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Severe asthma - A population study perspective

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Helena Backman^{1§}, Sven-Arne Jansson¹, Caroline Stridsman², Berne Eriksson^{3,4}, Linnea Hedman¹, Britt-Marie Eklund¹, Thomas Sandström⁵, Anne Lindberg⁵, Bo Lundbäck^{1,3}, Eva Rönmark¹

¹Dept of Public Health and Clinical Medicine, Division of Occupational and Environmental Medicine, the OLIN unit, Umeå university, Umeå, Sweden; ²Dept of Health Sciences, Luleå University of Technology, Luleå, Sweden; ³Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; ⁴Dept of Internal Medicine, Central County Hospital of Halland, Halmstad, Sweden; ⁵Dept of Public Health and Clinical Medicine, Division of Medicine, Umeå university, Umeå, Sweden

§Corresponding author information:

Helena Backman
Division of Occupational and Environmental Medicine, the OLIN unit
Dept of Public Health and Clinical Medicine
Umeå University
901 87 Umeå, Sweden

E-mail address: helena.backman@norrboten.se

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Abstract

Background: Severe asthma is a considerable challenge for patients, health care professionals and society. Few studies have estimated the prevalence of severe asthma according to modern definitions of which none based on a population study.

Objective: To describe characteristics and estimate the prevalence of severe asthma in a large adult population-based asthma cohort followed for 10-28 years.

Methods: N=1006 subjects with asthma participated in a follow-up during 2012-14, when 830 (mean age 59y, 56% women) still had current asthma. Severe asthma was defined according to three internationally well-known criteria: the ATS workshop definition from 2000 used in the US Severe Asthma Research Program (SARP), the 2014 ATS/ERS Task force definition and the GINA 2017. All subjects with severe asthma according to any of these criteria were undergoing respiratory specialist care, and were also contacted by telephone to verify treatment adherence.

Results: The prevalence of severe asthma according to the three definitions was 3.6% (US SARP), 4.8% (ERS/ATS Taskforce), and 6.1% (GINA) among subjects with current asthma. Although all were using high ICS doses and other maintenance treatment, >40% had uncontrolled asthma according to the asthma control test. Severe asthma was related to age >50 years, nasal polyposis, impaired lung function, sensitization to aspergillus, and tended to be more common in women. Further, neutrophils in blood significantly discriminated severe asthma from other asthma.

Conclusions and clinical relevance: Severe asthma differed significantly from other asthma in terms of demographic, clinical and inflammatory characteristics, results suggesting possibilities for improved treatment regimens of severe asthma. The prevalence of severe asthma in this asthma cohort was 4-6%, corresponding to approximately 0.5% of the general population.

Keywords: epidemiology; asthma; eosinophils; neutrophils; IgE; lung function

Introduction

Although the large majority of subjects with asthma can live their lives with limited or no restrictions when using adequate medication^{1,2}, a small but significant proportion of the asthma patients have a severe and poorly controlled disease despite using high doses of maintenance treatment³⁻⁵. Severe asthma is characterized by frequent symptoms, high comorbid burden, increased bronchial hyper-responsiveness and airflow variability accompanied by exacerbations of asthma⁴⁻⁸, all resulting in poor asthma control, lower quality of life, impaired lung function, increased health care utilization, and risk for asthma death^{8,9}. Furthermore, severe asthma is associated with high costs for the individuals and the society^{10,11}.

The medical scientific societies have published several documents on severe asthma over the past two decades including the *European Respiratory Society* (ERS), *American Thoracic Society* (ATS), *World Health Organization* (WHO) and *Global Initiative for Asthma* (GINA) consortium^{2,8,12-15}, and several projects and research programs on severe asthma have been initiated¹⁶⁻¹⁹. Specifically, the *US Severe Asthma Research Program* (SARP) was launched to improve the understanding of severe asthma^{13,16}. The two major terms used are *severe asthma* and *severe refractory asthma*, the former including also asthmatics among whom asthma can be controlled.

Almost all publications on severe asthma have been based on patient cohorts from hospitals or other health care units¹⁶⁻²¹, while population studies are scarce. The assumptions of the prevalence of severe asthma among asthmatics vary from a few percentages to at highest 10% by the *European Network For Understanding Mechanisms Of Severe Asthma* (ENFUMOSA)^{3,4,17}, while two studies based on prescription databases^{22,23} both reported 3-4% to have severe refractory asthma.

As a part of the epidemiological research program the *Obstructive Lung Disease in Northern Sweden* (OLIN) Studies, in progress since 1985²⁴, a large population-based adult asthma cohort was followed-up in 2012-14 using detailed clinical measures. In the present study, the aim was to describe characteristics and estimate the prevalence of severe asthma in a large adult population-based asthma cohort followed for 10-28 years, based on severe asthma definitions by the ATS workshop in 2000¹³, by ATS/ERS in 2014⁸ and by GINA in 2017².

Materials and Methods

Study population

The study sample consisted of adults with asthma identified at clinical examinations performed between 1986 and 2001 of four cohorts derived from the general population of the northernmost county of Sweden, Norrbotten²⁴⁻²⁷, and of adults with incident asthma identified in a case-referent study in the county²⁸. Studies of non-responders have shown none or only limited bias due to non-response^{29,30}, and the participation rates in the clinical examinations of the cohorts were 67%-91%³¹⁻³⁴. The asthma cohort included all patients with physician-diagnosed asthma, or report of ever having had asthma and, furthermore, those without asthma diagnosis prior to the surveys but who had a medical history of asthma together with physiologically verified bronchial variability or asthma medication, comprising all together 2055 adults. The origins of the cohort, the criteria for inclusion and mortality during follow-up have been described in detail elsewhere³⁰ and are summarized in Figure 1.

