Children with problematic severe asthma: A biopsychosocial perspective

Marieke Verkleij

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Cover

Front Davos, "Brücke bei Wiesen" (1926), painting by Ernst Ludwig Kirchner. Photo printed with permission.

Back *Anamorphosis*: A deformed image that appears in its true shape when viewed in some "unconventional" way. This image must be seen reflected in a distorting cylindrical mirror. Photo printed with permission.
Anamorfose (Grieks): "terug in beeld brengen." Rol de stellingen op en plaats de koker met de zilveren buitenkant op de cirkel.

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Children with problematic severe asthma: A biopsychosocial perspective

Kinderen met problematisch ernstig astma:
een biopsychosociaal perspectief
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 3 juni 2016 des middags te 4.15 uur

door

Marieke Verkleij
geboren op 2 januari 1973 te Bodegraven

Promotor: Prof.dr. R. Geenen

Laten wij zacht zijn voor elkander, kind –

Wij zijn maar als de bladeren in de wind
ritselend langs de zoom van oude wouden,
en alles is onzeker, en hoe zouden
wij weten wat alleen de wind weet, kind –

Veel liefde ging verloren in de wind,
en wat de wind wil zullen wij nooit weten;
en daarom – voor we elkander weer vergeten –
laten wij zacht zijn voor elkander, kind.

Uit: *Voorbij de wegen* (1920)
A. Roland Holst (1888-1976)

Voor Milan, Dante en Hebe

CONTENTS

Chapter 1

General introduction

INTRODUCTION

Asthma, a chronic inflammatory disease of the airways, is common in children and adolescents with a reported worldwide prevalence ranging from 5-15 %.[1] Most children respond well to treatment with safe and evidence-based medications, but in a small portion of pediatric patients with asthma (the precise prevalence is unknown) symptoms persist. These children are classified to have problematic severe asthma (PSA), i.e. asthma that is not under control despite optimal treatment. PSA comprises difficult-to-treat asthma and therapy resistant asthma and represents the most severe group of asthmatic children.[2] Pediatric asthma is a complex disease that is influenced by multiple factors,[3] but PSA –especially in children– is rarely studied.

Asthma control is considered an important indicator of disease activity in asthma. It is defined as the extent to which the various manifestations of asthma have been reduced, incorporating components of current control as well as future risks (e.g. worsening asthma symptoms, lung function decline and adverse effects of high dose asthma medications).[4, 5] Good current asthma control implies the absence of symptoms, normal lifestyle and activity levels, minimal airway obstruction and minimal use of rescue bronchodilators.[4] Adequate asthma control is closely associated with quality of life as definitions of quality of life commonly include asthma symptoms, wellbeing, functioning, and social participation.[6]

Psychosocial factors may influence asthma control and quality of life. Emotions and stress have been associated with physiological factors that play a role in asthma control[3, 7] and behavioral factors such as physical exercise, coping with asthma or adherence to medication will affect asthma control and quality of life.[8-10] However, it is unclear to what extent the quality of life of children with PSA is disturbed, and how behavioral and social problems impact on asthma control and quality of life.[9, 11] Multidisciplinary clinical treatment is considered a treatment option to improve asthma control. Improvements of both asthma control and quality of life have been shown for children treated in tertiary care clinics,[12, 13] but an encompassing evaluation including biological, psychological, and social variables is missing.

BIOPSYCHOSOCIAL MODEL

An assumption in this thesis is that a biopsychosocial model may take best account of PSA in children (Figure 1). First of all, biological factors such as underlying disease activity and other physiological processes affect asthma control, quality of life and psychosocial variables. Biological factors may be triggered and influenced by environmental factors such as viral infections and exposure to allergens or irritants (e.g. cigarette smoke and pollution). The biopsychosocial

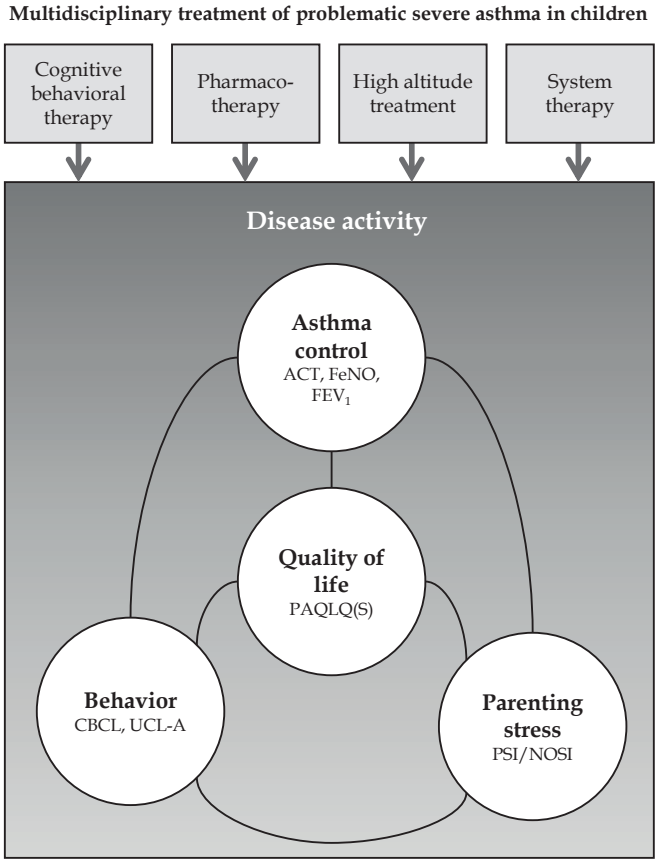

Figure 1. Biopsychosocial model of the psychological factor behavior and the social factor parenting stress in relation to asthma control and quality of life in children (bottom) and the effects of multidisciplinary treatment on all components of the model including disease activity (top). The variables that are studied in this thesis are asthma control using the Asthma Control Test (ACT), forced expiratory volume in 1 second (FEV_1) and fractional concentration of exhaled nitric oxide (FeNO), quality of life using the Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)], behavioral problems with the Child Behavior Checklist (CBCL) and coping with the Utrecht Coping List for Adolescents (UCL-A), and parenting stress with the Parenting Stress Index (PSI/NOSI).

perspective suggests that treatment of behavioral and social problems might improve quality of life and asthma control in pediatric asthma. Previous biopsychosocial models focused on the impact of social stress on childhood asthma by way of prenatal stress, and on specific family relational patterns impacting the child's emotional stress and asthma control.[3]

Figure 1 depicts the factors studied in this thesis and their possible relationships. Our biopsychosocial model suggests that multidisciplinary treatment influences disease activity, the underlying pathological process, as well as all other components of the model (asthma control and quality of life, behavior, and parenting stress). Moreover, relations between all components of the model are assumed to be reciprocal with mutually causal pathways of effect similar to a hanging mobile toy in which movement of one component causes movement of all other components. The multimodal model examined in this thesis could be of heuristic value in stimulating multilevel investigations promoting understanding and treatment of the complex biopsychosocial phenomena of childhood asthma. It is the hope that this thesis will ultimately reduce the asthma symptoms, morbidity, and mortality in children with PSA.

Guided by the biopsychosocial model as shown in Figure 1, the first part of this thesis focuses on the psychological factor behavior and the social factor parenting stress in relation to asthma control and quality of life, while the second part involves the effects of multidisciplinary treatment on the components of the model that may potentially affect each other.

PSYCHOSOCIAL FACTORS

Children's behavior

Although many children and adolescents with asthma function well, it has been observed that selected children and adolescents with asthma have a higher than normal risk at internalizing behavioral and emotional problems such as anxiety and depressive symptoms.[14, 15] 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,[15] psychosocial factors may trigger the expression of asthma through neuro-endocrine and immune mechanisms,[16] and behavioral problems may underlie poor adherence, poor asthma management, and poor functional health status.[17] It has been suggested that

psychological problems related to asthma attacks are associated with persistence of PSA,[18-20] but it is unclear whether these psychological problems are a cause or consequence of PSA, or both. From the perspective of the biopsychosocial model, disease activity will probably be influenced by children's behavior and vice versa, suggesting that a focus on children's behavior might be beneficial for disease activity. This mechanism may be particularly significant in children with PSA because of the severity of their asthma and resistance to asthma therapy. The aim of *chapter 2* was to quantify the behavioral problems in clinically treated children and adolescents with asthma and to examine the association of these behavioral problems with asthma severity and quality of life, which gives direction to the focus of treatment by health-care professionals. The study described in *chapter 3* focuses on the prospective association between behavioral problems at the moment of admission to multidisciplinary treatment and the asthma and quality of life outcomes at discharge.

Parenting stress

Parents play a crucial role in the social and autonomy development of their children. When parents establish a supportive, caring and positive environment, this will have a positive effect on developmental outcomes for children, also in a population of children growing up with a disease.[21] Some studies have indicated that parental physical, emotional, and social health influences the health and well-being of their children[22-24] and higher levels of parenting stress were shown to be related to lower psychosocial wellbeing in their children.[24] Thus, parenting stress is considered an important factor, both as a potential cause and consequence of disease activity, asthma control and quality of life and behavioral problems in children with PSA. Parenting stress can exert an influence on the disease through poor treatment adherence,[25] or through physiological stress response systems such as the sympathetic nervous system and the hypothalamic pituitary adrenal axis[26] as compliance with asthma management still largely depends upon caregivers in children.[2] Moreover, parenting stress might affect the disease through physiological stress response systems such as the sympathetic nervous system and the hypothalamic pituitary adrenal axis.[26] As parenting stress may play a role in perseverance of asthma, knowing its severity and the relationship between parenting stress in the parents and asthma control in their children is important. Guided by the biopsychosocial model, *chapter 4* examines parenting stress and its association with behavioral problems and disease severity in the child.

MULTIDISCIPLINARY TREATMENT

Most children with asthma respond well to treatment with safe and evidence-based medications.[27] Pediatric asthma patients that do not show an adequate response to medication may be admitted to specialized tertiary care. Often these children have an extensive treatment history and are still unable to gain sufficient control of their disease. It is not always clear whether treatment of asthma is difficult because the asthma is therapy-resistant or because of other reasons such as living in a house with detrimental environmental conditions for the asthma, or psychological factors that may obstruct treatment effects.[16, 28, 29] The biopsychosocial model suggests that biological, psychological and social variables in pediatric asthma may potentially improve after successful treatment.

The multidisciplinary approach in tertiary care centers includes medical and psychosocial evaluation and treatment, and educates the children and their parents using a stepwise approach to the management of asthma. Asthma control is the goal of asthma treatment, since asthma cannot be cured. Psychosocial assessment and intervention if needed is important because children need to learn to cope with the specific problems associated with living with a chronic disease. This will enhance quality of life and it may positively affect disease activity. Furthermore, children need to learn to adhere to strict medicinal regimes, which can be time consuming for caregivers and may yield parenting stress. In the second part of this thesis, it is examined whether asthma control and associated factors are improved by multidisciplinary interventions in pediatric patients with asthma that had turned out to be difficult-to-treat in primary and secondary care. To this aim, insight into the characterization of pediatric PSA is needed as well as insight into the effects of treatment on asthma, quality of life, behavior, and parenting stress. This will contribute to improvement of the treatment for the individual patient with PSA.

Pharmacotherapy and multidisciplinary treatment at high altitude

The mainstay of asthma treatment is pharmacological treatment with inhaled corticosteroids (ICS) and long-acting β2-adrenoceptor (LABA) agonists. High doses of ICS or oral steroids may be needed to stabilize asthma in children with PSA, 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. Multidisciplinary treatment at high altitude is one of the possible treatment options to reduce the dosage of ICS in children with PSA.[13] Several observational studies have shown significant improvement in quality of life, forced expiratory

volume in 1 second (FEV_1) and fractional concentration of exhaled nitric oxide (FeNO) in children with PSA after treatment at high altitude.[12, 13, 30, 31] Climatologic advantages, the absence of house dust mite allergen, lack of pollution and the removal of the child from his daily surroundings may be responsible for stabilization of the disease in the high altitude environment.[32-34] The aim of *chapter 5* is to investigate the effect of multidisciplinary high altitude treatment on the (minimum) dose of inhaled corticosteroid required to keep the asthma under control and to gain insight into possible factors predicting this tapering of the ICS dose, i.e., the demographic variables gender and age, and the asthma outcome variables at entrance: asthma control, FEV_1, FeNO, and quality of life.

Cognitive behavioral therapy and system therapy

Behavioral problems possibly affect the outcome of asthma treatment through multiple, complementary pathways. Some experts suggest that poor adherence and disease management are an explanation for poor asthma control,[2, 5, 35] while others believe that the role of stress in asthma morbidity is underestimated, not well understood, and therefore not adequately addressed in treatment.[7, 36] Theory postulates that not only the occurrence of stressors such as having an unpredictable disease and symptoms determine the levels of stress and quality of life, but also one's ability to deal with stressors, i.e., coping.[37] Uncontrolled asthma, especially exacerbation of asthma, is a high burden for psychosocial health, since patients need to manage their asthma and need to learn to cope with the consequences in daily life.[38] Psychological distress and decreased feelings of control were significantly more frequent in subjects with asthma in population-based studies.[39] Appropriate coping strategies are dependent on personal factors. Inappropriate coping strategies can lead to stress and distress such as frustration, depression and anxiety and result in an impaired health status.[40] 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. We expect that internalizing behavioral problems may reduce in connection with improvement of control of asthma, and coping may improve by multidisciplinary treatment. *Chapter 6* examines whether it is possible to establish a positive change in asthma control and psychosocial outcome variables during tertiary treatment in children with PSA because asthma control in common health care was problematic. This will reduce asthma morbidity and mortality and healthcare costs.

In multidisciplinary clinical treatment, all components will be assessed and – if possible – treated. In children with asthma, not necessarily PSA, interventions

incorporating cognitive behavioral techniques have shown to be successful in targeting variables such as self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation, social competence, and days absence from school.[41-43] However, in order to decide on the usefulness of cognitive behavioral therapy for adolescents with PSA and comorbid psychological stress, more evidence is needed. In *chapter 7* we will develop and evaluate psychological treatment customized to the individual. The chapter describes a 16-year-old adolescent with difficult-to-treat asthma, who was referred to the department of pediatric psychology because her pulmonologist recognized that psychological stress contributed to her uncontrollable asthma. Anamnestic examination suggested that asthma-specific fear induced by disturbed memories and distorted cognitions following frightening asthma attacks were factors driving her asthma exacerbations. A positive outcome of the intervention would be a proof-of-principle observation in support of the notion that PSA may be improved by psychological means in pediatric patients characterized by comorbid psychological stress or distress.

THESIS OUTLINE AND AIMS

The aim of this thesis is to get insight into PSA in children and its treatment from a biopsychosocial perspective. The thesis starts with examining behavioral problems in the child and parenting stress as reported by parents in relation to asthma control and quality of life of the child with asthma, while the following chapters evaluate the effects of multidisciplinary treatment on a broad set of biopsychosocial outcomes.

To clarify which behavioral problems in the child with asthma most severely deviate from normal, and to which extent behavioral problems impact on asthma control and quality of life, *chapter 2* quantifies behavioral problems in a selected group of children and adolescents with asthma from specialized multidisciplinary treatment clinics and examines the association of these problems and quality of life with being or not being classified as difficult-to-treat asthma.
Chapter 3 examines whether the child's behavioral problems at the start of therapy are associated with asthma control and quality of life after multidisciplinary treatment in a high altitude clinic.
The social component of the model is examined in *chapter 4*. Both the occurrence of parenting stress and its association with behavioral problems and disease severity are examined in children with PSA.

Chapter 5 analyzes the effect of multidisciplinary treatment at high altitude on the tapering of corticosteroids. To get an insight into possible factors influencing tapering, this chapter examines whether demographic variables, disease control, and quality of life at treatment entrance could predict the tapering of corticosteroids.

Adequate control of asthma symptoms is problematic in some children with asthma. For them, multidisciplinary clinical treatment in a tertiary care center might be a treatment option. *Chapter 6* evaluates the effects of multidisciplinary treatment of children with asthma in a tertiary clinical setting on biological, psychological, and social outcome variables.

In *chapter 7* cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) focusing on asthma-specific fear and disturbed memories are employed to try to reduce asthma symptoms and its burden in an adolescent with difficult-to-treat asthma. A sequential replicated single-case experimental design with multiple measurements was used for evaluation of therapy effectiveness.

The final *chapter 8* discusses the main findings of this thesis and presents future directions for research and clinical implications.

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Chapter 2

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

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Acknowledgement of author contributions: MV and RG designed the study; MV collected and processed the data; MV, AAK, and RG analyzed the data; EJvdG, LvEZ, and ED interpreted the medical data; MV wrote the paper with input from EJvdG, AAK, LvEZ, ED, and RG.

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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

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.

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

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.

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 $a < .05$ (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

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)	

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.

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.

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).

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.

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 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. 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.

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).

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.[6-8] 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 psychosocial 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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Chapter 3

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

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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 neuroendocrine 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 maneuvers was performed. Short or long acting β_2-adrenergic agonists were stopped at least 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,

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

	Netherlands Asthma Center Davos (n = 51)	High Altitude Clinic Davos (n = 48)	Asthma Center Heideheuvel (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)
Activity	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).

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).

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 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.

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**	
	FEV_1 (% pred)		**FeNO** (ppb)		**ACT**	
Predictor variable	***β***	**Adj R^2**	***β***	**Adj R^2**	***β***	**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	
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]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.

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	β	Adj R^2	β	Adj R^2	β	Adj R^2	β	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]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.

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).

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 se-

vere 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 hypo-allergenic 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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Chapter 4

Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma

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ABSTRACT

Our study examined parenting stress and its association with behavioral problems and disease severity in children with problematic severe asthma. Research participants were 93 children (mean age 13.4 ± 2.7 yrs.) and their parents (86 mothers, 59 fathers). As compared to reference groups analyzed in previous research, scores on the Parenting Stress Index in mothers and fathers of the children with problematic severe asthma were low. Higher parenting stress was associated with higher levels of internalizing and externalizing behavioral problems in children (Child Behavior Checklist). Higher parenting stress in mothers was also associated with higher airway inflammation (FeNO). Thus, although parenting stress was suggested to be low in this group, higher parenting stress, especially in the mother, is associated with more airway inflammation and greater child behavioral problems. This indicates the importance of focusing care in this group on all possible sources of problems, i.e., disease exacerbations and behavioral problems in the child as well as parenting stress.

INTRODUCTION

Asthma, a chronic inflammatory disease of the airways, is common in children and adolescents with a reported worldwide prevalence ranging from 5-15 %.[1] A small portion of pediatric asthma patients (the precise prevalence is unknown) has problematic severe asthma, defined as asthma that is not under control despite optimal treatment.[2] Psychosocial factors may influence disease progression and the psychological status of children with asthma. The focus of this article is on parenting stress in parents of children with problematic severe asthma. Parenting stress is both a potential cause and consequence of the disease status and behavioral problems in children with problematic severe asthma.

Open (family) systems models such as the BioBehavioral Family Model[3, 4] emphasize the interplay between physiological vulnerability, the family and involvement of the child in parental conflict in relation to symptom severity. Parenting stress can exert an influence on the disease through poor treatment adherence,[5] or through physiological stress response systems such as the sympathetic nervous system and the hypothalamic pituitary adrenal axis.[6] In support of the BioBehavioral Family model, in asthmatic children, the child's perception of parental conflict showed trends of association with insecure father-child relatedness and triangulation (indirect communication of one family member with another through a third family member).[3] Moreover, it was observed that these psychosocial systemic variables were associated with respiratory sinus arrhythmia, a measure of vagal activation that may underlie airway obstruction in asthma. Another study showed that children with asthma who simultaneously experienced acute and chronic stress exhibited a 5.5-fold reduction in glucocorticoid receptor mRNA and a 9.5-fold reduction in beta-2 adrenergic receptor mRNA relative to children with asthma without comparable stressor exposure.[7] Thus, stress was associated with physiological factors that play a role in asthma control. To the extent that reduction in glucocorticoid receptor mRNA reflects diminished sensitivity to the anti-inflammatory properties of glucocorticoids and the reduction in beta-2 adrenergic receptor mRNA reflects a reduction of bronchodilatory properties of beta-agonists, this physiological process could explain the increased asthma morbidity associated with stress that has been indicated in children with asthma.[8, 9] This mechanism may be particularly significant in children with problematic severe asthma because resistance to asthma therapy is a feature of problematic severe asthma.

