Original Article

Comorbidity Burden in Severe and Nonsevere Asthma: A Nationwide Observational Study (FINASTHMA)

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What is already known about this topic? Previous evidence shows that use of systemic corticosteroids (SCS) is prevalent in asthma management and is associated with a wide range of adverse effects, which may contribute to the comorbidity burden of patients with asthma.

What does this article add to our knowledge? Nationwide data demonstrated a dose-dependent association between SCS and inhaled corticosteroid (ICS) use and comorbidities, especially pneumonia, and significant impact on healthcare utilization, in severe asthma patients. The ICS, but not the SCS, had a safe dose range.

How does this study impact current management guidelines? Using SCS and high-dose ICS should be carefully evaluated in asthma management. Other treatment options (biologics) should be considered in severe asthma to potentially decrease comorbidity burden and excess health care resource utilization.

BACKGROUND: Asthma, affecting more than 330 million people worldwide, is associated with a high level of morbidity, mortality, and socioeconomic costs.
OBJECTIVE: In this cross-sectional study, we analyzed the comorbidity burden in patients with severe asthma compared with nonsevere asthma and investigated the role of corticosteroid use on the risk of comorbidities.
METHODS: All adults (≥18 y) with a diagnosis of asthma (International Classification of Diseases−10th revision code J45.x) between 2014 and 2017 were identified and data were collected until 2018 from Finnish nationwide registers. Asthma was defined as continuously or transiently severe or nonsevere based on annual dispensed inhaled corticosteroids (ICS), oral corticosteroids (OCS), and hospitalizations.
RESULTS: Of 193,730 adult identified patients diagnosed with asthma, 86.3% had nonsevere, 8.1% transiently severe, and 5.6% continuously severe asthma. Excess prevalence of pneumonia was observed in continuously (22%) and transiently severe (14%) compared with nonsevere patients after adjusting for age and sex. Cataract, osteoporosis, obesity, heart failure, and atrial fibrillation were also more frequent in severe asthma patients. The ICS and/or OCS use contributed to the risk of several comorbidities in a dose-dependent manner, particularly pneumonia, osteoporosis, obesity, heart failure, and atrial fibrillation.

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Abbreviations used
AF- Atrial fibrillation
BMI- Body mass index
COPD- Chronic obstructive pulmonary disease
FP eq.- Fluticasone propionate equivalents
GINA- Global Initiative for Asthma
HCRU- Health care resource utilization
HF- Heart failure
ICD-10- International Classification of Diseases−10th Revision
ICS- Inhaled corticosteroids
LABA- Long-acting β_2-agonist
OCS- Oral corticosteroids
PRED eq.- Prednisolone equivalents
SABA- Short-acting β2-agonist
SCS- Systemic corticosteroids
THL- The Finnish Institute for Health and Welfare

High OCS use and the presence of comorbidities were associated with increased health care resource use. CONCLUSIONS: Patients with severe asthma have a high burden of comorbidities, especially pneumonia. Many of the comorbidities have a strong dose-dependent association with ICS and OCS treatment, suggesting that corticosteroid doses should be carefully evaluated in clinical practice. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Severe asthma; Corticosteroids; Comorbidities; Health care resource use; Pneumonia; Cataract; Osteoporosis; Type 2 diabetes; Cardiac disease*

INTRODUCTION

Asthma, characterized by chronic airway inflammation, causes high levels of morbidity, mortality, and socioeconomic costs. It affects more than 330 million people worldwide and causes approximately 400,000 deaths annually.[1-3] It has been estimated that 4% to 9% of the patients have severe asthma, which is defined as a disease that remains uncontrolled despite optimized treatment with high-dose ICS/LABA (a combination of an inhaled corticosteroid and a long-acting β_2-agonist) or that requires a high-dose ICS/LABA or oral corticosteroid (OCS) to prevent it from becoming uncontrolled.[4,5]

More than half of asthma patients have 1 or more comorbid conditions.[6] Comorbidities are associated with worse asthma-related outcomes and they can complicate management of the disease.[6,7] Asthma-related comorbidities are associated with a significant increase in health care resource utilization (HCRU) and treatment costs.[8,9] In a Canadian cohort of asthma patients, comorbidity-attributable health care costs were 5 times higher than asthma-attributable costs.[9] Asthma patients with comorbidities also have an increased risk of long-term work disability and higher productivity losses than patients with no comorbidities.[10,11]

Systemic corticosteroids are widely used in asthma and 20% to 60% of patients with severe asthma receive long-term OCS therapy.[12] The OCSs are associated with a wide range of adverse effects, which may contribute to the comorbidity burden of patients with asthma.[13] Most commonly reported OCS-related acute complications include infections and gastrointestinal events, whereas chronic complications include metabolic, bone-related, and cardiovascular events.[12,14]

There is limited information on the comorbidity burden in severe compared with nonsevere asthma and the impact of corticosteroids on the comorbidity burden. Only a few studies have compared comorbidity burden of nonsevere and severe asthma in a population-based setting.[15] Furthermore, our knowledge on comorbidities linked to the use of the corticosteroids (pneumonia, osteoporosis, and cataract) and cardiometabolic diseases in severe asthma, as well as our understanding on factors that contribute to the excess HCRU in severe asthma, remain vague. The Finnish nationwide health care and prescription registries, which cover the whole population of 5.5 million and offer individual-level linkage between different registers, provide an excellent resource for evaluation of these questions. Thus, our aim was to analyze the comorbidity burden in patients with severe compared with nonsevere asthma and to investigate the role of corticosteroid use on the risk of comorbidities.

METHODS

Study design and participants

All adults (≥18 y) with an asthma diagnosis (International Classification of Diseases−10th Revision [ICD-10]: J45.x) recorded at any visit between January 1, 2014 and December 31, 2017 (the cohort formation period), were identified from the Finnish Care Register for Health Care and included in the study cohort (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org). The patients were included in the cohort if they had an asthma diagnosis recorded at any point during the cohort formation period. The index date was set to January 1, 2014 for everyone; hence, defining the start of the follow-up. The data were collected until December 31, 2018, yielding an equal length of follow-up for everyone. The following criteria, in line with the Global Initiative for Asthma (GINA) report,[3] were used to define study subgroups: (1) annual ICS purchases of fluticasone propionate equivalents (FP eq.) of 146,000 μg or higher (according to an assumption of 80% medication adherence and a daily dose of 500 μg FP eq., ie, 0.8 × 365 d × 500 μg of FP eq.); (2a) annual OCS purchases greater than 600 mg of prednisolone equivalents (PRED eq.); and (2b) 1 or more hospitalization during a year with J45.x or J46.x as the main diagnosis. Severe asthma was defined as fulfilling criteria 1 + 2a or 1 + 2b. Patients fulfilling the criteria for severe asthma as an annual average over the whole follow-up period were categorized in a continuously severe subgroup. Patients fulfilling the criteria for severe asthma at least once for a calendar year during the study period but not fulfilling the criteria for the continuously severe subgroup, were categorized as transiently severe. Other patients were categorized as nonsevere. Only asthma diagnoses (ie, not dispensed medications) were used as inclusion criteria for the cohort. If a patient did not have any dispenses, they were classified as nonsevere.

Variables

Data were collected from the nationwide registers with full coverage of the Finnish population, public health care providers, and pharmacies. Individual-level data from different registries were linked using unique personal identification numbers. The prevalence of comorbid conditions (based on ICD-10 codes) and HCRU were based on recordings in the Care Register for Health Care.

Medication usage was based on dispensed prescriptions and the data were collected from the Register for Reimbursed Drugs. The ICS dose was calculated as micrograms of FP eq./d and the cumulative OCS dose as milligrams of PRED eq./y (Tables E1 and E2; available in this article's Online Repository at www.jaci-inpractice.org). Details of the study variables are presented in the Online Repository.

Statistical analyses

The descriptive statistics were presented by number and proportion of patients for categorical variables, and by the mean, median, SD, and first and third quartiles for continuous ones. The prevalences of asthma and the comorbidities were calculated using data collected over the period from 2014 to 2018. The excess prevalence of comorbidities with 95% confidence intervals (CIs) were calculated as the weighted average of the age- and sex-specific differences in the prevalence. The age groups were 18 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, and older than 70 years. The weights used were based on the proportions of patients in the aforementioned age- and gender-stratified groups in the overall population.

The effect of corticosteroid use (exposure) on the prevalence of comorbidities was analyzed using a logistic regression model, in which all patients were included, such that the exposure was accounted for from the first 3 years of follow-up (2014−2016) and the outcomes were assessed during the last 2 years of follow-up (2017−2018). The comorbidities studied were based on previous literature related to severe asthma,[5] adult-onset asthma,[7,16] previous register-based studies on asthma in adults,[8,17] known or suspected adverse effects of ICS and OCS,[18,19] and clinical experience. Other covariates of interest (body mass index [BMI], smoking, and socioeconomic variables are not well covered in the data sources and were, therefore, not included. The period prevalence was calculated using all data in the study period and with an equal length of follow-up (until December 31, 2018) for each patient.

Because high ICS doses are known to be associated with pneumonia risk in chronic obstructive pulmonary disease (COPD)[15] and corticosteroids can also be prescribed for conditions other than asthma as well as the fact that the entire disease history was not available for all patients, 3 different sensitivity analyses were performed by excluding patients (1) with COPD, (2) having the following other indications (ICD-10 codes) for ICS and OCS use: 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 (3) not having a special reimbursement decision for asthma medication prior to January 1, 2014, and therefore, possibly having their onset of asthma after 2014. Asthma patients are entitled for special reimbursement when the specified diagnostic criteria are met after they have used a regular medication for a minimum of 6 months.

