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# Factors associated with the development of severe asthma
## A nationwide study (FINASTHMA)

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ABSTRACT

**Background:** Severe asthma presents a major challenge to health care and negatively affects the quality of life of patients. Understanding the factors predicting the development of severe asthma is limited.
**Objective:** To characterize patients with severe asthma and establish risk factors for the development of severe asthma in a Finnish sample with a nationwide coverage of population, health care, and drug register data.
**Methods:** We used data between January 1, 2014 and December 31, 2020. Pooled data over the years were used to identify characteristics of patients with severe asthma. Annual data were used in machine learning methods and logistic regression to identify factors predicting the development of severe asthma.
**Results:** Analysis of pooled data including 242,164 individuals revealed that patients with severe asthma were more often women, slightly older, multimorbid, and had higher body mass index values compared with patients with nonsevere asthma. They also had higher use of nonasthma-related medications, manifesting as polypharmacy. Annual data from 6908 patients revealed that the most significant predictors of the development of severe asthma were being aged 51 to 60 years (odds ratio [OR] 3.90 [95% CI: 3.42-4.47]), chronic sinusitis (OR 2.48 [95% CI: 2.12-2.89]), and higher blood eosinophil counts (≥600 cells/μL, OR 2.10 [95% CI: 1.56-2.28]). Increases in all medications (nonasthma and asthma medications) were observed in the year before the onset of severe asthma.
**Conclusion:** The results provide a clinically relevant risk factor profile for early identification of the patients at risk of developing severe asthma.


## Introduction

Asthma is a highly prevalent chronic respiratory disease that affects more than 300 million people worldwide,[1] thus presenting a substantial burden on public health care systems. According to recent estimates, 3.5% to 9.5% of patients with asthma remain refractory to the current standard treatment.[2-4] Severe uncontrolled asthma is characterized by persistent and poorly controlled symptoms with frequent exacerbations despite appropriate maintenance treatment with at least high-dose inhaled corticosteroid (ICS) and long-acting $\beta_2$-agonist (LABA) and possibly oral corticosteroids (OCS).[2,3] Severe asthma can be further divided into various phenotypes and endotypes, such as severe asthma with or without type 2 inflammation, of which the former is more common.[5,6]

Although patients with severe asthma constitute a fraction of the total patients with asthma, treatment of severe asthma contributes a high proportion to the total economic burden.[7,8] Severe asthma also negatively affects the quality of life of patients and their families.[9] Understanding the patient characteristics and factors underlying severe asthma is thus a key priority. Likewise, improving the care of patients with severe asthma and early identification of the individuals at the risk of developing severe asthma are major unmet medical needs. Previous research has identified predictors of asthma exacerbations, such as high fractional exhaled nitric oxide alone or in combination with eosinophilia,[10,11] and demonstrated that individuals follow different trajectories in the development of severe asthma.[12] However, research

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into the factors predicting the clinical course of asthma progressing to severe is scarce. This study aimed to assess the prevalence of severe asthma, characterize these patients and identify factors associated with the development of severe asthma in a nationwide Finnish adult population. Furthermore, to better understand the early signs of asthma progressing to severe, we analyzed the longitudinal patterns of the factors associated with the development of severe asthma.

## Methods

### *Study Design and Participants*

As described in detail in a previous publication of the same material,[13] all Finnish adults (>18 years of age) who had an asthma diagnosis in secondary care (International Classification of Diseases, 10th revision [ICD-10]: J45) or primary care (ICD-10: J45 or International Classification of Primary Care, second edition [ICPC-2]: R96) between January 1, 2014, and December 31, 2019, were identified from the Finnish Care Register for Health Care and included in this retrospective observational study (N = 278,172). The data were collected until December 31, 2020. Patients were followed up from January 1, 2014, to December 31, 2020, or death, whichever came first. Patients with a co-existing chronic obstructive pulmonary disease (COPD; ICD-10: J44, N = 36,008) were excluded from the main analysis. The study outline is presented in Figure 1.

### *Definition of Severe Asthma*

Severe asthma was defined according to the Global Initiative for Asthma report guidelines[14] as meeting criteria 1+2a, criteria 1+2b, or criterion 3 of the following: (1) average daily ICS dose of at least 400 μg (80% adherence to 500 μg) of fluticasone propionate equivalents and use of another controller (LABA, long-acting muscarinic antagonist [LAMA], or leukotriene receptor antagonist [LTRA]); (2a) annual OCS purchases more than 600 mg of prednisolone equivalents; (2b) more than or equal to 1 hospitalization during a year with J45 or J46 as the main diagnosis; and (3) use of biologics indicated only for severe asthma at the time of the study (mepolizumab, benralizumab, or reslizumab). Patients fulfilling the criteria for severe asthma for more than 1 calendar years across the follow-up period were categorized as “severe” and patients fulfilling the criteria (but no use of biologics) for only 1 calendar year were categorized as “transiently severe.” Patients not meeting the annual criteria at any year were categorized as “nonsevere.” For clarity, the definitions for these 3 asthma severity groups are also presented in eTable 1.

### *Study Variables*

The data were collected retrospectively from the following Finnish nationwide registers with full coverage of the population, public health care providers, and pharmacies: the Care Register for Health Care (demographics, secondary health care visits, and comorbidities as ICD-10 codes), the Register for Primary Health Care Visits (primary health care visits and comorbidities as ICD-10 and ICPC-2 codes), Prescription Centre (all prescribed medication purchases; the strength, dose, package size, number of purchased packages, purchase dates, and Anatomical Therapeutic Chemical [ATC] classification codes), Register for Medical Reimbursement Rights (reimbursement start date, reimbursement code, and underlying ICD-10 code), and laboratory databases/hospital data lakes (body mass index [BMI], smoking, and blood eosinophil count [BEC]). Dates and causes of deaths were acquired from Statistics Finland. Data from hospital data lakes have local coverage and are limited to the catchment area of the hospital district in question. A unique personal identification number was used to link the data. Details of the study variables are presented in eMethods 1.

### *Statistical Analyses*

To analyze the prevalence of severe asthma and characterize these patients, we used, for each person, pooled data over the individual years during the follow-up (Fig 1A). The period prevalence of asthma and severe asthma, as defined previously, was assessed together with descriptive statistics and statistical tests across these groups. Comorbidities were described as number and proportion of persons who had the specified condition ever during the follow-up. Medication use was described as ever use of specific medications, average dose, and number of different medications (polypharmacy) over the follow-up. For BMI and age, the most recent value before the end of follow-up was used. For smoking, the most frequently used value was reported, and for BEC, the maximum value. For continuous variables, the mean and SD or median and first and third quartiles were reported. Differences in the study variables between the patient groups were assessed using the $\chi^2$ test for categorical variables and the *t* test or Kruskal-Wallis test for continuous variables.

The analysis aiming to identify factors to predict severe asthma (Fig 1B) first included individuals who developed severe asthma during the follow-up, that is, who had at least 2 years of severe asthma (not necessarily consecutive), and who had at least 1 year of historic data without severe asthma before the first severe asthma year (N = 6,908). For these individuals, data from the historic year (the

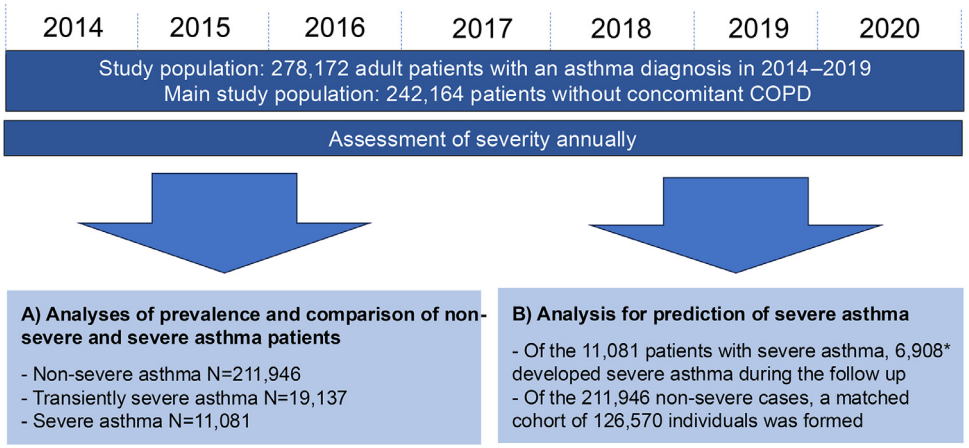


**Figure 1.** Study outline and analysis populations for the (A) analysis of prevalence and comparison between nonsevere and severe asthma and (B) analysis for prediction of severe asthma. Outcome was considered in the year asthma first became severe or matched control year for those who were constantly nonsevere. *Of the 11,081 severe cases, 4054 were severe already at the first year, and 119 were excluded owing to lack of data across 2 years, resulting in 6908 cases available for the analysis for prediction of severe asthma. COPD, chronic obstructive pulmonary disease.

year preceding the start of the first severe asthma year) were used to predict the development of severe asthma, that is, their outcome was defined as 1 at the beginning of the first severe year. Second, of the individuals who had no severe asthma years during the follow-up, a control population was formed by assigning a random outcome year (outcome defined as 0) from the observed distribution of the severe asthma years. After matching the outcome year distribution in this manner, it was similarly required to have at least 1 year of historic data and 2 follow-up years as for those who had outcome defined as 1. This procedure ensured similar outcome year distribution in both outcome groups and maintained the prevalence of the outcome.

After selection of the individuals for predictive analyses, we run a decision tree (XGBoost) to determine explanatory variables most strongly predicting the outcome (variable details in eMethods 1). Primary candidate predictive variables consisted of age, sex (male/female), calendar year, BEC, all diagnoses and medications (ICD-10, ICPC-2 codes, and ATC codes with a 3-digit accuracy excluding R03* and H02* codes), number of distinct diagnoses (primary or secondary) on 3-digit ICD-10 code accuracy, use of multiple groups of different medications (number of ATC code groups on 4-digit level), that is, nonasthma-related polypharmacy (excluding R*, J*, and H02* codes). In a secondary analysis, asthma medications (R03*, H02*, daily ICS amount, annual OCS amount, and polypharmacy without code restrictions) from the historic year, which were also part of the severity definition at the outcome year, were allowed to be in the set of candidate predictive variables. The aim of the secondary analysis was early detection of severe asthma rather than determination of independent predictive factors.

The tree-based model was performed using 80% of the data (training set), and the predictive performance (sensitivity, specificity, and positive and negative predictive values[15]) was tested using the remaining 20% of the data. Subsequently, using the full 100% data, the most influential variables from the tree-based model, and age and sex regardless of their selection were used in a logistic regression model to illustrate the strength of association on the development of severe asthma. Interaction terms in the logistic regression models were not considered. In addition, the longitudinal patterns of the selected variables were described. The analyses were performed using R version 4.3.1 (https://www.r-project.org/).

### *Risk Score Calculators*

We further turned the logistic regression model results into more practical risk score calculators, following methodologies applied in the past in different disease areas.[16,17] For the calculators, risk score points were allocated as 0 if the odds ratio (OR) was less than 1.20, 1 if OR was 1.20 to 1.49, 2 if OR was 1.50 to 2.49, 3 if OR was 2.50 to 3.49, 4 if OR was 3.50 to 4.49, and 5 if OR was more than or equal to 4.5. The Youden's criterion was used to determine the optimal number of risk point for the identification of high-risk patients.

### *Sensitivity Analyses*

Sensitivity analyses were performed by (1) including only patients with BEC available; (2) including also patients with COPD; (3) excluding patients having the following other possible indications (ICD-10 codes) for ICS and/or OCS: M05-14 (inflammatory polyarthropathies), M30-6 (systemic connective tissue disorders), K50-2 (noninfective enteritis and colitis), I80-4 (diseases of veins, lymphatic vessels, and lymph nodes), and D86 (sarcoidosis); and (4) excluding patients not having a special reimbursement for asthma medication before January 1, 2014. The last-mentioned criterion entails that the patients who had their onset of asthma after 2014 were excluded. The analysis aiming to identify factors to predict severe asthma (tree-based variable selection and logistic regression; Fig 1B) was repeated using logistic LASSO regression.

### *Ethical Considerations*

This study was approved by The Finnish Institute for Health and Welfare (THL/4/5.05.00/2020) and the Social Insurance Institution (Kela 1/522/2020).

## Results

### *Study Populations*

The study population included 278,172 adult patients with an asthma diagnosis, corresponding to a population prevalence of 6%, and of these, 242,164 did not have a co-existing COPD. The criteria of severe asthma were fulfilled by 11,081 (4.6%), whereas 19,137 had transiently severe asthma and 211,946 (87.5%) had nonsevere asthma (Fig 1). Of the 11,081 cases with severe asthma, 6,908 were eligible for predictive analysis using annual data (Fig 1), as they had at least 1 year of historic data before the first year with severe asthma, whereas 4,054 had severe asthma already at the first year and hence were not included in the analysis. In addition, 119 individuals lacked data due to death across the 2 years and were thus excluded. Patients with transiently severe asthma were excluded from analyses.

### *Comparison of Patients With Nonsevere and Severe Asthma*

In a purely descriptive characterization, which did not account for temporal sequences, patients differed in several aspects by asthma severity (Table 1). Patients with severe asthma were slightly older (median 65.8 vs 62.9 years), were more often women (70.6% vs 64.9%), and had higher BMI values (median 28.4 vs 27.8) compared with patients with nonsevere asthma ($P < .001$ for all comparisons) (Table 1). Correction coefficients for ICS in relation to fluticasone propionate and OCSs in relation to prednisolone are presented in eTables 2 and 3. Tabulation of the study variables for patients including a co-existing COPD diagnosis and the patient groups including transiently severe asthma are presented in eTables 4 and 5.

