Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality

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Oral corticosteroid use in asthma treatment is associated with an increase in morbidity and mortality even after low cumulative doses of ⩽500 mg (prednisolone-equivalent) and with evidence of dose–response relationships https://bit.ly/3gBSEAB

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Abstract

Background Long-term oral corticosteroid (OCS) treatment for severe asthma is known to cause significant adverse effects, but knowledge on effects of lower exposures in general asthma populations is limited. We aimed to explore this in a nationwide Danish asthma population.

Methods Users of asthma medication aged 18–45 years were identified in the Danish nationwide registers during 1999–2018 and followed prospectively in an open-cohort design. Incident OCS users were matched 1:4 to nonusers by propensity scores with replacement. Associations between OCS use and incident comorbidities were examined by Cox regression. Mortality rates, causes of death and rates of unscheduled hospital visits were assessed.

Results OCS users (n=30 352) had, compared with nonusers (n=121 408), an increased risk of all outcomes with evident dose–response relationships starting at cumulative doses of ⩽500 mg (prednisolone-equivalent). Hazard ratios ranged from 1.24 (95% CI 1.18–1.30) for fractures to 8.53 (95% CI 3.97–18.33) for adrenal insufficiency. Depression/anxiety had the highest incidence rate difference at 4.3 (95% CI 3.6–5.0) per 1000 person-years. Asthma-specific mortality rates were generally low at 0.15 (95% CI 0.11–0.20) and 0.04 (95% CI 0.02–0.06) per 1000 person-years for OCS users and nonusers, respectively. Mortality rates and unscheduled hospital visits increased with increasing OCS exposure.

Conclusion The study findings should be interpreted with their observational nature in mind. However, we found that even at low cumulative exposure, OCS use in asthma management was associated with increased risk of comorbidities, mortality and unscheduled hospital visits. Effective strategies for optimising asthma control and reducing OCS use are pivotal in asthma management.

Introduction

The introduction of systemic corticosteroids in asthma treatment in the 1950s fundamentally changed the management of asthma as an inflammatory disease, but the treatment is unfortunately associated with several severe side-effects [1]. Despite major advances in asthma management, oral corticosteroid (OCS) use is still very prevalent in asthma management [2] with a general nondeclining frequency of OCS users in European asthma populations [3–5]. Due to the potent anti-inflammatory effects and ability to reduce asthma symptoms and risk of exacerbation relapse [6, 7], OCS remain indispensable in the treatment of acute, uncontrolled asthma or severe asthma that remains uncontrolled despite otherwise optimised asthma treatment [8]. This continued dependence on OCS in asthma management imposes significant risks of adverse effects to the patients, which is why the benefit–risk profile must be frequently and carefully

considered. Of note, while severe asthma only constitutes 5–10% of the disease spectrum [9], it accounts for the majority of healthcare costs with >50% of the incremental costs attributed to comorbidities [10]. Overall, the increased risk of OCS-related comorbidities, such as diabetes, osteoporosis and psychiatric disorders, is thoroughly described in long-term OCS treatment in severe asthma [8, 11], while short-term courses for exacerbations have long been considered fairly safe [12]. However, recent studies on general asthma populations have found increased risks of many adverse outcomes starting at cumulative exposures of 500–1000 mg OCS (prednisolone-equivalent), corresponding to only two to four life-time exacerbation courses [13, 14]. Hence, it is important to consider the burden of OCS use in general asthma populations, but nationwide studies on this topic not restricted to severe cases or secondary care patients are scarce.

The aim of this study was to explore the association of OCS use on the morbidity burden in a general population of young adults with asthma over a 20-year period by use of Danish population-based nationwide registers, focusing on incidence of pre-specified OCS-related comorbidities and dose–response relationships, but also mortality rates, causes of death and rates of unscheduled hospital visits.

Materials and methods

Study design and data sources

We conducted a propensity score-matched open-cohort study by using information from several nationwide registers covering the entire Danish population (5.8 million inhabitants in 2018) [15], including: 1) the Danish National Prescription Registry, providing data on all pharmacy-dispensed prescriptions since 1995 [16], 2) the Danish National Patient Registry, covering hospital contacts including diagnoses since 1977 [17], 3) the Danish Register of Causes of Death established in 1970 [18], and 4) the Danish Civil Registration System, which provides basic demographic data and enables data linkage between registers on an individual level due to the unique civil registration number assigned to all Danish residents since 1968 [19]. Variables used from the registers are specified in supplementary table S1.

Study population

A nationwide asthma population was established based on previously validated methods [20, 21]. We included adults aged 18–45 years with at least two separate collections of asthma medication within a 12-month window during the study period (1 January 1999–31 December 2018). Asthma medication included inhaled corticosteroids (ICS), selective β_2-agonists, leukotriene receptor antagonists and xanthines. The upper age restriction limits the inclusion of patients with chronic obstructive pulmonary disease (COPD), but once included, patients were followed beyond the age of 45 years. We excluded patients with hospital diagnoses of COPD, cystic fibrosis and diseases commonly treated with OCS (supplementary table S1).

