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Early View

Original research article

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

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Take home message

Oral corticosteroid use in asthma treatment is associated with an increase in morbidity and mortality even after low cumulative doses of ≤500 mg (prednisolone equivalents) and with evidence of dose-response.

Abstract

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.

Users of asthma medication aged 18-45 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 non-users 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.

OCS-users (n 30,352) had, compared to non-users (n 121,408), an increased risk of all outcomes with evident dose-response relationships starting at cumulative doses of ≤500 mg (prednisolone equivalents). 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 1,000 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 1,000 person years for OCS-users and non-users, respectively. Mortality rates and unscheduled hospital visits increased with increasing OCS exposure.

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.

Word count: 250

Keywords: asthma, corticosteroids, systemic effects corticosteroids, morbidity, mortality

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 corticosteroids (OCS) use is still very prevalent in asthma management [2] with a general non-declining 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, 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 the healthcare costs with over 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 long have 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 equivalents), corresponding to only two to four lifetime 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 prespecified 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: I) The Danish National Prescription Registry, providing data on all pharmacy-dispensed prescriptions since 1995 [16], II) The Danish National Patient Registry, covering hospital contacts including diagnoses since 1977 [17], III) The Danish Register of Causes of Death established in 1970 [18], and IV) 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 **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 (January 1, 1999 – December 31, 2018). Asthma medication included inhaled corticosteroids, selective β2-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. We excluded patients with hospital diagnoses of COPD, cystic fibrosis, and diseases commonly treated with OCS (**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 four years leading up to the study period (i.e., January 1, 1995 – December 31, 1998). Non-users were assigned annual random index dates and were eligible for matching until filling an OCS prescription. Both OCS-users and non-users 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 below) until death, migration, first occurrence of disease commonly treated with OCS (**Table S1**), or end of study period. The study design is illustrated in **Figure 1**.

Covariates

Baseline characteristics (assessed at index date) included age, sex, and calendar year. Pre-existing asthma-related conditions and comedication (antihistamines, nasal corticosteroids, obesity, anti-obesity drugs, use of antipsychotics), and pre-existing OCS-related comorbidities (**Table 1**) were assessed any time prior to index date. Use of long-acting β2-agonists (LABA) and ICS stratified by mean daily dose as low dose (≤400 µg/day) and medium/high dose (>400 µg/day) in budesonide equivalents [8], was assessed during the baseline period.

Outcomes

The primary outcome of interest was incident occurrence of specific OCS-related comorbidities (osteoporosis, fractures, osteonecrosis, diabetes mellitus type 2, adrenal insufficiency, ischemic 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 **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 [22]. OCS-users were matched 1:4 to non-users using nearest neighbour matching with a calliper of 0.01 per calendar year and with replacement (meaning each non-user

could be matched to multiple OCS-users) using robust estimator techniques to account for non-users being sampled as comparators more than once. Standardised mean differences below 0.10 were considered balanced [23]. 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) in prednisolone equivalents (see **Table S2**). Incidence rates (IRs) were reported per 1,000 person years (py), and annual rates of unscheduled hospital visits per 100 py. All Cox regression models were, in addition the PS matching, adjusted for sex and age (time-varying in 5-year bands) and used to estimate the association between OCS exposure and comorbidity endpoints, reported as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard 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 index date were performed post hoc and added to the **Supplemental 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 non-users at baseline, we conducted a sensitivity analysis where all use of non-oral systemic corticosteroids was included as an exclusion/censoring criterion. Second, all individuals were followed to a maximum of five years to limit bias due to long observational time and differences in follow-up between the two cohorts. Third, individuals were censored after two 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 I) patients receiving biological treatment for asthma, and II) 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 non-users (comprising of 72,678 unique individuals due to re-sampling, median age 38 years, 60% women), see **Table 1**. The baseline parameters were well balanced as indicated by standardised mean differences (SMD) <0.1. The median time from being identified with asthma until inclusion as OCS-user was 3.8 years (interquartile range, IQR 0.8-8.9 years). The median follow-up time from index date was 8.0 years (IQR 3.6-13.1 years) for OCS-users and 3.5 years (IQR 1.6-7.3 years) for non-users. 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 endpoint than non-users with a HR of 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 1,000 py (**Table 2**). Depression/anxiety and fractures were the most frequent outcomes with, respectively, 3,364 and 2,867 cases among OCS-users. The corresponding HR for OCS-users compared to non-users was 1.41 (95% CI 1.35-1.47) for depression/anxiety and 1.24 (95% CI 1.18-1.30) for fractures. Adrenal insufficiency had the highest HR with an eightfold increased risk but was very infrequent with only 42 total incident cases reflected in a low IRD of 0.1 per 1,000 py (95% CI 0.1-0.2). Results from the subgroup analyses showed that males had a slightly higher risk of any comorbidity endpoint (HR 1.43, 95% CI 1.35-1.51) compared to 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 **Supplemental material**).