### *Identification of the Factors Associated With the Development of Severe Asthma*

Results of the primary multivariable logistic regression model without asthma medications (ATC codes R03* and H02*) demonstrated that BEC of more than or equal to 600 cells/μL, chronic rhinosinusitis, and several medication-related variables (antacids, antibacterials, antihistamines, cough preparations, nasal preparations, and immunosuppressants) were associated with an increased risk of developing severe asthma (Fig 2). Age was also associated with development of severe asthma, such that the risk was markedly elevated among those aged 41 years or older and highest among those aged 51 to 60 years (Fig 2). Sensitivity, specificity, and positive and negative predictive values of the primary model were 71.2%, 59.2%, 12.5%, and 96.2%, respectively.

In the secondary model that included also asthma medications, the associations of age and BEC remained largely the same, whereas ICS daily doses more than or equal to 500 μg fluticasone propionate equivalents, dispensed OCS, LABA, LAMA, or LTRA (at any dose), and polypharmacy were now introduced to the model with an increased risk of severe asthma (Fig 3). Use of lipid-modifying agents was associated with lower odds of developing severe asthma (Fig 3). Sensitivity, specificity, and positive and negative predictive values of the secondary model were 73.5%, 78.5%, 21.4%, and 97.4%, respectively

The results of the sensitivity analyses for individuals with BEC available (primary and secondary models) are presented in

**Table 1**
Descriptive Statistic of the Main Study Population, Using Data Over the Entire Follow-Up

| Characteristic | All (N = 223,027) | Nonsevere (N = 211,946) | Severe (N = 11,081) | *P* value |
|---|---|---|---|---|
| Female, N (%) | 145,345 (65.2) | 137,518 (64.9) | 7827 (70.6) | <.001 |
| Age | 63.1 (43.3-75.4) | 62.9 (42.7-75.4) | 65.8 (53.1-76.3) | <.001 |
| BMI (kg/m$^2$) | 27.8 (24.2-32.5) | 27.8 (24.1-32.5) | 28.4 (24.6-33.1) | <.001 |
| Missing, N (%) | 194,922 (87.4) | 187,073 (88.3) | 7849 (70.8) | <.001 |
| Smoking status, N (%) | | | | <.001 |
| Current | 9,999 (30.0) | 9260 (31.0) | 739 (21.0) | |
| Former | 5282 (15.8) | 4675 (15.7) | 607 (17.3) | |
| Never | 18,073 (54.2) | 15,903 (53.3) | 2170 (61.7) | |
| Missing | 189,673 (85.0) | 182,108 (85.9) | 7565 (68.3) | <.001 |
| Daily ICS dose FP eq. | 141 (28-315) | 119 (23-284) | 633 (424-949) | <.001 |
| Annual OCS dose, mg PRED eq. | 10 (0-171) | 0 (0-143) | 1143 (686-2171) | <.001 |
| SABA canisters per year | 1.0 (0.4-2.1) | 1.0 (0.4-2.0) | 2.6 (1.1-4.7) | <.001 |
| LABA, LAMA, or LTRA use, N (%) | 137,877 (61.8) | 126,812 (59.8) | 11,065 (99.9) | <.001 |
| ICS alone or in combination, N (%) | 204,875 (91.9) | 193,800 (91.4) | 11,075 (99.9) | <.001 |
| LABA alone or in combination, N (%) | 123,828 (55.5) | 113,041 (53.3) | 10,787 (97.3) | <.001 |
| LAMA alone or in combination, N (%) | 20,044 (9.0) | 14,841 (7.0) | 5203 (47.0) | <.001 |
| Nasal corticosteroids, N (%) | 127,856 (57.3) | 119,329 (56.3) | 8527 (77.0) | <.001 |
| No. of all medications (polypharmacy) | 20 (14-26) | 19 (14-26) | 28 (22-35) | <.001 |
| No. of nonasthma-related medications | 12 (8-18) | 12 (8-17) | 17 (12-23) | <.001 |
| Urticaria, N (%) | 5892 (2.6) | 5316 (2.5) | 576 (5.2) | <.001 |
| Atopic dermatitis, N (%) | 10,826 (4.9) | 10,174 (4.8) | 652 (5.9) | <.001 |
| Allergic rhinitis, N (%) | 19,386 (8.7) | 18,207 (8.6) | 1179 (10.6) | <.001 |
| Rhinosinusitis or nasal polyps, N (%) | 46,717 (20.9) | 42,431 (20.0) | 4286 (38.7) | <.001 |
| Allergic rhinoconjunctivitis, N (%) | 19,066 (8.5) | 17,874 (8.4) | 1192 (10.8) | <.001 |
| BEC, cells/μL (max) | 0.24 (0.14-0.42) | 0.23 (0.13-0.40) | 0.32 (0.17-0.63) | <.001 |
| Missing, N (%) | 203,221 (91.1) | 195,221 (92.1) | 8000 (72.2) | <.001 |

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; OCS, oral corticosteroid; PRED eq., prednisolone equivalents; Q1, quartile 1; Q3, quartile 3; SABA, short-acting $\beta_2$-agonist.
NOTE. The values are presented as median (Q1-Q3) unless otherwise indicated. Quantification of missing values is presented only for variables that have missing values.
Diagnoses are based on the International Classification of Diseases, 10th revision, diagnostic codes over the whole follow-up. The numbers of medications and number of nonasthma-related medications (excluding R*, J*, and H02* codes) are based on purchased drugs and considered at a 4-digit accuracy over the whole follow-up. The reported *P* value is for unadjusted comparison of severe and nonsevere groups which does not account for temporal sequence between the presented variables and asthma severity. For categorical variables, the *P* value is comparing all categories excluding the missing category, for which separate comparison was performed.

eFigures 1 and 2. The estimates of age and BEC were largely like the main population, whereas certain diagnoses and medications that were not significantly associated in the main population were associated with the development of severe asthma (eFigs 1 and 2) in the BEC group. The sensitivity analyses including patients having concomitant COPD diagnosis (eFigs 3 and 4), excluding patients having other indications for OCS use (eFigs 5 and 6), and excluding patients not having a special reimbursement for asthma medication before January 1, 2014 (eFigs 7 and 8) did not markedly alter the main findings. When the primary analysis was repeated using logistic LASSO regression, a few additional rare diagnoses associated with the development of severe asthma were found (polyarteritis [ICD-10: M30], disorders of white blood cells [D72], and eosinophilic pneumonia, [J82]), but otherwise the findings remained largely unchanged compared with the original analysis (data not revealed).

### *Risk Score Calculators*

On the basis of the model presented in Figure 2, the risk score calculator is found in eTable 6. The risk score can range from 0 to 21, and the optimal cutoff to determine high-risk patients was found to be 7 or more points. When assigning patients with 7 or more points into those who are predicted to have severe asthma, sensitivity was 62.1%, specificity 70.1%, positive predictive value 9.7%, negative predictive value 97.3%, and area under the receiver operating characteristic curve 0.66.

On the basis of the model presented in Figure 3, the risk score calculator is found in eTable 7. The risk score can range from 0 to 24, and the optimal cutoff to determine high-risk patients was found to be 9 or more points. When assigning patients with 9 or more points into those who are predicted to have severe asthma, sensitivity was 77.1%, specificity 69.5%, positive predictive value 11.5%, negative predictive value 98.2%, and area under the receiver operating characteristic curve 0.73

### *Longitudinal Patterns of the Factors Associated With the Development of Severe Asthma*

The results illustrating the longitudinal patterns of the factors associated with the development of severe asthma (medications and number of diagnoses) from 3 years before (−3) and 1 year after (+1) asthma turned severe are presented in Figures 4A-F and 5A-I. The same results but excluding patients not having a special reimbursement for asthma medication before January 1, 2014, are presented in eFigures 9A-F and 10A-I. The results revealed that, compared with nonsevere cases, the patients who developed severe asthma had significantly higher counts or values in most of the studied variables at 3 years before their asthma became severe. Most notable increases in these variables were observed in the year preceding the development of severe asthma. No marked increases were observed 2 years before asthma turning to severe.

## Discussion

This nationwide study characterized patients with asthma by disease severity and found that compared with nonsevere asthma, patients with severe asthma (4.6% of the patients with asthma) were more often women, slightly older, and had greater BMI values and more comorbidities compared with patients with nonsevere asthma. The factors associated with the development of severe asthma

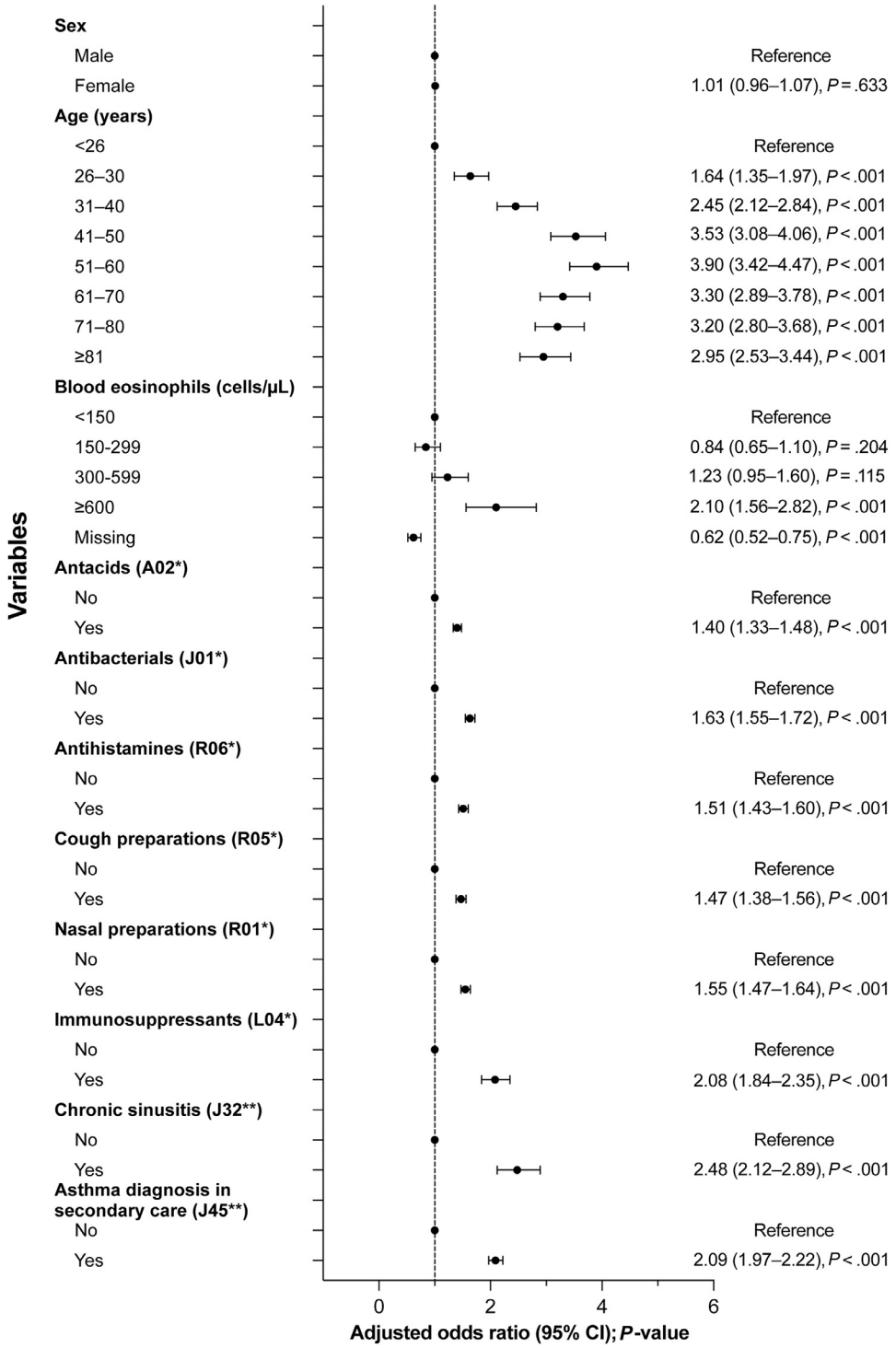


**Figure 2.** Logistic regression model to identify the factors associated with the development of severe asthma with asthma medications (ATC codes R03* and H02*) removed from the model predictors. The regression model included 6908 individuals with severe asthma and 126,570 nonsevere cases. The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision, code. ATC, Anatomical Therapeutic Chemical.

included age with highest risk in 51 to 60 years, BEC more than or equal to 600 cells/μL, chronic sinusitis, nasal preparations, immunosuppressants, antacids, antihistamines, cough preparations, and antibacterials. In the secondary model that included also used asthma medications, use of lipid-modifying agents was associated with a lower risk of developing severe asthma. Significant increases in the number of asthma and other medications and diagnoses were found most notably in the year preceding the development of severe asthma.