OCS users were defined by the date of their first filled OCS prescription (index date). To establish a new-user design, we excluded all individuals with any OCS use during a run-in period of 4 years leading up to the study period (*i.e.* 1 January 1995–31 December 1998). Nonusers were assigned annual random index dates and were eligible for matching until filling an OCS prescription. Both OCS users and nonusers were required to have at least two asthma medication collections during a baseline period of 12 months leading up to the index date as indicative of continued active asthma.

All individuals were followed prospectively for OCS use and outcomes (as specified in the Outcomes section) until death, migration, first occurrence of disease commonly treated with OCS (supplementary table S1) or end of study period. The study design is illustrated in figure 1.

Ethics and approvals

Register-based studies in Denmark do not require approval from ethical boards. All data were pseudonymised at the Danish Health Data Authority (record number 00001726) and data extraction approved by the Data Protection office at the University of Southern Denmark (record number 10.121). Recommendations from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) initiative were used in conducting and reporting results for this study [22].

Covariates

Baseline characteristics (assessed at the index date) included age, sex and calendar year. Pre-existing asthma-related conditions and comedication (antihistamines, nasal corticosteroids, obesity, anti-obesity drugs and use of antipsychotics) and pre-existing OCS-related comorbidities (table 1) were assessed any time prior to the index date. Use of long-acting β_2-agonists (LABA) and ICS stratified by mean daily dose as low dose ($\leqslant$400 $\mu g \cdot day^{-1}$) and medium/high dose (>400 $\mu g \cdot day^{-1}$) (budesonide-equivalent) [8] was assessed during the baseline period.

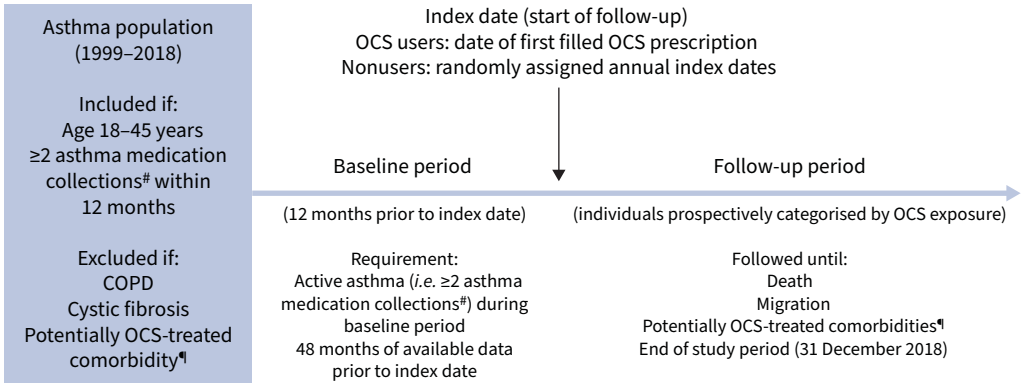

FIGURE 1 Study design. #: including inhalations of selective β_2-agonists, inhaled glucocorticoids, fixed combinations of β_2-agonists and glucocorticoids, leukotriene receptor antagonists, and theophylline (prescriptions redeemed at separate occasions); ¶: including sarcoidosis, primary adrenocortical insufficiency, pneumonitis, inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory spondylopathies and/or malignancy. COPD: chronic obstructive pulmonary disease; OCS: oral corticosteroids.

Outcomes

The primary outcome of interest was incident occurrence of specific OCS-related comorbidities (osteoporosis, fractures, osteonecrosis, diabetes mellitus type 2, adrenal insufficiency, ischaemic heart disease, heart failure, peptic ulcer, cataract and depression/anxiety) identified by first occurrence of a relevant hospital-given diagnosis. Diabetes mellitus type 2 and depression/anxiety could additionally be identified by dispensed prescriptions of oral antidiabetic drugs and antidepressants (only selective serotonin reuptake inhibitors included), respectively, as these diseases are more commonly diagnosed and managed in primary care from which we had no diagnosis data. Only individuals with no previous record of the comorbidity of interest were included in the analyses of the specific comorbidity outcome.

Secondary outcomes were mortality rates and cause of death, and rates of unscheduled hospital visits, *i.e.* hospitalisations and emergency department (ED) visits. Codes are specified in supplementary table S1.

Statistical analyses

Descriptive statistics were used to summarise baseline characteristics. Propensity scores were calculated by logistic regression and used as a matching parameter as a method of adjusting for measured confounders [23]. OCS users were matched 1:4 to nonusers using nearest-neighbour matching with a calliper of 0.01 per calendar year and with replacement (meaning each nonuser could be matched to multiple OCS users) using robust estimator techniques to account for nonusers being sampled as comparators more than once. Standardised mean differences <0.10 were considered balanced [24]. Cumulative OCS exposure was treated as a time-dependent variable, meaning that individual person-time during follow-up was prospectively categorised in three cumulative OCS exposure groups according to the total amount of redeemed OCS up until that moment in time. The exposure groups for the dose–response analysis were defined as low OCS use (⩽500 mg), medium OCS use (>500–2000 mg) and high OCS use (>2000 mg) (prednisolone-equivalent) (supplementary table S2). Incidence rates (IRs) were reported per 1000 person-years and annual rates of unscheduled hospital visits per 100 person-years. All Cox regression models were, in addition to the propensity score matching, adjusted for sex and age (time-varying in 5-year bands) and used to estimate the association between OCS exposure and comorbidity end-points, reported as hazard ratios with 95% confidence intervals The proportional hazards assumption was evaluated by visual inspection of log-log plots. The Kaplan–Meier estimator was used to calculate mortality risk and illustrate cumulative mortality functions. Subgroup analyses on the primary outcomes of interest with stratification by gender and calendar year of the index date were performed *post hoc* and added to the supplementary material. All data were analysed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Sensitivity analyses