HRs 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 2.20 (HR, 95% CI 1.99-2.43) times greater risk of death compared to non-users (**Table 3**). The higher the OCS exposure, the greater the cumulative all-cause mortality (**Figure 3**). Common causes of death were respiratory disease (260/794, 33%, for OCS-users and 82/815, 10%, for non-users) and cardiovascular diseases (130/794, 16%, for OCS-users and 137/815, 17%, for non-users). The risk of asthma-specific deaths was considerably higher among OCS users compared to non-users (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 1,000 py for OCS-users and non-users, respectively (**Table 3**).

Unscheduled hospital visits

OCS-users had greater frequency of ED visits and hospitalisations than non-users (**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 non-users, 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 non-users.

Sensitivity analyses

Results from the sensitivity analyses were overall consistent with findings to the main analysis (primary endpoints available in **Supplemental material**). Censoring users of injectable steroids produced very similar results to the main analyses with only minor changes observed in the specific comorbidity endpoints (**Table S5, Figure S1**). Correspondingly, analyses on mortality and healthcare utilisation displayed very similar results as the main analysis. The results were furthermore reproduced when limiting the follow-up period to 5 years (**Table S6, Figure S2**), censoring individuals with apparent remitted asthma (**Table S7, Figure S3**), or biological treatment (**Table S8, Figure S4**). Censoring individuals with asthma-related admissions and ED-visits generally yielded slightly lower

risks, e.g., risk of the combined endpoint for any comorbidity at 1.36 (HR, 95% CI 1.31-1.42) compared to the main analysis (HR 1.40, 95% CI 1.36-1.45) (**Table S9, Figure S5**).

Discussion

In this nationwide cohort study of young adults with asthma, we have observed an increased morbidity and mortality burden among individuals using OCS compared to non-users. OCS-users had an increased risk of all prespecified 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.

While it is fully recognised that long-term OCS use for severe asthma is associated with adverse effects [8, 11], the cumulative effects from also short-term OCS courses in general asthma populations have become of increasing interest [12, 24]. A growing amount of evidence indicates an increased risk of OCS-related comorbidities after four prescriptions [25] 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, though 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 [26]. However, it may be misleading only to evaluate asthma-specific mortality, as comorbid conditions contribute significantly to the overall excess asthma-related mortality. A study from Canada found that individuals with asthma during 1999 to 2008 had a persistently higher all-cause mortality compared to the general population with comorbid conditions comprising the majority of causes of excess death [27]. This may in part be attributed to treatment side effects. We found that nearly four in five died due to other causes 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 [27]. 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 [28]. A recent Swedish study found that regular OCS-users (≥5 mg/day/year) had three times the cost of health care resource utilisation than non-users with the primary cost driver being inpatient costs [29]. Noteworthy, we found individuals with high OCS use to have more than three times higher hospitalisation rates than non-users, 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 of several OCS-related complications applicable in health care planning. Our results emphasise that patients receiving even 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 patient with severe asthma and OCS use, poor adherence and/or inadequate inhaler technique is found to be as high as 78%, emphasising a substantial room for improvement [30]. According to the GINA guidelines, patients with severe uncontrolled asthma, long-term OCS use, or frequent OCS courses should be considered for specialist assessment [8]. However, only one third of patients with potential severe asthma in Denmark are managed in specialist care [31, 32], and among patients with indicators of low asthma control, only 27% with mild-moderate asthma and 44% with severe asthma receive specialist care within one year [32]. These findings suggest a 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 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 [33].

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 [34, 35].

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 recordings is a valid and utilised approach in Danish register-based studies [36, 37]. Although antidepressants are prescribed for various purposes, they are most commonly prescribed for depression and anxiety [38, 39] with selective serotonin reuptake inhibitors as the first-line treatment in Denmark. We would expect any potential underestimation of comorbidity outcomes to be non-differentially misclassified, which would bias our estimates towards the null.

OCS exposure was based on dispensed prescriptions, which is not necessarily synonymous with actual consumption [40]. 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. Though lifestyle factors are important risk factors for many of the OCS-related comorbidities, a recent Danish study have found that smoking, diet, and physical activity do not differ substantially according to systemic corticosteroids use in the general Danish population [41].

