracker or other device before and during the treatment period to elucidate this further. Finally, children were treated away from their systemic context, which might temporarily have altered their subjective scores on asthma control or quality of life. Despite these limitations, this study helps to characterize (scarcely reported) detailed aspects of PSA in children.

The importance of structural evaluation of all children with PSA has been emphasized.[24] Nurse-led home visits could elucidate a number of potentially modifiable factors in this population at risk. In our population we could at least stabilize the disease possibly by taking away home factors that might be harmful to the asthma and adding a structured, hypo allergenic environment.

In conclusion, our study shows improvement in FeNO, quality of life and asthma control in a group of mostly PSA patients which made the disease more treatable. Since correlations between these parameters were not found, we think that treatment of this selected group should focus on all possible determinants of the disease and functioning, preferably during one and the same admission. This means a comprehensive approach for the child with PSA. In future research on children with PSA, routine asthma measures should be combined with ACT, PAQLQ(S) and preferably psychosocial data. This will help us understand the nature of this complex disease and finally tailor the complex treatment of PSA in children.

This study provides detailed data on children with PSA before and after treatment at high altitude. The multidisciplinary treatment tailors treatment to several disease domains of the child with PSA. After treatment, improvement of control is observed while tapering the dose of inhaled steroids. This underlines that PSA is not synonymous to therapy resistant asthma. The results indicate that multidisciplinary treatment at high altitude might be considered a viable treatment option for children with PSA.

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6

Gain in lung function after weight reduction in severely obese children

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ABSTRACT

Aim

The primary objective of this prospective cohort study was to determine the effect of weight loss on pulmonary function values in extremely obese children.

Methods

Obese children participated in a 26-week in-hospital or outpatient multidisciplinary treatment programme. Waist circumference was measured and pulmonary function tests were performed at enrolment and after 6 months.

Results

The data of 112 children were analysed. The children had a mean age of 14.4 (range 8.5–18.9) years and 62.5% were girls. The mean SD score-body mass index (SDS-BMI) was +3.38 at baseline and +2.91 after the intervention. Lung function improved significantly: functional vital capacity increased by 3.08% (95% CI 1.16% to 5.00%) of the predicted value, forced expiratory volume in 1 s (FEV_1) by 2.91% (95% CI 1.11% to 4.71%) of the predicted value, total lung capacity by 2.27% (95% CI 1.16% to 5.00%) of the predicted value, and expiratory reserve volume (ERV) by 14.8% (95% CI 8.66% to 20.88%) of the predicted value. The increase in ERV correlated with the reduction in SDS-BMI and with the reduction in waist circumference. FEV_1 did not correlate with the reduction in either SDS-BMI or waist circumference.

Conclusions

Weight loss in severely obese children correlated with an improvement in lung function, especially ERV. The improvement in ERV correlated with the decrease in SDS-BMI and waist circumference.

INTRODUCTION

Obesity in children is a growing problem in Western countries as a substantial proportion of children are overweight or obese.[1] Obesity in children, as in adults, can lead to various health problems, such as insulin resistance, diabetes, cardiovascular disease, joint problems and decreased exercise tolerance. In addition, respiratory problems including upper airway disturbances such as obstructive sleep apnoea and breathlessness, have been reported.[2, 3]

Data on pulmonary function testing (PFT) in obese children are limited. In adults, obesity can affect lung function. Jones et al studied 373 adults using a cross-sectional study design and found that increased body mass index (BMI) was inversely correlated with lung function parameters.[4] The strongest impacts were seen on expiratory reserve volume (ERV) and functional residual capacity (FRC). Other studies in adults have demonstrated similar effects on ERV and FRC, as well as on total lung capacity (TLC) and vital capacity (VC).[5]

Data on PFT in obese children are less clear. In these children, a negative correlation was found between FRC and the degree of obesity when the percentage of body fat was measured using a DEXA scanner.[6] However, this association was less clear when correlated to BMI. Several small studies in obese children show lung function results in the normal range, although a recent national survey in Taiwanese schoolchildren demonstrated that dynamic volumes such as forced expiratory volume in 1 s (FEV_1) were reduced in obese children without asthma.[7]

Data on PFT after weight reduction in obese children with and without asthma are scarce, and the effect of weight reduction on changes in PFT has not, to our knowledge, been described in the literature. We hypothesised that weight reduction in extremely obese children would improve lung function parameters, particularly those indicating airflow obstruction and ERV. We aimed to evaluate the effects of weight reduction in extremely obese children, aged 8–18 years, on pulmonary function.

METHODS

Patients

Children aged 8–18 years with a BMI equivalent of 30 kg/m^2 or more and comorbidity related to obesity, or a BMI equivalent of 35 kg/m^2 or more, were eligible for participation. BMI was age adjusted according to the method described by Cole et al who developed BMI curves for children corresponding to the adult BMI cut-off points of 25 and 30 kg/m^2.[8] To obtain the curve for children corresponding to an adult BMI of 35, the vertical distance between the 25 and 30 curves on the graph was added to the 30

curve. All patients had primary obesity (i.e., obesity with an exogenous or alimentary cause). Exclusion criteria were overweight due to syndromes or chromosomal disorders, medication-induced overweight, endocrine disorders not secondary to the obesity, and overweight due to psychiatric problems and/or bulimia. Children with severe learning difficulties (as measured by an intelligence test) and unable to follow the educational programme, were also excluded.

Furthermore, all patients were asked if they had been diagnosed with asthma or if they regularly used inhaled corticosteroids. These were referred to as children with doctor 's diagnosed asthma (DDA) and were excluded from further analysis.

Procedures

We recruited a group of extremely obese children participating in a 26-week randomised controlled study (ISRCTN register no. NTR TC 1172) to evaluate the efficacy of a weight reduction programme and a group of extremely obese children meeting the same inclusion criteria and participating in the same weight reduction programme but not taking part in the randomised controlled study. The randomised intervention study ran from April 2004 to March 2006. The additional obese children were recruited directly after closure of enrolment into the randomised controlled study until September 2006. The results of the intervention study will be published elsewhere.

Weight reduction program

The weight reduction programme took place at a pediatric treatment centre for obesity and asthma in Hilversum, the Netherlands over a period of 6 months with a 24-month follow-up. All children followed the same weight reduction regime in an in-hospital setting or as ambulatory patients. The overall goals of both treatment regimes were loss of body fat, subsequent body weight maintenance and behavioral modification. The treatment included an exercise component, a nutritional education component and a behaviour modification programme. The complete weight reduction programme has been described in detail elsewhere[9].

Clinical evaluation

Data on history of coughing, wheezing, shortness of breath and use of (inhaled) medication were collected. One pediatrician (OHvdB-S) physically examined all patients. A complete physical examination including waist circumference measurement was performed on admission and at the end of the treatment programme. Waist circumference was defined as the mean of three measurements of the smallest torso circumference between the inferior margin of the last rib and the iliac crest at the end of normal expiration.[10] Spirometry was performed on admission and at the end of the treatment programme.

In addition to BMI, SD score (SDS)-BMI was calculated for each patient because of the expected increase in height during the treatment period.

Lung function

Lung function was measured using the MasterScreen PFT + body box (Jaeger Viasys, Wuerzburg, Germany). A standardised protocol was used and at least three technically correct manoeuvres were performed. Short or long acting β2-agonists were stopped 12 h before lung function measurements. The reversibility of airflow limitation was measured using 400 µg salbutamol delivered with a Nebuhaler (AstraZeneca, Macclesfield, UK). The following lung function parameters were obtained: FEV_1, maximal expiratory flow at 50% of forced vital capacity (MEF_{50}), ERV, FRC, TLC and VC. All lung function values are expressed as percentages of the predicted value.

The study was approved by the medical ethics committee of the Academic Medical Centre of Amsterdam and written informed consent was obtained from all patients or their parents or guardians.

Statistics

Descriptive statistics such as means (SD) or proportions in case of categorical variables, were used to describe patient data. Normality assumptions were visually checked using histograms. Correlations between continuous variables were assessed using Pearson's correlation coefficient after normality assumptions and linearity assumptions were checked. Differences between groups were tested using unpaired t-test after the normality of the data in each subgroup was visually checked using histograms. Changes in continuous variables over time such as BMI and lung function parameters, were analysed by repeated measurements analysis using the Linear Mixed Models procedure in SPSS V.15.1, with measurement and group as fixed variables. Figures only represent values without added values produced by repeated measurement analysis. Changes in ERV and waist circumference were correlated to changes in SDS-BMI using Pearson's correlation coefficient.

RESULTS

Eighty-six patients were randomised to two different groups: 43 to an in-hospital regime and 43 to an outpatient regime. After closure of the randomised trial, another 52 patients followed the same treatment regime, 37 of whom were in-hospital patients. The analysis therefore included 138 patients. However, four patients withdrew directly after randomisation due to refusal of further treatment, leaving the data of 134 patients to be analysed (table 1). Furthermore, 22 patients fulfilled criteria for DDA and were excluded.

The patients' mean age at the start of the study was 14.4 years (range 8.5–18.9 years) and 62.5% were girls (n=70). The mean weight at the start of treatment for the total group was 110.2 kg (range 52.3–192.2 kg). After the intervention, mean weight had decreased to 97.3 kg (range 43.7–200.3 kg). The mean SDS-BMI score of the total group at the start of treatment was +3.38 (range 2.50–4.62) and had decreased to +2.91 (range 1.67–4.79) after the intervention. The average SDS-BMI was reduced by 0.48 kg/m^2 (95% CI 0.41 to 0.56; p<0.001) (table 2).

Changes in lung function parameters as percentage of predicted of the total group after weight loss following 6 months of treatment are given in table 2. Functional VC (FVC) increased by 3.08%, FEV_1 showed an increase of 2.91%, TLC increased by 2.27% and ERV increased by 14.8%, all of which were statistically significant. Waist circumference highly correlated with SDS-BMI (Pearson correlation coefficient 0.70, p<0.001). Changes in waist circumference correlated with ERV but not with FEV_1 (table 3). Changes in SDS-BMI correlated with changes in ERV but not with changes in FEV_1 (figure 1; correlation-coefficients in table 3).

Table 1 Patient characteristics

Number	N=112
Mean age (years)	14.4 (2.4)
Female : male	62.5 : 37.5%
Waist circumference (cm)	122.2 (15.7)
Weight (kg)	110.2 (25.6)
Height (m)	1.67 (0.10)
BMI (kg/m^2)	39.1 (6.8)
SDS – BMI	3.38 (0.40)
FEV_1 % predicted	100.5 (13.4)
MEF_{50} %predicted	99.2 (21.7)
ERV %predicted	85.7 (31.3)
FVC %predicted	102.3 (12.5)
TLC %predicted	98.9 (10.6)
VCin %predicted	100.5 (13.4)

Data are presented as mean (SD) or as percentages, as appropriate.
BMI, body mass index; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; FVC, functional vital capacity; MEF_{50}, maximal expiratory flow at 50%; SDS, SD score; TLC, total lung capacity; VCin, forced inspiratory vital capacity

Table 2 Changes after treatment

	After treatment	Change (95% CI)	p Value
Weight (kg)	96.3 (24.1)	−13.85 (−13.87 to −11.83)	<0.001*
Height (m)	1.68 (0.10)	0.013 (0.01 to 0.016)	<0.001*
Waist circumference (cm)	110.9 (9.3)	−11.3 (−10.8 to −12.7)	<0.001*
BMI (kg/m^2)	34.0 (7.12)	−5.34 (−6.03 to −4.66)	<0.001*
SDS-BMI	2.91 (0.59)	−0.48 (−0.56 to −0.41)	<0.001*
FEV_1 %predicted	108.1 (13.7)	2.91 (1.11 to 4.71)	0.002*
MEF_{50} %predicted	99.7 (26.6)	−0.50 (−19.6 to 18.6)	0.80
ERV %predicted	98.4 (28.5)	14.8 (8.66 to 20.88)	<0.001*
FVC %predicted	104.7 (12.6)	3.08 (1.16 to 5.00)	0.001*
TLC %predicted	101.3 (10.0)	2.27 (0.86 to 3.68)	0.001*
VCin %predicted	100.8 (15.7)	1.36 (−1.83 to 4.56)	0.40

Data are presented as mean (SD) or as percentages, as appropriate
*p<0.01
BMI, body mass index; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; FVC, functional vital capacity; MEF_{50}, maximal expiratory flow at 50%; SDS, SD score; TLC, total lung capacity; VCin, forced inspiratory vital capacity

Table 3 Correlations between changes in FEV_1, ERV waist circumference and SDS-BMI

	Delta waist circumference	p Value	Delta SDS-BMI	p Value
Delta FEV_1	−0.05	0.65	−0.13	0.24
Delta ERV	−0.34*	0.002	−0.27*	0.01

Data are presented as Pearson correlations. p Value is two-tailed. Delta is the difference between before and after treatment.
*p<0.01
BMI, body mass index; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; SDS, SD score

DISCUSSION

To our knowledge, this is the first study to investigate the influence of weight reduction on lung function parameters in extremely obese children. Weight reduction after an intensive treatment programme in obese children was associated with significant increases in FVC, FEV_1, TLC and ERV. However, only the increase in ERV correlated with the decrease in SDS-BMI.

