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Increased Mortality in Patients with Corticosteroid-dependent Asthma: A Nationwide Population-based Study

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Abstract

Background: Chronic systemic corticosteroid (CS) therapy is associated with an increased risk of mortality in patients with many chronic diseases. However, it has not been elucidated whether chronic, systemic CS therapy is associated with increased mortality in patients with asthma. The aim of this study was to determine the effects of chronic, systemic CS therapy on long-term mortality in adult patients with asthma.

Methods: A population-based matched cohort study of men and women aged 18 years or older with asthma was performed using the Korean National Health Insurance Service database from 2005 to 2015. Hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality among patients in the CS-dependent cohort (CS use ⩾6 months during baseline period) relative to those in the CS-independent cohort (CS use <6 months during baseline period) was evaluated.

Results: The baseline cohort included 466,941 patients with asthma, of whom 8,334 were CS-dependent and 456,607 were CS-independent. After 1:1 matching, 8,334 subjects with CS-independent asthma were identified. The HR of mortality associated with CS-dependent asthma relative to CS-independent asthma was 2.17 (95% CI, 2.04–2.31). In patients receiving low-dose CS, the HR was 1.84 (95% CI, 1.69–2.00), and that for those receiving high-dose CS was 2.56 (95% CI, 2.35–2.80).

Conclusions: In this real-world, clinical practice, observational study, chronic use of systemic CS was associated with increased risk of mortality in patients with asthma, with a significant dose-response relationship between systemic CS use and long-term mortality.

Keywords: long-term mortality, chronic use, corticosteroid, severe asthma

Introduction

Asthma affects 5 to 10% of the population and contributes to approximately 0.4 million deaths annually, worldwide [1]. Although severe asthma affects only 4–10% of all asthma patients [2-4], that population has more asthma-related symptoms, increased risk of acute exacerbation, and higher morbidity compared to those with non-severe asthma [5]. Accordingly, severe asthma patients consume more healthcare resources than non-severe asthma patients [6-9].

Severe asthma is difficult to manage, and 20–60% of patients with severe asthma need regular use of a systemic corticosteroid (CS) [10, 11]. Despite the beneficial effects of systemic CS [12], chronic use in asthma patients is associated with many serious complications [8, 13-17].

Chronic systemic CS use is associated with an increased risk of mortality in patients with many chronic diseases, such as rheumatoid arthritis (RA) and inflammatory bowel disease [18, 19]. However, little evidence is available on the risk of mortality associated with chronic systemic CS therapy in asthmatic patients [20]. In addition, it is not known whether there is a dose-dependent relationship between chronic CS use and long-term mortality in these patients.

For this study, we followed a cohort of 8,334 patients with CS-dependent asthma using data from the Korean National Health Insurance Service (NHIS) to evaluate long-term mortality compared with a 1:1 matched cohort of CS-independent asthma patients. We also evaluated dose-dependency in the relationship between systemic CS dose and risk of mortality.

Methods

Data source and study population

This study was approved by the Institutional Review Board of Hanyang University Hospital (IRB number: HYUH 2017-09-051). The requirement of informed consent from the participants was waived because the NHIS database was constructed after anonymization. The NHIS provides mandatory health care for nearly all Korean citizens. The NHIS collects health data from nearly all 50 million of its insured subjects, including admission and outpatient visit records, diagnoses, drug prescriptions, national health examination data, and death. The NHIS provides all above-mentioned information for research purposes [21].

From January 1, 2005, to December 31, 2005, there were 751,180 asthma patients aged 18 years or older. Of those potential participants, we excluded 1,277 patients with only one visit associated with ICD J45-46 as a major or minor diagnosis. Of the remaining 749,903 patients, we further excluded 50,632 who had RA (M05-M06), systemic lupus erythematosus (M32), systemic sclerosis (L94) (n=29,300), inflammatory bowel disease (K50-K51) (n=2,053), or malignancy (C00-C99) (n=24,377) and those with no claims for asthma-related medications (n=232,330). Thus, a total of 466,941 patients was included (**Figure E1**).

Definitions

The index date was defined as 12 months from the first prescription of asthma-related medication with ICD codes J45-46 as a major or minor diagnosis between January 1, 2005, and December 31, 2005. The baseline period was defined as 12 months before the index date.

The follow-up period was from the index date to the date of death or December 31, 2015, whichever was sooner (**Figure E2**).

Asthma in adults was defined according to the following criteria: (1) aged 18 or older, (2) at least two claims under ICD-10 codes J45-46, and (3) at least one claim in the baseline period for prescription of asthma-related drugs such as inhaled or systemic CS, bronchodilators, leukotriene receptor antagonists, and xanthine derivatives [22-24]. CS-dependent asthma was defined as: (1) presence of asthma and (2) prescription of systemic CS under codes ICD-10 J45-46 for at least six months in the baseline period [8, 25, 26]. Otherwise, patients were classified as having CS-independent asthma. The proportion of patients who met the definition of both groups during the follow-up are summarized in **supplemental table E1**.

Baseline comorbidities were defined as comorbidities with at least one claim under ICD-10 codes as a major diagnosis during the baseline period. New-onset comorbidities were defined as at least one claim under ICD-10 codes as a major diagnosis during follow-up but not the baseline period, as follows: Diabetes mellitus (E10-14), Cushing disease (E24 and E24.2), adrenal insufficiency (E27.3-E27.4), bone necrosis (M87), osteoporosis (M80-M82), vertebral or pelvic bone fracture (S22.0-S22.2, S32.0, and M48.4), pneumonia (J12-J18), tuberculosis (A15-A19), hypertension (I10-I15), angina (I20), myocardial infarction (I21), heart failure (I50), peptic ulcer (K25-K27), gastrointestinal bleeding (K92.0, K92.1, and K92.2), glaucoma (H40 and H42), and cataract (H25, H26, and H28).

To analyse causes of death, we used mortality data provided by Statistics Korea, an initiative of the Ministry of Strategy and Finance of South Korea [21]. Causes of mortality were classified as respiratory diseases (J00-K00) including chronic lower respiratory diseases (J40-J47), cardiovascular diseases (I00-I99) including hypertension (I10-I15), ischemic heart

diseases (I20-I25), cerebrovascular diseases (I60-I69), malignant neoplasms (C00-C97), injury, poisoning, and external causes (S00-T98), endocrine diseases (E00-E90) including diabetes mellitus (E10-E14), gastrointestinal diseases (K00-K93), neurologic diseases (G00-G99), mental and behavioural disorders (F00-F99), musculoskeletal and connective tissue diseases (M00-M99) including osteoporosis (M80-M82), and others.

