

Original Article

The Prevalence of Severe Asthma and Low Asthma Control Among Danish Adults

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What is already known about this topic? The prevalence of severe asthma is unknown, but international expert statements assume that 5% to 10% of all patients with asthma have severe disease. The level of management within this group remains unknown.

What does this article add to our knowledge? In the present study, the prevalence of severe asthma was 8.1% among a nationwide population of young adults with asthma.

How does this study impact current management guidelines? Only a minority of patients with severe asthma were managed with specialist care, which indicates a significant unawareness of asthma severity and level of asthma control, and suggests a need for more attention to this patient group.

BACKGROUND: The prevalence of severe asthma is unknown. However, international expert statements estimate that severe asthma represents 5% to 10% of the entire asthma population.

OBJECTIVE: Based on register data from a nationwide population, we wanted to investigate the prevalence of severe asthma, the extent of asthma control, and contact with specialist care.

METHODS: A descriptive cross-sectional register study was performed. By using a nationwide prescription database, we identified current patients with asthma (age, 18–44 years) in 2010. Severity was classified as severe versus mild-moderate asthma according to the level of antiasthma treatment. We investigated prescription drug use, hospitalizations, emergency department visits, and outpatient clinic visits according to severity.

RESULTS: Among a nationwide population, we identified 61,583 current patients with asthma. Based on the level of antiasthma treatment, 8.1% of identified patients was classified as having severe asthma. Low asthma control (dispensed prescriptions of prednisolone, emergency department visits,

hospitalization, or excessive short-acting β_2 -agonist use) was more frequent in subjects with severe asthma (36.4% vs 25.2%, $P < .0001$); 63.8% with severe asthma and low asthma control were not managed by specialist care. Patients with severe asthma with specialist contact more frequently had impaired asthma control compared with subjects not treated by a specialist (44.4% vs 33.1%, $P < .0001$).

CONCLUSION: Based on the level of treatment, 8.1% of a nationwide population of current patients with asthma was classified as having severe asthma. Low asthma control was more frequent among subjects with severe asthma, and only a minority had access to specialist care. There is room for optimizing asthma management, particularly among patients with severe disease. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■–■)

Key words: asthma; Severe asthma; Asthma control; Asthma management; Prescription data

Several definitions of severe asthma have been proposed.^{1–7} Despite small variations, there is an agreement that severe asthma is asthma that requires high-intensity treatment to maintain adequate asthma control or when good asthma control is not achieved despite high-level therapy,^{1,3} which corresponds to treatment of the Global Initiative for Asthma steps 4 and 5 with high-dose inhaled corticosteroids (ICS) and concomitant treatment with a second controller or other systemic treatment.¹ The prevalence of severe asthma is uncertain and varies, depending on the criteria for defining asthma severity. However, expert statement estimates that severe asthma represents 5% to 10% of the entire asthma population.^{7,8}

Epidemiologic studies based on postal inquiries have shown that the proportion of patients with asthma and with severe disease ranges from 18% to 29%.^{9,10} These estimates are potentially biased because patients with more severe disease could be more likely to participate in epidemiologic studies that concern respiratory diseases.^{11,12} Results of previous studies have

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Abbreviations used

ACE- Angiotensin-converting-enzyme
 COPD- Chronic obstructive pulmonary disease
 ED- Emergency department
 GP- General practitioner
 ICS- Inhaled corticosteroid
 ICS-LABA- Fixed-dose combination of ICS and LABA
 LABA- Long-acting β_2 -agonist
 LAMA- Long-acting anticholinergic
 LTRA- Leukotrienantagonist
 OR- Crude odds ratio
 SABA- Short-acting β_2 -agonist
 ATC- Anatomical Therapeutic Chemical Classification
 ICD-10- International Classification of Diseases - Tenth Revision

indicated that persons with severe asthma represent the largest health economic burden due to an increased risk of hospitalizations, emergency department (ED) visits, loss of lung function, and low quality of life.^{8,13} Hence, this vulnerable group of patients is recommended to be assessed and treated by respiratory specialists,^{1-5,7} but it is not clear to what extent this is the case today. Despite asthma being a clinical diagnosis made by physicians on the basis of typical symptoms and clinical examination,¹ results of several studies have shown that prescription databases can be used to identify patients with asthma.¹⁴⁻¹⁶ In Denmark, every citizen is assigned a unique personal identification number, which provides a unique opportunity to crosslink several administrative health-related and socioeconomic databases for research on a nationwide population without the potential responder bias that may limit epidemiologic studies.

The aim of this study was to (1) investigate the prevalence of severe asthma based on the level of treatment, (2) describe the frequency of low asthma control among patients who receive antiasthma treatment equivalent to having severe asthma, and (3) describe the extent of contact with a respiratory specialist among subjects with low asthma control and subjects with severe asthma.

METHODS**Study design**

A register-based cross-sectional study was performed. To identify patients with asthma, we used information of redeemed asthma medication from a nationwide prescription database from years 2010 to 2011.

Data sources

The data in this study were received from different health and socioeconomic registers in Statistics Denmark. Statistics Denmark has detailed information at an individual level for the entire Danish population (www.dst.dk). In this study, we used the unique personal identification number to crosslink registers. For further information about the different registers, see [Text E1](#) in this article's Online Repository at www.jaci-inpractice.org.

