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Early View

Original article

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Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden (PACEHR)

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Take home message:

Room for improvement exists in identification and management of frequently exacerbating asthma patients in Sweden.

Plain Language Summary

In a Swedish primary care asthma population, 1.8% of the patients experienced frequent exacerbations yearly during the three-year observational period. Patients with frequent exacerbations were characterized by greater age, female predominance, high eosinophilic and neutrophilic count and high prevalence of comorbidities compared to non-exacerbators. Remarkably, the percentage of patients visiting health care in the group with frequent exacerbations decreased during the observational period, indicating that health care lack the efficiency to identity and optimally manage this patient group.

Study sponsor: AstraZeneca

ABSTRACT

Aim

To investigate prevalence, management and characteristics of asthma patients with frequent exacerbations.

Method

Data from asthma patients (≥18 years) identified in primary care medical records were linked to national Swedish health registries. Exacerbations defined as hospitalizations, emergency visits and/or collection of oral steroids. Frequent exacerbations defined as ≥2 exacerbations/year during the 3-year observation period.

Results

Of 18 724 asthma patients, 81.49% had no exacerbation and 6.43% had frequent exacerbations the year prior index. Frequent exacerbations yearly were observed for 1.8% of the patients. Frequent exacerbators were older, more often females, had increased eosinophil and neutrophil counts, lower lung function, and more comorbidities than patients without exacerbations. There was a slight increase in asthma medication claims and a slight decrease in physician visits compared to baseline, both in the group with and the group without frequent exacerbations.

Conclusion

Patients with frequent exacerbations were characterized by greater age, female predominance, high eosinophilic and neutrophilic count and high prevalence of comorbidities. This study indicates that the Swedish health care system lack efficiency to adjust treatment and management for this patient group. With new treatment options targeting severe asthma available, identification of these patients should be in focus to ensure reduction of exacerbations.

INTRODUCTION

Management of asthma has developed and undergone large changes during the last three decades, with new available treatment options and with established and continually updated international guidelines (1). Despite this, reports show that asthma still remains uncontrolled in a vast proportion of patients (2-5), have major negative effects on health-related quality of life (HRQOL) (6, 7), and causes a substantial economic burden on health care and society (8, 9). A large part of the disease burden is caused by asthma exacerbations (10), where frequent exacerbations may lead to a decline in lung function, resulting in more severe airway obstruction and airway remodelling (11).

In patients with chronic obstructive pulmonary disease (COPD), a large observational cohort study has reported an increased susceptibility to exacerbations reflecting a specific COPD patient phenotype [12]. This phenotype was associated with more severe disease and prior exacerbations, and independently also with a history of gastroesophageal reflux (GERD), poorer HRQOL, and elevated white blood cell counts (12). In asthma, a recent cohort study in adults and children with severe asthma found an association between exacerbations and blood eosinophils, bronchodilator responsiveness, body mass index (BMI), chronic sinusitis and GERD, indicating a distinct exacerbation prone phenotype also in asthma (13).

The association of high blood eosinophil counts and frequent exacerbations have been previously described (13-15), and eosinophilic inflammation is present in approximately 50% of patients with asthma (16). New anti-IL5 treatments targeting eosinophils, with different mode-of-actions, have shown to significantly reduce the number of exacerbations and the need for maintenance oral steroid treatment (16-18). For smokers and ex-smokers, high blood neutrophils have also been associated with frequent exacerbations, indicating that different types of systemic inflammation have an impact on the aetiology of frequent exacerbations in asthma patients (14).

Multi morbidity is common in patients with long-term disorders. A large Scottish primary care database consisting of almost 1.8 million individuals, showed that half of the patients with asthma had at least one comorbidity (19). This study did not include rhinitis among the comorbidities, but it is known that most asthma patients have comorbid upper airways disease (20, 21) and there is a strong association between perennial rhinitis and asthma [18]. Further, one third of elderly asthma patients have features of both asthma and COPD, implying increased disease severity and more frequent exacerbations compared with patients with either disease alone (22, 23). In addition, almost half of the asthma patients have chronic bronchitis, significantly more in smokers than in never-smokers, 50% versus 40% respectively (24). Other common comorbidities in asthma patients are stroke and diabetes (25), (26).