In 2012-2014, all subjects in the asthma cohort who were alive and still living in Norrbotten were invited to a clinical follow-up including a detailed structured interview including assessment of asthma treatment during the last 12 months, pre- and post-bronchodilator spirometry, skin prick testing, blood sampling, and measurements of height and weight³⁰. Of the 1425 invited, 1006 (71%) participated. The examinations of the asthma cohort were performed by specialized trained nurses.

Among the participants, 830 (56% women, mean age 59y, range 32-92y) had current asthma defined as report of wheeze, or attacks of shortness of breath, or asthma medication use last 12 months.

Patients reporting high dose ICS² or OCS as maintenance treatment in the 2012-2014 examinations were contacted by telephone in 2016 to verify adherence to treatment during the last 12 months. Patients with verified treatment adherence and severe asthma according to any of the three definitions below were additionally examined by a senior consultant in respiratory medicine in the research team including evaluation of treatment, inhalation technique, and assessment of comorbidities. Over the years preceding the current study, all severe asthma patients had also been subject to health care, either by respiratory specialists or by other physicians in close collaboration with respiratory specialists. The study was approved by the Regional Ethical Review Board at Umeå University, Sweden. Informed consent was obtained at the time of examinations.

Definitions

Three definitions of *severe asthma* were applied:

1/ *The ERS/ATS-definition*⁸: “High dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids)” is required “to prevent asthma from becoming uncontrolled or which remains uncontrolled despite this therapy”. Higher doses of ICS are required by the ERS/ATS than the GINA (e-Table 1).

2/ *The US SARP-definition*¹³: One major criterion out of two on use of either high dose ICS (as defined by ERS/ATS) or oral corticosteroids (OCS) and at least two out of seven minor criteria are required as defined by the ATS Workshop guidelines from 2000 which were used in US SARP 1-2 (e-Table 2).

3/ *The GINA-definition*²: Asthma on GINA step 4 or 5, but only those with high dose inhaled ICS as defined by GINA (e-Table 1) and those on regular OCS, not those on moderate ICS doses without concurrent OCS use.

Other asthma is all current asthma except *severe asthma* according to any of the three criteria above.

The *Asthma Control Test (ACT)* was used for defining asthma control³⁵, categorized as controlled (score 25), partly controlled (score 20-24), and uncontrolled (score <20).

Demography and clinical characteristics of severe asthma included symptoms, lung function, blood cells (eosinophil and neutrophil counts), specific-IgE, age of asthma onset, co-morbidity, age, sex, smoking, socio-economic status, and body mass index (BMI).

Smoking was categorized as current smokers, ex-smokers and non-smokers. Ex-smokers were defined as those who had smoked for at least one year but not during the last 12 months.

Socio-economic status classification was based on most recent occupation.

Lung function was measured using the Masterscope (Jaeger) spirometer. Swedish reference values for spirometry were used³⁶. *Airway obstruction* was defined both using $FEV_1/FVC < LLN$ and $FEV_1/FVC < 0.70$.

Allergic sensitization was measured using the ImmunoCap Phadiatop with 0.35 kU/L as cut-off.

Sensitizations to specific allergens were tested among those with a positive Phadiatop.

Statistical analyses

Statistical analyses were performed with the IBM Statistical Package for the Social Sciences Statistics 24. In bivariate analyses, the Chi-square test was used to test for differences in proportions and the T-test for differences in means. A p-value < 0.05 was considered statistically significant. Z-scores for the lung function variables were calculated as (observed value-reference value)/standard deviation³⁶. Receiver-operating characteristic (ROC) curves were constructed to determine areas under the curves (AUC) for the ability of blood eosinophil and neutrophil counts to separate severe asthma from other asthma.

Results

The prevalence of severe asthma

The prevalence of severe asthma among all patients with current asthma was 3.6% (95%CI 2.3-4.9), 4.8% (95%CI 3.4-6.3) and 6.1% (95%CI 4.5-7.8), according to the SARP-, ERS/ATS- and GINA-definitions, respectively (Table 1). The corresponding prevalence among those on asthma medication during the last 12 months (n=580) was 5.2% (95%CI 3.4-7.0), 6.9% (95%CI 4.8-9.0) and 8.8% (95%CI 6.5-11.1). All with severe asthma according to ERS/ATS also had severe asthma according to GINA, and all with severe asthma according to SARP also had severe asthma according to ERS/ATS. The prevalence was higher among women than men, however not significantly so, and among those aged >50 years (Table 1).

Asthma medication and asthma control

Asthma patients fulfilling any of the definitions of severe asthma were all using at least one further controller medicine in addition to high dose ICS or OCS (a specification of medications and doses is provided in e-Table 3). Four patients used OCS regularly in addition to ICS. At least one emergency room visit or hospitalization for asthma during the last 12 months was reported by 15.0%-20.0%, and 17.6%-26.7% had used ≥ 3 OCS bursts during the last 12 months (Table 2). Of those with severe asthma, >40% had uncontrolled asthma, and >90% had either uncontrolled or partly controlled asthma, regardless of severe asthma criteria. Only three patients had controlled asthma (ACT score=25) according to both the GINA and the ERS/ATS defined severe asthma, and only one according to SARP.