Differences in median follow-up time between exposure groups is another potential concern, however, sensitivity analyses with a limited 5-year follow-up demonstrated very similar results as the main analysis (**Table S4, 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 non-users, which would introduce a considerable bias due to non-comparability 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 indication of

allergic asthma), overall comorbidity status (CCI), and pre-existing OCS-related comorbidities. This allowed for identification of non-users with similar distribution in baseline variables and thereby higher comparability with the OCS-users, thus to some extent controlling for measured confounding factors [22]. 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 to non-users, 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, 24].

Conclusion

In conclusion, we have found that patients with asthma using OCS are at an increased and dose-dependent risk of incident comorbidities, mortality, and health care utilisation compared to patients not using OCS, a risk that is observed even after low cumulative exposure of ≤500 mg - equivalent to only one to two lifetime 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.

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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 no 00001726) and data extraction approved by the Data Protection office at the University of Southern Denmark (record no 10.121). Recommendations from The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative were used in conducting and reporting results for this study [42].

Data availability

The confidential health care data used in this study is 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 endpoints from the sensitivity analyses are available upon request.

Declaration of interest

IRS 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. Anton 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 work reported in this paper. JRD 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. HM, DPH and JHA have nothing to disclose.

Author contributions

JRD, DPH, HM, and IRS conceptualised the study. IRS and AP designed the study. Data were curated by DPH. JHA and AP performed the formal analyses. JRD, HM and IRS acquired the funding. IRS wrote the original draft. JRD was the main supervisor. All authors reviewed and approved the final version.

TABLES

Table 1: Baseline characteristics of the study population after matching

	Matched population		
Characteristics	OCS-users (n = 30,352)	Non-users (n = 121,408)	SMD
Female, n(%)	18,044 (59.4%)	72,958 (60.1%)	0.01
Age (years), median (IQR)	38 (30-45)	38 (30-45)	0.01
Age categories (years)			
18-25, n(%)	4723 (15.6%)	19,075 (15.7%)	0.00
26-35, n(%)	7669 (25.3%)	30,786 (25.4%)	0.00
36-45, n(%)	11,032 (36.3%)	44,152 (36.4%)	0.00
46-55, n(%)	5839 (19.2%)	23,168 (19.1%)	0.00
56-65, n(%)	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

ED: emergency department; IQR: interquartile range; OCS: oral corticosteroids; SMD: standardised mean difference
*based on diagnoses received any time prior to index, with exclusion of chronic pulmonary diseases

Table 2: Incidence rates and hazard ratios of OCS-related morbidities among adults with asthma, stratified by non-use of OCS vs. OCS-use

	Non-user (ref)			OCS-user			IRD/1,000 py (95% CI)	P-value	Hazard ratio (95% CI)	P-value
	Cases, n	py	IR/1,000 py (95% CI)	Cases, n	py	IR/1,000 py (95% CI)				
Any OCS-related comorbidity	10,032	332,808	30.1 (29.6;30.7)	5,426	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	5,394	443,685	12.2 (11.8;12.5)	2,867	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	2,183	589,324	3.7 (3.6;3.9)	1,489	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	1,140	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	6,214	461,086	13.5 (13.1;13.8)	3,364	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

CI: confidence interval; IR: incidence rate; IRD: incidence rate difference; OCS: oral corticosteroids; py: person years

Table 3: Mortality rates (deaths per 1,000 person year), hazard ratios, and causes of death among non-users and OCS-users stratified by cumulative OCS exposure (low use ≤500 mg, medium use >500-2000 mg, high use >2000 mg), adjusted for age and sex.

	Non-users (ref)		**OCS-users**				**Cumulative OCS exposure groups**								
							Low use, ≤500 mg			Medium use, >500-2000 mg			High use, >2000 mg		
	Cases, n	Mortality rate (95% CI)	Cases, n	Mortality rate (95% CI)	HR (95% CI)	P-value	Mortality rate	HR (95% CI)	P-value	Mortality rate	HR (95% CI)	P-value	Mortality rate	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 disease	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

CI: confidence interval; HR: hazard ratio; OCS: oral corticosteroids; py: person years

Table 4: Mean annualised rates of unscheduled hospital visits per 100 person years

	Non-users	**OCS-users**	**Cumulative OCS exposure groups**		
			Low use, ≤500 mg	Medium use, >500-2000 mg	High use, >2000 mg
	(n 121,408)	(n 30,352)	(n 28,791)	(n 10,679)	(n 4,612)
ED visits, per 100 py	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 py	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 py	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 py	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, OCS: oral corticosteroid, py: person years