In Sweden, the majority of asthma and COPD patients are managed in primary care. Research utilizing data extracted from electronic medical records from primary care, merged with national registry data, have previously been used to study patient management in COPD (27, 28). The aim of this study was to investigate the prevalence, management, and characteristics of patients with frequent exacerbations in a Swedish primary care asthma population.

METHOD

Study design

In this observational cohort study, primary care medical records data for asthma patients from 36 primary care centers were extracted using an established software system (Pygargus Customized eXtraction0, Program, CXP™) (29) and linked to data from Swedish national health registries, covering mandatory individual health data on a full population level. The unique personal identification numbers were replaced with study identification numbers prior to data processing. Morbidity data were collected from the National Patient Register, inpatient hospital care (admission and discharge dates, main and secondary diagnoses), and outpatient hospital care (number of contacts and diagnoses as specified by ICD-10-CM codes). Data on drug prescriptions were collected from the Swedish Prescribed Drug Register (collection date, drug type, dosage and reason for prescription). The data collection method has been described in detail previously (30). Data linkage was performed by the Swedish National Board of Health and Welfare, the linked database was managed by the Department of Medical Sciences, Respiratory Medicine at Uppsala University, Sweden. The study protocol was reviewed and approved by the regional ethics committee in Uppsala, Sweden (reference number 2014/446).

Study population

All patients ≥18 years with a record of drug collection for obstructive pulmonary diseases (Anatomical Therapeutic Chemical [ATC] code R03) during years 2011–2012, and a prior physician diagnosed asthma (ICD-10 code J45-J46) were eligible for inclusion (index date). All patients were observed during a 3-year period, where the baseline year was the year before the index date and year 2 and 3 are the years following the index date. Patients with a diagnosis of polymyalgia

rheumatica (ICD-10 code M35.3) or rheumatoid arthritis (ICD-10 code M05) were not included in order to exclude patients with potential continuous treatment with oral steroids for other reasons than asthma (Figure 1). Only oral corticosteroids (OCS) prescriptions intended for asthma exacerbation treatment were included, ascertained by individual and manual clinical verification.

Outcomes and variables

An exacerbation was defined as an asthma related inpatient hospitalization (asthma [J45, J46] as primary diagnosis) and/or asthma related emergency visit at hospital (J46.9) and/or a collection of oral corticosteroid in primary or secondary care due to an exacerbation of asthma. Repeated exacerbations occurring within 14 days were calculated as one single event.

The lung function measurements, forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), were recorded according to primary care routine and obtained from the medical records (31, 32).

Data on blood eosinophil and neutrophil counts were collected from the medical records.

Medications were defined by ATC codes (Inhaled corticosteroids (ICS) (R03BA), Long-acting β_2-agonists (LABA) (R03AC12-13,17-18, R03CC12), Fixed ICS/LABA combination (R03AK), Short-acting β_2-agonists (R3AC02-03), Leukotriene receptor antagonists (R03DC), Oral corticosteroids (H02AB).

Statistical analyses

Baseline characteristics was described as mean (SD) for continuous variables and absolute and relative frequencies for categorical variables. Comparisons between the two groups at baseline were performed using analysis of covariance (ANCOVA) for continuous variables and logistic regression for bivariate variables. All analyses (except age and sex) were adjusted for age and sex. Comparisons of within group changes from baseline to year two were performed using exact McNemar tests, and the comparison of changes in proportions over time were performed using a generalized estimation equation (GEE) model, using data for all 3 years, where the p-value for the interaction between group and time is presented. The GEE models were adjusted for age and gender.

The consistency of the classification of being non-user and frequent user over time is calculated as the positive predictive value (i.e. the likelihood that a frequent user remains a frequent), and the negative predictive value (i.e. the likelihood that a non-user remains a non-user). Statistical analyses were performed using SAS version 9.3 and R version 3.2.3.

RESULTS

Exacerbations history at index

The study included 18 724 asthma patients, of which 15 330 (81.45%) had no recorded exacerbations; 2219 (11.9%) had one recorded exacerbation; and the remaining 1175 (6.43%) patients had at least 2 exacerbations during the 12 months prior to index (Figure 1). Experiencing exacerbations prior to index were associated with greater mean age (56 vs 48 years), female sex (67 vs 62%), higher blood eosinophilic count (0.40 vs 0.31, x103 cells/μL), greater neutrophil count (6.1 vs 5.1 cells/mm3) respectively, and lower lung function compared to patients with no exacerbations. In addition, patients with exacerbations had a greater use of asthma medications than patients without exacerbations prior to index date, although 21% of the patients with two or more exacerbations had no recorded collection of ICS at index (Table 1).

