Severe asthma trajectories in adults: findings from the NORDSTAR cohort

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Data-driven techniques applied to a nationwide population of severe asthma patients identified four distinct and clinically relevant trajectories of severe asthma reflecting different patterns of progression in asthma severity https://bit.ly/3PRflDP

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Abstract

Background There is limited evidence on the pathways leading to severe asthma and we are presently unable to effectively predict the progression of the disease. We aimed to describe the longitudinal trajectories leading to severe asthma and to describe clinical events preceding disease progression in a nationwide population of patients with severe asthma.

Methods We conducted an observational study based on Swedish data from the NORdic Dataset for aSThmA Research (NORDSTAR) research collaboration platform. We identified adult patients with severe asthma in 2018 according to the European Respiratory Society/American Thoracic Society definition and used latent class analysis to identify trajectories of asthma severity over a 10-year retrospective period from 2018.

Results Among 169 128 asthma patients, we identified 4543 severe asthma patients. We identified four trajectories of severe asthma that were labelled as: trajectory 1 "consistently severe asthma" (n=389 (8.6%)), trajectory 2 "gradual onset severe asthma" (n=942 (20.7%)), trajectory 3 "intermittent severe asthma" (n=1685 (37.1%)) and trajectory 4 "sudden onset severe asthma" (n=1527 (33.6%)). "Consistently

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severe asthma" had a higher daily inhaled corticosteroid dose and more prevalent osteoporosis compared with the other trajectories. Patients with "gradual onset severe asthma" and "sudden onset severe asthma" developed type 2-related comorbidities concomitantly with development of severe asthma. In the latter group, this primarily occurred within 1–3 years preceding onset of severe asthma.

Conclusions Four distinct trajectories of severe asthma were identified illustrating different patterns of progression of asthma severity. This may eventually enable the development of better preventive management strategies in severe asthma.

Introduction

Despite effective biological therapies, severe asthma still presents a serious unmet need due to increased risk of exacerbations, high exposure to oral corticosteroids (OCS) and increased healthcare costs [1–3]. Overall, severe asthma is a heterogeneous condition affecting up to 8% of all asthma patients [1, 4–6]. Nevertheless, little is known about how severe asthma develops and we still cannot effectively predict or prevent the progression of asthma. Some patients experience severe asthma starting in early childhood [7], while others progress from a milder disease to a severe refractory asthma over time [8, 9]. Older age, loss of lung function and high comorbidity burden are all associated with increased risk of disease progression [8, 10–12]. However, evidence on longitudinal trajectories relating to developing severe asthma in nationwide populations is lacking and the underlying mechanisms driving asthma progression remain to be elucidated.

Understanding longitudinal trajectories of severe asthma is essential for several reasons. Different trajectories might have different underlying aetiologies, pathophysiological mechanisms and prognoses, and thus potentially a need for a different therapeutic approach. Latent class analysis (LCA) can provide important unbiased information about underlying groups in a population and has been used previously to identify disease patterns in asthma [11, 13–15]. However, previous studies have often been focused on asthma and wheezing trajectories from childhood to early adulthood [14, 15] and the trajectories of severe asthma in adulthood are not well understood.

Ideally, using data-driven research methods to delineate the natural course of severe asthma could improve our understanding of the underlying aetiology of severe asthma. Further, exploring the potential association between different severe asthma trajectories and specific asthma outcomes and comorbidities might enable identification of potential treatable traits. These results could ultimately be used to identify risk factors for developing severe asthma, to tailor treatment for different asthma subtypes and, through early interventions, even prevent disease progression for patients with asthma. According to clinical experience, the development and consistency of severe asthma over time is heterogenous. By using data-driven LCA trajectory methodology with prespecified indicators, such as time to severe asthma, minimum asthma treatment level and changes in asthma treatment over time, we hypothesised that different trajectories of severe asthma could be identified. Hence, by using nationwide data from the NORdic Dataset for aSThmA Research (NORDSTAR) research collaboration platform [16] with long-term follow-up and no selection bias, this study aimed to describe the longitudinal trajectories of developing severe asthma, and to examine the associations of different trajectories with asthma control measures and comorbidities. Further, an exploratory aim was to describe clinical events preceding disease progression in a large sample of patients with new onset of severe asthma, if such trajectories were identified.

Methods

Data source

The study is based on data from NORDSTAR, which is a unique research collaboration platform including complete nationwide data for all asthma patients in Denmark, Sweden, Norway and Finland [16]. Within each country, information between the registries is linked using the unique social identification number assigned to all individuals in the Nordic countries.

Patients are included in the NORDSTAR dataset if they have at least one International Classification of Diseases, 10th Revision (ICD-10) diagnosis of asthma (J45–J46) in secondary care or if they have filled at least two prescriptions for asthma medication (Anatomical Therapeutic Chemical classification code R03) in the last 12 months. The full inclusion and exclusion criteria in NORDSTAR are illustrated in figure 1.

Study population

We included only the Swedish data from NORDSTAR in the present study to enable a 10-year retrospective analysis of the severe asthma cohort, as data from the other Nordic countries were incomplete. We identified adult patients with prevalent severe asthma in Sweden in 2018, based on the European Respiratory Society/American Thoracic Society medication-based criteria [17]. Only patients aged ⩾18 years during the study period were included.