We classified CS-dependent asthma patients into high-dose and low-dose groups based on the median daily doses of systemic CS used. Low-dose systemic CS was defined as less than a median of 5.5 mg/day of a prednisolone equivalent dose, and high-dose CS was a median of 5.5 mg/day or higher prednisolone equivalent dose during the baseline period.

Asthma-related emergency department (ED) visit or hospitalisation was defined as a visit to an ED or admission to a hospital under ICD-10 codes J45-46 as a major or minor diagnosis during the follow-up period.

Main outcomes and measures

The primary outcome was all-cause mortality during the follow-up period. Secondary outcomes were healthcare use (all-cause or asthma-related ED visit or hospitalisation) and new comorbidities during the follow-up period. We additionally evaluated whether there were dose-dependent relationships between these clinical outcomes and systemic CS dose.

Statistical analysis

Baseline characteristics (age group, sex, type of insurances, Charlson comorbidity index [CCI] [27], comorbidities, and asthma-related medications) between the patients in CS-dependent and CS-independent cohort were compared using the McNemar test.

Controls were identified through 1:1 matching in which the nearest available neighbor for each case was selected as a control [28]. That is, within the same categories of sex and type of insurance, a control with similar age and CCI was matched for each CS-dependent asthma patient. To assess the effect of chronic CS use on the main outcomes of mortality, healthcare use (ED visits and hospital admissions), new comorbidities, and their incidence rates were calculated per 100,000 person-years (PYs) and compared between the two patient groups by the normal approximation test for binomials.

The Kaplan-Meier method was used to estimate survival curves during the follow-up period, and survival was compared among groups by the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for the main outcomes among patients in the CS-dependent cohort relative to those in the CS-independent cohort were evaluated using Cox proportional hazard regression model. To further adjust for the effects of comorbidities on mortality, we performed a Cox proportional hazard regression model with covariate adjustment using propensity scores based on the number of comorbidities.

We also determined HRs for each cause of mortality. We used a cause-specific and subdistribution proportional hazards regression model to account for competing risks caused by mortality from other causes [29].

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All tests were two-sided, and p values<0.05 were considered statistically significant.

Results

Population

The baseline cohort comprised 466,941 patients with asthma, of whom 8,334 (1.8%) were

CS-dependent and 458,607 were CS-independent (**supplementary figure E1**). After matching, the study cohort included 8,334 subjects with CS-dependent asthma matched with 8,334 subjects with CS-independent asthma. As shown in **table 1**, the baseline characteristics between the two cohorts were well balanced in age, sex, type of insurance, and CCI. However, compared with the CS-independent cohort, more patients in the CS-dependent cohort had the following comorbidities ($p<0.001$ for each comorbidity comparison except for angina); diabetes mellitus, Cushing's syndrome, and adrenal insufficiency, osteoporosis, vertebral or pelvic bone fracture, pneumonia, tuberculosis, angina ($p=0.033$), and congestive heart failure. Regarding asthma-related medications, the proportions of patients who received inhaled CS (ICS) (74.8% *versus* 55.1%; $p<0.001$) and long-acting β_2 agonist (LABA) (64.3% *versus* 42.3%; $p<0.001$) were higher in the CS-dependent cohort than in the CS-independent cohort.

Mortality

The overall mortality was 5,191/100,000 PY during a median of 9.5 years (interquartile range, 5.5-9.9 years) of follow-up. All-cause mortality was higher in the CS-dependent cohort than in the CS-independent cohort (6,760/100,000 PY *versus* 3,833/100,000 PY, $p<0.001$, **figure 1A**), which is consistent with our survival analysis ($p<0.001$ for log-rank test) (**figure 2**). Patients in the CS-dependent cohort were 2.17 (95% CI 2.04–2.31) times more likely to die during the follow-up period than those in the CS-independent cohort (**table 2).** Regardless of sex (**male in supplementary figure E3 and female in supplementary figure E4**) and age group (**age<65 years in supplementary figure E5 and age⩾65 years in figure E6**), there was a significant difference in survival between the two groups ($p<0.001$ for each sex and age group comparison). The HR of mortality in the CS-dependent cohort relative to the CS-independent cohort remained significant after adjustment for the number of comorbidities

(HR 2.10, 95% CI 1.97-2.23).

As shown in **figure 3**, the survival analysis found significant differences by systemic CS dose ($p<0.001$) in the proportion of subjects who survived. In a dose-dependent manner, those who received low-dose and high-dose CS had 1.84 (95% CI 1.69–2.00) and 2.56 (95% CI 2.35–2.80) times higher mortality rates, respectively, than patients in the CS-independent cohort (**table 2**). Survival analyses performed using three categories representing CS doses (<5mg, 5-10mg, and ⩾10mg of prednisolone equivalents) also showed significant differences in the proportion of subjects who survived (**Supplementary figure E7**).

The common causes of mortality in asthma patients were respiratory diseases (36.3%), cardiovascular diseases (19.3%), malignant neoplasms (16.6%), injury, poisoning, and external causes (5.1%), and endocrine diseases (3.4%) (**table 3**). The mortality risk associated with respiratory diseases (HR 3.12, 95% CI 2.85-3.42), cardiovascular diseases (HR 1.28, 95% CI 1.15-1.43), malignant neoplasms (HR 1.14, 95% CI 1.01-1.28), injury, poisoning, and external causes (HR1.40, 95% CI 1.13-1.74), and endocrine diseases (HR 1.71, 95% CI 1.30-2.23) were higher in the CS-dependent cohort than in the CS-independent cohort. When considering competing risks caused by mortality due to other diseases, mortality risks were especially significant for chronic respiratory diseases (subdistribution HR 2.96, 95% CI 2.70-3.24) and endocrine diseases (subdistribution HR 1.49, 95% CI 1.14-1.95).

Healthcare use

As shown in **figure 1**, the rates of annual ED visits (per 100,000 PY) (27,429 *versus* 18,794; $p<0.001$, **figure 1B**) including asthma-related ED visits (8,077 *versus* 2,681; $p<0.001$, **figure 1C**) and annual hospitalisations (68,454 *versus* 21,837; $p<0.001$, **figure 1B**) including

asthma-related hospitalisations (68,454 *versus* 21,837; p<0.001, **figure 1C**) were higher in the CS-dependent cohort than in the CS-independent cohort. The HRs of ED visit and hospitalisation showed a tendency to increase as the systemic CS dose increased (**table 2**).