We conducted three *a priori* sensitivity analyses to test the robustness of our findings. First, due to the frequency of injectable steroid use being 5.3% among OCS users and 2.6% among nonusers at baseline,

TABLE 1 Baseline characteristics of the study population after matching

	Matched population		SMD
	OCS users (n=30 352)	Nonusers (n=121 408)	
Female	18 044 (59.4)	72 958 (60.1)	0.01
Age (years)	38 (30–45)	38 (30–45)	0.01
Age categories (years)			
18–25	4723 (15.6)	19 075 (15.7)	0.00
26–35	7669 (25.3)	30 786 (25.4)	0.00
36–45	11 032 (36.3)	44 152 (36.4)	0.00
46–55	5839 (19.2)	23 168 (19.1)	0.00
56–65	1089 (3.6)	4227 (3.5)	0.01
Asthma treatment during baseline year			
No ICS	4567 (15.0)	17 775 (14.6)	0.01
Low-dose ICS	16 919 (55.7)	67 888 (55.9)	0.00
Medium/high-dose ICS	8866 (29.2)	35 745 (29.4)	0.01
LABA	15 339 (50.5)	61 879 (51.0)	0.01
Pre-existing asthma-related conditions (any time prior to index date)			
Use of antihistamines	18 494 (60.9)	74 373 (61.3)	0.01
Use of nasal corticosteroids	15 374 (50.7)	62 031 (51.1)	0.01
Obesity	1637 (5.4)	5698 (4.7)	0.03
Use of anti-obesity products	4793 (15.8)	18 794 (15.5)	0.01
Use of antipsychotics	2831 (9.3)	10 030 (8.3)	0.04
Pre-existing OCS-related conditions (any time prior to index date)			
Osteoporosis	88 (0.3)	293 (0.2)	0.01
Fractures	7374 (24.3)	29 170 (24.0)	0.01
Diabetes mellitus type 2	780 (2.6)	2215 (1.8)	0.05
Ischaemic heart disease	448 (1.5)	1251 (1.0)	0.04
Heart failure	72 (0.2)	185 (0.2)	0.02
Depression/anxiety	6328 (20.8)	24 971 (20.6)	0.01
Peptic ulcer disease	236 (0.8)	580 (0.5)	0.04
Cataract	149 (0.5)	432 (0.4)	0.02
Charlson Comorbidity Index[#]			
0	29 694 (97.8)	119 728 (98.6)	0.06
1	153 (0.5)	390 (0.3)	0.03
2	440 (1.4)	1126 (0.9)	0.05
⩾3	65 (0.2)	164 (0.1)	0.02

Data are presented as n (%) or median (interquartile range), unless otherwise stated. OCS: oral corticosteroids; LABA: long-acting β2-agonists; SMD: standardised mean difference. [#]: based on diagnoses received any time prior to the index date, with the exclusion of chronic pulmonary diseases.

we conducted a sensitivity analysis where all use of nonoral systemic corticosteroids was included as an exclusion/censoring criterion. Second, all individuals were followed to a maximum of 5 years to limit bias due to long observational time and differences in follow-up between the two cohorts. Third, individuals were censored after 2 consecutive years of not collecting any asthma medication to limit effects from patients with potentially remitted asthma using OCS for other reasons than asthma.

Two additional *post hoc* analyses were performed with exclusion/censoring of 1) patients receiving biological treatment for asthma, and 2) patients with asthma-related admissions and/or ED visits, in order to investigate specific effects from severe asthma and uncontrolled asthma populations, respectively.

Results

Baseline characteristics

The baseline cohort included 287 113 eligible individuals with asthma. The final study population after propensity score matching consisted of 30 352 incident OCS users (median age 38 years; 59% women) and a control group of 121 408 nonusers (comprising 72 678 unique individuals due to resampling: median age 38 years; 60% women) (table 1). The baseline parameters were well balanced as indicated by standardised mean differences <0.1. The median (interquartile range (IQR)) time from being identified with asthma

until inclusion as an OCS user was 3.8 (0.8–8.9) years. The median (IQR) follow-up time from the index date was 8.0 (3.6–13.1) years for OCS users and 3.5 (1.6–7.3) years for nonusers. Use of prescription antihistamines and nasal corticosteroids was common, while the overall comorbidity burden indicated by the Charlson Comorbidity Index was low in both groups (table 1).