Study population

The study population was identified in a stepwise manner, as illustrated in [Figure 1](#). In The Danish National Prescription Registry, we identified all the Danish residents between ages 18 to 44 years who had redeemed a prescription of medication with an Anatomical Therapeutic Chemical Classification (ATC) code R03 (drugs for obstructive pulmonary disease) in 2010. To verify that

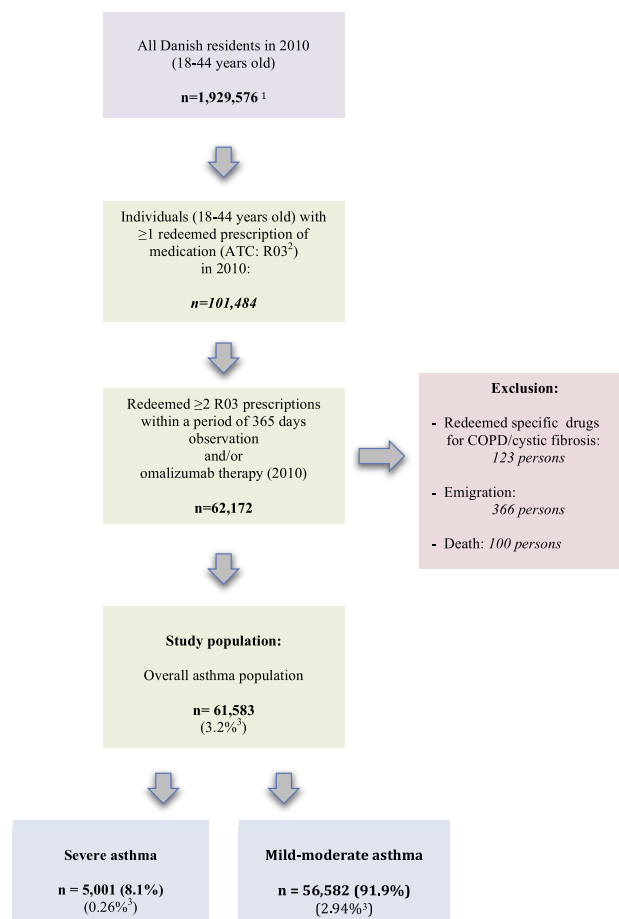


FIGURE 1. Flowchart: The selection of study population, and the proportion of patients with severe and those with mild-moderate asthma.¹The overall population in Denmark 2010 between 18 and 44 years old was calculated to consist of 1,929,576 individuals (analysis from Statistics Denmark www.dst.dk).²ATC R03: Drugs for pulmonary obstructive lung diseases.³Percentages from the overall population in Denmark.¹

the subjects truly had asthma, they were only included in the study population if they fulfilled one of the following 2 criteria: redeemed ≥ 2 prescriptions for drugs with an ATC R03 during 365 days of observation¹⁴ or had a registered code in The Danish National Patient Register for omalizumab therapy (*International Classification of Diseases, Tenth Revision* (ICD-10) code: B0HJ19A1) in 2010. The 365-day period of observation was defined as starting from an index date in 2010. The index date was chosen to be the first date where an ICS or a fixed-dose combination ICS and LABA (ICS-LABA) was redeemed. If the subjects had a code for omalizumab treatment, this was chosen to be the index date. If there was no use of ICS, ICS-LABA, or omalizumab in 2010, then we used the first date with redemption of an R03 drug as the index date. A data capture period of 365 days was selected to avoid any seasonal variation in asthma symptoms and drug redemption.

Because we wanted to exclude subjects with chronic obstructive pulmonary disease, we chose an upper age limit of 44 years. Furthermore, we also excluded individuals who had redeemed any specific medication for chronic obstructive pulmonary disease and cystic fibrosis (see [Table E1](#) in this article's Online Repository at

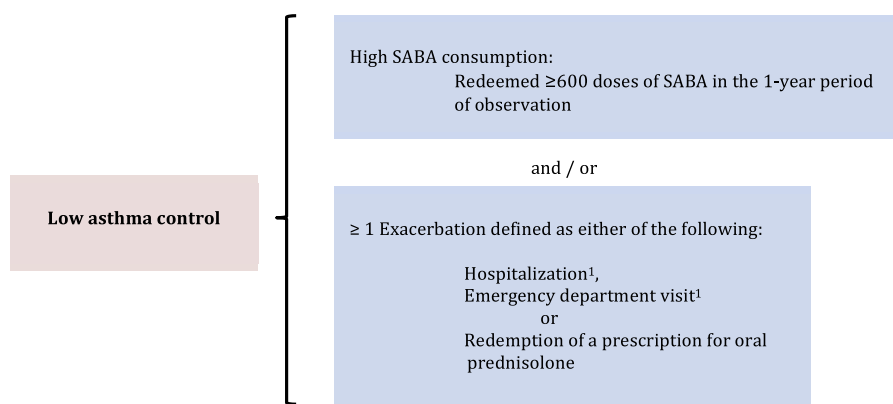


FIGURE 2. Definition of low asthma control: high SABA use and/or an exacerbation within the 1-year period of observation.¹Hospitalization or ED visit associated with an ICD-10 code for asthma, status asthmaticus, pneumonia, dyspnea, or respiratory insufficiency within the 1-year period of observation.

www.jaci-inpractice.org). Subjects who died or emigrated during the 365 days of observation were excluded.

Classification of asthma severity

The subjects were classified as having severe asthma if 1 of the following 2 criteria were fulfilled:

1. Redeemed ICS doses (single-container ICS or ICS-LABA) that corresponded to an average daily dose of >800 μg budesonide or equivalent and at least 1 dispensed prescription of a second controller: LABA, xanthines, or leukotrienantagonist (LTRA) in the 365-day period of observation; if ICS was redeemed as ICS-LABA, then there were no additional requirements for redemption of a second controller.
2. A code for omalizumab therapy. Omalizumab is only recommended in patients who have uncontrolled severe allergic asthma^{1,4,5}; to ensure that subjects with well-controlled asthma who received omalizumab therapy, with potentially less need of high-dose ICS, were included in the severe group, we chose omalizumab to be a criteria of severe asthma.

