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Introduction of a new paediatric asthma guideline: effects on asthma control levels.

Authors:

Hammer SC^{1*}, Sonneveld LJH^{1*}, van de Kant KDG¹, Hendriks HJ², Heynens JW³, Droog R⁴, Dompeling E¹, Jöbsis Q¹

¹Department of Paediatric Respiratory Medicine, Maastricht University Medical Centre (MUMC⁺), Maastricht, the Netherlands; ² Department of Paediatrics, Vie Curi Hospital Venlo, the Netherlands; ³Department of Paediatrics, Orbis Medical Centre, Sittard, the Netherlands; ⁴Department of Paediatrics, Elkerliek Hospital, Helmond, the Netherlands.

* Shared first author

Running title: Do patients perceive asthma control?

Address for correspondence:

Sanne Hammer

**Department of Paediatric Respiratory Medicine,
Maastricht University Medical Centre (MUMC+)**

P.O. Box 5800

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NL-6202 AZ Maastricht

Tel: +31 6 42154781

Email: sannehammer@gmail.com

Summary: Asthma control did not improve after the introduction of a new GINA based Dutch paediatric asthma guideline in 2008.

Abstract page:

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Title manuscript: Introduction of a new paediatric asthma guideline: effects on asthma control levels.

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Abstract:

Background: In 2008, a new national paediatric asthma management guideline based on the international Global Initiative for Asthma (GINA) guideline, was launched in the Netherlands. We studied whether asthma control and treatment regimens improved after introduction of the guideline by comparing survey data before and after the guideline introduction.

Methods: Two comparable groups of children (6-16 years) with asthma were included before (2004) and after (2013) the introduction of the guideline. Children, parents and paediatricians completed questionnaires about asthma symptoms, medication and healthcare use. Spirometry was performed.

Results: Data of 209 patients were analysed. Level of asthma control did not improve between 2004 and 2013 with a proportion of (partly) controlled asthmatics of 51% in 2004 and 59% in 2013 ($p=0.28$). In 2013, paediatricians characterised 76% of children as (partly) controlled, while 59% of children was (partly) controlled according to GINA criteria ($p<0.05$).

Step-down treatment in controlled patients was more applied by paediatricians in 2013 compared to 2004 (from 8 to 40%, $p<0.05$). Step-up treatment in uncontrolled patients did not improve.

Conclusions Asthma control did not improve after the introduction of the new guideline. Compared to 2004, an improvement was observed in step-down treatment in patients with controlled disease.

Key Words: Asthma, asthma control, asthma treatment, guideline, outpatient clinic, paediatrician,

Sanne Hammer
Department of Paediatric Respiratory Medicine,
Maastricht University Medical Centre (MUMC+)
P.O. Box 5800
6202 AZ Maastricht
The Netherlands

Introduction

Worldwide, asthma is considered the most common chronic disease among children (1). The major aim of asthma treatment is to achieve and maintain asthma control. Since the revision in 2006, the Global Initiative for Asthma (GINA) guideline focuses on asthma control rather than on asthma severity. Most patients can achieve control with a stepwise approach of the treatment (1-4). However, numerous surveys report suboptimal asthma control (5-13), which is associated with lower quality of life, more emergency care visits, increased health care costs, and airway inflammation causing remodelling (14).

In 2004, we assessed the level of asthma control in a Dutch paediatric outpatient population (15). In our study only one in ten patients was optimally controlled, which was comparable with other surveys. A limited number of children received step-up of their asthma treatment in case of uncontrolled asthma and step-down therapy in case of controlled disease.

In 2008, a national paediatric asthma management guideline, based on the international GINA guideline, was launched in the Netherlands. (16).

So far, no studies investigated the influence of this Dutch guideline on the level of asthma control in children. We hypothesised that an increase in asthma control has occurred due to the introduction of the guideline focusing on asthma control. We aim to assess: 1) the level of asthma control in a paediatric outpatient clinic; 2) the level of agreement of asthma control values as evaluated by patients, paediatricians, and the objective GINA criteria (gold standard); 3) the frequency of step-up and step-down treatment regimens by the paediatrician.