To assess the effect unmeasured confounding on the risk of comorbidities by corticosteroid use (the main analysis), we performed an E-value analysis[20] to determine the magnitude of unmeasured confounding that would attenuate the associations to null. The analysis is described in detail in the Online Repository Methods.

The associations between comorbidities, corticosteroid use, and the annual HCRU were analyzed using a linear regression model for the log-transformed number of in-person health care visits. For technical reasons, +1 visit was added to patients with 0 visits (only 0.1% of patients). The linear regression on the association between comorbidities and log(health care visits) was performed as a multivariable model in which all comorbidities were included simultaneously. All regression models were adjusted for age and sex. The data sources record essentially all utilized variables; therefore, records of missing data are not defined. Data were analyzed using R version 3.6.3 (https://www.r-project.org/).

RESULTS

Cohort description

A total of 193,730 adult patients diagnosed with asthma were identified and included in the cohort, corresponding to a population prevalence of 4.4% (Table I). Most of the patients were females (63.6%) and the mean age was 58.0 years (females 58.5 y; males 57.2 y). A total of 91.7% of patients were dispensed ICS and 54.7% were dispensed OCS at some point of the follow-up. Approximately one-third of the patients (35.2%; n = 68,174) had bought at least 2 OCS packages during the follow-up. Among cohort patients, 60.6% used LABAs, 27.3% used leukotriene receptor antagonists, and 16.6% used long-acting muscarinic antagonists.

Altogether 13.7% of the patients were defined to have severe asthma. A total of 5.6% (n = 10,754) of patients were classified in the continuously severe, 8.1% (n = 15,763) in the transiently severe, and 86.3% (n = 167,213) in the nonsevere subgroups.

Pneumonia

Significant excess prevalence of pneumonia was observed in continuously severe and transiently severe groups compared with patients in the nonsevere group. The age- and sex-standardized excess prevalence (95% CI) of pneumonia was 22.1% (21.2−23.0) in continuously severe ($P < .001$) and 13.9% (13.2−14.6) in transiently severe ($P < .001$) subgroups (Table II). The prevalence of comorbid pneumonia increased with age and the risk was associated with increasing ICS and OCS doses (Figures 1 and 2). Because high ICS doses are known to be associated with pneumonia risk in COPD,[15] the analyses were performed also by excluding the patients with coexisting COPD. The excess prevalence of pneumonia (18.8% in continuously severe [95% CI 17.7−19.9] and 11.3% [95% CI 10.5−12.1] in transiently severe) and dose-dependent added risks of ICS and OCS on pneumonia (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org) persisted when patients with coexisting COPD were excluded from the analyses.

Cataract and osteoporosis

The age- and sex-standardized excess prevalence (95% CI) of any cataract was 5.2% (4.5−5.9) in continuously severe ($P < .001$) and 2.1% (1.6−2.6) in transiently severe groups ($P < .001$) (Table II), but no significant sex difference was observed (Table E3; available in this article's Online Repository at www.jaci-inpractice.org). ICS and OCS had a modest but dose-dependent effect on the risk of cataract (Figure 2).

The age- and sex-standardized excess prevalence of osteoporosis (95% CI) was 4.2% (3.7−4.7) and 1.6% (1.3−1.9) in continuously severe ($P < .001$) and transiently severe ($P < .001$) groups (Table II), respectively, and was more prominent among female patients (Table E3). Increasing ICS and OCS doses were associated with a higher risk of comorbid osteoporosis. Increased risk of osteoporosis was observed starting from annual OCS doses greater than 600 mg and the risk was especially high (odds

TABLE I. Descriptive statistics of the study cohort*

Variable	Continuously severe (n = 10,754)		Transiently severe (n = 15,763)		Nonsevere (n = 167,213)		Total (n = 193,730)	
Sex	n	%	n	%	n	%	n	%
Female	7,102	66.0	10,519	66.7	105,581	63.1	123,202	63.6
Male	3,652	34.0	5,244	33.3	61,632	36.9	70,528	36.4
Co-existing COPD	2,972	27.6	3,509	22.3	18,062	10.8	24,543	12.7
Asthma medication reimbursement decision prior to 2014	8,741	81.3	10,502	66.6	78,449	46.9	97,692	50.4
No other potential indications for ICS or OCS use†	7,936	73.8	11,778	74.7	125,145	74.8	144,859	74.8
	Mean (Median)	**SD (Q1, Q3)**	**Mean (Median)**	**SD (Q1, Q3)**	**Mean (Median)**	**SD (Q1, Q3)**	**Mean (Median)**	**SD (Q1, Q3)**
Age (y)	64.6 (66.0)	14.8 (56.0, 76.0)	63.4 (66.0)	16.3 (54.0, 76.0)	57.1 (61.0)	19.8 (44.0, 73.0)	58.0 (62.0)	19.4 (44.0, 73.0)
Use of medication	n	%	n	%	n	%	n	%
ICS‡	10,754	100	15,763	100	151,094	90.4	177,611	91.7
OCS	10,519	97.8	15,578	98.8	79,913	47.8	106,010	54.7
LABA‡	9,735	90.5	13,040	82.7	94,579	56.6	117,354	60.6
LAMA‡	5,513	51.3	5,744	36.4	20,880	12.5	32,137	16.6
LTRA	6,156	57.2	7,369	46.7	39,279	23.5	52,804	27.3
ICS with LABA and/or LAMA and/or LTRA	10,066	93.6	13,943	88.5	103,919	62.1	127,928	66.0
Nasal corticosteroids	6,516	60.6	8,805	55.9	77,311	46.2	92,632	47.8
Dosing								
Daily ICS dose (μg FP eq.)	738 (666)	302 (510, 888)	465 (378)	295 (263, 592)	182 (96)	235 (14, 263)	236 (134)	284 (21, 356)
Annual OCS (mg PRED eq.)	1,328 (1,021)	1,058 (720, 1,721)	657 (460)	671 (280, 660)	159 (0)	376 (0, 150)	264 (60)	553 (0, 240)

LAMA, long-acting muscarinic antagonist; *LTRA,* leukotriene receptor antagonist; *Q1,* first quartile; *Q3,* third quartile.

*The following criteria were used to define study subgroups: (1) annual ICS purchases ≥ [0.8 (corresponding to ≥ 80% treatment adherence) × 365 (d/y) × 500 μg of FP eq.]; (2a) annual OCS purchases > 600 mg of PRED eq; and (2b) at ≥ 1 hospitalization with J45.x or J46.x as the main diagnosis. Severe asthma was defined as fulfilling criteria 1 + 2a or 1 + 2b. Patients fulfilling the criteria for severe asthma over the whole follow-up period were categorized in a continuously severe subgroup. Patients fulfilling the criteria for severe asthma at least once for a full calendar year during the study period but not fulfilling the criteria for the continuously severe subgroup were categorized as transiently severe. Patients who did not fulfill the criteria for continuously severe or transiently severe subgroups were categorized as nonsevere. Use of medication was evaluated over the whole follow-up period.

†Inflammatory polyarthropathies (ICD-10: M05-14), Systemic connective tissue disorders (ICD-10: M30-6), Noninfective enteritis and colitis (ICD-10: K50-2), Diseases of veins, lymphatic vessels and lymph nodes (ICD-10: I80-4), Sarcoidosis (ICD-10: D86).

‡Either a combination product or as a separate inhaler.

TABLE II. Excess prevalence of the selected comorbidities in 2014–2018

	Period prevalence								Excess prevalence*			
	Continuously severe		Transiently severe		Nonsevere		Total		Continuously severe		Transiently severe	
	(n = 10,754)		(n = 15,763)		(n = 167,213)		(n = 193,730)		(n = 10,754)		(n = 15,763)	
Comorbidity	n	%	n	%	n	%	n	%	% (95% CI)	*P* value†	% (95% CI)	*P* value†
Influenza or pneumonia	4,733	44.0	5,454	34.6	28,705	17.2	38,892	20.1	23.5 (22.6 to 24.4)	<.001	14.9 (14.1 to 15.7)	<.001
Pneumonia	4,390	40.8	5,010	31.8	25,293	15.1	34,693	17.9	22.1 (21.2 to 23.0)	<.001	13.9 (13.2 to 14.6)	<.001
Influenza	942	8.8	988	6.3	5,595	3.3	7,525	3.9	5.2 (4.7 to 5.7)	<.001	2.8 (2.4 to 3.2)	<.001
Osteoporosis	971	9.0	926	5.9	5,306	3.2	7,203	3.7	4.2 (3.7 to 4.7)	<.001	1.6 (1.3 to 1.9)	<.001
Any cataract	2,052	19.1	2,320	14.7	16,787	10.0	21,159	10.9	5.2 (4.5 to 5.9)	<.001	2.1 (1.6 to 2.6)	<.001
Senile cataract	1,728	16.1	1,914	12.1	14,088	8.4	17,730	9.2	4.3 (3.7 to 4.9)	<.001	1.5 (1.0 to 2.0)	<.001
Other cataract	524	4.9	627	4.0	4,237	2.5	5,388	2.8	1.5 (1.1 to 1.9)	<.001	0.8 (0.5 to 1.1)	<.001
Obesity	1,175	10.9	1,462	9.3	11,809	7.1	14,446	7.5	4.3 (3.7 to 4.9)	<.001	2.3 (1.8 to 2.8)	<.001
Type 2 diabetes	2,333	21.7	3,161	20.1	27,414	16.4	32,908	17.0	1.7 (1.0 to 2.4)	<.001	0.9 (0.3 to 1.5)	.010
Any circulatory system–related disease	7,657	71.2	10,615	67.3	92,349	55.2	110,621	57.1	6.0 (5.0 to 7.0)	<.001	3.7 (2.9 to 4.5)	<.001
Atherosclerosis	563	5.2	731	4.6	4,989	3.0	6,283	3.2	1.2 (0.8 to 1.6)	<.001	0.8 (0.5 to 1.1)	<.001
AF	2,325	21.6	3,156	20.0	21,445	12.8	26,926	13.9	4.4 (3.7 to 5.1)	<.001	3.6 (3.0 to 4.2)	<.001
Chronic ischemic heart disease	1,871	17.4	2,586	16.4	19,296	11.5	23,753	12.3	2.2 (1.5 to 2.9)	<.001	2.0 (1.4 to 2.6)	<.001
HF	2,194	20.4	2,867	18.2	15,302	9.2	20,363	10.5	7.1 (6.4 to 7.8)	<.001	5.7 (5.1 to 6.3)	<.001
Hypertension	5,282	49.1	7,133	45.3	63,507	38.0	75,922	39.2	2.5 (1.5 to 3.5)	<.001	0.5 (−0.3 to 0.3)	.770

*Age- and sex-standardized excess prevalence over the whole follow-up period compared with nonsevere asthma.
†Age-adjusted *P* value for severity, estimated using a logistic regression model.