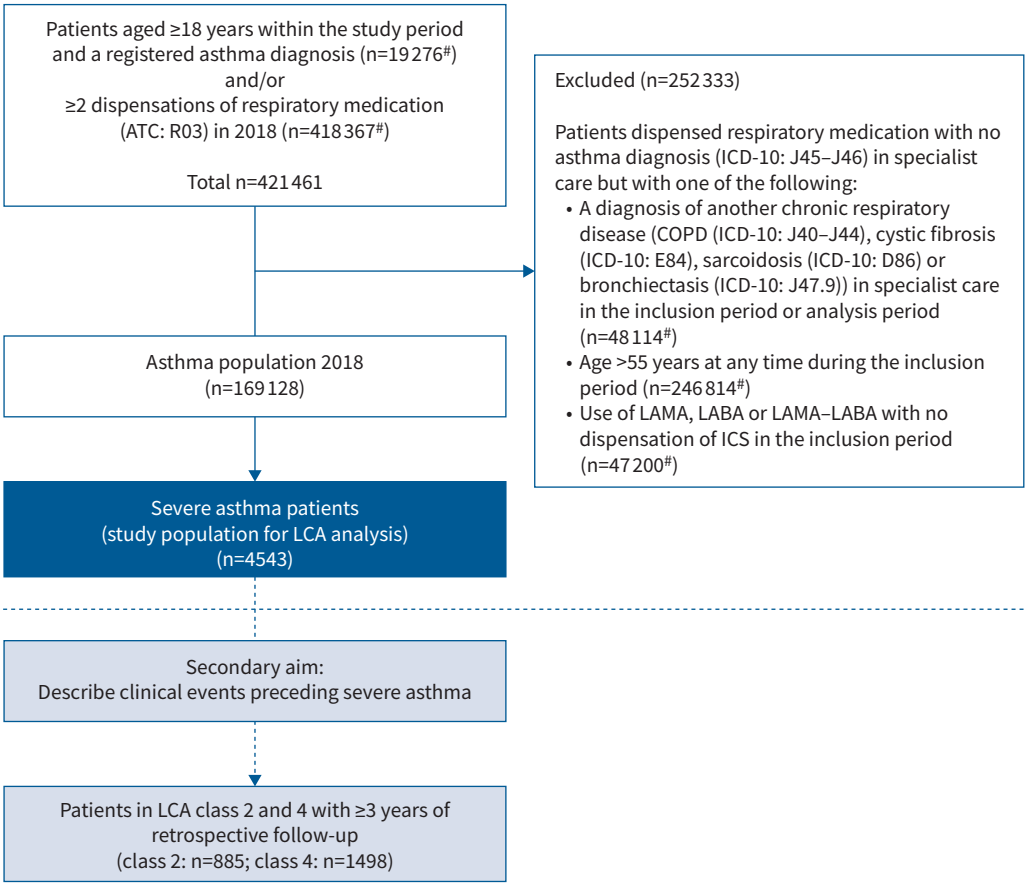


FIGURE 1 Flowchart of the study population including all severe asthma patients in 2018 identified from Swedish nationwide register data. #: not mutually exclusive. ATC: Anatomical Therapeutic Chemical; ICD-10: International Classification of Diseases, 10th Revision; LCA: latent class analysis; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid.

Study design

Patients with prevalent severe asthma in the index year of 2018 were tracked retrospectively over a 10-year period to identify trajectories leading to the development of severe asthma. During each year of the retrospective follow-up, the patients were classified according to asthma severity, based on their asthma treatment level for that calendar year [17, 18]. The included asthma treatment levels were: level 0: no asthma treatment; level 1: only short-acting β_2-agonist (SABA) (no ICS); level 2: low-dose ICS <400 µg budesonide average daily dose or equivalent; level 3: medium-dose ICS ⩾400–799 µg budesonide average daily dose or equivalent; level 4: ⩾800–1599 µg average daily dose budesonide or equivalent; level 5: ⩾1600 µg budesonide average daily dose or equivalent+second controller (high dose), or filled OCS (⩾1825 mg per year equivalent to 5 mg per day) in combination with ⩾800 µg budesonide average daily dose or equivalent, or ⩾1 dispensations of biological therapies (anti-IgE or anti-interleukin-5/5 receptor) (severe asthma).

Statistical analyses

Identification of trajectories

To identify trajectories of severe asthma, we used LCA, which is a finite mixture model that aims to describe the variance of a set of observed variables in a sample in terms of a set of latent variables (classes) [19]. It is a probabilistic approach which aims to identify the most likely model, where class membership is not a definitive assignment, but a probability for each class and each individual is determined instead.

To describe ways of developing severe asthma, it was necessary to describe the level of severity of asthma (based on asthma treatment) as well as the changes in asthma severity over time. Consequently, we

selected a set of prespecified indicators to be included in our LCA model, referred to as: time to severe asthma, minimum asthma treatment level and number of changes in progression of treatment levels. These variables were chosen 1) to enable the identification of different trajectories of asthma severity and 2) to find a model that could separate different trajectories observed in clinical practice, *e.g.* patients with consistent severe asthma *versus* patients having new development of severe asthma during the study period. Time to severe asthma was defined as the number of years it takes for a patient to go from asthma treatment level ⩽2 to level 5 (the first time this happens during the study period if there are several occasions). This variable was included to differentiate between patients who became severe over a short period of time from those who became severe over a longer period, with lower values indicating a more rapid increase in severity status. The variable was set to zero if the patient was never at or below level 2 during the analysis period or if the patient was at level 5 before being at level 2. Minimum asthma treatment level was defined as the minimum asthma treatment level during the analysis period, with higher values indicating consistently higher treatment levels. This variable was included to separate patients at lower treatment levels from those at higher levels throughout the analysis period. Changes in severity direction was defined as the number of directional changes in the evolution of severity (*e.g.* change from an increasing trend to a decreasing trend or vice versa), with higher values indicating more changes in severity status. A change in direction was defined as decrease in severity after an increase, or the opposite. Several changes in severity status in the same direction after each other were not considered as change in direction nor was a period of stationary state after a change in severity. Only when the progression switched from increasing to decreasing or from decreasing to increasing did we register a change in direction. This variable was chosen to differentiate patients at consistent treatment levels from those with several changes in their treatment status.