The subjects who did not fulfill the criteria for severe asthma were classified as having mild-moderate asthma.

Definition of indicators of low asthma control

We used surrogate markers of impaired asthma control, based on the high use of short-acting β_2 -agonist (SABA), use of prednisolone, ED visits, and hospitalizations. We defined high SABA use as redemption of ≥ 600 doses of SABA (1 dose = 1 puff) in the 365-day period of observation that corresponded to a mean weekly use of approximately 12 puffs of SABA.¹⁷ An exacerbation was defined as either a minimum of 1 redemption of an oral prednisolone prescription or hospitalization and/or ED visit associated with an ICD-10 code for asthma, status asthmaticus, pneumonia, dyspnea, or respiratory insufficiency.¹⁸⁻²⁰ Low asthma control was defined as high SABA use (≥ 600 doses of SABA) and/or at least 1 exacerbation in the 1-year period of observation, as illustrated in Figure 2.

Extent of contact with specialist care

Current management in specialist care was registered if the subjects had current contact with a respiratory outpatient clinic and/or with a private pulmonologist within the 1-year period

of observation. Contact with a respiratory outpatient clinic (hospital) was registered with the National Patient Register if the subject had a contact and a diagnosis of asthma, and, within the 365-day observation period, this was recorded as a specific service. Contact with a private pulmonologist was defined as a registered code in the National Health Insurance Service Registry for a specific pulmonary service (lung function with or without reversibility test, breath test, peak expiratory flow, bronchial provocation test, total lung capacity, lung volumes, and diffusing capacity) by the medical specialty internal medicine within the 1-year period of observation. The National Health Insurance Service Registry does not contain any diagnoses or specific codes for respiratory medicine.

Data analysis and statistics

Severity of disease was analyzed according to the level of asthma drug use, as described. Use of ICS (referred to as total ICS) was defined as redemption of ICS in a single container and/or as ICS-LABA. To calculate the average daily dose of ICS, we used an algorithm developed by Breton et al²¹ (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Baseline characteristics, including age and sex, for example, were compared between subjects with severe asthma and those with mild-moderate disease. Furthermore, categorical data, for example, high SABA use, exacerbations, and drug use, were summarized as percentages. Nonparametric data, for example, average ICS dose, were presented as the median, with 25% and 75% quartiles. A comparison of categorical variables was performed by using the χ^2 test. Numeric parametric data were tested by using the unpaired t test. For statistic significance, we used a P value of $<.05$. Because the severity classification was based on use of specific asthma medication (ICS, LABA, LTRA, xanthines, and omalizumab), we did not compare the use of these drugs between the mild-moderate and severe groups. All data analysis was performed by using SAS 9.3 (SAS Institute, Cary NC).

RESULTS

Overall description of study population according to severity classification

The selection of the study population is illustrated in Figure 1. A total of 101,484 individuals between the ages of 18 and 44 years had redeemed at least 1 prescription of drugs for pulmonary

TABLE I. Baseline characteristics categorized according to asthma severity

	Study population	Mild-moderate asthma	Severe asthma	P value*
Study population, no. (%)	61,583 (100)	56,582 (91.9)	5001 (8.1)	
Age (y), mean $\pm$ SD	33.38 $\pm$ 7.73	33.2 $\pm$ 7.8	35.4 $\pm$ 7.1	<.0001†
Age group, no. (%)				<.0001
18-24 y	10,954 (17.8)	10,427 (18.4)	527 (10.5)	
25-34 y	19,327 (31.4)	17,926 (31.7)	1401 (28.0)	
35-44 y	31,302 (50.8)	28,229 (49.9)	3073 (61.4)	
Sex, no. (%)				
Women	33,463 (54.3)	30,631 (54.1)	2832 (56.6)	.0007
Men	28,120 (45.7)	25,951 (45.9)	2169 (43.4)	.0007
Asthma medication, no. (%)				
ICS	28,085 (45.6)	26,300 (46.5)	1785 (35.7)	—
ICS-LABA	25,023 (40.6)	20,886 (36.9)	4137 (82.7)	—
Any ICS‡	49,534 (80.4)	44,551 (78.7)	4983 (99.6)	—
LABA	4570 (7.4)	3646 (6.4)	924 (18.5)	—
Only LABA§	797 (1.3)	797 (1.4)	—	—
SABA	41,912 (68.1)	38,796 (68.6)	3116 (62.3)	<.0001
LTRA	5710 (9.3)	4440 (7.9)	1270 (25.4)	—
Xanthines	193 (0.3)	109 (0.2)	84 (1.7)	—
LAMA	1094 (1.8)	754 (1.3)	340 (6.8)	<.0001
Omalizumab	79 (0.1)	—	79 (1.6)	—
Median daily ICS dose (μ g), median (25%,75% quartile)	—	270 (132, 460)	1172 (925, 1539)	—
Medication associated with comorbidities, no. (%)				
Nasal steroid	12,744 (20.7)	11,395 (20.1)	1349 (27.0)	<.0001
Antihistamine	13,465 (21.9)	12,000 (21.2)	1465 (29.3)	<.0001
Allergen immunotherapy	863 (1.4)	744 (1.3)	119 (2.4)	<.0001
Proton-pump inhibitors	7399 (12.0)	6547 (11.6)	852 (17.0)	<.0001
Antidepressants	8644 (14.0)	7776 (13.7)	868 (17.4)	<.0001
β -blockers	1272 (2.1)	1143 (2.0)	129 (2.6)	.008
ACE inhibitors	1658 (2.7)	1464 (2.6)	194 (3.9)	<.0001

ACE, Angiotensin-converting-enzyme; LAMA, long-acting anticholinergic; SD, standard deviation.