Incident OCS-related comorbidities

OCS users had higher risk of any comorbidity end-point than nonusers with HR 1.40 (95% CI 1.36–1.44) and an overall excess of 11.8 (*i.e.* incidence rate difference (IRD)) OCS-related comorbidities per 1000 person-years (table 2). Depression/anxiety and fractures were the most frequent outcomes with, respectively, 3364 and 2867 cases among OCS users. The corresponding hazard for OCS users compared with nonusers was HR 1.41 (95% CI 1.35–1.47) for depression/anxiety and HR 1.24 (95% CI 1.18–1.30) for fractures. Adrenal insufficiency had the highest hazard ratio with an eightfold increased risk but was very infrequent with only 42 total incident cases reflected in a low IRD of 0.1 (95% CI 0.1–0.2) per 1000 person-years. Results from the subgroup analyses showed that males had a slightly higher risk of any comorbidity end-point (HR 1.43, 95% CI 1.35–1.51) compared with females (HR 1.37, 95% CI 1.32–1.43). The differences in risk were most pronounced for osteoporosis and osteonecrosis (results available in the supplementary material).

Hazard ratios stratified by cumulative OCS exposure (figure 2) showed an increased risk for all outcomes starting at the lowest exposure group of ⩽500 mg with evidence of dose–response relationships, except for adrenal insufficiency, where dose–response analyses were hampered by low statistical precision.

Mortality and cause of death

OCS users had an overall 2.2 times (HR 2.20, 95% CI 1.99–2.43) greater risk of death compared with nonusers (table 3). The higher the OCS exposure, the greater the cumulative all-cause mortality (figure 3). Common causes of death were respiratory disease (260 out of 794 (33%) for OCS users and 82 out of 815 (10%) for nonusers) and cardiovascular disease (130 out of 794 (16%) for OCS users and 137 out of 815 (17%) for nonusers). The risk of asthma-specific deaths was considerably higher among OCS users compared with nonusers (HR 3.75, 95% CI 2.22–6.32), but absolute rates for asthma-specific mortality were generally low at 0.15 and 0.04 per 1000 person-years for OCS users and nonusers, respectively (table 3).

Unscheduled hospital visits

OCS users had greater frequency of ED visits and hospitalisations than nonusers (table 4). The annual rates of unscheduled hospital visits increased with increasing OCS exposure. Asthma-related visits constituted 4.1% (0.9/22.0) of all ED visits among OCS users and 1.3% (0.2/15.8) among nonusers, whereas asthma-related hospitalisations constituted 8.3% (2.3/27.6) of all hospitalisations among OCS users and 2.0% (0.3/15.3) among nonusers.

Sensitivity analyses

Results from the sensitivity analyses were overall consistent with the findings of the main analysis (primary end-points available in the supplementary material). Censoring users of injectable steroids produced very similar results to the main analyses with only minor changes observed in the specific comorbidity end-points (supplementary table S5 and supplementary figure S1). Correspondingly, analyses on mortality and healthcare utilisation displayed very similar results to the main analysis. The results were furthermore reproduced when limiting the follow-up period to 5 years (supplementary table S6 and supplementary figure S2), censoring individuals with apparent remitted asthma (supplementary table S7 and supplementary figure S3) or biological treatment (supplementary table S8 and supplementary figure S4). Censoring individuals with asthma-related admissions and ED visits generally yielded slightly lower risks, *e.g.* risk of the combined end-point for any comorbidity HR 1.36 (95% CI 1.31–1.42) compared with the main analysis HR 1.40 (95% CI 1.36–1.45) (supplementary table S9 and supplementary figure S5).

Discussion

In this nationwide cohort study of young adults with asthma, we observed an increased morbidity and mortality burden among individuals using OCS compared with nonusers. OCS users had an increased risk of all pre-specified comorbidities with evidence of dose–response relationships between increasing cumulative OCS exposure and risk of incident comorbidities. Increases in risk were observed even at low cumulative doses of ⩽500 mg OCS, equivalent to only one to two life-time exacerbation courses. Importantly, the increased risk of comorbidities was evident in our cohort of relatively young adults, despite many of these diseases often being associated with older age.

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TABLE 2 Incidence rates (IRs) and hazard ratios (HRs) of oral corticosteroid (OCS)-related morbidities among adults with asthma stratified by OCS nonusers *versus* OCS users

	Nonusers (reference)			OCS users			IRD per 1000 person-years (95% CI)	p-value	HR (95% CI)	p-value
	Cases (n)	Person-years	IR per 1000 person-years (95% CI)	Cases (n)	Person-years	IR per 1000 person-years (95% CI)				
Any OCS-related comorbidity	10 032	332 808	30.1 (29.6–30.7)	5426	129 353	41.9 (40.8–43.1)	11.8 (10.5–13.1)	<0.001	1.40(1.36–1.45)	<0.001
Osteoporosis	420	613 491	0.7 (0.6–0.8)	525	256 342	2.0 (1.9–2.2)	1.4 (1.2–1.6)	<0.001	2.51 (2.20–2.86)	<0.001
Fractures	5394	443 685	12.2 (11.8–12.5)	2867	189 312	15.1 (14.6–15.7)	3.0 (2.3–3.6)	<0.001	1.24 (1.18–1.30)	<0.001
Osteonecrosis	32	616 400	0.1 (0.0–0.1)	36	258 784	0.1 (0.1–0.2)	0.1 (0.0–0.1)	<0.001	2.66 (1.66–4.27)	<0.001
Diabetes mellitus type 2	2183	589 324	3.7 (3.6–3.9)	1489	246 816	6.0 (5.7–6.3)	2.3 (2.0–2.7)	<0.001	1.52 (1.42–1.62)	<0.001
Adrenal insufficiency	8	616 871	0.0 (0.0–0.0)	34	259 008	0.1 (0.1–0.2)	0.1 (0.1–0.2)	<0.001	8.53 (3.97–18.33)	<0.001
Ischaemic heart disease	1140	600 395	1.9 (1.8–2.0)	869	251 513	3.5 (3.2–3.7)	1.6 (1.3–1.8)	<0.001	1.67 (1.52–1.82)	<0.001
Heart failure	164	614 448	0.3 (0.2–0.3)	366	257 036	1.4 (1.3–1.6)	1.2 (1.0–1.3)	<0.001	5.06 (4.20–6.10)	<0.001
Depression/anxiety	6214	461 086	13.5 (13.1–13.8)	3364	189 136	17.8 (17.2–18.4)	4.3 (3.6–5.0)	<0.001	1.41 (1.35–1.47)	<0.001
Peptic ulcer disease	334	608 731	0.5 (0.5–0.6)	273	255 781	1.1 (0.9–1.2)	0.5 (0.4–0.7)	<0.001	1.89 (1.60–2.23)	<0.001
Cataract	570	611 200	0.9 (0.9–1.0)	509	255 879	2.0 (1.8–2.2)	1.1 (0.9–1.2)	<0.001	1.75 (1.56–1.98)	<0.001