We fitted models with an increasing number of classes to determine the best model fit from the Bayesian information criterion and Akaike information criterion. Model parameters were estimated by the expectation-maximisation algorithm, which iteratively searches for maximum-likelihood parameter values for which the data are more likely to be observed.

The identified trajectories were qualitatively interpreted into clinically meaningful trajectories based on the three model indicators. Furthermore, the trajectories were characterised by demographics, medication use, asthma control measures and comorbidities ascertained in the index year (2018) (see supplementary table S1 for definitions). Numbers were measured either as weighted sums, averages, medians, quantiles or standard deviations, with trajectory membership as the weight [20, 21]. The patient count for each trajectory was defined as the sum of weights for the corresponding trajectory, rounded to integer values. p-values for the comparison of outcomes were calculated using a generalised linear regression model (logistic for binary outcomes and linear for continuous outcomes) for the prediction of the outcome using trajectory membership probabilities as covariates. p-values were calculated using the first identified trajectory as the comparison group and not tested for all possible group by group comparisons to avoid the risk of type 1 errors. Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). LCA was performed using the package poLCA version 1.6.0.1. p-values <0.05 were considered statistically significant.

Clinical events preceding disease progression

A priori, it was decided to investigate the annual occurrence of clinical events and markers of disease progression leading up to severe asthma if trajectories with new onset of severe asthma in the 10-year retrospective period were identified. Clinical events included OCS use, high SABA use, respiratory infections and comorbidities (see supplementary table S1 for definitions). The occurrence of clinical events preceding severe asthma was evaluated in patients with ⩾3 years of retrospective follow-up available. Numbers were reported as proportions (%).

Results

Among 169 128 patients with asthma, we identified 4543 patients with severe asthma in 2018 (figure 1). Table 1 presents the characteristics of the study population in the index year.

Identification of severe asthma trajectories

The best-fit LCA model identified a four-trajectory model of severe asthma trajectories (examples of the trajectories are shown in supplementary figure S1). The trajectories were labelled as trajectory 1 “consistently severe asthma” (n=389 (8.6%)), trajectory 2 “gradual onset severe asthma” (n=942 (20.7%)), trajectory 3 “intermittent severe asthma” (n=1685 (37.1%)) and trajectory 4 “sudden onset severe asthma” (n=1527 (33.6%)) (figure 2). The proportions of individuals in each trajectory according to the three indicators (time to severe asthma, minimum severity level and changes in the drug treatment level) are

TABLE 1 Characteristics of adult patients (⩾18 years) with severe asthma in Sweden in 2018

	All severe asthma patients (n=4543 (100%))
Demographics	
Female	2766 (61)
Age (years) (mean±SD)	59±14
28–44 years	783 (17)
45–54 years	1160 (26)
⩾55 years	2600 (57)
Asthma medications	
SABA	3378 (74)
ICS+⩾1 controllers	4423 (97)
ICS+⩾2 controllers	2704 (60)
ICS+⩾3 controllers	737 (16)
Daily budesonide equivalent dose (µg) (median (IQR))	1841 (592)
LABA	4333 (95)
LAMA	1418 (31)
Xanthines	138 (3)
LTRA	2063 (45)
Any OCS[#]	3053 (67)
High OCS exposure[¶]	1298 (29)
Asthma control measures	
Exacerbations[+]	3056 (67)
Asthma-related ED visits	321 (7)
Asthma-related hospitalisation (severe exacerbation)	340 (8)
High SABA use[§]	2055 (45)
Respiratory infections	1564 (34)
T2 comorbidities[ƒ]	
Allergy	2691 (59)
Rhinitis	2289 (50)
Nasal polyps	524 (12)
Atopic dermatitis	162 (4)
Non-T2 comorbidities[ƒ]	
Anxiety–depression	673 (15)
Osteoporosis	284 (6)
Cardiovascular disease	1555 (34)
Diabetes	440 (10)
Gastro-oesophageal reflux disease	369 (8)

Data are presented as n (%), unless otherwise stated. SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; IQR: interquartile range; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; ED: emergency department; T2: type 2; ATC: Anatomical Therapeutic Chemical. [#]: at least one prescription with OCS (ATC: H02AB); [¶]: filled OCS prescriptions corresponding to an average of ⩾5 mg per day (⩾1825 mg total dispensed OCS), [+]: defined as either a dispensation with burst OCS (ATC: H02AB), or an asthma-related ED visit in 2018, or as an asthma-related hospital admission; [§]: ⩾600 doses (puffs); [ƒ]: see supplementary table S1 for codes used to define comorbidities.

shown in figure 3a–c. Trajectory 1 "consistently severe asthma" was characterised by severe asthma (treatment level 5) in 49% of the patients throughout the entire analysis period. Among the remaining, 31% had minimum treatment at level 4 (daily ICS ⩾800 µg budesonide or equivalent) and 21% had minimum treatment at level 3 (daily ICS ⩾400 µg budesonide or equivalent) during the analysis period. No patients in this trajectory were below treatment level 3 without changes in severity direction, indicating stable treatment levels over the 10-year analysis period. Trajectory 2 "gradual onset severe asthma" was characterised by an unclear pattern with respect to time to severe asthma, with 49% of the patients spending ⩾4 years going from treatment level ⩽2 to level 5 (severe asthma). All patients were on treatment levels 1–2 (SABA only or ICS <400 µg budesonide or equivalent) at one point during the analysis period together with several changes in severity direction. Trajectory 3 "intermittent severe asthma" was characterised by the majority of patients having minimum treatment levels 3–4, but in contrast to trajectory 1 with many changes in severity direction. Trajectory 4 "sudden onset severe asthma" was characterised by nearly all patients (99.6%) having minimum severity level 0, indicating no asthma treatment at some point during the analysis period. Further, 57% of the patients in trajectory 4 moved from treatment level 2 (ICS