*Unless other indicated, χ^2 test.†Unpaired *t* test.

‡ICS and/or ICS-LABA.

§Only LABA, redeemed LABA without any concomitant single-container ICS, or ICS-LABA during the period of observation.

||Patients were selected due to doses of ICS.

obstructive lung disease in 2010. In Denmark, in 2010, the entire asthma population, as per the present definition of redemption of at least 2 prescriptions, consisted of 61,583 patients, which corresponded to 3.2% of the overall population between ages 18 and 44 years ($n = 1,929,576$). One hundred patients were excluded because they died during the 1-year period and because information about cause of death was unavailable. However, only 7 of the deceased had a hospitalization due to asthma, dyspnea, or respiratory insufficiency within the last 7 days before the date of death. None of the deceased had an ED visit within the last 7 days before the date of death.

Categorization of asthma severity based on the level of treatment led to identification of 5001 subjects (8.1%) who had severe asthma and 56,582 subjects with mild-moderate asthma, which corresponds to 0.26% of the entire population in Denmark (age range, 18-44 years) who received asthma treatment at a level that indicates severe asthma. The baseline characteristics according to asthma severity categorization are given in Table I. The subjects with severe asthma were significantly older than those with mild-moderate asthma (mean age, 35.2 vs 33.2 years; $P < .0001$). There was a majority of women among

subjects with severe asthma in comparison with the subjects with mild-moderate asthma (mild-moderate asthma, 54.1%; severe asthma, 56.6%; $P < .0001$). Use of SABA (minimum of 1 redeemed prescription of SABA in the 1-year observation period) was significantly more frequent in the group with mild-moderate asthma compared with severe asthma (68.2 vs 62.3%, $P < .0001$). Use of medication related to potential comorbidities, such as rhinitis, gastroesophageal-reflux disease, or heart disease, psychiatric disease, was significantly more frequent among subjects with severe asthma (Table I).

Frequency of impaired asthma control according to asthma severity

All markers of impaired asthma control were significantly more frequent in the severe group in terms of excessive SABA use, ED visits, hospitalizations, and redemption of oral prednisolone prescriptions (Table II). Furthermore, the average days of hospital admissions, number of ED visits, and number of prednisolone redemptions were significantly more frequent among the subjects with severe asthma compared with those with mild-moderate asthma (data not shown). Notably, high SABA

TABLE II. Prevalence of markers for low asthma control

	Mild-moderate asthma, no. (%) (n = 56,582)	Severe asthma, no. (%) (n = 5001)	P value, χ^2 test	Severe asthma, OR (95% CI)
SABA > 600 doses	10,849 (19.2)	1214 (24.3)	<.0001	1.35 (1.26-1.45)
≥1 Prescription of antibiotics	23,779 (42.0)	2678 (53.5)	<.0001	1.59 (1.50-1.69)
≥1 Prescription of prednisolone	3903 (6.9)	894 (17.9)	<.0001	2.94 (2.71-3.18)
ED visit*	456 (0.8)	84 (1.7)	<.0001	2.1 (1.66-2.66)
Hospitalization*	984 (1.7)	199 (4.0)	<.0001	2.3 (2.01-2.73)
Exacerbation†	4616 (8.2)	980 (19.6)	<.0001	2.74 (2.54-2.96)
Low asthma control‡	14,252 (25.2)	1822 (36.4)	<.0001	1.70 (1.60-1.81)

OR, Crude odds ratio.

*Associated with a respiratory diagnosis: dyspnea, pneumonia, asthma, or status asthmaticus.

†At least 1 prescription of prednisolone or registered an ED visit or hospitalization within the 1-y period of observation.

‡Minimum of 1 exacerbation and/or redeemed SABA ≥600 doses in the 1-y observation period.

use (≥600 doses SABA in the period of observation) was frequent in both groups (19.2% mild-moderate vs 24.3% severe; $P < .0001$). Nearly 20% of the subjects with severe asthma had at least 1 exacerbation in the 1-year period of observation compared with only 8.2% among the subjects with mild-moderate asthma ($P < .0001$). Exacerbations were mostly driven by use of courses of oral prednisolone.

The distribution of asthma severity and the frequency of low asthma control are illustrated in Figure 3. More than a fourth of the entire study population (26%) had low asthma control (defined as a minimum of 1 exacerbation and/or high SABA use). The prevalence of low asthma control was 36.4% in the group with severe asthma vs 25.2% with the mild-moderate group (Table III). Three percent of the entire study population was patients with severe asthma who also had low asthma control (Figure 3). Independent of severity classification, the subjects with low asthma control were significantly older compared with subjects with controlled asthma (Table III). For the subjects with severe asthma, there was no difference in the sex distribution according to asthma control (men with severe asthma, 43.4% controlled vs 43.4% low asthma control; $P = .963$). Among subjects with severe asthma, the use of LTRA, omalizumab, long-acting anticholinergics, and xanthines were significantly more pronounced among those with low asthma control (Table III). Only 69.3% of subjects with mild-moderate asthma and concomitant low asthma control had redeemed any kind of ICS (single-container and/or ICS-LABA) within the 1-year of observation (Table III).