Methods

Study design and procedure

In 2004 and 2013, children with doctor-diagnosed asthma aged 6-16 years, who were treated by a paediatrician for at least 6 months from four outpatient clinics in the South-East region of the Netherlands, Maastricht, Venlo, Sittard and Helmond, were approached to participate in the study. While in Maastricht four paediatric pulmonologists were involved, in the other hospitals one paediatrician participated in the study. Patients attended the office because of a regular visit. The definition of asthma and the in- and exclusion criteria were comparable with the 2004 survey (15) All children and their parents received written and verbal information and signed informed consent before the start of the study. This study was

approved by the medical ethical committee of the Maastricht University Medical Centre (METC 12-4-122). The data of the 2004 survey were reported previously (15).

After selection, patients completed a questionnaire and performed spirometry (Figure 1). Thereafter, he/she visited the paediatrician. The paediatrician was not informed about the results of the patient questionnaire. After the consultation, the paediatrician completed a short questionnaire about asthma control and changes in treatment. An independent research assistant collected all data from the questionnaires and spirometry (Figure 1). The data of 2013 were compared with the data of 2004.

Questionnaires

Three questionnaires were used in the 2004 and the 2013 study. The first two questionnaires were filled in by the patient and parent(s). The first questionnaire consisted of items based on the GINA guideline and previous studies (1, 12, 15, 17). This questionnaire was used to determine the level of asthma control based on the GINA-guideline and was considered as gold standard in this study. The second questionnaire examined the level of asthma control, perceived by the patients, on a Visual Analogue Scale (VAS) of 0-100: a score of 0 reflected excellent asthma control, whereas 100 reflected no asthma control at all. The VAS score is a validated tool to measure asthma control and is frequently used in different paediatric studies (18-21). The third questionnaire was completed by the paediatrician, and contained items about level of asthma control (including a VAS score) and changes in asthma medication. Moreover, in the 2013 survey, the Childhood – Asthma Control Test (C-ACT, for children aged 6-11 years) and the Asthma Control Test (ACT, for children aged 12-16 years) were added as these were validated and commonly used after 2004 (22). The (C-)ACT were added to see if they accorded to our gold standard, the GINA-criteria. In a previous study the ACT and C-ACT correlated well with

GINA criteria (23). The validated cut-off point ≤ 19 for ACT and C-ACT was used to define uncontrolled disease (22, 24, 25).

Spirometry

In 2013, maximum expiratory flow-volume (MEFV) curves were performed according to ATS/ERS standards (26). From three technically correct MEFV-curves the highest Forced Expiratory Volume in one second (FEV_1) value was used, expressed as a percentage of the predicted value. Peak Expiratory Flow (PEF) was assessed with spirometry in 2013, compared to the personal best Peak flow device (Healthscan, Cedar Grove, NJ, USA) in 2004.

Predictors of asthma control

The influence of the following potential predictive covariates was analysed: sex, age, atopy, adherence to medication, consultation of an asthma nurse, instructions of the inhalation technique, and seasonal symptoms. Differences in symptoms might be expected such as complaints of hay fever due to pollen allergy during summer, or more complaints because of viral respiratory infections during the winter.

Sample size calculation and statistics

To establish a change in asthma control from 45% (partly) controlled asthma in 2004 ($n=112$) to at least 65% in 2013, 87 children are needed to assess this difference with a power of 80% and an alpha of 0.05. To study differences in 2004 and 2013, unpaired t-tests, Mann-Whitney U tests and Chi-squared tests were used to analyse parametric continuous variables, non-parametric continuous variables, and categorical variables, respectively. To compare doctor and patient judgment of control (VAS score) with asthma control based on the GINA criteria, categories of asthma control were defined: controlled (VAS score <20), partly controlled (VAS score 20-49), uncontrolled (VAS score ≥ 50) asthma. Cohen's kappa coefficients were used to compare the agreement between doctor and patient judgment of

asthma control. According to Cohen the results were interpreted (27). To identify predictors for asthma control in both populations, univariable and multivariable logistic regression analysis was used. P-values < 0.05 were considered statistically significant. The results were analysed with SPSS version 20.0 (SPSS Inc., Chicago IL, USA).