We found that ERV increased significantly after weight loss; moreover, we found that the increase in ERV significantly correlated with the decrease in SDS-BMI. A search of the literature revealed an open follow-up study showing that weight reduction in severely obese females with asthma was associated with less rescue medication use and improved lung function.[11] Pulmonary function was measured before and 1 year after gastric banding which resulted in a BMI decrease of more than 10 kg/m^2. FEV_1 and

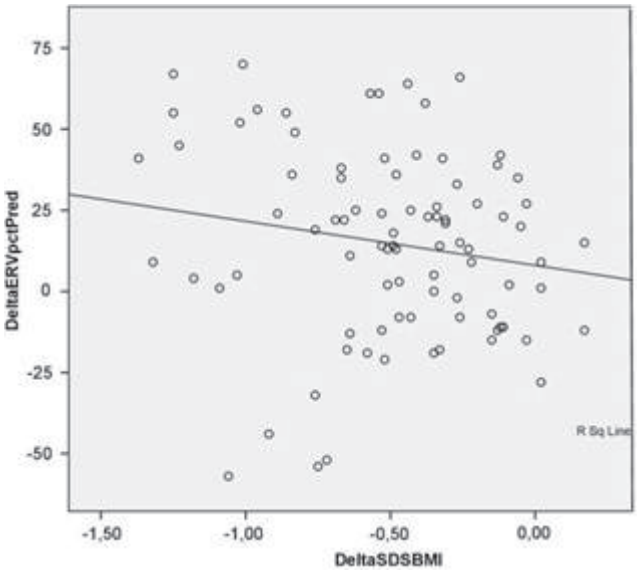

Figure 1 Correlation of Delta SDS- BMI and Delta ERV. BMI, body mass index; ERV, expatoiry reserve volume; SDS, SD score.

FVC improved by 5.1% and 8.4%, respectively. Unfortunately, changes in ERV were not mentioned in this study, which examined patients with asthma.

A second open follow-up study in adults who underwent surgery for gastric volume reduction also showed gains in FVC and FEV_1.[12] The group with the highest BMI showed the greatest gain, despite exhibiting the same degree of relative weight loss. Again, changes in ERV were not mentioned in this study. Our findings similarly show increases in FVC and FEV_1, and also a highly significant increase in ERV after weight loss.

A larger study, also in adults, was carried out by Jones et al.[4] In this open cross-sectional study, a group of 373 subjects who had to undergo PFT were analysed in relation to their BMI. Significant linear relationships were found between BMI and VC and TLC, although the mean values of the total group still fell within the normal ranges. However, FRC and ERV decreased dramatically with increasing BMI values. The results describe the association between pulmonary function and weight, and show the same relationship between BMI and ERV as in our study. However, this was not a longitudinal design, and did not investigate the effect of weight loss on lung function parameters. Moreover, this study was performed in adults, where chest wall compliance might be lower than in children.

Greater thorax compliance is probably the main reason for the increase in ERV after weight reduction. The correlation we found between an increase in ERV and a decrease in waist circumference supports this suggestion. Abdominal fat pushing upwards is decreased following weight loss, thus allowing more space for the thoracic compart-

ment to move, as implied by early experiments in adults without obesity or asthma who underwent mass loading of the thorax.[13] Another possible explanation for the changes in lung function include improved physical fitness as a training effect.

In children with severely compromised lung function (e.g., end-stage cystic fibrosis), clinicians recognise the difficulties of breathing close to residual volume. Likewise, obese children may find exercise difficult because of shortness of breath due to their breathing close to residual volume. Improvements in ERV could thus help children feel more comfortable taking exercise.

An association between obesity and asthma in children has been described by many authors.[3,7,14,15] Several mechanisms have been suggested to explain this association[9], but as shown in a recent review[16], the relationship is still unclear. We therefore excluded all children with DDA.

We found a significant but small and clinically irrelevant increase in vital capacity and FEV_1, and very little change in MEF_{50} values after weight reduction, suggesting that it is unlikely that obesity causes obstructive airflow limitation. In our opinion it seems more likely that the above-mentioned mechanical limitations are the major cause of shortness of breath in obese children.

A limitation of studies in this field is the observation that extremely obese patients are not used to lung function testing, resulting in severe problems producing a good flow–volume curve. We allowed extra time and a second attempt to combat this problem, using a standardised protocol. Some training effect of the spirometry procedure cannot be ruled out completely, but observation of the patient groups suggested this was very unlikely.

Our study is descriptive and was not designed as a randomised controlled trial, which might have given it greater weight. Despite this shortcoming, it is one of the first to provide data on PFT after weight loss in extremely obese children.

CONCLUSION

We hypothesised that weight reduction in extremely obese children would improve lung function parameters, especially those indicating ERV and airflow limitation. Airflow limitation was indeed less (as indicated by FEV_1 and MEF_{50}) after treatment, but did not correlate with weight loss and appears to be clinically irrelevant. This makes a mainly causal relationship between obesity and air flow limitation less probable. However, expiratory reserve volume was significantly improved after weight loss and was correlated to a decrease in waist circumference.

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7

Changes in lung function after weight reduction in children with asthma and severe obesity

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EJG, OBS and WVA designed the study, EJG analyzed the data and wrote the manuscript, JP performed all statistical analyses. All authors made substantial revisions to the manuscript. All authors revised and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

ABSTRACT

This prospective cohort study evaluated the effect of weight loss on pulmonary function children with asthma and extreme obesity. We analyzed lung function data of 22 obese children before and after weight reduction. Weight loss correlated highly with an increase in expiratory reserve volume (ERV) and a decrease in waist circumference. Functional Vital Capacity and Forced Expiratory Volume in one second did not increase significantly. Total Lung Capacity did not correlate with weight loss.

Weight loss in children with asthma and extreme obesity is associated with an increase in ERV but not a decrease in air flow limitation.

INTRODUCTION

Obesity in children is a large problem in Western countries, with a substantial proportion of children being overweight or obese[1]. Obese children have a greater risk of becoming obese adults. Already in childhood, obesity accounts for many health problems, such as a tendency towards insulin resistance, diabetes, cardiovascular disease, joint problems and decreased exercise tolerance. Among airway problems, upper airway disturbances like obstructive sleep apnoea and lower airway impairments such as shortness of breath are often reported[2].

Data on pulmonary function testing (PFT) before and after weight reduction in obese children are limited. In an earlier paper, we reported the results of a cohort of severely obese children without symptoms of asthma and their changes in waist circumference and lung function[3]. In this cohort, obstructive lung function measures such as forced expiratory volume in one second (FEV_1) hardly changed, even after extensive weight loss, whereas expiratory reserve volume (ERV) significantly increased, and the change in ERV correlated with the change in SDS-BMI and a decrease in central obesity as expressed by waist circumference.

Data on PFT after weight reduction in obese children with asthma are, to our knowledge, not available in the literature. We hypothesized that weight reduction in children with asthma and extreme obesity would improve lung function parameters, and especially lung function parameters indicating airflow obstruction and ERV.

METHODS

We included children with extreme obesity and a doctor's diagnosis of asthma (8-18 years, body mass index (BMI) equivalent to 30 kg/m^2 and comorbidity related to obesity, or having a BMI equivalent to 35 kg/m^2 or more). Participants followed a 26 weeks weight reduction program. Pulmonary function testing was performed on admission and discharge. Details on methods including statistics are described in the on-line repository facility.

RESULTS

Doctor's diagnosed asthma was present in 22 patients; of these 13 were girls (59.0%). Mean weight at start of treatment of the total group (n=22) was 106.6 (SD 24.3) kg. Four patients quit treatment or were unable to perform measurements at the end. Only complete pairs of data were analysed. After the intervention (n=18) mean weight

decreased to 90.5 (SD 22.0) kg. SDS-BMI score decreased from +3.39 (SD .33) to +2.82 (SD .54) after intervention. Changes in lung function before and after weight reduction are summarized in table 1. Change in weight correlated negatively with change in ERV %predicted (r= -0.66; p<0.01).

Table 1. Patient characteristics, results and correlations

N=22 participants	Pre treatment Mean (SD)	Post treatment Mean (SD)	Test of differences (p-value)	Pearson-correlation of change with change in SDS-BMI (p-value)
Mean age (years)	13.7 (2.1)			
Distribution female : male (%)	59 : 41			
Waist circumference (cm)	121.0 (15.7)	110.4 (14.4)	<0.01	0.70 (<0.01)
Weight (kg)	106.1 (24.3)	90.5 (22.0)	<0.01	0.79 (<0.01)
Height (m)	1.65 (0.09)	1.65 (0.08)	<0.01	-0.03 (0.92)
BMI (kg/m^2)	38.8 (6.1)	33.0 (6.77)	<0.01	0.88 (<0.01)
SDS-BMI	3.39 (0.33)	2.82 (0.54)	<0.01	-
FEV_1 (%predicted)	98.8 (13.3)	103.2 (13.5)	0.29	0.13 (0.67)
ERV (%predicted)	79.4 (32.6)	90.5 (27.3)	0.357	-0.66 (<0.01)
FVC (%predicted)	96.9 (14.1)	103.1 (11.6)	0.223	0.14 (0.63)
TLC (%predicted)	98.0 (12.0)	101.8 (9.4)	0.023	0.12 (0.67)
VC_{in} (%predicted)	96.1 (9.5)	99.7 (11.4)	0.511	-0.07 (0.82)

Data are presented as mean (SD) or as percentages, as appropriate. BMI, body mass index; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; FVC, functional vital capacity; SDS, standard deviation score; TLC, total lung capacity; VC_{in}, forced inspiratory vital capacity

DISCUSSION

Weight reduction after an intensive treatment program in obese children was associated with an increase in total lung capacity (TLC), but not with significant changes in forced vital capacity, FEV_1, or forced inspiratory vital capacity but we found an increase in ERV that significantly and highly correlated with the amount of weight loss.

We found a small increase in TLC which is probably not clinically relevant. This change did not correlate to the change in SDS-BMI. Perhaps some effect of training or increase in muscle mass may explain this increase, but these factors were not included in our analysis.

The main explanation for the increase in ERV after weight reduction is probably increased thorax compliance. Moreover, the abdominal obesity pushing upwards will decrease after weight loss, thus giving more space for movement of the thoracic com-

partment. Early experiments in adults without obesity or asthma who were loaded with weight on their thoracic and abdominal wall support this explanation[4].

Typically, obesity causes a modest reduction in total lung capacity (TLC), and a larger reduction in functional residual capacity (FRC)[5]. When breathing at lower FRC, an increase of hyperresponsiveness to methacholine is found in healthy subjects[6]. This might reinforce the airway symptoms in obesity.

An association between obesity and asthma in children has been described[7,8]. Although the precise mechanisms for this association are unknown, several mechanisms have been suggested to elucidate this association such as diet, gastro esophageal reflux or other biomechanical factors, immunological effects including atopy, or genetic or hormonal factors [8]. As shown in a review, their mechanistic interactions are still unclear and evidence for a causal relation is scant[9].

In adults with asthma, weight-loss and bariatric surgery studies have clearly shown that reduction of severe or moderate obesity is helpful in improving objective lung function parameters and in improving both the frequency and severity of respiratory symptoms[10]. Our study examined the effect of weight reduction on lung function parameters in extremely obese children. We did neither find a significant increase in vital capacity or FEV_1 after weight reduction, nor a change in Tiffeneau index (data not shown). The observation that considerable weight loss did not influence these classical "asthma" lung function parameters, suggests that the occurrence of obstructive airflow limitation as a consequence of obesity is less probable. To our view it seems more likely that the mechanical limitations, as explained above, are the major cause for changes in lung function parameters and complaints of shortness of breath in children with asthma and extreme obesity.

A limitation of studies in this field is the observation that patients with extreme obesity are not used to lung function testing. This results in problems in producing a good flow-volume curve, thereby challenging both lung function technicians and the patients. Therefore, we planned more time and allowed a second attempt to diminish this problem. Our small study is the first providing data on pulmonary function testing after weight loss in children with asthma and extreme obesity.

CONCLUSION

We hypothesized that weight reduction in children with asthma and extreme obesity would improve lung function parameters, especially expiratory reserve volume, TLC, VC and FEV_1. We only found a significant increase in expiratory reserve volume that significantly correlated with a reduction in SDS-BMI. This is most likely caused by the decrease of the obstructing abdominal mass.

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8

Applicability of evidence from previous systematic reviews on immunotherapy in current practice of childhood asthma treatment: a GRADE (Grading of Recommendations Assessment, Development and Evaluation) systematic review

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Contributor statement: EJG designed the study, chaired the guideline working group, provided clinical input (eg, defined clinically relevant outcome measures, judged the literature review from a clinical point of view), wrote and revised the manuscript, and approved the final version. MKT designed the study, was methodologist of the guideline working group, provided methodological input (provided literature search, selection, critical appraisal, GRADE evidence profiles), wrote and revised the manuscript, and approved the final version. HdG was member of the guideline working group, designed the study, revised the manuscript and approved the final version. PLPB provided clinical input, revised the manuscript and approved the final version. All authors meet full criteria for authorship, that is, all contributed substantially, revised, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

ABSTRACT

Background. Allergy plays a major role in both asthma and its common comorbidity allergic rhinitis. Immunotherapy is effective in the treatment of allergic rhinitis. Previous systematic reviews indicated its effectiveness in children with asthma. Because most children with persistent asthma now use ICS, the added benefit of immunotherapy in asthmatic children needs to be examined.