IRD: incidence rate difference.

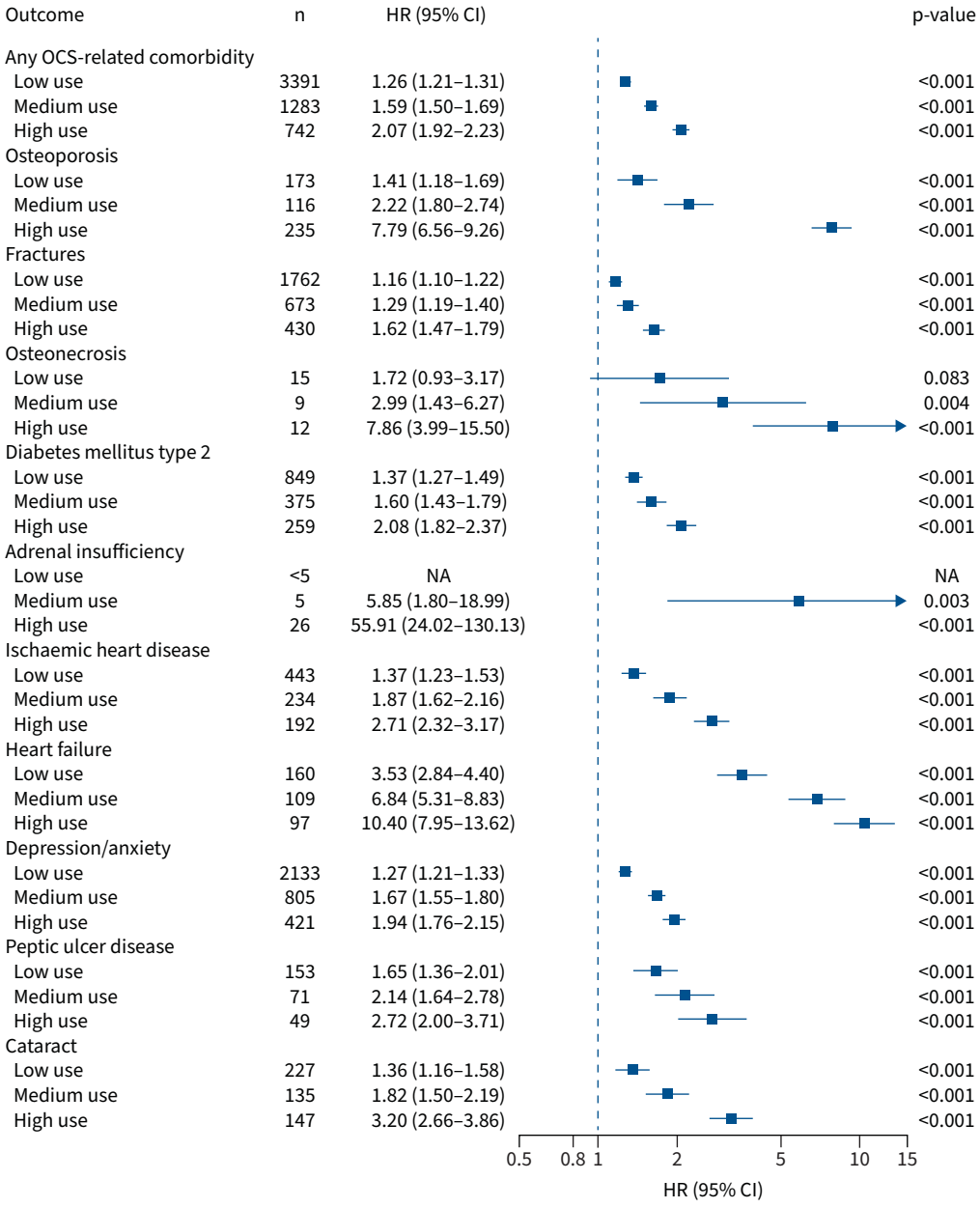

FIGURE 2 Risk of incident oral corticosteroid (OCS)-related comorbidity among adults with asthma estimated by hazard ratios (HR) adjusted for age and sex, and stratified by cumulative oral corticosteroid exposure (low use ⩽500 mg, medium use >500–2000 mg and high use >2000 mg) compared with nonusers. NA: not available.

