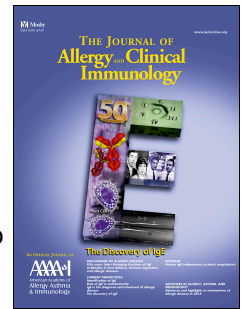


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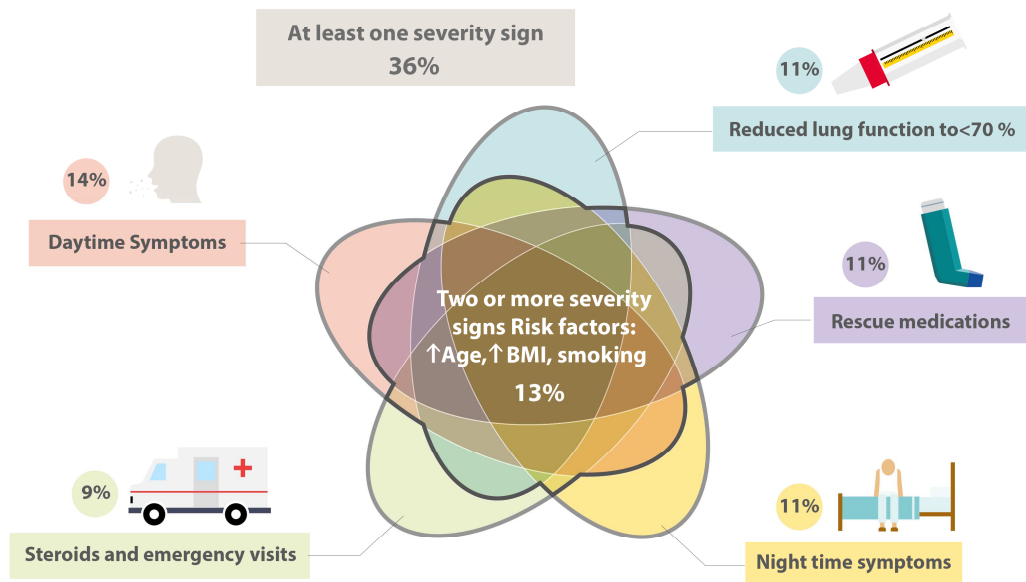
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Asthma severity phenotypes

A large random population study



ACCEPTED

High prevalence of severe asthma in a large random population study

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Abstract**Background**

The prevalence of asthma severity is not well described at a population level.

Objective

To determine the prevalence of phenotypic signs of asthma severity among individuals with asthma in a general population, and to describe risk factors for asthma severity.

Methods

Epidemiological study conducted between 2008 and 2012 (West Sweden Asthma Study). A postal questionnaire was sent to random population (N = 30,000) in West Sweden, with 18,087 responses. A total of 2,006 individuals were carefully phenotyped. Only individuals with “active asthma” (symptoms or medication in the last year, N = 744) were analyzed in this study, to determine degree of severity of the disease within an asthma cohort. Phenotypes of severity were calculated based on: 1) multiple symptoms during the day despite the ongoing use of asthma medications, 2) FEV1 below 70% of predicted value, 3) daily or almost daily use of rescue medications, 4) nighttime symptoms once a week or more, and 5) oral corticosteroid use/emergency room visits. Asthmatics were grouped as non-severe, one sign of severity or two or more signs of severity.

Results

A total of 36.2% of asthmatics expressed at least one sign of asthma severity, and 13.2% had two or more signs. The group with two or more signs was older in age, had higher BMI, a higher rate of tobacco smoking and lower lung function. Bronchial hyperreactivity, airway inflammation and sensitization were significantly different among the three groups. At a

population level, the prevalence of asthma severity was 3.1% for one sign, and 1.3% for at least two signs.

Conclusion

More than one in three asthmatics show at least one sign of asthma severity. The phenotypes of asthma severity are highly diverse, which is important to consider when implementing personalized medicine in asthma.

Clinical implications

Our data is based on a random population, which results in minimal bias vs patient selection, and argues that asthma severity is present in 13% to 36% of asthmatics.

Capsule summary

Every third asthmatic showed at least one sign of asthma severity which indicates that there are still many unmet needs in managing this disease. Asthma severity phenotypes are very diverse prompting an individualized approach to patients.

Key words

Asthma severity, prevalence, population study, phenotypic diversity

Abbreviations

ACT – Asthma Control Test;

FENO – Fraction of Exhaled Nitric Oxide;

FEV 1 – Forced Expiratory Volume in one second;

FVC – Forced Vital Capacity;

COPD – Chronic Obstructive Pulmonary Disease;

OR – Odds Ratio

INTRODUCTION

Asthma is a common disease with a prevalence of approximately 5–10% in Western countries¹⁻⁵. However, there are very little data available on how common severe asthma is, perhaps because of limited consensus in the international community in defining severity. It is well acknowledged that asthma severity has a disproportionate impact on both quality of life and health economics⁶⁻⁹. In the recent European Respiratory Society/American Thoracic Society guidelines, severe asthma was defined as the inability to achieve or maintain optimal disease control despite the use of a combination of high-dose medications and adequately addressing all possible comorbidities¹⁰. Although these guidelines hypothesized that the prevalence of severe asthma is approximately 5% to 10% of the total asthmatic population, it was acknowledged that the exact prevalence is unknown, again because of the lack of unified definitions and consensus on what exactly constitutes asthma severity¹¹. Previous relatively smaller general population studies have suggested that “severe asthma” prevalence ranges from 10% to 24%, although different definitions of severity were applied in these studies¹²⁻¹⁸. These estimates are imprecise, partly because the definitions are different between clinical and epidemiological studies. Importantly, a true prevalence of asthma severity can only be calculated from epidemiological studies of random populations, and not from selected hospital or clinic-based cohorts because of their inherent bias.