Exacerbations history during 3 years

Patients with two or more exacerbations at index were much more likely to have had frequent exacerbations also during the two following years (Figure 2). Of the 1175 patients with frequent exacerbations at baseline, 47% also had frequent exacerbations in the first year of follow-up (positive predictive value (95% CI) 0.47 (0.44-0.50)). Of those who had frequent exacerbations both at baseline and in the first year of follow-up, 63% had frequent exacerbations also in the second year of follow-up (positive predictive value (95% CI) 0.63 (0.58-0.67)). In total, 328 (1.8%) of the patients had frequent exacerbations during three consecutive years. A similar pattern, with a low likeliness of having exacerbations also during follow up, was observed for the patients who did not have any exacerbations prior to index (Figure 2). Of the 15,330 patients without exacerbations at baseline, 89% further had no exacerbations in the first year of follow-up (negative predictive value (95% CI) 0.89 (0.88-0.89)) and of those without exacerbation both at baseline and in the first year of follow-

up, 91% did not have any exacerbations in the second year of follow-up (negative predictive value (95% CI) 0.91 (0.90-0.91)).

Frequent exacerbations versus no exacerbations

There was an increase in the percentage of patients collecting an asthma medication during follow up, both in the group with frequent exacerbations and in the group without exacerbations compared with index (Table 2). The use of Leukotriene receptor antagonists and LABA increased more in the group with frequent exacerbations compared to those without exacerbations, but no other significant difference in medication change was found between the two groups (Table 2). During follow up, ICS in fixed combinations or as monotherapy, was collected by significantly more patients in the group with frequent exacerbations (90%) compared with those without exacerbations (54%) (Table 2).

Health care utilisation showed an opposite trend with a decreased percentage of patients visiting health care in both groups during follow up compared with the 12-months pre-index (Table 3). No significant difference in change in health care utilisation was found between the group with frequent exacerbations compared to the group without exacerbations (Table 3). The percentage of patients with a physician visit due to asthma during the follow up period, both in primary and secondary care, was however greater in the group with frequent exacerbations, 29% and 22% respectively, compared with 11% and 2% respectively, in the group without-exacerbations (Table 3).

The group with repeated frequent exacerbations was older (58 vs 47 years), were more often women (67 vs 61 %), had increased levels of eosinophils (0.46 vs 0.29 $x10^3$ cells/µL) and neutrophils (6.0 vs 4.9 cells/mm^3), lower FEV_1 (66 vs 87 % predicted) and lower FVC (86 vs 97 % predicted) than the group without exacerbations during study period (Table 4). In addition, the group with frequent

exacerbations had a greater multi morbidity prevalence, also after adjusting for age and sex differences compared to the group without frequent exacerbations. Comorbidities that differed in this aspect included nasal polyps, chronic sinusitis, chronic bronchitis, COPD, diabetes, hypertension, ischaemic heart disease, stroke, depression and osteoporosis (Table 4). Most of the association reported above remained also when excluding patients with concurrent COPD diagnosis, except that there was no significant difference between the groups regarding neutrophils, FVC, stroke and depression (Supplementary table S1-S3).

DISCUSSION

The main findings of the present observational study were that an exacerbation prone asthma phenotype could be identified in a Swedish primary care setting, corresponding to about 2% of the primary care asthma population, and that the health care system seems to be inadequately equipped to adjust the treatment and management in this group of patients with severe asthma. Patients with frequent exacerbations were somewhat older, more often women and they were more likely to have multi morbidity than those without exacerbations. The group with frequent exacerbations also had lower lung function and greater blood eosinophil and neutrophil counts than those without exacerbations.

This study indicates the existence of an exacerbations prone asthma phenotype. This is in accordance with what has been found in one previous study (13) and in line with what has been previously reported for COPD (12). This group with frequent exacerbations constitute a minority of the asthma patients managed in primary care, but as asthma is a common disease, these patients may still have a large impact on the costs of asthma management for both health care and society (10).