While it is fully recognised that long-term OCS use for severe asthma is associated with adverse effects [8, 11], the cumulative effects from short-term OCS courses in general asthma populations have also become of increasing interest [12, 25]. A growing amount of evidence indicates an increased risk of OCS-related comorbidities after four prescriptions [26] and life-time exposures of 500–1000 mg [13, 14]. Our study further adds that patients receiving even ⩽500 mg OCS should be considered at risk.

We found high OCS use to be associated with greater all-cause and asthma-specific mortality, although asthma-specific death was generally rare. The latter observation was expected as asthma-specific mortality has decreased in the last decades and is overall low in Western countries [27]. However, it may be misleading to only evaluate asthma-specific mortality, as comorbid conditions contribute significantly to overall excess asthma-related mortality. A study from Canada found that individuals with asthma during 1999–2008 had a persistently higher all-cause mortality compared with the general population, with

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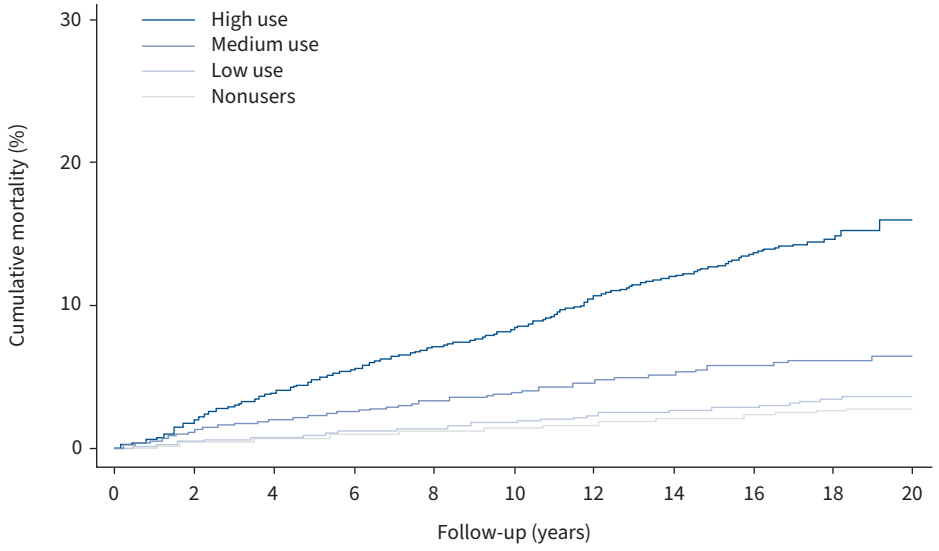
TABLE 3 Mortality rates (deaths per 1000 person-years), hazard ratios (HR) and causes of death among nonusers and oral corticosteroid (OCS) users stratified by cumulative OCS exposure (low use ⩽500 mg, medium use >500–2000 mg and high use >2000 mg) adjusted for age and sex

	Nonusers (reference)		OCS users				Cumulative OCS exposure groups								
							Low use			Medium use			High use		
	Cases (n)	Mortality rate (95% CI)	Cases (n)	Mortality rate (95% CI)	HR (95% CI)	p-value	Mortality rate (95% CI)	HR (95% CI)	p-value	Mortality rate (95% CI)	HR (95% CI)	p-value	Mortality rate (95% CI)	HR (95% CI)	p-value
All-cause mortality	815	1.3 (1.2–1.4)	794	3.1 (2.9–3.3)	2.20 (1.99–2.43)	<0.001	1.9 (1.7–2.1)	1.40 (1.23–1.60)	<0.001	3.6 (3.1–4.1)	2.52 (2.16–2.94)	<0.001	8.9 (7.9–10.0)	5.58 (4.83–6.44)	<0.001
Respiratory disease	82	0.13 (0.11–0.17)	260	1.0 (0.9–1.1)	6.74 (5.27–8.64)	<0.001	0.31 (0.23–0.40)	2.28 (1.61–3.22)	<0.001	1.1 (0.8–1.4)	7.21 (5.16–10.08)	<0.001	4.8 (4.1–5.7)	28.19 (21.20–37.50)	<0.001
Asthma-specific	23	0.04 (0.02–0.06)	38	0.15 (0.11–0.20)	3.75 (2.22–6.32)	<0.001	0.08 (0.04–0.13)	2.06 (1.04–4.08)	0.038	0.12 (0.06–0.25)	3.00 (1.27–7.06)	0.012	0.60 (0.38–0.95)	14.19 (7.39–27.23)	<0.001
Cardiovascular disease	137	0.22 (0.19–0.26)	130	0.50 (0.42–0.60)	2.07 (1.62–2.64)	<0.001	0.38 (0.30–0.49)	1.69 (1.26–2.28)	<0.001	0.59 (0.43–0.83)	2.33 (1.59–3.40)	<0.001	1.0 (0.7–1.4)	3.41 (2.28–5.11)	<0.001
Endocrine disease	43	0.07 (0.05–0.09)	26	0.10 (0.07–0.15)	1.33 (0.81–2.19)	0.254	0.06 (0.03–0.11)	0.83 (0.42–1.66)	0.605	0.12 (0.06–0.25)	1.52 (0.66–3.47)	0.326	0.30 (0.16–0.58)	3.42 (1.63–7.18)	0.001
Neurological disease	32	0.05 (0.04–0.07)	17	0.07 (0.04–0.11)	1.18 (0.64–2.15)	0.598	0.05 (0.02–0.09)	0.89 (0.41–1.94)	0.776	0.07 (0.03–0.18)	1.19 (0.42–3.39)	0.740	0.17 (0.07–0.40)	2.53 (0.92–6.97)	0.073
Mental and behavioural disorders	100	0.16 (0.13–0.20)	66	0.25 (0.20–0.32)	1.48 (1.08–2.02)	0.014	0.18 (0.12–0.25)	1.08 (0.72–1.63)	0.696	0.39 (0.26–0.59)	2.17 (1.37–3.43)	<0.001	0.43 (0.25–0.75)	2.14 (1.19–3.86)	0.012
Others	421	0.68 (0.62–0.75)	295	1.1 (1.0–1.3)	1.63 (1.41–1.89)	<0.001	0.89 (0.76–1.04)	1.31 (1.09–1.57)	0.005	1.4 (1.1–1.7)	1.93 (1.51–2.46)	<0.001	2.1 (1.7–2.7)	2.83 (2.17–3.70)	<0.001