Demography and clinical characteristics

Mean BMI, smoking habits, the proportion reporting current allergic rhinitis or ever having had rhinitis, and of sensitized to at least one airborne allergen did not differ between severe asthma and other asthma. However, the mean age was higher, and current and chronic respiratory symptoms

were all significantly and considerably more common among patients with severe asthma (Table 3, e-Table 4), and regardless of definition, severe asthma was also associated with low FEV₁, FEV₁/FVC<0.70 and FEV₁/FVC<LLN (Table 4).

Neutrophils both in terms of mean values and proportion of subjects having neutrophils >6 x 10⁹/l and >7 x 10⁹/l were significantly elevated in patients with severe asthma compared to other asthma (Table 3). ROC-curves exemplify how neutrophil counts significantly separated severe asthma from other asthma (Fig 2a-c). The proportion of patients with severe asthma with elevated eosinophils was higher than of elevated neutrophils, but the differences versus other asthma did not reach statistical significance.

Two separate phenotypes of severe asthma were detected: severe asthma with nasal polyposis, present in 13.7-20.0% of the patients with severe asthma (Table 3) among whom all but one had asthma onset in adulthood, and severe asthma with sensitization to moulds, particularly to aspergillus (Table 5). None of the patients with nasal polyposis were sensitized to moulds.

Discussion

This paper provides a population study perspective on severe asthma in terms of demography, clinical characteristics and prevalence, based on three well known and strictly defined criteria for severe asthma: the ATS 2000 workshop definition used in the first US SARP¹³, the definition by the 2014 ERS/ATS Task Force⁸, and finally according to GINA 2017². However, similar distinct clinical characteristics could significantly discriminate severe asthma from other asthma regardless of definition of severe asthma. Two completely separate phenotypes were detected: severe asthma with nasal polyposis and severe asthma with sensitization to moulds, and neutrophilia was more common in severe asthma than in other asthma. The prevalence of severe asthma according to the

three definitions ranged from 3.6% to 6.1% among subjects with current asthma. As the asthma prevalence among adults in Sweden is about 10%³⁷, our study indicates that about 0.5% of the adult population has severe asthma.

The increasing interest in severe asthma has resulted in development of terminology, definitions and management documents during the past two decades^{2,8,12-15}, most recently by GINA and ERS/ATS^{2,8}, but still both terminology and definitions vary. Major documents include the *ERS Task Force on Difficult/Therapy-Resistant Asthma* published in 1999¹² and *Proceedings of the ATS Workshop on Refractory Asthma* published in 2000¹³. Later on the WHO defined severe asthma somewhat broader by including also untreated severe asthma in the term^{1,14}. A workshop also in year 2000 organized by the US *National Institute of Health and the US National Heart, Lung, and Blood Institute* (NHLBI) resulted in the SARP aiming at studies for better understanding of severe asthma¹⁶. Also the ENFUMOSA characterized the condition and concluded neutrophil inflammation to be common in severe asthma¹⁷, and in 2009 the European *Unbiased BIOMarkers in PREDiction of respiratory disease outcomes* (U-BIOPRED) was initiated aiming at identifying biomarkers and mechanisms for the prediction of severe asthma¹⁹. U-BIOPRED and other studies have described characteristics of severe asthma^{6,16,17,18}, while precise estimates of prevalence cannot be made from these studies.

As terminology and definitions vary, we have chosen the strict US SARP definition which aims to identify severe refractory asthma in line with the ATS proceedings from 2000¹³, the slightly wider ERS/ATS Task Force definition⁸, and finally the GINA definition of severe asthma. The US SARP definition from the 2000 ATS proceedings¹³ is an older definition which preceded the 2014 ERS/ATS definition⁸, and which was replaced by this newer ERS/ATS definition⁸ in SARP 3. The GINA definition was slightly modified from the original version² by excluding those on moderate ICS doses without concurrent OCS use. This slight modification of the GINA definition made it somewhat more strict, but as GINA requires lower doses for defining high dose ICS than the ERS/ATS⁸ this definition is still

the widest of the three. However, because GINA does not require maximum ICS dose and thus may identify subjects with uncontrolled but not necessarily truly severe asthma, the 2014 ERS/ATS definition⁸ could be considered as most appropriate to identify truly severe asthma.

To shed light on population prevalence of severe asthma, population studies are warranted. From the clinicians, health economic and political point of view, it is important to increase the knowledge on how common this severe and costly disease is, recently particularly highlighted as new biological treatments are entering the market. Some previous epidemiological studies have suggested considerably higher prevalence of severe asthma than we found, even more than 20% among the studied asthmatics^{38,39}, but there was a significant proportion of subjects with far from optimal asthma treatment in these studies. Similarly, a French review has estimated a prevalence of 1-3% of severe asthma in the general population⁴⁰. Precise trends in prevalence of severe asthma cannot however be determined by comparing studies of today with earlier studies, as treatment has improved and as today's definitions of severe asthma are much stricter.