The extent of specialist care of patients with mild-moderate asthma and those with severe asthma

Fewer than a third of the subjects with severe asthma had contact with respiratory specialist care in the 1-year period of observation. Furthermore, only 10.4% of the patients with mild-moderate asthma were managed in specialist care (Table IV). The subjects with severe asthma and current contact with specialist care had a significantly greater burden of morbidity compared with subjects with severe asthma and with no specialist contact (Table IV). Approximately a third of this group had redeemed a prescription of prednisolone (29.5% specialist contact vs 13% no specialist contact, $P < .0001$). Nearly 10% of the subjects with severe asthma and specialist contact had a hospitalization in the period of observation (8.9% specialist contact vs 1.9% no specialist contact, $P < .0001$). Surprisingly, a substantial proportion of

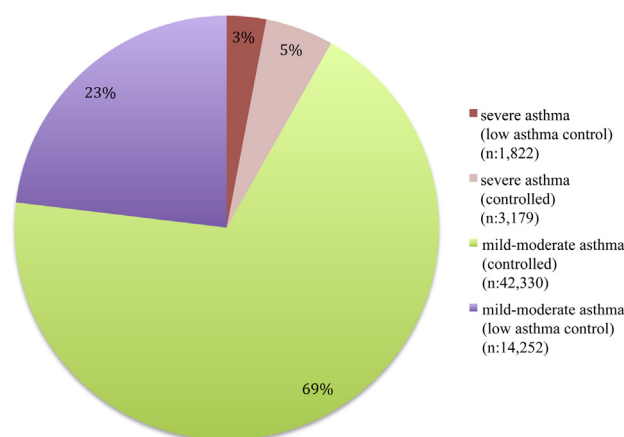


FIGURE 3. Distribution of asthma severity and low asthma control among a nationwide population of young subjects with asthma (study population, 61,583 subjects).¹Low asthma control, minimum 1 exacerbation (prednisolone redemption, ED visit, and/or hospitalization) and/or high SABA use (redeemed ≥600 doses) in the 1-year observation period.

subjects with severe asthma had high SABA use independent of specialist contact (24.3% specialist contact vs 24.3% no specialist contact, $P = .97$).

The frequency of overall low asthma control among subjects with severe asthma was 44.1% of the proportion with specialist contact vs 33.1% of the group without any specialist contact ($P < .0001$). A similar finding was observed in subjects with mild-moderate asthma, except that a significantly larger proportion of patients with high SABA use had no affiliation with a respiratory specialist. The extent of specialist care among patients with low asthma control was modest (Figure 4). Only 11.1% of the subjects with mild-moderate asthma and with low asthma control received specialist care versus 36.2% among the subjects with uncontrolled severe asthma, which corresponds to only 14% of the study population with low asthma control having had an affiliation with respiratory specialist care.

DISCUSSION

To our knowledge, this is the first database study that investigated the prevalence of severe asthma, level of control, and the

TABLE III. Distribution of age, sex, and asthma medication according to asthma severity and level of control

	Mild-moderate asthma			Severe asthma		
	Controlled	Low asthma control*	P value	Controlled	Low asthma control*	P value†
Distribution, no. (%)	42,330 (74.8)	14,252 (25.2)	—	3179 (63.6)	1822 (36.4)	—
Age (y), mean $\pm$ SD	32.8 $\pm$ 7.9	34.3 $\pm$ 7.2	<.0001‡	34.9 $\pm$ 7.3	36.2 $\pm$ 6.7	<.0001‡
Sex, no.						
Men	43.9	51.8	<.0001	43.4	43.4	.963
Women	56.1	48.2	<.0001	56.7	56.6	.963
Asthma medication, no. (%)						
ICS	19,893 (47.0)	6407 (45.0)	<.0001	1068 (33.6)	717 (39.4)	<.0001
ICS-LABA	16,622 (39.3)	4264 (29.9)	<.0001	2605 (81.9)	1532 (84.1)	.054
Total ICS§	34,680 (81.9)	9871 (69.3)	<.0001	3168 (99.7)	1815 (99.6)	.828
LABA	2862 (6.8)	784 (5.5)	<.0001	591 (18.6)	333 (18.3)	.783
SABA	25,437 (60.1)	13,359 (93.7)	<.0001	1501 (47.2)	1615 (88.6)	<.0001
LTRA	3428 (8.1)	1012 (7.1)	.0001	735 (23.1)	535 (29.4)	<.0001
Xanthines	47 (0.1)	62 (0.4)	<.0001	17 (0.5)	67 (3.7)	<.0001
LAMA	467 (1.1)	287 (2.0)	<.0001	114 (3.6)	226 (12.4)	<.0001
Omalizumab	—	—	—	32 (1.0)	47 (2.6)	<.0001

LAMA, Long-acting anticholinergic; SD, standard deviation.

*Minimum of 1 exacerbation (prednisolone redemption, ED visit, and/or hospitalization) and/or redeemed SABA $\geq$ 600 doses in the 1-y observation period.†Unless other indicated, χ^2 test.‡Unpaired *t* test.

§ICS + ICS-LABA.

TABLE IV. Markers of low asthma control according to whether the subject has been managed in special care within the 1 year of observation

	Mild-moderate asthma			Severe asthma		
	No specialist care, no. (%)	Specialist care, no. (%)	P value, χ^2 test	No specialist care, no. (%)	Specialist care, no. (%)	P value, χ^2 test
Subjects	50,709 (89.6)	5873 (10.4)	—	3516 (70.3)	1485 (29.7)	—
SABA > 600 doses	10,195 (20.1)	654 (11.1)	<.0001	853 (24.3)	361 (24.3)	.97
$\geq$ 1 Prescription of prednisolone	2944 (5.8)	959 (16.3)	<.0001	456 (13.0)	438 (29.5)	<.0001
ED visit*	304 (0.6)	152 (2.6)	<.0001	33 (0.9)	51 (3.4)	<.0001
Hospitalization*	588 (1.2)	396 (6.7)	<.0001	67 (1.9)	132 (8.9)	<.0001
Exacerbation†	3438 (6.8)	1178 (20.1)	<.0001	496 (14.1)	484 (32.6)	<.0001
Low asthma control‡	12,666 (25.0)	1586 (27.0)	.0007	1162 (33.1)	660 (44.4)	<.0001

*Associated with a respiratory diagnosis: dyspnea, pneumonia, asthma, status asthmaticus, or respiratory insufficiency.