Our findings on the prevalence and associated factors of severe asthma are in line with previous studies estimating the severe asthma prevalence among an asthma population at 3.5% to 9.5%[2-4] and linking higher age, female sex, higher BMI, ICS and OCS use, BEC, and nasal and sinus diagnoses to severe asthma.[3,4,18] We also observed a higher number of diagnoses (multimorbidity) and medications, both nonasthma-related and all (polypharmacy) among patients with severe asthma. Many characteristics of the patients with severe asthma, such as nasal and sinus diagnoses and higher

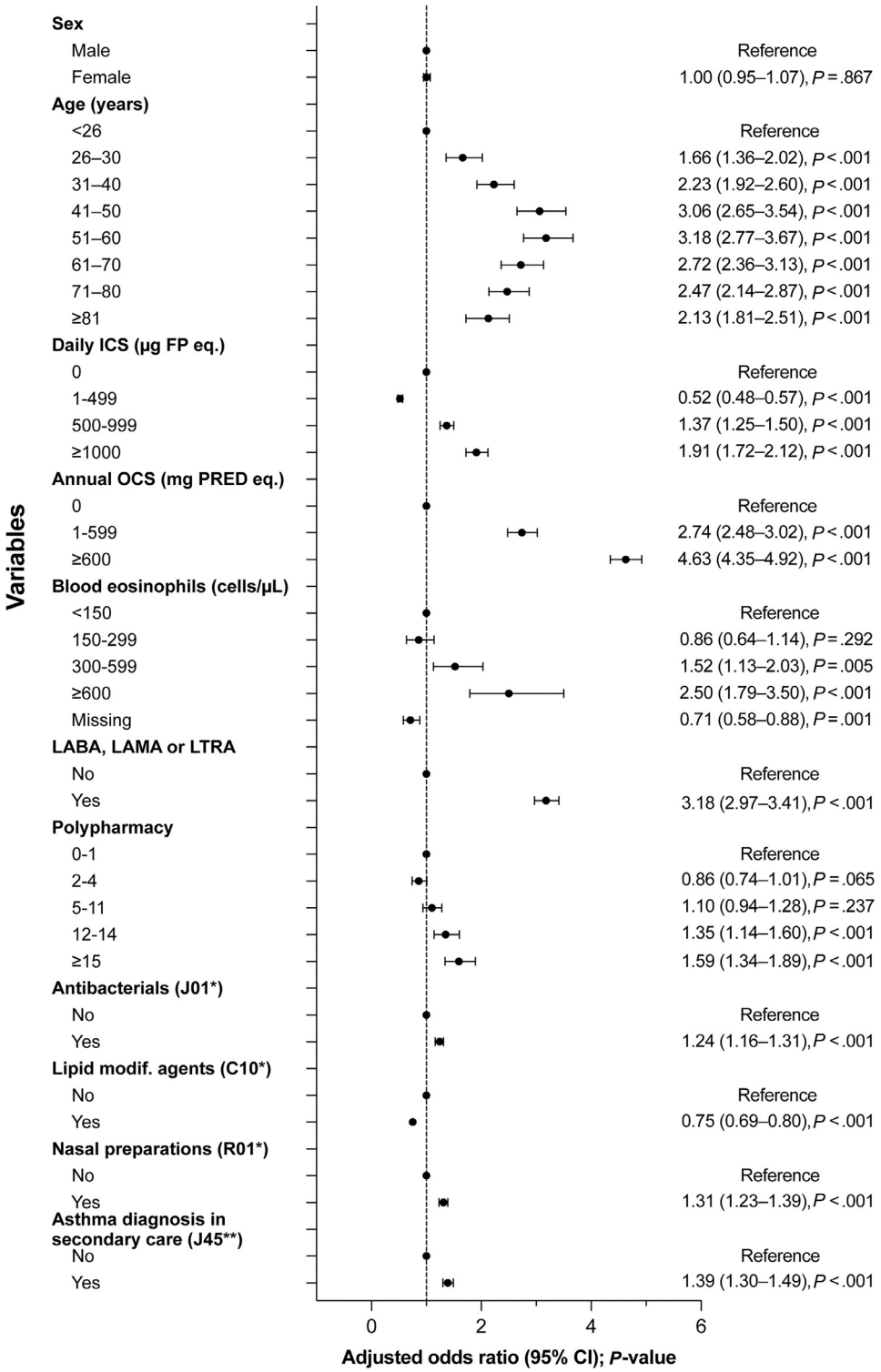


**Figure 3.** Secondary logistic regression model to identify the factors associated with the development of severe asthma, including asthma medications (ATC codes R03* and H02*). The regression model included 6908 individuals with severe asthma and 126,570 nonsevere cases. The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. ATC, Anatomical Therapeutic Chemical; FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRED eq., prednisolone equivalents.

BEC, are also common to patients with asthma exacerbations.[19,20] Overall, the results demonstrate that patients with severe asthma represent a distinct patient group with characteristics that require special attention in health care. However, asthma severity and poor asthma control are related, and it may be difficult to differentiate between loss of asthma control and shift in disease severity. As we defined severe asthma based on both treatment intensity and surrogates of exacerbations, we believe that the subjects truly represent severe asthma and not undertreated mild asthma with poor control.

To our knowledge, this is the first nationwide study assessing factors predicting the development of severe asthma; the findings thus provide new insights into how nonsevere asthma progresses to

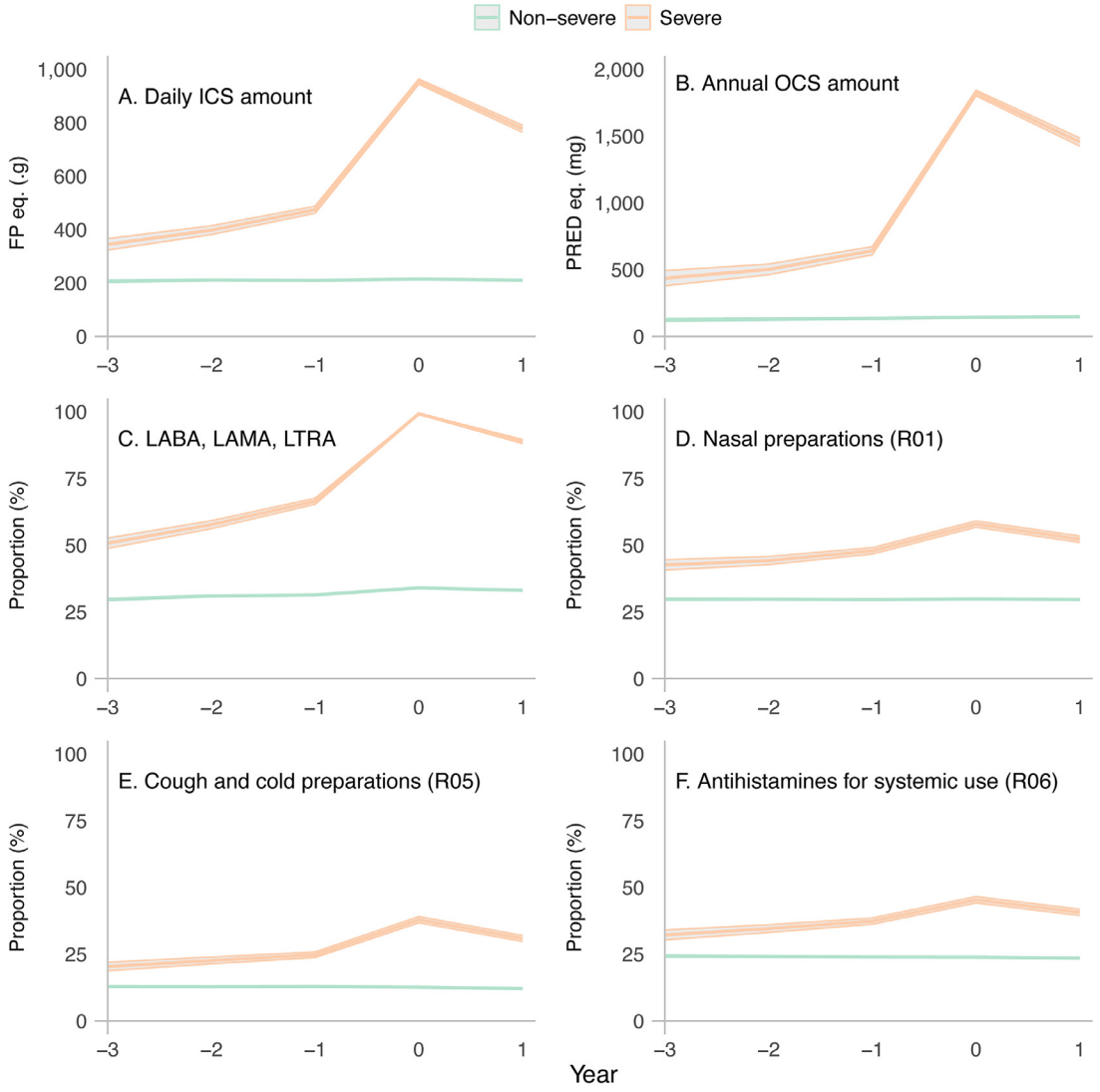


**Figure 4.** Longitudinal patterns of variables associated with the development of severe asthma. Year 0 indicates the first severe asthma year for severe and a matched control year for nonsevere. The *y*-axis values represent daily and annual averages (A and B) and proportions of patients purchasing the given medication (C-F). The lines bounding the trend line represent 95% CI. The analysis included 6908 individuals with severe asthma and 126,570 nonsevere cases. ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

severe asthma. The most prominent risk factors were being aged 51 to 60 years, having chronic sinusitis, and having BEC more than or equal to 600 cells/μL. Although previous studies have reported an increasing prevalence of severe asthma with age,[3,4,18] owing to the large sample size, our study was able to assess a more fine-grained association of age with severe asthma. We found that the risk was markedly elevated among those aged 41 years or older and was highest at ages 51 to 60 years. Zein et al[18] found an inflection point at age 45 years, such that the risk increased with each year of life until age 45 years, after which it increased at a much slower rate. A sex-stratified analysis revealed that after age 45 years, the risk continued to increase in men, but not in women.[18] Our findings thus support a nonlinear association between age and the risk of severe asthma. Regarding BEC, a study by Price et al[21] revealed that patients with asthma with BEC more than 400 cells per μL experience more severe exacerbations and have poorer asthma control. Our results concur with added value of BEC in the Global Initiative for Asthma control-based risk assessment. It should be noted though that BEC was measured more frequently in patients with severe asthma.

In addition to the previously discussed most prominent risk factors, also various medications, such as nasal preparations, immunosuppressants, antacids, antihistamines, cough preparations, and antibacterials were significantly associated with the development of severe asthma. As the use of antihistamines, nasal medications, and cough medicines is related to rhinitis and nasal symptoms, our findings could suggest that patients with severe asthma tend to have more severe forms of these diseases that required medication. The use of antibiotics is known to be associated with the occurrence of childhood asthma.[22] Increasing asthma incidence in relation to increased cumulative antibiotics prescription days and the number of antibiotic classes has recently been reported also for adults aged 40 years or older.[23] Higher dispensed antibiotics have also been associated with patients with neutrophilic and eosinophilic asthma.[24] However, it is important to note that associative and predictive analyses do not establish causation.

Longitudinal analysis on the risk factors revealed significant increases in the number of asthma and nonasthma-related medications and comorbidities in the year preceding the development of severe asthma. The patients who developed severe asthma had higher numbers of these medications and comorbidities already 3 years before their asthma progressed to severe, as compared with patients who did not develop severe asthma. In contrast, lipid-modifying agents were more frequently used by patients who did not develop severe asthma. This finding is in line with a previous meta-

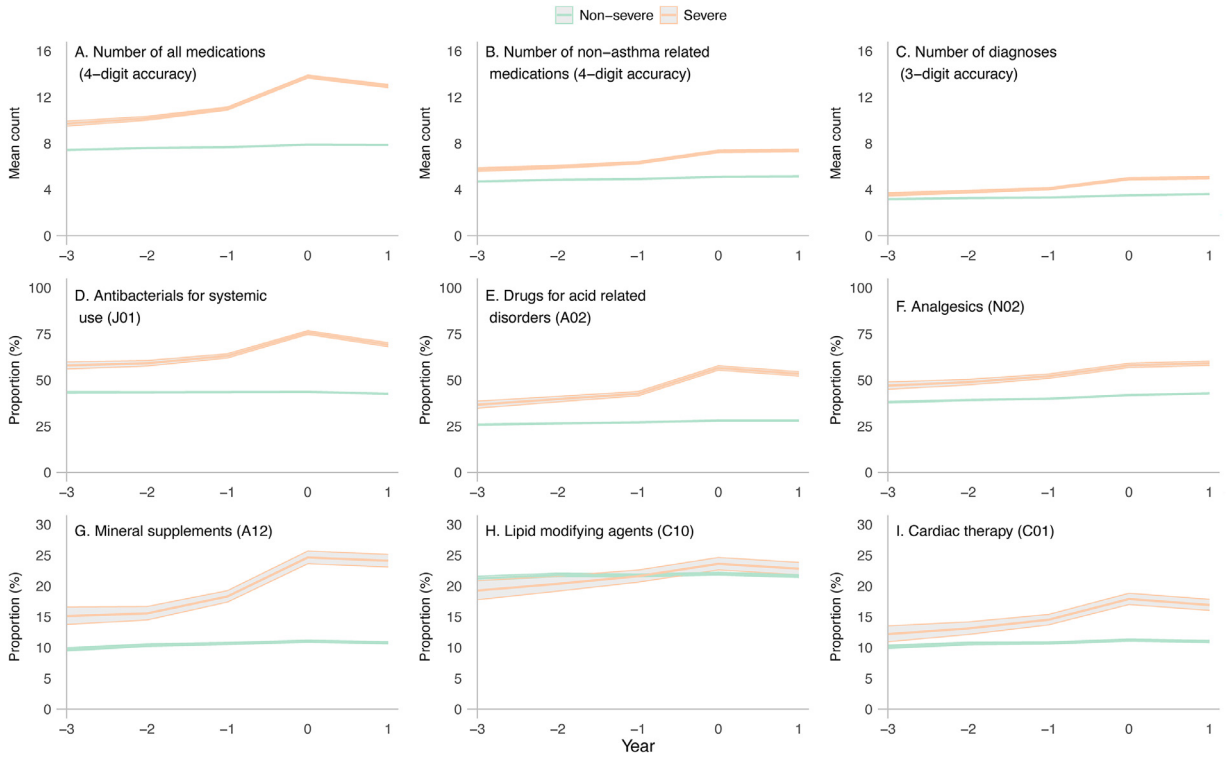


**Figure 5.** Longitudinal patterns of variables associated with the development of severe asthma. Year 0 indicates the first severe asthma year for severe and a matched control year for nonsevere. The analysis included 6908 individuals with severe asthma and 126,570 nonsevere cases. The lines bounding the trend line represent 95% CI. The *y*-axis values represent mean yearly counts (A-C) and proportions of patients purchasing the given medication (D-I).

analysis based on randomized controlled trials which reported that although statin use did not affect lung function of patients with asthma, it improved the symptoms of asthma and reduced inflammation.[25] The greater use of some medications, such as antibiotics[24] and antihistamines, is likely due to the management of more severe symptoms of asthma, whereas the greater use of medications for gastroesophageal reflux disease likely arises from the use of corticosteroids. Gastroesophageal reflux disease can also aggravate the symptoms of asthma. These findings indicate that cues to the development of severe asthma can be obtained already years before its onset.