We have identified only three studies on prevalence following recent criteria for severe asthma, one Danish, one Dutch, and one from Israel, all based on data bases and prescription registers. The prevalence of severe asthma and severe refractory asthma, respectively, was estimated to 8.1% and 3.0% among asthmatics aged 18-44 y based on the GINA criterion of high dose ICS in the Danish study²², and to 4.5% and 3.6% among asthmatics aged ≥ 18 y based on the ERS/ATS criteria for high dose ICS in the Dutch study²³. In the Israelic study⁴¹, 4.65% of the asthmatics were identified as having severe asthma based on a modified high dose ICS definition with levels in-between the GINA and ERS/ATS. Our slightly higher prevalence of severe asthma among medicine users can be related to our older sample, since there are reports indicating severe asthma to be more common among middle-aged and elderly than in younger asthmatics^{4,42}.

Regarding morbidity the year prior to our study, 15-20% of subjects with severe asthma (depending on criteria) had had emergency room visits or had been hospitalized for asthma and 18-27% had received at least three OCS bursts. In the Danish study only about 2% had emergency department visits, 4% had been hospitalized, and 18% had received at least one prednisolone prescription the year prior to the study²². The high morbidity among our severe asthmatics supports the validity of our classifications.

In contrast to the shortage of population studies, there are several studies focused on severe asthma in patient populations recruited from hospitals or other health care units^{6,7,17-19,21,42-44}. Knowledge about characteristics and phenotypes of severe asthma comes from these studies, while population prevalence cannot be estimated from them. Further, the majority in most of these studies have severe refractory asthma, for instance the ATS 2000 criterion for severe refractory asthma¹³ was applied at recruitment of the Belgian severe asthma cohort²¹. In our population study, >40% had uncontrolled asthma (ACT<20), which is lower than the >80% in the Belgian cohort²¹. It is also common that severe asthma patients develop severe chronic airway obstruction^{42,43}, which is associated with long disease duration and older age^{7,18}, as in our study. Further, mean BMI was high, almost 30, among our subjects with severe asthma, a finding also observed in severe asthma patients in the UK⁴⁴.

As found by others⁴², characteristics of allergy did not differ between severe asthma and other asthma, with one important exception. Sensitization to moulds, particularly aspergillus, was significantly more common among patients with severe asthma, and has previously been indicated as a specific asthma phenotype⁴⁶⁻⁴⁸. Our population-based results were in line with previous results from the ECRHS⁴⁹, but considerably lower compared to results from severe asthma patients participating in a clinical trial⁵⁰. Further, nasal polyposis was more common among those with severe asthma, a result also in line with others⁷. It would have been valuable to analyse aspirin or salicylate

hypersensitivity, but unfortunately such data was not available. Interestingly, none of the subjects with nasal polyposis were sensitized to moulds in our study, and these two phenotypes may be separate entities.

Several studies have reported increased eosinophils and/or neutrophils associated with severe asthma^{21,51-54}, although different cut-offs for the definition of increased levels were used in these studies, and in line with previous findings⁷ we found eosinophilia to be more common than neutrophilia. However, while blood neutrophils significantly separated severe asthma from other asthma in our study, blood eosinophils only tended to do so. Comorbidity is common among severe asthma patients, and blood neutrophilia may represent for instance frequent infections or even concomitant heart disease, and can also be explained by smoking or oral steroid use. Notably, smoking habits did not differ between subjects with severe and other asthma, and the prevalence of current smoking was particularly low among subjects with severe asthma. Thus, the higher levels of blood neutrophils among subjects with severe asthma are not explained by smoking.

Among the strengths of this population study are the high participation rates and limited selection bias^{29,30}, and that our asthma cohort seems to well reflect the distribution of asthma in the Swedish population of same age^{25-28,31-34,37}. A weakness when estimating prevalence might be the long recruitment period, but because both remission and incidence is low among adults we believe this bias is limited. Further, if a detailed medical history at recruitment had not been available, many asthmatics could in later stages have been classified as COPD instead of asthma due to impaired lung function. The asthma onset before age 40 and concomitant past or present allergic rhinitis in the majority of cases strongly support a correct asthma diagnosis. Importantly, the diagnosis of severe asthma cannot be based on one single examination but require long-term follow-ups and verification of treatment adherence. Despite these advantages of the current study, it is difficult to assess treatment adherence and there is still a risk that we not fully have been able to distinguish between

difficult-to-treat and truly severe asthma. Finally, it would indeed have been very interesting to study remission and complete occurrence of severe asthma during the entire study period along with mortality due to severe asthma per se, but data at inclusion was not detailed enough to enable identification of severe asthma according to current guidelines.

Conclusions

In conclusion, the prevalence of severe asthma in this large population-based asthma cohort was 4-6%, corresponding to approximately 0.5% of the adult general population. Regardless of definition, severe asthma was associated with impaired lung function, nasal polyposis, and tended to be more common among women and in older age. Further, the associations with blood neutrophils and sensitization to aspergillus suggest possibilities for new and improved treatment regimens of severe asthma.

Guarantor of the paper

HB is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Author contributions

HB had full access to all of the data in the study and takes full responsibility for the entire manuscript content including the integrity of the data and the accuracy of the data analysis. HB, CS, BE, LH, B-ME, TS, AL, BL, and ER all contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors provided important intellectual content to the manuscript and approved the final version.