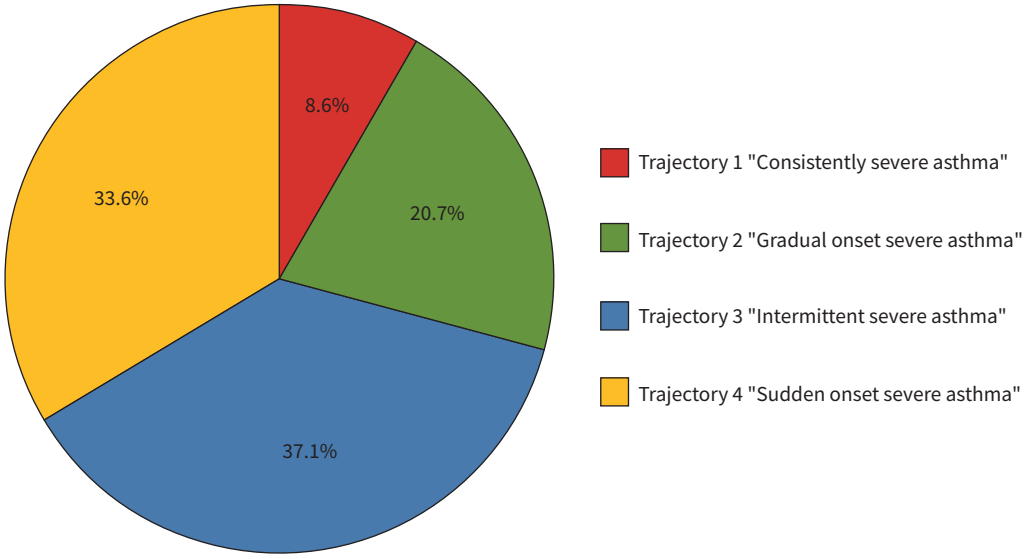


FIGURE 2 Proportions of severe asthma trajectories in a nationwide cohort of Swedish patients with severe asthma.

<400 µg budesonide) or below to severe asthma (level 5) within 1–2 years. Lastly, 28% had no changes in the severity direction and most patients (90%) had less than five changes.

Characteristics of the trajectories

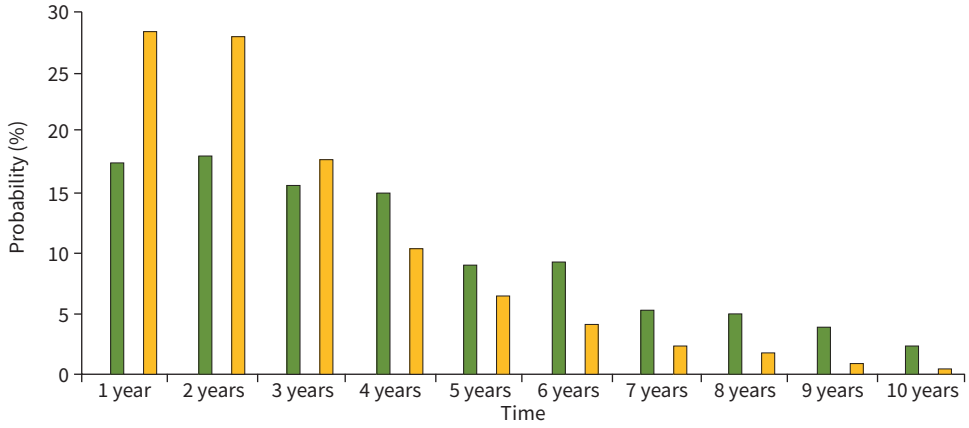
Weighted patient characteristics, assessed in the index year in 2018, are presented by each trajectory in table 2. The patients in trajectory 4 "sudden onset severe asthma" and trajectory 2 "gradual onset severe asthma" were significantly younger than those in trajectory 1 "consistently severe asthma" (reference group) (mean age 55 and 58 years, respectively, compared with 62 years; p<0.001). The patients in the "consistently severe asthma" trajectory had a significant higher average daily ICS dose compared with individuals in the other trajectories, but no differences were observed in high OCS exposure (annualised OCS ⩾1825 mg in 2018). Overall, no differences in asthma-related outcomes, such as exacerbations, hospitalisations, high SABA use or respiratory infections, were identified between either the "gradual onset severe asthma" or the "intermittent severe asthma" and the "consistently severe asthma" trajectories. In contrast, the "sudden onset severe asthma" trajectory had fewer respiratory infections (32% *versus* 40%; p<0.01) and asthma-related hospitalisations (7% *versus* 10%; p=0.02), as well as less frequent high SABA use (41% *versus* 48%; p=0.02) compared with the "consistently severe asthma" trajectory (table 2).

Most comorbidities were equally distributed in 2018 across the four trajectories (table 2). However, osteoporosis was most common in the "consistently severe asthma" trajectory (13%) compared with the other trajectories, with numbers ranging from 4% to 8% (p<0.05). Further, the "sudden onset severe asthma" trajectory had less allergy (54%), rhinitis (47%), atopic dermatitis (2%) and cardiovascular disease (27%) compared with the "consistently severe asthma" trajectory, with numbers of 61%, 55%, 6% and 38%, respectively (p<0.05 for all comparisons). In contrast, anxiety and depression were most common in the "sudden onset severe asthma" trajectory (18%) compared with "consistently severe asthma" (13%) (p<0.05).