Objective. We re-assessed the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient relevant outcome measures and children using ICS.

Methods. We used the GRADE approach to systematically search and appraise the evidence using predefined critical patient relevant outcomes (asthma symptoms, asthma control and exacerbations). We searched to retrieve systematic reviews and randomized controlled trials on immunotherapy for asthma in children (1960 - 2015). We assessed the quality of the body of evidence with GRADE criteria.

Results. The quality of the evidence for SCIT was very low due to a large risk of bias and indirectness (dated studies in children not using ICS). No effect of SCIT was found for asthma symptoms; no studies reported on asthma control. For asthma exacerbations, studies favoured SCIT. We have little confidence in this effect estimate, due to the very low quality of evidence. For SLIT, quality of the evidence was very low due to a large risk of bias, indirectness and imprecision. The outcome "asthma symptoms" could not be calculated due to lack of standardization and large clinical heterogeneity. Other predefined outcomes were not reported.

Conclusion. The beneficial effects of immunotherapy in childhood asthma found in earlier reviews are no longer considered applicable, because of indirectness (studies performed in children not being treated according to current asthma guidelines with inhaled corticosteroids). There was absence of evidence to properly determine the effectiveness or lack thereof of immunotherapy in childhood asthma treatment.

INTRODUCTION

Asthma affects 10-15% of school-aged children. For children with persistent asthma, all international guidelines recommend daily controller treatment with inhaled corticosteroids (ICS), and reliever medication (short-acting β-2-agonists) as needed.[1,2] Although many children achieve complete asthma control using this effective and safe treatment,[1] some need additional treatment to obtain disease control.[3,4] Identification and treatment of comorbidities in children with problematic severe asthma is part of the stepwise approach to improve asthma control in these children.[5,6]

The most common of these comorbidities in children with asthma is allergic rhinitis,[5] symptoms of which occur in 60-80% of asthmatic children.[7,8] Allergic rhinitis shares a common pathophysiological pathway with asthma, which has been described as the united airway concept.[9] Allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[7,10,11]

When symptoms of allergic rhinitis cannot be sufficiently controlled with nasal corticosteroids and oral antihistamines,[9,12] immunotherapy can be considered as additional treatment.[13] Subcutaneous immunotherapy (SCIT) requires repeated injections with an allergen extract and is available for allergens such as grass and tree pollen and house dust mite. After disappointing results of low-dose preparations in drops, effective high-dose sublingual immunotherapy (SLIT) has now become available with grass pollen allergen extract in a daily sublingual tablet.[14,15] A Cochrane systematic review, first published in 2000, and last updated in 2010, reported beneficial effects of immunotherapy in children with asthma.[16] Most studies in this review, however, were performed in the 1980s, when most children with asthma were not using ICS.

As part of the update of the Dutch pediatric guideline on childhood asthma, we evaluated the literature on the added value of SCIT and SLIT in childhood asthma.[17] Our structured clinical question was to assess whether immunotherapy (subcutaneous or sublingual), as an add-on to usual care with daily ICS, improves asthma outcomes in children (6-12 years) and adolescents (>12 years) with persistent asthma and sensitization to relevant aeroallergens (grass or tree pollen, house dust mite, or combinations), with or without symptoms of allergic rhinitis.

METHODS

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to appraise and summarize the body of evidence. GRADE is an

internationally approved standard for managing complex evidence reviews.[18] In contrast to former grading systems, GRADE focuses on the quality of the total body of evidence, instead of judging single studies. Another important characteristic of GRADE is that predefined outcomes with thresholds for clinical relevance are being used.[19] In earlier grading systems, the evidence was summarized using outcomes reported in studies, not necessarily being outcomes a guideline development group would be interested in.[20] GRADE avoids the use of surrogate or intermediate outcomes, and uses outcomes and differences that are more clinically relevant to patients instead. Starting from (several) randomized controlled trials or observational studies, for each outcome the quality of evidence can be downgraded or upgraded, for instance based on risk of bias, inconsistency, indirectness, possible publication bias, and dose-response relation.

The guideline development group included an epidemiologist, pediatric respiratory physicians, pediatricians, an allergist, an ear-nose-throat specialist, a family physician, a lung function technician, a youth public health care physician, and patient representatives. The guideline development group predefined clinically relevant outcomes and divided these into critical (contributing to the overall quality of evidence), important (also relevant to the content of the guideline) and not important outcomes. For each outcome, a minimal clinically important difference was defined *a priori*. The outcomes taken into account in our literature review are summarized in table 1, with corresponding minimal clinically important differences.[21-24]

Table 1. Patient relevant outcomes and clinical relevance

Outcome	Importance	Minimal clinically important difference
Asthma symptoms	Critical	ACT: 3 c-ACT: (2-)3*
(Severe) exacerbations	Critical	NNT n=10
Asthma control	Critical	ACT: 3 c-ACT: (2-)3*
(Disease-specific) quality of life	Important	PAQLQ: 0.5 (scale 0-7)*
Change in FEV_1	Important	>5%predicted

* or comparable differences on other valid scales representing this outcome
Abbreviations: ACT: asthma control test; c-ACT: child ACT; PAQLQ: Pediatric Asthma Quality of Life Questionnaire

We applied a sensitive search strategy to retrieve all available evidence addressing the clinical question, focusing on systematic reviews (SRs) and randomized controlled trials (RCTs) about asthma and immunotherapy in children. We searched for systematic reviews in the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness, and we searched The Cochrane Central Trial Register to update existing reviews. Literature searches were performed in March 2012 for the guideline (from 1960 onwards), and updated in April 2015 for the purpose of this review *(see table E1 in the Online Repository)*. Two reviewers (EJvdG, MKT) independently screened the

abstracts using predefined inclusion criteria: methodology (SRs and RCTs), patients (children with allergic asthma), and SCIT and/or SLIT as an intervention. Animal studies, conference abstracts, and studies published in languages other than English, Dutch and German were excluded. Differences between reviewers were resolved by consensus. Selected abstracts were critically appraised with respect to study population and methodological aspects (systematic search and selection, randomization of patients), which led to a further selection. An expert in the field (HdG) judged the selection for completeness.

All included studies were summarized in evidence tables by two reviewers (EJvdG, MKT). SRs were critically appraised using the AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews).[25] AMSTAR scores range from 0-11, a higher score indicating better quality (less bias). The Jadad scale was used to assess the methodological quality of each RCT.[26] This score ranges from 0-5, a higher score denoting a better quality. All eligible studies together defined the body of evidence, of which the quality was determined (per relevant outcome and overall quality) and GRADE Profiles were created. Results from SRs and RCTs were pooled, if possible, in meta-analyses using RevMan 5. We calculated standardized mean differences for continuous outcomes, because of the usage of different symptom scales in the underlying studies. We calculated risk ratios for dichotomous outcomes, to compare the probability of these outcomes between the intervention and control groups. In the meta-analyses we used random effects models, because of the possibility of generalization of the outcomes for different allergens, and tested the difference between intervention and control with the inverse variance method, since this method is typically used in meta-analyses to combine the results of independent studies. We reported 95% confidence intervals (pre-defined significance level: 0.05). Conclusions were drawn, based on quality and content, per outcome and discussed in the expert group until consensus was reached.

Patient involvement

The guideline development group included patient representatives who helped defining our clinical question, approved outcome measures and assessed its clinical relevancy. The burden of interventions and patient considerations were assessed as part of the GRADE evaluation. Patients were not directly involved in this systematic review since we reviewed published literature.

RESULTS

Literature search and selection

Screening of titles and abstracts yielded 83 eligible studies, 10 of which fulfilled the inclusion criteria.[16,27-35] After examining these 10 papers in full, 5 more studies were excluded (figure 1).

Experts in the guideline working group confirmed that no relevant publications were missed. The updated search (April 2015) revealed 43 additional studies, of which 2 fulfilled the inclusion criteria.[36,37] Full text examination resulted in exclusion of these 2 studies.

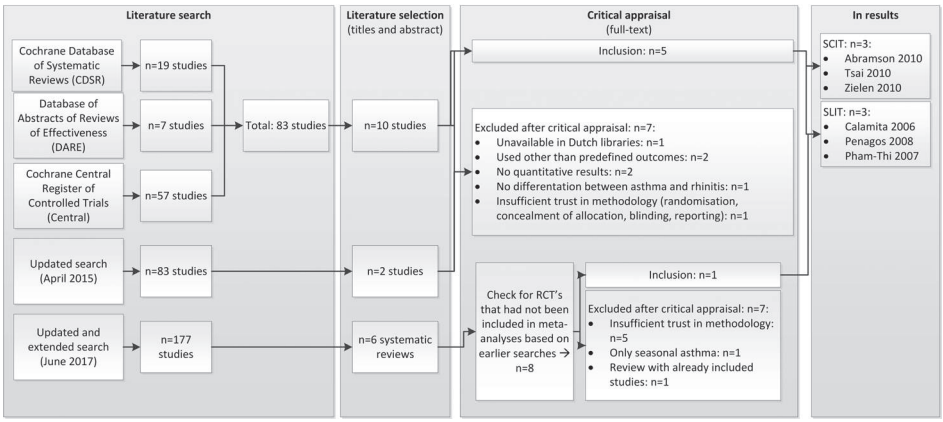

Figure 1. Literature search and selection

Results of SCIT

Description of studies

We retrieved one Cochrane SR on the effectiveness of SCIT in patients with asthma , including 90 RCTs with a total of 3,792 patients.[16] This was a high-quality review (AMSTAR score 10/11). Fourteen of the included RCTs were performed in children exclusively; another 24 included children and adults. In a few studies the age inclusion criteria were not clear. The characteristics of this review are summarized in an evidence table (*see table E2 in the Online Repository*). Only nine RCTs included in this review reported on our predefined outcomes in children. In these nine studies different allergens or combinations were studied (house dust mite (3), dog dander (1), grass pollen (1), mold (1), grass pollen/house dust mite (1), tailored combinations (2)). Two RCTs published after the 2010 Cochrane review were retrieved. In the first, the clinical efficacy of house dust mite-specific SCIT in 20 asthmatic children was compared to no intervention in 20 others; patients were followed up for six months.[34] In the other, the effects of allergen-specific

SCIT on corticosteroid dose in asthmatic children was evaluated.[35] Details of all included RCTs are summarized in the evidence table (*see table E3 in the Online Repository*).

Quality of the evidence

Little information was given about the included studies in the Cochrane review; e.g. follow-up was not stated. There were also other concerns about the quality of the literature, e.g. not all studies were double-blind and placebo-controlled, and randomization procedures were poor. Therefore we re-analyzed the individual pediatric studies in the Cochrane review, plus the added studies.[34,35] Jadad scores of the single studies are presented in table 2.

Table 2. Jadad scores of RCTs on SCIT

	Randomization*	Blinding**	Withdrawals#	Total
Adkinson 1997[38]	1	1	1	3
Altintas 1999[39]	1	1	1	3
Dreborg 1986[40]	1	-	-	1
Hill 1982[41]	1	-	-	1
Johnstone 1961[42]	2	1	-	3
Johnstone 1968[43]	2	1	1	4
Price 1984[44]	1	1	-	3
Tsai 2010[34]	1	-	1	2
Valovirta 1984[45]	1	-	1	2
Warner 1978[46]	1	1	1	3
Zielen 2010[35]	1	1	1	3

* 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate

** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate

1 point if the number and the reasons for withdrawal in each group are stated

The quality of the body of evidence for all critical and important outcomes was very low (table 3), mainly due to large risk of bias and indirectness. The large risk of bias was caused by a lack of allocation concealment, lack of information on follow-up, and loss to follow-up. The reason for downgrading for indirectness was the publication year of the underlying studies; populations and interventions were considered inapplicable to current clinical practice.

Critical outcomes

Asthma symptoms. Four small studies carried out in children only reported this outcome in the Cochrane review.[16] We extracted these results from the Cochrane review and updated these with the results from Tsai et al.[34] Results are presented in figure 2. The meta-analysis showed no significant effect of SCIT on asthma symptoms.