The clinically most important finding in this study is that the health care system does not seem to be able to neither identify, nor adjust the level of management in asthma patients with frequent exacerbations. It would be expected that the pharmacological treatment and the frequency of follow up visits would increase in asthma patients who continue to have frequent exacerbations over time. This was, however, not the case in the present study. There was a slight increase in pharmacological treatment, but this increase was at the same level as observed for the group with no exacerbations during the 3-year observational period. Concomitantly, there was a decrease in both primary and secondary care physician visits in both groups during the same time. According to international guidelines, patients with severe asthma should be managed by pulmonary specialists (1). In this study, only one third of the patients with frequent exacerbations was seen by a secondary care

specialist, indicating that the health care system has failed to identify and adjust the management of this patient population. We also found that 10% of those with frequent exacerbations had not collected ICS, which indicates that some of the patients in this group are undermedicated.

The finding that the group with frequent exacerbations was older is in accordance with several other studies, showing lower health-related quality of life (HRQOL) and less asthma control in older asthma patients (7, 33). In our study, women were more likely to have frequent exacerbations, which is in keeping with studies showing a lower HRQOL in women with asthma than in men with asthma (34), and that female sex is related to having uncontrolled asthma (35).

In the present study, the group with frequent exacerbations had lower FEV_1 and FVC compared with those without exacerbations. These results are in agreement with those of Bai and co-workers, who found that having frequent exacerbations was related to a more rapid decline of lung function in asthma patients (11). In addition, having frequent exacerbations was related to greater counts of both eosinophils and neutrophils. The association between exacerbations and eosinophil counts is well known (13-15), and the introduction of anti-IL5 treatment has shown that this is a relevant target for reducing exacerbations in some asthma patients (17). An association between greater neutrophil count and increased risk for exacerbations has also been shown in previous studies (14, 36), and it is possible that therapy that will target the neutrophilic inflammation may be relevant to reduce exacerbations in asthma in the future.

Several comorbidities were related to frequent exacerbations in the present study. The association between frequent exacerbations and upper airway diseases are in accordance with previous studies, showing an association between chronic rhinosinusitis and low asthma related quality of life (7), as well as studies showing that treating rhinitis with nasal corticosteroids may reduce exacerbations in asthma (37). In COPD, having chronic bronchitis is related to exacerbations (38), and chronic

productive cough has been related to frequent exacerbations in asthma (39). In the present study, the group with frequent exacerbations were more likely to have a concomitant diagnosis of COPD. This is in accordance with several other studies, reporting that patients with asthma and COPD overlap are more likely to have exacerbations than those with only one of the diseases (22, 23). The term asthma COPD overlap syndrome (ACOS) was introduced indicating that this is a group of patients that need special attention(40). The term has now been changed to asthma COPD overlap (ACO) in order to emphasise that having both asthma and COPD is not a distinct disease (41). The group with frequent exacerbations also had a higher prevalence of depression, cardiovascular disease and inflammatory bowel disease. In COPD, an association between health status and the number of comorbidities has been reported (42), but less is known of the role of comorbidities in asthma. One likely explanation for the association between multimorbidity and exacerbations in asthma may be that triggers, like viral infections, are more likely to cause an exacerbation in asthmatics whose health is already decreased by other diseases. The association between having frequent exacerbations and multimorbidity remained after excluding patients with concurrent COPD.

The strength of this study is that it is a large observational study with no selection bias, linking electronic primary healthcare data to mandatory national health registers with high coverage and quality. It can therefore be expected that the study results present a real-life picture of the management of asthma patients in a Swedish primary care setting. However, this is a retrospective, observational registry study, a design that has its limitations. Comprehensive phenotypic and personal characteristics, such as that lung function measurements and biomarkers, were only available for a limited number of patients, and data on allergic sensitisation and smoking was lacking. The exacerbations were identified by short courses of OCS, as manually verified. Still, it cannot be completely ruled out that some use of short courses of OCS was indicated by other chronic diseases than asthma.

In conclusion, we found that there is a group of asthma patients, also in a Swedish primary care setting, who have frequent exacerbations, characterized by greater age, female predominance, high eosinophilic and neutrophilic count and high level of comorbidities. In addition, the present study indicates that the health care system lacks the efficiency to adjust the level of treatment and management for this severe asthma population. With the availability of new treatment options targeting severe asthma, these patients would likely benefit from being identified and evaluated, to ensure reduced frequency of exacerbations and an increased health-related quality of life.