The current study reports the prevalence of different signs of asthma severity using a random cohort of individuals with active asthma selected from the West Sweden Asthma Study. The data were collected from a postal questionnaire sent to 30,000 random individuals aged 16–75 years with a 62% response rate after controlling for untraceable individuals². To avoid any biased prior definitions of “severe asthma”, asthma severity phenotypes were identified based on five parameters, including lung function, daytime symptoms, nighttime symptoms, use of rescue medications, and asthma exacerbations (oral corticosteroid use and/or emergency

109 health care visits due to asthma). Relationship between severity phenotypes and the presence
110 of comorbidities was tested and risk factors were determined.

METHODS

Study population and design

The current study was based on a large-scale population-based study conducted in West Sweden from 2008 to 2012 that has been thoroughly described previously^{2,15,19}. The study area of West Sweden includes the city of Gothenburg located on the North Sea. Gothenburg is the second largest city in Sweden and had a population of 494,000 at the end of 2007 and a population exceeding 700,000 including the urbanized areas surrounding the city. The population of the region was 1,547,000 in 2007, which corresponds to approximately 1/6 of the Swedish population. A postal questionnaire was sent in February 2008 to 30,000 inhabitants in the region aged 16–75 years. A random selection of 15,000 subjects was chosen from the population living in the urbanized area of Gothenburg and its surroundings. Similarly, a random sample of 15,000 subjects of the same age range was chosen from the rest of the region. The names and addresses were acquired from the Swedish Population Register. We received 18,087 completed questionnaires for a 62% response rate after correcting for individuals who could not be found or had passed away after acquiring their addresses. Subjects who reported ever having asthma or physician-diagnosed asthma along with a randomly selected group of subjects without asthma were invited to undergo clinical phenotyping, including interviews and multiple physiological tests. A total of 2,006 individual subjects underwent clinical examinations, which included pulmonary function tests (forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)) before and after bronchodilation, an inhaled provocation test with methacholine, a fractional exhaled nitric oxide (FENO) measurement, blood sampling, and a skin prick test against a panel of the eleven most common inhalant allergens. Prior to the examination and blood testing, a detailed clinical interview was also carried out, which included detailed questions about asthma

symptoms and use of asthma medications, upper and lower airway comorbidities, triggers or aggravating environmental factors, and socio-economic status. A detailed flow-chart of the selection of the participants, starting with the number of individuals that were invited to the questionnaire survey initially, is presented as Figure 1. The current analysis focuses primarily on 744 asthmatics who showed signs of active asthma, which was defined as ever having asthma or physician-diagnosed asthma and having used asthma medications or having had recurrent wheeze or attacks of shortness of breath with or without wheeze in the last 12 months. For comparisons of age, sex, BMI, and smoking status as well as lung function parameters, FENO, methacholine reactivity, and skin-prick test positivity, the different groups of asthmatics were compared with a control group of individuals who were considered to have healthy lungs. We included a respiratory healthy reference group consisting of 847 individuals who reported never having had physician-diagnosed asthma, asthma symptoms, chronic productive cough, use of asthma medications, COPD, chronic bronchitis, emphysema, or tuberculosis.

Defining asthma severity

To define asthma severity, we used five different asthma parameters aiming to cover a broad spectrum of asthma complaints coupled with a reduction in pulmonary function. Signs of asthma severity included 1) reporting four or more daytime asthma symptoms despite the ongoing use of medication (this is a definition of “multi-symptom asthma” used previously¹⁴), 2) impaired lung function corresponding to FEV1 below 70% of the predicted value, 3) daily or almost daily use of rescue medications, 4) nighttime symptoms occurring once or more per week, and 5) lung-related emergency unit visits or use of oral steroids regularly or during exacerbations.

The study was approved by the Regional Ethics Review Board in Gothenburg which has its chancellery at the University of Gothenburg.

Analysis

Statistical analyses on the examined cohort were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY). From whole questionnaire dataset, less than 1% of data was missing. For other parameters, the following percentage of data was missing: spirometry 3.8%, FENO was 11.3%, skin-prick test 27.6% (not performed because medications or age > 65 years), methacholine test 62% (not performed because of low lung function [FEV1 <70% predicted] age >65 years of age, lack of consent, or tested outside of clinic). Missing data was not included in the analysis. Three subgroups of asthmatics were defined, including subjects who presented with *one* of the asthma severity signs, subjects who had *two or more* signs of asthma severity (representing a higher level of severity), and subjects who were considered to have active asthma but who did not show any of the asthma severity signs and were regarded as *non-severe* asthmatics. Comparisons between groups were tested with a chi-square test, and the Mantel–Haenszel test was used for comparing trends when comparing more than two groups. Continuous variables were analyzed using an unpaired *t*-test to compare means between the groups. A *p*-value of <0.05 was regarded as statistically significant. Univariate analysis was performed as separate binary logistic regression models for each of the factors (age, gender, smoking, obesity, nasal blockage, rhinorrhea, allergic rhinitis, atopy, longstanding cough, morning cough and sputum production) as an independent variable and severity level as a dependent variable. The reference group for the dependent variable was non-severe asthma both for asthma with one severity sign and for two or more signs of asthma severity. Consequently, a multinomial logistic regression analysis was performed with the non-severe asthmatics as a reference group, including all the variables with significant ($p < 0.05$) and borderline significant ($p = 0.05$ -

183 0.10) association with severity from the unadjusted analysis including age, smoking status,
184 body mass index, nasal blockage, atopy, allergic rhinitis, rhinorrhea, sputum production,
185 morning and longstanding cough determining which factors are significantly associated with
186 increased level of severity. The results of these analyses are presented as the odds ratio (OR)
187 and 95% confidence interval (95% CI).

RESULTS

Prevalence of severity signs

The prevalence of each sign of asthma severity is presented in Table E1 in the Online Repository, and these varied from 8.9% to 13.7% in the active asthma group. The most common sign of severity was multiple daytime symptoms followed by low FEV1 and nighttime symptoms.

Description of asthma severity subgroups

We categorized the asthmatics into three groups according to the severity level of their asthma (Figure 2). Twenty-three percent of the asthmatics expressed only *one* of the five severity phenotype characteristics, and 13.2% had *two or more* features of severity. All in all, 36.2% (n = 269) of the asthmatics reported at least one sign of asthma severity. Only 5% of the asthmatics reported having three or more signs of asthma severity. (Table E2). The third group consisted of the remaining individuals with active asthma who did not show any of the described severity signs, and these were designated as *non-severe* asthmatics.