A meta-analytic review suggested that parenting stress is higher in caregivers of children with any chronic illness than in caregivers of healthy children.[10] However, findings about the occurrence of parenting stress in caregivers of children with asthma are equivocal. Most evidence indicates that parenting stress in children with asthma is in the normal range compared to healthy controls and norm reference groups.[11-13] Only in one study parenting stress was found to be slightly higher in parents of children with asthma as compared to parents of children with cystic fibrosis or cancer.[14] The authors suggested that higher parenting stress may follow from the daily demands that are placed on parents from children with asthma and diabetes. This could imply that parenting stress might be relatively high for parents of children with problematic severe asthma. However, the one study on controller medication in children with persistent asthma observed normal parenting stress levels.[15]

An innovative aspect of our study is that it uniquely focuses on problematic severe asthma, which is characterized by longer periods of unstable asthma, lower forced expiratory flow in 1 second (FEV_1), higher dose of inhaled steroids and more severe airway obstruction at the time of referral to a specialist.[2] Since problematic severe asthma comprises difficult-to-treat asthma and therapy resistant asthma, it represents the most severe group of asthmatic children. Parenting stress in caregivers of children with problematic severe asthma has not been investigated. Knowing the severity of parenting stress in this group is important because parenting stress may play a role in perseverance of asthma. Moreover, if the hypothesis of high parenting stress is also not verified in parents of children with problematic severe asthma (PSA), it indicates that parenting stress is likely not a factor playing a role in the persistence of PSA. We expected that parenting stress would be high in this group considering the great concern and responsibility of parents for children with problematic severe asthma.

Regarding the interplay between parenting stress and asthma severity, some previous studies in asthma did indicate that greater parenting stress was associated with higher asthma severity,[8, 16] poorer illness management, poorer adherence to medication,[17] and poor house dust mite control.[18] Moreover, it has been indicated that negative life events increase the risk of children's asthma attacks[19] and that caregiver stress predicts wheeze in early childhood.[20] However, other studies concluded that age of asthma onset, peak flow variability, and illness severity were unrelated to general parenting stress[12, 21] or even that greater parenting stress was correlated with greater medication (inhaler) adherence.[13] Thus,

studies of the association between asthma severity in children and parenting stress have not yielded uniform results.

Our previous study observed that, as compared to healthy reference groups, children and adolescents with problematic severe asthma had more internalizing behavioral problems such as being withdrawn/depressed and more severe somatic complaints.[22] Parental stress is a potential determinant of behavioral problems in the children as indicated by a study that observed a correlation between a negative family emotional climate and child internalizing symptoms.[23] As yet, however, in children with problematic severe asthma, the association of parenting stress with the child's behavioral problems has not been studied.

The aim of the current study was to examine the presence of parenting stress as related to the parent's own functioning and the functioning of the child in a sample of children with problematic severe asthma, and to examine the relation of parenting stress with disease severity and behavioral problems in their children. We hypothesized that the level of parenting stress is higher than in the general population and that parenting stress is associated with asthma severity and behavioral problems in their children.

METHODS

Study population

A cross-sectional study examined Dutch children and adolescents with asthma before the start of inpatient treatment in a high altitude asthma clinic with a hypo-allergenic environment in Switzerland, the *Merem Netherlands Asthma Center Davos (NAD)*, or an asthma clinic at sea level in the Netherlands, the *Merem Asthma Center Heideheuvel (ACH)*. These clinics were chosen because both are referral centers for children and adolescents with problematic severe asthma.[2, 24] As described in detail previously,[25] patients are admitted to the clinics when they have persistent symptoms as certified by a specialized pulmonologist (according to Global Initiative for Asthma 2012 criteria) despite treatment in step 3 (i.e. double dose of inhaled steroids and/or need for additional long acting beta-2 agonists or leukotriene receptor antagonist) or higher.[26] Although a reduction in forced expiratory volume in 1 second (FEV_1) supports the diagnosis of problematic severe asthma, many children with severe, therapy-resistant, asthma have normal spirometry in asymptomatic periods.[24] Allergy for one or more inhaled allergens and eczema or other presentations of the atopic syndrome are

commonly present. The reason for referral to one of the centers by the local or academic pediatric pulmonologist is the instability of the asthma and comorbidity such as allergic rhinitis, eczema, dysfunctional breathing and psychosocial problems. This needs an intensive multidisciplinary approach to therapeutically target these problems. A standard diagnostic program is performed with somatic and psychosocial investigations.[27] Both clinics provide highly integrated multidisciplinary treatment programs of 1 to 3 months duration. The children participate in a group psycho-educational asthma program that aims to increase knowledge, technical skills (inhalation technique), and coping strategies. Moreover, they have individual therapeutic contacts with a pediatric pulmonologist or pediatrician, pulmonary nurse, physical and sports therapist, pedagogical worker, psychologist, and social worker. 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 live in a hypo-allergenic environment due to a lower concentration of pollen and almost complete absence of house dust mite.[28] 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 that are treated in the Netherlands are at home every weekend.

Figure 1 shows the flow chart of the study. Of the 93 children in this study, 39 were from NAD and 54 from ACH. In the NAD population, 47 children were eligible for inclusion, 39 (83 %) were included; one child did not provide informed consent, seven did not return all questionnaires. Of the 62 children of ACH, 54 children were included (87 %); two children did not provide informed consent and 6 did not return all questionnaires. Eighty-six mothers and 59 fathers of the 93 children completed the PSI/NOSI-questionnaire; with 57 complete dyads.

From 2010-2012, all children aged 7-18 years who were referred to one of the two tertiary clinics because of problematic severe asthma were invited to participate in the study. The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. All parents and children aged 12 and older provided written consent, children younger than 12 provided oral assent.

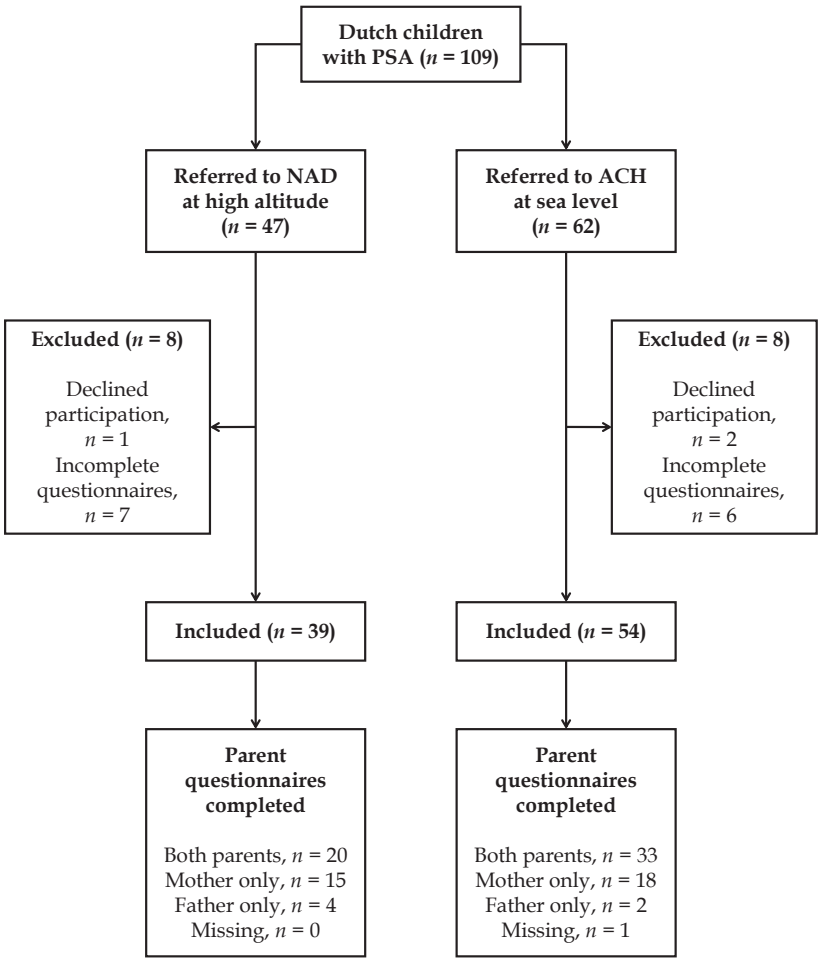

Figure 1. Flowchart

Procedure

Two weeks before the start of clinical treatment in one of the specialized asthma clinics, the patients and parents received questionnaires at their homes. Medical history and physical examination were performed on the day of arrival by the pediatrician. Medical history included atopic symptoms, exercise intolerance, medication, reliever therapy and adherence as derived from the clinical interview. Pulmonary function testing was performed.

Instruments

Descriptive variables

Demographic variables that were measured in the children were gender and age. For both parents, age, country of birth, relational status, number of children, chronic illness and education level were measured.

Parenting Stress Index (PSI/NOSI)

The Parenting Stress Index (PSI/NOSI) assesses the multidimensionality of parenting stress including such aspects as emotional distress in the parenting role, the parent's ability to cope with the task of parenting and the parents' perceptions of the child's demands.[29] We used the Dutch adapted version of the PSI, the "Nijmeegse Ouderlijke Stress Index,"[30] which is named PSI/NOSI in this paper. This self-report inventory measures parenting stress using 123 items divided into two major domains of 13 subscales. The "parent domain" that refers to perceived stress regarding family factors includes seven subscales: Sense of competence (e.g., "Parenting this child is more difficult for me than I expected"), Restriction of role (e.g., "I often get the feeling that my child needs to control my life"), Attachment (e.g., "I find it difficult to understand what my child wants or needs from me"), Depression (e.g., "Sometimes, I am so tired in the morning, that I don't feel like getting up to take care of my children"), Parent's health (e.g., "I had more health complaints in the past 6 months than normally"), Social isolation (e.g., "I feel alone and have no friends"), and Relationship with spouse (e.g., "My partner and I often disagree on how to manage our child"). The "child domain" that refers to stress evoked by their child's behavior and emotions contains six subscales: Adaptability (e.g., "My child gets upset in unexpected situations"), Acceptability (e.g., "It is difficult for me to accept my child as it is"), Demandingness (e.g., "Compared to other children, my child demands more of me"), Mood (e.g., "My child is often bad-tempered"), Distractibility-hyperactivity (e.g., "It is very difficult to my child to sit still for a period"), and Reinforcement to the child (e.g., "I often get the feeling that my child does not like me"). The items are scored on a six-point Likert-scale ranging from "totally disagree" = 1 to "totally agree" = 6.

The internal consistency reliability of the total parenting stress score in the clinical and non-clinical population is good (Cronbach's alpha = .94).[30] Concurrent validity ranges from "satisfactory" to "good" and discriminant validity is considered adequate.[30] Cronbach's alpha in our study sample showed good internal consistency reliability for the total parenting stress score in mothers (α = .92) and

fathers (α = .89), the parent domain mothers α = .89, parent domain fathers α = .87, child domain mothers α = .89, and child domain fathers α = .91. Cronbach's alpha for the subscales ranged from α = .84 ("Depression" of parent domain mothers) to α = .91 ("Reinforcement to the child" of child domain fathers). In the analyses, we used the domain scores (parent and child domain) for fathers and mothers separately.

The life events scale is part of the Dutch version of the PSI/NOSI. It consists of 40 life events. Respondents answered with "yes" or "no" to the question whether a life event occurred within the family during the past 12 months, such as divorce, discharge, debts, miscarriage, and bereavement. There was no psychometric evaluation available. The total sum score of life events was used in analysis (theoretical range 0-40).

Parental report: The Child Behavior Checklist (CBCL)

The CBCL is a standardized questionnaire that uses ratings by parents or caregivers to assess emotional and behavioral problems of children and adolescents.[31] Parents of the children and adolescents filled out the Dutch version of the CBCL (6-18 years).[31] The CBCL consists of 120 items to which participants respond on a 3-point Likert scale comprising 0 = "Not at all," 1 = "Somewhat or sometimes," and 2 = "Obvious or often." Results of the CBCL are expressed in a global score (120 items, range 0-240) and in scores for the domains internalizing (32 items, range 0-64) and externalizing (35 items, range 0-70) behavioral problems. Internalizing behavioral problems include the syndrome domains anxious/depressed, withdrawn/depressed and somatic complaints. Externalizing behavioral 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.

In all analyses CBCL *T*-scores were used. Higher scores indicate more behavioral problems. A *T*-score of 63 (90th percentile in the norm population) demarcates the clinical range, which is an indication that a child has clinically relevant symptoms and might need professional help. The Dutch version of the CBCL showed adequate psychometric values and good reliability.[31] Cronbach's alpha coefficients in our study sample were .87 for the total CBCL score (eight scales), .74 for internalizing behavioral problems (three scales), and .57 for externalizing behavioral problems (two scales).

Children's self-report: Asthma control

The childhood asthma control test (ACT)[32, 33] assesses the control of asthma at the moment of measurement, e.g., "How is your asthma today?", "How much of a problem is your asthma when you run, exercise, or play sports?", "Do you cough because of your asthma?", and "Do you wake up during the night because of your asthma?". The child completes these items using a 4-point response scale, with lower scores indicating poorer control. The summated total score ranges from 0 to 12.

Lung function

Pulmonary function testing was performed using the Masterscreen (Jaeger®, CareFusion Corporation). Children performed a maneuver of forced exhalation in a mouthpiece that was connected to a spirometer. According to the standardized protocol at least 3 technically correct maneuvers had to be performed. Short or long acting β_2-adrenergic agonists were stopped at least 12 hours before testing. The lung function parameter that was obtained and evaluated was forced expiratory volume in 1 second (FEV_1). Lung function measures were plotted in a reference set and expressed as percentage of the predicted (% predicted) value at this age, weight and height. In children, in between asthma attacks, even in severe asthma, lung function is often within a normal range of 80 to 120 % predicted. Sequential measurements are a valuable tool to evaluate change in bronchoconstriction in individual children with asthma; however, FEV_1 measures are not a valid variable to indicate individual differences. Therefore, no correlations between FEV_1 and parenting stress were computed.

Airway inflammation was measured with the NIOX®Flex Nitric Oxide Monitoring System (Aerocrine AB, Solna, Sweden) using the fractional concentration of exhaled nitric oxide (FeNO) according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.[34] Children exhaled quietly in a mouthpiece that was connected to an analyzer. A higher fraction of exhaled nitric oxide denotes more eosinophilic inflammation.[35] Eosinophils are blood cells that play an important role in the inflammatory response that finally leads to bronchoconstriction in allergic asthma. Normal values in children range from 10 to 25 parts per billion.

Statistical analysis

Statistical analyses were performed with SPSS 20 and Mplus 6.1.[36] The score distributions were checked for outliers and normality.

PSI/NOSI scores were categorized in classes derived from a Dutch non-clinical reference population.[30] In this non-clinical population of 161 mothers and fathers, 35, 30 and 35 % of the parents were classified to have lower than average [PSI/NOSI cut score: ≤ 226 for mothers and ≤ 214 for fathers], average [≤ 292 for mothers and ≤ 270 for fathers] and higher than average [≥ 293 for mothers and ≥ 271 for fathers] levels of PSI/NOSI parenting stress scores. Higher scores correspond to more parenting stress.

Moreover, Cohen's effect size estimates (d) were calculated for each parent using the mean and standard deviation of this non-clinical population[30] as reference values. The interpretation of these effect sizes is as follows: $0.2 \leq d < 0.5$ indicates a small effect, $0.5 \leq d < 0.8$ a medium effect, and $d \geq 0.8$ a large effect.[37] Since some effect sizes had skewed score distributions, deviations from the non-clinical reference groups were examined with the nonparametric one-sample Wilcoxon signed rank test. Pearson correlations were computed to reflect the univariate associations between the variables of interest.

Path analysis or structural equation modelling (SEM) was used to examine whether the parent variables, life events, and the child variables, internalizing behavioral problems, externalizing behavioral problems, and FeNO, were associated with the four measures of parenting stress, i.e., with mothers' and fathers' responses to PSI/NOSI parent domain items and child domain items. The advantage of SEM is that it accounts for the shared variance resulting from mothers and fathers reporting on the same child. A disadvantage of SEM is that it requires relatively large sample sizes.

To deal with this issue, the results were tested in two steps, starting with the usual approach using the maximum likelihood estimator robust to non-normality (MLR). The MLR estimation results in the same parameter estimates as maximum likelihood estimation (ML) but Chi Square is corrected for non-normality.[38] To deal with missing observations of either the mother or the father, full information maximum likelihood (FIML) was used to estimate these missing values, which allows the use of all available information.

In the next step, the same model was re-analyzed using the Bayesian estimator. The Bayesian approach is more appropriate to deal with small sample sizes and the underlying non-normal distribution of the data.[39, 40] Model fit was evaluated using the Chi Square statistic and three model fit indices: the Tucker Lewis Index (TLI), the comparative fit index (CFI), and the root mean square error of ap-

proximation (RMSEA).[41] Conventional guidelines suggest that model fit indices TLI and CFI between .80 and .90 and RMSEA between .05 and .08 represent a moderately fitting model, whereas TLI and CFI values >.90 and RMSEA <.05 represent good model fit. Chi Square should preferably be non-significant.[41]

Re-estimation of the model with the Bayesian estimator provides posterior estimates, the posterior *SD* and the 95 % asymmetric credibility intervals of this model. Credibility intervals, the Bayesian counterpart of the confidence intervals, offer information about the robustness of the findings. We used the default prior settings of the software (i.e., uninformative priors). The Bayesian estimator uses multiple chains and iterations to attain a stable posterior distribution.[39] The chain can start at any arbitrarily chosen point and iterates many times until it appears as coming from the target distribution. In this study, the starting values were based on the results from the MLR model, then 20,000 iterations were used with 15 chains to decide if the chains had reached their stationary distribution or desired posterior. The first 50 % of the iterations were ignored (i.e. burn-in phase) in the computation of the posterior to avoid any influence of the arbitrary chosen starting values. Convergence was assessed using the potential scale reduction (PSR) convergence criterion.[42] This criterion compares the variances within each chain and the variance between chains. Large deviations between the variances are indicative for non-convergence. The PSR was estimated to be < 1.02 of 50 % of the total number of iterations. This shows good convergence properties. Also all trace-plots were visually inspected for non-convergence. Trace-plots are useful in assessing convergence as it shows if the chain is mixing well and if the chain has reached stationarity when there is a relatively stable mean and variance. The trace-plots in this study were all doing well. The model was re-analyzed using twice as many iterations and the posterior estimates did not differ indicating convergence was reached.

RESULTS

Characteristics of the 93 children and adolescents

Table 1 shows the characteristics of the 93 children and adolescents with a complete data set. The mean FEV_1 measurement was in the normal range. Mean FeNO was slightly elevated (normal values range from 10 - 25 ppb). Overall, the mean for CBCL *T*-scores fell in the normal range, but for this sample of children with asthma: 29.4 % scored in the borderline clinical significant range on the total problem score (*T*-score ≥ 60; 84th percentile); 39.1 % in the borderline clini-

Table 1. Characteristics of the 93 children and adolescents

	Children *n* = 93
Female, number (%)	48 (51.6 %)
Age of child, mean (*SD*), range yrs	13.4 (2.7) 7-18
Behavioral problems (CBCL), mean *T*-scores (*SD*)[1]	
Total score	53.7 (9.7)
Internalizing	57.1 (9.7)
Externalizing	48.5 (10.1)
Lung function	
FEV_1 (*SD*) [2]	100.9 (15.5)
FeNO (*SD*) [3]	28.5 (25.6)
Control of asthma (ACT) [4]	
Total child score (*SD*)	6.1 (2.5)

[1] CBCL = Child Behavior Checklist (*T*-score ≥ 63; 90th percentile = clinical significant range; a higher score reflects more problems). [2] FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted (% pred). [3] FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb; normal range 10-25 ppb; a higher value corresponds with more eosinophilic inflammation). [4] ACT = Childhood Asthma Control Test (range 0-12; a higher score reflects better control).

cal significant range for internalizing behavioral problems; and for externalizing behavioral problems, 16.3 % fell within that range. On average, ACT scores reflected poor control of asthma.

Characteristics of the 145 parents

Table 2 shows the characteristics of the 145 fathers and mothers of the 93 patients before treatment in one of the two treatment centers. The number of parents with a chronic illness was high; 39.8 % of the children had at least one parent with a chronic illness, mostly a lung disease. Of the life events, events within the family (birth, divorce, death, and so on) were most frequently reported by the fathers and mothers.