The occurrence of new comorbidities

The occurrence of new comorbidities is summarized in **supplementary table E2**. As shown in **supplementary figure E8**, compared with the patients in the CS-independent cohort, those in the CS-dependent cohort were more likely to have the following comorbidities: diabetes mellitus, Cushing's syndrome, adrenal insufficiency, bone necrosis, osteoporosis, vertebral or pelvic bone fracture, pneumonia, tuberculosis, hypertension, myocardial infarction, congestive heart failure, gastrointestinal bleeding, and cataract. The HRs of all those comorbidities except for adrenal insufficiency and cataract showed a tendency to increase as the systemic CS dose increased.

Discussion

Using a large-scale, population-based, longitudinal cohort study, we demonstrated that long-term use of systemic CS correlates with increased risk of mortality, ED visits, hospitalisation, and development of new comorbidities in asthma patients in a dose-dependent manner.

With the development of new drugs, great improvements have been made in the treatment of patients with severe asthma, especially the T2 phenotype [30]. However, a substantial proportion of patients is still CS dependent [31], and despite some improvement

[12], these patients often suffer from adverse events associated with CS [8, 13-17, 32]. Although higher mortality is expected in patients with CS-dependent asthma, and mortality is one of the most important issues in these patients, few longitudinal data addressing their long-term mortality are available [33]. Recently, Bourdin and colleagues evaluated the long-term treatment outcomes of 52 patients with CS-dependent asthma and found that half of them died over 20 years [34]. It is also noteworthy that more than 60% of these patients died of fatal asthma, indicating the importance of mortality data in that population [34]. Extending those findings with a very large population-based longitudinal study, our study shows that about half of the patients died over 10 years, which is significantly higher than the percentage of CS-independent patients who died during the same period.

Another important finding of our study is that systemic CS use in asthma is associated with a dose-dependent increase in mortality rate. A dose-dependent relationship between systemic CS and the mortality rate was demonstrated in subjects with RA [35]. On the contrary, the use of CS-sparing drugs such as methotrexate decreased mortality in patients with RA [36]. In a similar fashion, CS-sparing therapy using antitumor necrosis factor-α–directed therapy in Crohn's disease reduced mortality [37]. These findings suggest that CS-sparing therapies using new biologics could have survival benefits for patients with severe asthma. Fortunately, recent studies showed that new biologics can significantly reduce severe acute exacerbations, providing systemic CS sparing effects for patients with severe asthma [30]. These promising outcomes will hopefully improve mortality in patients with CS-dependent asthma.

The major causes of mortality in patients with CS-dependent asthma were respiratory diseases, cardiovascular diseases, malignant neoplasms, injury, poisoning, and external causes, and endocrine diseases. Compared with patients in the CS-independent cohort, those

in the CS-dependent cohort were at higher risk to die due to the above-mentioned diseases, with the highest risk of mortality associated with chronic lower respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease, and pneumonia). When we considered competing risks caused by other causes of death, risks due to chronic respiratory diseases and endocrine diseases were especially significant, suggesting that improved treatment strategies for those diseases are urgently needed to effectively reduce mortality associated with chronic CS use.

As shown in previous studies [6-8, 38], chronic systemic CS use is associated with the occurrence of new comorbidities and healthcare use. We carefully suggest that the occurrence of these comorbidities might have contributed to the higher mortality of patients in the CS-dependent asthma cohort. In addition, a recent study showed that ⩾ four CS prescriptions are significantly associated with subsequent acute exacerbation of asthma [17]. In line with that result, our study showed that asthma-related ED visits and hospitalisations were significantly higher among patients with CS-dependent asthma than among those with CS-independent asthma. It is likely that the high exacerbation rate might also have been associated with the increased mortality we found in patients with CS-dependent asthma.

Whether systemic CS and doses thereof are appropriate should be discussed. Surprisingly, about 25% of CS-dependent patients did not use ICS or ICS/LABA, which suggests that systemic CS was inappropriately prescribed in Korea. There are a number of possible explanations for this phenomenon. First, the proportion of very old patients in our study was high. In real-world contexts, non-adherence regarding ICS use is an important problem in elderly patients [39]. Second, low prescription rates of ICS have been documented in real-world practice, especially in primary clinics in Korea [22-24]. Third, some physicians may believe that ICS is not necessary when a patient receives systemic CS, which is more

potent than ICS. However, regardless of the reasons, our results suggest that efforts to reduce systemic CS use and enhance ICS use are urgently needed to improve the treatment outcomes of CS-dependent asthma patients. CS doses are also an important issue. In our study, we observed a dose-dependent association between CS dose and unfavourable outcomes. Thus, CS-sparing strategies administering minimal doses of systemic CS are recommended.

This study has several limitations. First, it was performed in a single country, and the clinical characteristics of patients with CS-dependent asthma might vary by country or ethnicity. For example, patients with CS-dependent asthma in this study were relatively older than those in a previous study [10]. However, regardless of the age group, the mortality in the CS-dependent group was significantly higher than that in the CS-independent group. Second, Second, no current definition of chronic asthma has been validated using electronic health records [40]. Many previous studies defined chronic asthma using the US Healthcare Effectiveness Data and Information Set (HEDIS) criteria, which includes assessments for any of the following asthma-related events over periods of 12 and 24 months: 1) ED visits, 2) hospitalisation, 3) outpatient visits and two asthma prescriptions, or 4) four asthma prescriptions [40]. Since data associated with ED visits and hospitalisation are also included as claims data in the NHIS database, the definition of chronic asthma used in this study is very similar to that recognised by HEDIS criteria. In addition, we used the same definition used in several previous studies evaluating asthma in Korea using the NHIS database [22-24]. Thus, despite some limitations, the definition of asthma used in this study is acceptable in the current situation, as an internationally-accepted definition of chronic asthma is not available. Third, the proportion of patients who met the definition of CS-dependent asthma gradually decreased during follow-up, which might have attenuated the accumulating effects of systemic CS use. Despite this limitation, our results clearly show that even chronic CS use over a certain time period may be associated with very unfavourable treatment outcomes. In

addition, using a definition of CS-dependent asthma that has been used in previous studies [8, 25, 26] allowed us to identify a stable control group; more than 97% of the patients who were classified as CS-independent remained CS-independent during follow-up. The stable control group also underscores the reliability of our observations of higher mortality in our CS-dependent asthma cohort.

In summary, in this population-based retrospective cohort study, chronic systemic CS use was associated with a higher rate of mortality in a dose-dependent manner in asthma patients. CS-sparing treatment strategies are urgently needed to improve the treatment outcomes of patients with CS-dependent asthma.