Since the current study includes data from the random population, we were also able to calculate the prevalence of the severity signs at a population level. Thus, from the random population sample of 1172 individuals (Figure.1), the prevalence of at least *one* severity sign was 3.1%, those who had *two or more* signs were 1.3%, and 7.4% had *non-severe* asthma.

General characteristics

All three groups of asthma were compared with a reference group (n = 847) that did not report any signs of lung-related. The general characteristics of all groups are presented in Table 1. Between the three asthmatic groups, severity was associated with older age (mean age for two or more signs was 54.6 ± 14.9 years vs. 50.9 ± 15.1 years for one sign and 44.9 ± 15.1 years

for the non-severe group, $p < 0.001$), but all asthmatics combined did not differ in age when compared to the respiratory healthy reference group. Female gender was more prevalent in all three asthmatic groups compared to the reference group, but there was no difference among the three asthmatic groups. Obesity was significantly associated with greater asthma severity, and the proportions of individuals who had BMI above 30 were 40.8%, 29.8%, 20.7%, and 12.8% for the asthmatics with two or more severity signs, those with one severity sign, those with non-severe asthma, and respiratory healthy group respectively ($p < 0.001$). Smoking was reported by 21.5%, 17%, and 9.5% of the asthmatics with two or more signs of asthma severity, the asthmatics with one sign, and the non-severe asthmatics, respectively ($p < 0.05$). Asthmatics with two or more signs of asthma severity also had more pack-years compared to the other two groups of asthmatics.

Pulmonary function and clinical characteristics

The Forced Vital Capacity (FVC) and FEV1/FVC ratio was significantly lower in the groups with signs of asthma severity compared to the non-severe asthma group. Bronchial hyperreactivity was present in 88.2% of those with two or more signs of asthma severity, but this was not significantly different from the 77.6% and 67.9% seen in those with one sign and the non-severe asthmatics, respectively. Importantly, methacholine provocation was not performed in subjects with low lung function (FEV1 <70% predicted), in those older than 65 years of age, or in those who did not consent to the procedure, and this lowers the statistical power on this parameter. Significantly fewer individuals in the healthy reference group (32%) showed bronchial hyperreactivity ($p < 0.001$). FENO did not differ significantly between the asthmatic groups, but was significantly lower in the healthy reference group vs all asthma groups (Table I).

Regarding the allergic status, 61.5% of the non-severe asthmatics were skin prick test positive, and in this group 48.7% were sensitized to two or more aeroallergens. In the group with one sign of severity, 46.2% were skin prick positive, in this group 40.4% were sensitized to two or more allergens. Of those with two or more signs of asthma severity, 42.9 % had at least one positive on skin-prick test and in this group 34.7% were sensitized to two or more aeroallergens. In the healthy reference group, 33.1% were sensitized to at least one aeroallergen, and in this group 21.3% were sensitized to two or allergens. Sensitization status did not differ significantly between the different asthmatic groups, but significantly fewer respiratory healthy subjects were sensitized to mono or poly allergens ($p < 0.001$)

The mean values of blood eosinophilia differed significantly between the non-severe asthmatics and those with two or more severity signs (0.23×10^9 eosinophils/L vs. 0.28×10^9 eosinophils /L, respectively, $p < 0.05$) but not vs those with one sign of severe asthma (0.25×10^9 eosinophils/L). The healthy reference group had significantly lower blood eosinophilia (0.18×10^9 eosinophils/L, $p < 0.001$) than the asthmatics regardless of severity. Inhaled corticosteroids alone or in combination with a long-acting beta-2-agonist were used by 79.6% of the asthmatics with two or more signs of severity, which was significantly more than the non-severe asthmatics (53.1%, $p < 0.001$) but not significantly more than the group of asthmatics with one sign (70.2%, $p = 0.09$). The level of asthma control was approximated by the results from the Asthma Control Test (ACT). Only 28.8% of the individuals in the group with two or more signs of asthma severity were well controlled (as indicated by an ACT score greater than 19), while in the group with one sign 65.4% were well-controlled and in the non-severe group 84.4% were well controlled ($p < 0.001$). The mean ACT scores were 16.9, 20.2 and 22.1 for those with two or more signs of asthma severity, those with one sign, and non-severe asthmatics, respectively ($p < 0.001$) (Figure 3).

Factors associated with disease severity

Having signs of asthma severity was associated with several factors as presented in Table II and Table III. Older age increased the risk for both asthma severity subgroups in the univariate analysis. Smoking was a significant risk factor for having one sign of asthma severity (OR 2.07 (95% CI 1.22–3.51)) and even more strongly associated with having two or more signs of asthma severity (OR 3.46 (95% CI 1.85–6.46)). The other factors that were associated with asthma severity in the univariate analysis were obesity, longstanding cough, morning cough, and sputum production, while nasal blockage was only associated with two or more signs of asthma severity. Those factors were further included in the multinomial logistic regression using non-severe asthma as a reference group. From this analysis, which includes age, smoking, obesity, nasal blockage, sputum production, longstanding and morning cough, increasing age and sputum production were associated with having one sign of asthma severity. Increasing age, longstanding cough, obesity, and sputum production were all associated with having two or more signs of asthma severity (Table III). We also performed a bivariate analysis not only with those parameters significant at $p < 0.05$, but also those with borderline significance ($p = 0.05-0.10$). This did not change the results much, as for the one severity sign atopy and allergic rhinitis were borderline significant variables and for the group with two or more signs of severity, only rhinorrhea was a borderline significant variable. When these were consequently also incorporated into the multinomial logistic regression analysis, the only result that changes is that allergic rhinitis comes up as a significant factor for the group with one severity sign (data not shown).