†At least 1 prescription of prednisolone or registered an ED visit or hospitalization within the 1-y period of observation.

‡Minimum of 1 exacerbation and/or redeemed SABA $\geq$ 600 doses in the 1-y observation period.

extent of current contact with specialist care among a nationwide population of adults with asthma. We found that 8.1% of adults with asthma in the study population had redeemed asthma drugs equivalent to having severe disease. In spite of high-intensity treatment, approximately 40% of the subjects displayed signs of poor asthma control, and only one-third within this group had been in contact with a specialist during the past 12 months. The subjects with severe asthma more often used drugs associated with common asthma comorbidities, which suggests a greater burden of comorbidities within this group. Our findings demonstrate the significant morbidity associated with severe asthma and highlight the need for improvement in the level of asthma care.

In this study, the prevalence of severe asthma was 8.1%, which aligns closely with previous expert statements (5%-10%).^{7,8} However, our prevalence of severe asthma was rather low compared with other epidemiologic^{9,10} or register studies²⁰

(range, 18%-29%), which is most likely a result of less strict definitions of severe asthma in these studies, in which persons with untreated asthma and with impaired asthma control were also classified as having severe asthma. However, the current consensus is that asthma severity and asthma control are different constructs, which is why it would be inappropriate to say that patients with uncontrolled asthma necessarily have severe disease. Consequently, in this study, the classification of asthma severity was based on the intensity of treatment required to maintain good asthma control.^{1,22}

By using nationwide register data with high completeness and validity,²³⁻²⁵ we minimized potential responder and selection bias. These biases can potentially limit epidemiologic studies based on questionnaires^{9,10} or register studies that use databases only that cover patients with private health insurances.²⁰ However, different factors could cause potential over- or underestimation of the prevalence of severe asthma in this study. Because

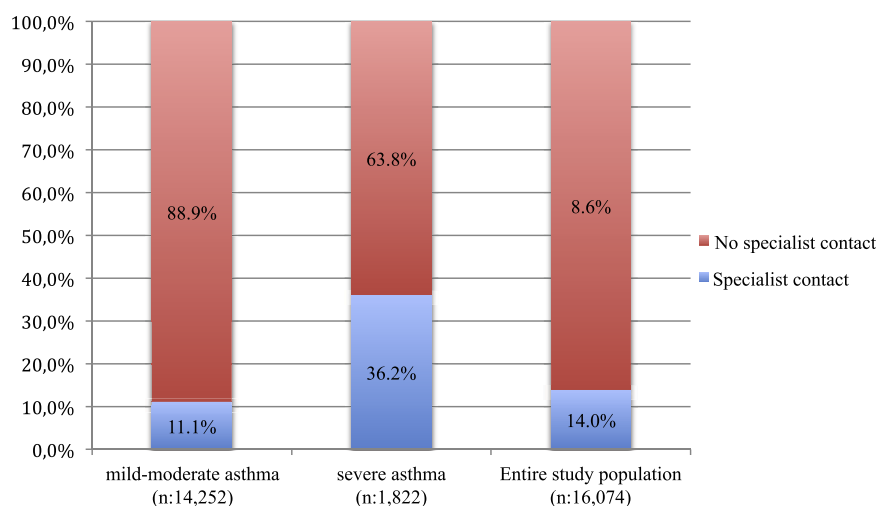


FIGURE 4. The prevalence of contact with a respiratory specialist among subjects with low asthma control. Specialist contact was defined as having contact to a respiratory specialist within the 365 days of observation. Low asthma control, minimum 1 exacerbation and/or redeemed SABA ≥ 600 doses in the 1-year observation period.

it was not possible to include undiagnosed and untreated patients with asthma in this study, the distribution of asthma severity could become skewed toward more-severe disease. Furthermore, 38% of persons with severe asthma did not redeem any kind of SABA within a year, and we could not distinguish whether they had true severe asthma that was successfully treated or over-treated mild-moderate asthma.

However, undertreatment could contribute to a potential underestimation of severe asthma. A significant proportion of the subjects with mild-moderate asthma displayed signs of poor asthma control. Most likely some of them could have severe asthma. Furthermore, our classification of asthma severity was based on rather strict criteria, which left no room for poor adherence. Some studies have demonstrated a significant lack of adherence, which ranged from 35% to 65% among patients treated as having severe asthma.^{26,27} As a result, some patients who should be classified with severe asthma were miscategorized as having mild-moderate disease due to either poor adherence or undertreatment.