Author's contribution

Literature search - All authors; study design - Hyun Lee, Jiin Ryu, Eunwoo Nam, Ji-Yoing Moon, Ho Joo Yoon, and Sang-Heon Kim; Data analysis - Hyun Lee, Jiin Ryu, Eunwoo Nam, and Sang-Heon Kim; Data interpretation - All authors; Writing - Hyun Lee, Jiin Ryu, Eunwoo Nam, and Sang-Heon Kim; Tables and figures - Hyun Lee, Jiin Ryu, and Sang-Heon Kim

Disclosure of potential conflict of interest

All authors have no conflict of interest to disclose.

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the study, analysis, and interpretation of data, and writing the current manuscript.

Ethics committee approval

This study was approved by the Institutional Review Board of Hanyang University Hospital (IRB number: HYUH 2017-09-051). The requirement of informed consent from the participants was waived because the NHIS database was constructed after anonymization.

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TABLE 1 Descriptive Characteristics of the Study Population

	Total (N=16,668)	CS-dependent asthma (n=8,334)	CS-independent asthma (n=8,334)	p-value
Age, years	66.0 ± 12.5	66.0 ± 12.5	66.0 ± 12.5	0.545
Twenties	144 (0.9)	72 (0.9)	72 (0.9)	1.0
Thirties	482 (2.9)	241 (2.9)	241 (2.9)	
Forties	1,161 (7.0)	580 (7.0)	581 (7.0)	
Fifties	2,602 (15.6)	1,301 (15.6)	1,301 (15.6)	
Sixties	4,934 (29.6)	2,467 (29.6)	2,467 (29.6)	
≥ Seventies	7,345 (44.1)	3,673 (44.1)	3,672 (44.1)	
Sex				1.0
Male	9,386 (56.3)	4,693 (56.3)	4,693 (56.3)	
Female	7,282 (43.7)	3,641 (43.7)	3,641 (43.7)	
Type of insurance				1.0
Self-employed health insurance	6,770 (40.6)	3,385 (40.6)	3,385 (40.6)	
Employee health insurance	9,090 (54.5)	4,545 (54.5)	4,545 (54.5)	
Medical aid	808 (4.9)	404 (4.9)	404 (4.9)	
Charlson comorbidities index	3.75 ± 2.3	3.75 ± 2.3	3.75 ± 2.3	1.0
Comorbidities				
Metabolic disease	5,104 (30.6)	2,709 (32.5)	2,395 (28.7)	<0.001
Diabetes mellitus	4,953 (29.7)	2,580 (31.0)	2,373 (28.5)	<0.001

Cushing’s syndrome	264 (1.6)	232 (2.8)	32 (0.4)	<0.001
Adrenal insufficiency	164 (1.0)	142 (1.7)	22 (0.3)	<0.001
Bone disease	2,877 (17.3)	1,717 (20.6)	1,160 (13.9)	<0.001
Bone necrosis	63 (0.4)	39 (0.5)	24 (0.3)	0.060
Osteoporosis	2,632 (15.8)	1,574 (18.9)	1,058 (12.7)	<0.001
Vertebral or pelvic bone fracture	628 (3.8)	406 (4.9)	222 (2.7)	<0.001
Infectious disease	4,833 (29.0)	2,743 (32.9)	2,090 (25.1)	<0.001
Pneumonia	4,469 (26.8)	2,558 (30.7)	1,911 (22.9)	<0.001
Tuberculosis	1,051 (6.3)	613 (7.4)	438 (5.3)	<0.001
Cardiovascular disease	9,811 (58.9)	4,981 (59.8)	4,830 (58.0)	<0.001
Hypertension	9,110 (54.7)	4,586 (55.0)	4,524 (54.3)	0.096
Angina	2,064 (12.4)	1,075 (12.9)	989 (11.9)	0.033
Myocardial infarction	463 (2.8)	242 (2.9)	221 (2.7)	0.311
Congestive heart failure	1,767 (10.6)	1,008 (12.1)	759 (9.1)	<0.001
Gastrointestinal disease	7,075 (42.5)	3,572 (42.9)	3,503 (42.0)	0.202
Peptic ulcer disease	7,032 (42.2)	3,547 (42.6)	3,485 (41.8)	0.252
Gastrointestinal bleeding	165 (1.0)	79 (1.0)	86 (1.0)	0.574
Ophthalmologic disease	740 (4.4)	380 (4.6)	360 (4.3)	0.442
Glaucoma	103 (0.6)	55 (0.7)	48 (0.6)	0.490
Cataract	661 (4.0)	337 (4.0)	324 (3.9)	0.599
Medication during follow-up[#]				

Any ICS	10,827 (65.0)	6,234 (74.8)	4,593 (55.1)	<0.001
Any LABA	8,888 (53.3)	5,360 (64.3)	3,528 (42.3)	<0.001
SABA	11,965 (71.78)	6,801 (81.61)	5,164 (61.96)	<0.001
LTRA	9,401 (56.40)	4,952 (59.42)	4,449 (53.38)	<0.001

Data are presented as frequency (%) and mean with standard deviation.
CS, corticosteroid; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist; LTRA, leukotriene receptor antagonist. [#]: Some patients received more than one medication.

TABLE 2 The Effects of Systemic CS Dose on Overall Mortality, ED visits, and Hospitalisations

	Mortality		Annual ED visits				Annual hospitalisations			
	All-cause		All-cause		Asthma-related		All-cause		Asthma-related	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All patients										
CS-independent asthma	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
CS-dependent asthma										
Low dose	1.84	1.69-2.00	1.26	1.17-1.37	3.12	2.64-3.69	1.54	1.44-1.64	2.48	2.28-2.70
High dose	2.56	2.35-2.80	1.43	1.32-1.55	3.61	3.06-4.25	1.78	1.67-1.91	3.24	2.97-3.53
Overall	2.17	2.04-2.31	1.34	1.27-1.42	3.37	2.99-3.78	1.65	1.58-1.73	2.84	2.67-3.01

CS: corticosteroid; ED: emergency department; HR: hazard ratio; CI: confidence interval; Ref: reference.