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The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Legends to figures

Figure 1. Study flow chart

Figures 2a-c. Receiver-operating characteristic (ROC) curves displaying the ability for blood eosinophils and neutrophils to discriminate severe asthma according to a) GINA, b) ERS/ATS, and c) SARP from other asthma. AUC=Area under the curve.

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Table 1. Prevalence of severe asthma according to different criteria, by age group and sex and among all subjects with asthma

Criteria	Age group				Sex				All		P-value by	
	<=50 y (n=220)		>50 y (n=610)		Women (n=462)		Men (n=368)		(n=830)		Age group	Sex
	n	%	n	%	n	%	n	%	n	%		
GINA	9	4.1%	42	6.9%	33	7.1%	18	4.9%	51	6.1%	0.139	0.180
ERS/ATS	5	2.3%	35	5.7%	25	5.4%	15	4.1%	40	4.8%	0.040	0.372
SARP	4	1.8%	26	4.3%	17	3.7%	13	3.5%	30	3.6%	0.096	0.910

P-value from chi-square test, bold figures indicate statistical significance

Table 2. Medicine use, daily symptoms, health care consumption and FEV1% among subjects with severe asthma according to different criteria

		Severe asthma according to different criteria		
		GINA (n=51)	ERS/ATS (n=40)	SARP (n=30)
High dose ICS according to GINA	n	50	39	29
	%	98.0%	97.5%	96.7%
High dose ICS according to ERS/ATS	n	38	38	28
	%	74.5%	95.0%	93.3%
OCS >50% of days	N	4	4	4
	%	8.0%	10.0%	13.3%
OCS periodically	N	8	7	7
	%	15.7%	17.5%	23.3%
Concurrent use of ≥ 1 controller medication (SARP minor criterion no 1)	n	51	40	30
	%	100.0%	100.0%	100.0%
Daily symptoms requiring treatment with SABA (SARP minor criterion no 2)	n	8	6	6
	%	15.7%	15.0%	20.0%
FEV1<80% of predicted (SARP minor criterion no 3)	n	27	21	21
	%	52.9%	52.5%	70.0%
≥ 3 OCS bursts past year (SARP minor criterion no 4)	n	9	8	8
	%	17.6%	20.0%	26.7%
≥ 1 urgent care visits past year* (SARP minor criterion no 5)	n	8	6	6
	%	15.7%	15.0%	20.0%

ICS = Inhaled corticosteroids, OCS = oral corticosteroids

*In our study defined as emergency room visit or hospitalization due to asthma

Table 3. Clinical characteristics among subjects with other asthma and severe asthma according to different criteria

Clinical characteristics		Other asthma n=779	Severe asthma according to different criteria			Difference (p-value) compared to other asthma		
			GINA n=51	ERS/ATS n=40	SARP n=30	GINA	ERS/ATS	SARP
Age	mean	58.45	63.31	64.73	65.60	0.006	0.001	0.002
BMI	mean	28.71	29.54	29.52	29.35	0.376	0.469	0.590
Blood eosinophils ($10^9/L$)	mean	0.22	0.26	0.27	0.28	0.066	0.070	0.061
Blood neutrophils ($10^9/L$)	mean	3.73	4.55	4.76	4.90	<0.001	<0.001	<0.001
Blood eosinophils > 0.22*	%	29.9%	41.7%	45.9%	46.4%	0.087	0.039	0.063
Blood eosinophils $\geq$ 0.3	%	27.5%	37.5%	40.5%	42.9%	0.136	0.086	0.076
Blood eosinophils $\geq$ 0.4	%	15.4%	22.9%	27.0%	28.6%	0.166	0.059	0.061
Blood eosinophils $\geq$ 0.5	%	7.2%	14.6%	16.2%	17.9%	0.062	0.044	0.037
Blood neutrophils $\geq$ 5.0	%	15.2%	29.2%	35.1%	39.3%	0.011	0.001	0.001
Blood neutrophils $\geq$ 6.0	%	5.5%	18.8%	24.3%	28.6%	<0.001	<0.001	<0.001
Blood neutrophils $\geq$ 7.0	%	2.5%	12.5%	16.2%	17.9%	<0.001	<0.001	<0.001
Ever rhinitis	%	66.4%	66.7%	62.5%	63.3%	0.965	0.614	0.730
Ever allergic rhinitis	%	47.4%	52.9%	52.5%	56.7%	0.440	0.526	0.317
Allergic rhinitis last 12 months	%	41.3%	47.1%	45.0%	46.7%	0.422	0.646	0.561
Nasal polyposis	%	6.0%	13.7%	15.0%	20.0%	0.031	0.025	0.002
Any wheeze last 12 months	%	88.8%	88.2%	87.5%	90.0%	0.896	0.795	0.842
Recurrent wheeze	%	31.8%	47.1%	50.0%	53.3%	0.025	0.017	0.014
Sputum production	%	47.5%	76.5%	77.5%	83.3%	<0.001	<0.001	<0.001
Chronic productive cough	%	15.9%	45.1%	45.0%	46.7%	<0.001	<0.001	<0.001
Dyspnea mMRC $\geq$ 2	%	21.7%	43.1%	45.0%	53.3%	<0.001	0.001	<0.001

Blood cell counts are available for n=709 subjects with current asthma, n=48 of the 51 subjects with GINA severe asthma, n=37 of the 40 subjects with ERS/ATS severe asthma, and n=28 of the 30 subjects with SARP severe asthma. *Blood eosinophils > 0.22 is calculated for comparison to reference 21. P-value= from Chi-square test or T-test, as appropriate, bold figures indicate statistical significance. mMRC=Modified MRC dyspnea scale (score range 0-4).

