

PSYCHOLOGICAL DISORDERS

Behavioral Problems in Children and Adolescents with Difficult-To-Treat Asthma

MARIEKE VERKLEIJ, M.Sc.,^{1,2,*} ERIK-JONAS VAN DE GRIENDT, M.D.,^{3,4} AD A. KAPTEIN, PH.D.,⁵ LIESBETH VAN ESSEN-ZANDVLIET, M.D., PH.D.,² ERIC DUIVERMAN, M.D., PH.D.,⁶ AND RINIE GEENEN, PH.D.^{7,8}

¹European Asthma and Allergy Center, Davos, Switzerland.

²Asthma Center Heideheuvel, Hilversum, The Netherlands.

³Dutch Asthma Center, Davos, Switzerland.

⁴Emma Children's Hospital Academic Medical Center, Amsterdam, The Netherlands.

⁵Unit of Psychology, Leiden University Medical Center, Leiden, The Netherlands.

⁶Department of Paediatrics, Division of Paediatric Pulmonology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, The Netherlands.

⁷Department of Clinical & Health Psychology, Utrecht University, Utrecht, the Netherlands.

⁸Department of Rheumatology & Clinical Immunology, University Medical Center, Utrecht, The Netherlands.

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 **Results.** Especially internalizing behavioral problems such as being withdrawn/depressed and somatic complaints were more severe in the asthmatic groups compared to the healthy reference groups.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. **Conclusions.** 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.

Keywords asthma, behavior, child, difficult-to-treat asthma, quality of life

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 neuroendocrine 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

*Corresponding author: Marieke Verkleij, M.Sc., Asthma Center Heideheuvel, Soestdijkerstraatweg 129, 1213 VX Hilversum, The Netherlands; E-mail: mverkleij@heideheuvel.nl

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 were 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 the task forces of the American Thoracic Society and European Respiratory Society, and ENFUMOSA study (Table 1) (13–16). A positive score on difficult-to-treat asthma denotes persistent or severe asthma and lack of adequate control of asthma symptoms (such as exercise intolerance, two or more times per week in need of extra reliever therapy, symptoms at night) despite high dose of maintenance therapy, adequate use of spacers and devices, confirmed diagnosis, and good compliance. Difficult-to-treat asthma according to these criteria was established on

the day of arrival by one pediatrician per clinic during a structured interview with the patients and their parents, and using data from the referring clinician about compliance history and pulmonary function testing at the time of diagnosis. Good compliance implicated no missing doses on 6 or 7 days per week. In case of doubt or an anamnestic compliance less than 6 days a week, compliance was regarded as ‘poor’ and thus criteria on difficult-to-treat asthma were not met. Intake of medication was supervised during the stay in the clinic.

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 12 hours before PFT. Lung function parameters that were obtained and evaluated were forced expiratory volume in 1 second (FEV₁) and maximal expiratory flow at 50% of forced vital capacity (MEF₅₀). 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).

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 $\geq 800 \mu\text{g}$ budesonide/beclometasone dipropionate or equivalent ($\geq 500 \mu\text{g}$ fluticasone of $\geq 400 \mu\text{g}$ beclometasone dipropionate extra-fine or $\geq 320 \mu\text{g}$ 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 ($\text{FEV}_1 < 80\%$ 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.

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 broadband scales internalizing (1 outlier) and externalizing problems (2 outliers); and the domain scales anxious/depressed (2), withdrawn/depressed (1), thought problems (1), attention problems (1), rule-breaking behavior (2), and aggressive behavior (2). These outlying variables were assigned a score that was one unit larger than the next most extreme score of the score distribution (24).

Statistical analyses were done with SPSS 16.0. The values of $\alpha < 0.05$ (two-sided) were considered statistically significant. Differences between groups were examined with independent samples *t*-tests and with a nonparametric test for lung function (Mann–Whitney *U* test). Cohen's effect size estimates (*d*) were calculated: $0.2 \leq d < 0.5$ indicates a small effect, $0.5 \leq d < 0.8$ a medium effect and $d \geq 0.8$ a large effect (25).

RESULTS

Patient Characteristics

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

Table 2 shows the characteristics of 83 patients with a complete data set and a certified diagnosis of asthma. The children and adolescents in the difficult-to-treat asthma ($n = 31$) and not-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, $d = 0.4$).

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.

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).