At risk (n):										
Nonusers	121 408	82 908	55 442	38 565	26 835	18 587	12 623	7974	4565	1873
Low use	28 885	19 550	14 953	11 693	8905	6569	4712	3116	1836	739
Medium use	487	4549	5000	4748	4189	3447	2719	1928	1195	549
High use	980	1745	2071	2196	2123	1941	1659	1303	881	437

FIGURE 3 Kaplan–Meier estimates of cumulative all-cause mortality among adults with asthma stratified by cumulative oral corticosteroid (OCS) exposure (nonusers, low use ⩽500 mg, medium use >500–2000 mg and high use >2000 mg) adjusted for age and sex.

comorbid conditions comprising the majority of causes of excess death [28]. This may in part be attributed to treatment side-effects. We found that nearly four out of five died due to causes other than respiratory disease, which emphasises the importance of assessing comorbidities as an integrated part of asthma management as these may contribute to worse outcomes [8] and an overall higher mortality [28]. We found that both mortality rates and rates of unscheduled hospital visits increased in a dose–response-like manner with increasing OCS exposure, in agreement with previous literature [29]. A recent Swedish study found that regular OCS users (⩾5 mg·day^{-1} per year) had three times the cost of healthcare resource utilisation than nonusers, with the primary cost driver being inpatient costs [30]. Noteworthy, we found individuals with high OCS use to have more than three times higher hospitalisation rates than nonusers, emphasising the high morbidity burden in this patient group.

Clinical perspectives

Although OCS are effective anti-asthmatic drugs [6, 7], it is important to weigh the harmful effects considering newer options of OCS-sparing strategies and therapies. This study has provided risk estimates

TABLE 4 Mean annualised rates of unscheduled hospital visits among nonusers and oral corticosteroid (OCS) users stratified by cumulative OCS exposure (low use ⩽500 mg, medium use >500–2000 mg and high use >2000 mg)

	Nonusers (n=121 408)	OCS users (n=30 352)	Cumulative OCS exposure groups		
			Low use (n=28 791)	Medium use (n=10 679)	High use (n=4612)
ED visits per 100 person-years	15.8 (15.7–15.9)	22.0 (21.8–22.1)	20.6 (20.4–20.9)	23.3 (22.9–23.7)	26.8 (26.2–27.4)
Asthma-related ED visits per 100 person-years	0.20 (0.16–0.18)	0.90 (0.91–0.99)	0.70 (0.68–0.77)	1.1 (1.0–1.2)	1.9 (1.7–2.1)
Hospitalisations per 100 person-years	15.3 (15.2–15.4)	27.6 (27.4–27.8)	21.7 (21.4–21.9)	30.7 (30.2–31.1)	54.7 (53.9–55.6)
Asthma-related hospitalisations per 100 person-years	0.30 (0.29–0.31)	2.3 (2.3–2.4)	1.5 (1.4–1.5)	2.9 (2.7–3.0)	6.2 (5.9–6.5)

ED: emergency department.

of several OCS-related complications applicable in healthcare planning. Our results emphasise that patients receiving even a few OCS courses are at increased risk of adverse outcomes and thus should be prioritised and reassessed, both to reduce unwanted OCS-related effects and to assess their clinical situation in general. Among patients with severe asthma and OCS use, poor adherence and/or inadequate inhaler technique is found to be as high as 78%, emphasising substantial room for improvement [31]. According to the Global Initiative for Asthma guidelines, patients with severe uncontrolled asthma, long-term OCS use or frequent OCS courses should be considered for specialist assessment [8]. However, only a third of patients with potential severe asthma in Denmark are managed in specialist care [32, 33], and among patients with indicators of low asthma control, only 27% with mild-to-moderate asthma and 44% with severe asthma receive specialist care within 1 year [33]. These findings suggest room for improvement in the selection of patients, referral pathways and access to hospital care.