Table 4. Lung function among subjects with other asthma and severe asthma according to different criteria

		Other asthma n=779	Severe asthma according to different criteria			Difference (p-value) compared to other asthma		
			GINA n=51	ERS/ATS n=40	SARP n=30	GINA	ERS/ATS	SARP
Pre-BD FEV1 % of predicted	mean	86.53	77.39	76.63	70.42	0.004	0.006	<0.001
Pre-BD FVC % of predicted	mean	93.37	88.62	87.29	82.57	0.095	0.055	0.001
Pre-BD FEV1 Z-score	mean	-1.10	-1.68	-1.74	-2.19	0.013	0.014	<0.001
Pre-BD FVC Z-score	mean	-0.51	-0.79	-0.89	-1.22	0.170	0.098	0.002
Pre-BD FEV1/FVC	mean	0.71	0.66	0.66	0.65	0.009	0.025	0.009
Pre-BD FEV1/FVC Z-score	mean	-1.03	-1.72	-1.65	-1.98	0.026	0.079	0.022
Delta FEV1 (ml)	mean	13.02	11.40	10.69	12.25	0.490	0.376	0.798
Delta FEV1 (%)	mean	5.26	5.66	5.39	6.30	0.693	0.908	0.420
Post-BD FEV1/FVC	mean	0.72	0.67	0.67	0.65	0.007	0.012	0.005
Post-BD FEV1/FVC Z-score	mean	-0.85	-1.58	-1.58	-1.90	0.019	0.040	0.013
Pre-BD FEV1 <80% of predicted	%	29.4%	52.9%	52.5%	70.0%	<0.001	0.002	<0.001
Post-BD FEV1/FVC<0.7	%	31.5%	52.9%	57.5%	63.3%	0.002	0.001	<0.001
Post-BD FEV1/FVC<LLN (Z<1.645)	%	23.3%	47.9%	47.4%	55.2%	<0.001	0.001	<0.001

n=763 of the 779 subjects with other asthma participated in spirometry, of which n=709 also in reversibility testing

n=48 of the 51 subjects with GINA severe asthma participated in spirometry, of which n=42 also in reversibility testing

n=38 of the 40 subjects with ERS/ATS severe asthma participated in spirometry, of which n=33 also in reversibility testing

n=29 of the 30 subjects with SARP severe asthma participated in spirometry, of which n=25 also in reversibility testing

p-value= from Chi-square test or T-test, as appropriate, bold figures indicate statistical significance

Delta FEV1= Change in FEV1 after bronchodilation, BD=bronchodilator, Z=Z-score (standardized residual)

Table 5. Prevalence of allergic sensitization and multi-sensitization based on Phadiatop and specific IgE comparing subjects with other asthma and severe asthma according to different criteria

	Severe asthma according to different criteria								Difference (p-value*) compared to other asthma		
	Other asthma (n=753)		GINA (n=50)		ERS/ATS (n=39)		SARP (n=29)				
	n	%	n	%	n	%	n	%	GINA	ERS/ATS	SARP
Any allergen	269	35.7%	16	32.0%	10	25.6%	8	27.6%	0.594	0.199	0.369
Any dust mite	44	5.8%	3	6.0%	3	7.7%	2	6.9%	0.964	0.634	0.813
Any furred animal	187	24.8%	13	26.0%	8	20.5%	7	24.1%	0.854	0.541	0.932
Any pollen	189	25.1%	9	18.0%	6	15.4%	4	13.8%	0.259	0.170	0.166
Any mould	20	2.7%	5	10.0%	5	12.8%	5	17.2%	0.004	<0.001	<0.001
<u>Specific moulds</u>											
Cladosporium herbarum	10	1.3%	2	4.0%	2	5.1%	2	6.9%	0.132	0.058	0.017
Aspergillus fumigatus	16	2.1%	5	10.0%	5	12.8%	5	17.2%	0.001	<0.001	<0.001
Alternaria alternata	6	0.8%	2	4.0%	2	5.1%	2	6.9%	0.027	0.008	0.001
<u>Multi-sensitized</u>											
≥2 allergens	206	27.4%	12	24.0%	9	23.1%	7	24.1%	0.605	0.558	0.702
≥3 allergens	136	18.1%	9	18.0%	7	17.9%	5	17.2%	0.991	0.986	0.910
≥4 allergens	81	10.8%	7	14.0%	5	12.8%	4	13.8%	0.477	0.686	0.606

*P-value from chi-square test, bold figures indicate statistical significance. IgE data measured by Phadiatop available for n=753 with current asthma and for all but one subject with severe asthma according to all three definitions. Subjects positive on Phadiatop (>35kU/L) were tested for specific allergens. Dust mites=D.pteronyssinus and D.farinae. Furred animals=horse, cat and dog. Pollens=timothy, birch and mugwort. Moulds=cladosporium herbarum, aspergillus fumigatus and alternaria alternata.