Parenting Stress Index (PSI/NOSI)

Using the categories derived from a non-clinical population,[30] more than half of the fathers and mothers of our sample reported parenting stress scores reflecting lower than average levels of parenting stress (Table 3), while 15 to 20 % obtained higher than average levels of parenting stress. In Table 4, columns 2 and 10 show the median of effect size deviation scores of the parents on parenting stress as compared to the reference scores of a non-clinical population of 161 mothers and 84 fathers.[30] The scores (*d*) reflect the difference in standard deviation units

Table 2. Characteristics of the parents of the 93 children and adolescents

Total group fathers and mothers	***n* = 145**	
Relational status (%)		
Married and living together	76.3 %	
Living apart together	2.2 %	
Divorced and living apart, single	21.6 %	
Widowed	0 %	
Mean number of children per family (*SD*)	2.43 (.88)	
Mean number of children per age category (*SD*)		
Age < 4	.08 (.30)	
Age 4-12	.82 (.88)	
Age 12-18	1.25 (.87)	
Age > 18	.27 (.71)	
Child with parent with chronic illness, *n* (%)	37 (39.8 %)	
	Mothers, *n* = 86	**Fathers, *n* = 59**
Parent with chronic illness, *n* (%)	26 (30.2 %)	18 (30.5 %)
Lung disease, *n*	15	12
Rheumatic disease, *n*	3	0
Diabetes, *n*	1	0
Cardiovascular disease, *n*	1	2
Psychiatric or psychological, *n*	1	0
Other disease, *n*	7	5
Age, mean (*SD*)	42.6 (4.6)	45.0 (5.5)
Country of birth		
Netherlands/ unknown/other country (*n*)	77/1/8	56/0/3
Education level [1]		
Low/middle/high (*n*)	14/53/19	8/29/22
Life events [2]**,** mean (*SD*) range	2.2 (1.9) 0-7	2.0 (2.0) 0-8

[1] Education level, "Low": Primary school or lower vocational secondary education, "Middle": intermediate general secondary education or intermediate vocational education, and "High": higher general secondary education, higher vocational education, or university education.
[2] The Life Events Scale included 40 life events.

between the observed scores of the parents of children with asthma (our sample) and the parents of the non-clinical population, and thus are Cohen's *d* effect sizes. Overall, the parents of children and adolescents with asthma reported less parenting stress than the non-clinical reference group: most effect sizes were medium to large. On the total PSI/NOSI-score, mothers showed a large deviation ($d = 0.8$, $p < .001$) and fathers a medium deviation ($0.5 \leq d < 0.8$, $p < .001$) from the non-clinical reference group.

Table 3. Percentages of mothers and fathers of children with asthma reporting lower than average, average, and higher than average levels of parenting stress as compared to parents from a non-clinical population

	Percentages		
PSI/NOSI scale	**Lower than average**	**Average**	**Higher than average**
Mothers (n = 86)			
Parent domain total score	55.8	30.2	14.0
Child domain total score	54.7	29.1	16.3
Total score	58.1	27.9	14.0
Fathers (n = 59)			
Parent domain total score	52.5	32.2	15.3
Child domain total score	55.9	23.7	20.3
Total score	54.2	25.4	20.3
Non-clinical population (n = 245)			
Total score	35	30	35

PSI/NOSI Parenting stress index

The deviation of the total score of parenting stress (parent domain) was medium for mothers and fathers ($0.5 \leq d < 0.8$, $p < .001$). On the stress evoked by their child's behavior and emotions (child domain), mothers showed a medium deviation ($0.5 \leq d < 0.8$, $p < .001$) and fathers a large deviation ($d \geq 0.8$, $p < .001$) from the non-clinical reference group.

On most subscales of the parent domain, both mothers and fathers showed a medium to large deviation from the reference comparison group in the direction of lower levels of stress, especially with respect to "sense of competence," "attachment," "depression," "parent's health," and "social isolation." On the child domain subscales, deviations were large for "reinforcement to parent" (mothers) and "mood" (fathers) and medium for "acceptability" (mothers), "distractibility-hyperactivity" (fathers) and "reinforcement to parent" (fathers). Because our design lacked a matched control group and the parenting stress of our study group was unexpectedly low as compared to parenting stress in the non-clinical reference group, we decided to compare the parenting stress scores to scores of other clinical and non-clinical samples that used the Dutch version of the PSI/NOSI (Table 4). Compared to the Dutch reference scores of the clinical sample of the PSI/NOSI (mothers n = 68, fathers n =40),[30] effect size deviations were even larger than the deviation from reference scores of the non-clinical population (see Table 4). Compared to a study sample of parents with children with enuresis (n =78, aged 5-13 years) using the PSI/NOSI,[43] our study sample

Table 4. Medians of effect sizes (*d*-scores) of the parenting stress index (PSI/NOSI) of mothers and fathers of the current sample compared to a non-clinical sample of the original validation article[30] and the mean scores of the current sample, the non-clinical and clinical samples of the original validation article, and samples of children with and without enuresis[43] and with normal weight and overweight[44]

	Mothers *n* = 86								Fathers *n* = 59					
PSI	**Median effect size deviation**	**Current sample**	**Non-clinical sample[a]**	**Clinical sample[a]**	**Children with enuresis[b]**	**Children without enuresis[b]**	**Normal weight group[c]**	**Overweight group[c]**	**Median effect size deviation**	**Current sample**	**Non-clinical sample[a]**	**Clinical sample[a]**	**Children with enuresis[b]**	**Children without enuresis[b]**
Parent domain														
Total score	−.71**	98.2 (30.8)	121.0 (34.9)	151.8 (42.6)	125.4 (45.1)	102.3 (35.4)	113.6 (34.9)	125.7 (40.1)	−.79**	92.5 (28.7)	108. 1 (28.1)	128.0 (37.2)	110.1 (36.6)	92.2 (31.1)
Sense of competence	−1.1**	21.4 (6.7)	29.4 (9.1)	38.1 (11.2)	27.4 (11.1)	20.8 (9.3)			−.96**	20.8 (7.2)	25.9 (7.2)	32.3 (9.2)	23.5 (10.4)	18.0 (7.6)
Restriction of role	−.40*	13.4 (6.1)	14.3 (5.8)	16.9 (7.2)	17.1 (7.6)	13.6 (6.1)			−.62*	12.2 (6.0)	13.1 (5.0)	16.0 (7.0)	16.1 (7.1)	12.2 (6.0)
Attachment	−1.0**	9.4 (3.0)	12.3 (4.3)	16.5 (5.3)	15.0 (3.5)	13.3 (2.8)			−1.1**	9.9 (3.4)	12.2 (3.7)	14.6 (5.5)	14.6 (3.5)	13.3 (2.7)
Depression	−.81**	19.5 (7.6)	26.8 (9.6)	33.4 (11.1)	25.2 (10.7)	20.3 (8.7)			−.85**	17.7 (5.4)	21.6 (6.6)	25.5 (9.7)	19.8 (7.0)	17.8 (6.4)
Parents health	−.52*	11.9 (5.6)	13.6 (5.0)	15.8 (6.2)	14.2 (6.7)	11.5 (5.3)			−.38*	10.1 (3.7)	11.4 (3.7)	13.1 (4.7)	11.3 (5.2)	9.6 (4.1)
Social isolation	−.90**	9.1 (4.1)	10.8 (4.2)	11.8 (4.8)	11.6 (5.3)	9.3 (4.2)			−.72*	9.5 (4.5)	11.4 (4.7)	11.1 (5.2)	11.3 (4.8)	9.1 (4.0)
Relationship with spouse	−.22	13.4 (6.4)	13.5 (6.8)	19.0 (8.9)	15.0 (8.2)	13.5 (7.2)			−.27	12.2 (6.7)	12.2 (4.4)	14.4 (6.8)	13.6 (6.1)	12.3 (7.1)
Child domain														
Total score	−.78**	126.1 (40.6)	145.3 (37.3)	201.1 (43.1)	152.5 (53.2)	119.2 (34.5)	144.6 (49.6)	151.9 (49.8)	−.87**	121.5 (39.1)	142. 2 (37.1)	186.2 (42.0)	141.1 (43.0)	111.1 (27.1)

Table 4. (continued)

	Mothers $n = 86$								Fathers $n = 59$					
PSI	**Median effect size deviation**	**Current sample**	**Non-clinical sample[a]**	**Clinical sample[a]**	**Children with enuresis[b]**	**Children without enuresis[b]**	**Normal weight group[c]**	**Overweight group[c]**	**Median effect size deviation**	**Current sample**	**Non-clinical sample[a]**	**Clinical sample[a]**	**Children with enuresis[b]**	**Children without enuresis[b]**
Adaptability	−1.20**	25.1 (10.9)	32.3 (8.6)	42.2 (10.2)	30.8 (12.0)	26.2 (8.7)			−1.2**	25.0 (10.2)	32.4 (8.7)	41.5 (10.0)	28.3 (9.2)	24.5 (6.5)
Acceptability	−.74**	18.9 (6.5)	22.6 (7.6)	32.6 (9.5)	23.3 (10.5)	16.9 (6.2)			−.46*	19.0 (6.7)	21.2 (7.0)	28.3 (9.3)	21.3 (9.0)	15.8 (4.7)
Demandingness	−.14	21.5 (8.5)	20.8 (7.3)	32.5 (8.0)	24.7 (11.6)	16.6 (7.5)			−.52	20.6 (8.8)	20.3 (6.4)	29.4 (9.7)	21.5 (9.5)	15.0 (6.0)
Mood	−.75**	18.5 (9.0)	21.7 (7.6)	30.6 (9.0)	24.2 (9.2)	20.3 (6.4)			−1.0**	16.5 (7.4)	20.7 (6.7)	28.0 (7.8)	22.7 (7.1)	18.7 (5.2)
Distractibility-Hyperactivity	−.46*	28.1 (9.5)	30.6 (11.0)	42.7 (11.5)	33.8 (13.0)	25.4 (9.4)			−.65**	25.6 (7.7)	31.0 (10.7)	40.5 (11.8)	32.1 (10.1)	24.6 (8.7)
Reinforcement to Parent	−.83**	14.03 (4.7)	17.3 (5.2)	20.7 (6.2)	15.9 (5.8)	13.8 (4.8)			−.55*	14.8 (5.9)	16.6 (4.7)	18.5 (4.9)	15.2 (5.4)	12.6 (4.1)
Total score	−.81**	224.3 (66.9)	266.5 (66.9)	353.2 (78.5)	277.9 (91.3)	221.5 (65.0)	258.3 (78.7)	277.6 (11.5)	−.67**	214.0 (64.6)	250.4 (60.7)	314.5 (72.1)	251.1 (74.9)	203.3 (54.3)

[a] Reference population scores of the PSI/NOSI.[30]

[b] Population scores of 78 children with enuresis vs 110 without enuresis,[43] wherein parenting stress was measured with the PSI/NOSI.

[c] Population scores of 100 children with overweight and 97 with normal weight,[44] wherein parenting stress of mothers was measured with the PSI/NOSI.

The effect size (*d*) reflects the magnitude of deviation from the non-clinical reference population in standard deviation units; a negative score indicates that the parents of children with asthma are judged to have less stress than the reference population. The *d* values have the following common effect sizes: values smaller than 0.2 reflect no deviation from the reference population; values between 0.2 and 0.5 reflect small deviations; values between 0.5 and 0.8 reflect medium deviations; and values greater than 0.8 reflect large deviations. The significance of these median effect size deviations from the non-clinical reference population were tested using one-sample Wilcoxon signed rank tests.

A significant score reflects that the number of parents with lower scores than the mean score of the reference population exceeds chance; * $p < .05$, ** $p < .001$. The significance of differences between the mean parenting stress scores of the current sample and other samples is reported in the text.

*SD*s associated with means are shown in parentheses.

showed significantly less parenting stress in fathers and mothers on all domains ($p < .001$). The population of our study was comparable with the control group without enuresis ($n = 110$, aged 5-15 years) in this study[43] on all domains in mothers: parent domain ($t = -1.24$, $p = .22$), child domain ($t = 1.57$, $p = .12$) and total score ($t = .38$, $p = .70$). The same was true for the fathers parent domain ($t = .09$, $p = .93$) and total score ($t = 1.27$, $p = .21$), while the fathers of the current sample scored significantly higher than the fathers of the control group without enuresis on the child domain ($t = 2.04$, $p = .046$). Compared with a cross-sectional study of 197 families with children with normal weight ($n = 97$) and overweight ($n = 100$) aged 6-14 years,[44] our study sample showed significantly less parenting stress in mothers on all domains ($p < .001$).

Path analysis examining variables associated with parenting stress

In the first step of path analysis, associations of parental life events, child internalizing behavioral and externalizing behavioral problems, and FeNO with parenting stress reported by both the mother and father were examined. The model included 93 families of which 57 reports from both mother and father were available. The model using MLR estimation showed the five variables to be statistically significantly related to parenting stress and provided a moderate to good fit ($\chi^2 = 6.99$, $df = 4$, $p = .14$; RMSEA = .09; CFI = .99; TLI = .91). The model using Bayes estimation showed the same results excluding the associations of externalizing problem behavior with maternal parenting stress and of FeNO with the child domain of parenting stress as reported by mothers that did no longer reach statistical significance. As the credibility interval did not include zero in any of the estimated parameters, it can be concluded that the results reflect robust findings.

The Bayesian outcomes are presented in Figure 2, which shows paths that were significant using the Bayesian analysis that adjusts for small sample size. Attached to each path are four associated numerical values: the posterior estimate with significance level; the *SD* linked to that posterior estimate; and the lower and upper 95 % asymmetric credibility intervals for that path in this model. For example, the uppermost path in Figure 2 shows that, the path from FeNO to parenting stress of the mother (parent domain) was significant at the .05 level; the posterior estimate = .22, with *SD* = .06, and 95 % credibility interval ranging from .03 to .39. For the model as a whole, the 95 % credibility interval for the difference between the observed and the replicated Chi-square values was estimated to be −23.98 to 38.46, and the posterior predictive *p*-value was .34, both indicating a good posterior-predictive model fit. A higher score on internalizing

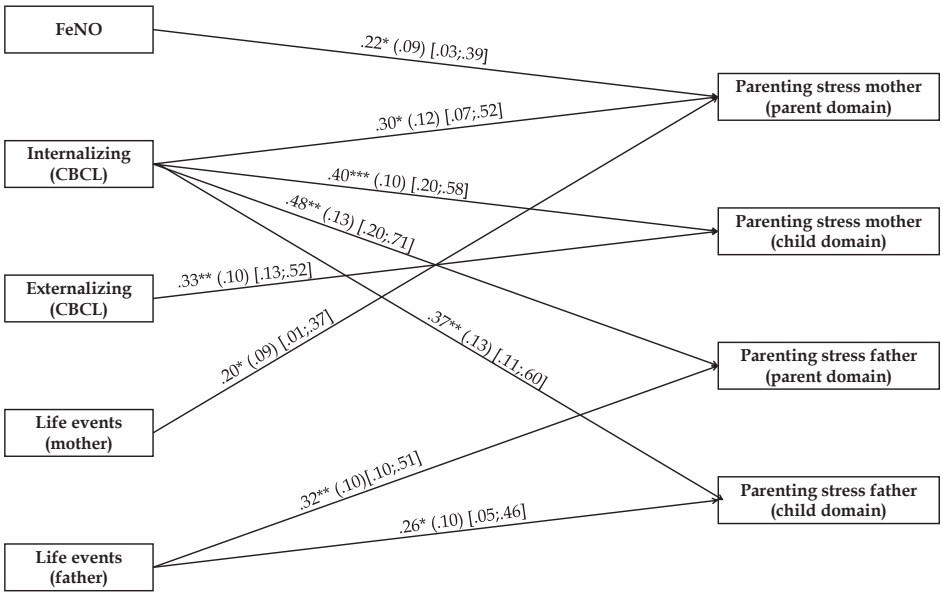

Figure 2. Associations of airway inflammation (FeNO) of the child, internalizing and externaling behavioral problems of the child, and life events of the parents with parenting stress. The posterior estimates, the posterior *SD* and the 95 % a-symmetric credibility intervals of the model are given. **p* < .05, ***p* < .01, ****p* < .001

behavioral problems of the child was associated with more parenting stress in all parenting stress domains. More externalizing behavioral problems were associated with higher parenting stress scores in the child domain reported by the mother. Regarding lung function assessment, the FeNO indication of greater inflammatory activity in the child was associated with higher maternal parenting stress. The association between FeNO and the child domain as reported by the mother fell just short of significance in the model when other relationships were taken into account, and yielded the following estimate: .16 (.08) [−0.00; .33], $p = .052$. Finally, life events of the parents were associated with higher parenting stress scores in the mother domain whereas in fathers, it was associated with both the parent and child domain.

The Pearson correlations of the variables that were tested in path analysis are shown in Table 5. The significance of the univariate correlations (not corrected for other variables) largely reflect the adjusted estimates as calculated in the path analysis.

Table 5. Univariate Pearson correlations (and *p*-values) between the variables

	Internalizing behavioral problems	Externalizing behavioral problems	FeNO (ppd)	Life events
Mothers' observation				
Parent domain	.47 ($p < .001$)	.43 ($p < .001$)	.20 ($p = .06$)	.29 ($p = .007$)
Child domain	.62 ($p < .001$)	.61 ($p < .001$)	.13 ($p = .23$)	.28 ($p = .009$)
Fathers' observation				
Parent domain	.40 ($p = .002$)	.13 ($p = .34$)	.04 ($p = .78$)	.28 ($p = .03$)
Child domain	.51 ($p < .001$)	.45 ($p < .001$)	.03 ($p = .84$)	.27 ($p = .04$)

FeNO fractional concentration of exhaled nitric oxide, *ppb* = parts per billion.

DISCUSSION

This study examined parenting stress in parents of children with problematic severe asthma and the association of parenting stress with behavioral problems and disease severity in their children. To our knowledge, this is the first study that observed a significant association between parenting stress and airway inflammation in this group of children beyond the well-established association between parenting stress and behavioral problems of the child. Moreover, the comparison with samples from previous research suggested that both in mothers and fathers, parenting stress scores were on average low showing a medium to large deviation from a non-clinical reference group.

In accordance with our hypothesis, higher levels of parenting stress were associated with the observation of more behavioral problems in their children. This is in agreement with previous studies of children with asthma,[4, 6, 23] cystic fibrosis[45] and other chronic diseases (cancer, arthritis, diabetes and sickle cell disease) as indicated in a recent systematic review.[10] Higher levels of parenting stress have been found to be related to lower psychosocial well-being[46] and more externalizing problems,[47] internalizing problems[48] and depressive symptoms[49] in the child. Our cross-sectional data do not establish causality. Likely the relationship between parenting stress and child behavioral problems is bidirectional, which can lead to an upward cycle that has negative consequences for both parent and child, i.e., higher levels of parental stress may increase a child's behavioral problems, and the child's increased behavioral problems may increase parental stress.[50, 51] It is in agreement with open systems models that parenting stress and the child's behavior affect one another.[4, 52, 53] The association between parenting stress and behavioral problems in the child

indicates the importance of a family approach to deal with problems of both the parent and the child.

A main finding of our study is that parenting stress in mothers was associated with airway inflammation of their children as measured by FeNO, which confirms our hypothesized relation between parenting stress and asthma severity in the child with problematic severe asthma. Two possible interpretations of the correlation between parenting stress and FeNO exist. First, as psychosocial stressors may trigger the expression of asthma,[9] parenting stress of the mother may lead to stress in the child that is a possible vulnerability factor for inflammation through neuro-endocrine and immune mechanisms. A second possible explanation is that recurrent episodes of inflammation are especially difficult to handle by the mother. It is a common finding that mothers as compared to fathers are more distressed by negative life events happening to their child, be it a disease or accident[54, 55] and use other ways of coping.[56] It is conceivable that particularly in mothers of children with problematic severe asthma, more frequent episodes of inflammation in the child lead to increased helplessness, negative emotions, and other aspects of stress. Longitudinal studies are needed to examine the directionality of the association between episodes of exacerbation in the child and parenting stress in mothers.

Our study lacked a matched control group of parents. Comparison with all available samples using the PSI/NOSI indicated that levels of parenting stress in parents of tertiary treated children with problematic severe asthma are low, suggesting that raising a child with problematic severe asthma does, in general, not necessarily lead to enhanced parenting stress. This low level of parenting stress is surprising, because parenting stress may depend –among other influences– on the child's problems and caregiver demands,[57] which are higher in our group than in the general population.[22] Although results of previous studies were not uniform, our hypothesis, guided by the BioBehavioral Family Model, was that parenting stress in our population would be high instead of low. Afterwards, it is possible to mention some complementary explanations that may explain the low levels of parenting stress observed in the current study. According to the stress-appraisal model, parenting stress is not only determined by the severity of stressors but also by one's capability to deal with stressors.[58] In general, this group of parents may have learned to cope well with the disease of their child and have grown accustomed to their way of living and caring for their child. However, this would not explain why parenting stress for parents in our sample was lower than in reference groups whose children were not suffering

from severe chronic disease. One possible way to understand this unexpected finding is by turning to concepts that assume stressors can have positive as well as negative consequences, as described under such headings as positive reappraisal,[59] positive reinterpretation,[60] and benefit finding or growth.[61] Some parents described caring for a chronic disabled child as a "commitment" that gave their life content and meaning[62] or the feeling of achieving a mission in life.[63, 64] Thus, besides being a possible source of stress, caring for a child with a chronic illness like asthma may be a means to discover and create meaning and purpose in life, or it may increase the bond between parents and between the parents and the child. These ad hoc speculations should be further investigated in research.