Results

Patient population

Data of 209 children were analysed: 97 children in 2013, and 112 children in 2004. No patients participated in both surveys. In 2013, 102 patients were approached to participate, 5 of them refused. No data are available of total number of contacted patients in 2004. Only regular control (no exacerbation) visits were included. The patient characteristics of the 2013 and 2004 surveys were comparable (Table 1). Only children were younger in the 2004 population. The peak flow values were statistically significantly higher in the 2013 study population.

Table 1: Baseline characteristics of the 2004 and 2013 surveys

	2004	2013
Patients (n)	112	97
Age (median (yrs.) (IQR))	9.7 (4.3)	11.2 (4.5)*
Sex (Female n (%))	38 (34)	32 (33)
Atopy, n (%) §	74 (66)	72 (74)
PEF (median, (IQR)) % of predicted value §§	84.3 (25.9)	91 (19.5)*
FEV1 % (mean ± s.d.) % of predicted value	-	94.3 ± 15.7
ICS use, n (%)	104 (95)	90 (93)
Use of long-acting beta-2 agonists, n (%)	44 (41)	48 (50)
LTA use, n (%)	8 (7)	8 (8)

*p < 0.05

§ Atopy Group 2004: atopy is defined as a positive Phadiatop, or 1 or more RAST classes > 2. Group 2013: atopy is defined as a positive Phadiatop

§§ PEF was determined with spirometry in 2013, compared to a personal best Peak Flow device in 2004

Abbreviations: FEV1: Forced Expiratory Volume in 1 second; ICS: Inhaled Corticosteroids; IQR: Interquartile Range; LTA: Leukotriene Receptor Antagonist; PEF: Peak Expiratory Flow; s.d.: standard deviation

Asthma control according to GINA, paediatricians, patients and ACT / C-ACT scores

In general, asthma control in the 2013 survey was equal to the 2004 study (Table 2). In 2013, 13% of the patients was optimally controlled, 46% had partly controlled asthma, and 41% had uncontrolled asthma (in 2004: respectively 13%, 39% and 48%). Patients' perception of asthma control was significantly more optimistic than the paediatrician-assessed control in both groups (Chi-square p<0.01). Agreement between asthma control according to patients (VAS) and GINA criteria was poor (k = 0.154 (95% CI, .055 to .254), p < 0.01). Moreover, there was no agreement between asthma control according to paediatricians (VAS) and GINA criteria (k = .053 (95% CI, 0 to 0.177), p = 0.380).

In 2013, all patients completed the ACT / C-ACT. According to these questionnaires 62% of the children were classified as well or partly controlled.

Table 2: Number of patients with (partly) controlled asthma

	2004	2013
GINA criteria, n (%)	57 (51)	57 (59)
VAS score (patient), n (%)	93 (83)	85 (88)
VAS score (paediatrician), n (%)	82 (73)	74 (76)
ACT/C-ACT, n (%)	-	60 (62)

This table presents the number of patients with controlled and partly controlled asthma (add together) measured with the different instruments.. If the VAS score was ≤ 49 , asthma control was considered as (partly) controlled.

VAS score: Controlled asthma: VAS score <20 ; Partly controlled asthma: VAS score: 20-49;
Uncontrolled asthma: VAS score ≥ 50

Abbreviations: ACT: Asthma Control Test; C-ACT: Childhood-Asthma Control Test; GINA: Global Initiative for Asthma; VAS: Visual Analogue scale

Ability to discriminate between asthma control levels

Both in 2004 and 2013, patients with uncontrolled asthma (assessed with the GINA questionnaire) scored significantly higher on their reported VAS score than patients with (partly) controlled disease (Figure 2, $p < 0.001$). However, VAS scores reported by patients with partly controlled and controlled asthma did not differ ($p = 0.13$). This indicates that these patients could not perceive the difference between partly controlled and controlled disease. In accordance to patients, paediatricians scored the VAS scores of patients with uncontrolled asthma significantly higher than patients with partly controlled and controlled asthma ($p < 0.001$), but not between patients with controlled and partly controlled asthma (Figure 3, $p = 0.29$).