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Table 1. Baseline patient characteristics of the study population, grouped by the number of exacerbations during 12-months prior to index

	No exacerbations n=15330 (81.49%)	**One exacerbation n=2219 (11.9%)**	**≥2 exacerbations n=1175 (6.3%)**	**p-value***
Age, mean (sd)	48.3 (19.3)	51.4 (18.5)	55.6 (17.9)	<0.001
Female, n (%)	9470 (61.8)	1503 (67.7)	792 (67.4)	<0.001
Neutrophils, cells/mm3, mean (sd), n	5.1 (2.7), 1407	5.6 (2.8), 370	6.1 (3.0), 291	<0.001
Eosinofils, $x10^3$ cells/µL, mean (sd), n	0.31 (0.39), 2362	0.33 (0.52), 482	0.40 (0.62), 351	0.001
BMI, mean (sd), n	27.6 (6.0), 8109	27.8 (6.0), 1182	27.5 (6.0), 668	0.304
FEV_1 % predicted, mean (sd), n	85.1 (20.6), 1176	81.7 (23.3), 272	70.8 (26.0), 167	<0.001
FVC % predicted, mean (sd), n	95.9 (18.6), 1049	95.1 (19.1), 224	87.6 (20.8), 136	<0.001
Short-acting ß2-agonists, n (%)	4642 (30.3)	1053 (47.5)	683 (58.1)	<0.001
Long-acting ß2-agonists, n (%)	1554 (10.1)	351 (15.8%)	244 (20.8)	<0.001
Inhaled corticosteroids, n (%)	4211 (27.5)	814 (36.7)	447 (38.0)	<0.001
Fixed ICS/LABA combination, n (%)	3709 (24.2)	827 (37.3)	607 (51.7)	<0.001
Any ICS, n (%)	7610 (49.6)	1530 (68.9)	932 (79.3)	<0.001
Leukotriene receptor antagonists, n (%)	718 (4.7)	207 (9.3)	229 (19.5)	<0.001
Long acting anticholinergics, n (%)	576 (3.8)	184 (8.3)	183 (15.6)	<0.001

*Adjusted for age and sex
BMI = body mass index

Table 2. Percentage of patients collecting at least one claim of asthma medication at baseline and during follow-up, grouped in patients with and without frequent exacerbations during the observation period.

	No exacerbations n=12036				Frequent exacerbations n=328				Group*time interaction p-value*
	Baseline	**Follow-up**	**Diff* (95% CI)**	**p-value**	**Baseline**	**Follow-up**	**Diff* (95% CI)**	**p-value**	
Short-acting ß2-agonists, %	28.5	34.2	5.72 (4.85, 6.58))	<0.001	64.3	68.0	3.66 (-1.49, 8.47)	0.18	0.46
Long-acting ß2-agonists (LABA), %	9.1	10.0	0.95 (0.48, 1.40)	<0.001	20.4	25.3	4.88 (0.95, 8.01)	0.015	0.045
Inhaled corticosteroids (ICS), %	26.9	30.9	3.95 (3.18, 4.72)	<0.001	38.1	38.7	0.61 (-4.32, 5.48)	0.90	0.15
Fixed ICS/LABA combination, %	21.8	25.1	3.32 (2.71, 3.91)	<0.001	54.9	61.0	6.10 (1.55, 9.92)	0.008	0.29
Any ICS	47.0	54.2	7.22 (6.37, 8.06)	<0.001	83.5	89.6	6.10 (1.74, 9.67)	0.006	0.30
Leukotriene receptor antagonists, %	3.7	4.1	0.35 (0.04, 0.65)	0.024	23.5	29.9	6.40 (2.21, 9.71)	0.003	<0.001
Long acting anticholinergics, %	2.8	3.7	0.91 (0.66, 1.14)	<0.001	21.0	25.6	4.57 (1.02, 7.21)	0.012	0.25

*Adjusted for age and sex

Table 3. Health care utilisation at baseline and during the 3-year observation period, grouped by patients that have frequent exacerbations and those without exacerbations.