Strengths and limitations

A major strength of this study is the use of population-based registries with high data validity and complete follow-up on an individual level [15]. The healthcare system in Denmark is publicly financed which ensures equal access to all citizens, thus providing complete nationwide coverage on all Danish residents [15]. The registers provide "real-world data" which are collected systematically and independently of researchers, thereby ensuring a high level of external validity. By use of an open-cohort and incident user design with a prospective analysing approach, this study allowed for appropriate classification of individual follow-up time, thereby reducing the risk of time-related bias [34].

There are, however, several important limitations to the study. The unavailability of information on diagnoses from primary care and spirometry data may limit the specificity of the asthma case definition. However, our approach is based on validated definitions of active asthma [20, 21] utilised in several larger Scandinavian asthma studies and databases [35, 36].

The lack of diagnostic data from primary care may result in an underestimation of the development of comorbidities. The majority of the comorbidities in question are, however, conditions primarily diagnosed and/or managed in secondary care, thereby limiting the risk of underestimation. Diabetes mellitus type 2 and depression/anxiety were additionally identified by relevant medication use, as these conditions are often managed exclusively in primary care. Identifying diabetes by use of antidiabetic dispensing records is a valid and utilised approach in Danish register-based studies [37, 38]. Although antidepressants are prescribed for various purposes, they are most commonly prescribed for depression and anxiety [39, 40], with selective serotonin reuptake inhibitors as the first-line treatment in Denmark. We would expect any potential underestimation of comorbidity outcomes to be nondifferentially misclassified, which would bias our estimates towards the null.

OCS exposure was based on dispensed prescriptions, which are not necessarily synonymous with actual consumption [41]. This would, however, more likely result in an underestimation rather than overestimation of the estimated associations.

Data on lifestyle factors and asthma control were not available. Although lifestyle factors are important risk factors for many of the OCS-related comorbidities, a recent Danish study found that smoking, diet and physical activity do not differ substantially according to systemic corticosteroid use in the general Danish population [42].

Differences in median follow-up time between exposure groups is another potential concern; however, sensitivity analyses with a limited 5-year follow-up demonstrated results very similar to the main analysis (supplementary table S4 and supplementary figure S2).

Observational studies are generally vulnerable to selection bias due to the absence of randomisation. We expected, for instance, asthma severity to differ substantially between OCS users and nonusers, which would introduce a considerable bias due to noncomparability between groups. We used propensity scores designed to mitigate this problem by matching on baseline characteristics, which included among other things markers of the level of asthma severity (*i.e.* ICS dose and LABA use), asthma phenotype (*e.g.* use of prescription antihistamine as an indication of allergic asthma), overall comorbidity status (Charlson Comorbidity Index) and pre-existing OCS-related comorbidities. This allowed for identification of nonusers with a similar distribution in baseline variables and thereby higher comparability with the OCS users, thus to some extent controlling for measured confounding factors [23]. However, due to the observational nature of our study, residual differences between the cohorts are expected and thus a direct causal interpretation that the observed increases in risks can be attributed solely to OCS use should be

discouraged. However, even when interpreted strictly as associations, our findings document increased risks among OCS users compared with nonusers, also after adjusting for numerous clinical covariates, supporting existing recommendations that patients receiving even a few OCS courses should be frequently assessed regarding optimised strategies to improve their asthma control and considered for specialist referral [8, 12, 25].

Conclusions

We have found that patients with asthma using OCS are at an increased and dose-dependent risk of incident comorbidities, mortality and healthcare utilisation compared with patients not using OCS, a risk that is observed even after low cumulative exposure of ⩽500 mg (equivalent to only one to two life-time exacerbation courses). These findings thus emphasise that OCS users constitute a vulnerable group of patients and a need for elevated awareness of the high morbidity burden associated with even low exposures of OCS.

Author contributions: J.R. Davidsen, D.P. Henriksen, H. Madsen and I.R. Skov conceived the study. I.R. Skov and A. Pottegård designed the study. Data were curated by D.P. Henriksen. J.H. Andersen and A. Pottegård performed the formal analyses. J.R. Davidsen, H. Madsen and I.R. Skov acquired the funding. I.R. Skov wrote the original draft. J.R. Davidsen was the main supervisor. All authors reviewed and approved the final version.

Data availability: The confidential healthcare data used in this study are available from the Danish Health and Medicines Authority upon relevant request and a data extraction fee. In accordance with Danish law, individual-level data is not publicly accessible. Secondary end-points from the sensitivity analyses are available upon request.

Conflict of interest: I.R. Skov reports grants paid to her institution from AstraZeneca, Teva, Novartis, the Odd Fellow Lodge of Haderslev Denmark, the Region of Southern Denmark and the University of Southern Denmark; and personal fees for lectures from Roche, outside the submitted work. A. Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the submitted work. J.R. Davidsen reports grants and personal fees for advisory board participation and lectures from Roche and Boehringer Ingelheim, and personal fees for lectures from Chiesi, outside the submitted work. H. Madsen, D.P. Henriksen and J.H. Andersen have nothing to disclose.

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