Table 3. GRADE Evidence Profile SCIT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SCIT	No intervention	Relative (95%CI)	Absolute (95%CI)		
Asthma symptoms (assessed with: Asthma symptom scores)												
5[a]	RCT	Very serious[b]	Not serious	Serious[c]	Not serious	None	136	286	-	Standardized Mean Difference 0.04 lower (0.42 lower to 0.33 higher)	OOO VERY LOW	CRITICAL
Exacerbations (assessed with: Symptomatic deterioration)												
5[a]	RCT	Serious[d]	Not serious	Very serious[e]	Not serious	None	64/253 (25.3%)	92/153 (60.1%)	Risk ratio 0.43 (0.34 to 0.56)	343 fewer per 1000 (from 265 fewer to 397 fewer)	OOO VERY LOW	CRITICAL
Asthma control – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Lung function – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Abbreviations: 95%CI: 95% confidence interval; RCT: randomized controlled trials; SCIT: subcutaneous immunotherapy

a. *Studies in Cochrane review Abramson + Tsai*
b. *The underlying studies had a quite large risk of bias, due to lack of allocation concealment, problems with blinding, and lack of information on follow-up (and loss-to-follow-up)*
c. *We downgraded for indirectness, because the included studies are quite old and maintenance medication may have changed probably; thus, study populations may alter from nowadays patients with moderate to severe asthma*
d. *We downgraded for risk of bias, because of problems with blinding and loss-to-follow-up*
e. *We assessed very serious indirectness, because most included studies for this outcome are very old, and carried out before the ICS-era; thus, patients nowadays differ from study populations*

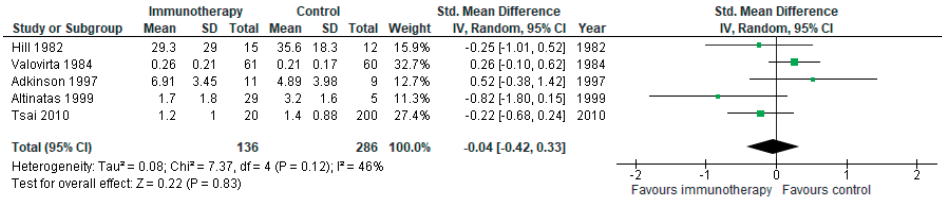

Figure 2. Meta-analysis of SCIT versus placebo, outcome asthma symptoms. IV, inverse variance; Random, random effect model; SCIT, subcutaneous immunotherapy; Std, standardised.

Asthma exacerbations. Five studies (published 1961-1984) in the Cochrane review, carried out in children only, reported this outcome.[16] No relevant studies of sufficient quality were published afterwards. Our meta-analysis included 253 patients on immunotherapy and 153 on placebo. The pooled risk ratio was 0.47 (95%CI: 0.31 – 0.72), favouring immunotherapy (see *figure 3*). The absolute risk reduction was 35%, giving a number needed to treat of 3.

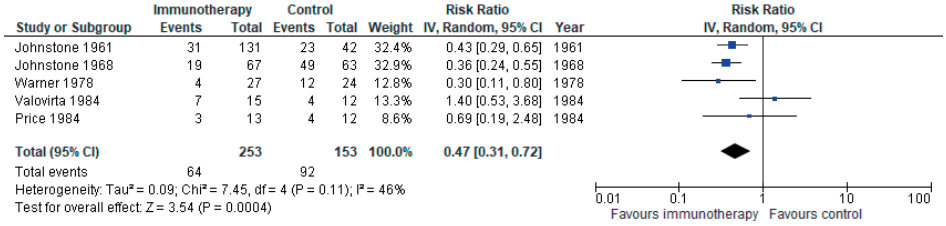

Figure 3. Meta-analysis of SCIT vs placebo, outcome asthma exacerbations. IV, inverse variance; SCIT, subcutaneous immunotherapy.

No studies reported results on the critical outcome asthma control.

Important outcomes

No studies reported results on quality of life and lung function (FEV_1).

Results of SLIT

Description of studies and quality of the evidence

We retrieved two SRs on SLIT in patients with asthma.[29,32] The characteristics of these SRs are summarized in evidence table *E2 (Online Repository)*. The quality of the reviews was moderate; both had an AMSTAR score of 7/11. Weaknesses included the absence of an 'a priori design', exclusion of grey literature, not assessing the likelihood of publication bias and not mentioning conflicts of interest in one review,[29] and the absence of an 'a priori design', no information about excluded studies, too firm conclusions compared to the weak evidence, and not assessing the likelihood of publication bias in the other.[32] One review included both children and adults, and patients with asthma and/or rhi-

nitis.[29] Because of the quality concerns of both existing SRs, we set out to perform a meta-analysis of the original studies that fulfilled our selection criteria. Jadad scores of selected studies, as well as an overview of the outcomes of those studies, are presented in table 4. Study characteristics are summarized in the evidence table (*see table E4 in the Online Repository*). We rated the quality of evidence to be very low, due to a large risk of bias, imprecision and indirect evidence.

Table 4. Summary of quality and outcome measures of selected RCT's in reviews Calamita et al and Penagos et al.[29,32]

Review	RCT	Eligible	Jadad-score: Randomization*	Blinding**	Withdrawals#	Total	Reported on asthma symptoms	Reported on exacerbations	Reported on asthma control	Reported on disease specific quality of life	Reported on lung function (FEV_1)
Calamita[29]	Bahceciler 2001[47]	Yes	1	1	1	3	+	-	-	-	-
	Hirsch 1997[48]	Yes	2	1	1	4	+	-	-	-	-
	Niu 2004[24]	No, conference abstract									
	Novembre 1991[49]	No, Italian language									
	Pajno 2003[50]	Yes	2	1	1	4	+	-	-	-	-
	Pajno 2004$ [51]	Yes	2	1	1	4	-	-	-	-	+
	Rodriguez Santos 2004[52]	No, Spanish language									
	Rolinck-Werninghaus 2004[53]	Yes	1	2	0	3	+	-	-	-	-
	Yuksel 1999[54]	No, Spanish language									
Penagos[32]	Bahceciler 2001[47]	Overlap with Calamita									
	Caffarelli 2000[55]	No, children with asthma not separately analyzed									
	Hirsch 1997[48]	Overlap with Calamita									
	Ippoliti 2003[56]	Yes	1	1	0	2	+	-	-	-	+
	Niu 2006[57]	Yes	1	1	1	3	+	-	-	-	+
	Pajno 2000[58]	Yes	2	1	0	3	+	-	-	-	-
	Rolinck-Werninghaus 2004[53]	Overlap with Calamita									
	Tari 1990[59]	No, Spanish language									
	Vourdas 1998[60]	No, children with asthma not separately analyzed									
Total							7	0	0	0	3

Abbreviations: FEV_1: forced expiratory volume in 1 second; RCT: randomized controlled trial

** 1 point if randomization is mentioned; 1 additional point if the method of randomization is appropriate; minus 1 point if the method of randomization is inappropriate*

*** 1 point if blinding is mentioned; 1 additional point if the method of blinding is appropriate; minus 1 point if the method of blinding is inappropriate*

 # 1 point if the number and the reasons for withdrawal in each group are stated

$ Same patients as Pajno 2003[50]

Critical outcomes

Asthma symptoms. Seven of the included studies reported on asthma symptoms. Different symptom scores were used, none of them standardized or validated. Clinical differences in asthma scores were not defined and most studies reported improvement in the treatment group as well in the control group. Due to this large clinical heterogeneity we were not able to compile a meta-analysis of the results of the individual studies. Since studies did not report results in a clearly comparable way, reporting the results of the individual studies was considered unreliable.

Other critical outcomes. No studies reported results on the critical outcomes exacerbations and asthma control.

Important outcomes

Quality of life. No studies reported results on the outcome disease specific quality of life**.**

Lung function. Three studies reported results on lung function (FEV_1). One of the studies reported no numeric data on lung function.[57] One study reported no variance (standard deviation), and no comparison of the baseline data.[56] The only remaining study reported on FEV_1 percentage predicted,[51] and reported no significant differences between treatment groups, neither at baseline nor at follow-up.

DISCUSSION

Summary of main results

Our GRADE systematic review showed no evidence of a significant difference in asthma symptoms between SCIT and placebo in children with allergic asthma, but some evidence for a significant and clinically relevant reduction in asthma exacerbations was found in SCIT-treated children. We have little confidence in the effect estimate, however, due to a large risk of bias and indirectness. Thus, the true effect of SCIT on exacerbations and asthma symptoms in the target population of interest is likely to be substantially different from the estimate of effect. There was absence of evidence on the effects of SCIT on lung function, asthma control, and quality of life in children with allergic asthma. There was no evidence for a beneficial effect of SLIT in reducing asthma symptoms and exacerbations, quality of life and lung function in children with allergic asthma. Our review does not address the efficacy of immunotherapy in children regarding complaints of allergic rhinitis and/or conjunctivitis, without having asthma.

Quality of the evidence / GRADE methodology

The overall quality of the evidence about the effectiveness of SCIT and SLIT was very low. This implicates that our confidence in the effect estimates is very limited. The true

effect of SCIT and SLIT on patient relevant asthma outcomes in children with asthma may be substantially different from our estimates of the effect. We cannot conclude that the possible desirable effects of SCIT and SLIT outweigh the undesirable effects (e.g. influence on quality of life, adverse events, or increased resource expenditure), nor can we reject that hypothesis. Our concerns about the quality of evidence are based on (very) serious risk of bias and indirectness in the underlying primary studies. Firstly, the quality of many studies had to be downgraded because of risk of bias due to lack of allocation concealment, lack of information on follow-up, and loss to follow-up. Secondly, included studies were heterogeneous in the patients included and allergen extracts used, with different dosing regimens and duration being studied, targeting different inhaled allergens. We have concerns about the potential different responses and the generalizability of the evidence. Thirdly, and most importantly, for SCIT, the quality of the body of evidence was downgraded because of indirectness, since patients in the original studies long ago are likely to differ considerably from patients nowadays.

Thirdly, different studies used variable definitions of asthma exacerbations. We had to use 'worsening of asthma', which may not represent real-life patient relevant exacerbations. This may decrease the applicability of the evidence. In addition, there were no studies using the predefined important outcomes quality of life and asthma control.

Finally, and most importantly, several included studies dated from the 1980s or earlier, when allergic rhinitis treatment with selective antihistamines and nasal corticosteroids was not available. As a result, the allergic rhinitis patients in these studies cannot be compared to patients in clinical practice today. Similarly, widespread use of ICS was not introduced in childhood asthma treatment until the 1990s.[61] Most studies on SCIT in children with asthma were published decades ago, during the pre-ICS era. The patients in the described studies represent an incomparable group compared to the child with asthma in contemporary clinical practice. Specifically, it is unclear whether the beneficial effects found in the systematic review of earlier studies is applicable to children with asthma treated according to contemporary guidelines with daily ICS controller therapy.[16]

In our opinion and that of others, the GRADE approach is superior to former methods of SRs, because it focuses on predefined patient relevant outcomes, predefined minimally clinical important differences and because it judges the complete body of evidence. One RCT among pediatricians studied the influence of different guideline grading systems on decisions.[62] GRADE showed the largest change in direction on the clinical decision. However, the added value of GRADE on guideline implementation or patient care, has not been formally evaluated, the GRADE approach is still rather complex for non-methodologists.

To formulate recommendations for clinical practice, not only the body of evidence concerning effectiveness of an intervention is important. Recommendations should balance the benefits and harms of the intervention of interest, and take patient preferences

and resource use into account. Since (after critical evaluation) no benefits of SCIT and SLIT for children with asthma were determined, we consider it unlikely that the benefits will exceed the harms. Patient preferences were included in the formulation of our guideline recommendations.

Agreements and disagreements with other studies or reviews

Using GRADE and re-analyzing data from children with allergic asthma only, we came to different conclusions on the effectiveness of SCIT and SLIT in children with asthma than the authors of the original SRs. We believe this highlights the importance of using GRADE methodology to systematically review evidence for patient relevant outcomes, not focusing on levels of evidence, but on underlying study validity, precision, directness, and applicability in current clinical practice. The 2009 position paper on SLIT describes history, use and applicability of this treatment for allergic rhinitis.[63] It positions SLIT in children as a safe and useful therapy above and after more regular treatment for allergic rhinitis. Potential positive treatment outcome for allergic asthma is however mainly based on literature in adults. We show the lack of evidence and lack of applicability of treatment of immunotherapy for asthma in children. Since we have worries on the applicability of evidence in adults on children (who are still developing their immune system), we think further studies that compare immunotherapy for the contemporary treatment of asthma in children are urgently needed to fill in this gap.

Recently, a Cochrane SR on SLIT for asthma found a similar lack of data for important outcomes (e.g. exacerbations, symptom scores, quality of life) as we did. [64] Contrary to our study, the authors did no separate analysis for adults and children, and patients with asthma were not separately analyzed from patients without asthma.

CONCLUSIONS

Focusing on predefined patient relevant outcomes, and critically appraising the body of evidence using original studies and GRADE methodology, our systematic review on the effects of immunotherapy in children with asthma came to different conclusions than previous systematic reviews. We believe that this underscores the importance of using GRADE methodology in systematically reviewing evidence.

We found absence of valid applicable evidence on improvement of clinically relevant asthma outcomes in children with allergic asthma using SCIT or SLIT. This absence of evidence is due to serious risk of bias, large clinical heterogeneity between studies, and most importantly due to lack of applicability because studies were performed in the pre-ICS era.