Comorbidities

Asthmatics with at least two signs of asthma severity reported other pulmonary symptoms and comorbidities more frequently than all other groups (Figure 4), including cough, nasal

283 obstruction and COPD, but neither rhinorrhea nor gastroesophageal reflux were associated
284 with asthma severity.

DISCUSSION

The presented data, emerging from a random population study, argue that asthma severity is more common than often suggested¹⁰, with prevalence from 13.2% up to 36.2% among those with active asthma, depending on the definition. The indicators of asthma severity used in the current study were selected based on previous studies showing these to be indicative of asthma severity. The lack of unified and categorical definitions on what constitutes asthma severity might indeed make it prone to being underestimated. Our results further show that 13.2% of the asthmatic population has two or more signs of asthma severity, and the various combinations of these signs represent a broad array of different phenotypes indicative of asthma severity. In the current study, factors associated with asthma severity include age, obesity, and tobacco smoking. Cough was not included in the definition of asthma severity, but it was recognized to be a sign of more severe disease.

Using the definitions of asthma severity phenotypes selected for this study, we report a higher prevalence of asthma severity than any previous publication^{17,20-22}. We realize that this might be a controversial finding, but it is exceptionally important to note that our data are based on a population study, and there is no bias in patient selections from, for example, clinically selected patient cohorts or web-based recruitments. Clearly, asthma severity is an exceedingly complex concept to define and to apply in clinical practice²³, which is why we were inclusive to choose multiple phenotypic signs of severity in our calculations. Many patients experience a mixture of complaints, and this can muddle their interpretation even more and make it difficult to determine how severely ill the individual patient truly is. However, dissecting the different phenotypes of asthma severity might eventually allow us to deal with the specific problems of an individual asthma patient, resulting in more successful personalized asthma management. Since the studied population is randomly selected, it could be speculated that approximately 300,000 Swedish people have some sign of asthma severity, since the

population of Sweden is 10 million. It is unclear whether these data translate to other countries such as the US.

The relevance of epidemiological data for determining asthma severity could also be criticized because the cohort does not include only patients who are under full and professional asthma management plans. This might be a fair argument, but it should also be considered that Sweden is a country that early and efficiently implemented inhaled corticosteroid (ICS) use, and prescription rates are high¹⁹. Furthermore, based on the epidemiological data, a higher proportion of asthmatics with greater disease severity reported taking ICS alone or in combination with a long-acting bronchodilator (Table I). Thus, it cannot be concluded from this study that the severity signs reported were due to the lack of adequate treatment in that group overall, except possibly in a limited portion of patients. Further, increasing age is a significant risk factor for having more severe disease, which may reflect structural changes in the lungs over time^{27,28}.

Female sex has been reported to be associated with more severe asthma^{7,29-32}. In this analysis, we did not find female sex to be a risk factor for more severe disease, even though women were more represented in all asthma groups. From a mechanistic viewpoint, it is unclear whether sex hormones³³, perception and behavior trends³⁴, or various internal and external factors can explain the often-reported increased severity of asthma in women vs. men.

Obesity was significantly associated with more severe asthma, which has also been documented in several previous reports³⁵⁻³⁸. There are many hypotheses that link obesity with increasing asthma severity, including underlying genetic factors, accompanying comorbidities, or inflammatory mediators secreted by adipose tissue^{39,40}. Indeed, a previous study from the OLIN studies in the North of Sweden showed that obesity is a risk factor for both allergy-associated and non-allergy-associated asthma^{41,42}. Epidemiological studies might

facilitate the explanation for why severe asthma is more common in obese patients, but bariatric surgery associated with a dramatic weight loss can in some individuals even eliminate signs of asthma⁴³. This suggests that a mechanism of asthma in the obese can be simply due to being overweight, whereas in others, obesity is a comorbidity that increases severity^{44,45}. Indeed, in some individuals undergoing bariatric surgery, asthma is only improved but not eliminated, suggesting that the individual's obesity influenced the degree of severity but was not the cause of their asthma⁴⁶. Thus, there might be several underlying mechanisms behind the association between obesity and asthma severity.

We found that tobacco smoking was associated with more severe asthma, and this is in agreement with some previous studies^{47,48}; whereas some studies have not observed such an association^{49,50}. It is well known that smoking changes the phenotype of asthma, including reducing the therapeutic response to ICS^{51,52} and reducing the level of nitric oxide in exhaled air⁵³. It cannot be excluded that the individuals with a severe asthma phenotype along with a history of tobacco smoking have varying degrees of COPD-associated pathology in the lung together with the asthma and that this contributes to an overlap of COPD and asthma in the same patient.

In our asthma cohort, allergic sensitization was not associated with more severe disease, which is an observation that supports several previous studies^{49,54,55}. By contrast, we observed a negative association between atopy and both levels of asthma severity, and the proportion of non-sensitized individuals was higher in the group with two or more signs of asthma severity compared to asthmatics with one sign of asthma severity or non-severe asthma. Self-reported allergic rhinitis, as a surrogate estimate of self-reported allergies, was also negatively associated with asthma severity, especially among the group with two or more signs of asthma severity. Thus, it is possible that non-allergic asthma is in general more closely associated with characteristics of increased asthma severity than allergic asthma is.

The most characteristic asthma symptoms, such as wheezing or shortness of breath, were included in the definition of the severity signs from the beginning of the analysis, but other complaints such as longstanding cough and morning cough as well as sputum production were studied in relation to other severity signs. Indeed, all of these cough-related problems were significantly more prevalent in the group of asthmatics having two or more signs of asthma severity. Several other studies have also related the presence of cough to more severe disease with more persistent symptoms despite anti-inflammatory therapy^{56,57}. This observation suggests that cough has a complex presentation in asthma and that it might involve other pro-inflammatory pathways that are different from the pathophysiological mechanisms behind the other asthmatic symptoms that can be treated with conventional asthma therapies. It is important, therefore, that these complaints are not taken lightly.