TABLE 3 Hazard ratios (95% confidence intervals) for mortality in the CS-dependent cohort relative to the CS-independent cohort

	Mortality rate			Cause-specific HR (95% CI)	Cause-specific subdistribution HR[¶] (95% CI)
	Total[#] (N = 6,547)	CS-dependent cohort (n = 3759)	CS-independent cohort (n = 2590)		
Respiratory diseases	**2,379 (36.3)**	**1,740/2,379 (73.1)**	**639/2,379 (26.9)**	**3.12 (2.85-3.42)**	**2.96 (2.70-3.24)**
Chronic lower respiratory diseases	1,928 (29.4)	1,467/1,928 (76.1)	461/1,928 (23.9)	3.63 (3.27-4.03)	3.41 (3.07-3.78)
Asthma	553 (8.4)	437/553 (79.0)	116/553 (21.0)	4.27 (3.48-5.24)	3.83 (3.13-4.71)
COPD	1,332 (20.3)	999/1,332 (75.0)	333/1,332 (25.0)	3.42 (3.02-3.88)	3.13 (2.77-3.54)
Pneumonia	247 (3.8)	132/247 (53.4)	115/247 (46.6)	1.37 (1.07-1.76)	1.14 (0.89-1.47)
Cardiovascular diseases	**1,266 (19.3)**	**664/1,266 (52.4)**	**602/1,266 (47.6)**	**1.28 (1.15-1.43)**	**1.11 (0.99-1.23)**
Hypertension	139 (2.1)	73/139 (52.5)	66/139 (47.5)	1.28 (0.92-1.79)	1.10 (0.79-1.53)
Ischemic heart disease	365 (5.6)	196/365 (53.7)	169/365 (46.3)	1.33 (1.08-1.63)	1.16 (0.94-1.42)
Heart failure	137 (2.1)	77/137 (56.2)	60/137 (43.8)	1.49 (1.06-2.08)	1.27 (0.91-1.78)
Cerebrovascular disease	411 (6.3)	199/411 (48.4)	212/411 (51.6)	1.09 (0.90-1.33)	0.94 (0.77-1.14)
Malignant neoplasms	**1,084 (16.6)**	**535/1,084 (49.4)**	**549/1,084 (50.6)**	**1.14 (1.01-1.28)**	**0.97 (0.86-1.09)**
Lung cancer	422 (6.4)	217/422 (51.4)	205/422 (48.6)	1.23 (1.02-1.49)	1.05 (0.87-1.28)
Other cancer	662 (10.1)	318/662 (48.0)	344/662 (52.0)	1.08 (0.93-1.26)	0.92 (0.79-1.07)
Injury, poisoning, and external causes	**331 (5.1)**	**181/331 (54.7)**	**150/331 (45.3)**	**1.40 (1.13-1.74)**	**1.21 (0.97-1.50)**
Endocrine diseases	**221 (3.4)**	**132/221 (59.7)**	**89/221 (40.3)**	**1.71 (1.30-2.23)**	**1.49 (1.14-1.95)**
Diabetes mellitus	206 (3.1)	123/206 (59.7)	83/206 (40.3)	1.71 (1.29-2.25)	1.49 (1.12-1.96)
Gastrointestinal diseases	**146 (2.2)**	**75/146 (51.4)**	**71/146 (48.6)**	**1.24 (0.90-1.72)**	**1.06 (0.76-1.46)**
Neurologic diseases	**119 (1.8)**	**48/119 (40.3)**	**71/119 (59.7)**	**0.79 (0.55-1.14)**	**0.66 (0.46-0.95)**
Mental and behavioural disorders	**59 (0.9)**	**31/59 (52.5)**	**28/59 (47.5)**	**1.31 (0.78-2.18)**	**1.10 (0.66-1.84)**

Musculoskeletal and connective tissue diseases	**38 (0.6)**	**22/38 (57.9)**	**16/38 (42.1)**	**1.59 (0.84-3.03)**	**1.37 (0.72-2.62)**
Osteoporosis	20 (0.3)	11/20 (55.0)	9/20 (45.0)	1.40 (0.58-3.39)	1.22 (0.51-2.95)
Others	**904 (13.8)**	**529/904 (58.5)**	**375/904 (41.5)**	**1.63 (1.43-1.86)**	**1.42 (1.25-1.62)**

Data are presented as number frequency (%) and risk ratios (95% CI).

CS: corticosteroid; HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease.

[#]: Sixty two patients who did not have information regarding cause of mortality were excluded; [¶]: Subdistribution HR of the disease-specific cause of mortality was calculated with other cause of mortality as a competing risk.

Figure legends

FIGURE 1 Comparison of all-cause mortality, ED visits, and hospitalisations during follow-up.

A) All-cause mortality; B) All-cause ED visits and hospitalisations; C) Asthma-related ED visits and hospitalisations

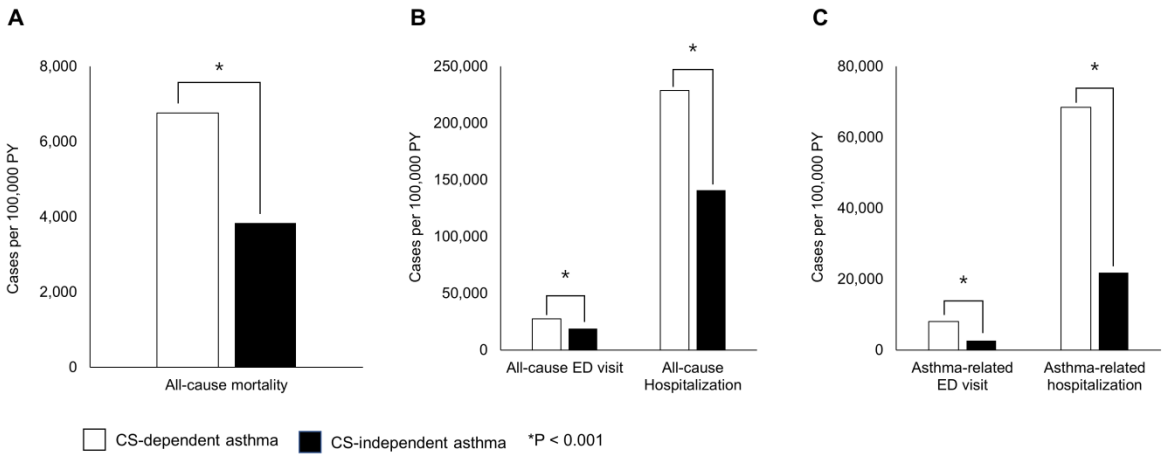
CS: corticosteroid; PY: person-years; ED: emergency department

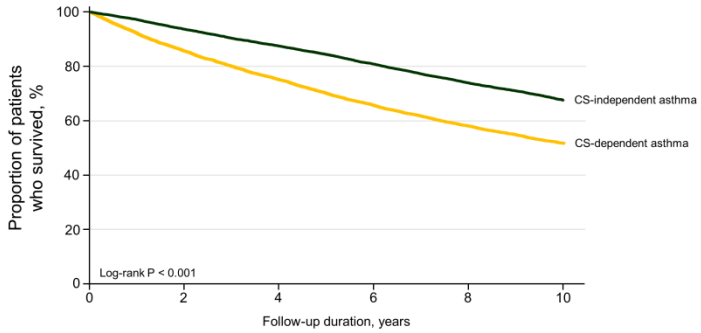
FIGURE 2 Kaplan-Meier survival plot of time to death.