A previous Finnish cross-sectional study on adult-onset severe asthma found that male sex, ever smoking, chronic comorbidities, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, and having more than or equal to 2 siblings (describing early life factors) were associated with severe asthma.[26] In our study, we did not find smoking to be an important predictor. This and the observed differences in smoking status for patients with nonsevere and severe asthma can be potentially explained by the high proportion of missingness or by a phenomenon that fewer patients with severe asthma smoke due to their poor condition. A cohort study on Swedish adults with asthma identified impaired lung function, wheeze, dyspnea, and nighttime awakenings due to respiratory symptoms as long-term risk factors for severe asthma.[27] Another study in Sweden used a class analysis and identified 4 distinct trajectories of severe asthma: consistently severe asthma, gradual-onset severe asthma, intermittent severe asthma, and sudden-onset severe asthma.[12] Defining features of the classes were high ICS use and prevalent osteoporosis in the consistently severe asthma class, development of comorbidities, such as allergy, rhinitis, nasal polyps, and atopic dermatitis concomitantly with the severe asthma onset in the gradual-onset severe asthma and sudden-onset severe asthma classes.[12] The authors also found that once severe asthma is established, the morbidity burden of the disease appears similar across the classes.[12] Similar risk factor profiles, including recurrent respiratory infections, gastroesophageal reflux, and severe sinus disease, have also been identified in another study on asthma exacerbations in patients with severe asthma.[20]

Although several of the risk factors for severe asthma identified in this study overlap with those of asthma exacerbations and the distinct severe asthma classes, the risk factor profile we identified can be considered clinically meaningful and used to single out high-risk patients at early stages. Such tools are currently lacking in health care yet urgently needed as severe asthma is associated with a high economic burden[7,8] and psychological distress of the patients.[28] The negative predictive values of our models and risk score calculators were very high, indicating that patients not fitting the risk profile are very unlikely to develop severe asthma. However, the calculators had relatively low positive predictive values, and they were based on a single data set from one country with limitations on several potentially informative variables. For better clinical applicability and generalizability, validation with heterogeneous data sets and varying variable availability should be done. With correct tools, resources could be potentially dedicated to patients exhibiting the risk factors, allowing for closer monitoring and clinical evaluation.

The strengths of this register-based study include a large nationwide sample covering practically all Finnish citizens. Furthermore, the data-driven approach we used to identify the predictors of severe asthma provided a combination of the most significant factors, while controlling for collinearity and overfitting. As these variables were not predetermined, it enabled the discovery of new associations. We also performed a series of sensitivity analyses that supported the main findings. This study has also some limitations. Our data did not capture information on the frequency of severe exacerbations, clinical examinations, and laboratory tests other than BEC, and we did not have information on socioeconomic variables, family history, allergic triggers, or environmental factors, limiting the type of predictors considered in our models. The positive predictive value of our model and risk score calculator was also relatively low, although comparable to other risk scores.[16,17] The study population covered only 1 country,

and to ensure the applicability of the findings in practice, data from other countries and diverse data sets would be needed. Finally, we used the term severe asthma through the paper, but as information content in the registers is not directly available as guidelined,[14] our definition could also be referred to as severe uncontrolled asthma.

In conclusion, the findings of this study identify the risk profile for the development of severe asthma and demonstrate that many of these factors are observed a year before the onset of severe asthma. Specifically, being 51 to 60 years old, having chronic sinusitis, and having BEC more than or equal to 600 cells/μL conferred the highest risk of developing severe asthma in the following years. More research is needed to establish practices on how these factors could be considered in care decisions of individual patients.

## Acknowledgment

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## Disclosures

Dr Ilmarinen and Dr Idänpään-Heikkilä are employees of GSK Oy. Dr Ylisaukko-oja is owner of MedEngine Oy. Dr Mehtälä and Dr Jylhävä are employees of MedEngine Oy. Dr Viinanen reports receiving personal fees for lectures, advisory board meetings, and consulting from Airsonett AB, ALK, AstraZeneca, Boehringer-Ingelheim, Chiesi Pharma, Sanofi, and GlaxoSmithKline, outside the current work. Dr Kankaanranta reports receiving personal fees for lectures and providing consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi Pharma, Covis Pharma, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Orion Pharma, and SanofiGenzyme, outside the current work. Dr Lehtimäki reports receiving personal fees for lectures, advisory board meetings, and consulting from ALK, AstraZeneca, Berlin Chemie, Boehringer-Ingelheim, Chiesi Pharma, GlaxoSmithKline, Menarini, Novartis, Orion Pharma, and SanofiGenzyme, outside the current work.

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## Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2025.03.002.

## References

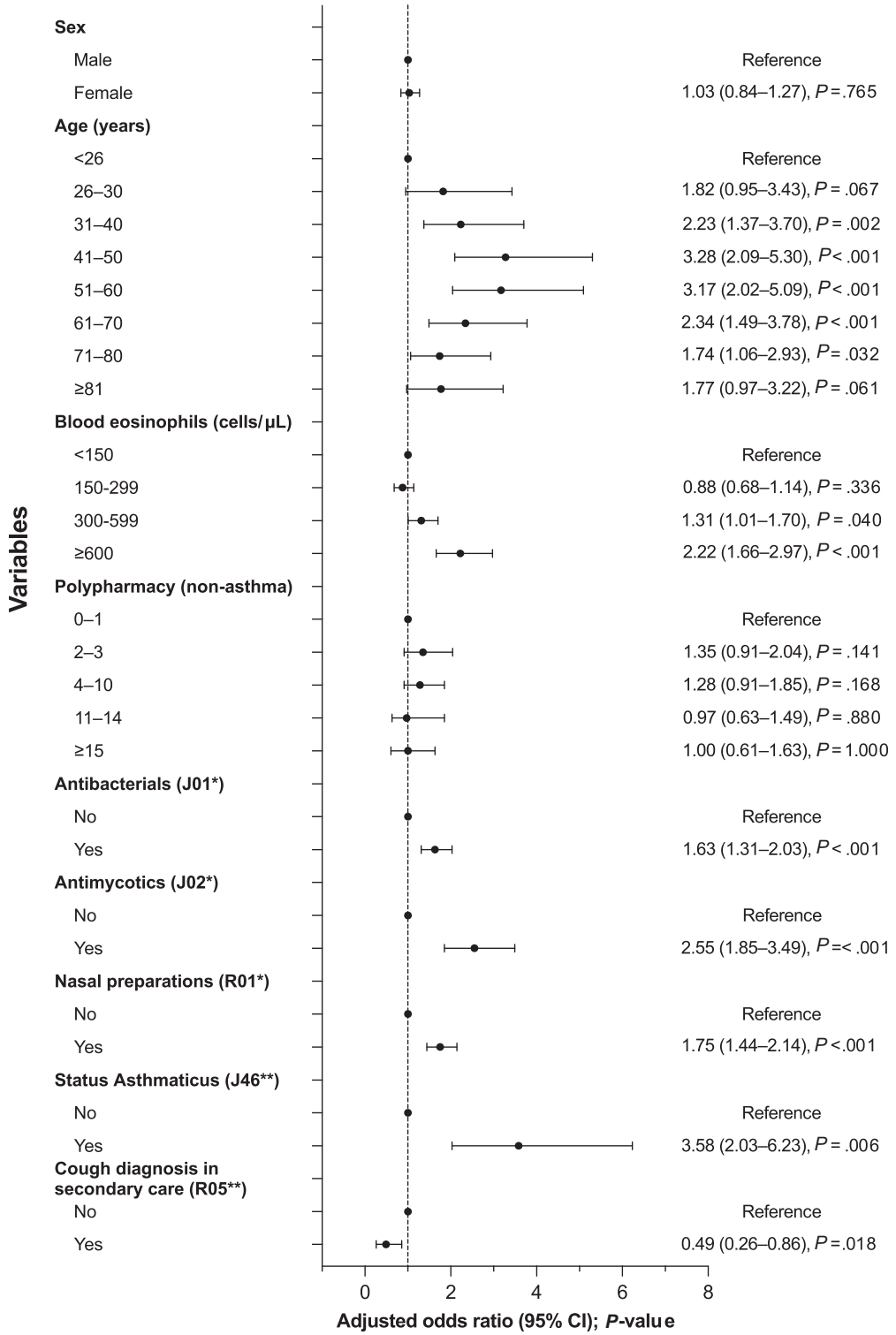
1. The global asthma report. Accessed September 14, 2023. Available at: http://globalasthmareport.org/2018/index.html.
2. Hekking PPW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135(4):896–902.
3. Rönnebjerg L, Axelsson M, Kankaanranta H, Backman H, Rådinger M, Lundbäck B, et al. Severe asthma in a general population study: prevalence and clinical characteristics. *J Asthma Allergy*. 2021;14:1105–1115.
4. Hansen S, von Bülow A, Sandin P, Ernstsson O, Janson C, Lehtimäki L, et al. Prevalence and management of severe asthma in the Nordic countries: findings from the NORDSTAR cohort. *ERJ Open Res*. 2023;9(2):00687–02022.
5. Heaney LG, Perez De Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and noneosinophilic asthma. *Chest*. 2021;160(3):814–830.
6. Ilmarinen P, Tuomisto LE, Niemelä O, Kankaanranta H. Prevalence of patients eligible for anti-IL-5 treatment in a cohort of adult-onset asthma. *J Allergy Clin Immunol Pract*. 2019;7(1). 165-174.e4.
7. Sullivan PW, Campbell JD, Ghushchyan VH, Globe G, Lange J, Woolley JM. Characterizing the severe asthma population in the United States: claims-based analysis of three treatment cohorts in the year prior to treatment escalation. *J Asthma*. 2015;52(7):669–680.
8. Inoue H, Kozawa M, Milligan KL, Funakubo M, Igarashi A, Loefroth E. A retrospective cohort study evaluating healthcare resource utilization in patients with asthma in Japan. *NPJ Prim Care Respir Med*. 2019;29(1):13.
9. Hossny E, Caraballo L, Casale T, El-Gamal Y, Rosenwasser L. Severe asthma and quality of life. *World Allergy Organ J*. 2017;10(1):28.
10. Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax*. 2022;77(2):199–202.
11. Kimura H, Konno S, Makita H, Taniguchi N, Shimizu K, Suzuki M, et al. Prospective predictors of exacerbation status in severe asthma over a 3-year follow-up. *Clin Exp Allergy*. 2018;48(9):1137–1146.
12. von Bülow A, Hansen S, Sandin P, Ernstsson O, Janson C, Lehtimäki L, et al. Severe asthma trajectories in adults: findings from the NORDSTAR cohort. *Eur Respir J*. 2023;62(3):2202474.
13. Kankaanranta H, Viinanen A, Ilmarinen P, Hisinger-Mölkänen H, Mehtälä J, Ylisaukko-Oja T, et al. Comorbidity burden in severe and nonsevere asthma: a nationwide observational study (FINASTHMA). *J Allergy Clin Immunol Pract*. 2024;12(1). 135-145.e9.
14. Global Initiative for Asthma - GINA. GINA main report: global strategy for asthma management and prevention 2024; 2024. Accessed July 31, 2024. Available at: https://ginasthma.org/2024-report/.
15. Monaghan TF, Rahman SN, Agudelo CW, Wein AJ, Lazar JM, Everaert K, et al. Foundational statistical principles in medical research: sensitivity, specificity, positive predictive value, and negative predictive value. *Medicina (Kaunas)*. 2021;57(5):503.
16. Brindle PM, McConnachie A, Upton MN, Hart CL, Davey Smith G, Watt GCM. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. *Br J Gen Pract*. 2005;55(520):838–845.
17. Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care*. 2003;26(3):725–731.
18. Zein JG, Dweik RA, Comhair SA, Bleecker ER, Moore WC, Peters SP, et al. Asthma is more severe in older adults. *PLoS One*. 2015;10(7):e0133490.
19. Akuthota P. Asthma exacerbations: patient features and potential long-term implications. *Adv Exp Med Biol*. 2023;1426:253–263.
20. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J*. 2005;26(5):812–818.
21. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med*. 2015;3(11):849–858.
22. Gold M, Bacharier LB, Hartert TV, Rosas-Salazar C. Use of antibiotics in infancy and asthma in childhood: confounded or causal relationship? A critical review of the literature. *J Allergy Clin Immunol Pract*. 2024;12(10):2669–2677.
23. Choi J, Park SJ, Park YJ, Hong J, Jeong S, Chang J, et al. Association between antibiotics and asthma risk among adults aged over 40 years: a nationally representative retrospective cohort study. *BMJ Open Respir Res*. 2023;10(1):e001643.
24. Flinkman E, Vähätalo I, Tuomisto LE, Lehtimäki L, Nieminen P, Niemelä O, et al. Association between blood eosinophils and neutrophils with clinical features in adult-onset asthma. *J Allergy Clin Immunol Pract*. 2023;11(3). 811-821.e5.
25. Zhang QX, Zhang HF, Lu XT, Zhao J, Xu QX. Statins improve asthma symptoms by suppressing inflammation: a meta-analysis based on RCTs. *Eur Rev Med Pharmacol Sci*. 2022;26(22):8401–8410.
26. Toppila-Salmi S, Lemmetyinen R, Chanoine S, Karjalainen J, Pekkanen J, Bousquet J, et al. Risk factors for severe adult-onset asthma: a multi-factor approach. *BMC Pulm Med*. 2021;21(1):1–11.
27. Backman H, Stridsman C, Jansson SA, Hedman L, Kankaanranta H, Lindberg A, et al. Risk factors for severe asthma among adults with asthma. *Eur Respir J*. 2020;56(suppl 64):4642.
28. Dafauce L, Romero D, Carpio C, Barga P, Quirce S, Villasante C, et al. Psycho-demographic profile in severe asthma and effect of emotional mood disorders and hyperventilation syndrome on quality of life. *BMC Psychol*. 2021;9(1):3.