Clinical events preceding disease progression in trajectories with new onset of severe asthma

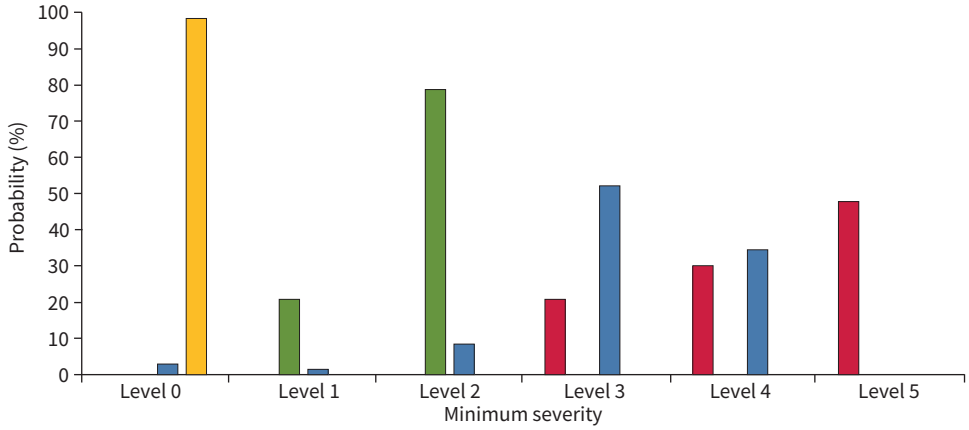
To explore in detail what occurs before patients develop severe asthma, the following analysis was performed in trajectories with new onset of severe asthma, including trajectory 2 "gradual onset severe asthma" and trajectory 4 "sudden onset severe asthma". In these two trajectories, clinical events preceding disease progression to severe asthma were assessed over a 10-year period before the first year of having severe asthma. In both trajectories, markers of uncontrolled asthma, including high SABA use, respiratory infections and OCS use, increased in the 10 years preceding severe asthma (figure 4a and supplementary table S2). In the "gradual onset severe asthma" trajectory, 10 years prior to severe asthma, 34% had used OCS, 35% had high SABA use and 29% had respiratory infections treated with antibiotics, which

a) Time to severe asthma



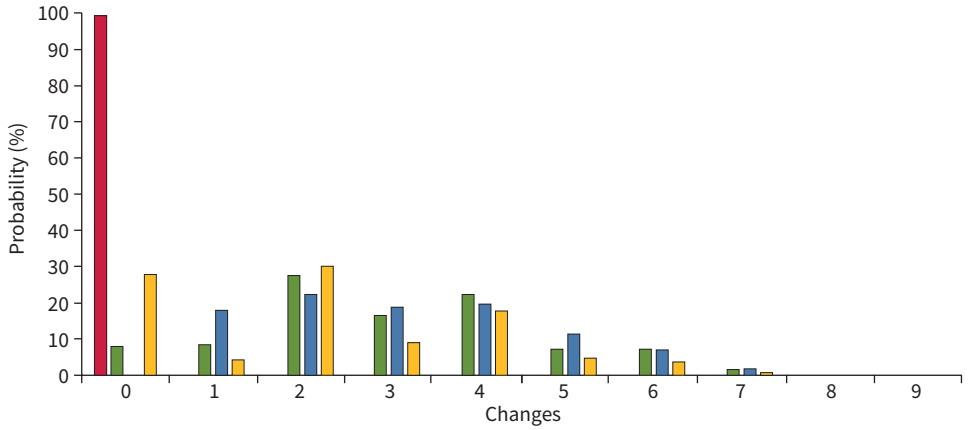
	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Trajectory 1	0	0	0	0	0	0	0	0	0	0
Trajectory 2	17	18	16	15	9	9	5	5	4	2
Trajectory 3	0	0	0	0	0	0	0	0	0	0
Trajectory 4	29	28	18	10	7	4	2	2	1	0

b) Minimum severity level



	Level 0	Level 1	Level 2	Level 3	Level 4	Level 5
Trajectory 1	0	0	0	21	31	49
Trajectory 2	0	21	79	0	0	0
Trajectory 3	3	1	9	52	35	0
Trajectory 4	100	0	0	0	0	0

c) Number of changes in treatment level



	0	1	2	3	4	5	6	7	8	9
Trajectory 1	100	0	0	0	0	0	0	0	0	0
Trajectory 2	8	9	28	17	23	7	7	2	1	0
Trajectory 3	0	18	22	19	20	11	7	2	0	0
Trajectory 4	28	5	30	9	18	5	4	1	1	0

FIGURE 3 Item response probabilities in the three model dimensions in the identified four trajectories (trajectory 1 "consistently severe asthma", trajectory 2 "gradual onset severe asthma", trajectory 3 "intermittent severe asthma" and trajectory 4 "sudden onset severe asthma") for patients with severe asthma identified by latent class analysis: a) time to severe asthma, b) minimum severity level and c) number of changes in treatment level. a) Time to severe asthma: number of years it takes for a patient to go from level ⩽2 to level 5 (the first time this happens during the study period if there are several occasions). This variable is 0% if the patient is never below level 2 during the analysis period or if the patient is at level 5 before they are at level 2. A low value indicates a rapid increase in severity status. b) Minimum severity level: minimum asthma treatment level during the analysis period. Level 0: no asthma treatment; level 1: only short-acting β_2-agonist (no inhaled corticosteroid (ICS)); level 2: low-dose ICS <400 µg budesonide average daily dose or equivalent; level 3: medium-dose ICS ⩾400–799 µg budesonide average daily dose or equivalent; level 4: ⩾800–1599 µg budesonide average daily dose or equivalent; level 5: ⩾1600 µg budesonide average daily dose or equivalent+second controller (high dose), or filled oral corticosteroid (⩾1825 mg per year) in combination with ICS ⩾800 µg budesonide average daily dose or equivalent, or ⩾1 dispensations of biological therapies (anti-IgE or anti-interleukin-5/5 receptor) (severe asthma). c) Number of changes in treatment level: number of directional changes in the evolution of severity (*e.g.* change from a higher treatment level to a lower treatment level), with higher values indicating more changes in severity status.

gradually increased until the year they developed severe asthma for the first time (figure 4a and supplementary table S2). Likewise, 10 years prior to onset of severe asthma, 26% had allergy and rhinitis, and the prevalence gradually increased throughout the 10-year period.