Pharmacotherapy according to different asthma control levels

There was a significant relationship between prescription of medication and doctor-assessed asthma control (VAS) (Table 3, $p < 0.001$). This relationship was less pronounced when level of asthma control according to GINA criteria and prescribed pharmacotherapy was assessed ($p = 0.09$). In 2013, in 40% of well controlled patients, step-down therapy was performed, which was significantly higher than in 2004 ($p = 0.02$). In 2013, step-up therapy was applied in 23% of uncontrolled patients, compared to 22% in 2004 ($p = 0.73$).

Table 3: Adjustment of prescribed asthma medication according to asthma control

	Step down		No change		Step up	
	VAS	GINA	VAS	GINA	VAS	GINA
Controlled, n (%)	16 (35)	6 (40)	3 (7)	7 (47)	27 (59)	2 (13)
Partly controlled, n (%)	3 (11)	11 (26)	6 (21)	24 (56)	19 (68)	8 (19)
Uncontrolled, n (%)	1 (4)	3 (8)	10 (44)	27 (69)	12 (52)	9 (23)

Assessment of asthma control by the paediatrician (VAS score) and by GINA criteria in the 2013 population

VAS score: Controlled asthma: VAS score < 20 ; Partly controlled asthma: VAS score: 20-49;

Uncontrolled asthma: VAS score ≥ 50

Abbreviations: GINA: Global Initiative for Asthma; VAS Visual Analogue Scale

GINA items and aspects of education, knowledge and management in both groups.

None of the separate GINA items differed between both groups (data not published).

Adherence was decreased significantly in 2013 from 91% to 72% ($p < 0.001$). The knowledge of patients on pathogenesis and therapy of asthma in 2013 was comparable to 2004, except for knowledge on the effect of inhaled corticosteroids which decreased from 55% to 34% ($p < 0.001$).

Predictors of asthma control

Univariable regression showed that only atopy was a significant predictor of uncontrolled asthma ($p=0.04$). Multivariable regression analysis showed atopy and age as predictors of asthma control (resp. $p = 0.01$ and $p = 0.01$).

Discussion

In this study we showed that the introduction of a new national asthma guideline based on GINA criteria has not resulted in an overall improvement in the level of asthma control in a paediatric outpatient population. Paediatricians assessed asthma control significantly more optimistic than asthma control according to the GINA criteria. Besides, asthma control was perceived even more optimistic by children, compared to paediatricians and GINA criteria. Patients and doctors were not able to discern the difference between partly controlled and controlled asthma according to GINA criteria. Step-down treatment in patients with controlled asthma did improve significantly compared to 2004, whilst step up treatment in uncontrolled asthma did not improve.

The lack of improvement in asthma control after the introduction of the new guideline can be the result of various factors:

First, we can question whether the new guideline was successfully implemented. The guideline was published on the website of the Dutch Society of Paediatrics and discussed during the 4-monthly national meetings of paediatric pulmonologists. Moreover, the guideline was frequently discussed during weekly meetings of paediatricians and paediatric pulmonologists in our region. However to improve guideline implementation in the future (28), probably other actions should be undertaken, such as offering an interactive guideline course. Because of the discrepancy between GINA and paediatrician assessed levels of asthma control, a GINA based asthma scores of each patient at each visit integrated in the electronic patient dossier may help (29).

As far as we know, there are no other studies executed which assessed asthma control after introduction of a new paediatric asthma guideline. Moreover, studies comparing different information sources (patients, parents, paediatricians) with GINA guideline are limited. Deschildre et al published the results of comparison between GINA/NAEPP guidelines, C-ACT, and physician's rating (30). They observed discrepancies between the different tools applied to assess asthma control in children, which resemble the results of our study.

Secondly, we can argue whether it is feasible to achieve completely controlled asthma in all patients. Asthma control in the 2013 population improved to 59% compared to 2004, which implies that still 41% has uncontrolled disease.

Thirdly, the effect of change in paediatric asthma care between 2004 and 2013 can be argued. Introduction of omalizumab for patients with severe asthma is an important change. However, this medication is not prescribed in children with mild-intermediate asthma, and there has is no significant change in care in this patient group.

Fourth, one may speculate that the decreased adherence to asthma medication in 2013 negatively influenced asthma control. However, in our analysis, adherence was not a predictor of uncontrolled asthma, and in our view the reported adherence rate of 91% in 2004 by patients might overestimate real adherence rates, as adherence levels are generally low (31).