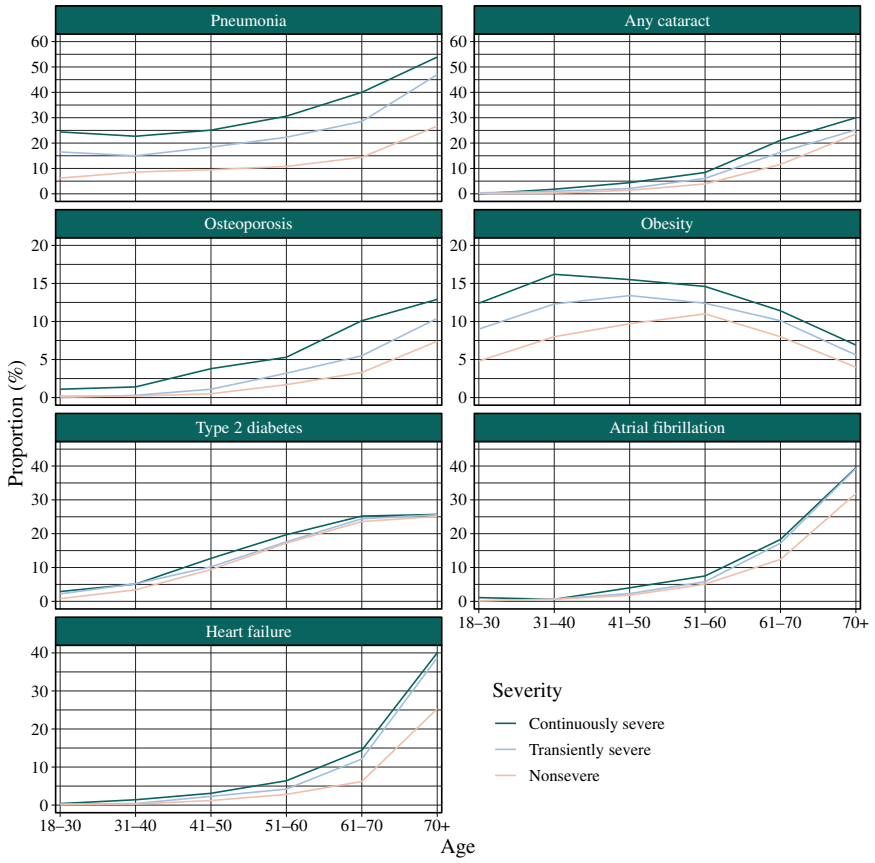

FIGURE 1. Comorbidity prevalence in patients with asthma by age groups.

ratio [OR] 3.48; 95% CI 3.18-3.81; $P < .001$) in patients with the highest annual OCS doses of greater than 1,200 mg (Figure 2).

Metabolic comorbidities

Prevalence of obesity was higher in continuously severe and transiently severe groups compared with the nonsevere group (Figure 1) with age- and sex-standardized excess prevalence (95% CI) of 4.3% (3.7−4.9) and 2.3% (1.8−2.8), respectively (Table II). The highest prevalence of obesity was observed among women aged 31 to 40 years (Figure E3; available in this article's Online Repository at www.jaci-inpractice.org). Annual OCS doses greater than 300 mg (PRED eq.) were associated with an increased risk of obesity (Figure 2).

Only modest excess prevalence of type 2 diabetes was observed in continuously severe (1.7%; 95% CI 1.0−2.4) and transiently severe (0.9%; 95% CI 0.3−1.5) groups (Table II). However, a greater excess prevalence (95% CI) was observed in females than in males in both continuously severe (2.4% vs 0.4%; $P = .013$) and transiently severe (1.3% vs 0.2%; $P = .055$) groups (Table E3). Only the highest ICS (>1,000 μg FP eq.) and OCS (>1,200 mg PRED eq.) doses were modestly associated with the risk of type 2 diabetes in this cohort (Figure 2).

Cardiovascular comorbidities

Continuously severe and transiently severe groups had a significant ($P < .001$) age- and sex-standardized excess prevalence of any circulatory system−related diseases (continuously severe 6.0%; transiently severe 3.7%; Table II). The highest excess prevalence of cardiovascular comorbidities was observed in heart failure (HF; continuously severe 7.1%; transiently severe 5.7%) and atrial fibrillation (AF; continuously severe 4.4%; transiently severe 3.6%). In the continuously severe group, a greater excess prevalence of HF was observed for female versus male patients (7.6% vs 6.1%; $P = .004$) (Table E3).

The ICS use was associated with the increased risk of AF and HF in a dose-dependent manner. The greatest risks were observed for the highest daily doses of greater than 1,000 μg FP eq. for both AF and HF, but considerable effect sizes were observed already at daily doses of greater than 500 μg (FP eq.) (Figure 2). The OCS use was significantly associated with the increased risk of HF throughout the dose range, the highest risk being for the highest annual OCS doses (>1,200 mg PRED eq.). Because it is possible that the cardiac adverse effects relate to use of β_2-agonists rather than ICS/OCS in severe asthma, we evaluated the risk of all these adverse events in relation to the combined short-acting β2-agonists and long-acting β_2-agonists (SABA/LABA) use, defined as annual defined daily doses. Whereas SABA/LABA use was associated with some increased risk of cardiac adverse effects, the effect of increasing doses of OCS was clearly higher (Figure E4; available in this article's Online Repository at www.jaci-inpractice.org).

Modest excess prevalence of comorbid atherosclerosis, chronic ischemic heart disease, and hypertension was also observed (Table II and Figure E5; available in this article's Online Repository at www.jaci-inpractice.org).

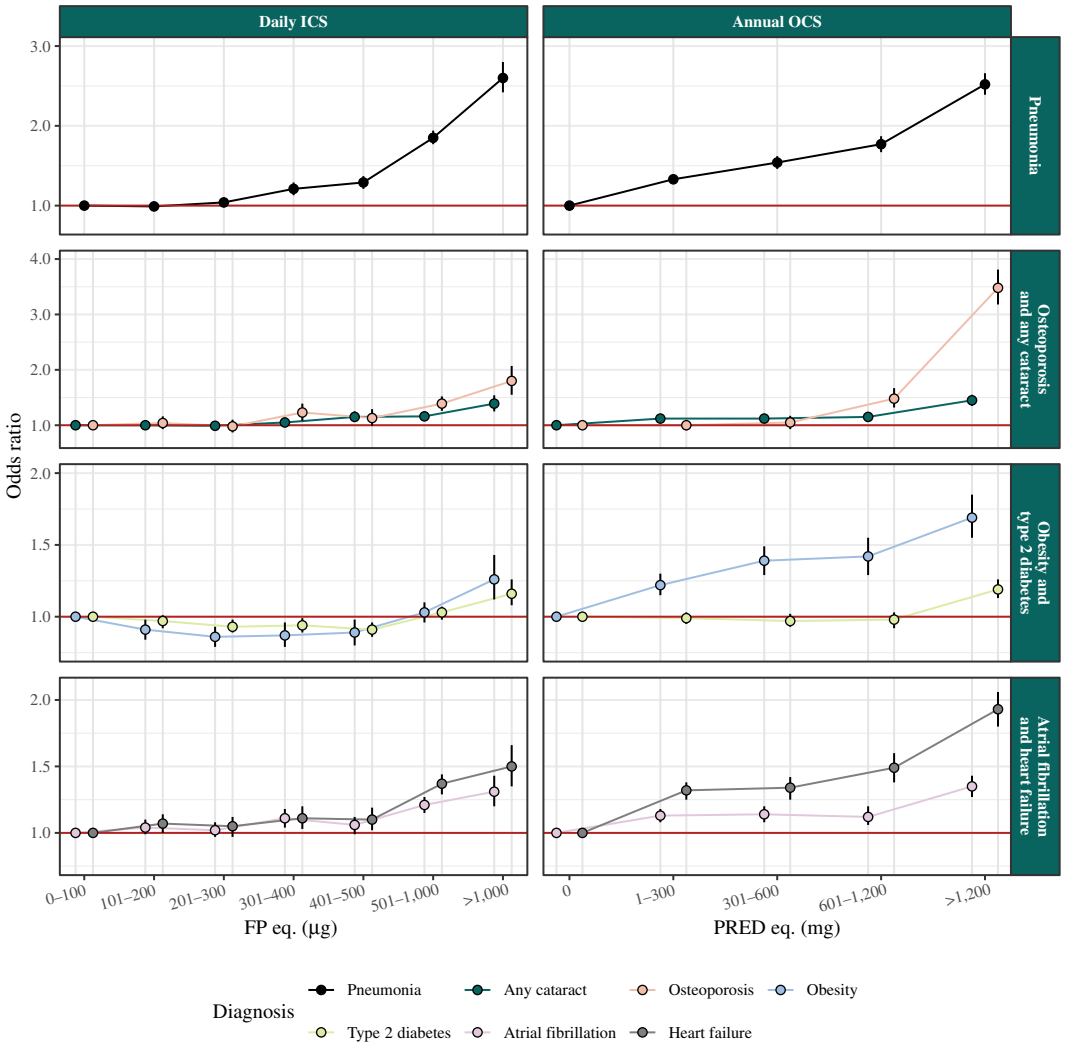

FIGURE 2. The effect of ICS and OCS use on the prevalence of comorbidities, estimated using a logistic regression model. Exposure was accounted from the first 3 years of follow-up and the outcomes assessed during last 2 years of follow-up. The models were age- and sex-adjusted. The figure presents odds ratios with 95% confidence intervals.