A significant aspect of asthma severity is the extent of medication utilization and medication adherence. It is complicated to objectively estimate the level of adherence to treatment in epidemiology, partly because of the lack of standardized methods to measure adherence, but also because each method has limitations^{58,59}. However, previous data from our cohort¹⁹ and other studies^{18,60-62} suggest that individuals with more severe disease report greater use of medications, although a subgroup reports that they are not taking any medication on a regular basis. Overall, however, we should assume that the increased level of severity is not likely to depend simply on under-treatment.

One of the drawbacks that epidemiological studies face is the potential bias of over-estimation of disease severity because the patients with more severe asthma might be more prone to participate in studies concerning respiratory morbidity^{63,64}. However, from a validation study on the non-responders and late responders in this study⁶⁵, symptom estimates were not biased to the study population vs. non-respondents. Another potential disadvantage of our study could be its cross-sectional design, which only provides a snapshot of the separate severity

signs and their degree of overlap without determining the dynamics of disease and ageing. However, even though patients might go in and out of the defined “severity phenotypes” over time, it is unlikely that the overall prevalence of severity in the population would change. Lastly, we should note that the term “asthma control”, which is determined either by the ACT or the “asthma control questionnaire”²⁴⁻²⁶, could overlap to some degree of the definition of asthma severity in the current study. For example, the frequent use of a symptom-relieving beta-2-agonist without any other sign of severity, is part of the definition of “asthma control”. In conclusion, asthma severity, albeit challenging to define and evaluate, is far from uncommon. Every third asthmatic in our study showed at least one sign of asthma severity, and this clearly indicates that there are still many unmet needs in managing this disease. Our study also points out the complexity and overlap of the asthma severity parameters, which indicates that severe asthma is not a uniform type of asthma, but consists of a mixture of many different phenotypic variables. Some of the phenotypic indicators of asthma severity are only found together in a small number of patients, while other indicators are found in combination in a greater number of severe asthmatics. Overall, this study illustrates the importance of phenotyping asthma patients with signs of more severe disease, which can guide individualized severe asthma management and future clinical study design.

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581 **Table legends**

582 Table I. Characterization of all groups in terms of age, gender, BMI, smoking, pack-years,
 583 clinical characteristics, asthma medications, and level of control.

Characteristics	Respiratory healthy group	Non-severe asthma	One sign of severity	Two or more signs of severity	p-value (within asthma groups)	p-value (asthma groups vs. healthy)
No of individuals	847	475	171	98		
Age	49.9 ± 15.5	44.9 ± 15.1	50.9 ± 15.1	54.6 ± 14.9	<0.001	0.002
Sex (female) (%)	53.2	60.2	63.2	67.3	NS	<0.001
BMI (%)						
<20	4.5	3.4	2.3	3.1		
20-24	39.7	35.8	27.5	25.5		
25-29	43.0	40.1	40.4	30.6	<0.001*	<0.001*
≥30	12.8	20.7	29.8	40.8		
Smoking (%)						
Non-smokers	54.1	56.5	48.5	36.7		
Ex-smokers	35.4	34.0	34.5	41.8	<0.05*	NS*
Smokers	10.5	9.5	17.0	21.5		
Pack years (%)						
1 to 5	32.5	32.5	28.7	16.1		
6-15	34.3	39.3	27.6	24.2	<0.001*	<0.001*
Over 16	33.2	28.2	43.7	59.7		
FVC (in litres)	4.34 ± 1.08	4.35 ± 1.08	3.86 ± 1.11	3.36 ± 1.21	<0.001	<0.001
FENO ppb	19.0 ± 11.0	26.4 ± 21.4	27.1 ± 24.6	28.6 ± 26.9	NS	<0.001

FEV1/FVC < 0.70 (%)	4.0	6.4	25.7	32.0	<0.001	<0.001
Positive methacholine test) (%)	32.0	67.9	77.6	88.2	NS	<0.001
Positive SPT (%)	66.9	38.5	53.8	57.1	NS*	<0.001*
0	11.8	12.8	5.8	8.2		
1	21.3	48.7	40.4	34.7		
≥2						
ICS / ICS+LABA (%)	N/A	53.1	70.2	79.6	<0.001**	N/A
"Well controlled asthma" ACT _{≥20} (%)	N/A	84.4	65.4	28.8	<0.001	N/A

A *p*-value <0.05 was considered significant. NS, non-significant. * test for trend, ** the difference between having one sign of severe asthma and having two or more signs was not significant (*p* = 0.09).

PD20 – provocation dose of methacholine which causes a 20% fall of the forced expiratory volume in one second, SPT – skin-prick test, ICS – inhaled corticosteroid, LABA – long-acting beta-2 agonist, ACT – asthma control test

584 **Table II. Unadjusted odds ratios associated with signs of asthma severity among**
 585 **subjects with current asthma. Data are presented as the odds ratio (OR) and 95%**
 586 **confidence interval (CI).**

Associated factors	One sign of severity (n=171)	Two or more signs of severity (n=98)
OR (CI), significant are bold		
Age (years)	1.03 (1.02 – 1.04)	1.04 (1.02 – 1.05)
Gender (female)	1.13 (0.79 – 1.63)	1.36 (0.86 – 2.06)
Smoking	2.07 (1.22 – 3.51)	3.46 (1.85 – 6.46)
BMI > 30	1.63 (1.10 – 2.42)	2.65 (1.67 – 4.19)
Nasal blockage	0.96 (0.66 – 1.40)	1.58 (1.02 – 2.47)
Rhinorrhea	1.31 (0.95 – 1.81)	1.47 (0.94 – 2.29)
Allergic rhinitis	1.08 (0.77 – 1.52)	0.66 (0.42 – 1.04)
Atopy	0.68 (0.45 – 1.06)	0.69 (0.39 – 1.22)
Longstanding cough	1.48 (1.02 – 2.15)	3.51 (2.24 – 5.48)
Morning cough	1.81 (1.27 – 2.57)	3.29 (2.09 – 5.18)
Sputum production	2.66 (1.84 – 3.82)	6.38 (3.97 – 10.24)

The **reference group** used in the analysis was **non-severe** asthmatics.