	No exacerbations n=12028				Frequent exacerbations n=328				Group*time interaction p-value*
	Baseline	**Follow-up**	**Diff* (95% CI)**	**p-value**	**Baseline**	**Follow-up**	**Diff* (95% CI)**	**p-value**	
Primary care									
Doctor visits, %	58.1	48.3	-9.83 (-10.76, -8.88)	<0.001	70.1	60.4	-9.76 (-13.53, -5.01)	<0.001	0.95
Doctor visit due of asthma, %	18.2	10.7	-7.49 (-8.23, -6.73)	<0.001	34.5	28.7	-5.79 (-10.94, -0.20)	0.043	0.052
Secondary care									
Outpatient visit, %	14.8	12.5	-2.32 (-3.03, -1.60)	<0.001	53.7	51.2	-2.44 (-8.42, 3.70)	0.48	0.62
Outpatient visit due to asthma, %	3.8	2.1	-1.69 (-2.02, -1.33)	<0.001	25.9	21.6	-4.27 (-8.85, 0.73)	0.099	0.45
Hospitalisation, all cause, %	7.4	6.9	-0.51 (-1.08, 0.07)	0.086	30.5	29.9	-0.61 (-6.85, 5.67)	0.92	0.83
Hospitalisation due to asthma, %	0	0	0	-	4.3	4.0	-0.30 (-3.25, 2.72)	>0.99	0.84

*Adjusted for age and sex

Table 4 Patient characteristics of patients without any exacerbations compared with those with frequent exacerbations every year during the observational period

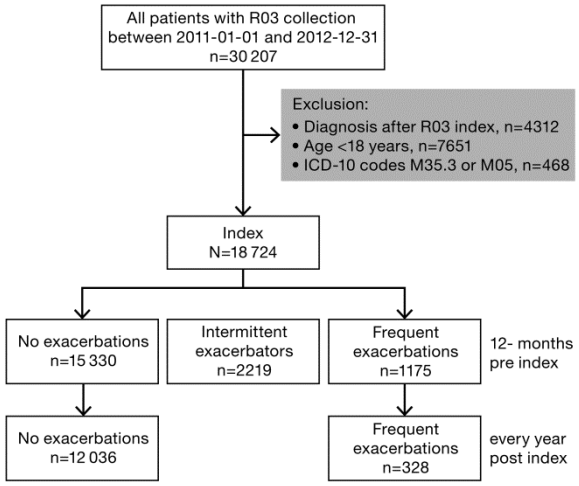
	No exacerbations n=12036	Frequent exacerbations n=328	p-value*
Age, mean (sd)	46.9 (18.9)	58.0 (16.5)	<0.001
Female, n (%)	7295 (60.6)	218 (66.5)	0.031
Neutrophils, cells/mm3, mean (sd), n	4.9 (2.5), 979	6.0 (2.6), 84	<0.001
Eosinophils, $x10^3$ cells/µL, mean (sd), n	0.29 (0.33), 1640	0.46 (0.75), 109	<0.001
BMI, mean(sd), n	27.6 (6.0), 6239	26.5 (5.2), 186	0.017
FEV1 % predicted, n	87.2 (19.1), 867	65.9 (26.6), 45	<0.001
FVC % predicted, n	96.9 (17.6), 787	86.0 (18.1), 33	<0.001
Rhinitis/sinusitis, n (%)	2527 (21.0)	84 (25.6)	0.048
Non-allergic rhinitis, n (%)	530 (4.4)	19 (5.8)	0.248
Allergic rhinitis, n (%)	1944 (16.2)	55 (16.8)	0.766
Chronic rhinitis, n (%)	317 (2.6)	21 (6.4)	<0.001
Chronic sinusitis, n (%)	110 (0.9)	10 (3.0)	0.002
Nasal polyps, n (%)	275 (2.3)	26 (7.9)	<0.001
Chronic bronchitis, n (%)	222 (1.8)	28 (8.5)	<0.001
COPD, n (%)	854 (7.1)	109 (33.2)	<0.001
Type 2 diabetes, n (%)	709 (5.9)	38 (11.6)	<0.001
Hypertension, n (%)	2620 (21.8)	115 (35.1)	<0.001
Ischaemic heart disease, n (%)	709 (5.9)	53 (16.2)	<0.001
Cerebrovascular diseases, n (%)	301 (2.5)	16 (4.9)	0.001
Anxiety, n (%)	1174 (9.8)	38 (11.6)	0.283
Depression, n (%)	1734 (14.4)	62 (18.9)	0.028
Osteoporosis, n (%)	202 (1.7)	19 (5.8)	<0.001
Inflammatory bowel disease, n (%)	322 (2.7)	14 (4.3)	0.105