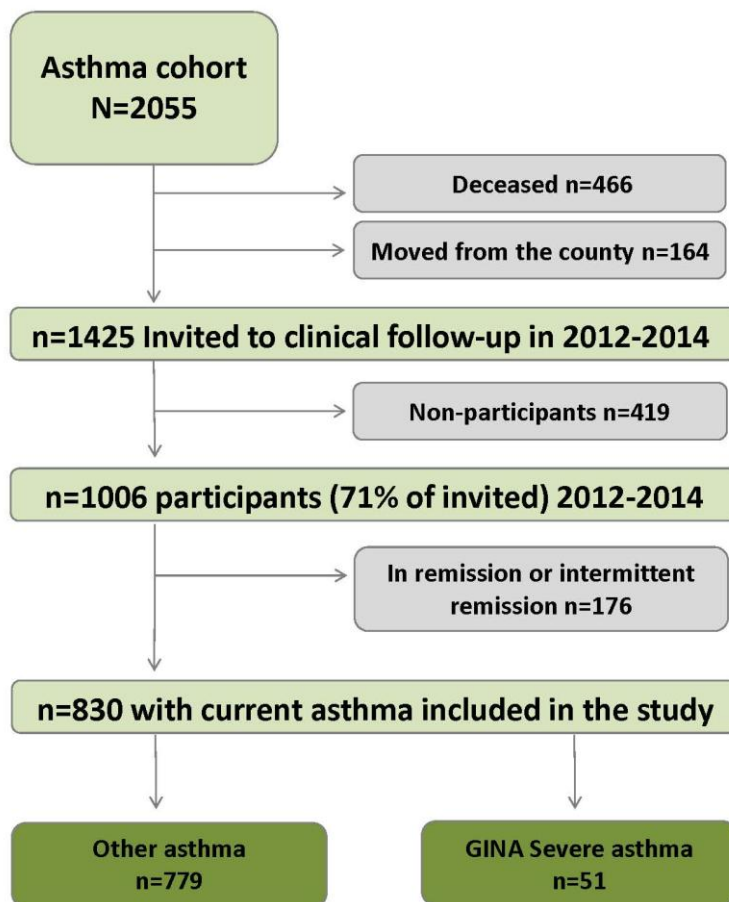


Fig 1

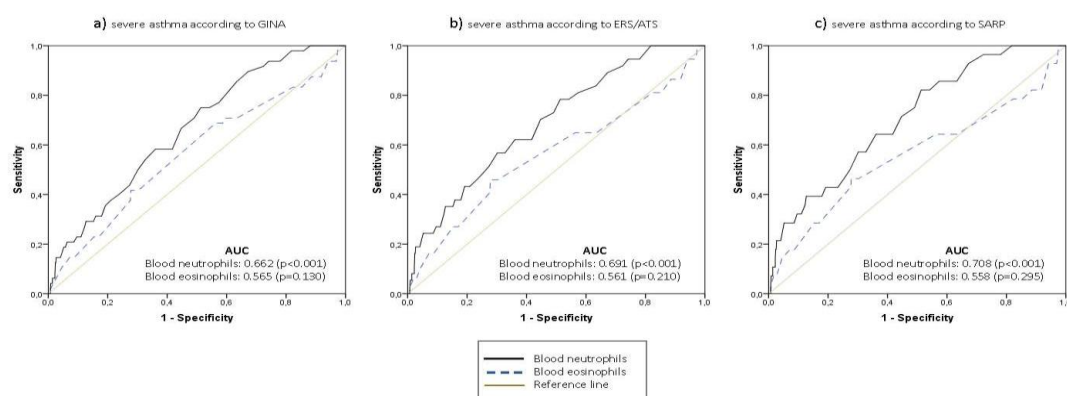


Fig 2

Supplemental Material

Manuscript title: Severe asthma - A population study perspective

Authors:

Helena Backman¹, PhD, Sven-Arne Jansson¹ PhD, Caroline Stridsman² PhD, Berne Eriksson^{3,4} MD, PhD, Linnea Hedman¹ PhD, Britt-Marie Eklund¹ MSc, Thomas Sandström⁵ MD, PhD, Professor, Anne Lindberg⁵ MD, PhD, Associate Professor, Eva Rönmark^{1§} PhD, Professor, Bo Lundbäck³ MD, PhD, Professor

E-Table 1. Definitions of high dose (micrograms) inhaled corticosteroids according to the GINA 2017 and the ERS/ATS 2014 Task Force documents*

Inhaled corticosteroid	<i>GINA 2017</i>	<i>ERS/ATS 2014</i>
Beclometasone dipropionate (DPI, CFC, MDI)	>1000	≥2000
Beclometasone dipropionate (HFA, MDI)	>400	≥1000
Budesonide (DPI, MDI)	>800	≥1600
Fluticasone propionate (DPI, HFA, MDI)	>500	≥1000
Mometasone furoate (HFA, DPI)	>440	≥800
Ciclesonide (HFA, MDI)	>320	≥320

*Summarized from references 2 and 8

E-Table 2. ATS Workshop and the US SARP definition of severe refractory asthma*

Major criteria (must have at least 1):
• Oral corticosteroids for > 50% of days past year • Continuous high-dose inhaled corticosteroids (ICS) as maintenance treatment
Minor criteria (must have at least 2):
• Concurrent use of at least 1 other controller medication • Daily symptoms requiring treatment with SABA • $FEV_1 < 80\%$ of predicted • Need of at least 3 oral corticosteroid bursts in the past year • One or more urgent care visit in past year • Deterioration with $\leq 25\%$ reduction in oral or inhaled corticosteroid dose • A history of a near-fatal event
<i>Further:</i> Diagnosis and treatment of co-morbidities required.