The **reference categories** were: younger age, male gender, no smoking, BMI of 20-24, no nasal blockage, no rhinorrhea, no allergic rhinitis, no atopy, no longstanding cough, no morning cough and no sputum production.

587 **Table III. Multinomial logistic regression analysis with non-severe asthmatics as a**
 588 **reference group. Data are presented as the adjusted odds ratio (OR) with 95 %**
 589 **confidence intervals (CI).**

Associated factors	One sign of severity (n=171)	Two or more signs of severity (n=98)
OR (CI), significant are bold		
Age	1.02 (1.01 – 1.04)	1.03 (1.01 – 1.05)
Smoking	1.50 (0.86 – 2.62)	1.76 (0.89 – 3.50)
BMI > 30	1.51 (0.99 – 2.26)	2.27 (1.38 – 3.75)
Nasal blockage	1.12 (0.76 – 1.66)	1.34 (0.82 – 2.18)
Longstanding cough	1.03 (0.68 - 1.55)	2.01 (1.22 - 3.33)
Morning cough	1.06 (0.69 - 1.63)	1.14 (0.65 - 2.01)
Sputum production	2.15 (1.37 – 3.35)	4.60 (2.29 – 7.58)

The **reference group** used in the analysis was **non-severe** asthmatics

The **reference categories** were: younger age, no smoking, BMI of 20-24, no nasal blockage, no sputum production, no longstanding cough, no morning cough.