Sensitivity analyses

The excess prevalence of pneumonia (18.8%; 95% CI 17.7−19.9 in continuously severe and 11.3%; 95% CL 10.5−12.1 in transiently severe) and dose-dependent added risks of ICS and OCS on pneumonia persisted when patients with coexisting COPD were excluded from the analyses (Figure E2). In the sensitivity analysis excluding patients (48,871 of 193,730) with other conditions for which corticosteroids can be used, 125,145 (86%) were classified as nonsevere, 11,778 (8%) as transiently severe, and 7,936 (5%) as continuously severe. A similar dose-response trend was observed as in the main population (Figure E6; available in this article's Online Repository at www.jaci-inpractice.org). In the sensitivity analysis on the prevalence of comorbidities by corticosteroid use in patients without a reimbursement decision for asthma medication prior to January 1, 2014, 96,038 of 193,730 patients were excluded. Of the remaining patients, 78,449 (80%) were classified as nonsevere, 10,502 (11%) as transiently severe, and 8,741 (9%) as continuously severe. A similar dose-response trend was observed as in the main population (Figure E7; available in this article's Online Repository at www.jaci-inpractice.org).

E-value analysis

The E-value analysis showed that some of the findings in Figure 2 with lower effect sizes, such as the use of OCS on type 2 diabetes mellitus may be explained by unmeasured confounding, whereas the findings with higher effect sizes, such as use of OCS on osteoporosis, are unlikely to be explained by unmeasured confounding. The results of the E-value analysis are presented in detail the Online Repository Results.

Health care resource use

Continuously severe (rate ratio 1.64; 95% CI 1.61−1.67; $P <$ .001) and transiently severe (rate ratio 1.35; 95% CI 1.33−1.37; $P <$ .001) asthma were associated with a higher number of total health care visits compared with nonsevere asthma. The median

TABLE III. Median (Q1, Q3) number of annual health care visits

	Continuously severe (n = 10,754)		Transiently severe (n = 15,763)		Nonsevere (n = 167,213)		Total (n = 193,730)	
Visit type	**Median**	**Q1, Q3**	**Median**	**Q1, Q3**	**Median**	**Q1, Q3**	**Median**	**Q1, Q3**
All health care visits	16.4	9.6, 27.0	13.2	7.4, 22.6	8.8	4.6, 16.0	9.4	4.8, 17.2
Secondary care	4.2	2.2, 8.0	3.2	1.4, 6.2	1.8	0.8, 4.0	2.0	0.8, 4.4
Inpatient visits	0.4	0.0, 0.8	0.2	0.0, 0.6	0.0	0.0, 0.4	0.0	0.0, 0.4
Outpatient visits	3.8	1.8, 7.2	2.8	1.2, 5.6	1.6	0.6, 3.6	1.8	0.6, 4.0
Primary care visits	10.6	5.0, 19.4	8.8	4.2, 16.2	6.0	2.8, 11.4	6.4	3.0, 12.2
Asthma-related visits	1.0	0.4, 2.2	0.6	0.4, 1.4	0.4	0.2, 0.8	0.4	0.2, 0.8
Non−asthma-related visits	14.8	8.0, 25.0	12.0	6.4, 21.2	8.2	4.0, 15.2	8.8	4.2, 16.2

Q1, First quartile; *Q3,* third quartile.

number of annual health care visits was 16 in continuously severe, 13 in transiently severe, and 9 in nonsevere patients (Table III). Patients in the continuously severe group also had a higher proportion of asthma-related visits (6.1% of all visits) than patients in transiently severe (4.5%), or nonsevere (4.5%) groups.

Higher annual OCS doses were associated with increased HCRU, but only a modest effect was observed with ICS use (Figure 3, *A*). In addition, all comorbid conditions of interest were associated with increased HCRU. The largest effects were observed for AF followed by osteoporosis and type 2 diabetes (Figure 3, *B*).

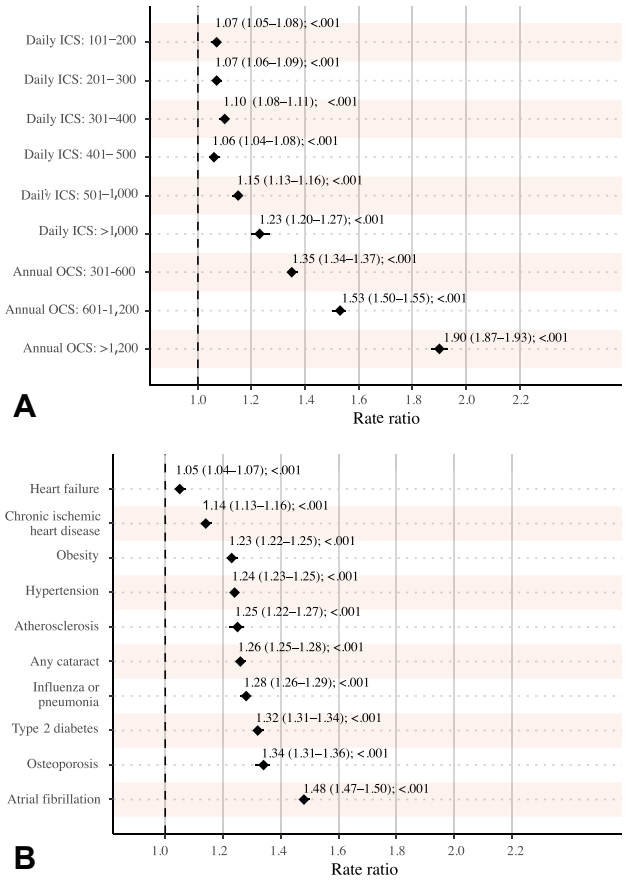

FIGURE 3. Associations between annual HCRU and (**A**) ICS (FP eq. [μg]) and OCS (PRED eq. [mg]) use and (**B**) presence of comorbidities in asthma patients; estimated using a linear regression model for the log-transformed number of all health care visits (with +1 visit added to 0.1% of patients with 0 visits). The models were age- and sex-adjusted. The figure presents rate ratios with 95% confidence intervals.

DISCUSSION

In this nationwide, retrospective, observational cohort study, we demonstrated a significant excess prevalence of several comorbid conditions in severe asthma, including pneumonia, cataract, osteoporosis, obesity, atrial fibrillation, and heart failure. The OCS and ICS use contributed to the risks of most comorbidities in a dose-dependent manner. High doses of OCS and the presence of comorbidities were associated with increased HCRU.

There are only a few earlier large-scale population-based long-term studies investigating the comorbidity burden in severe and nonsevere asthma. In this cohort, disease severity was assessed retrospectively based on the type and duration of pharmacological treatment and hospitalizations, in line with the GINA report.[3] Owing to a long follow-up time and changes in patients' asthma medication over time, we generated 3 classes of asthma severity: continuously severe, transiently severe, and nonsevere asthma. This seems to be a valid method for classifying asthma severity because the groups had distinct comorbidity and HCRU profiles. Altogether, 5.6% of patients were classified as continuously severe and 8.1% as transiently severe.

Pneumonia had the highest excess prevalence of the comorbidities included in the analyses and the use of both ICS and OCS showed a strong dose-dependent added risk. Pneumonia is a common complication of patients with COPD,[21] but the excess prevalence of pneumonia and added risk from ICS and OCS persisted when patients with coexisting COPD were removed from the analyses.

There is limited earlier evidence available on the impact of disease severity and the role of corticosteroid use for the risk of comorbid pneumonia in asthma. A U.S. study found that pneumonia was reported more frequently in subjects with the lowest lung function and highest exposure to corticosteroid treatment.[22] There have been somewhat mixed results concerning the association between ICS use and pneumonia. Several studies have identified association only with fluticasone propionate but not with budesonide, whereas others have reported

dose-dependent association for both fluticasone proprionate and budesonide.[23,24] In this study, association to pneumonia was not evaluated for different ICS. Our results provide evidence that ICS use increases the risk of pneumonia in a dose-dependent manner in asthma. A dose-dependent effect was observed also for OCS use supporting results presented in the U.S. claims database.[25]

We observed excess prevalence of both osteoporosis and cataract in patients with continuously and transiently severe asthma. It is well established that the use of systemic corticosteroids increases the risk of osteoporosis and cataract.[26,27] In addition to OCS, we also identified a dose-response relationship between cumulative ICS doses and the risk of both comorbidities. A cumulative annual OCS dose of greater than 1,200 mg (PRED eq.) had a major impact on the risk of osteoporosis, which is in line with earlier reports.[28] The excess prevalence of osteoporosis was significantly higher among female than male patients and prevalence started to increase swiftly with age, highlighting that postmenopausal women using OCS are at significant risk.