CS: corticosteroid

FIGURE 3 Kaplan-Meier survival plot of time to death according to systemic CS dose.

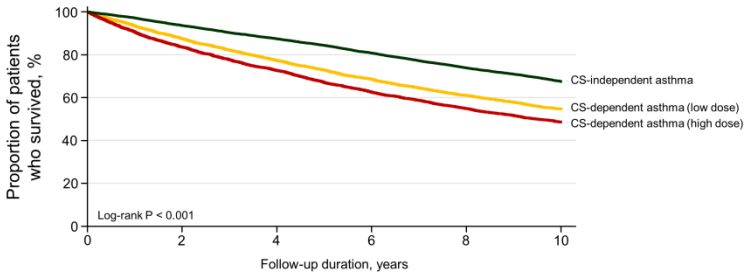
CS: corticosteroid


A
B
C
8,000
6,000
4,000
2,000
0
Cases per 100,000 PY
*
All-cause mortality
250,000
200,000
150,000
100,000
50,000
0
All-cause ED visit
All-cause Hospitalization
80,000
60,000
40,000
20,000
Asthma-related ED visit
Asthma-related hospitalization
CS-dependent asthma
CS-independent asthma
*P < 0.001



No. at risk

CS-independent asthma	8334	7904	7297	6735	6159	29
CS-dependent asthma	8334	7129	6249	5462	4835	47



No. at risk

CS-independent asthma	8334	7904	7297	6735	6159	29
CS-dependent asthma (low dose)	4167	3646	3220	2855	2544	18
CS-dependent asthma (high dose)	4167	3483	3029	2607	2291	29

Supplementary TABLE E1 The proportion of patients who met the definition of CS-dependent asthma or CS-independent asthma during the follow-up period

Supplementary TABLE E2 The occurrence of new comorbidities

Supplementary FIGURE E1 Flow chart of the study population

CS: corticosteroid.

Supplementary FIGURE E2 Study design schema

Index date was defined as 12 months from the first prescription of asthma-related medication with ICD codes J45-46 as a major or minor diagnosis between January 1, 2015, and December 31, 2005· Baseline period was defined as 12 months before the index date· Follow-up duration was from the index date to death or December 31, 2015, whichever was sooner.

Supplementary FIGURE E3 Kaplan-Meier survival plot of time to death from index date to the end of the 10-year follow-up in males.

Supplementary FIGURE E4 Kaplan-Meier survival plot of time to death from index date to the end of the 10-year follow-up in females.

Fig E5 in the supplement. Kaplan-Meier survival plot of time to death from index date to the end of the 10-year follow-up in patients aged < 65 years.

Fig E6 in the Supplement. Kaplan-Meier survival plot of time to death from index date to the end of the 10-year follow-up in patients aged ⩾ 65 years.

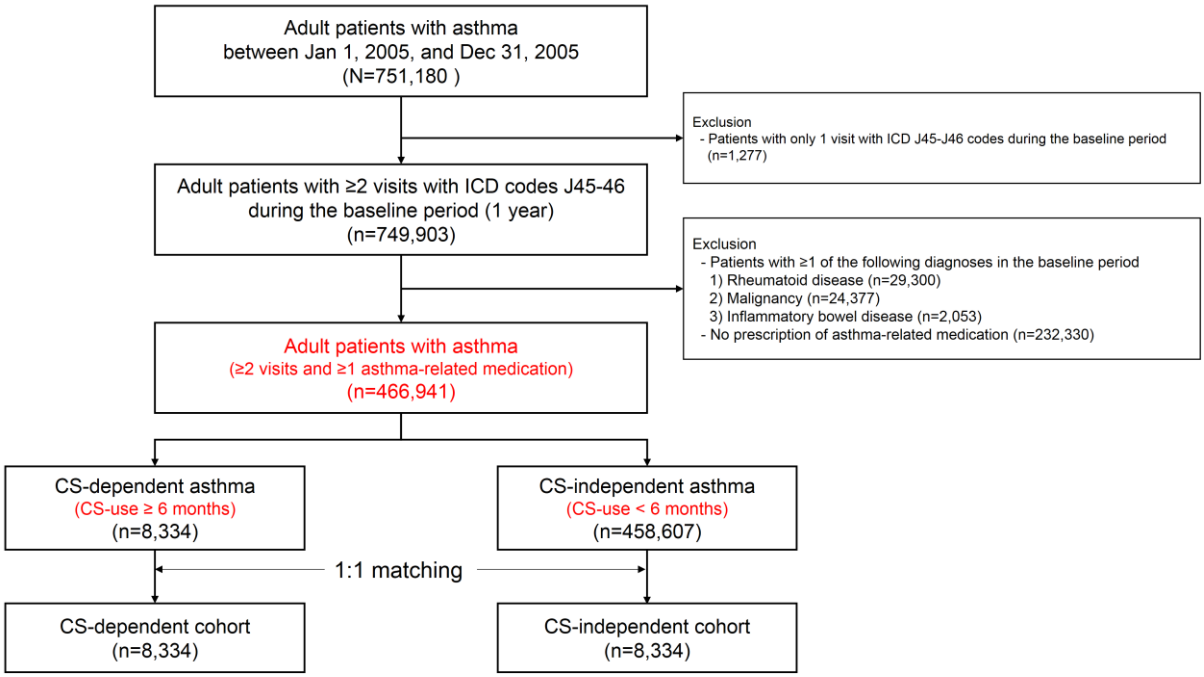
Fig E7 in the supplement. Kaplan-Meier survival plot of time to death according to systemic CS dose.