*Shortened version of the definition published in the review paper by Wenzel (reference 4), and the original document (reference 12).

E-Table 3. Asthma medication among subjects fulfilling the GINA severe asthma criterion.

Criteria	ICS	Dose	N	Regular maintenance treatment		Periodical
ATS/ERS	Fluticasone	2000	1	Salmeterol	Formoterol, Montelukast PO terbutaline	OCS Theophylline
ATS/ERS	Fluticasone	2000	1	Salmeterol		OCS
ATS/ERS	Fluticasone	2000	1	Salmeterol		
ATS/ERS	Fluticasone	1000	3	Salmeterol	Montelukast	
ATS/ERS	Fluticasone	1000	2	Salmeterol	Tiotropium	
ATS/ERS	Fluticasone	1000	2	Salmeterol	Regular SABA/SAMA ¹	
ATS/ERS	Fluticasone	1000	1	Salmeterol	OCS	
ATS/ERS	Fluticasone	1000	3	Salmeterol		OCS
ATS/ERS	Fluticasone	1000	19	Salmeterol		
ATS/ERS	Fluticasone	1000	1	Formoterol	Montelukast	
ATS/ERS	Fluticasone	1000	1	Tiotropium		OCS
ATS/ERS	Budesonide	1600	1	Formoterol	OCS	
ATS/ERS	Budesonide	1600	2	Formoterol		
ATS/ERS	Budesonide	800	1	Formoterol	OCS	
ATS/ERS	Budesonide	160-640	1	Formoterol	OCS, Montelukast	
GINA	Budesonide	1280	1	Formoterol	Tiotropium	
GINA	Budesonide	1280	1	Formoterol	Montelukast	
GINA	Budesonide	1280	1	Formoterol		OCS
GINA	Budesonide	1280	1	Formoterol		
GINA	Budesonide	1200	1	Formoterol		
GINA	Budesonide	1200	1	Salmeterol		
GINA	Budesonide	1200	2	Regular SABA ¹		
GINA	Budesonide	1000	1	Regular (SABA/SAMA) ¹		
GINA	Budesonide	960	1	Formoterol		
GINA	Fluticasone	500-750	1	Salmeterol		

ATS/ERS-criteria=fulfills both the ERS/ATS and GINA criteria for severe asthma, GINA=fulfills the GINA criterion for severe asthma but not the ERS/ATS criterion, ICS=inhaled corticosteroid, OCS=oral corticosteroid, ¹ Four patients used SABA or SABA/SAMA regularly as controller medication via nebulizer. All on Fluticasone and Budesonide used DPI. 37 used the Fluticasone/Salmeterol combination and 7 the Budesonide/Formoterol combination.

E-Table 4. Demographics (%) among subjects with other asthma and severe asthma according to different criteria

		Other asthma	Severe asthma			Difference (p-value*) compared to other asthma		
Demographics		n=779	GINA n=51	ERS/ATS n=40	SARP n=30	GINA	ERS/ATS	SARP
Sex	Women	55.1%	64.7%	62.5%	56.7%	0.180	0.357	0.863
Smoking habits	Never-smokers	47.6%	45.1%	47.5%	46.7%	0.726	0.988	0.918
	Ex-smokers	39.9%	51.0%	50.0%	50.0%	0.119	0.205	0.270
	Current smoker	12.5%	3.9%	2.5%	3.3%	0.069	0.059	0.133
ETS exposure from mother during pregnancy		11.2%	11.8%	7.5%	10.0%	0.896	0.469	0.842
Low birth weight (<2500g)		2.4%	7.8%	5.0%	6.7%	0.023	0.319	0.154
Grew up on a farm		37.4%	39.2%	42.5%	43.3%	0.796	0.516	0.511
Furry pet before 7 years of age		69.4%	56.9%	55.0%	56.7%	0.060	0.055	0.138
Age at asthma onset	<20 years of age	34.3%	33.3%	30.0%	33.3%	0.884	0.573	0.910
	20-39 years of age	37.1%	35.3%	37.5%	36.7%	0.799	0.957	0.964
	≥40 years of age	28.6%	31.4%	32.5%	30.0%	0.671	0.595	0.867
Manual workers in industry		12.6%	7.8%	5.0%	6.7%	0.318	0.153	0.334
Manual workers in service		26.8%	29.4%	27.5%	26.7%	0.687	0.926	0.984
Assistant non-manual employees		21.1%	23.5%	27.5%	26.7%	0.675	0.332	0.461
Intermediate non-manual employees		25.7%	21.6%	22.5%	20.0%	0.514	0.653	0.484
Professionals and executives		5.5%	7.8%	7.5%	6.7%	0.487	0.596	0.788
Self-employed		4.5%	7.8%	7.5%	10.0%	0.273	0.378	0.162
Others		1.8%	0.0%	0.0%	0.0%	0.334	0.392	0.459
Socio-economy N/A		2.1%	2.0%	2.5%	3.3%	0.964	0.847	0.632

*P-value from chi-square test, bold figures indicate statistical significance