In the "sudden onset severe asthma" trajectory, high SABA use, OCS use and frequency of respiratory infections slowly increased until 2 years prior to the onset of severe asthma, whereafter all three outcomes became more frequent. Likewise, type 2 (T2)-related comorbidities mostly developed in the 1–3 years prior to the development of severe asthma (figure 4b and supplementary table S2).

Discussion

In this nationwide population-based NORDSTAR study, our data-driven approach using LCA methodology over a 10-year retrospective period resulted in four distinct and clinically relevant severe asthma trajectories: trajectory 1 "consistently severe asthma", trajectory 2 "gradual onset severe asthma", trajectory 3 "intermittent severe asthma" and trajectory 4 "sudden onset severe asthma". The two most common trajectories were "intermittent severe asthma" (37.1%) and "sudden onset severe asthma" (33.6%), followed by "gradual onset severe asthma" and "consistently severe asthma" (20.7% and 8.6%, respectively). Comparisons showed that all four trajectories had high burden of disease with only few clinically relevant differences in asthma medication use, asthma control outcomes and comorbidities, suggesting that morbidity of severe asthma overall appears to be similar irrespective of trajectory to disease. From a clinical point of view, we believe this finding is intuitive and highlights that once severe asthma has occurred the morbidity of disease is critical regardless of different ways of developing severe asthma. The "consistently severe asthma" trajectory was characterised by higher average ICS dose and had more prevalent osteoporosis compared with the other trajectories. However, no differences in OCS use or exacerbations were identified between the different trajectories. Moreover, patients with "sudden onset severe asthma" were less likely to have allergy, rhinitis, atopic dermatitis, osteoporosis and cardiovascular disease compared with the "consistently severe asthma" trajectory. The higher prevalence of comorbidities in the latter trajectory may be a consequence of a higher age average (62 *versus* 55 years) or of side-effects from OCS exposure.

To gain further insight into what occurs before patients develop severe asthma, we described clinical events preceding disease progression in patients with new onset of severe asthma (trajectory 2 "gradual onset severe asthma" and trajectory 4 "sudden onset severe asthma"). These analyses showed a concomitant linear increase in asthma control measures and T2-related comorbidities with increasing severity of asthma, whereas non-T2-related comorbidities (except cardiovascular disease) were relatively stable over the 10-year retrospective period. Patients with "gradual onset severe asthma" had, in general, higher markers of uncontrolled asthma, respiratory infections and T2-related comorbidities 10 years prior to developing severe asthma compared with patients with "sudden onset severe asthma", who had low levels of these markers until 1–3 years before developing severe asthma. The development of T2-related comorbidities just before the onset of severe asthma suggests that the disease progression in the "sudden onset severe asthma" trajectory is driven by T2 inflammation. Interestingly, when severe asthma occurred, the prevalence of most T2-related comorbidities was similar in both trajectories. This indicates that the

TABLE 2 Weighted characteristics of the four severe asthma trajectories identified by latent class analysis

	Trajectory 1 "consistently severe asthma" (n=389 (8.6%))	Trajectory 2 "gradual onset severe asthma" (n=942 (20.7%))	Trajectory 3 "intermittent severe asthma" (n=1685 (37.1%))	Trajectory 4 "sudden onset severe asthma" (n=1527 (33.6%))
Demographics				
Female	228 (59)	585 (62)	1049 (62)	904 (59)
Age (years) (mean±SD)	62±13	58±15**	62±14	55±14**
28–44 years	46 (12)	180 (19)**	171 (10)	386 (25)**
45–54 years	74 (19)	260 (28)**	364 (22)	462 (30)**
⩾55 years	269 (69)	502 (53)**	1150 (68)	679 (45)**
Asthma medications				
SABA	298 (77)	703 (75)	1290 (77)	1087 (71)*
ICS+⩾1 controllers	385 (99)	927 (98)	1668 (99)	1443 (95)**
ICS+⩾2 controllers	254 (65)	540 (57)**	1067 (63)	843 (55)**
ICS+⩾3 controllers	76 (20)	133 (14)*	309 (18)	219 (14)*
Daily budesonide equivalent dose (µg) (median (IQR))	2192 (1074)	1797 (589)**	1907 (570)**	1775 (769)**
LABA	377 (97)	908 (96)	1645 (98)	1403 (92)
LAMA	127 (33)	278 (30)	574 (34)	439 (29)
Xanthines	24 (6)	20 (2)**	62 (4)*	32 (2)**
LTRA	194 (50)	402 (43)*	779 (46)	688 (45)
Any OCS[#]	263 (68)	641 (68)	1183 (70)	966 (63)
High OCS exposure[¶]	116 (30)	256 (27)	516 (31)	410 (27)
Asthma control measures				
Exacerbations[+]	265 (68)	635 (67)	1182 (70)	974 (64)
Asthma-related ED visits	23 (6)	75 (8)	113 (7)	110 (7)
Asthma-related hospitalisation	40 (10)	70 (7)	128 (8)	102 (7)*
High SABA use[§]	187 (48)	435 (46)	805 (48)	628 (41)*
Respiratory infections	155 (40)	313 (33)*	609 (36)	487 (32)*
T2 comorbidities[f]				
Allergy	237 (61)	571 (61)	1058 (63)	825 (54)*
Rhinitis	215 (55)	460 (49)*	892 (53)	722 (47)**
Nasal polyps	52 (13)	104 (11)	203 (12)	165 (11)
Atopic dermatitis	23 (6)	49 (5)	57 (3)*	33 (2)**
Non-T2 comorbidities[f]				
Anxiety–depression	49 (13)	158 (17)	198 (12)	268 (18)*
Osteoporosis	51 (13)	40 (4)**	131 (8)**	62 (4)**
Cardiovascular disease	148 (38)	320 (34)	677 (40)	410 (27)**
Diabetes	50 (13)	92 (10)	185 (11)	113 (7)**
Gastro-oesophageal reflux disease	32 (8)	84 (9)	152 (9)	101 (7)