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	Not-Difficult-to-treat asthma	<i>p</i>
Total group <i>n</i> (%)	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] years	12.7[2.6]	13.0[3.0]	.59 ^b
Dutch sample [SD]	12.5[2.4]	13.3[2.0]	
German sample [SD]	13.8[3.3]	13.0[3.1]	
Mean FEV ₁ [SD] ^c	106.7[14.6]	99.8[14.4]	.04 ^d
Dutch sample [SD]	107.3[14.2]	101.5[12.9]	
German sample [SD]	102.8[18.5]	99.4[14.8]	
Mean MEF ₅₀ [SD] ^c	97.0[25.9]	87.6[23.9]	.06 ^d
Dutch sample [SD]	97.1[23.3]	89.0[27.4]	
German sample [SD]	96.4[41.7]	87.3[23.6]	
Mean FeNO [SD] ^e	39.5[30.0]	33.8[31.6]	.21 ^d
Dutch sample [SD]	38.8[27.5]	35.7[19.6]	
German sample [SD]	45.9[55.5]	33.4[33.9]	

Note. FEV₁ (forced expiratory volume in 1 second) and MEF₅₀ (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 (FEV₁ and MEF₅₀).

^aChi² test for gender and country; ^bIndependent samples *t*-test; ^c% pred, percentage predicted; ^dMann–Whitney *U* test; ^eppb, parts per billion.

TABLE 3.—Quality of life of patients with difficult-to-treat asthma (*n* = 31) versus not-difficult-to-treat asthma (*n* = 52).

	Quality of life (range 1–7) ^a		<i>t</i>	<i>p</i>
	Difficult-to-treat asthma (<i>n</i> = 31)	Not-difficult-to-treat asthma (<i>n</i> = 52)		
Overall, mean ± SD	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 (range)	5.1 ± 1.5(1.8–7.0)	5.7 ± 1.2(2.3–7.0)	–1.95	.06

^aA higher score on the quality of life scales reflects a better quality of life.

TABLE 4.—Behavioral problems of patients with difficult-to-treat asthma and not-difficult-to-treat asthma. The mean scores reflect deviations from healthy CBCL norms.

Group	Difficult-to-treat asthma <i>n</i> = 31			Not-difficult-to-treat asthma <i>n</i> = 52			Comparison between groups	
	Mean ± SD	<i>t</i>	<i>p</i>	Mean ± SD	<i>t</i>	<i>p</i>	<i>t</i>	<i>p</i>
CBCL ^a								
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

^aMean 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.

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 neuroendocrine 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 not-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 FEV₁ 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 not-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, we 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 the 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 not-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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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med* 2001; 163:1093–1096.
2. Hayden ML, Dolan CM, Johnson C, Morris SM, Bleecker ER. High level health care utilization in severe and difficult-to-treat asthma. *J Allergy Clin Immunol* 2002; 109:292–293.
3. Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998; 12: 1209–1218.
4. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet L. Severe asthma in adults: What are the important questions? *J Allergy Clin Immunol* 2007; 119:1337–1348.
5. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003; 22:478–483.
6. Goldbeck L, Koffmane K, Lecheler J, Thiessen K, Fegert JM. Disease severity, mental health, and quality of life of children and adolescents with asthma. *Pediatr Pulmonol* 2007; 42:15–22.
7. Katon W, Lozano P, Russo J, McCauley E, Richardson L, Bush T. The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared to controls. *J Adolesc Health* 2007; 41:455–463.
8. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: A meta-analysis. *J Dev Behav Pediatr* 2001; 22:430–439.
9. Marin TJ, Chen E, Munch JA, Miller GE. Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. *Psychosom Med* 2009; 71:378–384.
10. Rhee H, Belyea MJ, Czurzynski S, Brasch J. Barriers to asthma self-management in adolescents: Relationships to psychosocial factors. *Pediatr Pulmonol* 2009; 44:183–191.
11. Spieksma M, Zuidema P, Leupen M. High altitude and house-dust mites. *BMJ* 1971; 1:82–84.
12. Boehmer ALM, Brackel HJL, Duiverman EJ, van Essen-Zandvliet EEM, van Ewijk BE, van de Griendt EJ, Hugen CAC, Landstra AM, Versteegh FGA. Moeilijk behandelbaar astma: diagnostiek en behandelopties [Difficult-to-treat asthma: Diagnosis and treatment]. *Tijdschr Kindergeneesk* 2009; 77:255–262.
13. Proceedings on the ATS workshop on refractory asthma: Current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000; 162:2341–2351.
14. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, Bel E, Burney P, Chanez P, Connett G, Corrigan C, de Blic J, Fabbri L, Holgate ST, Ind P, Joos G, Kerstjens H, Leuenberger P, Lofdahl CG, McKenzie S, Magnussen H, Postma D, Saetta M, Salmeron S, Sterk P. Difficult/therapy-resistant asthma: The need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS task force on difficult/therapy-resistant asthma. *Eur Respir J* 1999; 13:1198–1208.
15. The ENFUMOSA cross sectional European multicentre study on the clinical phenotype of chronic severe asthma. European network for understanding mechanisms of severe asthma. *Eur Respir J* 2003; 22:470–477.
16. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). 2008. Available at: www.ginasthma.org
17. ATS/ERS Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005; 171:912–930.
18. Barreto M, Rennerova Z, Montesano M, Alterio A, Trubacova D, Ronchetti R, Pia Villa M. Variations in exhaled nitric oxide in children with asthma during a 1-week stay in a mountain village sanatorium. *J Asthma* 2008; 45:453–458.
19. Achenbach TM, Rescorla LA. Manual for the Child Behavior Checklist (CBCL), multicultural supplement to the manual for the ASEBA school-age forms & profiles, and scoring program Form Version Upgrade 2007. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families, 2007.
20. Arbeitsgruppe Deutsche Child Behavior Checklist. Elternfragebogen über das Verhalten von Kindern und Jugendlichen: Deutsche Bearbeitung der Child Behavior Checklist (CBCL/4-18). Einführung und Anleitung zur Handauswertung. 2. Auflage mit Deutschen Normen. Arbeitsgruppe Kinder-, Jugend-, und Familiendiagnostik, Köln, Germany 1998.