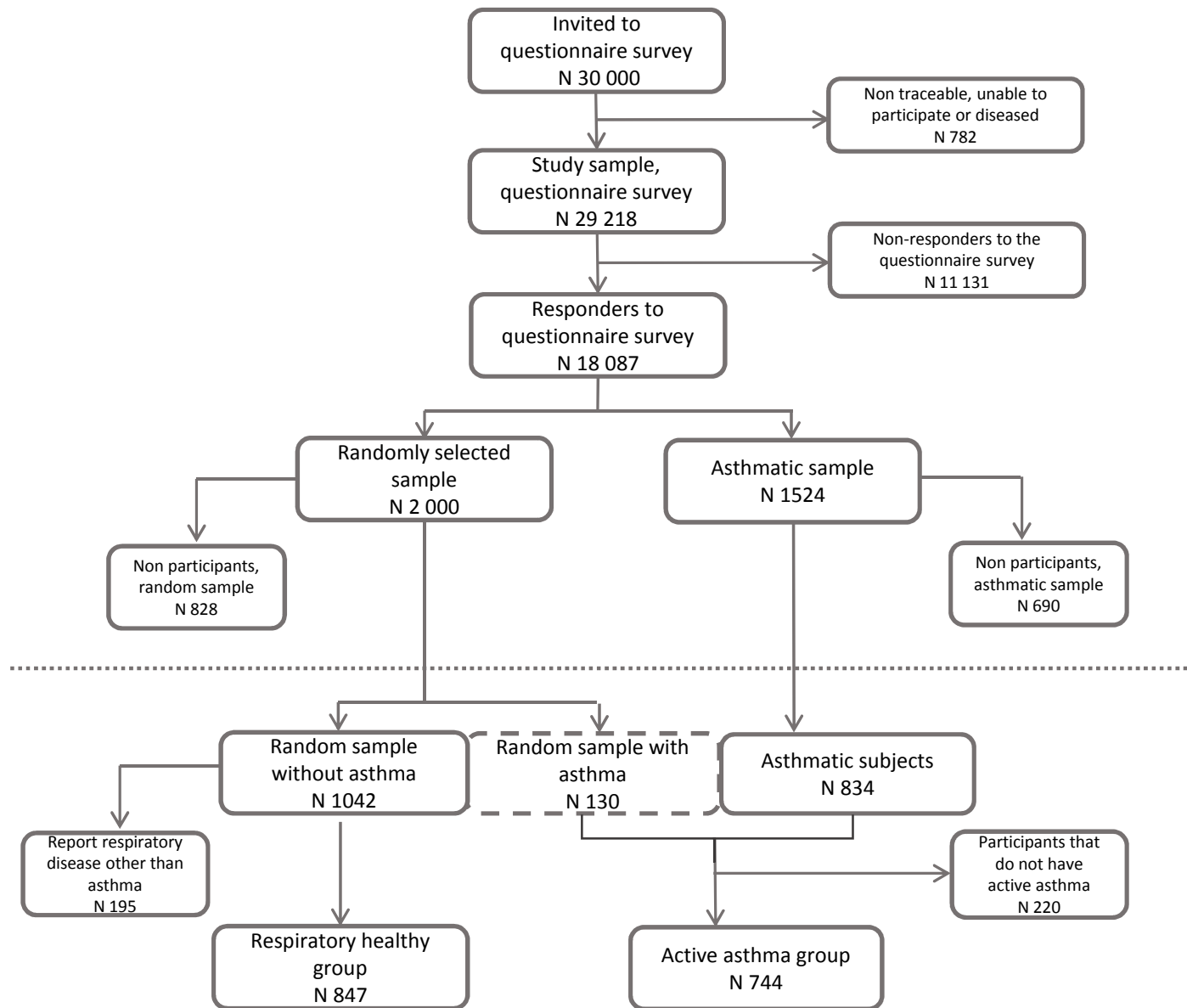
Figure legends

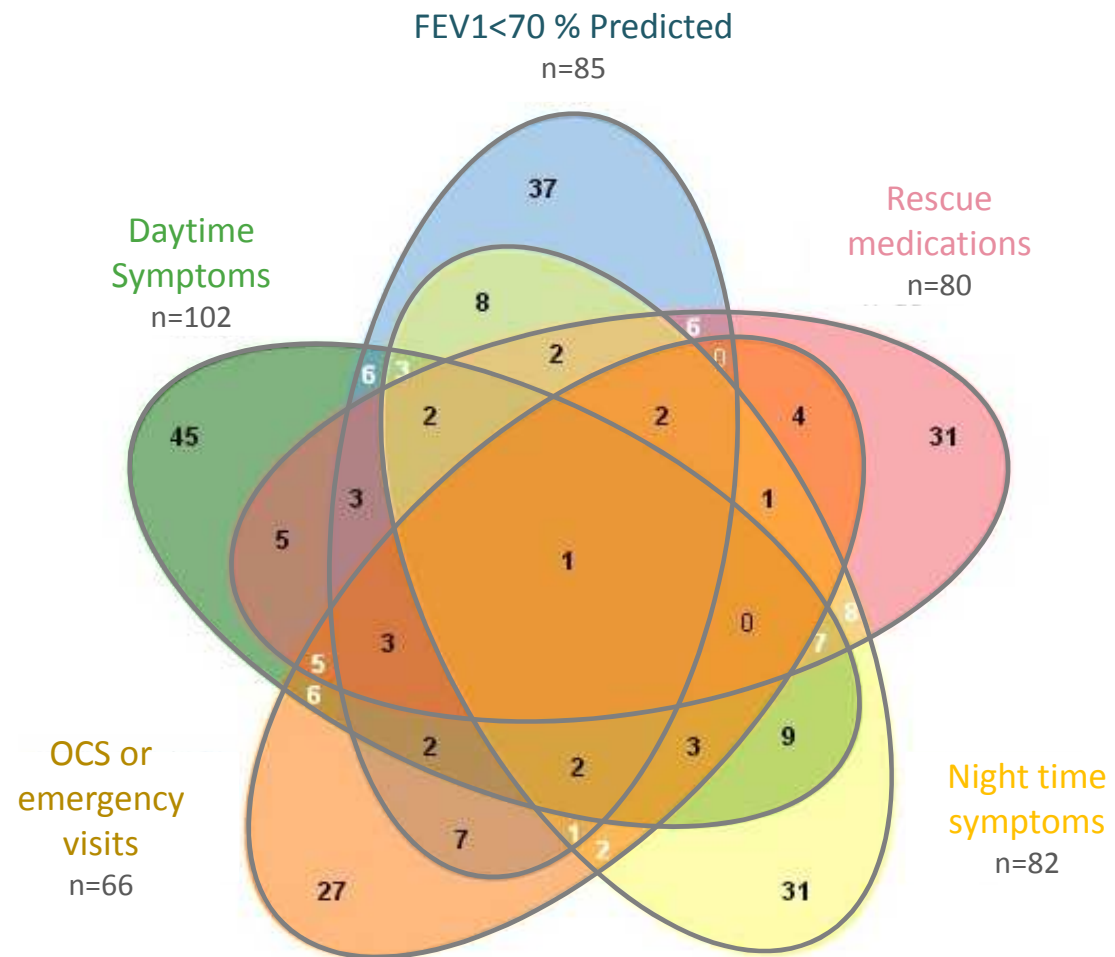
Figure 1. Flow-chart showing the study design and the selection of the asthmatic and control groups

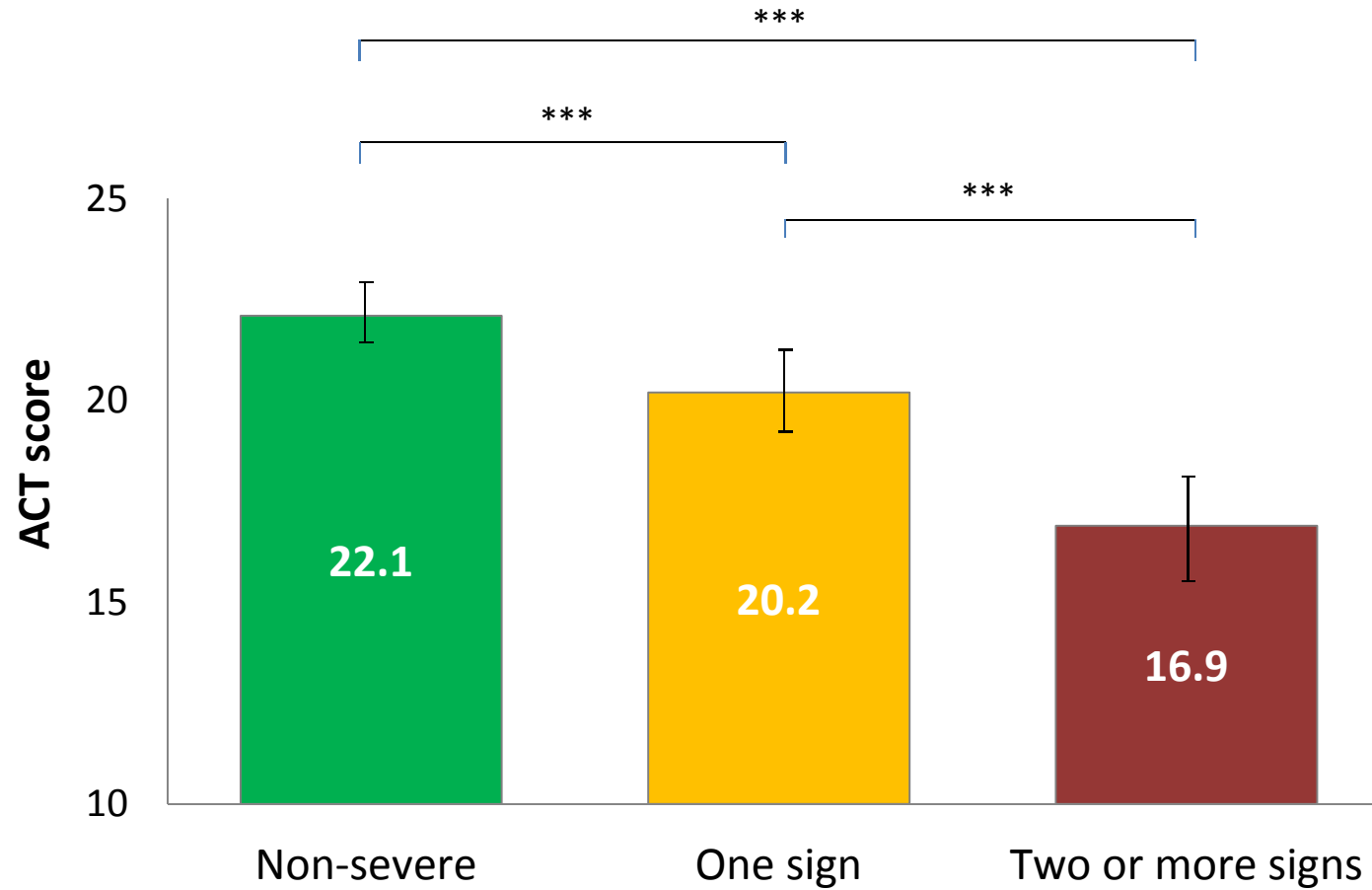
Figure 2. Venn diagram showing the proportions of the active asthmatics who present with the individual severity signs as well as their degree of overlap.