Data are presented as n (%), unless otherwise stated. SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; IQR: interquartile range; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; ED: emergency department; T2: type 2; ATC: Anatomical Therapeutic Chemical. [#]: at least one prescription with OCS (ATC: H02AB); [¶]: filled OCS prescriptions corresponding to an average of ⩾5 mg per day (⩾1825 mg total dispensed OCS), [+]: defined as either a dispensation with burst OCS (ATC: H02AB), or an asthma-related ED visit in 2018, or as an asthma-related hospital admission; [§]: ⩾600 doses (puffs); [f]: see supplementary table S1 for codes used to define comorbidities. *: p<0.05; **: p<0.01, with trajectory 1 as reference.

"gradual onset severe asthma" trajectory as well as the "sudden onset severe asthma" trajectory mainly end up having T2-high severe asthma, but with a different trajectory leading up to this. Clinically, we believe that these two trajectories suggest that for both "gradual onset severe asthma" and "sudden onset severe asthma", the period of increasing loss of asthma control prior to developing severe asthma seems to be concomitant with an increase in T2 comorbidities. This may suggest that patients with a combination of increasing loss of asthma control and development of T2 comorbidities represent an at-risk group for severe asthma development, and a possible group to target for earlier interventions [22, 23]. Further, it is

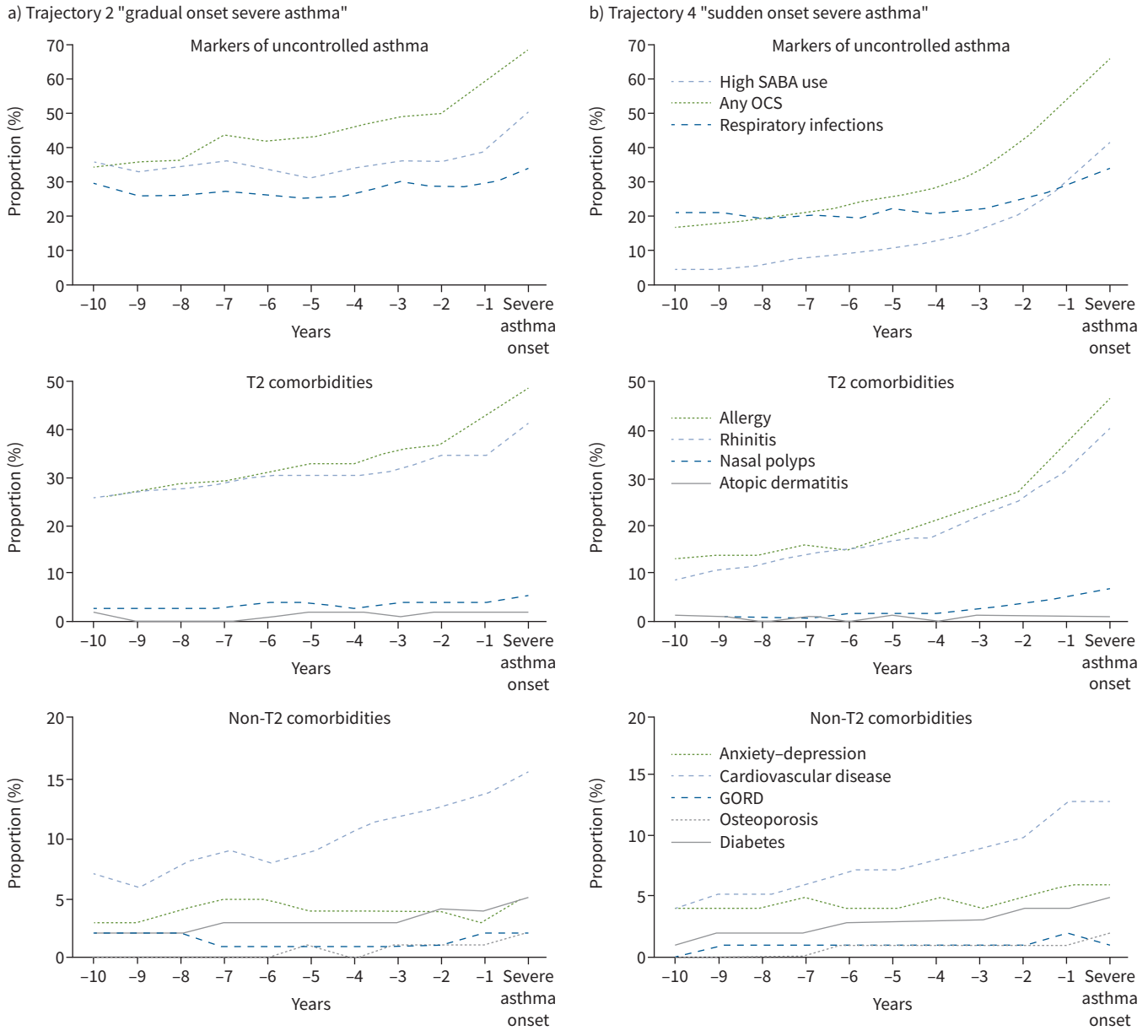


FIGURE 4 Proportion of clinical events 10 years preceding the first year with incident severe asthma in a) trajectory 2 "gradual onset severe asthma" and b) trajectory 4 "sudden onset severe asthma". SABA: short-acting β_2-agonist; OCS: oral corticosteroid; T2: type 2; GORD: gastro-oesophageal reflux disease.

interesting that respiratory infections are relatively more common than T2-related comorbidities prior to development of severe asthma in the "sudden onset severe asthma" trajectory, whereas in the "gradual onset severe asthma" trajectory the frequency of respiratory infections follows that of T2-related comorbidities. This could suggest that the "gradual onset severe asthma" trajectory is dominated by patients with an early onset allergic asthma with increased risk of infections as previously shown by Woehlk *et al.* [24], whereas in the "sudden onset severe asthma" trajectory frequent respiratory infections seem to precede the development of T2-related comorbidities and severe asthma, suggesting a possible causative role. Overall, these findings have a direct clinical benefit for our patients, as they point out the potential role of T2 comorbidities and respiratory infections in the development of severe asthma, ultimately providing us with a point for an early and effective intervention to prevent development of severe asthma.