Besides the possible explanations mentioned in the previous paragraph, also the specific population and moment of measurement may have played a role. The children in this study were on average 13 years old. At this age, children may be better able to communicate their health problems and take care of themselves than children who are younger. Parents of younger children may report higher levels of parenting stress as found in studies of parents of children under the age of five with asthma symptoms; these parents reported feeling frightened, helpless, frustrated, uncertain, vulnerable, and worried by symptoms that seem never to end.[65] Furthermore, the timing of the measurement, right before the start of treatment, when the child was already accepted for treatment at the clinic, could have influenced parenting stress. Given that these children have chronic problems that could not be effectively managed at more routine levels of care, one would assume that these parents have been distressed and searching for better, higher level of care for their sick child. Once the child has been admitted for the treatment specialized tertiary care program, but before treatment has actually begun, one might expect that these parents would experience a sense of relief and a boost in their morale and hopefulness that now, at last, their child will get the best treatment possible. This sense of relief could be reflected in lower ratings of parenting stress. Overall, considering the effect sizes of differences with references groups, our finding of low levels of parenting stress in parents of children with problematic severe asthma tentatively indicated that parenting stress is low in this group.

There are some limitations to our study. First, we did not compare the parenting stress levels of our sample to parenting stress levels of a control sample matched on relevant demographic characteristics. Instead, we used all available reference groups that used this parenting stress questionnaire (PSI). These samples were

obtained at a different time using a different sampling frame. This methodology is weaker than being able to directly compare our group of parents to a control group, which may pose a challenge to our interpretation – even though a wide range of comparisons indicated low parenting stress scores in our group. Second, the parents and children participated on a voluntary basis after having been informed about the purpose of the study. It is unknown whether our sample was representative for the population of parents of clinically treated children and adolescents with problematic severe asthma. However, non-participation among parents –especially among mothers– was low. Third, socially desirable responding may have occurred as in a previous study showing that 22 % of parents of children with asthma were responding defensively,[13] i.e., parents' responses may have been influenced by a tendency to minimize negative aspects of their family situation and/or parental behavior. Fourth, the findings generalize only to parents of tertiary treated children with problematic severe asthma. As none of the demographic variables such as education level of the parents were related to the outcome variable, it is unlikely that demographic variables such as social economic status explain the findings.

With respect to implications for research, our results partially support the notion that, parents having lower control of their child's asthma, as revealed in the child's higher level of airway inflammation, is a stress factor for parents; alternatively, perhaps, parenting stress can aggravate the child's asthma. Moreover, the behavioral problems of their children may be both a source for and a consequence of parenting stress. Longitudinal research is needed to get more insight regarding the direction of and mechanisms behind these associations.

With respect to clinical implications, high levels of parenting stress can lead to harsh or withdrawn parenting with consequences for child development.[66] Professionals should be alert to parenting stress and behavioral problems in the child. When observing psychological problems in the parents or child, professionals can help to provide appropriate support in the relevant domains to reduce the primary sources of stress and improve well-being of the whole family.[11] Interventions aimed at empowerment and improving parenting skills of parents will benefit their chronically ill child[67] in terms of a reduction of behavioral problems and asthma severity. Most important, our study indicates that care in this group involves a focus on all possible sources of problems, i.e., disease exacerbations and behavioral problems in the child as well as parenting stress.

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Chapter 5

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

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Acknowledgement of author contributions: MV and RG designed the study; MV, EJvdG and MD collected and processed the data; MV, EJvdG, MD, WvA, and RG analyzed the data; EJvdG and MV wrote the paper with input from MD, WvA, and RG.

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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

Table 1. Criteria of problematic severe asthma[11]

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.

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

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 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 predesigned 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 β2-agonists were stopped at 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 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 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 ($p < .001$).

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]
FEV_1[a]	41	105.1 (14.7)	108.1 (13.9)	−1.5	.14
FEV_1 / 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.

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

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).

	FEV_1 (n = 41)		**FeNO (n = 41)**		**ACT (n = 34)**		**PAQLQ(S) (n = 35)**	
	β	**Adj R^2**	β	**Adj R^2**	β	**Adj R^2**	β	**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).

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.

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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Chapter 6

Multidisciplinary clinical treatment in a tertiary setting for children with asthma: A prospective evaluation

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ABSTRACT

Objective: For children with problematic severe asthma, achieving adequate control of asthma symptoms is difficult. The aim of this prospective observational study was to evaluate the effect of multidisciplinary treatment in a tertiary care setting in children with asthma.

Methods: Research participants were 89 children with asthma (mean age 13.6 ± 2.5 yrs.) treated in tertiary care clinics at high altitude in Switzerland or at sea level in the Netherlands and their parents (85 mothers, 55 fathers). Outcome variables were asthma control (C-ACT), forced expiratory volume in 1 sec (FEV_1), fractional concentration of exhaled nitric oxide (FeNO), quality of life [PAQLQ(S)], children's coping (UCL-A) and behavioral problems (CBCL), and parenting stress (PSI/NOSI). Evaluations were taken at pre- and post-treatment and at 3-6 months follow-up.

Results: The vast majority of the children (80 %) showed an improvement on asthma control with 4 % showing a deterioration. On asthma control, FeNO, quality of life, and behavioral problems, more children had a better score after the intervention than before and the improvement was large; scores generally remained at a functional level at follow-up. Children's coping and parenting stress in parents did not change during the intervention.

Conclusions: The improvement in asthma control and other outcome variables suggests that multidisciplinary treatment in a tertiary care setting is an effective approach for a heterogeneous group of children with asthma that remained uncontrolled in secondary care.

INTRODUCTION

Asthma, a chronic inflammatory disease of the airways, is common in children with a reported prevalence ranging from 5-15 %.[1] Most children respond well to safe and evidence-based pharmacological treatment. In the Netherlands, pediatric asthma patients that do not show an adequate response to standard care with medication can be referred to specialized tertiary care.

It is not always clear whether treatment of asthma is difficult because the asthma is therapy-resistant or because of other reasons such as living in a house with detrimental environmental conditions for the asthma. Psychological factors may also obstruct treatment effects, but it is unclear whether psychological problems are a cause or consequence of asthma.[2-4] Some studies suggest that poor adherence and disease management are an explanation for poor asthma control,[5-7] while others underline that stress should be addressed in treatment.[8-10] Several models of pediatric asthma specify mutually causal interrelations between biological variables, psychological variables such as behavioral problems and poor coping, and social variables such as parenting stress.[11] This biopsychosocial model suggests that all these variables may potentially improve after successful treatment.

Given the alleged multiple factors that may play a role in persistence of asthma, multidisciplinary clinical treatment in tertiary care is a treatment option to improve asthma control. Studies evaluating a small set of outcome variables in children treated in tertiary care clinics – mainly regarding treatment at high altitude – indicated an improvement of quality of life and control of asthma as measured with questionnaires.[9, 12-14] Lung function FEV_1 yielded equivocal results; some studies showed no significant improvement in FEV_1 during tertiary clinical treatment,[9, 12, 14] but in other studies FEV_1 improved.[13, 15] As yet, an encompassing evaluation including biological, psychological and social variables of multidisciplinary treatment in tertiary care is missing.

Our current prospective observational study offers an evaluation of the effects of tertiary multidisciplinary clinical treatment on multiple outcome variables in children with asthma. Asthma control is the main goal of asthma treatment and patients are only referred to tertiary multidisciplinary clinical treatment when asthma control is low. We hypothesized that asthma control and the associated quality of life outcomes improve after tertiary multidisciplinary clinical treatment.

METHODS

Participants

Our prospective study examined children with asthma before and after the start of multidisciplinary clinical treatment in a tertiary care high altitude asthma clinic with a hypo-allergenic environment in Switzerland, the *Merem Netherlands Asthma Center Davos (NAD),* or a tertiary care asthma clinic at sea level in the Netherlands, the *Merem Asthma Center Heideheuvel (ACH)*. The main reason for referral to one of the clinics by a pediatrician or pediatric pulmonologist was the lack of disease control or the co-existence of multiple asthma-related problems and the need for an intensive multidisciplinary approach to therapeutically target these problems. These patients commonly had persistent symptoms despite treatment in step 3 according to Global Initiative for Asthma 2012 criteria (double dose of inhaled steroids and/or need for additional long acting β_2-adrenergic agonists or leukotriene receptor antagonist) or higher.[16]

From 2010-2012, all children aged 7-18 years who were referred to one of the two multidisciplinary clinical treatment clinics were invited to participate in the study. The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. All parents and children aged 12 and older provided written consent, children younger than 12 provided oral assent.

Treatment

The participating clinics provide similar care. The population consists of children with problematic severe asthma,[6] the majority of them presenting with several components of atopic disease.[17] Both clinics provide highly integrated, personalized multidisciplinary clinical treatment programs of 1 to 3 months. A standard diagnostic program is performed with somatic and psychosocial assessments.[9] The children participate in a group psycho-educational asthma program that aims to increase knowledge, technical skills (inhalation technique), and coping strategies. Besides, patients 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.

Procedure

Two weeks before the start of clinical treatment in one of the specialized asthma clinics, the patients and parents received questionnaires at their homes. Medical

history and physical examination were performed on the day of arrival by the pediatrician. Medical history included atopic symptoms, exercise intolerance, medication, reliever therapy and adherence as derived from the clinical interview. Pulmonary function testing was performed. At discharge, the self-report questionnaires of patients and their parents as well as assessments of lung function and airway inflammation were repeated. At 3-6 months follow-up, the same self-report questionnaires were administered to the children.

Instruments

Descriptive variables

Demographic variables that were measured in the children were gender and age, length of stay, sensitization to inhaled allergens, ICU admission in history, medication including history, exacerbations with need for oral prednisolone in the past year, and school absence.

Outcome variables

Childhood Asthma Control Test (C-ACT)

The childhood Asthma Control Test (C-ACT)[18, 19] is a 7-item checklist, with a maximum score of 27. This questionnaire shows the control of asthma at the moment of measurement, reported by the child (4 questions) and their caregivers (3 questions) using a 4-point Likert response scale. The questionnaire has been validated for children from the age of 4-12 years with relatively mild, controlled asthma.[19] A cut-off point of ≤ 19 indicates uncontrolled asthma.[20] A minimal important difference (MID) of the C-ACT of 2 points has been recommended.[21] In the current study, Cronbach's alpha of the ACT scores by parents and children was .74, reflecting good reliability.

Lung function

Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Germany). A standardized protocol for spirometry according to the ATS and ERS guidelines[22] with at least 3 technically correct maneuvers was performed. Short and long acting β_2-adrenergic agonists were stopped the day before, which was at least 12 hours before PFT. Forced expiratory volume in 1 second (FEV_1) before β_2-agonists was obtained and evaluated. In children with asthma, even in case of severe asthma, FEV_1 is in between asthma attacks often within a normal range of 80 to 120 % predicted. FEV_1 of < 80 % predicted is considered abnormal. Airway inflammation was measured with the Niox Flex (Aerocrine, Sweden) using the fractional concentration of exhaled nitric oxide

(FeNO) according to the ATS guideline.[23] Normal values in children range from 10 to 25 parts per billion. The cut-off score for problematic airway inflammation in children of ≥ 35 ppb was used.[23]

Quality of life [PAQLQ(S)]

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.[24] The Dutch PAQLQ(S) has adequate psychometric properties and excellent responsiveness, which supports longitudinal and cross-sectional construct validity.[25] The PAQLQ(S) is responsive to change of asthma control and has strong measurement properties.[26] 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[24] and a cut-off score for uncontrolled asthma is ≥ 5.9. A change in PAQLQ(S) score of 0.5 has been defined a clinically significant and relevant change.[21, 24]

Coping (UCL-A)

The UCL-A (Utrecht Coping List for Adolescents) questionnaire measures stress coping in adolescents (27, 28). It has 47 items on the following 7 domains: "confrontation" (7 items e.g., "seeking a way to solve the problem"), "palliative reaction" (8 items; e.g., "looking for distraction"), "avoidance" (8 items; e.g., "avoiding difficult situations"), "seeking social support" (6 items; e.g., "asking someone for help"), "passive reaction pattern" (7 items; e.g., "worrying about the past"), "expression of emotions" (3 items; e.g., "expressing angers and annoyance"), "reassuring thoughts" (5 items; e.g., "imagining that things could be worse") and 3 extra items not being part of the score. The scores are reported on a 4-point Likert-scale; a higher score reflects that the behavior is more prominent. Although this cannot generalize to all individuals in all situations, the domains "confrontation" and "seeking social support" are considered to be adequate coping strategies in the long term and the other five coping strategies are considered less adequate.[28] For this questionnaire, there is no cut-off score differentiating between dysfunctional and functional coping and no "minimal important difference" or "clinically relevant change" have been defined.

Child Behavior Checklist (CBCL)

The CBCL is a standardized questionnaire that uses ratings by parents or caregivers to assess emotional and behavioral problems of children and adolescents.[29] Parents filled out the Dutch version of the CBCL (6-18 years).[29] The CBCL

consists of 120 items with a 3-point Likert scale response format. Results of the CBCL are expressed in a global score and in scores for the domains internalizing and externalizing behavioral problems.
In all analyses CBCL *T*-scores were used. Higher scores indicate more behavioral problems. The Dutch version CBCL showed adequate psychometric values and good reliability.[29] A *T*-score of ≥ 63 (90th percentile in the norm population) demarcates the clinical range, which is an indication that a child has clinically relevant symptoms and might need professional help. No criteria for minimal important or clinically relevant change have been defined.

Parenting Stress-Index (PSI/NOSI)
The Parenting Stress Index (PSI) assesses the multiple dimensions of parenting stress.[30] We used the Dutch adapted version of the PSI, the "Nijmeegse Ouderlijke Stress Index" (NOSI),[31] which is named PSI/NOSI in this paper. This self-report inventory measures parenting stress using 123 items divided into two major domains: the "parent domain" that refers to perceived stress regarding family factors (58 items), and the "child domain" that refers to stress evoked by their child's behavior and emotions (65 items). The items are scored on a six-point Likert-scale; a higher score reflects more stress. The internal consistency reliability of the total parenting stress score in the clinical and non-clinical population is good (Cronbach's alpha = .94).[31] Cut-off criterion for more than average total parenting stress in mothers is ≥ 293 and in fathers ≥ 271.[31] No criteria for minimal important or clinically relevant change have been defined.

Statistical analysis
The score distributions were checked for outliers and normality. Asthma outcome scores (C-ACT, FEV_1 and FeNO) at baseline were compared with norm reference scores using descriptive statistics. The variables quality of life [PAQLQ(S)], coping (UCL-A) and behavior (CBCL) and social variable parenting stress (PSI/NOSI) scores were compared with norm reference population values using one sample *t*-tests.
Attrition analyses using independent *t*-tests for parametric and Mann-Whitney *U* test for nonparametric variables were used to reveal the differences between the participating children and the children with incomplete records.
Group pre- and post-treatment and follow-up changes were evaluated by paired samples *t*-tests or Wilcoxon signed rank test in case of non-normal distributed data.
To quantify the number of children with scores below and above a clinically relevant cut-off, established criteria were used. Change was quantified for the

C-ACT using a "minimal important difference" criterion of 2 points[21] and for FEV_1, using a change of > 9 % predicted, for FeNO a cut-off point of ≥ 35 was used. Statistical analyses were performed with SPSS 23. *P*-values < .05 (2-sided) were considered statistically significant.

RESULTS

Characteristics of the 89 children at baseline

In the study period, 45 children were admitted to NAD of whom 37 (82 %) were included; one child did not provide informed consent, and seven did not return the questionnaires. Of the 60 children admitted to ACH, 52 children were included (87 %); two children did not provide informed consent and 6 did not return the questionnaires. Eighty-five mothers and 55 fathers of the 89 children completed the PSI/NOSI-questionnaire.

Attrition analyses. No post-treatment or follow-up measurements were received from about one third of the total group of 89 children at baseline and their parents. Attrition analyses revealed no differences between the 55 participating children and the 23 children with incomplete records with respect to FEV_1, FeNO, C-ACT, PAQLQ, CBCL and PSI/NOSI-scores (all *p*'s > .05). On the UCL-A, most domains did not show difference with two exceptions. The attrition group scored lower on "confrontation" (mean 13.2 ± 3.3, $n = 28$ vs. mean 16.0 ± 3.5, $n = 55$, $p = .001$) and "reassuring thoughts" (mean 9.8 ± 2.8, $n = 28$ vs. mean 12.0 ± 2.8, $n = 55$, $p = .001$).

Asthma control. Table 1 shows the asthma outcome variables at baseline of the 89 children. Most children had sensitization to inhalation allergens, while in 10 children (12 %) no sensitization could be shown. The mean total C-ACT-score of 14.2 reflects poor control of asthma (≤ 19), despite intensive treatment with medication. The mean daily equivalent of budesonide dose was 1037 µg/day, with higher doses up till 4000 µg/day, 89 % of the children used long-acting β_2-adrenergic (LABA) agonists, 83 % leukotriene receptor antagonists (LTRA), and 10 % used omalizumab. Most children (70 %) underwent at least 2 courses with prednisolone in the past year, and in total 10 % of the group had an intensive care admission in their history. Regarding participation in daily activities; 54 % of the children were > 4 weeks absent from school because of their asthma in the year before admission.

While the group mean of FEV_1 (100.5 % predicted) and the median of FeNO (19.5 ppb) were in the normal range, 10.1 % of the children had a FEV_1 < 80 % predicted and 36.8 % a FeNO score > 35 ppb. In general, the children in this group had severe asthma, with poor asthma control despite high dosages of medication and with high impact on their school presence.

Table 1. Characteristics and asthma outcome variables of the 89 children at baseline

Female, number (%)	46	(52 %)
Age of child, mean (*SD*), range yrs	13.6 (2.5)	7-18
Length of stay, mean (*SD*) days, range	66.8 (24.8)	7-131
Lung function measures		
FEV_1, mean (*SD*) (*n* = 89)	100.5	(15.6)
FeNO, median (interquartile range) (*n* = 88)	19.5	(23.8)
Control of asthma (C-ACT) total score, mean (*SD*) (*n* = 82)	14.2	(5.8)
Allergy (sensitization), number (%)		
House dust mite (*n* = 81)	60	(74 %)
Pollen (*n* = 82)	52	(63 %)
Animals (*n* = 82)	56	(68 %)
Non-allergic (*n* = 81)	10	(12 %)
Medication		
Daily inhaled budesonide-equivalent, mean (*SD*) µg, (*n* = 88)	1037	(666)
Daily use of LABA, number (%)	79	(89 %)
Daily use of LTRA, number (%) (*n* = 76)	63	(83 %)
Omalizumab, number (%)	9	(10 %)
ICU admission in history, number (%)	8	(9 %)
Exacerbations with need for oral prednisolone ≥ 2 per year, number (%) (*n* = 77)	53	(69 %)
School absence in past year ≥ 4 weeks, number (%) (*n* = 80)	43	(54 %)

FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted (% pred).
FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb; normal range 10-25 ppb; a higher value corresponds with more eosinophilic inflammation).
C-ACT = Childhood Asthma Control Test (total score range 0-27; a higher score reflects better control). LABA = long acting β_2-agonists. LTRA = leukotriene receptor antagonist.

Quality of life. Table 2 shows the baseline values of quality of life [PAQLQ(S)], coping (UCL-A), behavioral problems (CBCL) and parenting stress (PSI/NOSI). One-sample *t*-tests showed that mean PAQLQ-scores in our study sample were lower than scores from the reference population with many respiratory symptoms (25); total score ($t = -4.31$, $p < .001$), and domains "symptoms" ($t = -4.05$, $p < .001$), "activities" ($t = -2.37$, $p = .02$) and "emotions" ($t = -3.87$, $p < .001$).