Since the effect of immunotherapy added to contemporary asthma treatment with daily controller therapy is not clear, the drawbacks of immunotherapy should be considered carefully. SCIT is a complex and intensive form of treatment, associated with a (very) long duration of treatment, and considerable burden to the patient with (monthly) injections under adequate medical supervision due to potential (however rare) dangerous side effects, and may have relatively high costs and resource use. In SLIT the risk of serious side-effects is considerably smaller, but the other drawbacks of immunotherapy apply equally to this treatment. In our opinion therefore, when balancing the absence of evidence on a clear beneficial effect of SCIT or SLIT on clinically relevant patient outcomes in children with asthma with the considerable burden and costs of SCIT and SLIT, we do not recommend this treatment to children with asthma until further high-quality evidence from well-designed RCTs in children comparing SCIT or SLIT to contemporary asthma treatment becomes available.

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9

General discussion

GENERAL DISCUSSION

The aim of this thesis was to get insight in difficulties in the treatment of asthma in children from different viewpoints. The first part of the thesis focused on the role of behavior, multidisciplinary treatment at high altitude and prediction of treatment success mainly for children with problematic severe asthma. The second part examined pathophysiology and possible treatment options for two common comorbidities in children with asthma: obesity and allergic rhinitis.

This chapter summarizes our most important findings, provides an embedding and discussion of lessons of the individual studies and considers clinical implications and possible treatment options. It provides a checklist for problematic severe asthma which integrates evidence and clinical practice and gives treatment clues in a deadlocked situation. Considerations on directions for future research are given in every section.

The main findings of the studies of this thesis are summarized in the box below.

- A state of the art guideline with current insight into diagnosis and treatment of asthma in children is provided (chapter 2).
- Internalizing behavioral problems such as depressive mood or withdrawal behavior and somatic complaints are more severe in tertiary referred children with asthma compared to healthy reference groups (chapter 3).
- Behavioral problems and a lower quality of life appear to be more pronounced in clinically treated children and adolescents with difficult-to-treat asthma than in asthma patients who are not classified as difficult-to-treat (chapter 3).
- In clinically treated children with difficult asthma, admitted to a specialized clinic, internalizing behavioral problems before treatment are associated with a lower increase in quality of life during treatment (chapter 4).
- During clinical multidisciplinary treatment at high altitude, medication level can be reduced while fractional concentration of exhaled nitric oxide (FeNO), asthma control and quality of life improve (chapter 5).
- It is not possible to predict the degree of tapering off inhaled corticosteroids from health status variables at treatment entrance (chapter 5).
- Weight loss in children with severe obesity correlates with an improvement in lung function, especially expiratory reserve volume (ERV). The improvement in ERV correlates with a decrease in standard deviation score of the body mass index (SDS-BMI) and waist circumference. This favors a mechanical explanation (chapter 6).

- Weight loss in children with severe obesity *and asthma* is not associated with a decrease in air flow limitation but it is related to an increase in ERV. This increase in ERV in obese children with asthma is most likely caused by a reduction in obstructing abdominal mass (chapter 7).
- So far, there is no scientific evidence that supports a positive advise for the treatment of childhood allergic asthma by means of immunotherapy, either subcutaneous or sublingual, when balancing patient outcomes, costs and disadvantages following Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology (chapter 8).

Considerations on an asthma guideline

The first part of of this thesis starts with the current Dutch guideline on pediatric asthma (**chapter 2**). This guideline is partly based on the BTS (British Thoracic Society) guideline[1] and updated and adapted to the Dutch situation. We applied GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology in our evidence reports on controversial subjects and made recommendations as transparent as possible following this grading system.[2] Knowledge gaps were identified and described separately,[3] giving direction for future research in this field. Moreover, this guideline crosslinked and integrated other initiatives and practice guidelines on asthma in children.

Guidelines are subject to changes and should best be dynamic documents. The first version of the Dutch guideline on pediatric asthma went back to the nineties of the last century and resulted in a consensus-based printed book, distributed and partly financed by the pharmaceutical industry. Our current guideline (**chapter 2**) is independent and transparent. Future initiatives on the process of publishing guidelines should tend towards dynamic (online) documents, that can be updated frequently, guaranteeing its content by means of an expert panel free from conflicts of interest and support from the latest systematic literature searches.

Guidelines are commonly based on the combination of solid evidence and subsequent expert opinion. Randomized controlled trials and aggregated evidence in systematic reviews as reported in **chapter 8** are cornerstones of evidence-based guidelines like we developed in **chapter 2**. A crucial step in developing recommendations is the balancing of solid evidence. Patient relevant outcome measures should be weighed for benefits and harms, costs and (dis)advantages, in order to be useful for the individual patient.[2] Writing medical guidelines has become a high-standard profession that needs specialized skills and knowhow and should be performed in combined approaches: experts from the field working together with guideline methodologists in order to reach this

standard. This process should, in an early phase, be completed with patient and public involvement (PPI) to weigh patient interests best.[4]

A most promising trend in asthma treatment is personalized medicine in contrast to the "trial and error" strategy that is presently recommended in three steps of the guideline (steps 3, 4 and 5). Personalized or tailored treatment can target the asthma phenotype. As an example 300 children with asthma and need for daily controller therapy (step 2) were studied.[6] Three crossover periods with daily inhaled corticosteroid, daily leukotriene receptor antagonist, and as-needed ICS treatment co-administered with albuterol were compared and best differential response (based on a composite measure of asthma control) was predicted by pre-specified features (aeroallergen sensitization, previous exacerbations, sex).

Important first steps in precision medicine by means of pharmacogenetics of asthma have also been made. In pharmacogenetics, genetic variations and their influence on drug response are being studied. Individual differences in genetic loci may account for (lack of) efficacy in medication response in individual patients (for example in children carrying the Arg16 variant in the β2-adrenoreceptor gene show a attenuated response to β2-agonists) or account for difference in experienced side-effects.[6]

We expect and recommend that future guidelines and practice on pediatric asthma will incorporate more individualized approaches, once this field has evolved by showing more evidence for patient-specific recommendations.

Overviewing challenges in pediatric asthma treatment

Should we focus on behavioral problems?

In a tertiary referred group of children and adolescents with asthma, we found more behavioral problems than in general population-based reference groups (**chapter 3**). This finding was more pronounced in children with problematic severe asthma (PSA). The problems found were mainly internalizing (withdrawn behavior, depressive mood) and somatic complaints (such as nightmares, dizziness, tiredness, (head)aches, nausea, and stomach problems). Somatic complaints and thought problems (hearing things, sleep problems and strange behavior) were more prevalent in difficult-to-treat asthma. The observation that behavioral problems were associated with more severe asthma, suggests that a focus on behavioral problems might be beneficial for asthma control.

When followed prospectively during a treatment period, we found that internalizing behavioral problems before treatment are associated with a lower increase in disease-specific quality of life during treatment (**chapter 4**), specifically a less positive change in the domains symptoms and emotions. Behavioral problems were not associated with a change of lung function measurements (FEV_1 and FeNO) and asthma control (ACT) during treatment.

The explanation of the effect of behavioral problems on asthma outcome is enigmatic, since multiple complementary mechanisms might contribute. The higher severity of behavioral problems in children and adolescents with asthma can theoretically be due to the asthma, to medication related to the treatment of asthma, or to psychosocial effects. Adverse effects of asthma medications are rare.[7] Adverse effects of inhaled corticosteroids (ICS) are mild and sporadic and ICS should not be avoided for that reason.[8,9] Poor adherence might be a general obstructing factor as described in chapter 1, and behavioral and thought problems might contribute to low adherence and morbidity of asthma in this age group.[10] Double stress (chronic family stress in combination with acute stress) may cause a higher expression of asthma-related cytokines (IL-4, IL-5, IL-13 and IFN-gamma), suggesting a higher risk of asthmatic events.[11] This might implicate the contribution of neuro-immune mechanisms that have to be elucidated yet.

We think asthma control, physiological parameters, and psychosocial problems are integrated domains of the health status of the individual patient in her or his family system.[12] Assessments on asthma control, quality of life and behavioral and thought problems add unique and valuable information that might help in asthma management for the individual patient, especially in PSA. Treatment of the latter group should focus on all domains in order to disentangle the experienced difficulties in treatment and make the disease treatable again. Future research should clarify whether a compound score or asthma impact score that integrates all domains is helpful in tailoring treatment.

Should we treat in multidisciplinary centers?

The studies presented in **chapter 3, chapter 4** and **chapter 5** were performed in a multidisciplinary treatment center. Although it is difficult to find evidence for multidisciplinary treatment, from a clinician's view it makes sense to target the multiplicity of problems of a patient with asthma in a multidisciplinary team. Especially in situations where symptoms overlap, for example different kinds of dyspneic attacks as possible in asthma with comorbidity dysfunctional breathing, a combined treatment approach will fit in best. A biopsychosocial model has been postulated which describes the dynamic system of (and around) the patient as a hanging pendulum or mobile in which movement of one of the elements will influence (disturb) the other elements.[13] Elements in this biopsychosocial model can be asthma control, quality of life, asthma symptoms, behavior, external influences such as parenting stress, compliance. Comorbid factors such as symptoms of allergic rhinitis or obesity and its implications on daily activities can (easily) be fit into this model, thus underlining the need for a dynamic and comprehensive approach.

In a prospective follow-up in adolescents, multidisciplinary treatment of asthma was suggested to be an effective approach for children with uncontrolled asthma in secondary care, although indication of which elements of treatment are most contribu-

tive remained difficult.[14] However, no randomized controlled studies are available for multidisciplinary pediatric asthma treatment. In other chronic diseases of childhood such as constipation there is also lack of high quality research on treatment effect of a multidisciplinary approach.[15] Future research should focus on multidisciplinary treatment and define good comparison groups.

Should we recommend high altitude treatment?

Treatment at high altitude (over 1500m above sea level) has been subject of several studies.[16,17,18] In theory, allergic exposition, as expressed by the concentration of tree pollen in air will be lower, and air pollution is measurably lower. Although a more recent study sheds doubt on this issue,[19] early studies conclude that house dust mite is hardly found at 1600m altitude.[20] If allergy is a destabilizing factor in allergic asthma and allergic triggers are difficult to avoid, an allergen-free (or low allergen) environment might be beneficial. The fraction of nitric oxide in exhaled breath (FeNO) is a known marker for eosinophillic inflammation in asthma and allergy.[21] During a 2 weeks stay in the mountains FeNO showed a normalizing trend in both allergic and non-allergic asthmatic adults, without changing the asthma treatment regimen.[22] However, these are observational data without blinding or a control group. In adolescents, a small but controlled follow-up study showed better results for asthma patients who had been treated 10 weeks at high altitude, when compared to those who stayed at sea level.[23] Again, the measured changes were surrogate outcome markers like bronchial hyper responsiveness or markers of inflammation in the urine of asthma patients which are not typical clinical relevant patient outcomes.

Regrettably, recent practical decisions (mainly based on financial matters and Dutch Health Insurances and the very small group of pediatric patients that need this treatment) will make future treatment of and research on pediatric PSA in the Dutch high altitude asthma clinic in Davos, Switzerland, most insecure. In the Netherlands one multidisciplinary treatment option for pediatric lung revalidation is available to date, in Hilversum, while multidisciplinary assessment for pediatric asthma is also possible in Groesbeek, both being part of a lung revalidation setting.

The designs of the studies in part 1 of this thesis were neither controlled nor blinded. In daily practice, treatment at very different locations – like an Alp climate in the mountains versus treatment in the Netherlands – will never be subject to the possibility of blinding for the subject. The best possible design to forestall this problem would be a cross-over design. Only one trial has been performed for atopic patients with eczema.[18] Future research should be adequately designed to truly compare different treatment modalities in order to decide best treatment locations in the future.

Why would we focus on and treat obesity?

Obesity in childhood is an important problem population wide, with a substantial proportion of children being overweight or being obesity.[24] Obese children experience shortness of breath and may lack exercise tolerance. In **chapter 6** we showed the beneficial consequences on pulmonary function after weight loss. Severely obese children followed a multidisciplinary treatment program comprising nutritional education, physical activity and behavior. Weight loss in severely obese children correlated with an improvement in pulmonary function, especially expiratory reserve volume (ERV). This improvement in ERV correlated with the decrease in SDS-BMI and waist circumference. Obstructive lung function parameters (FEV_1, Tiffeneau) showed small, clinically irrelevant improvement. We were limited in our observation regarding measurement of subjective signs of breathlessness, fatigue or dyspnea because of difficulties in standardization. However, we assume that the improvement of ERV after weight loss will help in less breathlessness.

In **chapter 7** we described a small sample of asthmatic children with severe obesity. We saw the same improvement in pulmonary function after massive weight loss as observed in children without asthma. Again, the ERV improved after weight loss, and only small, clinically irrelevant, improvement of obstructive measures were found.

Asthma and obesity have a complex interaction and several mechanisms have been suggested to clarify this correlation. Possible mechanisms may play a role at different ages.[25] Main explanations for the asthma-obesity correlation are, first, inflammatory or endocrine and, second, mechanical. An association between inflammatory mediators of obesity and asthma has been found by several authors as summarized in review that recognizes obesity as a low-grade inflammatory state.[26] Th1/Th2 helper balance is thus disturbed via pro-inflammatory adipocytokines, leading to more bronchial hyper responsiveness and obstruction. Correlations as described in these studies do not automatically represent a unidirectional causal relation.