To the best of our knowledge, this is the first study using LCA methodology describing longitudinal adult severe asthma trajectories in a nationwide population. Existing studies have mainly focused on longitudinal changes in lung function and on phenotypic changes from childhood to adulthood [10, 15], exacerbation trajectories in patients with problematic asthma [11] or the consistency of severe asthma over time [25]. CHEN *et al*. [25] found that 10 years after incident severe asthma, 83% of the individuals had transitioned into mild-to-moderate asthma, which aligns well with our finding of <10% being in the "consistently severe asthma" trajectory over our 10-year period of analysis. However, other studies have indicated that approximately half of the patients with severe or difficult-to-treat asthma had very poorly controlled asthma within 10 years of the diagnosis [12]. In our study, only a few clinically relevant differences were observed between severe asthma patients in the four trajectories. This finding supports that once severe asthma develops, the morbidity of disease appears to be similar irrespective of trajectory to disease. Hence, although the trajectories were good at differentiating severe asthma patients with different patterns of disease progression, it may not be easy to distinguish between the underlying endotypes. Future studies are highly warranted to investigate more specific groups of patients at high risk of developing severe asthma and clinical predictors of disease progression, and this ought to be explored further in clinical cohorts with biospecimen data available. Lastly, since the long-term prognosis of the four different trajectories is unknown, it would be highly relevant to prospectively explore the morbidity and consistency of the different trajectories to gain more knowledge about the natural history of severe asthma, and hopefully facilitate identification of those patients being on track to develop persistently severe disease.

Our study has several strengths. We analysed trajectories of severe asthma in a large, unselected cohort of severe asthma patients based on nationwide complete register data and our study therefore has a low risk of selection bias. We furthermore used LCA to analyse our data to identify trajectories of severe asthma, which to the best of our knowledge has not been done previously. However, our study is not without limitations. First, the aim of this study was to describe the longitudinal trajectories of developing severe asthma using a retrospective time period of 10 years. Hence, within that timeframe we were able to identify four distinct trajectories of severe asthma. However, it is important to recognise that patients would not necessarily belong in the same trajectory if they were investigated at another time-point. Furthermore, the age variable may potentially be a driver of some of the identified trajectories, as we did not analyse the statistical significance of explanatory variables, including age, in the prediction of trajectories. Moreover, for trajectories 1 and 3 ("consistently severe asthma" and "intermittent severe asthma"), we are not able to conclude anything in terms of how severe asthma developed in these trajectories, as we were unable to identify the onset of severe asthma throughout our 10-year follow-up period. Further research using a life-course approach starting follow-up from onset of asthma is needed to confirm these trajectories. Consequently, our results should therefore be regarded as descriptive in nature, with further research needed to verify our results.

Further, in this study we used the national disease registries in Sweden to assess severe asthma and no objective assessments, such as lung function, smoking status and biomarkers, were available. Hence, our definition of severe asthma is an approximation for the clinical definition with no opportunity to distinguish between true severe asthma and difficult-to-treat asthma. Thus, we may have included subjects with diagnostic uncertainty, where asthma medication could have been prescribed due to other conditions that mimic asthma symptoms or where medication has been used in excessive doses despite well-treated patients. Furthermore, misclassification of the different drug treatment levels is a possibility since the definitions relied on information on filled prescriptions. Non-compliant patients will therefore likely have been misclassified into lower severity levels, which potentially could influence which trajectory class they were assigned. An upper age limit of 55 years was applied as an exclusion criterion in patients without any asthma diagnosis to avoid interference with COPD. Consequently, older patients with severe asthma only managed in primary care were not included in this study and we cannot exclude that this can have influenced the trajectory model. Most comorbidities were defined by ICD-10 diagnoses, which were obtained only from secondary care. This can also explain the rather low prevalence of certain comorbidities like nasal polyposis in our study. Lastly, since our analyses were based on Swedish population-based registries, it remains unknown how generalisable our results are outside of Northern Europe.

In conclusion, using LCA methodology, we identified four distinct clinically relevant longitudinal trajectories of severe asthma: "consistently severe asthma", "gradual onset severe asthma", "intermittent severe asthma" and "sudden onset severe asthma". Comparisons showed that once severe asthma is developed the morbidity of disease appears to be similar irrespective of trajectory to disease. This emphasises the need for early identification of patients at high risk of progressing to severe asthma as well as the importance of future development of early interventions to prevent asthma progressing to severe

disease. Lastly, we examined clinical events preceding severe asthma and found that the "gradual onset severe asthma" as well as the "sudden onset severe asthma" trajectories mainly develop T2-high severe asthma, but with different trajectories leading up to this. Our findings suggest that a combination of increasing loss of asthma control together with presence of T2 comorbidities represents an at-risk group for severe asthma development, and a possible group to target for earlier interventions. Overall, this study illustrates different patterns of progression of asthma severity, which may eventually enable the development of better preventive management strategies. Future studies focusing on specific markers and profiles of patients who are at high risk of developing severe asthma are highly warranted.

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