An excess prevalence of obesity and type 2 diabetes was observed in continuously and transiently severe asthma. The risk of type 2 diabetes was more pronounced in female patients, but a clear sex-specific effect was not observed in obesity. Earlier studies have shown that asthma is associated with an increased risk of type 2 diabetes in women regardless of BMI, potentially because chronic inflammation contributes to the pathogenesis of diabetes.[29] We observed only modestly increased risk with the highest cumulative ICS and OCS doses, although earlier retrospective cohort studies have suggested an association between ICS and OCS use and type 2 diabetes.[25,30] The overall prevalence of obesity was significantly lower in this study than reported earlier indicating that ICD-10 codes for obesity may not be comprehensively recorded.[31] Annual cumulative OCS doses greater than 300 mg (PRED eq.) and the highest mean ICS daily doses (>1,000 μg FP eq.) contributed to the risk of comorbid obesity, supporting prior findings by Sullivan and colleagues.[32]

In aggregate, there is limited research on the role of cardiovascular diseases in severe asthma, and data from large-scale population-based studies are largely absent. An earlier limited study (2,332 patients with asthma) showed that cardiovascular diseases are very common asthma comorbidities in the Finnish working population.[10] Recently, 1 Swedish population-based sampling study (744 patients with asthma) reported a higher prevalence of HF among severe compared with nonsevere asthma patients.[5]

In this study, 1 or more circulatory system—related diseases were present in 57% of patients with asthma. Importantly, we observed a considerable excess prevalence of HF and AF in severe asthma. The OCS use was significantly associated with the increased risk of HF throughout the dose range, but only a modest effect was observed in AF. The ICS use contributed modestly to the risk of both AF and HF in a dose-dependent manner. Our results are supported by earlier findings suggesting that persistent and/or uncontrolled asthma might be associated with an increased risk for incident AF[33,34] and that high-dose corticosteroids are associated with increased risk of cardiovascular diseases in general and specifically with the risk of AF and HF.[35,36]

Although our study setting did not allow us to establish causality, previous experimental evidence exists to support the biological plausibility of the findings. Glucocorticoids are well known to stimulate glucocorticoid receptor activation, resulting in hyperglycemia and insulin resistance via increased hepatic glucose production and inhibition of peripheral glucose uptake, leading to metabolic complications, such as type 2 diabetes mellitus and central obesity in long-term use.[37] In bone cells, glucocorticoids are known to interfere with proliferation, differentiation, and apoptosis, such that the balance is shifted to enhanced osteoclastogenesis (bone resorption) and reduced osteoblastogenesis (bone formation), leading to an increased risk of osteoporosis.[38] Regarding the risk of pneumonia, the mechanistic link has been studied mostly in COPD patients in whom the risk is attributed to inhibition of macrophage-mediated bacterial clearance, suppression of antimicrobial peptides, and alterations in the lung microbiome due to long-term ICS use.[39]

Patients with continuously and transiently severe asthma used more health care resources than patients in the nonsevere group. Importantly, the main excess burden in severe asthma was due to a higher number of non—asthma-related visits. We observed that OCS use had a strong dose-dependent impact on HCRU. Furthermore, all comorbidities of interest contributed to the excess HCRU, with AF, osteoporosis, and type 2 diabetes having the highest impact. Therefore, it is evident that high corticosteroid use and comorbidities contribute significantly to the high use of health care resources and the economic burden of severe asthma.

The main strength of this study is the real-world setting with complete nationwide coverage of Finnish health care and prescription registries with no loss to follow-up. All Finnish citizens are included in these registries regardless of social status, income, or insurance. Therefore, the data are representative of the entire population with a negligible selection bias, offering a major benefit compared with the registries that rely on insurance or survey data. Furthermore, Finland has publicly funded, universal, and high-quality health care available to all citizens. In addition, lung function tests are considered necessary for making an asthma diagnosis in Finland. However, we did not capture detailed clinical and covariate data of the patients, such as BMI, smoking, and socioeconomic variables, which might have provided useful additional information. Hence, the effect of unmeasured confounding cannot be completely excluded. As in all studies, this study has findings that can be explained by unobserved confounding as demonstrated by the E-value analysis. However, it seems implausible that all the findings, especially those with large effect sizes, could be explained by unmeasured confounding. Moreover, as for most outcomes, the pattern of OCS and ICS use has a clear trend, and the unobserved confounding should also follow a similar trend in the different OCS and ICS groups, a scenario that is unlikely. Furthermore, as pertinent to all studies involving medication data, secondary nonadherence (a patient filling a prescription but not taking the medication as prescribed) cannot be ruled out. Lastly, in an observational study, causal relationship between corticosteroid use and comorbidity cannot be fully established and variations in health care systems and treatment practices may affect the generalizability of these results.

Our results from this nationwide study highlight the importance of pneumonia as a major comorbid condition in severe asthma but also provide evidence that there is an increased risk of cataract, osteoporosis, obesity, type 2 diabetes, AF, and HF among patients with severe asthma. The ICS and OCS

contributed significantly to the comorbidity burden in a dose-dependent manner. However, our results suggest that ICS has a safe range, in contrast to OCS. Furthermore, severe asthma is associated with excess HCRU and comorbidities contribute to health care burden. The OCS use had a strong dose-dependent impact on HCRU. Therefore, treatment with OCS as well as long-term treatment with high-dose ICS should be carefully considered by weighing the risk of the comorbidities and consequences of potential asthma exacerbations. Other treatment options, such as biologics, should be considered in clinical practice for patients with severe asthma.

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Contributors

H. Kankaanranta was involved in conception and study design, methodology, visualization, and interpretation of the data and participated in writing of the manuscript. A. Viinanen was involved in conception and study design, methodology, and interpretation of the data and participated in writing of the manuscript. P. Ilmarinen was involved in conception and study design, methodology, and interpretation of the data and participated in writing of the manuscript. H. Hisinger-Mölkänen was involved in conception and interpretation of the data. J. Mehtälä was lead statistician, was involved in conception, design, management, and analysis, and wrote sections of the final draft. T. Ylisaukko-oja was involved in conception, study design, management, interpretation of the data, and writing of the manuscript. J.J. Idänpään-Heikkilä was involved in conception, study design, and interpretation of the data and writing of the manuscript. L. Lehtimäki had access to data, verified statistical analyses, and was involved in conception, study design, methodology, interpretation of the data, and writing of the manuscript. All authors read, revised, and approved the final manuscript.

Institutional review board approval

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). The study was performed in accordance with the Declaration of Helsinki and in compliance with applicable national laws. The study was based on existing data and no interventions were performed.

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ONLINE REPOSITORY

METHODS: VARIABLES

The following diagnoses were collected from the Care Register for Health Care (The Finnish Institute for Health and Welfare [THL]) and included in the assessment of individual comorbidities: influenza (J09-11), pneumonia (J12-18), influenza or pneumonia (J09-18), osteoporosis (M80-M82), cataract (any cataract, H25-H26, Q120; senile cataract, H25; other cataract, H26), any circulatory system-related disease (any I-code), atherosclerosis (I70), atrial fibrillation (I48), chronic ischemic heart disease (I25), heart failure (I50), primary hypertension (I10), obesity (E65-E68), and type 2 diabetes (E11).

The following health care resource utilization (HCRU) data were collected from the Care Register for Health Care (THL): the number of primary, secondary, and tertiary public health care outpatient visits, and hospitalization periods.

The following data were collected from the Register for Reimbursed Drugs (The Social Insurance Institution of Finland) on dispensed medications: category (Anatomical Therapeutic Chemical codes R01AD [corticosteroids], R03 [drugs for obstructive airway diseases], H02AB [glucocorticoids]), date of purchase, package size, number of packages per claim, strength, and cost of purchase (€).

The data collected had a complete nationwide coverage of Finnish health care and prescription registries with no loss to follow-up. All Finnish citizens are included in these registries regardless of social status, income, or insurance. Therefore, the data are representative of the entire population with a negligible selection bias.

METHODS: E-VALUE ANALYSIS

We used the E-value calculator (https://www.evalue-calculator.com/) to determine how strong unmeasured confounding would attenuate the main results on the corticosteroid use and risk of comorbidities to null. The E-value, defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain away a specific exposure-outcome association.

RESULTS: E-VALUE ANALYSIS

Pertaining to the results in Figure E3, in which the strongest result is for the increased risk of osteoporosis (odds ratio [OR} 3.48; 95% CI 3.19−3.79; $P < 0.001$) in patients with the highest annual oral corticosteroids (OCS) doses of greater than 1,200 mg, the E-value for the point estimate (OR 3.48) to turn to 1.00, is 6.42. Similarly, the E-value for the weakest finding in Figure E3 (type 2 diabetes OR 1.16; 95% CI 1.08−1.26; $P < .001$ for annual inhaled corticosteroids [ICS] > 1,000 mg) is 1.37. These findings indicate that, for the estimated OR 3.48 to turn to 1.00, there should be an unmeasured confounder that has an effect of magnitude 6.42 on the outcome (osteoporosis) and that is 6.42 times more common in the OCS 0 mg group (than in OCS > 1,200 mg group). For the estimated OR 1.16 (type 2 diabetes mellitus) to turn to 1.00, there should be an unmeasured confounder that has an effect of magnitude 1.37 on the outcome and that is 1.37 times more common in the ICS 0 to 100 mg group (than in the ICS > 1,000 mg group).