## Supplementary Data

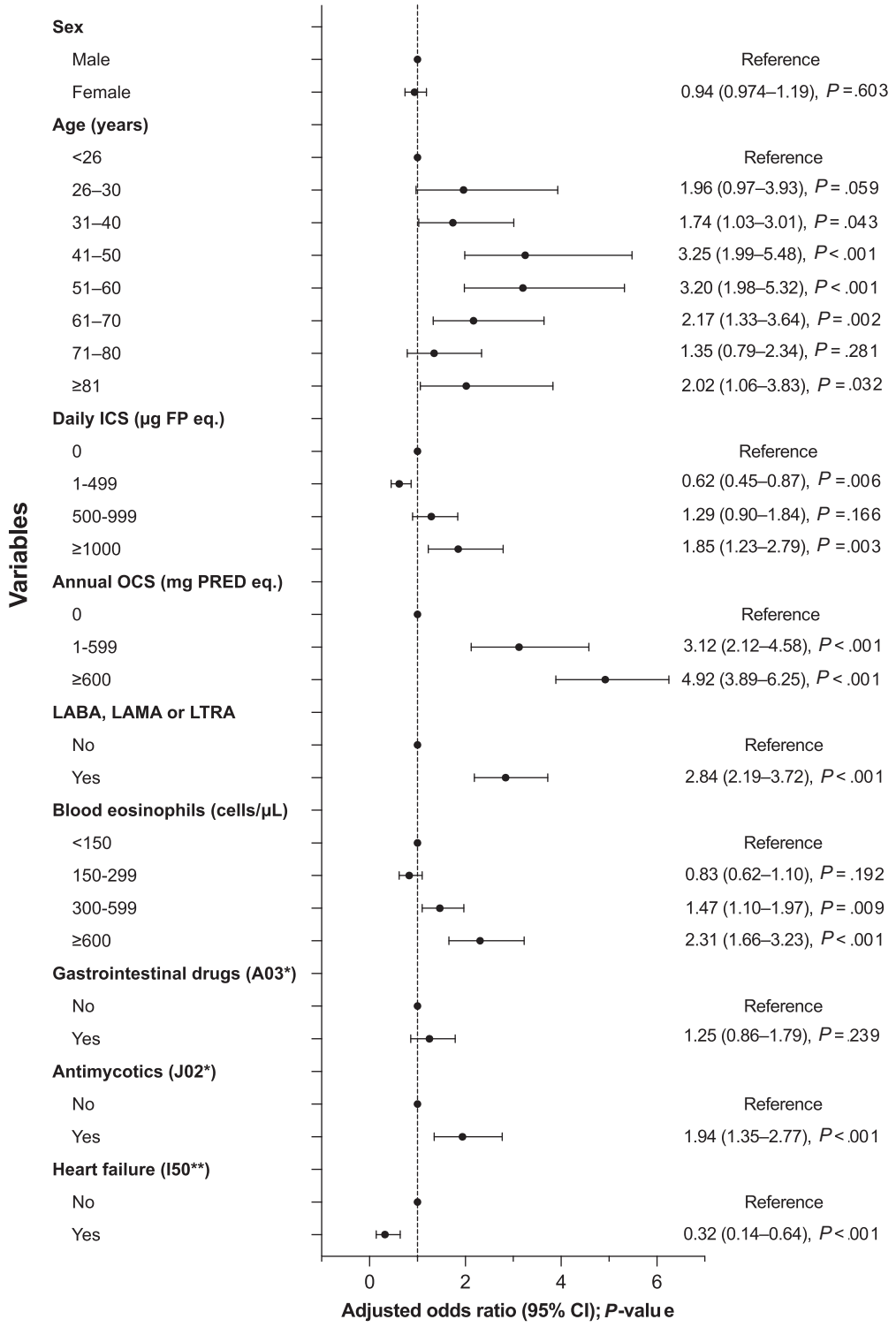
### eMethods

*Variables*

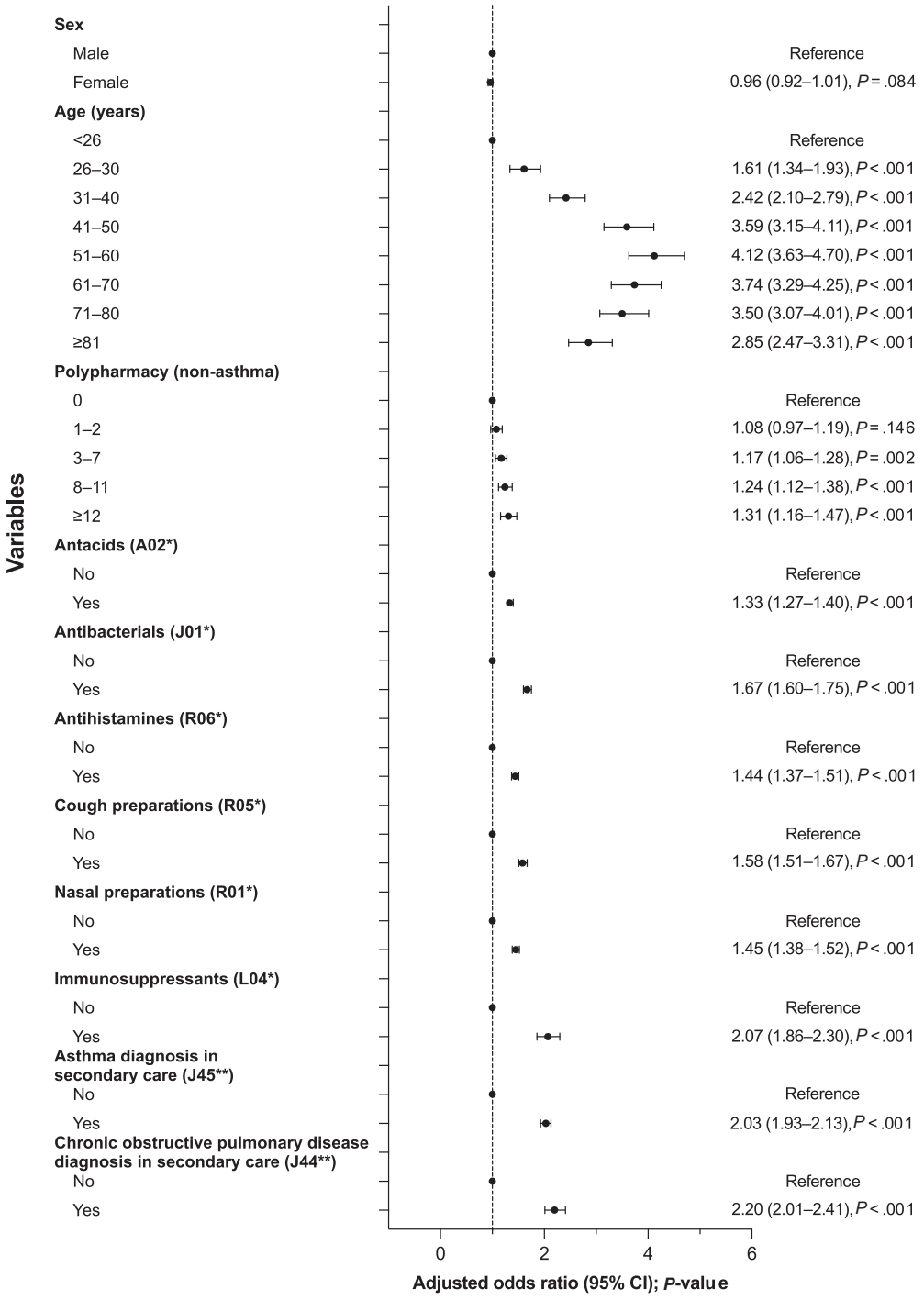
- For each patient, the inhaled corticosteroid dose was calculated as micrograms of fluticasone propionate equivalents per day and the cumulative oral corticosteroid dose as milligrams of prednisolone equivalents per year. Correction coefficients for inhaled corticosteroids in relation to fluticasone propionate and oral corticosteroids in relation to prednisolone are presented in eTables 1 and 2, respectively.
- Data on diagnoses (not including the private sector) were collected from the Care Register for Health Care (The Finnish Institute for Health and Welfare).
- Number of diagnoses was counted with a 3-digit diagnosis code accuracy (International Classification of Diseases, 10th Edition codes).
- All medications were collected from the Prescription Centre (The Social Insurance Institution of Finland) and used with specific accuracy or as Anatomical Therapeutic Chemical (ATC) categories.
- Reimbursement decisions, their start date, reimbursement codes, and underlying diagnosis were collected from the Register for Medical Reimbursement Rights (The Social Insurance Institution of Finland).
- Polypharmacy was defined as the number of all different medications (ATC codes considered with a 4-digit accuracy).
- Nonasthma-related polypharmacy was defined as the number of different medications (ATC codes with 4-digit accuracy) excluding R*, J*, and H02* codes.
- Asthma medications were defined as ATC codes R03* and H02*.
- Dates and causes of deaths were acquired from the Causes of Death Register (Statistics Finland).
- All the above-mentioned data have a complete nationwide coverage of the Finnish health care and drug prescription registries without any loss to follow-up. In Finland, all citizens are included in these registries regardless of social status, income, or insurance; hence, the data can be considered representative of the entire population with a negligible selection bias. However, the private sector is not covered by the Care Register of Health care.
- Body mass index, smoking status (current, former, or never), and blood eosinophil count were ascertained from the local hospital data lakes.
- Data on eosinophil counts (cells per microliter) have been obtained from laboratory data contained in the electronic health record systems.



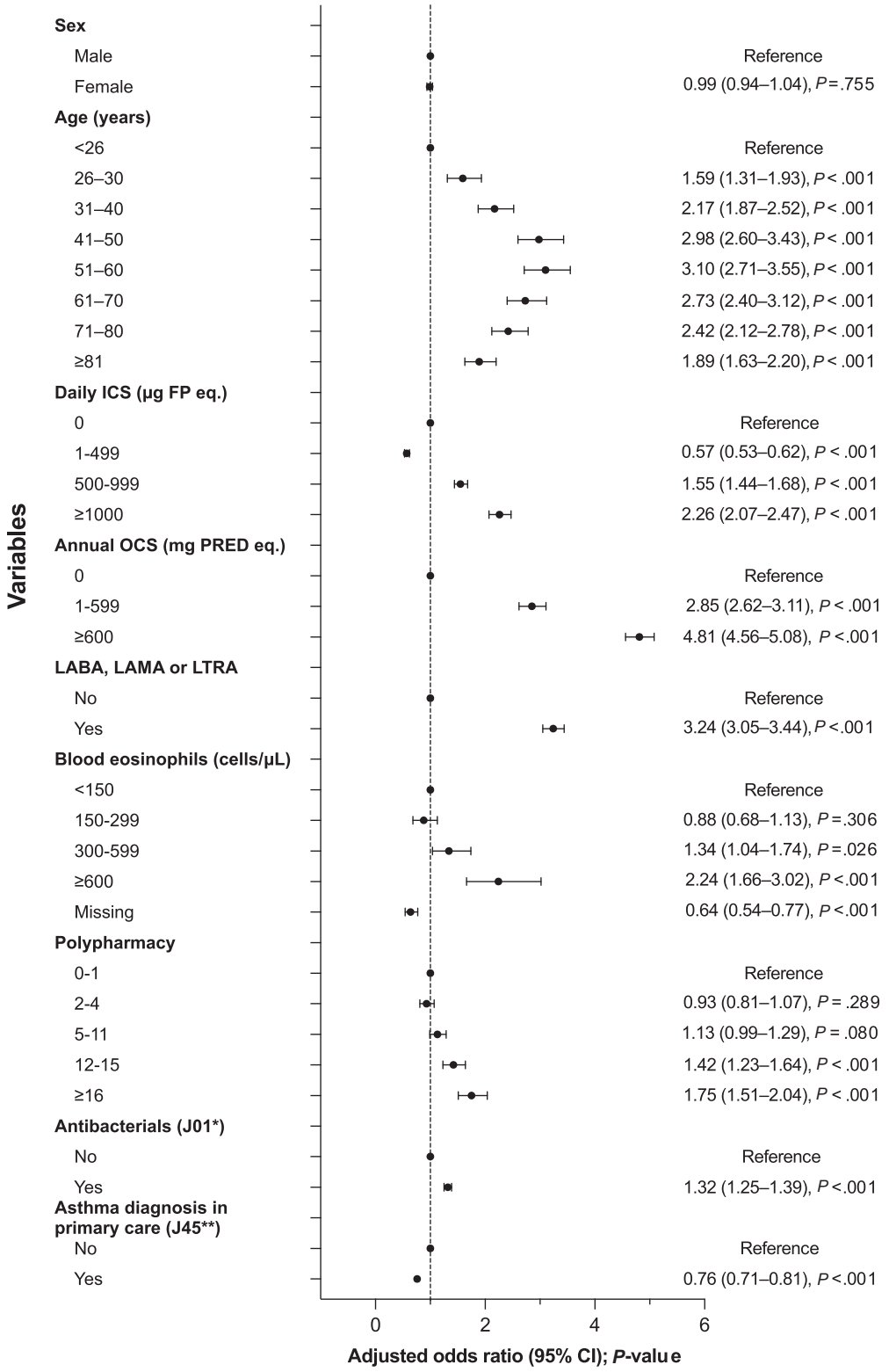

**eFigure 1.** Logistic regression model to identify the factors associated with the development of severe asthma in the population that had blood eosinophil counts available and no co-existing chronic obstructive pulmonary disease (primary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code.