21. Achenbach TM. Manual for the Child Behavior Checklist/ 4–18 and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry, 1991.
22. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996; 5:35–46.
23. Raat H, Bueving HJ, Jongste de JC, Grol MH, Juniper EF, Wouden van der JC. Responsiveness, longitudinal- and cross-sectional construct validity of the paediatric asthma quality of life questionnaire (PAQLQ) in Dutch children with asthma. *Qual Life Res* 2005; 14:265–272.
24. Tabachnick BG, Fidell LS. Using multivariate statistics. Boston, MA: Allyn and Bacon, 2001.
25. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press, 1977.
26. Bussamra MH, Stelmach R, Rodrigues JC, Cukier A. A randomized, comparative study of formoterol and terbutaline dry powder inhalers in the treatment of mild to moderate asthma exacerbations in the pediatric acute care setting. *Ann Allergy Asthma Immunol* 2009; 103:248–253.
27. Garcia-Marcos L, Ros-Lucas JA, Sanchez-Solis M. Inhaled corticosteroids in asthmatic children: Are they as safe in infants and preschoolers as in older children? A review. *Curr Drug Saf* 2008; 3:35–45.
28. Bender BG, Iklé DN, DuHamel T, Tinkelman D. Neuropsychological and behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. *Pediatrics* 1998; 101: 355–360.
29. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: A systematic review. *Patient Educ Couns* 2009; 75:162–168.
30. Sawyer MG, Spurrier NJ, Waites L, Kennedy D, Martin AJ, Baghurst P. The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma. *Qual Life Res* 2000; 9:1105–1115.
31. Visser-van Balen H, Sinnema G, Geenen R. Growing up with idiopathic short stature: Psychosocial development and hormone treatment: A critical review. *Arch Dis Child* 2006; 91:433–439.
32. Döpfner M, Schmeck K, Poustka F, Berner W, Lehmkuhl G, Verhulst F. Behavioral symptoms of children and adolescents in Germany, the Netherlands and USA. A cross-cultural study with the child behavior checklist. *Nervenarzt* 1996; 67:960–967.
33. Schmeck K, Poustka F, Döpfner M, Pluck J, Berner W, Lehmkuhl G, Fegert JM, Lenz K, Huss M, Lehmkuhl U. Discriminant validity of the child behavior checklist CBCL 4/18 in German samples. *Eur Child Adolesc Psychiatry* 2001; 10:240–247.
34. Ivanova MY, Dobrea A, Döpfner M, Erol N, Fombonne E, Fonseca AC, Frigerio A, Grietens H, Hannesdottir H, Kanbayashi Y, Lambert M, Achenbach TM, Larsson B, Leung P, Liu X, Minaei A, Mulatu MS, Novik TS, Oh KJ, Roussos A, Sawyer M, Simsek Z, Dumenci L, Steinhausen HC, Metzke CW, Wolanczyk T, Yang HJ, Zilber N, Zukauskiene R, Verhulst FC, Rescorla LA, Almqvist F, Weintraub S, Bilenberg N, Bird H, Chen WJ. Testing the 8-syndrome structure of the CBCL in 30 societies. *J Clin Child Adolesc Psychol* 2007; 36:405–417.