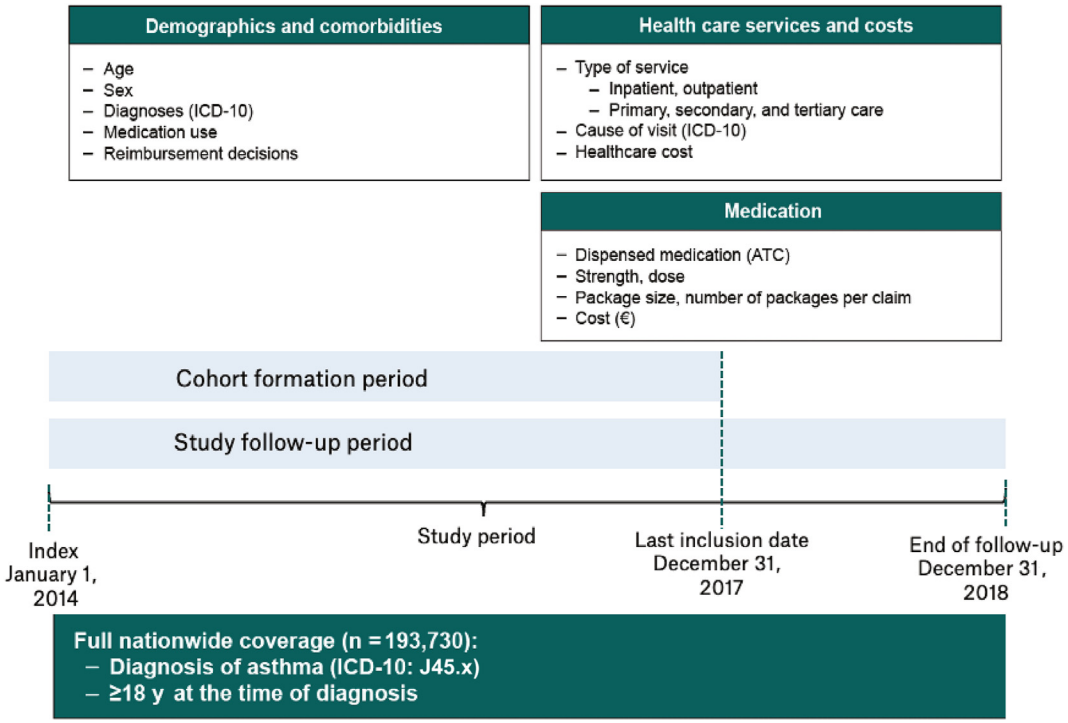

FIGURE E1. Overview of the study design. The patients were included in the cohort if they had an asthma diagnosis recorded at any point during the cohort formation period. The index date was set to January 1, 2014, for everyone; hence, defining the start of the follow-up and yielding an equal length of follow-up for everyone.

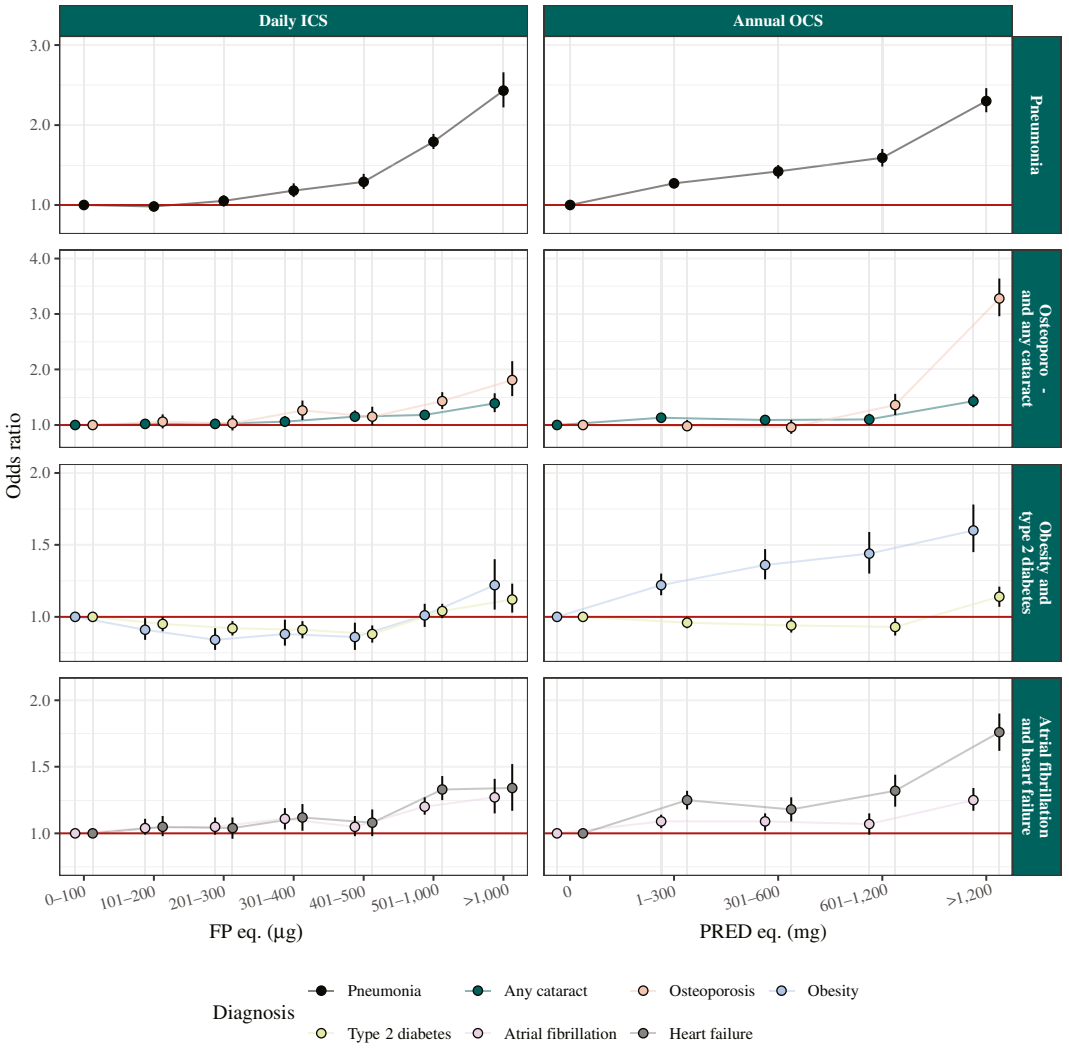

FIGURE E2. The effect of inhaled corticosteroid (ICS) and oral corticosteroid (OCS) use on the prevalence of comorbidities when patients with chronic obstructive pulmonary disease (COPD) were excluded. The estimates were made using a logistic regression model in which exposure was accounted from the first 3 years of follow-up and the outcomes were assessed during the last 2 years of follow-up. The models were adjusted for age and sex. Patients with COPD were excluded. The figure presents odds ratios with 95% confidence intervals. When error bars are not visible, they are inside the symbol. *FP eq.,* Fluticasone proprionate equivalents; *PRED eq.,* prednisolone equivalents.

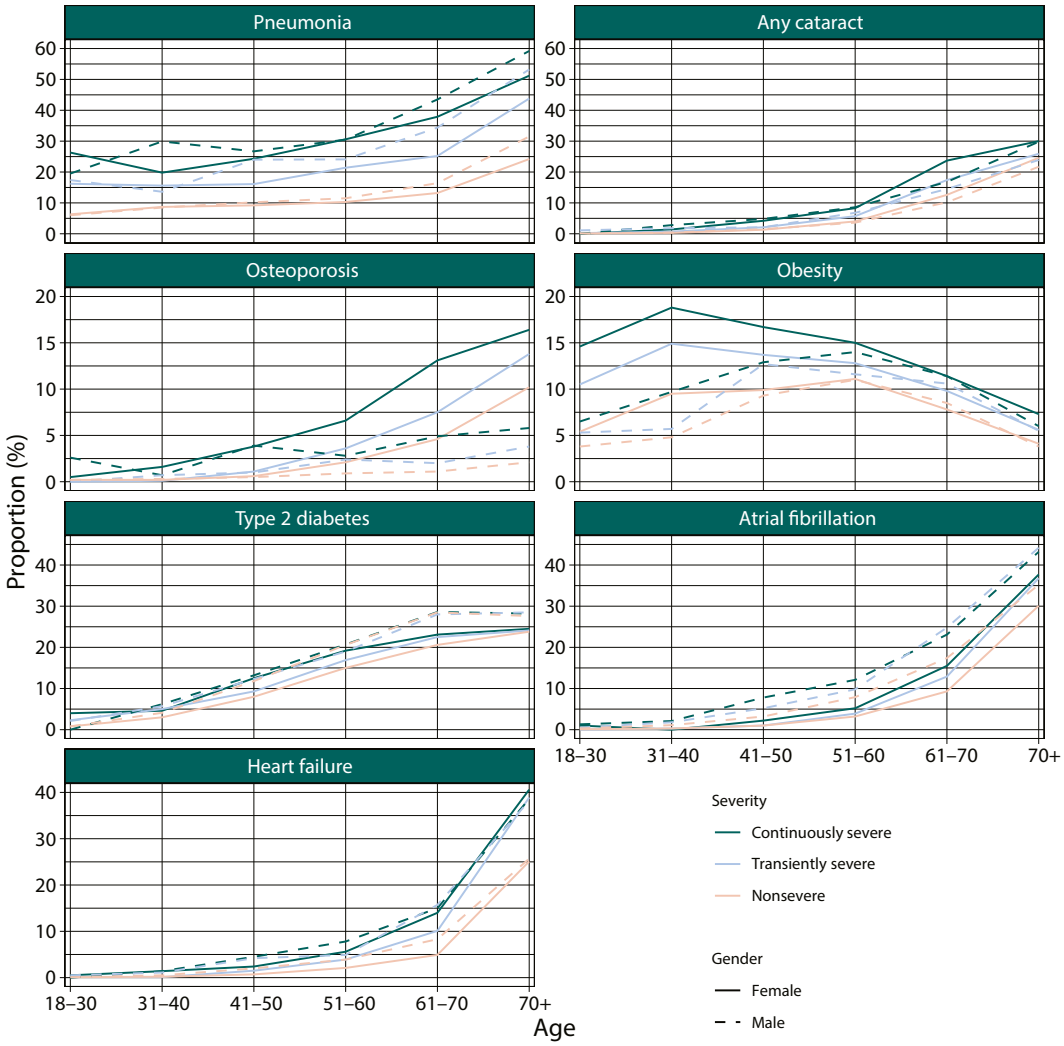

FIGURE E3. Comorbidity prevalence of pneumonia, cataract, osteoporosis, obesity, type 2 diabetes, atrial fibrillation, and heart failure in female and male patients with asthma, by age group.