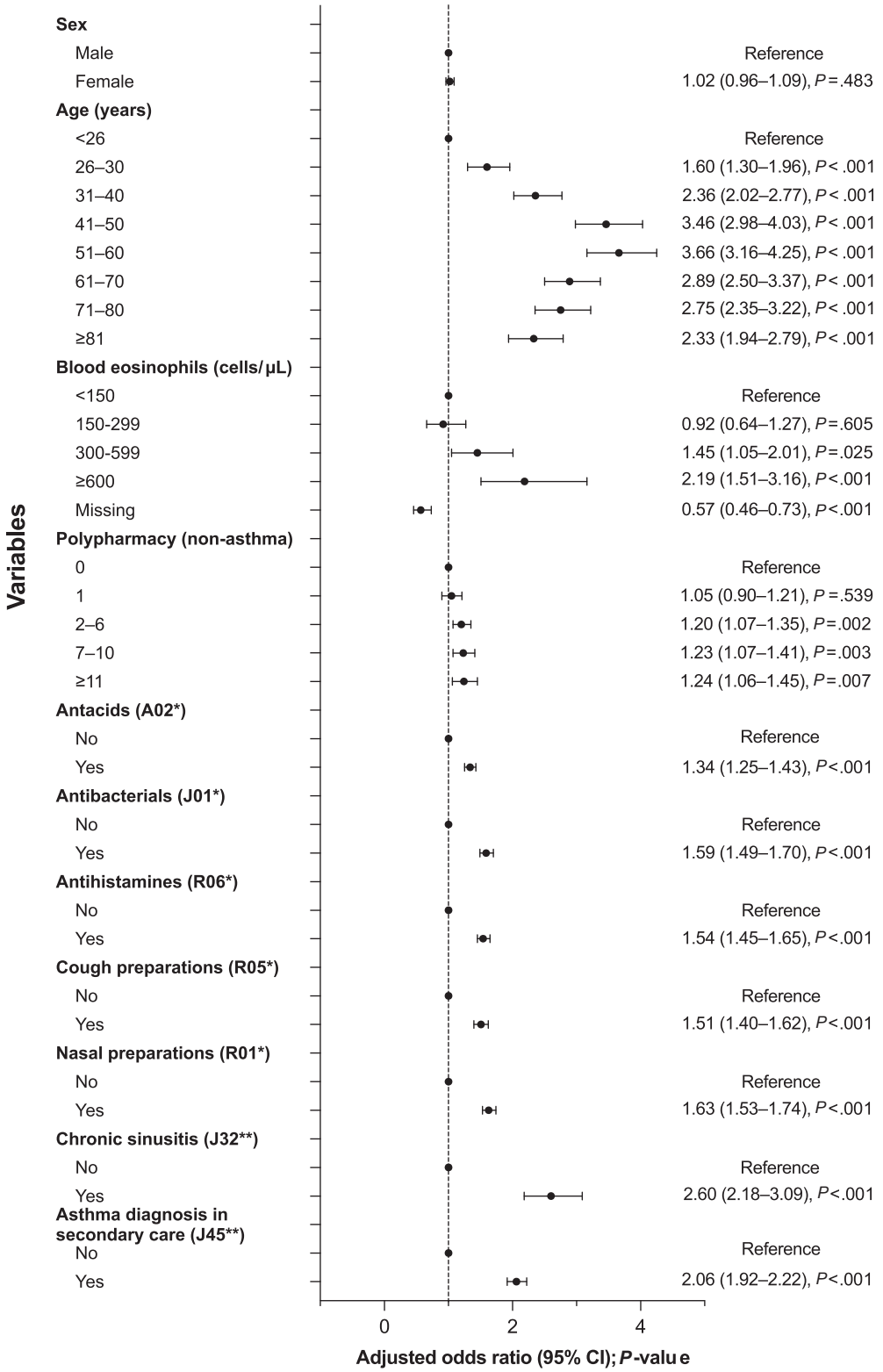

**eFigure 2.** Logistic regression model to identify the factors associated with the development of severe asthma in the population that had blood eosinophil counts available, no co-existing chronic obstructive pulmonary disease, and asthma medications added to the model predictors (the secondary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRED eq., prednisolone equivalents.



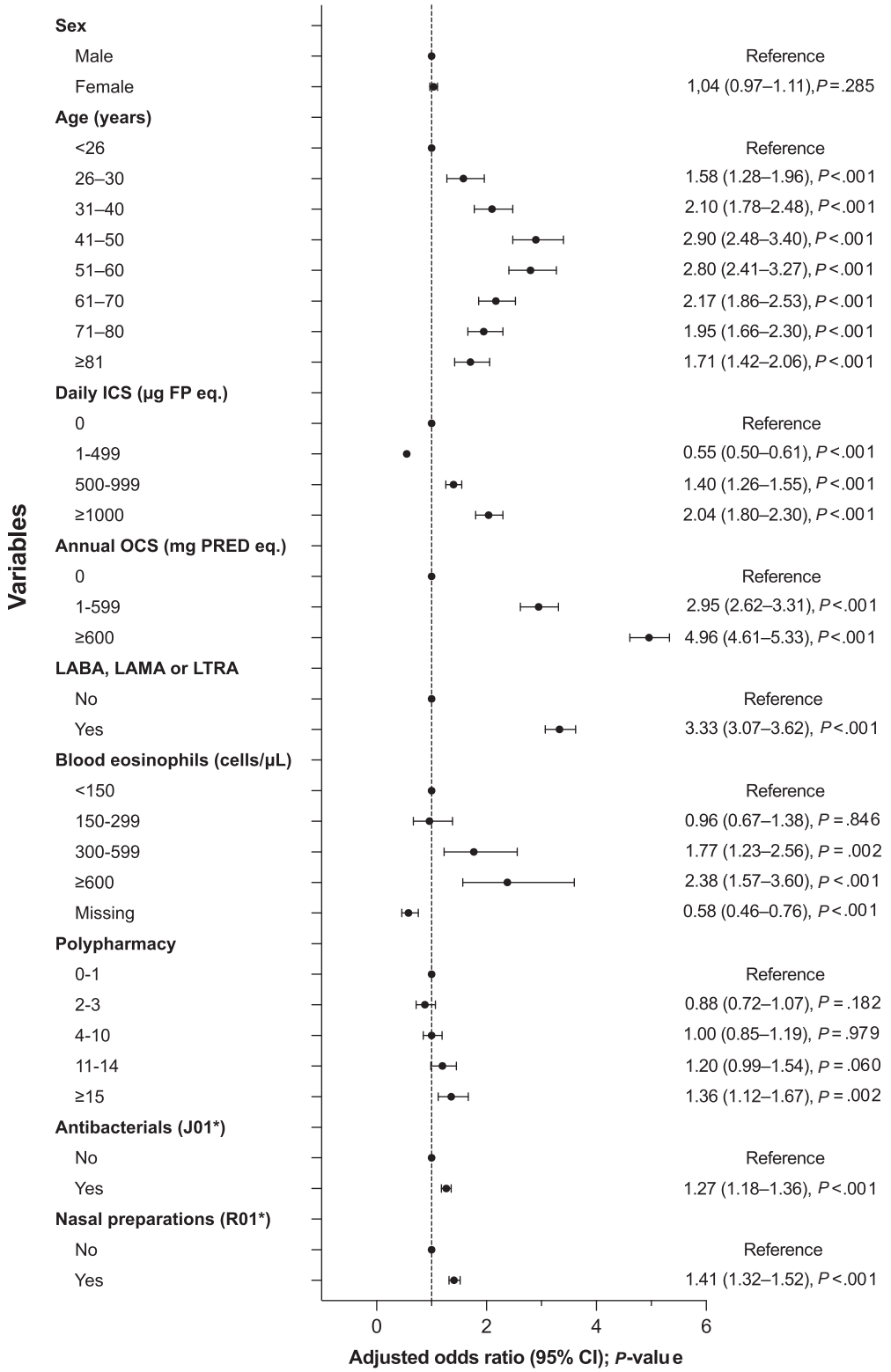

**eFigure 3.** Logistic regression model to identify the factors associated with the development of severe asthma in the population including patients with chronic obstructive pulmonary disease (the primary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code.



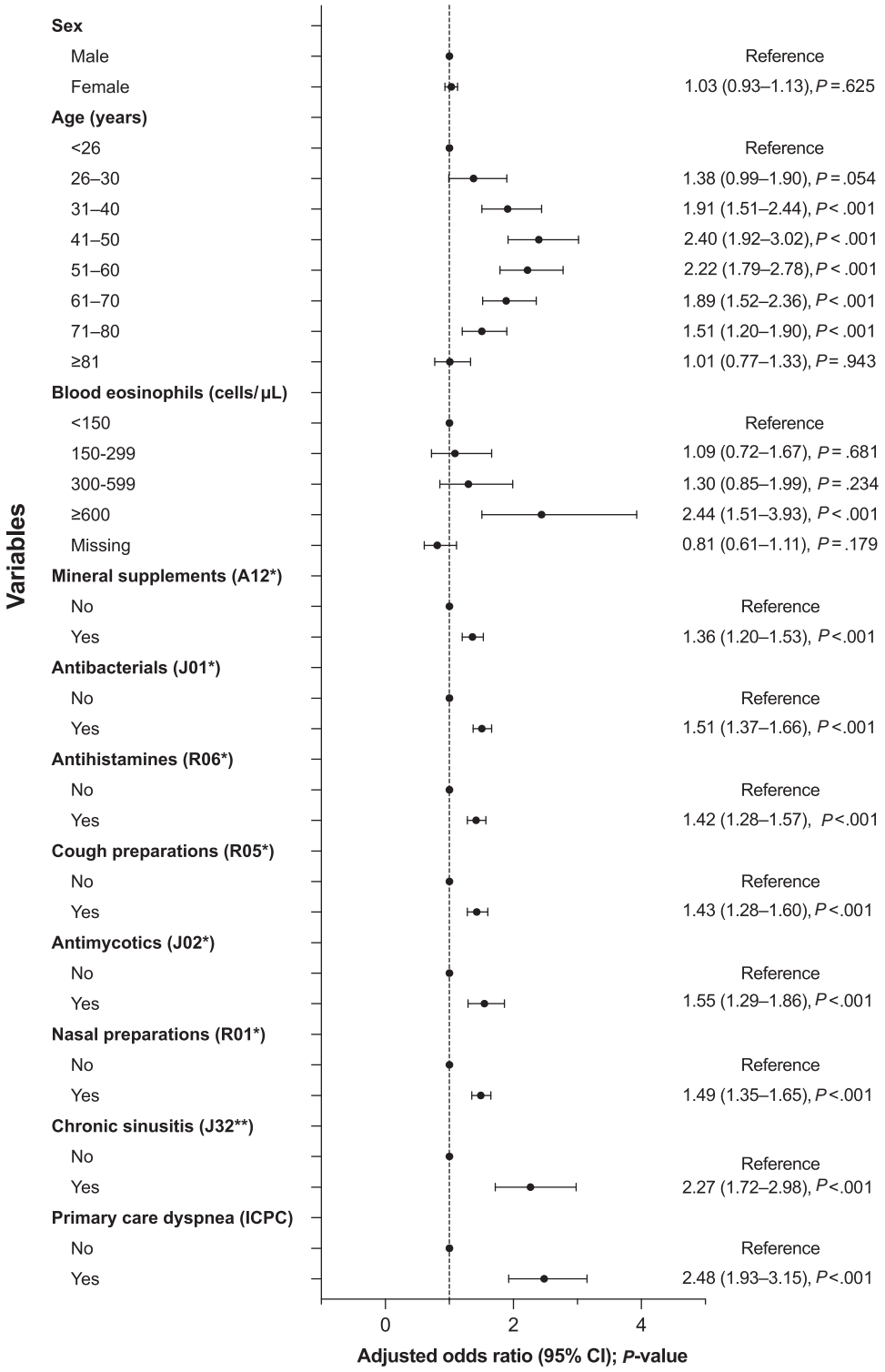

**eFigure 4.** Logistic regression model to identify the factors associated with the development of severe asthma in the population including patients with chronic obstructive pulmonary disease (the secondary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRED eq., prednisolone equivalents.