Figure 3. Difference in the mean Asthma Control Test (ACT) score between the groups of non-severe asthmatics, asthmatics with one sign of severe asthma, and those with two or more signs.

Figure 4. Prevalence of symptoms in the non-severe asthmatics, asthmatics who report one sign of severe asthma, and those who report two or more signs of severity.







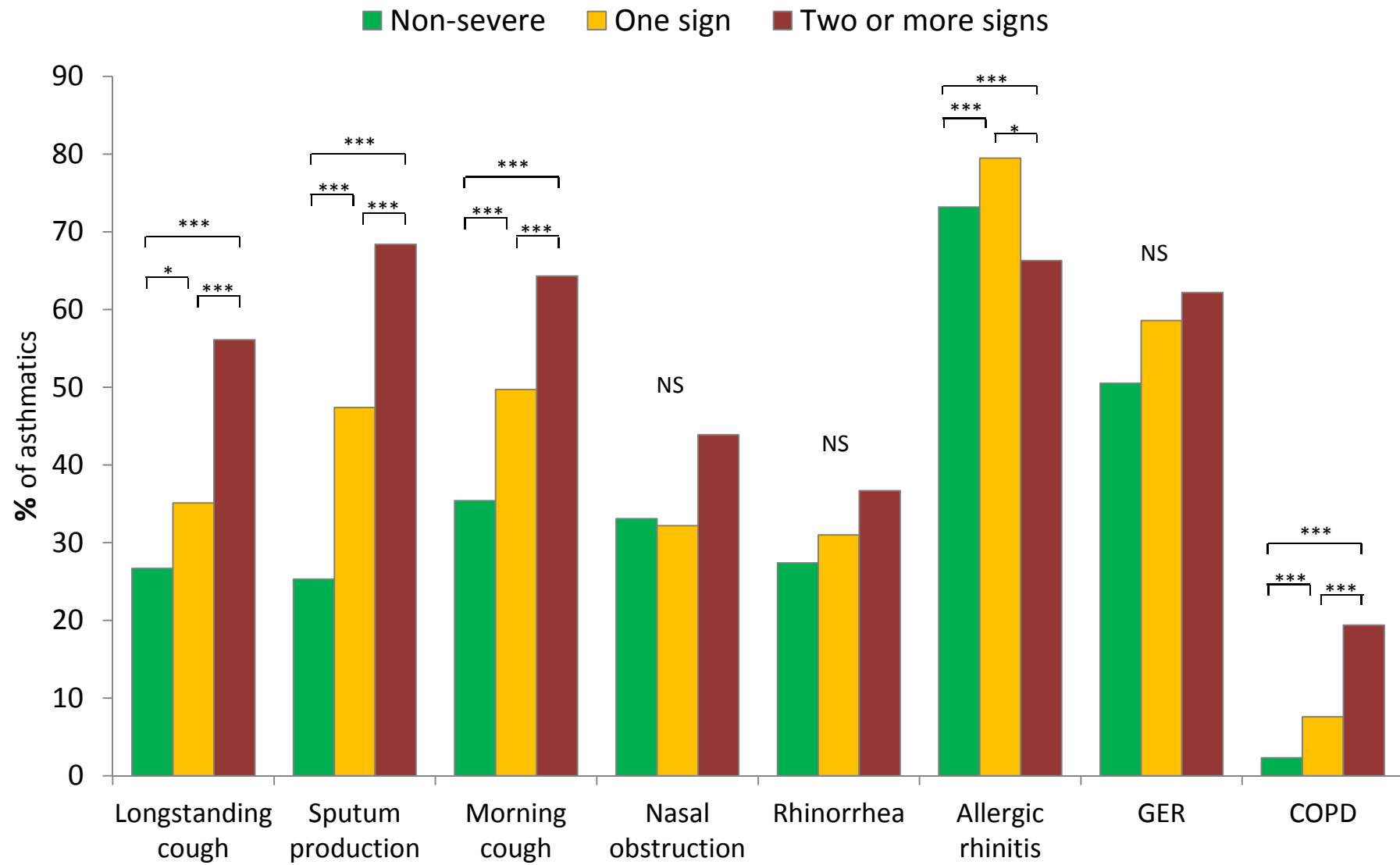


Table E1. Prevalence of each of the chosen asthma severity signs.

Severity signs	Number (% from active asthmatics, n=744)
Multiple daytime symptoms (Recurrent wheeze, attacks of shortness of breath, dyspnea, breathlessness on exertion or cold, all while using asthma medications)	102 (13.7)
FEV1 below 70% of predicted value	85 (11.4)
Daily or almost daily use of rescue medications (SABA)	80 (10.8)
Night-time symptoms at least once a week or most nights of the week	82 (11.0)
Respiratory problems-related emergency visits or/and use of oral steroids regularly or during exacerbations	66 (8.9)

Description of the chosen asthma severity signs. Results are presented with the number of the individuals as well as the percentage they represent from the active asthma group (744 individuals).

Table E2. The amount of individuals that express the one, two, three, four or five severity signs and proportion from the asthmatic population

Number of severity signs expressed by the subjects	Number of individuals (% from active asthmatics, n=744)
One sign	171 (23)
Two signs	61 (8.2)
Three signs	25 (3.4)
Four signs	11 (1.5)
All five signs	1 (0.1)