We can question whether the way of monitoring and the type of parameters in children with asthma is optimal in paediatric care. In a previous study we demonstrated that prospective monitoring of symptoms and lung function by a home monitor lead to better detection of less controlled asthma than retrospective assessment of asthma control (32). Moreover, prospective monitoring of biomarkers of airway inflammation, e.g. exhaled volatile organic compounds, might provide valuable information during the monitoring of asthma in children (33, 34), which in turn could increase the level of asthma control.

Moreover, we found that only step-down therapy in controlled patients, did increase. Possibly the paediatrician assessed other items such as seasonal symptoms, influences of

infections or exacerbations, side effects of intensifying medication, in the decision of increasing medication therapy. This is in line with the reasoning of Price et.al that asthma guidelines are not written for the individual needs of asthma patients and do not consider the full heterogeneity of asthma (35).

This is the first study in which the effect of implementation of a new Dutch asthma guideline on asthma control was evaluated. A strength of this study is that, both subjective parameters (symptoms) and objective parameters (lung function measurements) were used (6, 7, 10-12). Failure of previous studies to include lung function measurements as a part of the control index can overestimate asthma control (8). Moreover, studies comparing different information sources with GINA guideline are limited.

A limitation of the study is that in 2004 PEF measurements were performed while in 2013 we performed dynamic spirometry. This did not substantially influence our results as classification of asthma control with PEF values did not significantly change overall asthma control levels compared to classification with FEV1 values (data not reported). Another possible limitation is that patients in the 2013 study visited the outpatient clinic between November and March, while patients of the 2004 survey visited the outpatient clinic during the entire year. We do not expect that this difference affected results significantly, because experiencing most symptoms during the winter was not a predictor of uncontrolled asthma in our analysis. A third potential limitation is that there are no records of 2004 how many patients were approached and refused to participate.

Conclusions and implications for clinical practice

The introduction of the new Dutch asthma guideline did not improve the level of asthma control in children from outpatient clinics in the southern part of the Netherlands. Patient's and paediatricians' perception were significantly more optimistic regarding asthma control

than objective GINA criteria. By using the VAS score, patients and doctors could not specify the difference between partly controlled and controlled asthma as indicated by the GINA criteria.

Compared to 2004, significantly more children with controlled asthma in the 2013 survey received step-down treatment.

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Figures:

Figure 1: Study design:

This figure shows the inclusion and exclusion criteria and the instruments which were used in the study. The visit to collect patient data (instruments of patient) was ahead of the doctor's visit. Except for lung function, the paediatrician was not informed about these patient data (marked with *)

Abbreviations: ACT: Asthma Control Test; C-ACT: Childhood Asthma Control Test; FEV1: Forced Expiratory Volume in 1 second; PEF: Peak Expiratory Flow; VAS: Visual Analogue Scale

Figure 2: Comparing asthma control assessed by the GINA criteria and by the patient (VAS score):

Patients asthma control according to the GINA guideline (gold standard) on the x-axis, versus asthma control perceived by the patients on a (mean) VAS score (y-axis). Mean VAS-score and 95% CI are presented per asthma control group in 2004 and 2013. It appears that patients are not able to discriminate between controlled and partly controlled asthma

* $p < 0.05$

VAS score: Controlled asthma: VAS score <20 ; Partly controlled asthma: VAS score: 20-49; Uncontrolled asthma: VAS score ≥ 50

Abbreviations: GINA: Global Initiative for Asthma; VAS: Visual Analogue Scale

Figure 3: Comparing asthma control assessed by the GINA criteria and by the paediatrician (VAS score):

Patients asthma control according to the GINA guideline (gold standard) on the x-axis, versus asthma control perceived by the paediatrician on a (mean) VAS score (y-axis). Mean

VAS-score and 95% CI are presented per asthma control group in 2004 and 2013. It appears that the paediatrician is not able to discriminate between controlled and partly controlled asthma

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VAS score: Controlled asthma: VAS score <20 ; Partly controlled asthma: VAS score: 20-49;