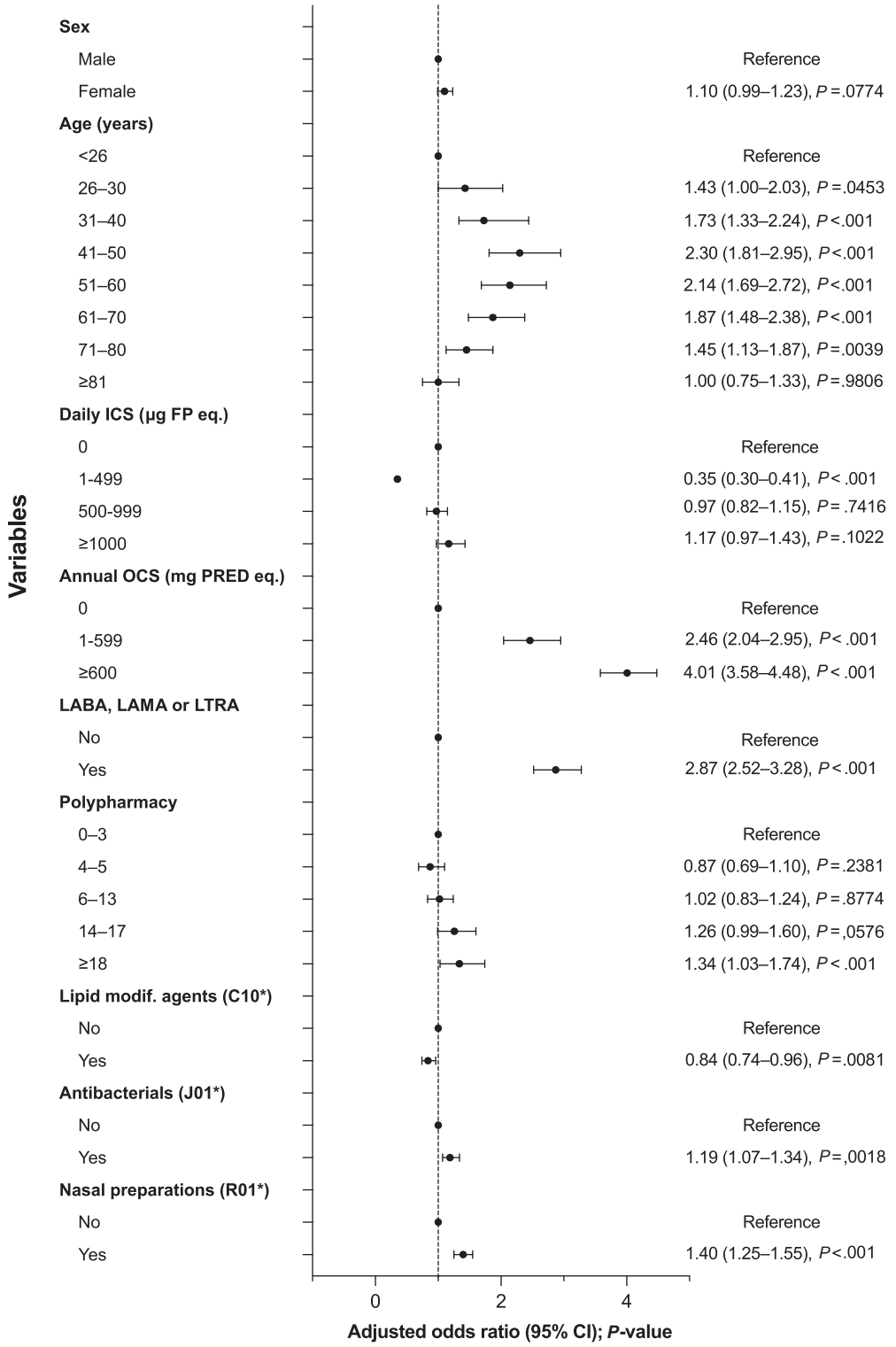

**eFigure 5.** Logistic regression model to identify the factors associated with the development of severe asthma in the population excluding patients having other indications for oral corticosteroid use (the primary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code.



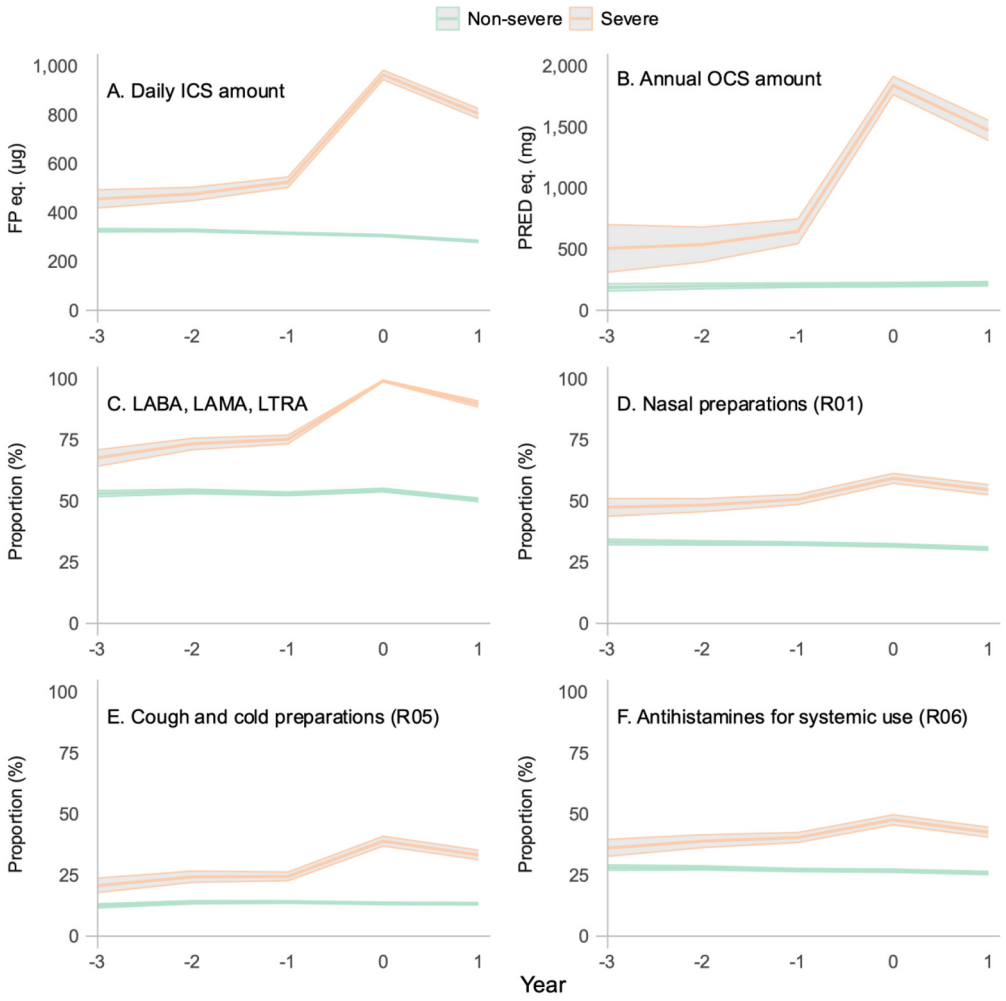

**eFigure 6.** Logistic regression model to identify the factors associated with the development of severe asthma in the population excluding patients having other indications for oral corticosteroid use (the secondary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; OCS, oral corticosteroid; PRED eq., prednisolone equivalents.



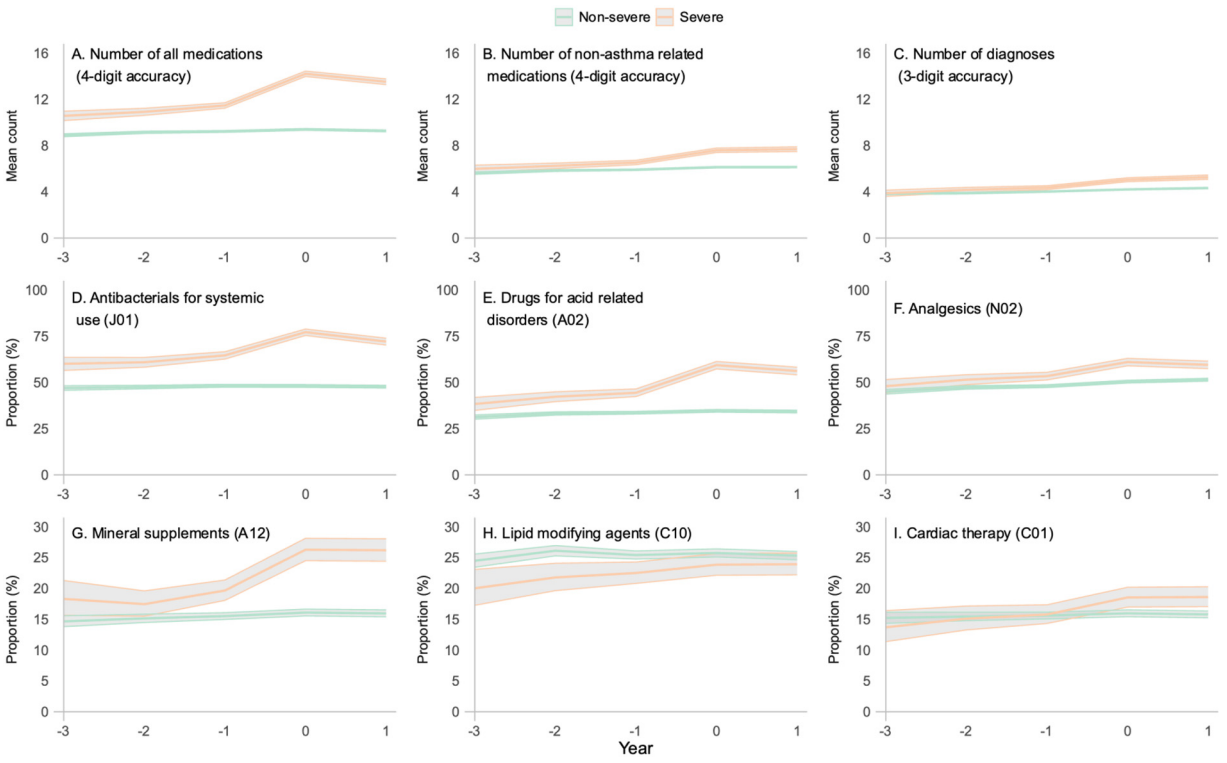

**eFigure 7.** Logistic regression model to identify the factors associated with the development of severe asthma in the population excluding patients not having a special reimbursement decision for asthma medication before January 1, 2014 (the primary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. ICPC-2, International Classification of Primary Care, second edition.




**eFigure 8.** Logistic regression model to identify the factors associated with the development of severe asthma in the population excluding patients not having a special reimbursement decision for asthma medication before January 1, 2014 (the secondary model). The figure illustrates adjusted odds ratios from a single model including all the presented variables. *Anatomical Therapeutic Classification code; **International Classification of Diseases, 10th revision code. FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; max, maximum; OCS, oral corticosteroid; PRED eq., prednisolone equivalents.




**eFigure 9.** Longitudinal patterns of variables associated with the development of severe asthma. Year 0 indicates the first severe asthma year for severe and a matched control year for nonsevere. Patients not having a special reimbursement decision for asthma medication before January 1, 2014, were excluded. The *y*-axis values represent yearly averages (A and B) and proportions of patients purchasing the given medication (C-F). The lines bounding the trend line represent 95% CIs. ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA; OCS, oral corticosteroid.




**eFigure 10.** Longitudinal patterns of variables associated with the development of severe asthma. Year 0 indicates the first severe asthma year for severe and a matched control year for nonsevere. Patients not having a special reimbursement decision for asthma medication before January 1, 2014, were excluded. The *y*-axis values represent mean yearly counts (A-C) and proportions of patients purchasing the given medication (D-I). The lines bounding the trend line represent 95% CIs.