Mechanical changes that obstruct full expansion of the lungs have been described in early experiments in adults.[27] Here the effect of mass loading – more or less comparable to the abdominal mass in obesity – was explored. Men with obesity showed the same tendencies as healthy persons with an abdominal mass load. When breathing at a higher functional residual capacity (FRC), as is typical in obesity, bronchial hyper responsiveness increased.[28]

More recently, the phenomenon of dysanapsis has come into focus of research. Dysanapsis is the incongruence between the growth of the lungs and the airways.[29] Obesity is associated with airway dysanapsis in children. Dysanapsis is associated with increased morbidity among obese children with asthma, and may partly explain their reduced response to inhaled corticosteroids.[29] In our studies (**chapter 6, 7**), children had a normal Tiffeneau index, reflecting no obvious dysanapsis. Moreover after significant weight

loss, we did not see an improvement in FEV_1/FVC, thus reflecting no improvement in dysanapsis. If this phenomenon of dysanapsis is thought to play a major role in obesity in asthma, we would have expected it to be present in patients in our study or at least to improve at the end of treatment. However, it did not. A possible explanation for this finding could be that dysanapsis is thought to be a structural change in lung growth, which is irreversible or that the study period was too short to elucidate a difference.

Also regarding mechanical changes in obesity and its link with obesity, a solid and complete causal explanation fails. We tentatively conclude that the mechanical explanation as expressed above is the most likely causative factor since obese children without asthma showed the same changes in lung function.

What can we expect of treatment of obesity regarding childhood asthma?

Bariatric surgery was shown to have positive effects on asthma control, lung function and bronchial and systemic inflammation in severe obese adults with asthma.[30] Stomach reduction is however not allowed in patients below 18 years in the Netherlands. Several programs for weight intervention have been described including ours (**chapter 6**).[31,32] Long-term success of a combined lifestyle intervention in obese children can sometimes be reached, but is difficult and takes huge efforts by patients, caregivers and clinicians.[33,34]

From a behavioral point of view obesity may be linked to poor self-regulation and lack of discipline. These factors may also have negative consequences for asthma self management. Due to the combination of asthma and obesity, the patient is often compromised in exercise tolerance, thus lacking physical fitness. These factors may strengthen each other.

Frey postulates an interesting approach for treatment of the combination of asthma and obesity. [25] Here, a ´small step multi-dimensional treatment´ is advocated (figure 1). This treatment approach recommends small and positive steps to increase physical activity and includes family and peers. Although the underlying mechanisms are not fully understood, our findings suggest that severe obesity contributes to the (experienced) symptoms of asthma thus advocating prompt treatment of this heavy problem.

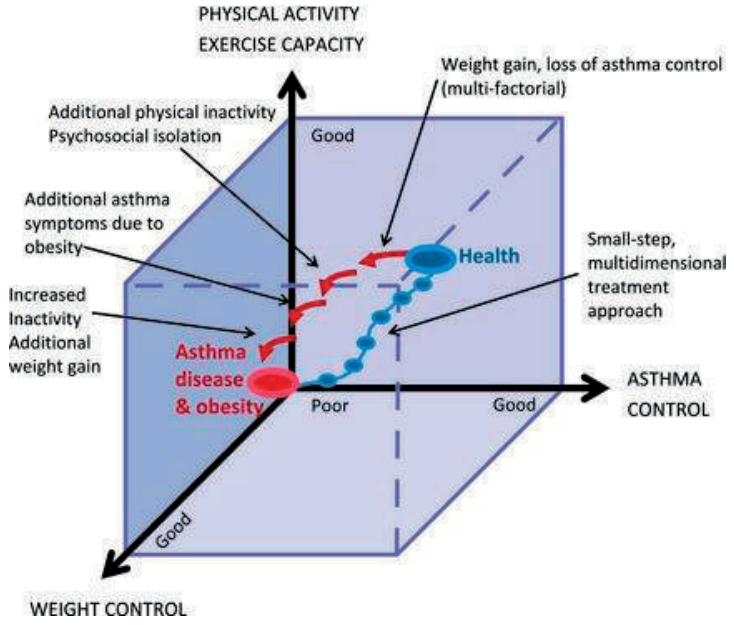

Figure 1. Small step multi-dimensional treatment model. Reprinted with permission from the author.[25]

Should we treat childhood allergic asthma by means of immunotherapy?

Treatment of asthma by means of immunotherapy has been recommended in a Cochrane review.[35] In **chapter 8** we provide a state of the art GRADE systematic review to evaluate this recommendation when comparing it to actual treatment standards for pediatric asthma. The main finding of this study is the difference (incomparability) of modern asthma treatment for children, with ICS as cornerstone, versus the regimen used in the period the burden of evidence for the Cochrane review was collected (mainly seventies to nineties of the 20th century).

The most common comorbidity in childhood asthma is allergic rhinitis,[36,37] symptoms of which occur in 60-80% of asthmatic children.[38,39] Allergic rhinitis shares a common pathophysiological pathway with allergic asthma, which has been described as the united airway concept.[40] Cornerstones for the treatment of allergic rhinitis are antihistaminics and local steroids.[40,41] Above this, immunotherapy can be used when symptoms of allergic rhinitis cannot be sufficiently controlled with nasal steroids and oral histaminics. There is evidence for the efficacy of treatment with immunotherapy for allergic rhinitis.[42,42,44] Allergic rhinitis is associated with worse asthma control in children, and accumulating evidence suggests that treatment of allergic rhinitis with intranasal steroids improves not only rhinitis, but also asthma symptoms in these patients.[41,45]

When using GRADE methodology,[2] not only transparent and systematic weighing of the evidence is needed, but also a careful evaluation of practical implications, benefits and harms for the patient and resource utility is included.[46] In former critical evaluations

of Dutch childhood asthma recommendations this transparent process made a significant difference in outcome.[47] By applying GRADE and focusing on important patient outcomes and transparent, explicit other considerations, recommendations on pediatric asthma differed from those in other international guidelines in 2011. For example the order of step-up in step 3 of the treatment scheme, or the preferred first choice medication for preschool wheeze (ICS instead of leukotriene receptor antagonist) was different from former recommendations.[47]

In addition to quality of evidence, the process of balancing desirable and undesirable consequences of the treatment options is essential, which is recognized by GRADE. Patient and clinicians' values and preferences should play a role in this process. For a large part of pediatric illnesses high quality evidence for important clinical relevant outcomes is scarce. Thus treatment options in daily practice are often based on other considerations or deliberations. We strongly advocate that recommendations mention these considerations explicitly so that a most adequate decision can be made for the patient.

From our critical appraisal of the literature regarding immunotherapy for asthma, we cannot recommend its efficacy for pediatric asthma.

Difficulties in pharmacological treatment – focus on the basics in asthma treatment

As shown in the medication scheme in the current guideline, inhaled steroids are the cornerstones for the treatment of asthma, from step 2 (**chapter 2**), or even in step 1.[48] Correct inhalation technique, compliance, self-management education and treatment of a co-morbidity such as allergic rhinitis, is recommended as part of the basic approach. Adding long acting β_2 agonist or leukotriene receptor antagonists and/or doubling the dose of inhaled steroids can be necessary to gain control (step 3).[49] Quadrupling the dose of inhaled steroids is recommended in step 5 of asthma treatment (**chapter 2),** however even then, prevention of exacerbations can sometimes be difficult.[50]

Medical treatment options in problematic severe asthma include high dosed nebulized inhaled steroids (eventually with smart jet nebulizer), systemic corticosteroids, macrolide antibiotics for non-eosinophilic asthma, anti-IgE injections (Omalizumab) and other (new) anti-inflammatory drugs, and are beyond the scope of this thesis.

Supported by the findings in this thesis, we strongly suggest to balance the potential benefits and disadvantages from more intensive, time-consuming or rather expensive pharmacological treatment options.

Concluding remarks and final recommendations

Due to the complexity of pediatric asthma and its treatment, we suggest to pay attention to all different domains until the asthma that was (thought to be) difficult to treat is treatable again.

Such an approach needs different dedicated experts in their fields (e.g. pediatric asthma nurse, pediatric pulmonologist, child psychologist, physiotherapist and so on), preferably working closely together in one team. Before that, (local) pediatric caregivers should first screen systematically and focus on several practical aspects like inhaler technique, adherence to medication, allergen exposure (at home), passive smoking, patient believes and concordance between patient and caregiver.

If lack of disease control remains after getting the aforementioned basics right, referral to specialized pediatric asthma teams is recommended. Here supportive or invasive tests can be added when estimated necessary, like steroid responsiveness, imaging, bronchoscopy or phenotyping the asthma, and co-morbidities can be demonstrated, including challenges in the psychosocial domain. Also, intervening emotional (like fear or mood disturbances), behavourial or family problems can be diagnosed. Shared decision making should be advocated since it can help in obtaining concordance at all stages. Likewise, treatment difficulties can become challenges and will possibly be targeted effectively.

In this stepped approach difficult to treat pediatric asthma will become treatable again in a lot of cases. In a scarce portion of children real therapy resistant asthma will be diagnosed. It is essential that this small group will be treated in few specialized treatment centers in order to obtain pediatric experience with this group.

Although treatment options are refining (biologicals) and targeting better to the right group (phenotyping), we expect future numbers of therapy resistant asthma in children, albeit small, not to decrease due to the prevalence of childhood asthma and the increase of obesity among children with asthma. We expect the most important benefit for this group from personalized treatment more precisely targeting the exact asthma phenotype. This stepped approach and personalized treatment could best be organized in specialized pediatric asthma clinics.

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Checklist problematic severe asthma

based on Bush,[1] NVK 2013,[2] BTS 2019[3]

Definitely

Reassure diagnosis of asthma

Check inhaler technique and improve wherever possible

Check compliance, ask permission to request pharmacy's report on provided medication, identify obstructing factors

Check concordance and patient believes

Check comorbidities and treat wherever necessary

- Skin prick test aero-allergens and/or RAST (grass and tree pollen, house dust mite, cockroach, cat, dog), fungi
- Eczema
- Dysfunctional breathing (refer to a respiratory physiotherapist, perform hyperventilation provocation test)
- Psychosocial and/or behavioral problems (refer to a dedicated psychologist)
- BMI and waist circumference

Perform spirometry and capture bronchodilator response

Plan a specialist respiratory nurse home visit (including signs of smoking, persistent exposure to allergic and aspecific triggers, humidity, ventilation, pets, and so on)

Capture limitations in exercise tolerance, nonattendance at school and learning disabilities due to asthma

Possibly

Perform measurement of fraction of exhaled nitric oxide (FeNO)

Measure induced sputum cell counts if FEV_1 is more than 70% predicted

Perform a bronchial hyperresponsiveness test, if in a stable situation (in a child with normal spirometry and reported severe symptoms, a negative challenge would make uncontrolled asthma unlikely)

Capture response on Triamcinolone i.m.

Consider performing skin prick test and/or RAST food allergens (peanut, milk, egg), in case of exacerbations that might mimic anaphylaxis

Collect saliva for cotinine concentrations as an objective measure of exposure to tobacco smoke

Measure blood concentrations of the drugs if Prednisolone or Theophylline have been prescribed

Consider HRCT scanning, but only in case of diagnostic doubt (obliterative bronchiolitis; bronchiectasis). There is no evidence to recommend routine HRCT as a clinical test in true severe, therapy-resistant paediatric asthma.[1]

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Summary

SUMMARY

Treatment of problematic severe asthma in children

This thesis examines difficulties in the treatment of asthma in children both from a psychosocial (behavioral) and a pathophysiological point of view. It aims to illuminate clues for further treatment in a deadlock situation for young patients with asthma.

Chapter 1, General Introduction, gives an overview of the field, it defines pediatric asthma and current treatment steps. Multiple factors can influence pediatric asthma treatment, such as differential diagnosis, adequate dose of prescribed medication, correct inhaler technique and dose deposition, compliance, exposure to allergens or tobacco smoke, co-morbidities like obesity or allergic rhinitis, psychological and behavioral problems. Most children respond well to treatment, however a small share is classified to have problematic severe asthma (PSA). Obesity is a growing problem in children and has been thought to play a contributing role in pediatric asthma, which is not completely elucidated yet. Allergic rhinitis should be treated if interfering with daily activities and destabilizing asthma control, sometimes using immunotherapy. We do not have evidence from studies with high enough quality to apply immunotherapy in the treatment of asthma. Also, multidisciplinary treatment (at sea level or high altitude) for PSA is practiced, but the added value for this approach is not clear yet.

The first part of this thesis starts with current insights in pediatric asthma diagnosis and treatment. **Chapter 2** shows the topical Dutch Guideline on Pediatric Asthma and provides the outcome of a thorough guideline writing process following modern guideline development standards.

Beyond this starting point, challenging difficulties in the treatment are being faced, specifically behavioral problems in children with problematic severe asthma and obesity and its possible link with asthma.