The Danish health care system is a fully tax-financed public service and gives free access to general practice, outpatient clinics, and hospitals.²⁸ All asthma medications have to be prescribed by a medical physician. Outpatient drugs are not free of charge but are partially reimbursed according to the total cost of prescribed drugs per year. The higher use of reimbursable drug expenditure, the higher is the reimbursement percentage.²⁹ Despite this, a low socioeconomic position could be a barrier to being classified as having severe asthma in our study, because a previous study demonstrated that Danish patients with asthma and with low income were more unlikely to be treated with ICS.³⁰

International guidelines highlight that asthma control (prevention of asthma symptoms, no exacerbations, no emergency care visits) is the major goal of long-term asthma management.^{1,4} Despite receiving high-dose therapy, a substantial proportion of subjects with severe asthma had low levels of asthma control with high SABA use and frequent severe asthma exacerbation with either use of at home treatment with oral prednisolone or acute admission to the hospital. To minimize subjects who have antiasthmatic drugs due to causes other than asthma (eg, chronic

obstructive pulmonary disease), our study population was limited to individuals up to the age of 44 years. However, severe asthma is common among elderly patients with asthma,³¹ and if it were possible to include older subjects with asthma in the study, we would likely have seen even poorer levels of asthma control^{32,33} among persons with severe asthma due to a higher risk of age-related comorbidities and lower lung function in the elderly.³⁴

Among the subjects with severe asthma, the use of LTRA, xanthines, long-acting anticholinergic, and omalizumab was more pronounced among those having low asthma control, which indicates that, to some extent, impaired asthma control reflects true refractoriness to therapy within this group.⁷ By contrast, ICS, ICS-LABA, LABA, and LTRA were more commonly dispensed to subjects with controlled versus those with uncontrolled and mild-moderate disease, which supports both the effectiveness of therapy for patients who have mild-moderate asthma and the responsiveness to controllers as potential determinants of severity. Approximately two-thirds of the subjects with severe asthma and low asthma control had no current contact with a respiratory specialist, despite the fact that several guidelines^{1-4,7} recommend that severe asthma should be managed and treated with specialist care. Even though some patients with severe asthma have true refractoriness to therapy, this also suggests a significant unawareness of asthma severity and inadequate asthma treatment among a substantial proportion of patients with asthma as well by their treating general practitioners (GP).

Even among subjects with asthma who were categorized as having mild-moderate asthma, serious markers of low asthma control were common, especially in terms of excessive SABA use, which presumably reflects unawareness of asthma symptoms and asthma control not only among subjects with asthma alone but also among physicians who provide treatment. In addition, these findings indicate a serious undertreatment within this group of subjects with mild-moderate asthma and with low asthma control because a substantial proportion of these subjects (30%) did not receive any kind of treatment with ICS. The consequence of mismanaged asthma is lower quality of life,³⁵ higher mortality,³⁶ and more excessive decline in lung function.³⁷

Our findings are consistent with other epidemiologic studies that had demonstrated that a lack of asthma control is frequent among patients with asthma (35%-54%).^{32,33,38-41} In this context, it is worth noting that these studies assessed the level of asthma control based on questionnaires that concerned the frequency of symptoms, limitation in daily activities, and so forth according to the definition of asthma control from the Global Initiative for Asthma guidelines^{38,40} or used validated symptom scores, for example, the Asthma Control Test.^{32,33} By using only administrative databases, this study did not include any clinical information (eg, daily symptoms, smoking, lung function). Instead, we used prednisolone use, ED visits, hospitalizations, and excessive SABA use as surrogate markers of uncontrolled asthma.^{17,19,20} All of the above markers are serious indicators of low asthma control.^{1,42} We believe that using these markers gives a safe but also rather conservative estimate of poor asthma control compared with when asthma control is assessed in the classic way, by extent of daily symptoms, limitations in physical activity, low lung function, and so forth.^{1,4}

As mentioned earlier in the Discussion, asthma control can be assessed in many ways. We found it reasonable to categorize subjects to have low asthma control if they had at least 1 marker of a moderate-to-severe exacerbation (a prescription of oral prednisolone, an ED visit, or hospitalization).^{17,19,20} Although Expert Panel Report 3 guidelines define poor asthma control based on exacerbations as 2 or more in a 12-month period,⁴³ it could be problematic to use 2 prescriptions of prednisolone as a cutoff for low asthma control in this register study because 1 prescription may include treatment for more than 1 exacerbation.

Only a minority of patients with severe asthma had current access to a respiratory specialist. The subjects with severe asthma who received specialist care had significantly more frequent markers of exacerbations. The exact reasons for this are not possible to determine from our cross-sectional study design. However, we do not believe that specialist care led to a deteriorated outcome. We think it reflects the fact that patients with the greatest morbidity of asthma fortunately have more specialist contact. It seems obvious that subjects who have severe disease with many symptoms and frequent exacerbations would be more likely to be referred to a respiratory specialist.^{44,45} In addition, a randomized study demonstrated that patients with asthma managed by a respiratory specialist were less likely to be undertreated, had fewer symptoms, and better quality of life compared with patients treated by GPs.^{46,47}

Our results are supported by previous studies that demonstrate that inconsistent use of asthma guidelines with undertreatment of asthma^{9,38,39,41,48} and unawareness of asthma symptoms³⁸ and asthma severity⁹ is a significant problem. As mentioned earlier in the Discussion, general practice and specialist care is free of charge but referral to specialist care goes through the GP.²⁸ Consequently, the lack of specialist management may be caused by inadequate and rare follow-up visits in general practice, which causes poor assessment of symptoms, rare lung function measurements, and a lack of patient education.^{9,38,39,41,48} Other contributing factors might be an overestimation of the level of asthma control by GPs and specialists^{9,39,46,49} but also the well-known tendency among patients with asthma to underestimate their level of asthma symptoms.^{38,39} Overall, this could be an explanation of why only a minority of subjects with severe asthma and low asthma control were referred to specialist care.