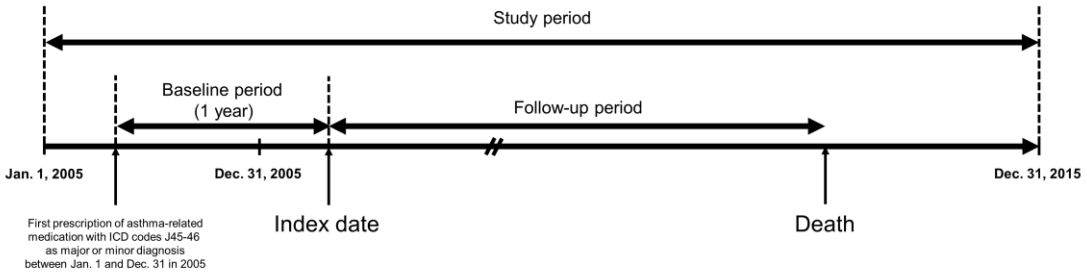
CS: corticosteroid

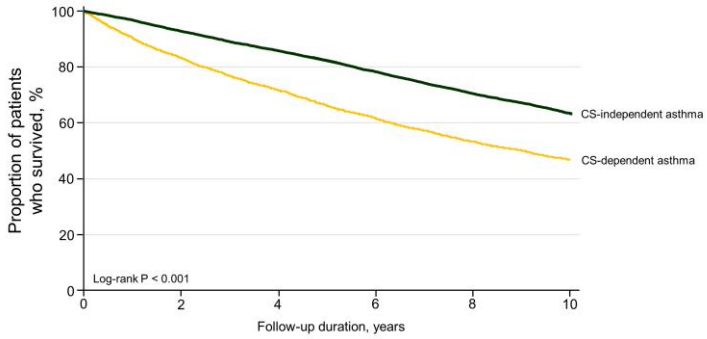
Low-dose, moderate-dose and high-dose systemic CS were defined as less than a median of 5.0 mg/day, 5.0-10.0 mg/day, and 10.0 mg/day or higher prednisolone equivalent dose during the baseline period, respectively.

Fig E8 in the supplement. Forest plot of the hazard ratios for the occurrence of new comorbidities in patients with CS-dependent asthma according to systemic CS dose relative to CS-independent asthma.

CS: corticosteroid; HR: hazard ratio

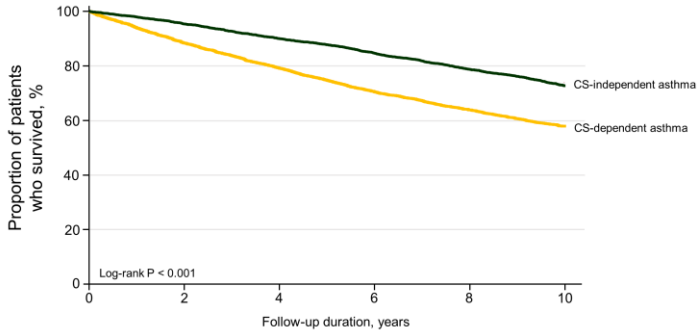

Adult patients with asthma
between Jan 1, 2005, and Dec 31, 2005
(N=751,180)
Exclusion
- Patients with only 1 visit with ICD J45-J46 codes during the baseline period (n=1,277)
Adult patients with ≥2 visits with ICD codes J45-46 during the baseline period (1 year)
(n=749,903)
Exclusion
- Patients with ≥1 of the following diagnoses in the baseline period
1) Rheumatoid disease (n=29,300)
2) Malignancy (n=24,377)
3) Inflammatory bowel disease (n=2,053)
- No prescription of asthma-related medication (n=232,330)
Adult patients with asthma
(≥2 visits and ≥1 asthma-related medication)
(n=466,941)
CS-dependent asthma
(CS-use ≥ 6 months)
(n=8,334)
CS-independent asthma
(CS-use < 6 months)
(n=458,607)
1:1 matching
CS-dependent cohort
(n=8,334)
CS-independent cohort
(n=8,334)


Study period
Baseline period
(1 year)
Follow-up period
Jan. 1, 2005
Dec. 31, 2005
Dec. 31, 2015
First prescription of asthma-related medication with ICD codes J45-46 as major or minor diagnosis between Jan. 1 and Dec. 31 in 2005
Index date
Death



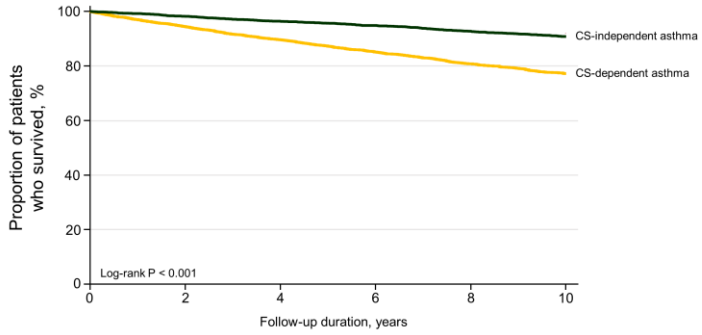
No. at risk

CS-independent asthma	4693	4334	4013	3655	3294	21
CS-dependent asthma	4693	3911	3367	2895	2507	26



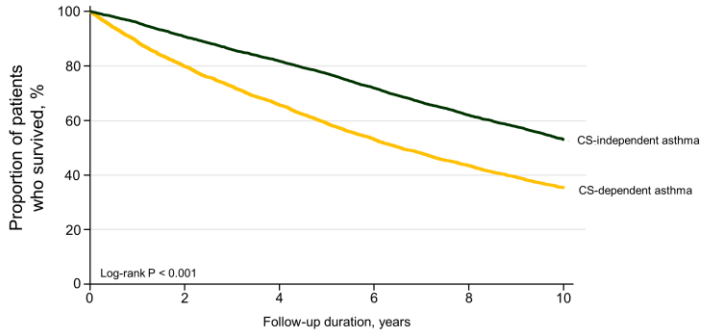
No. at risk

CS-independent asthma	3641	3470	3274	3080	2865	9
CS-dependent asthma	3641	3218	2882	2567	2328	21



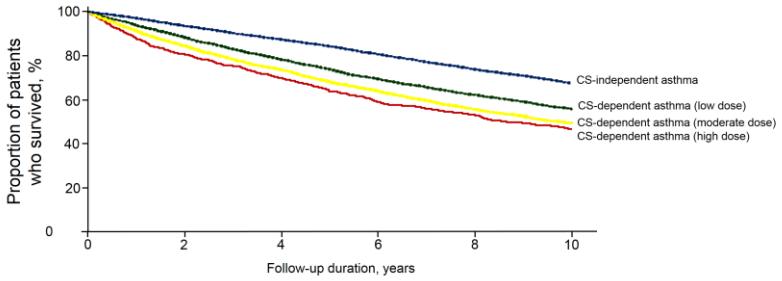
No. at risk

CS-independent asthma	3245	3187	3128	3079	3010	14
CS-dependent asthma	3245	3064	2909	2764	2622	27