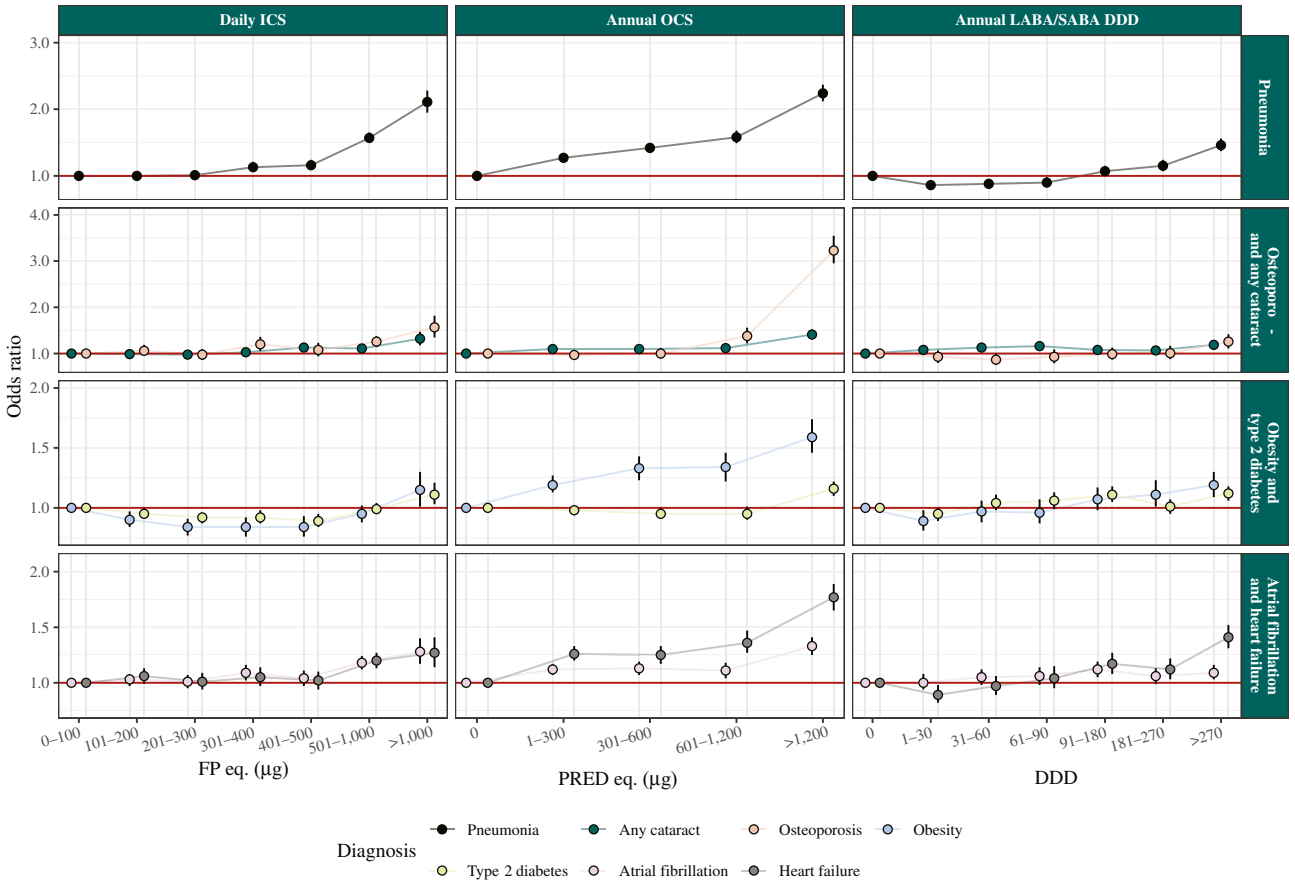

FIGURE E4. The effect of inhaled corticosteroid (ICS), oral corticosteroid (OCS), and long-acting β_2-agonist/short-acting β_2-agonist (LABA/SABA) defined daily dose (DDD) use on the prevalence of comorbidities, estimated using a logistic regression model in which exposure was accounted from the first 3 years of follow-up and the outcomes were assessed during the last 2 years of follow-up. The models were adjusted for age and sex. The figure presents odds ratios with 95% confidence intervals. When error bars are not visible, they are inside the symbols. *FP eq.,* Fluticasone proprionate equivalents; *PRED eq.,* prednisolone equivalents.

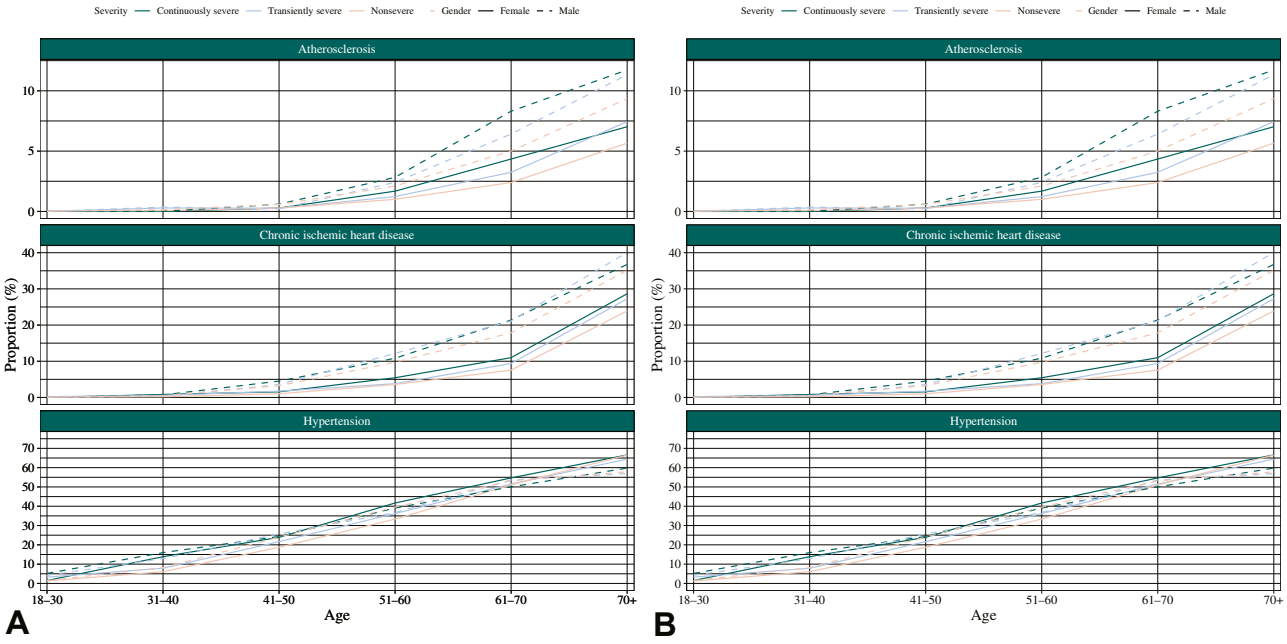

FIGURE E5. Comorbidity prevalence in patients with asthma (**A**) in both sexes combined and (**B**) separately in female and male; by age groups for atherosclerosis, chronic ischemic heart disease, and hypertension.