Conclusion

Based on the level of treatment, 8.1% of a nationwide population of adult patients with asthma could be classified as having severe asthma. Among these, a substantial proportion had serious markers of impaired asthma control, and only a minority had current contact with specialist care. Notably, low asthma control also was frequent among subjects with mild-moderate asthma. In a nationwide perspective, the outcome of this study indicated substantial room for improvement, such as optimizing the extent of assessment, treatment, and level of asthma control, particularly among subjects with asthma and with severe disease.

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TEXT E1. DATA SOURCES

Data on pharmacotherapy was extracted by using The Danish National Prescription Registry, which serves as a national prescription database. The Danish National Prescription Registry contains information on every medication sold on prescription in Denmark. For every medical product there is information concerning the following: the patient's identifier, a list of drug names, the ATC code, strength of the drug, date of dispensing, form of the drug, code of reimbursement, prescribed daily doses, and so forth. Redemption of asthma drugs and oral antibiotics were identified in the prescription database accordingly to the specific ATC codes and drug names (see Table E1).

Data regarding ED visits, hospitalization, outpatient visit, and omalizumab treatment in a hospital setting was extracted from the Danish National Patient Register. The register contains

administrative and clinical information on all patients in Danish hospitals by every ED visit or hospitalization, the Civil Personal Registration Number diagnosis (ICD-10), date of admission, and discharge. Information regarding diagnosis (ICD-10) and dates for specific services are registered for every patient in the outpatient clinic. Omalizumab treatment (Xolair, Novartis Healthcare A/S; Copenhagen, Denmark) is restricted to delivery to hospitals and is not registered at an individual level in the prescription database. Omalizumab treatment instead was extracted from the National Patient Register.

The National Health Insurance Service Registry contains information of every service performed in general practice and by private practice specialists. Demographic data were obtained from the Population Register. Register-based studies do not require ethics approval in Denmark. Permission to access data was given by Statistics Denmark and the Danish Medicines Agency.

TABLE E1. Medication and the Related Anatomical Therapeutic Chemical Classification (ATC) codes.

Medications	ATC codes
Asthma drugs	
ICS	R03BA02, R03BA01, R03BA05, R03BA07, R03BA08
ICS-LABA	R03AK07, R03AK06
SABA	R03AC02, R03AC03
LABA	R03AC12, R03AC13
LTRA	R03DC03
Xanthines	R03DA04
Short-acting anticholinergics	R03BB01
LAMA	R03BB04
Oral SABA	R03CC02, R03CC03
Oral LABA	R03CC12
Prednisolone	H02AB06
Antibiotics	
Penicillin	J01CE02, J01CA02, J01CA04, J01CA01
Penicillin combined with β -lactamase inhibitor	J01CR02
Macrolides	J01FA10, J01FA06, J01FA09, J01FA01
Quinolones	J01MA14, J01MA02
Cephalosporines	J01DB01
Specific COPD drugs	
Daxas (Takeda Pharma; Roskilde, Denmark)	R03DX07
Specific drugs for cystic fibrosis	
Pulmozyme (Roche; Hvidovre, Denmark)	R05CB13
Promixin (Swedish Orphan Biovitrum A/S; Lyngby, Denmark)	J01XB01
Tobi (Novartis Healthcare A/S; Copenhagen, Denmark)	J01GB01
Causton (Gilead Sciences Sweden A/S, Solna, Sweden)	J01DF01
Drugs associated with asthma comorbidities	
Nasal steroid	R01AD12, R01AD01, R01AD05, R01AD08, R01AD09, R01AD11, R01AD12, R01AD58
Antihistamine	R06AX27, R06AE07, R06AX26, R06AX18, R06AX13, R06AX22, R06AE09
Allergen immunotherapy	V04CL, V01AA02
Proton-pump inhibitor	A02BC05, A02BC03, A02BC01, A02BC02, A02BC04.
Antidepressants	N06AB10, N06AB04, N06AB08, N06AB03, N06AB05, N06AB06, N06AX18, N06AX21, N06AX16, N06AX11, N06AX03, N06AA09, N06AA04, N06AA02, N06AA21, N06AA10, N06AA16, N06AA12
β -blockers	C07AA03, C07AA05, C07AA07, C07AB03, C07AB07, C07AB09, C07AB12, C07AB02, C07AG02, C07AG01, C07BB12, C07CB03, C07BB02
ACE inhibitors	C09AA06, C09AA01, C09AA03, C09AA02, C09AA04, C09AA10, C09AA05, C09BA02, C09BA04, C09BA03, C09BA05

ACE, Angiotensin-converting-enzyme; COPD, chronic obstructive pulmonary disease; LAMA, long-acting anticholinergic.

TABLE E2. Algorithm to calculate the average daily dose of ICS during the 1-year period of observation*

1. All redemptions of ICS (single container and/or ICS-LABA) in 2010 were identified.
2. The beginning the 1-y period of observation was chosen to be the first date in 2010 with redemption of an ICS prescription.
3. The duration of the ICS prescription was equal to the number of days between 2 successive renewals.
4. The duration of the last ICS redemption within the 1-y period of observation was calculated from the daily dosage and the number of doses written on the prescription.
5. If the daily dosage was not specified, then the duration of the prescription was equal to the number of the mean duration of the previous prescriptions.
6. The number of micrograms dispensed per redeemed prescription was calculated. If the last day of the prescription was beyond the end of the 1-y period of observation, the number of micrograms was adjusted accordingly.
7. The different ICS products were recalculated to a budesonide equivalence according to the Global Initiative for Asthma guidelines.
8. The total number of micrograms dispensed during the 1-year observation period was calculated by summing the number of micrograms for all prescriptions during the observation period.
9. The average number of micrograms per day was calculated by dividing the total number of micrograms by the length of the observations period (365 days).

*From Ref. 21.