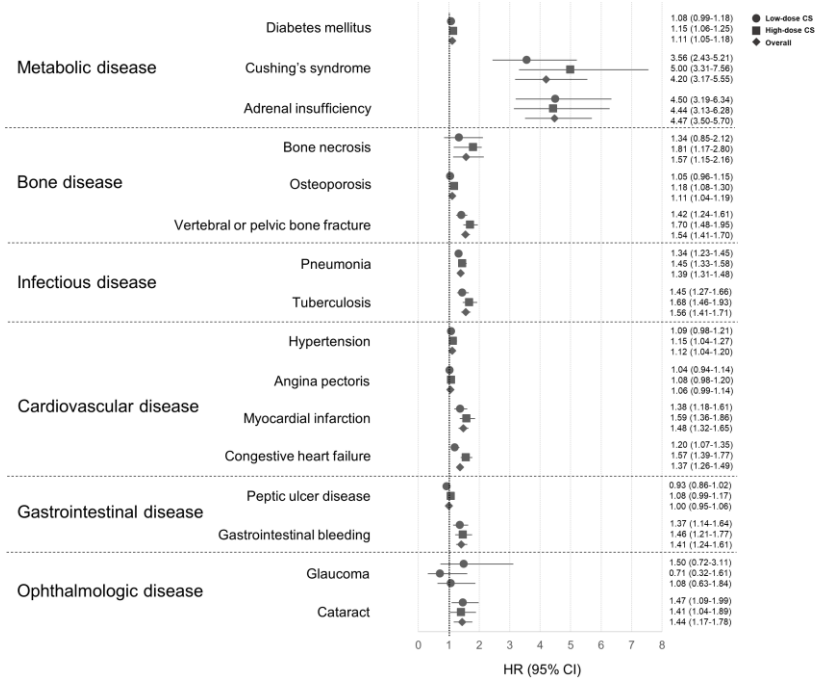
No. at risk

CS-independent asthma	5089	4617	4159	3656	3149	15
CS-dependent asthma	5089	4065	3341	2700	2213	20



No. at risk

CS-independent asthma	8334	7804	7287	6735	6159	29
CS-dependent asthma (low dose)	3239	2862	2534	2250	2019	14
CS-dependent asthma (moderate dose)	4146	3501	3053	2651	2312	24
CS-dependent asthma (high dose)	949	766	662	561	504	9


Metabolic disease
Diabetes mellitus
1.08 (0.99-1.18)
1.15 (1.06-1.25)
1.11 (1.05-1.18)
Cushing's syndrome
3.56 (2.43-5.21)
5.00 (3.31-7.56)
4.20 (3.17-5.55)
Adrenal insufficiency
4.50 (3.19-6.34)
4.44 (3.13-6.28)
4.47 (3.50-5.70)
Bone disease
Bone necrosis
1.34 (0.85-2.12)
1.81 (1.17-2.80)
1.57 (1.15-2.16)
Osteoporosis
1.05 (0.96-1.15)
1.18 (1.08-1.30)
1.11 (1.04-1.19)
Vertebral or pelvic bone fracture
1.42 (1.24-1.61)
1.70 (1.48-1.95)
1.54 (1.41-1.70)
Infectious disease
Pneumonia
1.34 (1.23-1.45)
1.45 (1.33-1.58)
1.39 (1.31-1.48)
Tuberculosis
1.45 (1.27-1.66)
1.68 (1.46-1.93)
1.56 (1.41-1.71)
Cardiovascular disease
Hypertension
1.09 (0.98-1.21)
1.15 (1.04-1.27)
1.12 (1.04-1.20)
Angina pectoris
1.04 (0.94-1.14)
1.08 (0.98-1.20)
1.06 (0.99-1.14)
Myocardial infarction
1.38 (1.18-1.61)
1.59 (1.36-1.86)
1.48 (1.32-1.65)
Congestive heart failure
1.20 (1.07-1.35)
1.57 (1.39-1.77)
1.37 (1.26-1.49)
Gastrointestinal disease
Peptic ulcer disease
0.93 (0.86-1.02)
1.08 (0.99-1.17)
1.00 (0.95-1.06)
Gastrointestinal bleeding
1.37 (1.14-1.64)
1.46 (1.21-1.77)
1.41 (1.24-1.61)
Ophthalmologic disease
Glaucoma
1.50 (0.72-3.11)
0.71 (0.32-1.61)
1.08 (0.63-1.84)
Cataract
1.47 (1.09-1.99)
1.41 (1.04-1.89)
1.44 (1.17-1.78)
Low-dose CS
High-dose CS
Overall
0
1
2
3
4
5
6
7
8
HR (95% CI)

Supplementary TABLE E1 The proportion of patients who met the definition of CS-dependent asthma or CS-independent asthma during the follow-up period

Year	CS-dependent asthma	CS-independent asthma
1	57.9	98.8
2	46.6	97.9
3	39.4	97.8
4	34.2	97.8
5	31.3	97.7
6	29.1	97.7
7	26.8	97.7
8	24.8	97.6
9	23.2	97.6

Data are presented as percentages. The proportion of patients who met the definition of each group was calculated, except for those who died in the previous year.

Supplementary TABLE E2 Occurrence of New Comorbidities in CS-dependent and CS-independent cohort

	Total (N=16,668)	CS-dependent asthma (n=8,334)	CS-independent asthma (n=8,334)	p-value
Metabolic diseases	6,258	6,784	5,800	< 0.001
Diabetes mellitus	5,745	5,950	5,563	0.007
Cushing disease	273	437	129	< 0.001
Adrenal insufficiency	402	657	181	< 0.001
Bone disease	6,145	6,518	5,818	< 0.001
Bone necrosis	141	175	110	0.001
Osteoporosis	4,907	5,025	4,802	0.093
Vertebral or pelvic bone fracture	1,983	2,307	1,702	< 0.001
Infectious disease	6,998	8,067	6,105	< 0.001
Pneumonia	5,916	6,726	5,234	< 0.001
Tuberculosis	1,788	2,124	1,496	< 0.001
Cardiovascular disease	9,328	9,883	8,838	< 0.001
Hypertension	3,592	3,760	3,443	0.004
Angina	3,579	3,608	3,553	0.616
Myocardial infarction	1,274	1,475	1,097	< 0.001
Congestive heart failure	2,514	2,789	2,272	< 0.001
Gastrointestinal disease	7,061	7,232	6,908	0.052
Peptic ulcer disease	6,233	6,303	6,169	0.385
Gastrointestinal bleeding	934	1,058	824	< 0.001
Ophthalmologic disease	330	391	276	< 0.001
Glaucoma	42	46	38	0.466
Cataract	294	354	241	< 0.001

Data are presented as frequency (cases/100,000 person-years).
CS: corticosteroid.