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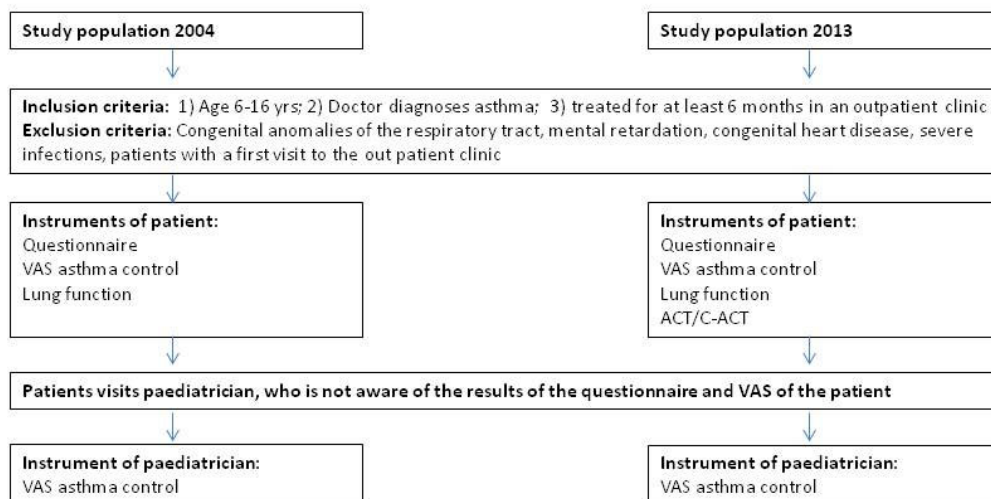


Fig 1

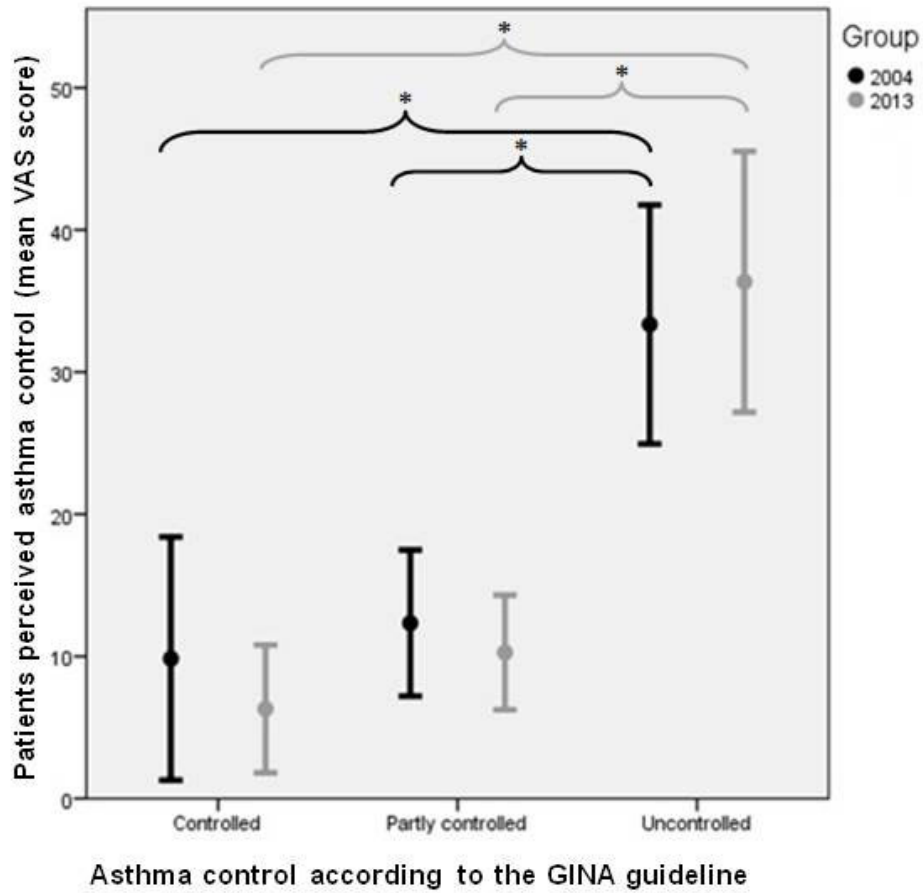
Fig 2:

Fig 3: