

## ORIGINAL RESEARCH

## Asthma severity in primary care asthma patients: a comparative study of four different approaches to severity classification

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**Abstract****Aims:** To explore the factor structure of asthma severity and asthma control and to compare the results of different approaches to asthma severity classification on the distribution of costs of asthma medication.**Methods:** Comparison of four different approaches to asthma severity classification and factor analysis of asthma control descriptors. A correlation analysis between costs and the different approaches to severity classification was performed.**Results:** The factor analysis suggests that asthma control consists of at least two factors. Four approaches to severity classification were explored and all except the 'GINA EXPANDED' classification tended to place patients in the most severe category. The pharmaceutical costs varied between 0 and 75 SEK per day (0 and 5.31 GBP; 0 and 7.68 EURO ).**Conclusions:** There is a considerable overlap between asthma control and asthma severity. None of the approaches used in this study present a superior satisfactory solution to the classification problem.

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**Keywords** Asthma severity, classification, costs, asthma control**Introduction**

Disease severity classification is crucial in research, providing an opportunity to compare important variables across different severity levels or to select populations. Severity classification is also fundamental for economic evaluation and development of reimbursement systems, and for priority-setting and development of health care programs and guidelines.

The ideal system for asthma severity classification should be easily applicable in various clinical and research situations and should produce reliable and valid results. The most widely accepted severity classification in adult asthma patients so far is probably the Global Initiative for Asthma (GINA) guidelines.<sup>1</sup> Nevertheless, the GINA classification has a number of

limitations.<sup>2-4</sup> Previous studies using the GINA severity classification system on patients on inhaled corticosteroid (ICS) treatment have suggested that the system tends to overestimate severity in these patients.<sup>5</sup> In the revised GINA guidelines (Nov 2006), severity classification is regarded as suitable only for classification of patients who are not on ICS treatment – which seems to exclude severity classification of most asthmatics seeking care or participating in clinical trials. It is still unclear whether any classification system can be used to classify asthma severity reliably in patients receiving drug treatment. An alternative view of asthma severity has been suggested by Cockcroft and Swystun,<sup>6</sup> where the minimum medication required to maintain control of asthma reflects the overall severity of the condition.

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The aims of this study were twofold:

- firstly, to explore the relationships between the components used to describe asthma control and disease severity, and to compare the results of four different approaches to asthma severity classification
- and secondly, to explore the impact of classifications on treatment costs

## Methods and Materials

### Study design

We used a database constructed from two primary care studies in which asthma-specific quality of life and conventional measures of clinical asthma and pharmaceutical costs were measured in a similar and standardised manner.<sup>7,8</sup> Both studies were carried out during 2003 and 2004, in a similar fashion, and only data from the first of two visits was used in this study so that the outcomes would not be influenced by the trial interventions. The two separate studies as well as the present data analysis were approved by the regional ethics committee of the Karolinska Institutet.

### Study subjects

The database constructed for this study consists of 246 patients in total. The inclusion and exclusion criteria in both studies are reported elsewhere.<sup>7,8</sup>

### Measures

We measured asthma control with the Asthma Control Questionnaire (ACQ).<sup>9</sup> Other instruments were not available in a Swedish version at the time for data collection. Disease specific Quality of Life (QoL) was measured with the Mini Asthma Quality of Life Questionnaire (MiniAQLQ).<sup>10</sup>

The costs of drugs per day were retrieved from the original databases. The cost of the daily dose of each drug was calculated per patient and summarised to total daily pharmaceutical costs per patient. Anti-asthmatic drugs and dosages used during the week preceding the visit were recorded. The details have been presented fully elsewhere.<sup>5</sup>

Asthma severity was classified according to four different approaches. The GINA guideline<sup>11</sup> approach was used as a basis for three of the classifications. According to GINA, asthma severity is classified as intermittent, mild persistent, moderate persistent, or severe persistent, based on the combined assessments of symptoms, lung function and activity restrictions. Before treatment is begun, asthma severity classification rests entirely upon clinical features, whereas the classification of severity should be based on the clinical features present and the daily medication regimen when the patient is already on treatment.

### Classification methods used

In this study, classification was performed both with and without consideration of current pharmaceutical treatment. The **first** approach that combines medical regimen and

clinical features is referred to as 'GINA'. The **second** approach, where the medical regimen is neglected, is referred to as 'GINA-NAÏVE'. The **third** classification, referred to as 'GINA EXPANDED', was carried out with the intention of elaborating the GINA classification system by subdividing the fourth step, yielding two additional classes, on the basis of the following criteria:

Class 4 = normal pulmonary function (FEV<sub>1</sub>% predicted > 80%)

Class 5 = impaired pulmonary function (FEV<sub>1</sub>% predicted < 80%)

Class 6 = treatment with oral corticosteroids

The **fourth** classification, referred to as 'TREATMENT INTENSITY', was carried out on the basis of two parameters: treatment steps, as defined in the GINA guidelines; and lung function. When the results of the two parameters differed, severity was defined by the parameter that yielded the most severe classification outcome. Lung function, measured as the forced expiratory volume in one second (FEV<sub>1</sub>) expressed as % predicted, was classified into four categories according to the following:

1 = FEV<sub>1</sub>% predicted > 80%

2 = FEV<sub>1</sub>% predicted > 70% ≤ 80%

3 = FEV<sub>1</sub>% predicted > 60% ≤ 70%

4 = FEV<sub>1</sub>% predicted ≤ 60%

On the basis of the ACQ scores, we identified patients having poor control and good control,<sup>12</sup> using a score of 1 as a cut-off. Those patients scoring below 1 were considered to have good control and those above 1 poor control.<sup>12</sup>

### Statistical analysis

Due to a skewed distribution of the variable "cost of drugs per day", the variable was transformed by taking the square root of costs. The distributions of the transformed cost were close to normal.

Comparison of the results from the different approaches to severity classification was made by calculating Cohen's kappa, in order to find out whether or not the different approaches yielded similar results.

### Factor analysis

The objective of using factor analysis in this study was to determine whether asthma control variables, (FEV<sub>1</sub> % predicted, diurnal asthma symptoms frequency, nocturnal asthma symptom frequency), activity impact of asthma, treatment intensity, and the four MiniAQLQ domains (symptoms, activities, emotions, and environment), would reduce to one or more common factors.

Factor analysis was performed by means of principal component analysis followed by varimax rotation. The number of factors chosen for the varimax rotation was based on the Eigenvalues of the factors in the principal component analysis, criterion Eigenvalue > 1. Significant loading was

considered to be greater than 0.40. Bartlett's Test of Sphericity and Kaiser-Meyer-Olkin Measure of Sampling Adequacy were performed to assess if the data were suitable for factor analysis.

## Results

The demographics of the study population are shown in Table 1. In the study population, 67% of the 246 patients were females. The population mean age was 47.9 years, which is a little higher than in other studies on asthma. The smoking habits matched our expectations and the mean lung function after bronchodilation fell within the normal range. The pharmaceutical costs varied between 0 and 75.34 Swedish krona (SEK) and the median cost was lower in the non-smoking group.

### Factor analysis of asthma descriptors

On the basis of the Eigenvalues of the factors in the principal component analysis, a 2-factor model, which explained 54.2% of the variability, was chosen.

The second step of the factor analysis was to examine the variables with high loadings on each factor in order to identify the element that seemed to be common to those variables. The first factor extracted contained diurnal and nocturnal asthma symptoms, impact on activity and the four domains of the MiniAQLQ. The three first-mentioned variables are all related to asthma control assessment, and the four others to disease specific QoL. This factor accounted for approximately 42% of the total variance. The second factor contained two

variables; FEV<sub>1</sub> % predicted and treatment intensity. These two variables are components in assessment of asthma severity. This factor accounts for approximately 11.5% of the total variance.

### Different approaches to classification of severity

The different approaches yielded quite different proportions of persons identified as having mild (2-12%), mild persistent (9-20%), moderate (23-58%), and severe asthma (12-66%). Both the GINA-NAIVE and the TREATMENT INTENSITY classifications included more patients in the milder levels than the other two. The GINA method identified 89% of the subjects as having moderate or severe asthma. The GINA-EXPANDED was the only method yielding symmetry in the distribution of subjects (see Figure 1).

When taking asthma control into account, the GINA-NAIVE and the TREATMENT INTENSITY classifications were still the methods that included the largest number of subjects in the milder levels. The GINA method still identified a large proportion of subjects as severe. The distribution of subjects in each category identified by the GINA EXPANDED lost some of its symmetry.

To evaluate further the extent of agreement between the three severity methods with the same number of categories, Kappa was calculated. GINA EXPANDED was left out, since it has more different categories. Table 2 illustrates that the agreement between the three compared methods was generally low. This indicates that the methods rate the same patients differently. In a worst case scenario, a patient might

**Table 1. Demographic characteristics of the study population (n=246).**

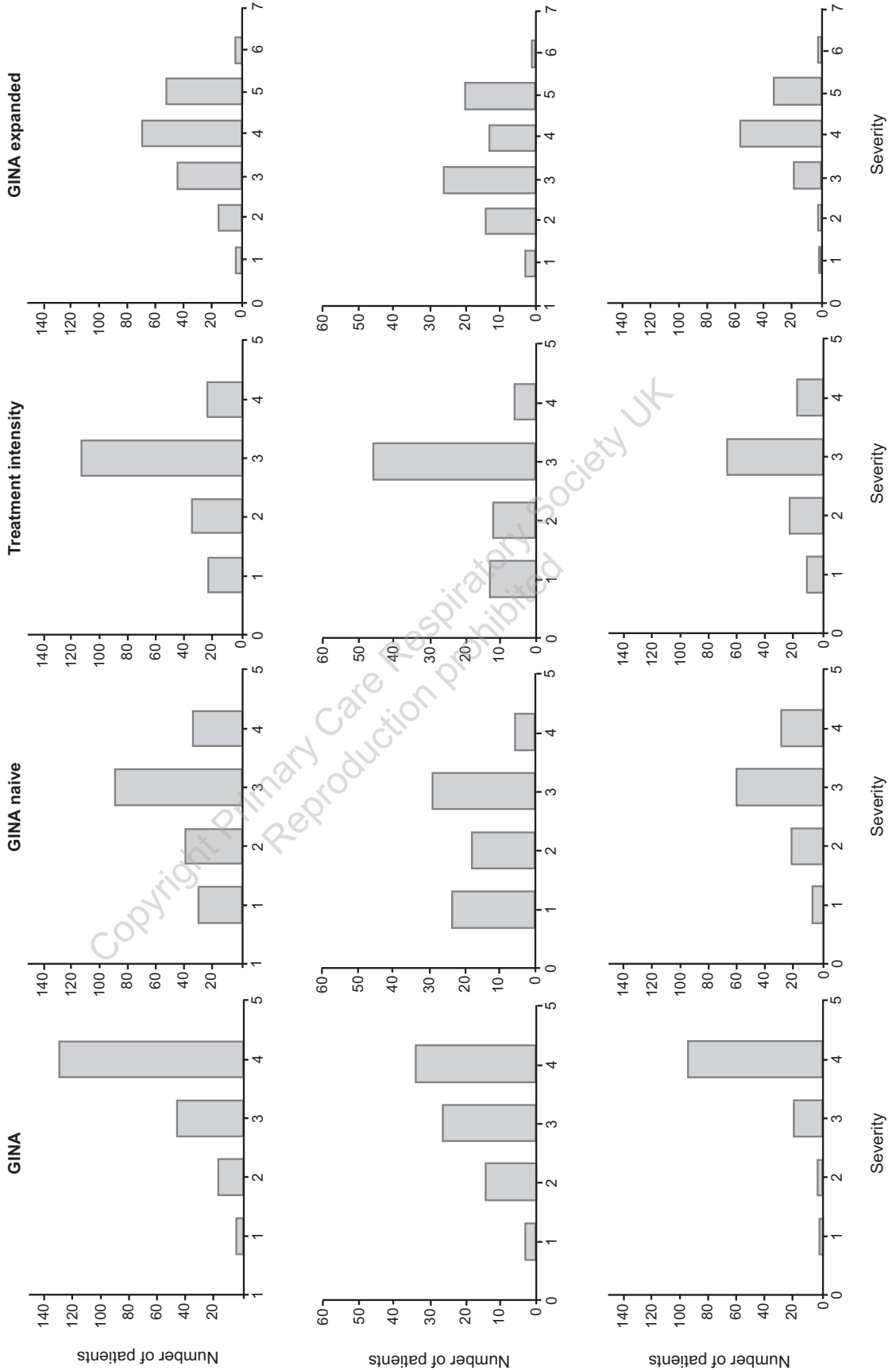
	Total	Smokers	Non smokers	Ex smokers
Sex (male/female); n	82/164	8/37	33/71	39/56
Age	49.7	45.4	48.7	52.5
mean (min-max); years	(18-87)	(18-75)	(18-87)	(19-80)
Asthma Control; mean (SD)	1.53 (1.04)	1.67 (1.03)	1.47 (1.05)	1.49 (0.96)
Smoking habits, n (%)				
Smokers	45 (18.3)	45	-	-
Ex-smokers	95 (38.6)	-	-	95
Non-smokers	104 (42.3)	-	104	-
Missing data	2 (0.8)			
Lung function				
FEV <sub>1</sub> , % of predicted; mean	86	89	87	84
(min-max; n)†,	(33-136;196)	(42-127;39)	(45-136;79)	(33-119;76)
Costs				
Total daily costs of drugs per patient SEKmean/median	11.89/10.24	11.62/11.54	11.64/9.52	12.09/10.24
Range, min-max	0-75.34	0-41.22	0-75.34	0-52.82

FEV<sub>1</sub> = forced expiratory volume in one second.

1 EUR= 9,12 SEK (2003); 1 USD= 8,1 SEK (2003); 1 GBP= 13,19 SEK (2003)

† Due to lack of spirometer at some PHCCs, pulmonary function data was not obtained for the entire groups

Figure 1. Distribution of Asthma severity when classified according to different classification systems. First row: all study subjects included in classification. Second row: only the study subjects with good asthma control are classified. Third row: only the study subjects with poor asthma control are classified.



**Table 2. Agreement among 3 of the classification methods.**

Classification methods	GINA NAÏVE			TREATMENT INTENSITY		
	all	good	poor	all	good	poor
GINA	0.046	0.039	0.023	0.041	0.074	0.008
GINA NAÏVE	-	-	-	0.154	0.083	0.191

\*all refers to that the entire study population data has been used, good refers to the subpopulation that has good asthma control, poor refers to the subpopulation that has poor asthma control.

**Table 3. Correlation between pharmaceutical costs and severity classes (Spearman).**

Classification	Costs All Subjects	Subjects with	
		Good asthma control	Poor asthma control
GINA	0.393	0.243	0.402
GINA NAÏVE	0.170	n.s	0.221
GINA EXPANDED	0.345	0.230	0.348
TREATMENT INTENSITY	0.626	0.606	0.638

p < 0.05

be classified as having mild asthma by one method and as having severe asthma by another.

**Exploring the impact of the classification on pharmaceutical treatment costs**

The pharmaceutical costs varied between 0 and 75.34 (SEK) per day. The median cost was lower in the non-smoking group but the range between 0 and 75.34 (SEK) was the widest (Table 1).

The correlation between costs of medication and the

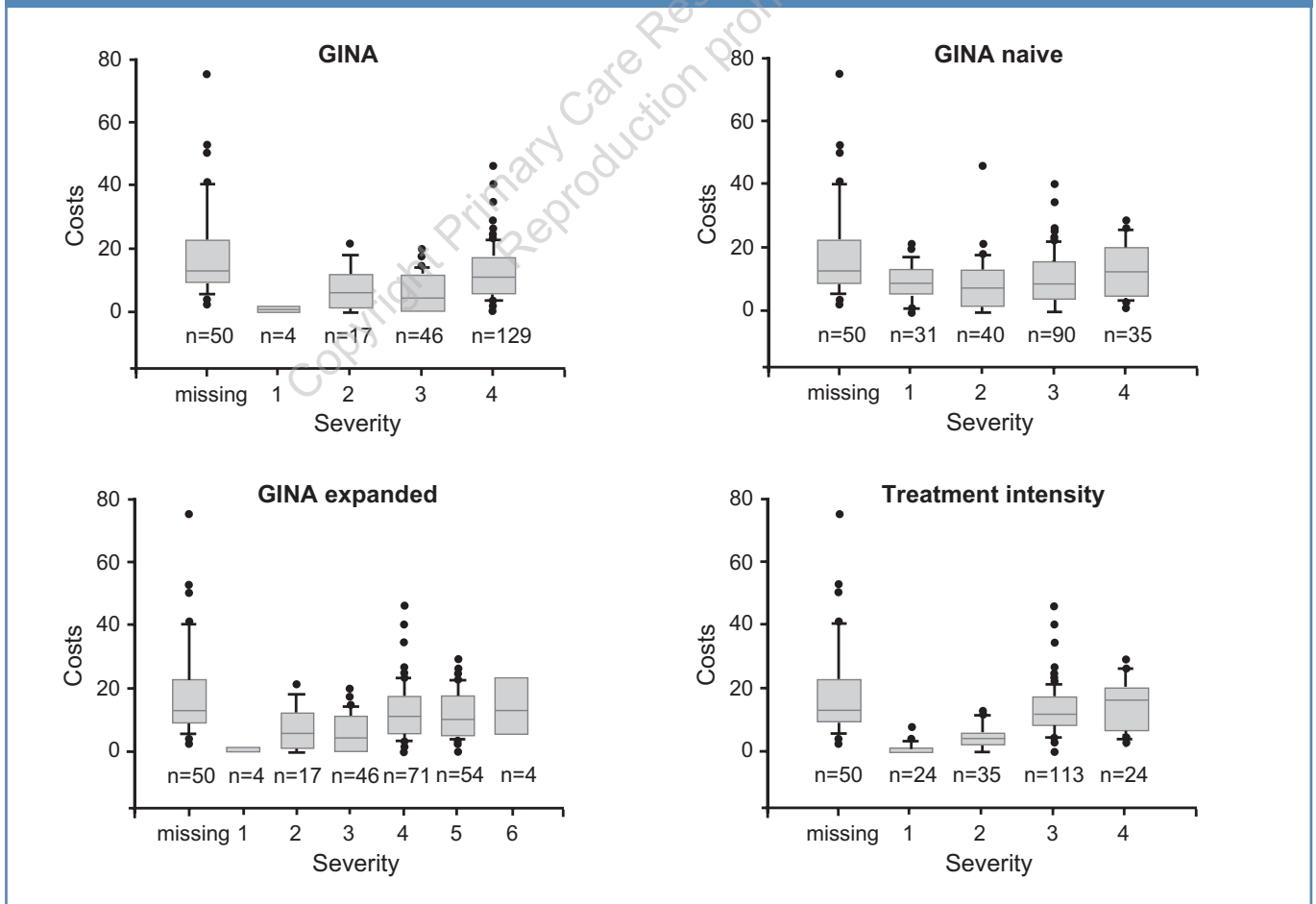
different approaches to classify is presented in Table 3. Treatment intensity has a major impact on costs (0.626, p < 0.05) even when divided into good and poor asthma control.

Figure 2 shows the correlation between costs of asthma medication per day and the severity according to the four different methods. In the GINA classification, the costs of medication per day range from 0 to 46.08 SEK with a median of 11.46 SEK among severe asthmatics.

**Figure 2. Box plot of the costs (SEK) of asthma medication per day and the four asthma severity classifications.**

(Missing= no pulmonary function data)

1 EUR= 9,12 SEK (2003). 1 USD= 8,1 SEK (2003). 1 GBP= 13,19 SEK (2003).



## Discussion

The aims of this study were twofold: firstly, to explore relationships between the components of asthma control and disease severity, and to compare different approaches to severity classification of asthmatics already receiving treatment; and secondly, to explore the impact of these classifications on treatment costs.

To our knowledge this is the first study exploring the relationships between asthma control and severity in asthmatic patients who are actively being treated for their asthma and to test different approaches to classifying the severity of the patients' asthma in primary care. There is no gold standard for measuring or classifying asthma control. We measured asthma control with the ACQ.<sup>9</sup> Other instruments to measure asthma control – for example, the Asthma Control Test (ACT)<sup>13</sup> – were not available in a Swedish version at the time for data collection. However, the impact of an alternative approach to measurement such as the ACT would probably not have been substantial since the item contents are relatively similar.<sup>9,13</sup> Alternative approaches to classification of control have also been shown to have moderate agreement.<sup>14</sup>

The factor analysis suggested a two-factor model that accounted for approximately 54% of the variability. The most prominent rotated factor (42% of variability) of the two included asthma control-related variables (diurnal asthma symptoms, nocturnal asthma symptoms, impact on activity) and disease specific QoL (the MiniAQLQ subscales). We labelled this factor "asthma control". The other factor (11.5% of variability) included FEV<sub>1</sub> % predicted and treatment intensity. This factor we have labelled "asthma severity". Other similar studies have found a larger number of factors.<sup>15,16</sup> Similar to the results of Juniper *et al.*,<sup>15</sup> our results suggest that lung function is clearly separate from symptoms and QoL.

Three out of the four different approaches we used to classify asthmatic patients already on treatment demonstrated a negative skewed result – i.e. a tendency to designate patients to the worst category. This can be understood in terms of a lack of discriminative ability in the classification methods or in terms of an inherent predisposition of the study population. In Scandinavia, treatment with ICS and long-acting  $\beta_2$ -agonists are started quite early in the course of the disease,<sup>17</sup> which could account for some of the tendency to identify the patients as having severe asthma. Only the GINA EXPANDED classification did not yield these skewed results.

As seen in Figure 1, poor control seems to influence the results equally. This would suggest a lack of discriminative ability due to confounding. It has been claimed that important distinctions between asthma severity and asthma control exist.<sup>18,19</sup> Nevertheless, there is significant overlap between the parameters by which severity and control are defined.<sup>19</sup> Thus, if asthma control is not taken into account, it is almost impossible to

distinguish poorly controlled patients from patients with severe disease who manage to maintain good asthma control with extensive treatment. If one were to choose a classification method on the basis of discriminative ability, the choice should preferably be either the GINA EXPANDED or GINA NAÏVE classifications.

We have shown that the costs vary between the four approaches. This highlights the importance of well defined classification systems when performing economic evaluations and creating reimbursement systems for health care. The correlation between pharmaceutical costs and severity using the different classification approaches shows that the method for classifying treatment intensity has a major influence on the distribution of cost data. However, there is a very large variation in costs between different patients considered as having equally severe disease, possibly indicating that clinical practice is a more important determinant of pharmaceutical costs than disease severity.<sup>5,20-22</sup>

An interesting view on the classification problem was presented by Cockcroft & Swystun<sup>6</sup> who suggest that the asthma severity of patients on treatment is reflected by the amount of medication needed to reach disease control. This view on severity is also adopted by Taylor *et al.*<sup>23</sup> and both the American Thoracic Society and The European Respiratory Society.<sup>24</sup> However, our attempt to incorporate this notion by including treatment step in combination with the FEV<sub>1</sub> % predicted was unsuccessful. Other suggested disease markers such as exhaled nitric oxide and sputum eosinophilia might be useful in future classifications, but these measurements have hitherto not been included in routine use in primary care.

## Conclusion

It is still unclear whether it is possible to classify reliably the severity of asthma in patients receiving drug treatment. In this study we explored the relationships between the components used to describe asthma control and compared the results of four different approaches to classifying disease severity in asthma patients on treatment. All of the classifications except the GINA EXPANDED system tended to allocate patients to the severest category. None of the approaches represent a superior satisfactory solution to the classification problem, and further research is needed to find a more appropriate classification.

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**Conflict of interest**

No financial or other potential conflicts of interest related to the subject of the manuscript exist for any of the authors.

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