Table 2. Psychological and social variables of children with asthma (*n* = 89) and their parents (85 mothers, 55 fathers) at baseline

Children reports	
Quality of life [PAQLQ(S)] (*n* = 87)	
Total score, mean (*SD*)	4.8 (1.2)
Symptoms, mean (*SD*)	4.4 (1.4)
Activities, mean (*SD*)	4.2 (1.5)
Emotions, median (interquartile range)	6.0 (1.5)
Coping (UCL-A), mean (*SD*) (*n* = 83)	
Confrontation	15.1 (3.6)
Palliative reaction	19.5 (3.6)
Avoidance	16.8 (3.4)
Seeking social support	13.1 (4.0)
Passive reaction pattern	11.2 (3.5)
Expression of emotions	6.2 2.1)
Reassuring thoughts	11.2 (3.0)
Behavioral Problems (CBCL), mean (*SD*) (*n* = 87)	
Total score	53.9 (9.8)
Internalizing	57.3 (9.7)
Externalizing	48.7 (10.3)
Parent reports	
Parenting Stress (PSI/NOSI)	
Mothers (*n* = 85) total score, mean (*SD*)	225.7 (67.3)
Parent domain, mean (*SD*)	98.5 (31.0)
Child domain, mean (*SD*)	127.2 (41.1)
Fathers (*n* = 55) total score, median (interquartile range)	207 (100)
Parent domain, median (interquartile range)	84.0 (45.7)
Child domain, mean (*SD*)	119.7 (38.2)

PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (range 1-7; a higher score reflects better quality of life). UCL-A = Utrecht Coping List for Adolescents (range confrontation 7-28, palliative reaction 8-32, avoidance 8-32, seeking social support 6-24, passive reaction pattern 7-28, expression of emotions 3-12, reassuring thoughts 5-20). CBCL = Child Behavior Checklist: a higher score reflects more problems (*T*-score ≥ 60 borderline clinical significant, *T*-score ≥ 63 = clinical significant). PSI/NOSI = Parenting Stress Index (total score ranges from 123-738; parent domain 58-348, child domain 65-390).

Psychological variables. On most domains, UCL-A-scores did not show deviations from the healthy Dutch reference group,[27] except for the higher scores of our group on the domains "palliative reaction" ($t = 2.53$, $p = .01$) and "avoidance" ($t = 5.62$, $p < .001$); "passive reaction pattern" did not reach significance ($t = -1.69$, $p = .09$).

The CBCL total and internalizing *T*-scores were higher than the healthy norm reference population[29] indicating more behavioral problems; total score ($t = 3.95$, $p < .001$), internalizing ($t = 6.84$, $p < .001$). Externalizing behavioral problems did not deviate from the norm reference population ($t = -1.30$, $p = .20$).

Parenting stress. According to the scores derived from a non-clinical Dutch reference population,[31] parenting stress scores (PSI/NOSI) were low on all domains in mothers: total score ($t = -5.59$, $p < .001$), parent domain ($t = -6.70$, $p < .001$) and child domain ($t = -4.07$, $p < .001$) and fathers: total score ($t = -4.49$, $p < .001$), parent domain ($t = -4.14$, $p < .001$) and child domain ($t = -4.36$, $p < .001$). Compared to the Dutch reference scores of the clinical sample of the PSI/NOSI, deviations were even larger than the deviation from reference scores of the non-clinical population.

Overall baseline assessment. The population admitted for tertiary clinical treatment showed low control of asthma, low quality of life, and a coping style characterized by palliative reaction and avoidance in combination with internalizing behavioral problems.

Treatment outcomes

Table 3 shows the number of children with a functional score at baseline, after treatment, and at follow-up. Table 4 shows the changes at post-treatment and at follow-up.

Asthma control. Figure 1 shows the score of each individual child on the primary outcome C-ACT at pre- and post-treatment. Before therapy, the scores of 9 (18 %) children were > 19, indicating normal asthma control in the past four weeks, while 40 (82 %) scored in the uncontrolled asthma range. For the children that provided post-therapy assessments, after therapy the scores of 34 (69 %) children were > 19. At follow-up, 26 of 59 (44 %) were in the controlled range (> 19). Using the MID criterion of 2 points[21] on the C-ACT, 80 % of the children showed an improvement from admission to discharge, 4 % showed a deterioration, and 16 % did not reach the minimal important difference. At follow-up, 11 (23 %) of the children showed an improvement compared to post-treatment while 21 (45 %) showed a deterioration compared to post-treatment scores. The mean improvement between pre- and post-treatment (6.3) on the C-ACT was highly significant ($p < .001$) and the drop (1.9) at follow-up ($p = .02$) only involved part (30 %) of the increase between admission and discharge.

Table 3. Percentage of children having a satisfactory score at pre-therapy, post-therapy and follow-up

	Cut-off criterion	Pre-therapy	Post-therapy	Follow-up
C-ACT total	> 19	18 %	69 %	44 %
FEV_1	≥ 80 % pred.	90 %	94 %	n.a.
FeNO	< 35 ppb	75 %	97 %	n.a.
PAQLQ total	> 5.9	23 %	56 %	41 %
CBCL total	< 63	76 %	89 %	n.a.
PSI/NOSI total mothers	< 293	86 %	93 %	87 %
PSI/NOSI total fathers	< 271	82 %	88 %	84 %

C-ACT = Childhood Asthma Control Test. FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted (% pred). FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb). PAQLQ(S) = Pediatric Asthma Quality of Life Questionnaire (Self-Report). CBCL= Child Behavior Checklist. PSI/NOSI = Parenting Stress Index.

Lung function. On the lung function measurement FEV_1, before therapy, the scores of 80 children (90 %) were above the cut-off criterion of 80 % predicted. After therapy, 67 of the children (94 %) with post-therapy assessments had a score > 80 %. Using a 9 % change in predicted FEV_1 as clinical significant change criterion, 15 (21 %) had improved at post-therapy and 7 (10 %) of the children deteriorated. The mean FEV_1 value was in the normal range at baseline. Nevertheless, a mean significant improvement of 2.9 % predicted after treatment occurred (p = .02).

Before therapy, FeNO scores of 66 of 88 children (75 %) were below the cut-off criterion of 35 ppb for problematic airway inflammation. After therapy, the scores of 61 of 63 children (97 %) had values < 35 ppb. The median observed improvement of 8.2 ppb was highly significant (p < .001).

Quality of life. On the PAQLQ total score, before therapy, 20 children (23 %) were above the cut-off criterion of 5.9 for uncontrolled asthma[21], after therapy 31 of 55 children (56 %) scored > 5.9 according to this criterion, and at follow-up 26 of 63 children (41 %).
After therapy, 33 children (60 %) showed an improvement according to a MID score[26] > 0.5 while 5 (9 %) showed a deterioration. At follow-up, 9 children (18 %) showed an improvement compared to post-treatment while 19 (39 %) showed a deterioration compared to post-treatment scores.

The mean improvement of the PAQLQ total score between pre- and post-treatment (0.9) was highly significant (p < .001), but there was a reduction (0.4)

Table 4. Analyses of pre-to-post therapy and post-therapy to follow-up changes: Means and *p*-values of paired samples *t*-tests for parametric data or medians and *p*-values of Wilcoxon signed rank test for nonparametric data

	Pre-and post-treatment comparison				Post-treatment and follow-up (FU) comparison			
	N	Mean (*SD*)[a] Pre	Mean (*SD*)[a] Post	*p*	*N*	Mean (*SD*)[a] Post	Mean (*SD*)[a] FU	*p*
C-ACT total	49	14.1 (6)	20.4 (5)	<.001	47	20.6 (4)	18.7 (5)	.02
FEV_1	71	100.8 (16)	103.7 (16)	.02	-	-	-	-
FeNO*[a]	63	21.5 (25)	13.3 (11)	<.001	-	-	-	-
PAQLQ total	55	4.9 (1)	5.8 (1)	<.001	49	5.8 (1)	5.4 (1)	.04
Symptoms		4.4 (1)	5.4 (1)	<.001		5.4 (1)	5.0 (1)	.12
Activities		4.3 (2)	5.4 (1)	<.001		5.4 (1)	5.1 (1)	.14
Emotions		5.8 (1)	6.5 (1)	<.001		6.5 (1)	6.2 (1)	.02
UCL-A	55				49			
Confrontation		16.0 (4)	16.1 (4)	.79		16.2 (4)	15.6 (4)	.20
Palliative reaction*		19.7 (3)	19.0 (5)	.22		19.3 (5)	19.3 (4)	.99
Avoidance*		16.6 (3)	15.6 (3)	.07		15.8 (3)	16.6 (4)	.18
Seeking social support		13.5 (4)	14.3 (4)	.10		14.2 (4)	14.2 (4)	.97
Passive reaction pattern*		11.3 (4)	10.8 (3)	.28		11.2 (3)	11.5 (3)	.44
Expression of emotions*		5.9 (2)	6.2 (2)	.36		6.3 (2)	5.9 (2)	.33
Reassuring thoughts*		12.0 (3)	11.9 (3)	.90		12.0 (3)	11.7 (3)	.34
CBCL total*	63	53.5 (10)	48.9 (11)	<.001		-	-	
Internalizing*		57.7 (10)	52.0 (13)	<.001		-	-	
Externalizing*		47.7 (10)	45.5 (10)	.04		-	-	
PSI/NOSI								
Mothers total score*	54	217.3 (59)	211.1 (59)	.25	50	216.6 (61)	207.8 (65)	.10
Parent*		95.1 (27)	92.2 (29)	.26		94.3 (30)	91.6 (34)	.31
Child*		122.2 (36)	119.0 (33)	.31		122.4 (34)	116.2 (35)	.04
Fathers total score*	33	203.5 (63)	193.2 (60)	.08	30	194.3 (64)	196.2 (60)	.68
Parent*		88.4 (30)	84.3 (28)	.16		85.4 (30)	85.9 (30)	.81
Child*		115.1 (36)	109.0 (35)	.07		108.9 (36)	110.3 (33)	.64

* a higher score indicates a lower functional status. [a] Median (interquartile range). Differences between pre- and post-therapy and between post-therapy and follow-up were examined with Wilcoxon signed rank test. Scores of FEV1, FeNO, and CBCL were not collected at the follow-up assessment. FEV_1 (forced expiratory volume in 1 second) is expressed as percent of predicted (% pred). FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb; normal range 10-25 ppb; a higher value corresponds with more eosinophilic inflammation). C-ACT = Childhood Asthma Control Test (total score range 0-27; 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). UCL-A = Utrecht Coping List for Adolescents (range confrontation 7-28, palliative reaction 8-32, avoidance 8-32, seeking social support 6-24, passive reaction pattern 7-28, expression of emotions 3-12, reassuring thoughts 5-20). CBCL = Child Behavior Checklist: a higher score reflects more problems (*T*-score ≥ 60 borderline clinical significant, *T*-score ≥ 63 = clinical significant). PSI/NOSI = Parenting Stress Index (total score ranges from 123-738; parent domain 58-348, child domain 65-390).

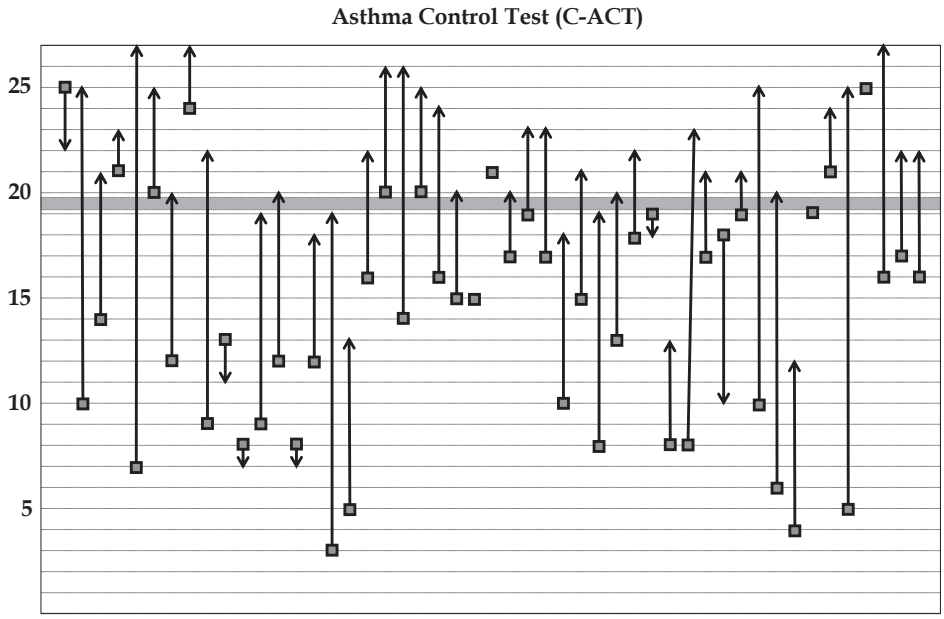

Figure 1. Arrows showing the scores on the Asthma Control Test (C-ACT) for each individual child at pre- and post-treatment, $n = 49$. A score ≤ 19 is considered uncontrolled asthma.

at follow up ($p = .04$). The domains of the PAQLQ improved highly significantly after treatment and were maintained (domain "symptoms") or deteriorated (domains "activities" and "emotions") at follow-up.

Psychological outcomes. For the coping variable, no clear cut-off criterion between functional and dysfunctional scores exists for the total score. None of the scores showed a significant change between pre-therapy and post-therapy, and scores remained stable at follow-up.

On the total score of the CBCL, before therapy the scores of 66 of 87 children (76 %) were below the cut-off criterion for clinically significant behavioral problems of 63. After therapy, 56 of 63 children (89 %) with post-therapy assessments had a score < 63.

The mean observed improvement of the CBCL total score (4.6) was highly significant ($p < .001$) as well as the improvement (5.7) of the domain internalizing behavioral problems.

Parenting stress. On the PSI/NOSI total score for mothers, before therapy, the scores of 73 of 85 mothers (86 %) were below the cut-off criterion of 293 for more than average parenting stress,[31] after therapy 50 of 54 of the mothers (93 %) had less than average parenting stress according to this criterion, and at follow-up 54 of 62 mothers (87 %). None but one of the scores showed a significant change between pre- and post-treatment, and overall scores remained stable at follow-up. Only the child domain of the mothers improved a little (6.2) at follow-up (p = .04).

On the PSI/NOSI total score for fathers, before therapy, the scores of 45 of 55 fathers (82 %) were below the cut-off criterion of 271 for more than average parenting stress,[31] after therapy 29 of 33 fathers (88 %) had less than average parenting stress according to this criterion, and at follow-up 32 of 38 fathers (84 %). No significant improvements were found. Scores remained stable during the follow-up interval.

DISCUSSION

This prospective observational study evaluated the effects of multidisciplinary treatment in a tertiary care in children with problematic severe asthma in whom adequate control of asthma could not be achieved in secondary care. Overall, the vast majority of children improved on asthma control and quality of life, while also reductions in airway inflammation and behavioral problems were obtained.

While the emphasis in asthma management has been shifted to achieving full control of asthma,[5] in a subgroup of children with asthma this target appears too farfetched. Nevertheless, our study demonstrated that a large improvement on asthma and FeNO from pre- to posttreatment in this group *is* possible. This is in agreement with previous studies.[9, 12-14, 32-34] FEV_1 was in most children already in the normal range at pre-treatment, but nevertheless showed a small improvement at post-treatment. Compared to previous studies, our study is unique regarding three characteristics: it was done in a large cohort of children, the design was prospective, and the effect of multidisciplinary treatment on multiple outcomes was examined.

Consistent with the biopsychosocial model and previous studies,[35-37] our study confirmed that children with asthma are at risk of having internalizing behavioral problems. After treatment, internalizing behavioral problems had been reduced

and the percentage of children with clinically relevant behavioral problems was comparable to the percentage in the general population.

This kind of improvement was not reached with other psychosocial variables. Although also the coping domains palliative reactions and avoidance behavior at treatment entrance reflected internalizing problems, they did not significantly change during therapy. A possible reason is that the profile of coping styles was too heterogeneous with many children having an adequate score already at the start of treatment. Also parenting stress did not change. Our previous study in this group showed that parenting stress was low but associated with more airway inflammation and greater child behavioral problems at pre-treatment.[38] The current study confirms that parenting stress levels were low. This observation as well as the observation that parenting stress levels did not change after therapy, suggests that in the overall group parental stress is not an important issue. This does not exclude that parenting stress might be an important target of treatment in selected cases.

Our study has several limitations. As recommended,[39] we included next to the self-reported asthma control test,[19] also objective measurement of lung function (FEV_1) and airway inflammation (FeNO), but it is a limitation inherent to the complex and heterogeneous nature of asthma that our primary outcome measure –the asthma control test– was a self-report measure. To increase its reliability, we wanted this measure to be scored by children as well as by parents. Therefore, we used the child version of the asthma control test also for the part of the group that was older than 12 years. Another reason for this choice was that we wanted a uniform outcome measure for the whole group. A limitation, however, is that the scores of our older subsample cannot be compared to ACT scores in this age group in other populations. Another limitation was that non-participation in post-therapy evaluation was lower than desired, and a really long-term follow-up was lacking. A limitation of any observational study is that there is no control group to differentiate between "real" effects and regression to the mean. Another limitation is that it was not possible to quantify all changes using similar change measures such as the MID criterion. A final limitation is that we were not able to examine the separate effects of the clinics at sea level and high altitude because the trial was not randomized and the detailed reasons to refer to one of these clinics were not documented and may involve aspects such as homesickness. In future research, new interventions can be compared to the currently evaluated treatment, which can then be considered the treatment-as-usual control group.

Patients are heterogeneous in the sense that different pathological processes maintain the asthma and that different psychological, environmental and social processes may play a crucial role in maintaining uncontrolled asthma in children. Therefore, treatment customized to the individual patient is of great importance. Overall, the observed improvements in asthma control, airway inflammation, quality of life, and behavioral problems suggest that multidisciplinary treatment in a tertiary care setting is a useful approach for a heterogeneous group of children with asthma that remained uncontrolled in secondary care.

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Chapter 7

Cognitive behavioral therapy and eye movement desensitization and reprocessing in an adolescent with difficult-to-treat asthma: A single-case experimental design

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ABSTRACT

Stress and distress have been suggested to maintain difficult-to-treat asthma (DTTA), i.e., asthma that is not under control despite optimal medical treatment. A pediatric pulmonologist referred a 16-year-old girl with DTTA in whom asthma-specific fear induced by disturbed memories and distorted cognitions following frightening asthma attacks were driving asthma exacerbations. We examined whether Cognitive Behavioral Therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR) focusing on asthma-specific fear and disturbed memories could reduce asthma symptoms and its burden. The single-case experimental design included 48 weekly repeated assessments of primary outcomes during baseline, therapy and follow-up phases of 16 weeks each, and four repeated assessments of secondary outcomes at intake, pre-therapy, post-therapy, and follow-up. Analysis of the time series data with a piecewise regression model demonstrated that the level or slope (trend) showed an improvement during the intervention and a sustained improvement during follow-up compared to the baseline phase on all primary outcomes: burden of asthma exacerbations, physical activities, social activities, physical complaints, and worrying. Analyses using the Reliable Change Index, showed significant pre-to-post therapy changes on most domains of questionnaires measuring secondary outcomes: Asthma Control Test, Pediatric Asthma Quality of Life Questionnaire, Child Behavior Checklist and Youth Self Report. Moreover, medication use reduced and lung function (FEV_1) was just in the normal range at follow-up. Thus, the study showed that asthma symptoms and the burden of asthma were reduced after CBT and EMDR. This proof-of-principle study suggests that DTTA may be improved by psychological interventions in pediatric patients characterized by having psychological stress or distress.

INTRODUCTION

Asthma, a chronic inflammatory disease of the airways, is common in children and adolescents with a reported worldwide prevalence ranging from 5-15 %.[1] A small portion of pediatric asthma patients (the precise prevalence is unknown) has difficult-to-treat asthma (DTTA), i.e. asthma that is not under control despite optimal medical treatment.[2, 3] It is unclear why control of asthma is not possible in case of DTTA.[3, 4] It has been suggested that psychological problems related to asthma attacks may maintain DTTA,[5-8] but it is unclear whether these psychological problems are a cause or consequence of DTTA, or both.

Because emotional stress may precipitate or exacerbate asthma,[9, 10] it has been recommended to develop and evaluate psychological treatment in children and adolescents with DTTA in whom psychological comorbidity may play a role.[11] The recent decade has witnessed surging interest in behavioral interventions that target the psychological pathways that might influence asthma.[11] Among these, education, breathing training, stress-reduction through relaxation techniques, hypnotherapy, and behavioral therapy have been indicated useful[12] and have indicated a decrease in anxiety and asthma symptoms, an increase in quality of life,[13-15] and a reduction of hospital admissions and length of stay.[16] In children with asthma, not necessarily DTTA, interventions incorporating cognitive behavioral techniques have shown to be successful in targeting variables such as self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation, social competence, and days absence from school.[17-19] The one previous evaluation of the effects of cognitive behavioral therapy in two adults with DTTA indicated favorable effects,[5] as did the one study using self-hypnosis for anxiety in a child with severe asthma.[20] However, in order to decide on the usefulness of cognitive behavioral therapy for youth with DTTA and comorbid psychological stress, more evidence is needed.

"Sarah" is a 16-year-old adolescent with DTTA. She was referred to the department of pediatric psychology, because psychological stress was recognized by her pediatric pulmonologist as contributing to her uncontrollable asthma. Anamnestic examination suggested that asthma-specific fear induced by disturbed memories and distorted cognitions following frightening asthma attacks were factors driving asthma exacerbations (Box 1).