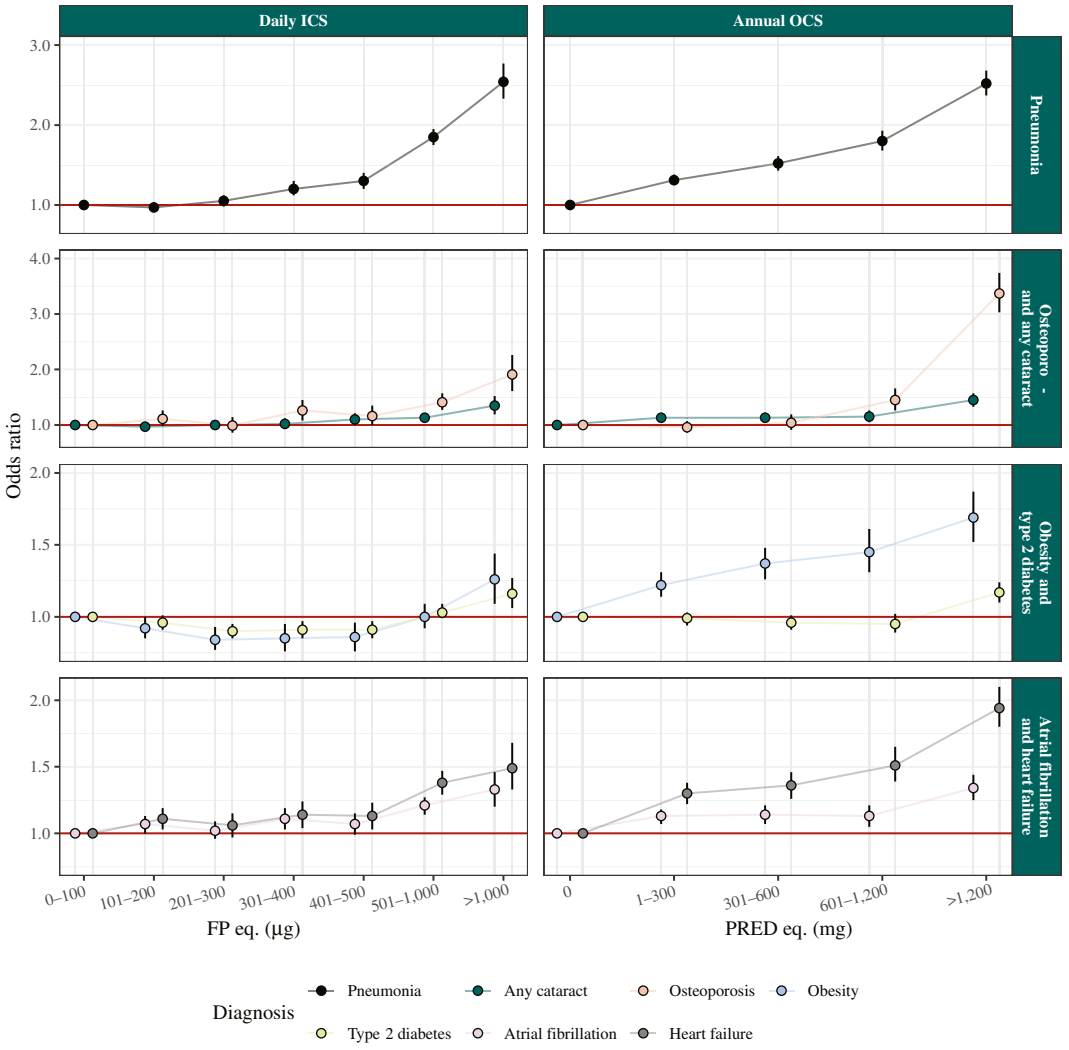

FIGURE E6. The effect of inhaled corticosteroid (ICS) and oral corticosteroid (OCS) use on the prevalence of comorbidities when patients with other indications for OCS and ICS use were excluded. The estimates were obtained from a logistic regression model in which exposure was accounted from the first 3 years of follow-up and the outcomes were assessed during the last 2 years of follow-up. The models were adjusted for age and sex. The figure presents odds ratios with 95% confidence intervals. When error bars are not visible, they are inside the symbol. *FP eq.,* Fluticasone proprionate equivalents; *PRED eq.,* prednisolone equivalents.

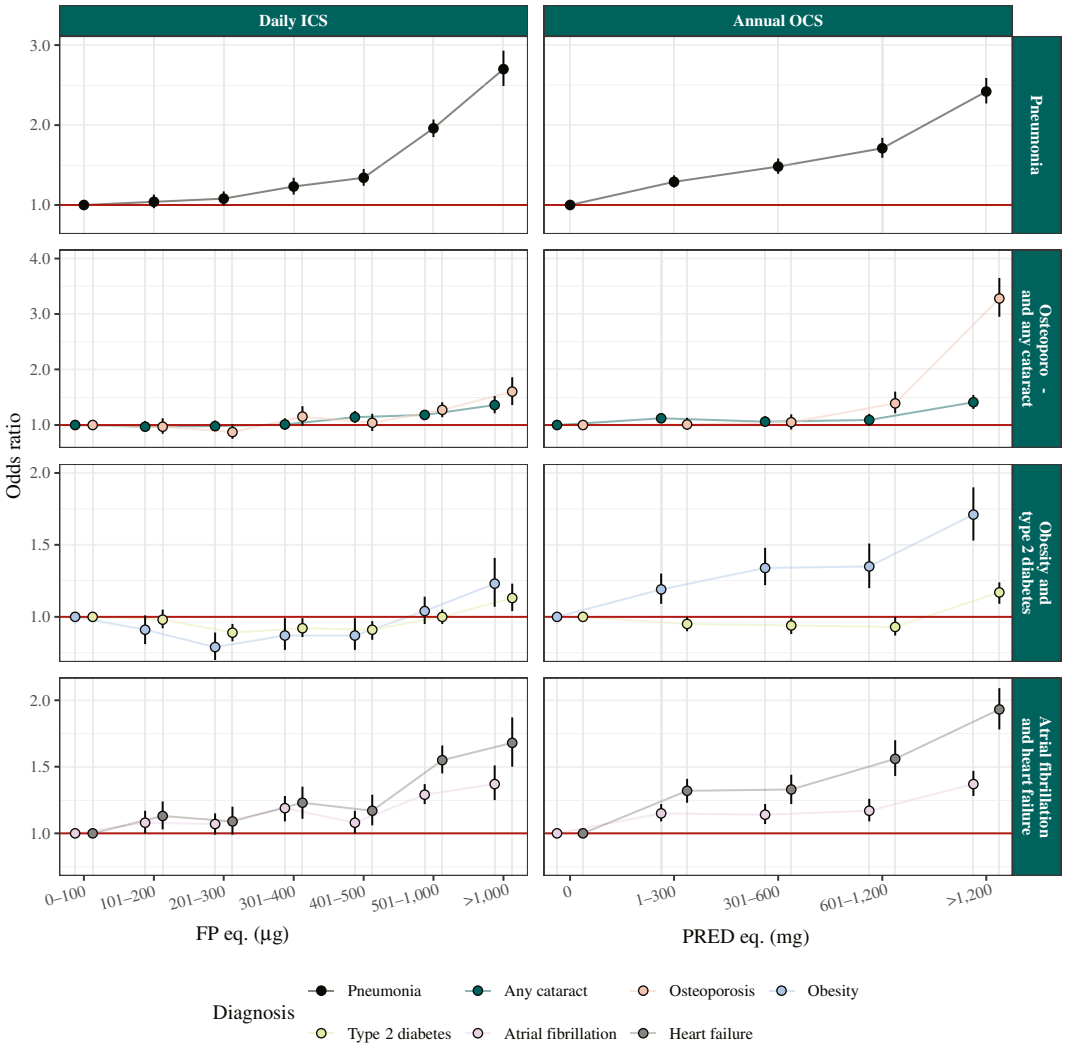

FIGURE E7. The effect of inhaled corticosteroid (ICS) and oral corticosteroid (OCS) use on the prevalence of comorbidities when patients without a reimbursement decision for asthma medication prior to January 1, 2014 were excluded. The estimates were obtained from a logistic regression model in which exposure was accounted from the first 3 years of follow-up and the outcomes were assessed during the last 2 years of follow-up. The models were adjusted for age and sex. The figure presents odds ratios with 95% confidence intervals. When error bars are not visible, they are inside the symbol. *FP eq.,* Fluticasone proprionate equivalents; *PRED eq.,* prednisolone equivalents.

TABLE E1. Correction coefficients for inhaled corticosteroids in relation to fluticasone propionate

Inhaled corticosteroid	Correction coefficient	Equipotent dose (µg) with 1,000 µg fluticasone propionate
Beclomethasone	0.625	1,600
Beclomethasone small-particle	1.25	800
Budesonide	0.625	1,600
Ciclesonide	1.5625	640
Mometasone	1.25	800
Fluticasone furoate	5.4348	184

TABLE E2. 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

TABLE E3. Excess prevalence of selected comorbidities among female and male patients*

	Continuously severe (n = 10,754)			Transiently severe (n = 15,763)		
Comorbidity	**Female***	**Male***	***P* value†**	**Female***	**Male***	***P* value†**
Influenza or pneumonia	23.8 (22.8−24.8)	23.0 (21.4−24.6)	.817	13.9 (13.2−14.6)	16.6 (15.6−17.6)	.002
Pneumonia	21.8 (20.8−22.8)	22.5 (20.9−24.1)	.822	12.9 (12.3−13.5)	15.8 (14.8−16.8)	.007
Influenza	5.8 (5.3−6.3)	4.3 (3.5−5.1)	.989	2.6 (2.3−2.9)	3.0 (2.5−3.5)	.055
Osteoporosis	5.0 (4.5−5.5)	3.0 (2.4−3.6)	<.001	2.0 (1.7−2.3)	1.0 (0.7−1.3)	.043
Any cataract	5.2 (4.7−5.7)	5.1 (4.3−5.9)	.485	1.9 (1.6−2.2)	2.5 (2.1−2.9)	.189
Senile cataract	4.3 (3.8−4.8)	4.2 (3.4−5.0)	.728	1.4 (1.2−1.6)	1.6 (1.3−1.9)	.396
Other cataract	1.5 (1.2−1.8)	1.5 (1.0−2.0)	.335	0.8 (0.6−1.0)	1.0 (0.7−1.3)	.322
Obesity	5.1 (4.6−5.6)	3.0 (2.4−3.6)	.286	2.7 (2.4−3.0)	1.7 (1.4−2.0)	.904
Type 2 diabetes	2.4 (2.0−2.8)	0.4 (0.2−0.6)	.013	1.3 (1.1−1.5)	0.2 (0.1−0.3)	.055
Any circulatory system −related disease	7.0 (6.4−7.6)	4.4 (3.6−5.2)	.024	3.5 (3.1−3.9)	4.2 (3.7−4.7)	.061
Atherosclerosis	0.9 (0.7−1.1)	1.5 (1.0−2.0)	.980	0.8 (0.6−1.0)	0.9 (0.6−1.2)	.338
Atrial fibrillation	4.2 (3.7−4.7)	4.9 (4.1−5.7)	.574	2.9 (2.6−3.2)	4.8 (4.2−5.4)	.080
Chronic ischemic heart disease	2.6 (2.2−3.0)	1.6 (1.1−2.1)	.003	1.6 (1.4−1.8)	2.6 (2.2−3.0)	.775
Heart failure	7.6 (7.0−8.2)	6.1 (5.2−7.0)	.004	5.7 (5.3−6.1)	5.7 (5.1−6.3)	.368
Hypertension	3.4 (3.0−3.8)	0.9 (0.5−1.3)	<.001	0.6 (0.5−0.7)	0.3 (0.2−0.4)	.107

*Age- and sex-standardized excess prevalences (%) [95% CI] are presented.

†Age-adjusted *P* value for the interaction term between sex and severity, estimated using a logistic regression model separately for continuously severe and transiently severe asthma and using the nonsevere group as the reference group.