**eTable 1**
Definition of the 3 Asthma Severity Groups

| Subgroup | Definition |
|---|---|
| Severe asthma | Patients fulfilling the criteria for severe asthma (1+2a or 1+2b) for >1 calendar years between January 1, 2014 and December 31, 2020 or 3 at any time point. |
| Transiently severe asthma | Patients fulfilling the criteria for severe asthma (1+2a or 1+2b) for 1 calendar year between January 1, 2014 and December 31, 2020 |
| Nonsevere asthma | Patients with asthma not meeting the annual criteria for severe or transiently severe asthma at any year between January 1, 2014 and December 31, 2020 |

**eTable 2**
Correction Coefficients for Inhaled Corticosteroids in Relation to Fluticasone Propionate

| Inhaled corticosteroid | Correction coefficient | Equipotent dose (μg) with 1000 μg fluticasone propionate |
|---|---|---|
| Beclomethasone | 0.625 | 1600 |
| Beclomethasone small-particle | 1.25 | 800 |
| Budesonide | 0.625 | 1600 |
| Ciclesonide | 1.5625 | 640 |
| Mometasone | 1.25 | 800 |
| Fluticasone furoate | 5.4348 | 184 |

**eTable 3**
Correction Coefficients for Oral Corticosteroids in Relation to Prednisolone

| Oral corticosteroid | Correction coefficient | Equipotent dose (mg) with 10 mg prednisolone |
|---|---|---|
| Dexamethasone | 6.7 | 1.5 |
| Hydrocortisone | 0.3 | 33.3 |
| Methylprednisolone | 1.3 | 7.7 |
| Prednisolone | 1.0 | 10 |
| Prednisone | 1.0 | 10 |

**eTable 4**
Characteristics of the Main Study Population With Patients With a Co-Existing Chronic Obstructive Pulmonary Disease Included

| Characteristic | All (N = 253,165) | Nonsevere (N = 237,600) | Severe (N = 15,565) | *P* value |
|---|---|---|---|---|
| Female, N (%) | 159,032 (62.8) | 148,795 (62.6) | 10,237 (65.8) | <.001 |
| Age | 65.0 (46.1-76.2) | 64.8 (45.2-76.1) | 68.2 (56.7-77.4) | <.001 |
| BMI (kg/m$^2$), continuous | 27.8 (24.1-32.6) | 27.8 (24.0-32.5) | 28.2 (24.3-33.1) | <.001 |
| Missing, N | 219,367 (86.6) | 208,277 (87.7) | 11,090 (71.2) | <.001 |
| Smoking status, N (%) | | | | <.001 |
| Current | 13,736 (34.2) | 12,329 (35.0) | 1407 (28.6) | |
| Former | 7594 (18.9) | 6469 (18.3) | 1125 (22.9) | |
| Never | 18,865 (46.9) | 16,474 (46.7) | 2391 (48.6) | |
| Missing | 212,970 (84.1) | 202,328 (85.2) | 10,642 (68.4) | <.001 |
| Daily ICS dose, FP eq. | 142 (29-333) | 123 (23-286) | 629 (424-943) | <.001 |
| Annual OCS dose, mg PRED eq. | 21 (0-171) | 0 (0-171) | 1186 (691-2229) | <.001 |
| SABA canisters per year | 1.0 (0.4-2.14) | 1.0 (0.4-2.0) | 2.7 (1.3-5.3) | <.001 |
| LABA, LAMA, or LTRA use, N (%) | 165,396 (65.3) | 149,847 (63.1) | 15,549 (99.9) | <.001 |
| ICS alone or in combination, N (%) | 233,721 (92.4) | 218,162 (91.8) | 15,559 (100.0) | <.001 |
| LABA alone or in combination, N (%) | 149,703 (59.1) | 134,465 (56.6) | 15,238 (97.9) | <.001 |
| LAMA alone or in combination, N (%) | 39,794 (15.7) | 30,701 (12.9) | 9093 (58.4) | <.001 |
| Nasal corticosteroids, N (%) | 139,694 (55.2) | 128,642 (54.1) | 11,052 (71.0) | <.001 |
| No. of all medications (polypharmacy) | 20 (14-27) | 20 (14-26) | 29 (23-35) | <.001 |
| No. of nonasthma-related medications | 13 (8-18) | 12.00 (8-18) | 18 (13-23) | <.001 |
| Urticaria, N (%) | 6418 (2.5) | 5712 (2.4) | 706 (4.5) | <.001 |
| Atopic dermatitis, N (%) | 11,593 (4.6) | 10,793 (4.5) | 800 (5.1) | .003 |
| Allergic rhinitis, N (%) | 20,233 (8.0) | 18,896 (8.0) | 1337 (8.6) | .018 |
| Rhinosinusitis or nasal polyps, N (%) | 51,003 (20.1) | 45,661 (19.2) | 5342 (34.3) | <.001 |
| Allergic rhinoconjunctivitis, N (%) | 21,217 (8.4) | 19,605 (8.3) | 1612 (10.4) | <.001 |
| BEC, cells/μL (max) | 0.25 (0.14-0.42) | 0.24 (0.13-0.40) | 0.31 (0.17-0.57) | <.001 |
| Missing, N | 229,224 (90.5) | 217,837 (91.7) | 11,387 (73.2) | <.001 |

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRED eq., prednisolone equivalents; Q1, quartile 1; Q3, quartile 3; SABA, short-acting $\beta_2$-agonist.

NOTE. Values are presented as median (Q1-Q3), unless otherwise indicated. Quantification of missing values is presented only for variables that do have missing values.

Diagnoses are based on the International Classification of Diseases, 10th revision diagnostic codes over the whole follow-up. The number of medications and number of nonasthma-related medications (excluding R*, J*, and H02* codes) are based on purchased drugs and considered at a 4-digit accuracy over the whole follow-up. The reported *P* value is for comparison of severe and nonsevere groups. For categorical variables, the *P* value is comparing all categories excluding the missing category, for which separate comparison was performed.

**eTable 5**
Characteristics of the Main Study Population With Patients With Transiently Severe Asthma Included

| Characteristic | All (N = 242,164) | Nonsevere (N = 211,946) | Transiently severe (N = 19,137) | Severe (N = 11,081) | *P* value |
|---|---|---|---|---|---|
| Female, N (%) | 158,694 (65.5) | 137,518 (64.9) | 13,349 (69.8) | 7827 (70.6) | <.001 |
| Age | 63.4 (43.9-75.6) | 62.9 (42.7-75.4) | 65.2 (51.3-77.0) | 65.8 (53.1-76.3) | |
| BMI (kg/m$^2$), continuous | 27.9 (24.2-32.7) | 27.8 (24.1-32.5) | 28.4 (24.7-33.2) | 28.4 (24.6-33.1) | <.001 |
| Missing, N (%) | 209,842 (86.7) | 187,073 (88.3) | 14,920 (80.0) | 7849 (70.8) | <.001 |
| Smoking status, N (%) | | | | | <.001 |
| Current | 11,243 (29.4) | 9260 (31.0) | 1244 (25.4) | 739 (21.0) | |
| Former | 6117 (16.0) | 4675 (15.7) | 835 (17.0) | 607 (17.3) | |
| Never | 20,892 (54.6) | 15,903 (53.3) | 2819 (57.6) | 2170 (61.7) | |
| Missing | 203,912 (83.2) | 182,108 (85.9) | 14,239 (74.4) | 7565 (68.3) | <.001 |
| Daily ICS dose, FP eq. | 148 (35-352) | 119 (23-284) | 379 (226-610) | 633 (424-949) | <.001 |
| Annual OCS dose, mg PRED eq. | 21 (0-229) | 0 (0-143) | 374 (236-700) | 1143 (686-2171) | <.001 |
| SABA canisters per year | 1.0 (0.4-2.1) | 1.0 (0.4-2.0) | 1.7 (0.9-3.3) | 2.6 (1.1-4.9) | <.001 |
| LABA, LAMA or LTRA use, N (%) | 157,014 (64.8) | 126,812 (59.8) | 19,137 (100.0) | 11,065 (99.9) | <.001 |
| ICS alone or in combination, N (%) | 224,012 (92.5) | 193,800 (91.4) | 19,137 (100.0) | 11,075 (99.9) | <.001 |
| LABA alone or in combination, N (%) | 142,067 (58.7) | 113,041 (53.3) | 18,239 (95.3) | 10,787 (97.3) | <.001 |
| LAMA alone or in combination, N (%) | 25,254 (10.4) | 14,841 (7.0) | 5210 (27.2) | 5203 (47.0) | <.001 |
| Nasal corticosteroids, N (%) | 141,189 (58.3) | 119,329 (56.3) | 13,333 (69.7) | 8527 (77.0%) | <.001 |
| No. of all medications (polypharmacy) | 20 (14-27) | 19 (14-26) | 25 (20-32) | 28 (22-35) | <.001 |
| No. of nonasthma-related medications | 13 (8-18) | 12 (8-17) | 16 (11-21) | 17 (12-23) | <.001 |
| Urticaria, N (%) | 6588 (2.7) | 5316 (2.5) | 696 (3.6) | 576 (5.2) | <.001 |
| Atopic dermatitis, N (%) | 11,747 (4.9) | 10,174 (4.8) | 921 (4.8) | 652 (5.9) | <.001 |
| Allergic rhinitis, N (%) | 21,272 (8.8) | 18,207 (8.6) | 1886 (9.9) | 1179 (10.6) | <.001 |
| Rhinosinusitis or nasal polyps, N (%) | 52,520 (21.7) | 42,431 (20.0) | 5803 (30.3) | 4286 (38.7) | <.001 |
| Allergic rhinoconjunctivitis, N (%) | 20,899 (8.6) | 17,874 (8.4) | 1833 (9.6) | 1192 (10.8) | <.001 |
| BEC, cells/μL (max) | 0.24 (0.14-0.42) | 0.23 (0.13-0.40) | 0.25 (0.14-0.45) | 0.32 (0.17-0.63) | <.001 |
| Missing, N (%) | 218,848 (90.4) | 195,221 (92.1) | 15,627 (81.7) | 8000 (72.2) | <.001 |

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; FP eq., fluticasone propionate equivalents; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PRED eq., prednisolone equivalents; Q1, quartile 1; Q3, quartile 3; SABA, short-acting $\beta_2$-agonist.
NOTE. Values are presented as median (Q1, Q3), unless otherwise indicated. Quantification of missing values is presented only for variables that do have missing values.
Diagnoses are based on the International Classification of Diseases, 10th revision diagnostic codes over the whole follow-up. The number of medications and number of nonasthma-related medications (excluding R*, J*, and H02* codes) are based on purchased drugs and considered at a 4-digit accuracy over the whole follow-up. The reported *P* value is for comparison of severe, transiently severe and nonsevere groups. For categorical variables, the *P* value is comparing all categories excluding the missing category, for which separate comparison was performed.

**eTable 6**
Risk Score Calculator Based on Regression Coefficients of a Model Which Identified the Factors Associated With the Development of Severe Asthma With Asthma Medications (Anatomical Therapeutic Chemical codes R03* and H02*) Removed From the Model Predictors (Fig 2)

| Criterion | Options | OR | Points |
|---|---|---|---|
| Age | <26 | Ref. | 0 |
| | 26-30 | 1.64 | 2 |
| | 31-40 | 2.45 | 2 |
| | 41-50 | 3.53 | 4 |
| | 51-60 | 3.90 | 4 |
| | 61-70 | 3.30 | 3 |
| | 71-80 | 3.20 | 3 |
| | ≥81 | 2.95 | 3 |
| Blood eosinophils | Not available | | 0 |
| (cells per μL) | <150 | 1.19 | 0 |
| | 150-299 | Ref. | 0 |
| | 300-599 | 1.46 | 1 |
| | ≥600 | 2.50 | 3 |
| Use of antacids in the past year | Yes | 1.40 | 1 |
| Use of antibacterials in the past year | Yes | 1.63 | 2 |
| Use of antihistamines in the past year | Yes | 1.51 | 2 |
| Use of cough preparations in the past year | Yes | 1.47 | 1 |
| Use of nasal preparations in the past year | Yes | 1.55 | 2 |
| Use of immunosuppressants in the past year | Yes | 2.08 | 2 |
| Chronic sinusitis | Yes | 2.48 | 2 |
| Asthma-related secondary care visit in the past year | Yes | 2.09 | 2 |

Abbreviation: OR, odds ratio; Ref., reference.
NOTE. Risk score points were allocated as 0 if the OR was less than 1.20, 1 if OR was 1.20 to 1.49, 2 if OR was 1.50 to 2.49, 3 if OR was 2.50 to 3.49, 4 if OR was 3.50 to 4.49, and 5 if OR was more than or equal to 4.5.

**eTable 7**
Risk Score Calculator Based on Regression Coefficients of a Model Which Identified the Factors Associated With the Development of Severe Asthma, Including Asthma Medications (Anatomical Therapeutic Chemical codes R03* and H02*; Fig 3)

| Criterion | Options | OR | Points |
|---|---|---|---|
| Age | <26 | Ref. | 0 |
| | 26-30 | 1.66 | 2 |
| | 31-40 | 2.23 | 2 |
| | 41-50 | 3.06 | 3 |
| | 51-60 | 3.18 | 3 |
| | 61-70 | 2.72 | 3 |
| | 71-80 | 2.47 | 2 |
| | ≥81 | 2.13 | 2 |
| Current daily ICS dose | 0 | 1.92 | 2 |
| (μg of fluticasone propionate equivalents) | 1-499 | Ref. | 0 |
| | 500-999 | 2.63 | 3 |
| | ≥1000 | 3.67 | 4 |
| OCS doses used in the past year | 0 | Ref. | 0 |
| (mg of prednisolone equivalents) | 1-599 | 2.74 | 3 |
| | ≥600 | 4.63 | 5 |
| Blood eosinophils | Not available | - | 0 |
| (cells per μL) | <150 | 1.16 | 0 |
| | 150-299 | Ref. | 0 |
| | 300-599 | 1.77 | 2 |
| | ≥600 | 2.91 | 3 |
| LAMA, LABA, or LTRA use | Yes | 3.18 | 3 |
| No. of concomitant medications | 0-1 | 1.16 | 0 |
| | 2-4 | Ref. | 0 |
| | 5-11 | 1.28 | 1 |
| | 12-14 | 1.57 | 2 |
| | ≥15 | 1.85 | 2 |
| Use of antibacterials in the past year | Yes | 1.24 | 1 |
| Use of lipid-modifying agents in the past year | No | 1.33 | 1 |
| Use of nasal preparations in the past year | Yes | 1.31 | 1 |
| Asthma-related secondary care visit in the past year | Yes | 1.39 | 1 |

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; OR, odds ratio; Ref., reference.
NOTE. Risk score points were allocated as 0 if the OR was less than 1.20, 1 if OR was 1.20 to 1.49, 2 if OR was 1.50 to 2.49, 3 if OR was 2.50 to 3.49, 4 if OR was 3.50 to 4.49, and 5 if OR was more than or equal to 4.5.