To target Sarah's worries that she might "die of an asthma attack," cognitive behavioral therapy (CBT) was indicated.[5] Eye Movement Desensitization and

Box 1. Patient description and history

"Sarah" is a 16-year-old Dutch girl from parents with a Mediterranean ethnic background living in the Netherlands. Asthma was diagnosed at age 3 years with regular exacerbations and hospitalizations. During early childhood, Sarah's asthma was not well handled by her parents and adherence to medication was poor. The past years, adherence had improved and the asthma was better accepted by Sarah and her parents.
At the intake, Sarah showed a lack of motivation for psychological therapy. She was convinced that only the pulmonologist could help her. Sarah was convinced of a biomedical basis of her asthma and was preoccupied with its severity. The overreaction, demonstrated by excessive worrying about symptoms of asthma, had led to medication overuse and deficient self-management, as mentioned by the pulmonologist. Frequent exacerbations and hospital admissions were part of a perpetuating cycle including symptom hypervigilance, distress, and significant disruption of functioning for the past years including many days of asthma-related absence from school, social isolation, and lack of social competence. Sarah had learned to fear her symptoms and had developed distorted perceptions of them. She described a preoccupation with worrying thoughts and feelings concerning her asthma and expressed anxiety about the course of her asthma and inadequate coping with asthma attacks. This was central to cycles of isolation, avoidance of pleasurable activities and anxiety which aggravated Sarah's breathing difficulties and prevented her from leading a normal life. The illness was influencing all family members. Her overprotecting mother was extremely aware of triggers and signs of asthma exacerbations. Sarah showed difficulties in separation and individuation from her parents which obstructed her development of independence and of adequate coping strategies. She also had a lack of knowledge about asthma self-management. She was insecure and helpless, depending highly on her mother and physician who had a leading and prescribing role.

Reprocessing (EMDR) was included to treat her asthma-specific fear caused by disturbed memories.[21, 22] The aim of the current study was to evaluate whether CBT including EMDR would reduce the burden of asthma and worrying in a 16-year old female adolescent with DTTA and comorbid psychological problems. A sequential replicated single-case experimental design with multiple measurements was used for evaluation of therapy effectiveness.[23] A positive outcome of the intervention would be a proof-of-principle observation in support of the notion that DTTA may be improved by psychological means in pediatric patients characterized by comorbid psychological stress or distress.

METHODS

Procedure

The study was approved by the medical ethics committee of the VU University Medical Center (VUmc), Amsterdam, the Netherlands. Sarah signed informed consent. Therapy by a cognitive behavioral therapist (also qualified as an EMDR-therapist) was provided for 20 one-hour weekly sessions of individual therapy within three phases (Table 1). EMDR was carried out on the basis of the children's protocol.[24] Box 2 presents an overview of the contents of the therapy.

Design

To evaluate the therapy, a sequential replicated single-case experimental design with multiple measurements was used. This procedure is able to examine clinically meaningful and statistically reliable changes in outcome variables as a function of the intervention.[23] The design included 48 weekly repeated assessments of five *primary outcomes* during baseline, therapy and follow-up phases of 16 weeks each (Table 1, P01-P48). *Secondary outcomes* involved self-report scores of control of asthma, quality of life, behavioral problems, and lung function measurement, measured on four repeated assessments at intake, pre-therapy, post-therapy, and follow-up.

Instruments

Primary outcomes. Five individual outcomes as indicated most important by Sarah were set during the first intake visit and monitored weekly using Visual Analogue Scales (VAS): "Asthma exacerbations" (burden of asthma exacerbations), "physical activities" (suffocative and wheezed breathing during physical activities), "social activities" (suffocative and wheezed breathing during activities with family and friends), "physical complaints" (suffering from other physical complaints) and "worrying" (worrying and being concerned and anxious).

Secondary outcomes. The *Asthma Control Test* (ACT)[25] assesses the control of asthma from the past four weeks. The patient rates 5 questions on a 5-point scale ranging from 1 ("not controlled at all") to 5 ("completely controlled"). The items are: 1) "Asthma keeps you from getting much done at work/school," 2) "Shortness of breath," 3) "Asthma symptoms wake you up," 4) "Use of rescue medication" and 5) "Patient rating of control." The summated total score ranges from 5 to 25; a higher score reflects better control. A score of 20 or higher denotes good disease control, 15-20 partly controlled asthma and 5-15 uncontrolled asthma. ACT-scores were shown to be reliable and valid.[25]

Table 1. Design and therapy sessions

Week number	Phase	Therapy		Outcome assessments	
		Session	Main contents	Primary	Secondary
01	Baseline	Intake	Getting acquainted, anamnesis	P01	S1
02		Intake	Explanation of therapy	P02	
03-16				P03-P16	
17	Therapy	CBT	Explanation of therapy plan	P17	S2
18		CBT	Cognitive behavioral therapy plan	P18	
19		CBT	Explanation of the nature of asthma & asthma management	P19	
20		CBT	Cognitive restructuring	P20	
21		CBT	Replacing dysfunctional with functional behavior and thoughts	P21	
22		CBT	Learning to recognize and control hyperventilation	P22	
23		CBT	Continuation exercises of adequate breathing technique	P23	
24		CBT	Exposure and response prevention	P24	
25		CBT	School: learning to make better planning and overview of problems and stress	P25	
26		CBT	Developing skills in problem-solving: coping strategies	P26	
27		CBT	Reducing dysfunctional somatic preoccupation: mindfulness training	P27	
28		CBT	Stress-management: Relaxation exercises and muscle relaxation	P28	
29		CBT	Interoceptive exposure exercise	P29	
30		EMDR	EMDR explanation and timeline targets	P30	
31		EMDR	EMDR desensitization target 1	P31	
32		EMDR	EMDR desensitization target 2	P32	
33	Follow-up	T & RP	Termination and relapse prevention	P33	S3
34		T & RP	Relapse prevention plan and evaluation of therapy	P34	
35-47				P35-47	
48				P48	S4

Primary outcomes: 48 weekly assessments (P01 to P48) with Visual Analogue Scales (VAS).
Secondary outcomes: 4 assessments (S1 to S4) with questionnaires.
Asthma Control Test (ACT), Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)], Child Behavior Checklist (CBCL), Youth Self Report (YSR), and FEV_1 (forced expiratory volume in 1 second, expressed as percent of predicted (% pred)). Cognitive Behavioral Therapy (CBT). Eye Movement Desensitization and Reprocessing (EMDR).

Box 2. Overview of therapy

Step 1: Getting acquainted, anamnesis and explanation therapy (session 1-2)
The initial intake session included assessments and discussing Sarah's goals for therapy. The second intake session was focused on educating Sarah about asthma management and psychotherapy in general, the importance of practicing and doing exercises at home, taking responsibility for change, and discussing expectations. Initially, it was challenging for Sarah to consider that physical and psychological circumstances are related. A collaborative understanding of Sarah's difficulties was developed and the intervention was based on this.

Step 2: Explaining therapy plan and motivating (session 3-4)
The therapy plan was explained and what could be gained through therapy. Based on analysis of the functional relationship between situational triggers, asthma-related cognitions, and physiological fixation, cognitive behavioral explanations were given of Sarah's asthma-specific fear, and of the impact of helpful thoughts on psychological wellbeing, physical health, and better asthma management.

Step 3: Education about asthma management and symptom discrimination (session 5 & 8)
Explanation of the nature of breathing difficulties in asthma, and promoting awareness of cognitions through self-monitoring, particularly catastrophic misinterpretations of somatic sensations (symptom education). Specific instances of asthma exacerbations experienced by Sarah were discussed. Sarah was helped to recognize the consequences of different ways of personally experiencing asthma exacerbations for dysfunctional breathing. Instead of experiencing all asthma attacks as life-threatening, Sarah was learned to differentiate asthma symptoms, dysfunctional breathing, and hyperventilation. She learned techniques to remain calm in an effort to prevent anxiety induced asthma symptoms, and had a prescribed asthma management plan to use.

Step 4: Cognitive restructuring and teaching positive thoughts (session 6-7)
Cognitive restructuring skills were introduced to decrease Sarah's general anxiety and distress. She was taught to replace dysfunctional with functional thoughts and behavior, how to develop adaptive explanations for anxiety-provoking events, as opposed to maladaptive, self-harmful explanations, and how to manage stress.

Step 5: Relaxation exercises (session 9, 13-14)
The therapist taught Sarah how to respond to panic versus asthma symptoms, and how to recognize and control hyperventilation. Adequate breathing

technique, postural adjustments, and relaxation techniques such as progressive muscle relaxation together with visualization of relaxing situations were taught. To reduce dysfunctional somatic preoccupation, mindfulness was taught to retrain focus of attention and to concentrate on the present moment rather than worry about what might happen or about what happened before.

Step 6: Coping strategies (session 11-12)

Sarah was taught problem solving skills in an effort to reduce her general level of anxiety and distress as well as her asthma-specific anxiety. Concerning her school, an overview of problems and school-related stress was made and Sarah created a better planning system.

Step 7: Response prevention and interceptive exposure (session 10 & 15)

To reduce dysfunctional safety-seeking, techniques to control exposure to anxiety and increase anxiety tolerance (response prevention) were introduced. With physician's approval, Sarah practiced relaxation skills during an asthma attack at home or school to diminish the severity and duration. Sarah practiced interceptive exposure by breathing quickly in and out of a straw until she reported experiencing some of the physical sensations of a panic attack. This exercise re-exposed Sarah to her physical sensations during an asthma attack and allowed her to endure these sensations and realize that nothing catastrophic resulted. The exercise also allowed her to practice the relaxation skills that were most effective for her. Sarah was asked to practice this exercise at home (when an adult was in the house). Asthma rescue medication was available in the session and at all subsequent practice sessions at home in the event that Sarah experienced sustained difficulty with breathing as a result of asthma; however, Sarah never needed to use the medication during the interceptive exposure exercises.

Step 8: EMDR (session 16-18)

One goal of EMDR is to alleviate negative cognition during the desensitization phase and to replace it by positive cognition during the reprocessing phase. To achieve this, many aspects of Sarah's cognition were stimulated in an eight-phase approach that included having Sarah's recall distressing images while receiving bilateral sensory input.[22] The eight phases were: history taking, preparation, assessment, desensitization, installation, body scan, closure and reassessment. Sarah had experienced two traumatic asthma exacerbations, at the age of 13 and 16 years. The therapist started with the asthma exacerbation at age of 13. In the reprocessing phases, Sarah was instructed to recognize a picture that represents the most terrible part of this asthma exacerbation and a negative unreasonable self-belief related with the picture (a negative belief currently held). Next step was to add a desired positive belief, current

emotion, and physical sensation. Then, first, Sarah was guided, according to standardized protocols to simultaneously move her eyes back and forward, following the therapist's finger as they moved across their field of vision for a set of about 24–36 seconds. This procedure continued until the target memory was desensitized. After that, more eye movement sets were used, while Sarah was thinking of a recognized adaptive belief. This was repeated until the new belief felt good to Sarah and physiological arousal was dissipated.

Step 9: Relapse prevention and termination (session 19-20)

Because of Sarah's steady progress based on her report and VAS-scales, and her wish to end the therapy, the therapy could be terminated. Two termination sessions focused on reviewing the most effective components of therapy, relapse prevention, and practicing self-skills-management.

The *Pediatric Quality of Life Questionnaire (Self-report)* [PAQLQ(S)][26] is a disease-specific health-related quality of life self-report measure for children and adolescents aged 7-17 years. 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. The Dutch PAQLQ(S) is responsive to change of asthma control and has strong measurement properties.[27]

The Child Behavior Checklist (CBCL) *and Youth Self Report* (YSR)[28] are standardized questionnaires for assessing emotional and behavioral problems filled out by parents (CBCL) or adolescents (YSR). The CBCL and YSR consist of 120 questions. Results are expressed in a global score and scores for internalizing and externalizing behavioral problems. In all analyses CBCL *T*-scores were used, with higher scores indicating more behavioral problems. The Dutch versions of the CBCL and YSR showed good reliability.[28]

To assess *lung function*, standardized pulmonary function testing was performed using the Masterscreen (Jaeger®, CareFusion Corporation). Short or long acting β_2-adrenergic agonists were stopped at least 12 hours before testing. Forced expiratory volume in 1 second (FEV_1) was obtained. In children, in between asthma attacks, even in severe asthma, lung function is often within a normal range of 80 to 120 % predicted.

Data analysis

Several statistical techniques have been applied to analyze single-case data with as a guiding criterion that the method should complement visual analysis.[23, 29, 30] To analyze the change in primary outcomes, we used a change point model (also known as structural break or turning point model). Analysis consisted of estimating a piecewise regression model to the time series data.[31] Specifically, the level and slope (trend) during the baseline were compared to the level and slope during therapy and during the follow-up phase. In addition to changes in trend across the three phases, also sudden changes were allowed when moving from one phase to another. The linear regression procedure of SPSS version 22 was used.

To evaluate the change in secondary outcomes, the Reliable Change Index (RCI)[32] was used. The RCI expresses the change relative to measurement error. For post-therapy versus pre-therapy measurements, the formula is: RCI = $(X_{post\text{-}therapy} - X_{pre\text{-}therapy}) \; / \sqrt{(2*SEM^{\,2})}$, in which X is the score before and after therapy and SEM is the standard error of measurement that can be computed knowing the standard deviation (SDx) and reliability (r_{xx}) of a test (x), $SEM = SDx \sqrt{(1\text{-}r_{xx})}$. A RCI larger than 1.96 reflects a significant improvement ($p < .05$).

To compute the RCI's, reliabilities (test-retest or internal consistency) and standard deviations were derived from norm population articles. For the ACT, the internal consistency reliability for not controlled asthma was α = .83 and SD = 4.4.[25] For the PAQLQ(S), test-retest reliability (intraclass correlation, ICC) for Dutch adolescents aged 15-18 years was .66 and SD = 0.99 for the total score, ICC = .42 and SD = 1.22 for symptoms, ICC = .73 and SD = 1.25 for activities and ICC = .80 and SD = 0.94 for emotions.[27] For the CBCL, r = .94 and SD = 10.0 for the total score was used, r = .91 and SD = 9.7 for internalizing, and r = .92 and SD = 9.5 for externalizing behavioral problems.[28] For the YSR, r = .87 and SD = 9.9 for the total score was used, r = .80 and SD = 10.1 for internalizing, and r = .89 and SD = 10.0 for externalizing behavioral problems.[28]

RESULTS

Primary outcomes

Figure 1 presents the weekly measurements of the five primary outcome variables. All five visual analogue scales reflected a high burden of asthma during baseline with average values ranging from 7.2 to 7.9. At the end of baseline,

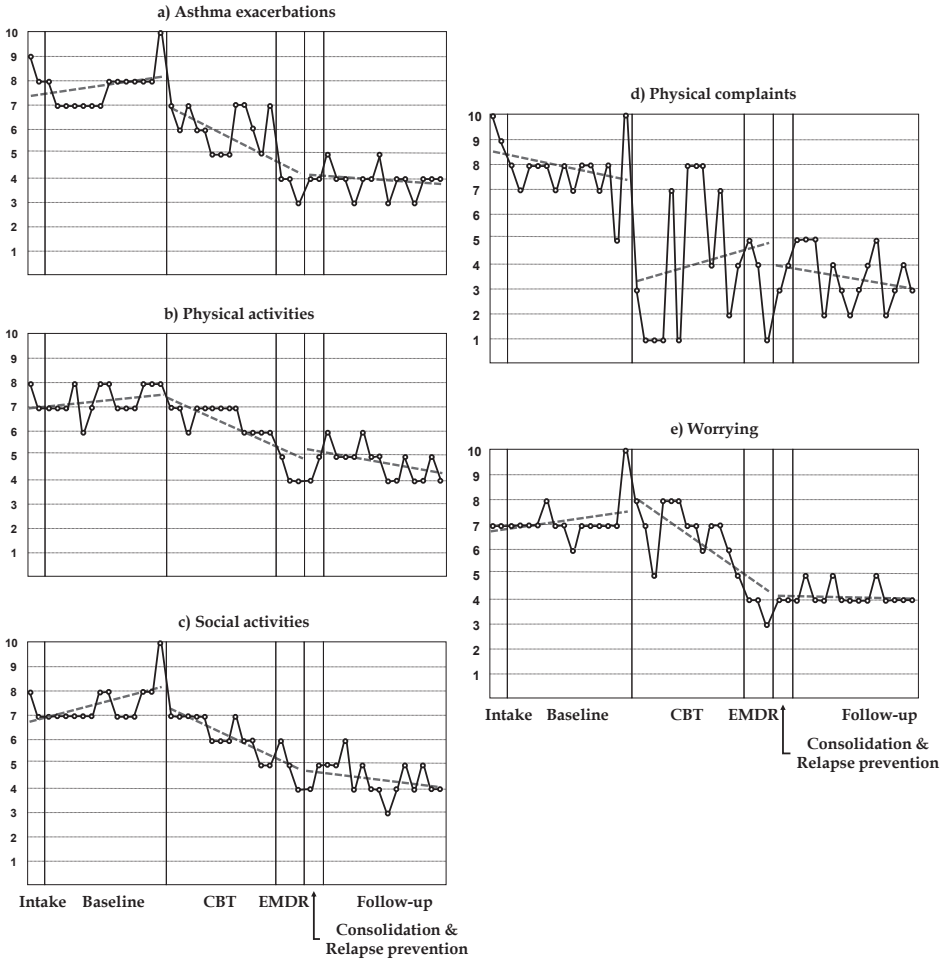

Figure 1. Weekly assessments during baseline, therapy and follow-up of observed (straight line) and predicted (dotted line) a) burden of asthma exacerbations, b) suffocative and wheezed breathing during physical activities, c) suffocative and wheezed breathing during activities with family and friends, d) suffering from other physical complaints, and e) worrying and being concerned and anxious. CBT = Cognitive Behavioral Therapy; EMDR = Eye Movement Desensitization and Reprocessing. A higher score reflects worse functioning.

Sarah had an asthma exacerbation and was hospitalized for three days with use of oral prednisolone.

Table 2 shows the statistics of the time-series analysis comparing the level and slope (trend) of the outcomes during baseline with the level and slope during and after therapy. A significant effect of "Time" reflects a linear change across 32 repeated measurements (baseline and therapy phase or baseline and follow-up

Table 2. Estimates (*b*) from linear regression analysis comparing the level and slope (trend) of primary outcomes during the baseline with the level and slope during therapy and follow-up

	Baseline vs. Therapy						Baseline vs. Follow-up					
	Time		Level		Slope		Time		Level		Slope	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Asthma exacerbations	.35	.24	−.49	.02	−.74	.003	.26	.15	−1.01	<.001	−.20	.14
Physical activities	.35	.28	−.10	.66	−1.04	<.001	.24	.27	−.85	<.001	−.34	.046
Social activities	.71	.02	−.41	.049	−1.13	<.001	.46	.04	−1.00	<.001	−.40	.02
Physical complaints	−.26	.51	−.68	.02	.30	.31	−.30	.21	−.65	.001	.03	.85
Worrying	.40	.29	.18	.50	−1.16	<.001	.33	.11	−1.05	<.001	−.20	.20

Time reflects the linear change of the outcome across conditions; Level refers to differences in outcome levels between conditions; Slope refers to differences in linear change of outcome levels between conditions.

phase) while adjusting for the other effects (level and slope); it is used in this analysis as a control variable to adjust for changes across time that are independent of changes within the conditions (baseline vs. therapy or follow-up).

A significant negative *b*-value for "Level" reflects that the level of the outcome during therapy or follow-up was lower than the level during baseline, while adjusting for the other effects (time and slope). A lower value of the outcome reflects improvement. The results show that the levels of three outcomes (asthma exacerbations, social activities, and physical complaints) were lower during therapy than during baseline and that the levels of all outcome variables were lower during follow-up than during baseline.

A significant negative *b*-value for "Slope" reflects that the decrease during therapy or follow-up was higher than the decrease during baseline, while adjusting for other effects (time and level). Significant decreases during the intervention were observed for all outcomes but physical complaints. During the follow-up a further decrease was observed for physical activities and social activities.

Thus, during the intervention –as compared to the baseline– the level or slope of all primary outcomes reflected an improvement, while during the follow-up phase as compared to the baseline phase, all outcome levels reflected an improvement and two outcomes showed an ongoing positive change.

Secondary outcomes

Table 3 shows the secondary outcomes at intake, pre- and post-therapy, and follow-up. For example, in the first line, the scores of the ACT are shown at intake (T0), pre-therapy (T1), post-therapy (T2), and follow-up (T3). The RCI at post-therapy compared to intake was 1.95 ($p > .05$) and compared to pre-therapy 2.34 ($p < .05$). The RCI at follow-up compared to intake was 1.56 ($p > .05$) and compared to pre-therapy 1.95 ($p > .05$). Thus, the ACT score significantly improved from pre-therapy till post-therapy but it did not improve further from post-therapy to follow-up. Sarah reported improvements on all items (e.g. "Asthma keeps you from getting much done at work/school," "Shortness of breath," "Asthma symptoms wake you up," "Use of rescue medication" and "Patient rating of control"). However, her scores at post-therapy and follow-up were still in the uncontrolled asthma range (total score 5 to 15).