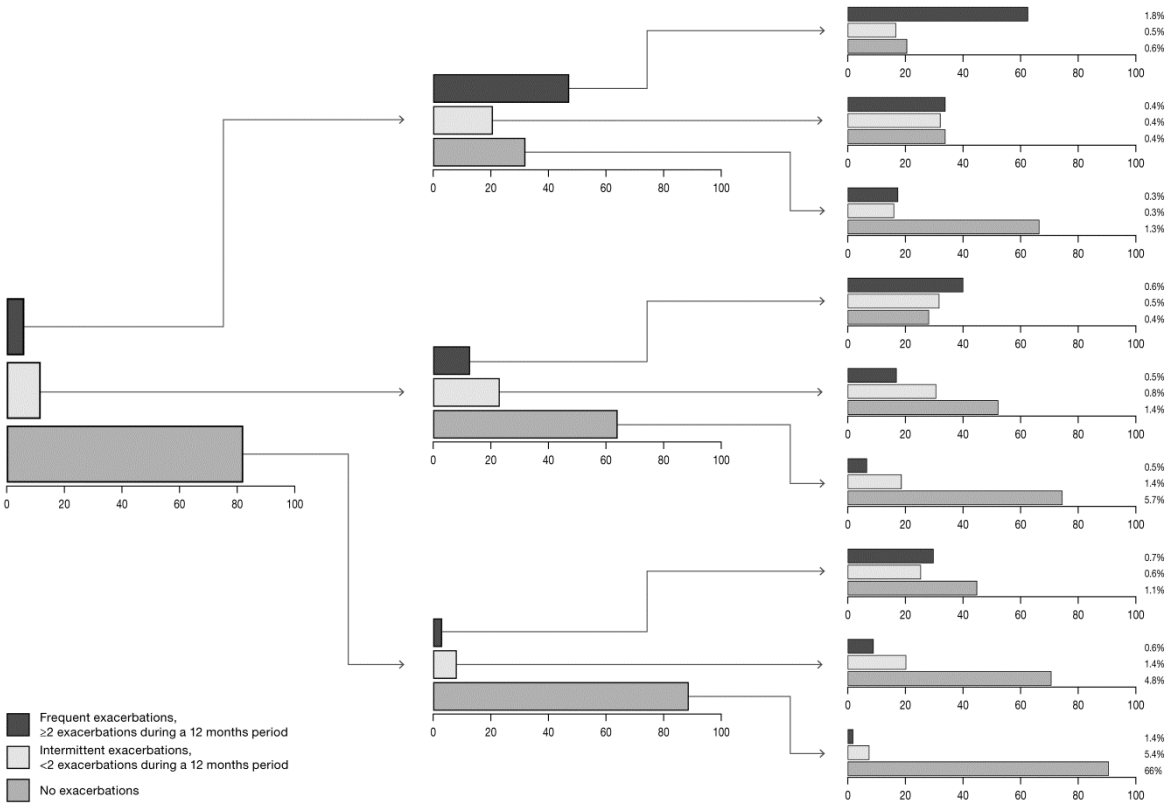
*Adjusted for age and sex
BMI = Body Mass Index

FIGURE LEGENDS

Figure 1. Patient flow chart.

Figure 2. Prevalence of exacerbations during each year of the follow-up period for patients with frequent, intermittent and no exacerbations during the baseline year.





Online Data Supplement

SUPPL Table 1. Percentage of patients without concomitant COPD diagnosis collecting at least one claim of asthma medication at baseline and during follow-up, grouped by patients with and without frequent exacerbations during the observation period.

	No exacerbations n=11182			Frequent exacerbations n=219		
	Before	**Follow-up**	**OR* (95% CI)**	**Before**	**Follow-up**	**OR* (95% CI)**
Short-acting ß2-agonists, %	27.9	33.7	1.62 (1.50-1.75)	60.7	67.1	1.74 (0.96-3.23)
Long-acting ß2-agonists (LABA), %	8.4	9.4	1.37 (1.17-1.59)	20.1	26.0	3.17 (1.22-9.69)
Inhaled corticosteroids (ICS), %	26.8	30.9	1.54 (1.42-1.68)	40.6	45.2	1.59 (0.83-3.11)
Fixed ICS/LABA combination, %	20.1	23.4	1.77 (1.58-1.98)	47.0	53.0	1.93 (0.98-3.98)
Any Inhaled corticosteroid, %	45.3	52.6	1.85 (1.71-2.00)	79.0	88.1	3.22 (1.49-7.74)
Leukotriene receptor antagonists, %	3.7	4.0	1.29 (1.03-1.62)	25.1	33.8	4.17 (1.67-12.42)
Long acting anticholinergics, %	8 0.8	1.3	3.07 (2.01-4.80)	3.7	7.3	5.00 (1.07-46.93)