Chapter 3 examines behavioral problems in 82 tertiary referred, clinically treated pediatric asthma patients with (n=31) or without (n=52) PSA by quantifying behavioral problems and quality of life. We related quality of life with the qualification of PSA by use of 2 questionnaires (Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and the Child Behavior Checklist (CBCL) to assess behavioral problems). Especially internalizing behavioral problems such as being withdrawn/depressed and somatic complaints are more severe in the asthmatic groups compared to the healthy reference group. The behavioral problems 'somatic complaints' and 'thought problems' as well as a lower quality of life are more severe in children and adolescents with PSA than in those who do not fulfill criteria for PSA.

In **Chapter 4** the association of the child's behavioral problems and asthma control and quality of life after multidisciplinary treatment in a high altitude clinic is examined. Here we prospectively study different asthma domains in 134 patients: disease specific

quality of life, asthma control, lung function, fraction of exhaled nitric oxide (FeNO), behavioral problems and its mutual association by means of multiple regression. Patients were tertiary referred patients from 2 high altitude and 1 sea level asthma clinics in Switzerland and the Netherlands. More severe internalizing behavioral problems are found to be associated with less improvement of total quality of life. Behavioral problems are not associated with a change of lung function measurements and asthma control (ACT) during treatment. We conclude that a focus of healthcare professionals on the treatment of internalizing behavioral problems may optimize the quality of life in clinically treated pediatric asthma patients.

Chapter 5 analyzes the possibility of reducing maintenance medication in severe asthmatic children in multidisciplinary treatment at a high altitude clinic. Here we prospectively study 43 children aged 8–17 years referred to a specialized high altitude treatment center, regarding lung function (FEV_1, Tiffeneau), eosinophilic inflammation (as measured by FeNO), medication level, asthma control (ACT) and quality of life (PAQLQ) on admission and at discharge. We aim to predict which patients can be tapered from inhaled corticosteroids on the basis of asthma control, pulmonary function testing and disease specific quality of life at entrances. We find a significant decrease in dosage of inhaled corticosteroids (ICS) after treatment, also oral steroid maintenance therapy can be stopped in all patients. FeNO, ACT and PAQLQ show significant improvement from admission to discharge. However, apart from ICS levels at entrance, multiple regression analyses do not show any associated factor predicting the reduction of ICS dosage during treatment.

A massive and growing problem in Western countries is childhood obesity, which interferes with many aspects of health and quality of life in children. In **chapter 6** we examine lung function changes related to severe obesity. Here we show lung function data of 112 children 8-18 years old with obesity before and after significant weight loss in a prospective cohort study. There is significant improvement of lung function parameters (functional vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), total lung capacity and expiratory reserve volume (ERV). The increase in ERV correlates with the reduction in body weight (SDS-BMI) and with the reduction in waist circumference. FEV_1 does not correlate with the reduction in either SDS-BMI or waist circumference. We hypothesize this favors a mechanical explanation for lung function decline in severe obesity.

In **chapter 7** we describe a small group of children with asthma and obesity and their changes in lung function after massive weight loss. Here we try to find some clues to disentangle the asthma–obesity problem. We present a prospective cohort study examining the effect of weight reduction on pulmonary function in 22 extremely obese children with asthma. Weight loss and a waist circumference decrease correlate highly with an ERV increase. FVC and FEV_1 did not increase significantly. Total lung capacity does not correlate with weight loss. We conclude that weight loss in children with asthma

and extreme obesity is associated with an increase in ERV but not a decrease in air flow limitation.

Chapter 8 has the viewpoint of adjuvant therapies, targeting the common allergenic pathway in childhood asthma and its common comorbidity allergic rhinitis. In a systematic review we critically examine evidence for immunotherapy and its adjuvant value for children with asthma and allergic rhinitis using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) to rate the level of quality of studies. We reassess the effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) in childhood asthma treatment focusing on studies with patient-relevant outcome measures and children using ICS. We use predefined critical patient-relevant outcomes (asthma symptoms, asthma control and exacerbations). We searched to retrieve systematic reviews and randomized controlled trials on immunotherapy for asthma in children (1960–2017). The quality of the evidence for SCIT is very low due to a large risk of bias and indirectness (dated studies in children not using ICS). No effect of SCIT is found for asthma symptoms; no studies report on asthma control. For asthma exacerbations, studies favor SCIT. However, we have no confidence in this effect estimate, due to the very low quality of evidence. For SLIT, quality of the evidence is very low due to a large risk of bias, indirectness and imprecision. The outcome 'asthma symptoms' could not be calculated due to lack of standardization and large clinical heterogeneity. Other predefined outcomes are not reported. We conclude that in childhood asthma the beneficial effects of immunotherapy found in earlier reviews are no longer applicable, because these studies were performed in children who were not treated with ICS, as is advocated in current asthma guidelines.

The final **chapter 9** discusses the main findings of this thesis and its implications for clinical practice, and offers suggestions on asthma treatment in difficult settings and problematic severe asthma. In addition, we present directions for future research. We emphasize the importance of a transparent guideline writing process, including careful considerations. More personalized treatment strategies should find their way into future guidelines and practice. In difficult asthma behavioral problems (mainly internalizing and somatic complaints other than asthma symptoms) are important to consider, especially in PSA. The observation that behavioral problems were associated with more severe asthma, suggests that a focus on behavioral problems might be beneficial for asthma control and quality of life. We suggest that asthma control, physiological parameters, and psychosocial problems are integrated domains of the health status of the patient. Future research should clarify whether a compound score or asthma impact score, that integrates all domains, is helpful to tailor treatment. From the biopsychosocial model, it makes sense to treat in a multidisciplinary setting. Weight loss in severely obese children has significant effect on improvement of several lung function parameters. In children without asthma, weight loss and improved expiratory reserve volume show a positive

correlation. In children with asthma we found the same improvement. The asthma-obesity link in children is discussed but remains to date rather enigmatic. We think the mechanical explanation of the abdominal mass is an important aspect and – from a clinical viewpoint – recommend treatment of obesity in asthma patients. Albeit proven effective for allergic rhinitis, the evidence for immune therapy for asthma in children is neither direct nor clear. Critical appraisal of the literature combined with transparent considerations can make an important difference in guideline recommendations. From our critical appraisal of the literature regarding immunotherapy for asthma, we cannot recommend its efficacy for pediatric asthma.

Considering difficulties in treatment of childhood asthma, especially PSA, as supported by the findings in this thesis, we strongly suggest to balance the potential benefits and disadvantages from more intensive, time-consuming or rather expensive pharmacological treatment options. We advise to focus on the basics in asthma treatment. We recommend a stepped approach if treatment remains difficult after getting the basics right. Preferably, specialized multidisciplinary asthma teams should be consulted. We provide a checklist for PSA (Appendix 1) which may be helpful in the search for clues to make the asthma treatable again.

Samenvatting

SAMENVATTING

Behandeling van problematisch ernstig astma bij kinderen

Dit proefschrift onderzoekt problemen in de behandeling van astma bij kinderen, zowel vanuit een psychosociaal (gedragsmatig) als vanuit een pathofysiologisch gezichtspunt. Het heeft tot doel om mogelijke oplossingen te belichten in een vastgelopen situatie bij jonge patiënten met astma.

Hoofdstuk 1, algemene introductie, geeft een overzicht over het veld, definieert astma bij kinderen en actuele stappen in de behandeling. Multipele factoren kunnen de behandeling beïnvloeden van astma bij kinderen, zoals de differentiaal diagnose, adequate dosering van voorgeschreven medicatie, correcte inhalatortechniek en dosis-depositie, therapietrouw, blootstelling aan allergenen of tabaksrook, comorbiditeit zoals obesitas of allergische rinitis, psychologische en gedragsmatige problemen. De meeste kinderen reageren goed op behandeling, een klein gedeelte echter wordt geclassificeerd als problematisch ernstig astma (PEA). Obesitas is een groeiend probleem bij kinderen en speelt waarschijnlijk een bijdragende rol bij astma bij kinderen. Deze rol is nog niet volledig opgehelderd. Allergische rinitis moet behandeld worden als deze interfereert met dagelijkse activiteiten en de astmacontrole instabiel maakt, soms door behandeling met immunotherapie. We hebben geen bewijs van studies van voldoende kwaliteit om immunotherapie aan te kunnen bevelen in de behandeling van astma. Ook wordt multidisciplinaire behandeling (op zeeniveau en in het hooggebergte) toegepast voor PEA, maar de toegevoegde waarde van deze aanpak is nog niet duidelijk.

Het eerste deel van dit proefschrift begint met de huidige inzichten in diagnostiek en behandeling van astma bij kinderen. **Hoofdstuk 2** toont de actuele Nederlandse Richtlijn voor Astma bij Kinderen en voorziet in de uitkomsten van een grondig richtlijn schrijfproces naar moderne richtlijn maatstaven.

Vanaf dit startpunt worden uitdagingen in de behandeling onder de loep genomen, vooral gedragsproblemen bij kinderen met PEA, en obesitas en de mogelijke link daarvan met astma.

Hoofdstuk 3 onderzoekt gedragsproblemen bij 82 tertiair verwezen, klinisch behandelde patiënten met astma met (n=31) en zonder (n=52) PEA door gedragsproblemen en kwaliteit van leven te kwantificeren. We relateerden kwaliteit van leven aan de kwalificatie PEA door gebruik te maken van 2 vragenlijsten (*Pediatric Asthma Quality of Life Questionnaire* (PAQLQ) en de *Child Behavior Checklist* (CBCL) om gedragsproblemen in kaart te brengen). Vooral internaliserende gedragsproblemen zoals zich terugtrekken/somber zijn en lichamelijke klachten zijn ernstiger in de astmagroepen vergeleken met de gezonde normgroep. De gedragsproblemen 'lichamelijke klachten' en 'denkproblemen' evenals lagere kwaliteit van leven zijn ernstiger bij kinderen en adolescenten met PEA dan bij degenen die niet voldoen aan de criteria voor PEA.

In **hoofdstuk 4** wordt de associatie onderzocht tussen gedragsproblemen, astmacontrole en kwaliteit van leven na multidisciplinaire behandeling in het hooggebergte. Hier bestuderen we prospectief verschillende domeinen bij 134 patiënten: ziektespecifieke kwaliteit van leven, astmacontrole, longfunctie, fractie van uitgeademde stikstofmonoxide (FeNO), gedragsproblemen en hun wederzijdse associaties door middel van multiple regressie analyse. Patiënten waren tertiair verwezen patiënten uit 2 hooggebergteklinieken in Zwitserland en 1 astmabehandelcentrum op zeeniveau in Nederland. Ernstiger internaliserende gedragsproblemen zijn geassocieerd met minder verbetering van kwaliteit van leven. Gedragsproblemen zijn niet geassocieerd met een verandering in longfunctiemetingen en astmacontrole gedurende de behandeling. We concluderen dat aandacht van behandelaren voor de behandeling van internaliserende gedragsproblemen de kwaliteit van leven van klinisch behandelde kinderen met astma zou kunnen optimaliseren.

Hoofdstuk 5 analyseert de mogelijkheid van afbouwen van onderhoudsmedicatie bij kinderen met ernstig astma tijdens multidisciplinaire hooggebergtebehandeling. Hier onderzoeken we 43 kinderen van 8-17 jaar die werden verwezen naar een gespecialiseerd hooggebergtebehandelcentrum op longfunctie (FEV_1, Tiffeneau), eosinofiele inflammatie (gemeten met FeNO), medicatie, astmacontrole (ACT) en kwaliteit van leven (PAQLQ) bij opname en ontslag. Doelstelling is om te voorspellen welke patiënten afgebouwd kunnen worden met betrekking tot hun inhalatiecorticosteroïden op basis van astmacontrole, longfunctie, en ziektespecifieke kwaliteit van leven bij binnenkomst. We vinden een significante dosisreductie van de inhalatiecorticosteroïden (ICS) na behandeling. Ook onderhoudsbehandeling met systemische steroïden kan worden gestopt bij alle patiënten. FeNO, ACT en PAQLQ laten significante verbetering zien van opname naar ontslag. Echter, behalve bij ICS-niveau bij binnenkomst, laat multiple regressie analyse geen geassocieerde factor zien die de afbouw van ICS dosering tijdens de behandeling voorspelt.

Een massief en groeiend probleem in Westerse landen is obesitas bij kinderen. Obesitas interfereert met meerdere aspecten van gezondheid en kwaliteit van leven bij kinderen. In **hoofdstuk 6** onderzoeken we veranderingen in longfunctie in relatie tot ernstige obesitas. In een prospectieve cohortstudie laten we hier longfunctie gegevens zien van 112 kinderen van 8-18 jaar met obesitas, voor en na significante gewichtsreductie. Er is significante verbetering van longfunctieparameters (functionele vitale capaciteit (FVC), geforceerd expiratoir volume in 1 s (FEV_1), totale longcapaciteit (TLC) en expiratoir reservevolume (ERV). De toename in ERV correleert met de afname in lichaamsgewicht (SDS-BMI) en met de afname in buikomtrek. FEV_1 correleert niet met de afname in SDS-BMI en ook niet met de afname in buikomvang. We hypothetiseren dat deze bevindingen een mechanische verklaring voor longfunctieverlies bij ernstige obesitas ondersteunt.