Table 3. Scores at four questionnaires during intake (T0), pre-therapy (T1), post-therapy (T2) and at follow-up (T3) as well as the Reliable Change Index (RCI) which indicates whether the change after therapy and at follow-up –as compared to the intake and pre-therapy assessment– exceeds chance

	Intake	Pre-therapy	Post-therapy			Follow-up		
	Score	Score	Score	RCI	RCI	Score	RCI	RCI
	T0	T1	T2	T2-T0	T2-T1	T3	T3-T0	T3-T1
ACT	7	6	12	1.95	2.34*	11	1.56	1.95
PAQLQ(S)								
Total	3.2	2.9	5.2	2.45*	2.82**	5	2.2*	2.57*
Symptoms	2.7	1.5	4.8	1.6	2.51*	4.4	1.29	2.21*
Activities	2.0	2.4	4.2	2.4*	1.96*	4	2.18*	1.74
Emotions	4.6	5.0	6.5	3.20**	2.52*	6.5	3.20**	2.52*
CBCL								
Total *T*-score	51	50	41	−2.89**	−2.60**	42	−2.60**	−2.31*
Internalizing	60	55	45	−3.64***	−2.43*	52	−1.94	−0.73
Externalizing	40	44	40	−0.00	−1.05	40	−0.00	−1.05
YSR								
Total *T*-score	49	38	34	−2.97**	−0.79	37	−2.38*	−.20
Internalizing	56	45	37	−2.97**	−1.25	43	−2.04*	−.31
Externalizing	42	34	32	−2.13*	−0.43	35	−1.49	0.21

* $p < .05$ (RCI > 1.96), ** $p < .01$ (RCI > 2.58), *** $p < .001$ (RCI > 3.29)
ACT (Asthma Control Test): Range 5-25; 5-15 uncontrolled asthma, 15-20 partly controlled asthma, 20-25 controlled asthma. PAQLQ(S) (Pediatric Asthma Quality of Life Questionnaire (Self Report)): Range 1-7; a higher score indicates better quality of life. CBCL (Child Behavior Checklist) and YSR (Youth Self Report): A higher score reflects more problems (*T*-score ≥ 60 borderline clinical significant, *T*-score ≥ 63 = clinical significant).

Overall, a reliable decrease in all domains of quality of life [PAQLQ(S)], especially emotional functioning, was found. Also, a reliable decrease in total behavioral problems and internalizing symptoms was found at the CBCL and the YSR.

Lung function and medication

Lung function measurements (FEV_1) at the four occasions were 72 (intake), 60 (pre-therapy), 61 (post-therapy), and 81 (follow-up) % predicted. At follow-up, the value was just in the normal range of 80 to 120 % predicted.

Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment. Long-acting β2-adrenoceptor (LABA) agonists are commonly prescribed for moderate to severe persistent asthma patients, combined with ICS. For Sarah, during all phases, intensive medical treatment with high dosage of inhaled ICS and LABA (both twice a day), leukotriene antagonists and antibiotic maintenance treatment remained stable. In addition, Sarah reduced daily use of short-acting β_2-agonists (Salbutamol). During therapy, Salbutamol could be reduced to a maximum of 4 times a day with at least 3 hours in between in comparison with the baseline phase when she used Salbutamol every hour. Sarah had no exacerbations with need for oral prednisolone during the therapy or follow-up phases, but she needed oral prednisolone due to exacerbations three months before intake and at the end of the baseline phase.

DISCUSSION

The hypothesis of the current proof-of-principle study was that CBT including EMDR would be able to reduce the burden of asthma and worrying in a 16-year old female adolescent with DTTA and comorbid psychological problems. In agreement with the hypothesis, weekly assessments of asthma symptoms and the burden of asthma showed an improvement after CBT and EMDR, focusing on cognitions and asthma-specific fear. Also most secondary outcomes showed an improvement. Overall, Sarah's physical health, as well as her psychosocial well-being, improved substantially.

Although asthma guidelines consider the potential role of nonpharmacological interventions in DTTA and recommend the assessment of psychological co-morbidity, they do not indicate how identified psychological morbidity is best managed.[5] In adults, there is only one previous study that evaluated CBT in DTTA. "Third wave" CBT (Acceptance and Commitment Therapy; Compassion

Focused Therapy) was given to two adults with DTTA.[5] One patient with denial of asthma severity demonstrated an improved psychological status, improved well-being, and a reduction of prednisolone and hospital admissions. The other patient with over-identification with asthma demonstrated improvements in well-being and psychological symptoms. In our current study, the techniques used (especially EMDR) were different, and our study involved an adolescent. However, both the study in adults and our study in an adolescent clearly indicate how CBT may bring relief of DTTA.

In clinical practice and research, self-reports and reports by parents, such as the asthma control test (ACT),[25,33] are common outcome variables in the standardized and multidimensional evaluation of children with asthma.[34] In a clinical setting, spirometry and other pulmonary function tests are often used of which FEV_1 is the most frequently used index for airway obstruction. However, in children and adolescents, even in severe asthma, FEV_1 is often within a normal range of 80 to 120 % in between asthma attacks. In the current study, FEV_1 of Sarah had improved to a level that was just in the normal range at follow-up giving some indication of improvement. A clear indication of improvement of asthma was given by the significantly reduced daily use of short-acting β_2-agonists and prednisolone during therapy and follow-up without hospital admission. The improvement during intervention and sustained improvement during follow-up on all primary outcomes was convincing. Overall, our results indicated that CBT and EMDR treatment positively impacted on asthma symptoms and the burden of asthma in this adolescent with DTTA and psychological comorbidity.

All secondary outcomes showed significant improvement. However, although Sarah's control of asthma improved as measured by the asthma control test, her asthma remained in the uncontrolled range according to the norms of this test,[25] showing that CBT did not cure her DTTA. Both quality of life, especially emotional functioning and behavioral problems, especially internalizing behavioral problems, showed a significant improvement. Unfortunately, when children and adolescents with asthma and severe psychological problems are presented to primary care and emergency departments, treatment often focuses on medical management only, which leads to medication overuse and increased admittance to hospital,[20] especially in children who overreact emotionally to the symptoms of asthma.[35] Therefore, it is important to identify and treat psychological problems in DTTA. This study and a previous study[36] support the recommendation that psychological evaluation and intervention should be considered early in the course of management of a patient with DTTA because it may help avoid

unnecessary overmedication and investigation, and it may yield rapid improvement in the patient's clinical condition.

Our study did not examine why anxiety and stress can exacerbate asthma. In response to stress and anxiety, the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) are commonly activated and these variables may be critically involved in asthma as well. Children with asthma who simultaneously experienced stress showed marked reductions in glucocorticoid receptor mRNA (HPA) and beta-2 adrenergic receptor mRNA (ANS),[9] and stress was associated with respiratory sinus arrhythmia (ANS) that may underlie airway obstruction in asthma.[37] To the extent that reduction in glucocorticoid receptor mRNA reflects diminished sensitivity to the anti-inflammatory properties of glucocorticoids and the reduction in beta-2 adrenergic receptor mRNA reflects a reduction of bronchodilatory properties of beta-agonists, this physiological process could play a role in resistance to therapy in patients with difficult-to-treat asthma and comorbid stress. Inclusion of physiological stress variables in experimental studies can test this notion.

Our study design has strengths and limitations. A strength is the use of a single-case experimental design with multiple repeated measurements, which allowed to thoroughly evaluate the effects of the intervention. A limitation inherent to assessment in asthma is the lack of objective measures of asthma exacerbations outside the hospital and the need to rely most on reports of exacerbations by the patient. Self-reports are subject to recall and other forms of biases. A potential way to obtain an indication of asthma exacerbations at home using repeated objective measures is to continuously assess oxygen saturation, heart rate, and respiration with ambulatory devices. However, this would be very cumbersome in a study that lasts such a long time. Moreover, for the specific case in our study, not the real occurrence of exacerbations appeared the problem, but perceiving any instance of shortness of breath as an exacerbation was the core problem for which she was treated with CBT.

This single-case study suggests that a psychological intervention customized to the individual psychological comorbidity is beneficial to adolescents with DTTA. A realistic option for future research is a design with small groups using multiple repeated measures as in this single-case experimental design. A sufficiently powered randomized controlled trial customized to individual patients with DTTA and with as severe psychological comorbidity as in the case of Sarah is only possible if multiple centers participate.

Conclusion

Our study tested the notion that psychological problems related to asthma attacks may maintain DTTA. It was shown that asthma symptoms and the burden of asthma were reduced after CBT and EMDR. Therefore, this proof-of-principle study suggests that DTTA may be improved by psychological interventions in pediatric patients characterized by having psychological stress or distress.

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Chapter 8

General discussion

Box 1. Main findings

The six studies of this thesis yielded the following main findings:

- 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 (chapter 2).

- In clinically treated children with asthma, internalizing behavioral problems before treatment are associated with a lower increase in quality of life during treatment (chapter 3).

- Parenting stress in parents of children with problematic severe asthma is low, but higher parenting stress, especially in the mother, is associated with more airway inflammation and greater behavioral problems in the child (chapter 4).

- After clinical multidisciplinary treatment at high altitude, medication level reduced and fractional concentration of exhaled nitric oxide (FeNO), asthma control and quality of life improved. However, it was not possible to predict inhaled corticosteroids tapering off from health status variables at treatment entrance (chapter 5).

- Before clinical multidisciplinary treatment, more children with problematic severe asthma had a dysfunctional score on asthma control, FeNO, quality of life, and behavioral problems. At post-treatment, the improvement was large and generally remained at a functional level at follow-up. Coping and parenting stress did not change after treatment (chapter 6).

- The single-case experimental design showed that asthma symptoms and the burden of asthma were reduced after cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) in an adolescent with difficult-to-treat asthma. Also medication use reduced and forced expiratory flow in 1 s (FEV_1) was just in the normal range at follow-up (chapter 7).

GENERAL DISCUSSION

This thesis examined behavioral problems and parenting stress in relation to asthma control and quality of life in children with problematic severe asthma, and evaluated the effects of multidisciplinary treatment on a broad set of biopsychosocial outcomes. The main findings (Box 1) are discussed in this section after which implications for future research and clinical practice are given.

The thesis was guided by a biopsychosocial model, assuming interrelatedness between biological and psychosocial variables similar to a hanging mobile toy in which movement of one component causes movement of all other components. This model was also the fundament of multidisciplinary treatment. It is obvious that only part of the multiple factors that affect the heterogeneous population of children with PSA could be investigated. The first part of the thesis assessed the presence of behavioral problems and parenting stress in relation to asthma control and quality of life of the child with PSA, while the second part evaluated the effects of multidisciplinary treatment on a broad set of biopsychosocial outcomes.

PSYCHOSOCIAL FACTORS

Children's behavior

With respect to children's behavior, we assumed that disease activity is influenced by children's behavior and vice versa. To clarify the possible role of behavioral problems of the child in relation to asthma, we examined whether behavioral problems were more often present in PSA. Besides, we examined whether behavioral problems were concurrently and prospectively associated with asthma severity and quality of life.

The results suggested that especially internalizing behavioral problems such as being withdrawn/depressed and somatic complaints are more pronounced in children with difficult-to-treat asthma than in children who did not fulfill the criteria of difficult-to-treat (chapter 2). Moreover, a low control of asthma and an associated lower quality of life were observed and associated with behavioral problems (chapter 2, 3, 5, 6, 7). A strong example indicating a link of cognitions and behavior with asthma control was suggested by a single-case study (chapter 7).

There are multiple explanations for the higher severity of behavioral problems in children with asthma. This can theoretically be due to the disease, to medication related to the asthma, or to psychosocial effects such as being treated differently by parents due to the disease. At first, the higher prevalence of somatic problems in our sample of children may suggest that more severe asthma is a risk factor for more internalizing problems, e.g., as a consequence of symptoms that are uncontrollable and unpredictable, or because immune and neuroendocrine parameters induce a passive state including internalizing behavior.[1] Secondly, adverse effects of asthma medications are rare[2] and adverse effects of inhaled corticosteroids are mild and sporadic.[3] Thus, effects of asthma medication do not seem to play a role in behavioral problems. Thirdly, in a previous study, psychosocial systemic variables were shown to be associated with stress in children and the child's perception of parental conflict in asthmatic children showed trends of triangulation (indirect communication of one family member with another through a third family member).[4] Thus, parenting stress is considered a possible factor in children's behavior. Besides, other psychosocial stressors may trigger the expression of asthma in children.[5] Finally, it is possible that more severe internalizing behavioral problems intensify the severity of asthma through poor adherence.[6, 7] Our results showed that behavioral problems linked to disease activity and all components of the biopsychosocial model (control of asthma, quality of life and parenting stress) of children with asthma. However, we did not prove the causal direction of the associations and it remains difficult to disentangle cause and effect. Likely, the group of children is heterogeneous with respect to the predominance of these influences. While in one child the one variable has a snowball effect on other variables, in other children other variables are important, or variables are hardly associated. Overall, it appears important to focus on behavioral problems of children in care. Even if improvement of behavioral problems does not influence asthma, then it is still valuable to focus treatment on behavioral problems because it may contribute to amelioration of the daily life of children.

Parenting stress

Among the social variables, parenting stress was considered a factor that may play a role in the perseverance of PSA. We examined the presence of parenting stress and its association with behavioral problems and disease severity in children with PSA. We hypothesized –first– that the level of parenting stress would be higher than in the general population and –second– that parenting stress would be associated with behavioral problems and disease severity in their children.

Overall, unexpected and in disagreement with our first hypothesis, the levels of parenting stress in our group were low. This is surprising, because parenting stress may depend –among other influences– on the child's problems and caregiver demands,[8] which are higher in our group than in the general population (chapter 2). Thus, these results were inconsistent with prediction from our biopsychosocial model. There are several possible explanations to explain the low level of parenting stress found in this study. According to the stress-appraisal model, parenting stress is not only determined by the severity of stressors but also by one's capability to deal with stressors.[9] In general, this group of parents may have learned to cope well with the disease of their child and have grown accustomed to their way of living and caring for their child. However, this would not explain why parenting stress for parents in our sample was lower than in reference groups of parents of children without a (severe) chronic disease. One possible way to understand this unexpected finding is by turning to concepts that assume stressors can have positive as well as negative consequences, as described under such headings as positive reappraisal,[10] positive reinterpretation,[11] and benefit finding or growth.[12] Some parents described caring for a chronic disabled child as a "commitment" that gave their life content and meaning[13] or the feeling of achieving a mission in life.[14, 15] Thus, besides being a possible source of stress, caring for a child with a chronic illness like asthma may be a means to discover and create meaning and purpose in life, or it may increase the bond between parents and between the parents and the child. This thesis did not include methods and variables to examine these ad hoc speculations.

However, we were able to examine associations of parenting stress with child variables. In agreement with the second hypothesis based on our biopsychosocial model, we found that parenting stress and the children's behavior are associated (chapter 4), but our cross-sectional data do not establish causality. The relationship between parenting stress and children's behavioral problems is commonly considered bidirectional, which can lead to an upward cycle that has negative consequences for both parent and child, i.e. higher levels of parenting stress and children's behavioral problems may fuel each other.[16, 17]

Also in agreement with the second hypothesis, parenting stress in mothers was associated with airway inflammation of their children (FeNO) (chapter 4). Parents having lower control of their child's asthma –as revealed in the child's higher level of airway inflammation– could be a stress factor for parents; alternatively, parenting stress can have aggravated the child's asthma.

In conclusion, our thesis supports the importance of the social component parenting stress as part of our biopsychosocial, since parenting stress is associated with behavioral problems and disease severity in children with PSA.

MULTIDISCIPLINARY TREATMENT

In the second part of the thesis, we examined whether asthma control and associated factors can improve after multidisciplinary interventions. Pediatric asthma patients who turned out to be difficult-to-treat in primary and secondary care were participants in these series of studies. Effects on asthma control, quality of life, behavior and parenting stress were evaluated.

Our study indicated that asthma control and associated quality of life showed large improvements after multidisciplinary treatment and that the reduction of behavioral problems was highly significant (chapter 5, 6 and 7). In disagreement with our biopsychosocial model, children's coping and parenting stress did not change for the total group of children with PSA (chapter 6). The profile of coping styles may have been too heterogeneous with many children having an adequate score at the start of treatment to be able to observe a mean change in coping. Also, overall parenting stress was low and heterogeneous at pre-treatment (chapter 6).

Although behavioral problems were found to be a predictor of quality of life after treatment, they did not predict the change in asthma control (chapter 3). Moreover, asthma control and quality of life at pre-treatment did not predict the reduction of medication after treatment at high altitude (chapter 5).

Overall, the results indicated that multidisciplinary treatment is a useful approach for a heterogeneous group of children with asthma that remained uncontrolled in secondary care. These analyses were based on evaluation of multiple outcome measures in the total group of children. In clinical practice, the program was customized to the individual children. Improvement may have been observed because of the focus on the primary factors that were assumed to maintain the asthma in an individual child. Treatment in any child was aimed at improving asthma control, and our evaluation showed that for most children this was successful. Improvement of other variables was not an issue in any child, and it is therefore not surprising that effect sizes of other outcomes were lower. In a future evaluation, multiple variables –including therapeutic modalities– should be documented better in research. Moreover, not only the therapy

but also the outcome variables should –before the start of therapy– be customized to the individual patient.

A clear example of a design in which both the treatment and treatment-evaluation were customized to the individual, was provided by the proof-of-principle study involving a 16-year-old girl with difficult-to-treat asthma (chapter 7). In this patient, asthma-specific fear induced by disturbed memories and distorted cognitions following frightening asthma attacks were driving asthma exacerbations. After cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR), asthma symptoms and its burden were significantly reduced. The study indicated that psychological interventions customized to the individual may be beneficial to selected adolescents with difficult-to-treat asthma.

In the introduction, the model of a hanging mobile toy was presented in which movement of one component causes movement of the other components. In PSA, it appears that both the components and connections of such a model are different between patients. That is, patients are heterogeneous in the sense that different pathological processes maintain the asthma and that different psychological, environmental and social processes may play a crucial role in maintaining PSA. For some patients, e.g., the adolescent who was evaluated in chapter 7, cognitive behavioral factors are crucial, for others a specific immunoglobulin might drive the asthma, and for others still other factors are crucial. Therefore, treatment customized to the individual patient with PSA is of great importance. Overall, our results indicated that it is possible to achieve an improvement of asthma control in children with PSA who remained uncontrolled in secondary care.

METHODOLOGICAL LIMITATIONS AND FUTURE RESEARCH

First, our studies did not include research of mediating variables. For instance, we did not examine why anxiety and stress can exacerbate asthma and vice versa. Possible mediators could be the sympathetic nervous system and the hypothalamic pituitary adrenal axis,[18] since stressful life events can cause exacerbation of asthma symptoms[19] and stress is associated with these physiological stress systems that play a role in asthma.[4, 5, 20, 21] Inclusion of physiological and psychological stress variables could have tested this notion.

Another mediator could have been adherence. Psychosocial problems can negatively interfere with adherence to inhaled steroids, especially in adolescence.[7, 22, 23] Being similar to peers is important in adolescence, while the disease and its consequences may cause a differentiation from healthy peers.[24] Oppositional behavior, current smoking, poor planning capabilities, and incorrect health beliefs about medication and illness are associated with non-adherence[25] and can be common problems in adolescence.

Also, environmental factors including exposure to allergic factors should be taken into account. The pathogenic mechanisms of asthma include eosinophilic and non-eosinophilic pathways, potentially induced by allergens, viral infections and other non-allergic sensitizing triggers. Air pollution and microbes may lead to airway inflammation and hyper-responsiveness.[26] Also cigarette smoke may trigger biological factors in children with asthma. We did not measure environmental factors like allergen exposure, air pollution or smoking in the home environment of children in this study.

Second, the children of our study represented a population that was referred to specialized asthma clinics. The parents and children participated on a voluntary basis after having been informed about the purpose of the study. It is unknown whether our samples were representative for the population of clinically treated children with PSA. We also were not able to examine the separate effects of the clinics at sea level and high altitude, because the detailed reasons to refer to one of those clinics were not documented and may involve aspects such as homesickness. Thus, confounding by indication may have occurred. Only randomization would have offered the possibility to make this comparison.

Third, a limitation inherent to assessment in asthma is the lack of generic objective measures of asthma control. This is due to the heterogeneous physiological substrate of asthma. Although questionnaire reports are subjective and subject to recall bias and other forms of bias, they are the best option available at the moment to evaluate asthma control.