*OR - Odds ratios refers to the ratio of the odds of changing category within patient (from no to yes, vs yes to no)

SUPPL Table 2. Health care utilisation at baseline and during the 3-year observation period in patients without concomitant COPD diagnosis, grouped by patients that have frequent exacerbations and those without exacerbations

	No exacerbations n=11182			Frequent exacerbations n=219		
	Before	**Follow-up**	**OR* (95% CI)**	**Before**	**Follow-up**	**OR* (95% CI)**
Primary care						
Doctor visits, %	56.8	47.1	0.52 (0.48-0.56)	68.5	59.4	0.39 (0.19-0.77)
Doctor visit due of asthma, %	18.0	10.4	0.45 (0.41-0.50)	35.2	31.5	0.76 (0.43-1.31)
Secondary care						
Outpatient visit, %	14.0	11.9	0.76 (0.69-0.83)	50.7	47.9	0.82 (0.48-1.40)
Outpatient visit due to asthma, %	3.9	2.1	0.43 (0.36-0.53)	28.8	23.3	0.57 (0.29-1.09)
Hospitalisation, all cause, %	6.0	5.8	0.95 (0.84-1.07)	21.9	22.4	1.03 (0.61-1.77)
Hospitalisation due to asthma, %	0.0	0.0	NA (0.00-Inf)	4.6	3.7	0.75 (0.21-2.46)

*OR - Odds ratios refers to the ratio of the odds of changing category within patient (from no to yes, vs yes to no)

SUPPL Table 3. Characteristics of patients without concurrent COPD diagnosis, patients without any exacerbations compared with those with frequent exacerbations every year during the observational period

	No exacerbations n=11182	**Frequent exacerbations n=219**	**p-value***
Age, mean (sd)	45.3 (18.4)	53.4 (16.9)	<0.001
Female, n (%)	6767 (60.5%)	153 (69.9%)	0.004
Neutrophils, cells/mm3, mean (sd), n	4.79 (2.37), 852	5.26 (1.99), 50	0.176
Eosinophils, $x10^3$ cells/µL, mean (sd), n	0.29 (0.34), 1464	0.39 (0.43), 72	0.012
BMI, mean (sd), n	27.5 (6.0), 5625	27.1 (5.1), 116	0.474
FEV1 % predicted, (sd), n	91.1 (16.0), 745	82.0 (14.7), 22	0.008
FVC % predicted, (sd), n	99.0 (16.0), 672	91.4 (14.7), 13	0.087
Rhinitis/sinusitis, n (%)	2458 (22.0%)	67 (30.6%)	0.003
Non-allergic rhinitis, n (%)	506 (4.5%)	13 (5.9%)	0.342
Allergic rhinitis, n (%)	1913 (17.1%)	44 (20.1%)	0.256
Chronic rhinitis, n (%)	296 (2.6%)	17 (7.8%)	<0.001
Chronic sinusitis, n (%)	97 (0.9%)	7 (3.2%)	0.005
Nasal polyps, n (%)	251 (2.2%)	17 (7.8%)	<0.001
Chronic bronchitis, n (%)	153 (1.4%)	6 (2.7%)	0.129
COPD, n (%)	0 (0.0%)	0 (0.0%)	1.000
Type 2 diabetes, n (%)	552 (4.9%)	21 (9.6%)	0.005
Hypertension, n (%)	2144 (19.2%)	64 (29.2%)	<0.001
Ischaemic heart disease, n (%)	528 (4.7%)	20 (9.1%)	0.007
Cerebrovascular diseases, n (%)	223 (2.0%)	7 (3.2%)	0.247
Anxiety, n (%)	1087 (9.7%)	25 (11.4%)	0.414
Depression, n (%)	1567 (14.0%)	41 (18.7%)	0.057
Osteoporosis, n (%)	143 (1.3%)	12 (5.5%)	<0.001
Inflammatory bowel disease, n (%)	288 (2.6%)	10 (4.6%)	0.097

*Adjusted for age and sex
BMI = Body Mass Index