In **hoofdstuk 7** beschrijven we een groep kinderen met astma en obesitas en hun veranderingen in longfunctie na forse gewichtsreductie. Hier proberen we enkele aanwijzingen te vinden om het obesitas-astma probleem te ontrafelen. We presenteren een prospectieve cohortstudie die het effect onderzoekt van gewichtsverlies op longfunctie bij 22 kinderen met ernstige obesitas en astma. Afname van gewicht en afname van buikomtrek correleren in hoge mate met een toename van ERV. FVC en FEV_1 verbeteren niet significant. TLC correleert niet met gewichtsverlies. We concluderen dat gewichtsverlies bij kinderen met astma en extreme obesitas geassocieerd is met een toename in ERV maar niet met een afname in *air flow* limitatie.

Hoofdstuk 8 heeft de insteek van adjuvante therapieën die mikken op de gemeenschappelijke allergische route bij astma bij kinderen en de frequent voorkomende comorbiditeit allergische rinitis. In een systematische review onderzoeken we op kritische wijze het bewijs voor immunotherapie en de toegevoegde waarde daarvan voor kinderen met astma en allergische rinitis door gebruik te maken van GRADE (*Grades of Recommendation, Assessment, Development and Evaluation*) om het kwaliteitsniveau van de studies vast te stellen. We evalueren opnieuw de effectiviteit van subcutane (SCIT) en sublinguale immunotherapie (SLIT) in de behandeling van astma bij kinderen door het focus te leggen op studies met patiënt-relevante uitkomstmaten en op studies met kinderen die ICS gebruiken. We gebruiken vooraf gedefinieerde kritische patiënt-relevante uitkomstmaten (astmasymptomen, astmacontrole en exacerbaties). We zochten op systematische reviews en gerandomiseerde gecontroleerde onderzoeken op gebied van immunotherapie voor astma bij kinderen (1960-2017). De kwaliteit van bewijs voor SCIT is erg laag ten gevolge van een groot risico op *bias* en indirectheid (gedateerde studies uit de tijd dat kinderen geen ICS gebruikten). Voor SCIT werd geen effect gevonden op astmasymptomen; over astmacontrole rapporteerde geen enkele studie. SCIT komt beter uit de studies voor de uitkomst astma exacerbaties. Echter, we hebben geen vertrouwen in deze effectschatting, ten gevolge van de zeer lage kwaliteit van bewijs. Voor SLIT is de kwaliteit van bewijs heel laag ten gevolge van een groot risico op *bias*, indirectheid en imprecisie. De uitkomst 'astmasymptomen' kon niet worden berekend ten gevolge van een gebrek aan standaardisatie en grote klinische heterogeniteit. Andere vooraf gedefinieerde uitkomsten werden niet gerapporteerd. We concluderen dat bij kinderen met astma het gunstige effect van immunotherapie zoals dat in eerdere reviews werd gevonden niet langer van toepassing is, omdat deze studies werden uitgevoerd bij kinderen die niet werden behandeld met ICS, zoals in actuele richtlijnen wel wordt aangeraden.

Het laatste **hoofdstuk 9** bediscussieert de bevindingen uit dit proefschrift en de daaruit voortvloeiende implicaties voor de klinische praktijk, en doet aanbevelingen voor astmabehandeling in moeilijke situaties en bij problematisch ernstig astma. Daarnaast presenteren we richtingen voor toekomstig onderzoek. We onderstrepen het belang

van een transparant richtlijnproces, inclusief zorgvuldige overwegingen. Meer gepersonaliseerde behandelstrategieën zouden hun weg moeten vinden naar toekomstige richtlijnen en de praktijk. Bij moeilijk astma, vooral bij PEA, is het belangrijk aandacht te besteden aan gedragsproblemen (vooral internaliserende gedragsproblemen en lichamelijke klachten anders dan astmasymptomen). De observatie dat gedragsproblemen meer geassocieerd waren met ernstiger astma, suggereert dat aandacht voor gedragsproblemen gunstig kan zijn voor astmacontrole en kwaliteit van leven. Wij suggereren dat astmacontrole, fysiologische parameters, en psychosociale problemen geïntegreerde domeinen zijn van de gezondheidsstatus van de patiënt. Toekomstig onderzoek moet uitwijzen of een samengestelde (*compound*) score of astma-impact score, die alle domeinen integreert, helpend is om de behandeling meer op maat te maken. Vanuit het biopsychosociaal model is het logisch om te behandelen in een multidisciplinaire setting. Gewichtsreductie bij kinderen met ernstige obesitas heeft significant effect op de verbetering van verschillende longfunctieparameters. Bij kinderen zonder astma laten gewichtsreductie en toename van ERV een positieve correlatie zien. Bij kinderen met astma vonden we dezelfde verbetering. De astma-obesitas link bij kinderen wordt bediscussieerd maar blijft tot op heden tamelijk enigmatisch. We denken dat de mechanische verklaring van de abdominale massa een belangrijk aspect is en bevelen – vanuit een klinisch perspectief – behandeling van obesitas bij astmapatiënten aan. Ofschoon bewezen effectief voor allergische rinitis, is het bewijs voor immunotherapie voor astma bij kinderen noch direct noch duidelijk. Kritische weging van de literatuur gecombineerd met transparante afwegingen kan een belangrijk verschil maken in de aanbevelingen in een richtlijn. Vanuit onze kritische weging met betrekking tot immunotherapie voor astma, kunnen we de werkzaamheid van deze therapie voor astma bij kinderen niet aanbevelen.

Bij problemen in de behandeling van astma bij kinderen, vooral bij PEA, zoals ondersteund door de bevindingen in dit proefschrift, raden wij sterk aan de mogelijke voor- en nadelen af te wegen van meer intensieve, tijdrovende of tamelijk dure farmacologische behandelopties. We adviseren om te focussen op de *basics* in de astmabehandeling. We raden aan om een stapsgewijze aanpak te doen als de behandeling lastig blijft nadat deze *basics* op orde zijn. Bij voorkeur zou een gespecialiseerd multidisciplinair team geconsulteerd moeten worden. We publiceren een *checklist* voor PEA (appendix 1) die van pas kan komen in de zoektocht naar aanknopingspunten om het astma weer behandelbaar te maken.

List of abbreviations

LIST OF ABBREVIATIONS

95%CI	95% confidence interval
ACT	asthma control test
AMSTAR	A Measurement Tool to Assess Systematic Reviews
BMI	Body Mass Index
CBCL	Child Behavior Checklist
ERV	expiratory reserve volume
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FVC	forced vital capacity
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICS	inhaled corticosteroids
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PFT	pulmonary function testing
%pred	percentage of the predicted value
PSA	problematic severe asthma
RCT	randomized controlled trial
SCIT	subcutaneous immunotherapy
SD(S)	standard deviation (score)
SLIT	sublingual immunotherapy
SR	systematic review
TLC	total lung capacity
VC	vital capacity

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Met de collega's uit Almere ervaar ik bijna (werk)dagelijks hoe belangrijk de toepassing van wetenschappelijk werk in de klinische praktijk is. Of is het nou andersom? Aan de directe collega's in Hilversum veel dank voor de ruimte en ondersteuning op precies de juiste momenten. Dit proefschrift is daardoor precies geworden waar ik voor sta, verbinding tussen alle behandelaren van verschillende disciplines met patiënt en

ouders. En laat dat nu net de werkomgeving zijn waarin ik tegenwoordig dagelijks in mag werken.

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Erik-Jonas van de Griendt
Hilversum, maart 2020

Bibliography, PhD Portfolio & Curriculum Vitae

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PHD PORTFOLIO

Name PhD student: E.J. van de Griendt
PhD period: external 2011-2016, AMC Graduate School for Medical Sciences 2016-2020
Name PhD supervisor: Prof. dr. W.M.C. van Aalderen

1. PhD training	Year	Workload (ECTS credits)
General courses		
- GCP/BROK course	2017	0.25
Specific courses		
- EBRO (evidence based guideline development), FMS	2011	0.25
Seminars, workshops and master classes		
- 2-monthly pediatric pulmonology meetings, incl journal articles	2011-2020	
- 2-monthly problematic severe asthma meeting	2016-2020	9
Presentations		
- Poster Changes in lung function after weight loss in severely obese children, Wetenschapssymposium EKZ, Amsterdam, 2011	2011	0.5
- NVK congress interactive session on allergic rhinitis	2014	0.2
- NVK congress interactive session on GRADE methodology and inhalation allergy, 2018	2018	0.2
(Inter)national conferences		
- ERS, ATS, NVK, CF-Killarney	2011-2020	6.75
Other		
- Guideline Pediatric Asthma NVK 2011-2013, chair	2011-2013	4
- Guideline Lower respiratory tract infections NVK 2013-2015	2013-2015	2
- Guideline Pediatric Asthma NVK 2018-2020	2018-2020	2

2. Teaching	Year	Workload (ECTS)
Lecturing		
- Trends in asthma and allergy, 'Workshop inhalation technology' (2-days)	2013-2014	0.8
- WinterKLAS, Davos, Switzerland, 'Workshop the new Dutch asthma Guideline' (5-days)	2014-2015	0.8
- GP (kaderhuisartsen) Radboud Nijmegen 2015	2015	0.1
- National pulmonary congress 2012-2019, 'Workshop the new Dutch asthma Guideline', 'Workshop challenges in adolescent asthma treatment', 'Workshop difficult to treat asthma', 'Workshop a uniform written action plan for asthma in children'	2012-2019	1.6
Tutoring, Mentoring		
- Tutoring 2 nurses on the job training pediatric pulmonology ('kinderlongconsulent'): N. van der Valk, M.Benasskar	2016-2018	2
Supervising		
- Supervising outpatient clinics		
Total		30.45

CURRICULUM VITAE

Erik-Jonas van de Griendt werd geboren in Vlijmen op 11 februari 1970. Tijdens het gymnasium in 's-Hertogenbosch volgde hij de vooropleiding viool van het Conservatorium Tilburg. Na het eindexamen studeerde hij aanvankelijk verder aan het conservatorium maar verruilde dat al snel voor biologie en later geneeskunde aan de Universiteit Utrecht. Tijdens deze laatste studie vonden enkele buitenlandstages plaats in Londen en Kaapstad, vooral gericht op de kindergeneeskunde. Als basisarts werkte hij in de jeugdzorg en de kinderpsychiatrie. Vanaf 2000 volgde hij de opleiding tot kinderarts in het VU medisch centrum (Prof. John Roord en Prof. Willem Fetter), registratie in 2005. Tijdens de opleiding kreeg hij de kans om samen met Alike Kamerbeek en Frank Kneepkens de Leidraad Kindergeneeskunde voor co-assistenten te schrijven, die werd uitgegeven bij BSL in een reeks.

Werkervaring als algemeen kinderarts deed hij op in het Diakonessenhuis te Utrecht en als aandachtsgebieder kinderlongziekten bij het toenmalige Astmacentrum Heideheuvel (tegenwoordig Merem) en het Amsterdam Universitair Medisch Centrum. Vanaf 2007 werkte hij enkele jaren in Zwitserland, als kinderarts in het Nederlands Astmacentrum Davos, waar tevens een eerste kiem werd gelegd voor het wetenschappelijk onderzoek. Daarna kreeg hij de kans om zich in Amsterdam verder te specialiseren in de kinderlongziekten bij Prof. Wim van Aalderen. Hier werd een multidisciplinair spreekuur voor moeilijk behandelbaar astma opgezet. In 2011 registreerde hij zich als kinderarts-pulmonoloog.

Als projectleider van de Richtlijn Astma bij Kinderen, kreeg hij vanaf 2011 de mogelijkheid om zich te verdiepen in richtlijnmethodologie. Daarbij werd samenwerking gezocht met diverse andere initiatieven op het gebied van behandeling van astma bij kinderen (onder andere de NHG-Standaard astma bij kinderen onder leiding van Prof. Patrick Bindels). Dit resulteerde in de Richtlijn zoals opgenomen in dit proefschrift en enkele publicaties.

Sinds 2011 werkte hij als kinderlongarts in DeKinderkliniek en het Flevoziekenhuis Almere. Hij was als docent en organisator betrokken bij de landelijke kinderartsen cursus Trends in Astma en Allergie en schreef mee aan de Richtlijn Onderste Luchtweginfecties. In 2018 maakte hij de overstap naar Merem medische revalidatie in Hilversum, met een project voor de patiëntengroep met chronische buikpijn. Daarnaast is hij als consulent kinderarts-pulmonoloog werkzaam in Almere.

This thesis on treatment of problematic severe asthma in children aims to illuminate clues for further treatment. It promotes a stepped approach in which all of the involved health domains get attention. Multidisciplinary treatment is advocated, focusing on the basics as well as comorbidities and behavioral problems. Patients and their families should 'dance' with their doctors, psychologists and other team members to bridge treatment challenges in order to have a clear view on the path to wander.