Fourth, in research and clinical practice, many terms refer to asthma being uncontrolled, e.g. difficult-to-control asthma, difficult-to-treat asthma, difficult asthma, severe asthma, problematic asthma, uncontrolled asthma, severe therapy-resistant asthma etc. Studies are difficult to compare, because the highly overlapping definitions nevertheless differ a little bit. The abundance of terms should be reduced and the clinical definition should be improved. In this thesis,

we used the definition of Hedlin[27] who coined the term "Problematic severe asthma" to describe children with any combination of chronic symptoms, acute severe exacerbations and persistent airflow limitation despite prescription of multiple therapies. The approach to PSA may vary with the age of the child, but, in general, three steps need to be taken in order to separate difficult-to-treat asthma from severe therapy-resistant asthma. First, confirmation that the problem is really due to asthma requires a complete diagnostic re-evaluation. Secondly, the pediatrician needs to systematically exclude comorbidity, as well as personal or family psychosocial disorders. The third step is to re-evaluate medication adherence, inhaler technique and the child's environment.[27] There is a clear need for a common international classification of pediatric asthma, since there is currently no uniform agreement regarding how best to approach children with PSA.

Our conclusions need substantiation in future studies in children with PSA. Randomized controlled experimental research focusing on systematic evaluation of long-term effects of all variables is needed to get insight in the direction and mechanisms behind the associations and possible mediators. A randomized study comparing comprehensive customized treatment of children with moderate to severe atopic dermatitis (and asthma) at high altitude treatment with that at sea level is recently started, and will inform us better about the specific contribution of the mountain climate.[28] A sufficiently powered randomized controlled trial customized to individual patients with PSA and with severe psychological comorbidity is only possible if multiple centers participate. However, also a design with small groups could be useful, e.g., a series of experimental single case studies or cross-over design, using validated outcomes and multiple repeated measures customized to the individual, and including a long follow-up period.

CLINICAL IMPLICATIONS

Our results suggested that health psychosocial variables such as behavioral problems and parenting stress can be important in children with PSA. Therefore, we recommend a systematic screening of these variables to be part of asthma care. This could be screening in clinical consults or by using generic or disease-specific questionnaires. In children, assessments should be adapted to developmental ages. Not only the way in which children are able to provide adequate feedback about how they feel or think about specific subjects change over time, but also the specific tasks they face regarding their developmental age and self-

management. Web-based applications can be used to systematically monitor the child or adolescent with asthma and their parents, and give the opportunity to define customized outcome measures before the start of treatment.

The evaluation of multidisciplinary clinical treatment in the cohort of children with PSA as well as the individual outpatient treatment in an adolescent (single-case study) indicated the importance of focusing care in this group of children with PSA on all possible sources of problems, i.e., disease exacerbations and behavioral problems in the child as well as parenting stress. Treatment of internalizing behavioral problems may optimize the quality of life in children with PSA. The associations of parenting stress with behavioral problems and inflammatory activity in the child indicated that a systems approach including caregivers may be useful in selected cases.

Motivated by the promising results of our proof-of-principle study, we recommend to include methods of the single-case experimental design to evaluate the outcome with repeated assessments, customized to the individual patient with PSA. In this way, changes in outcomes can be detected in time and could be tackled immediately by adequate interventions. Technology applications (E-health) could be used to support such an approach.

CONCLUDING REMARKS

This thesis examined problematic severe asthma in children from a biopsychosocial perspective. The results indicated that multiple biopsychosocial contributing factors should be considered when asthma is poorly controlled. Therefore, regular screening of asthma control and disease activity variables as well as psychosocial variables (behavioral problems in the child and parenting stress) is recommended, customized to the individual patient with PSA.

Moreover, it was indicated that multidisciplinary treatment and individualized psychological interventions offer the opportunity to improve asthma control. Importantly, control of asthma can be achieved even in children with "uncontrolled" asthma. Multidisciplinary treatment customized to children's personal profile may have been crucial to achieve this effect.

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Samenvatting

Dutch summary

INLEIDING

Astma is een chronische ontsteking van de longen. De mate waarin de astma onder controle is (verder aangeduid als "astmacontrole"), is van groot belang voor het dagelijks leven van het kind en zijn omgeving. Bij kinderen met "problematisch ernstig astma" lukt het niet om de astma onder controle te krijgen, ondanks optimale medische behandeling.

Gezondheid wordt bepaald door een complexe wisselwerking tussen lichamelijke en psychische processen. Vanuit het biopsychosociaal model (Figuur 1) wordt verondersteld dat biologische en psychosociale variabelen nauw met elkaar verbonden zijn. Het evenwicht tussen deze variabelen kan gezien worden als een mobile: speelgoed met aan touwtjes hangende voorwerpen, waarin disbalans van één van de componenten een verandering teweeg brengt in alle andere componenten.

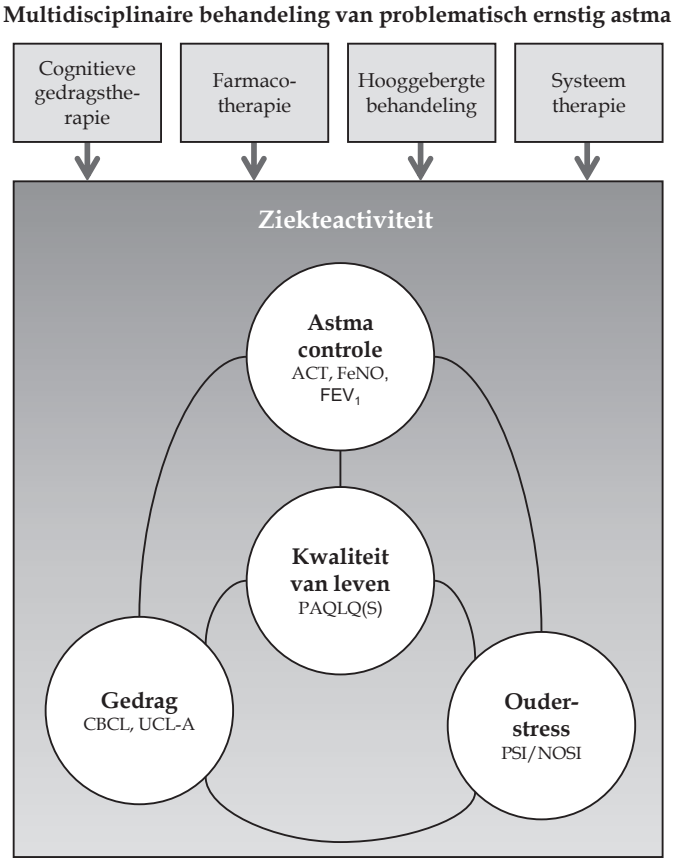
Dit proefschrift bevat onderzoek naar gedragsproblemen bij kinderen met problematisch ernstig astma en stress bij de ouders in samenhang met astmacontrole en kwaliteit van leven, evenals een evaluatie van de effecten van multidisciplinaire behandeling.

PSYCHOSOCIALE FACTOREN

Gedrag van het kind

Het was onduidelijk hoe vaak gedragsproblemen voorkomen bij kinderen met problematisch ernstig astma. In hoofdstuk 2 bleek dat een aanzienlijk aantal kinderen internaliserende gedragsproblemen heeft, zoals teruggetrokken gedrag en somberheid. Deze gedragsproblemen gaan soms gepaard met een lagere kwaliteit van leven en onvoldoende astmacontrole. Een sterk verband tussen gedachten, gedrag en astmacontrole werd beschreven in een onderzoek naar het effect van behandeling bij een adolescent met problematisch ernstig astma (hoofdstuk 7). Ook de resultaten uit de hoofdstukken 3, 4, en 6 lieten zien dat gedragsproblemen een rol spelen bij ziekteactiviteit en de andere componenten uit het biopsychosociaal model (astmacontrole, kwaliteit van leven en stress bij de ouders).

We hebben echter geen onderzoek kunnen doen naar de richting van oorzakelijke verbanden. De groep kinderen met problematisch ernstig astma is heterogeen, wat wil zeggen dat in ieder kind verschillende factoren een rol kunnen spelen



Figuur 1. Biopsychosociaal model van de psychologische factor gedrag en de sociale factor ouderstress in samenhang met astmacontrole en kwaliteit van leven in kinderen (onder) en de effecten van multidisciplinaire behandeling op alle componenten van het model inclusief ziekteactiviteit (boven). De variabelen die in dit proefschrift zijn onderzocht zijn astmacontrole (ACT), longfunctie (FEV_1) en luchtwegontsteking (FeNO), kwaliteit van leven [PAQLQ(S)], gedragsproblemen (CBCL) en coping (UCL-A), en ouderstress (PSI/NOSI).

waarbij oorzaak en gevolg niet altijd scherp zijn te onderscheiden. De bevindingen geven wel aan dat het nuttig lijkt om in de behandeling van kinderen met problematisch ernstig astma ook aandacht te besteden aan gedragsproblemen.

Ouderstress

Het was niet bekend welke rol ouderstress speelt bij kinderen met problematisch ernstig astma. In hoofdstuk 4 hebben we onderzocht of er sprake is van ouderstress en of ouderstress samenhangt met gedragsproblemen en ziekteactiviteit in het kind. We hadden de verwachting dat ouderstress veel zou vóórkomen, vanwege de ernst van de astma. Dat blijkt echter niet het geval. De ouders gaven

over het algemeen zelfs minder stress aan dan ouders van gezonde kinderen. Wel bleek sprake van meer ouderstress als de kinderen naast astma ook gedragsproblemen hadden. Ook de moeders van kinderen met luchtwegontsteking ervoeren meer stress. De sociale component ouderstress binnen het biopsychosociale model kan dus wel degelijk een rol spelen waar rekening mee gehouden moet worden, maar in de totale groep van kinderen met problematisch ernstig astma lijkt het mee te vallen.

MULTIDISCIPLINAIRE BEHANDELING

In het tweede deel van dit proefschrift hebben we onderzocht in hoeverre astmacontrole en andere factoren kunnen verbeteren na multidisciplinaire behandeling. Het onderzoek richtte zich op kinderen bij wie binnen de zorg van de eerste of tweede lijn geen goede controle van de astma mogelijk bleek. Deze kinderen werden naar de derdelijnszorg voor gespecialiseerde multidisciplinaire behandeling verwezen.

In hoofdstuk 3, 5 en 6 laten we zien dat astmacontrole en de daarmee samenhangende kwaliteit van leven duidelijk verbeterden na multidisciplinaire behandeling. Ook verminderden de gedragsproblemen van kinderen na multidisciplinaire behandeling. Stress van ouders en coping van het kind lieten over het algemeen geen verandering zien.

Hoewel gedragsproblemen een belangrijke voorspeller zijn van kwaliteit van leven na de behandeling, hebben wij niet aan kunnen tonen dat gedragsproblemen ook de verandering in astmacontrole voorspellen (hoofdstuk 3). Ook voorspellen astmacontrole en kwaliteit van leven bij opname niet de afbouw van medicatie tijdens de behandeling (hoofdstuk 5).

Over het algemeen kunnen we concluderen dat na multidisciplinaire behandeling sprake is van een goede astmacontrole bij de meeste kinderen, die individueel verschillen voor wat betreft alle componenten die in figuur 1 werden gepresenteerd, inclusief de precieze onderliggende pathologie. Waarschijnlijk is het daarbij belangrijk geweest dat de behandeling werd afgestemd op het individuele kind en zijn systeem.

Een voorbeeld voor een individuele op maat gemaakte behandeling is het onderzoek bij een patiënte van 16 jaar met problematisch ernstig astma (hoofd-

stuk 7). Dit meisje had last van angst voor een astma aanval en door haar astma ondervond zij in haar dagelijks leven problemen en stress. De behandeling bestond uit 20 bijeenkomsten, waarin Cognitieve Gedragstherapie (CGT) en Eye Movement Desensitization and Reprocessing (EMDR) werden geboden. Na de behandeling waren de astma aanvallen afgenomen en bleek minder medicatie nodig. De patiënte had geleerd om op een betere manier met haar astma om te gaan en had minder last van stress en piekergedachten. Het onderzoek gaf aan dat het nuttig kan zijn om naast de astmabehandeling met medicatie ook een op maat gemaakte psychologische behandeling te bieden als sprake is van problematisch ernstig astma en er tegelijkertijd ook psychische problemen zijn.

BELANGRIJKSTE CONCLUSIES

- Bij kinderen met problematisch ernstig astma komen vaak internaliserende gedragsproblemen voor en een lagere kwaliteit van leven.
- Internaliserende gedragsproblemen hangen samen met een lagere kwaliteit van leven gedurende de behandeling.
- Ouderstress is over het algemeen laag, maar ouderstress hangt samen met gedragsproblemen en de ziekteactiviteit van het kind.
- Na multidisciplinaire behandeling blijkt sprake van een verbeterde astmacontrole, kwaliteit van leven en gedragsproblemen.
- Behandeling die goed op het individu is afgestemd laat verbetering zien in astma symptomen, gedachten en gedrag.

Slotopmerking

In dit proefschrift is problematisch ernstig astma in kinderen onderzocht vanuit een biopsychosociaal perspectief. De resultaten bevestigen dat er meerdere psychosociale factoren samenhangen met een slechte astmacontrole. Daarom is het belangrijk dat er in deze groep regelmatig screening plaatsvindt van astmacontrole en variabelen die ziekteactiviteit betreffen, maar ook van psychosociale variabelen (gedrag van het kind en ouderstress). Deze screening zal afgestemd moeten zijn op het individuele kind met problematisch ernstig astma.

Multidisciplinaire behandeling, systemische behandeling en individuele psychologische interventies geven de mogelijkheid om astmacontrole te verbeteren. Zelfs in kinderen met ongecontroleerd astma kan adequate astmacontrole worden bereikt. Om een optimaal behandeleffect te krijgen, is het belangrijk dat de behandeling goed op het individuele kind is afgestemd.

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Ik hoop dat dit werk zal bijdragen aan een beter leven voor kinderen met problematisch ernstig astma en hun ouders.

Marieke Verkleij
Hilversum, maart 2016

[1] E. Erikson (1902-1994)
[2] Oud Afrikaans gezegde
[3] Uit: Die Mutter (1931), Bertolt Brecht (1898-1956)
[4] Confucius, Chinese filosoof (551-479 v. Chr)

Bibliography & Curriculum vitae

INTERNATIONAL PEER REVIEWED PUBLICATIONS

- **Verkleij M**, van de Griendt EJ, Kaptein AA, van Essen-Zandvliet LE, Duiverman EJ, Geenen R (2011). Behavioral problems in children and adolescents with difficult-to-treat asthma. J Asthma; 48: 18-24.
- **Verkleij M**, van de Griendt EJ, Kaptein AA, van Essen-Zandvliet LE, Duiverman EJ, Geenen R (2013). The prospective association between behavioural problems and asthma outcome in young asthma patients. Acta Paediatr; 102: 504-9.
- Van de Griendt EJ, **Verkleij M**, Douwes JM, van Aalderen WM, Geenen R (2014). Problematic severe asthma in children treated at high altitude: Tapering the dose while improving control. J Asthma; 51: 315-9.
- **Verkleij M**, van de Griendt EJ, Colland V, van Loey N, Beelen A, Geenen R (2015). Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma. J Clin Psychol Med Settings; 22: 179-93.

SUBMITTED MANUSCRIPTS

- **Verkleij M**, Maric M, Colland V, Geenen R. Cognitive behavioral therapy and eye movement desensitization and reprocessing in an adolescent with difficult-to-treat asthma: A single-case experimental design.
- **Verkleij M**, van Ewijk B, Beelen A, Geenen R. Multidisciplinary clinical treatment in a tertiary setting for children with asthma: A prospective evaluation.

INTERNATIONAL SCIENTIFIC CONGRESS AND CONFERENCE ABSTRACTS

- Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma. *Longdagen, Ermelo, 2016.* **Poster presentation.**
- Cognitive behavioral therapy and EMDR in an adolescent with difficult-to-treat asthma: A single-case experimental design. *Vijfde Amsterdam Kindersymposium, Amsterdam, 2016.* **Oral presentation.**
- Prevalence of symptoms of depression and anxiety in adolescents with Cystic Fibrosis and their parents in a single CF Center in the Netherlands.

Symposium "Van hielprik tot donorlong," Nederlandse Cystic Fibrosis Stichting, Utrecht, 2016. **Poster presentation.**

- Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma. *European Respiratory Society (ERS), Amsterdam, 2015.* **Poster presentation.**
- Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma. *Vierde Amsterdam Kindersymposium, Amsterdam, 2015.* **Oral presentation.**
- Parenting stress related to behavioral problems and disease severity in children with problematic severe asthma. *The 2nd International Conference in Pediatric Psychology, Amsterdam, 2014.* **Poster presentation.**

AWARDS

- Cystic Fibrosis Innovation Award 2014. *CF-Centrale, Den Haag, 2014.*

SCIENTIFIC PRESENTATIONS

- Pilot study CF My Way. *CF-Centrale Erasmus University, Rotterdam, 2015.*
- Adherence and adolescence. *Nationaal Pulmonaal Lustrumcongres, Ede, 2015.*
- Mental health screening in the Netherlands. *European Cystic Fibrosis Society (ECFS), Brussels, Belgium, 2015.*
- Adolescents with asthma. *Netwerk Longverpleegkundigen Noord-Holland, Purmerend, 2015.*
- Psychopathology in adolescents with asthma. *2e Nationaal Pulmonaal Congres, Ede, 2012.*
- Psychopathology in adolescents with asthma. *Scientific congress, University Medical Center Groningen, Groningen, 2012.*
- Development of children with asthma and comorbid behavioral problems. *Symposium Kinderlongverpleegkundigen, Zwolle, 2012.*
- Behavioral problems in children with asthma. *1e Nationaal Pulmonaal Congres, Ede, 2011.*

CURRICULUM VITAE

Marieke Verkleij was born on January 2nd, 1973 in Bodegraven, the Netherlands. After completing secondary education in 1991, she studied orthopedagogy at Utrecht University which she combined with her study of music (viola) at the Conservatory of Utrecht. She won scholarships for studying viola in Czech Republic, Japan and the USA. In 1998 she received her master's degree in orthopedagogy at Utrecht University and in music at the Conservatory of Utrecht. She continued her viola study in performing arts at the Conservatory of Amsterdam and Utrecht and graduated in 2000. From 2007-2009 she lived in Davos, Switzerland, where she started her PhD research project in the Netherlands Asthma Center Davos (NAD). From 2009-2014 she worked as a child psychologist at the department of child psychiatry of Zonnehuizen, the Netherlands, and received her postmaster degree as a health-care psychologist in 2014. Since 2014, she is working at the VU University Medical Center Amsterdam as a psychologist specialized in pediatric pulmonology. In 2015 she graduated as a Cognitive Behavioral Therapist and Eye Movement Desensitization and Reprocessing (EMDR) therapist. She is member of the EMDR-Special Interest Group Somatic Disorders and European Cystic Fibrosis Mental Health Working Group.

Marieke Verkleij werd geboren op 2 januari 1973 te Bodegraven. Na het behalen van haar VWO diploma in 1991 combineerde zij de studie orthopedagogiek aan de Universiteit Utrecht met docerend musicus altviool aan het Utrechts Conservatorium. Zij won studiebeurzen waarmee ze altviool studeerde in o.a. Tsjechië, Japan en de VS. In 1998 behaalde zij haar doctoraal orthopedagogiek en diploma conservatorium docerend musicus. Zij vervolgde de opleiding tot uitvoerend musicus altviool aan de conservatoria van Amsterdam en Utrecht, waar zij in 2000 afstudeerde. De daaropvolgende jaren wijdde zij zich aan de kamermuziek en haar eigen lespraktijk, in combinatie met haar baan als orthopedagoog in het speciaal basisonderwijs.
Van 2007-2009 woonde zij met haar gezin in Davos, Zwitserland, en in die periode heeft zij dit onderzoeksproject vanuit het Nederlands Astmacentrum Davos opgestart. Na terugkomst in Nederland in 2009 was zij werkzaam als orthopedagoog in de kinder- en jeugdpsychiatrie van Zonnehuizen te Zeist, van waaruit zij van 2011-2013 de GZ-opleiding volgde. Na het behalen van de GZ-opleiding volgde zij het opleidingstraject tot Cognitief Gedragstherapeut VGCt. Sinds 2014 werkt zij als medisch psycholoog met aandachtsgebied kinderlongziekten in het VU Medisch Centrum te Amsterdam. In 2015 behaalde zij haar registraties tot Cognitief Gedragstherapeut en EMDR therapeut. Zij is lid van de EMDR-Special Interest Group Somatiek en de European Cystic Fibrosis Mental Health Working Group.