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FIGURE LEGENDS

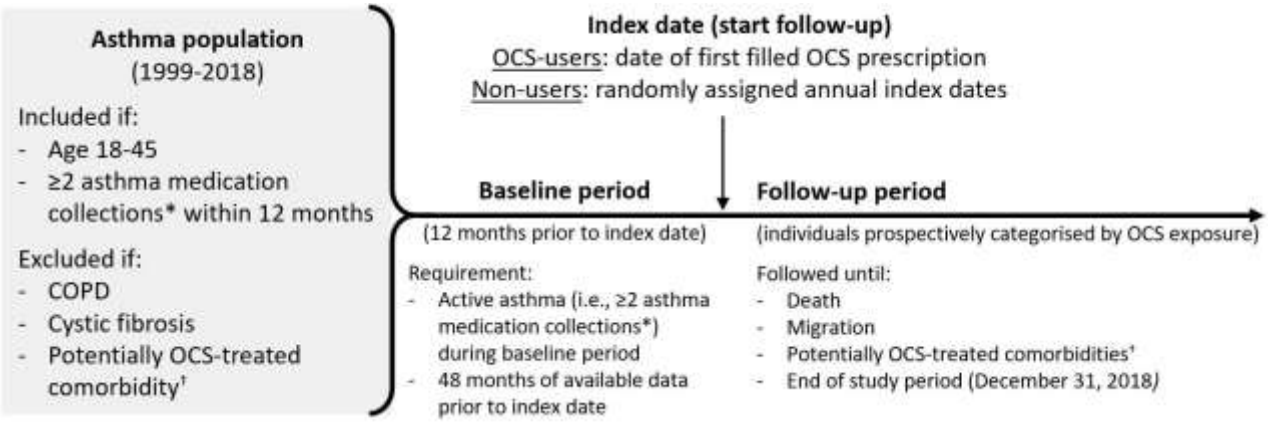

Figure 1: Study design

Legend:
COPD: chronic obstructive pulmonary disease; OCS: oral corticosteroids
*including inhalations of selective β2-agonists, inhaled glucocorticoids, fixed combinations of β2-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.

Outcome	No. of outcomes	HR (95% CI)	P-value
Any OCS-related comorbidity			
Low use	3391	1.26 (1.21;1.31)	<0.001
Medium use	1283	1.59 (1.50;1.69)	<0.001
High use	742	2.07 (1.92;2.23)	<0.001
Osteoporosis			
Low use	173	1.41 (1.18;1.69)	<0.001
Medium use	116	2.22 (1.80;2.74)	<0.001
High use	235	7.79 (6.56;9.26)	<0.001
Fractures			
Low use	1762	1.16 (1.10;1.22)	<0.001
Medium use	673	1.29 (1.19;1.40)	<0.001
High use	430	1.62 (1.47;1.79)	<0.001
Osteonecrosis			
Low use	15	1.72 (0.93;3.17)	0.083
Medium use	9	2.99 (1.43;6.27)	0.004
High use	12	7.86 (3.99;15.50)	<0.001
Diabetes mellitus type 2			
Low use	849	1.37 (1.27;1.49)	<0.001
Medium use	375	1.60 (1.43;1.79)	<0.001
High use	259	2.08 (1.82;2.37)	<0.001
Adrenal insufficiency			
Low use	(n<5)	NA	NA
Medium use	5	5.85 (1.80;18.99)	0.003
High use	26	55.91 (24.02;130.13)	<0.001
Ischaemic heart disease			
Low use	443	1.37 (1.23;1.53)	<0.001
Medium use	234	1.87 (1.62;2.16)	<0.001
High use	192	2.71 (2.32;3.17)	<0.001
Heart failure			
Low use	160	3.53 (2.84;4.40)	<0.001
Medium use	109	6.84 (5.31;8.83)	<0.001
High use	97	10.40 (7.95;13.62)	<0.001
Depression/anxiety			
Low use	2133	1.27 (1.21;1.33)	<0.001
Medium use	805	1.67 (1.55;1.80)	<0.001
High use	421	1.94 (1.76;2.15)	<0.001
Peptic ulcer disease			
Low use	153	1.65 (1.36;2.01)	<0.001
Medium use	71	2.14 (1.64;2.78)	<0.001
High use	49	2.72 (2.00;3.71)	<0.001
Cataract			
Low use	227	1.36 (1.16;1.58)	<0.001
Medium use	135	1.82 (1.50;2.19)	<0.001
High use	147	3.20 (2.66;3.86)	<0.001

Figure 2: Risk of incident oral corticosteroid-related comorbidity among adults with asthma estimated by hazard ratios (HR) adjusted for age and sex, and stratified by cumulative oral corticosteroid exposure groups (low use ≤500 mg, medium use >500-2000 mg, high use >2000 mg) compared to non-users

Legend:
CI: confidence interval, HR: hazard ratio, OCS: oral corticosteroid

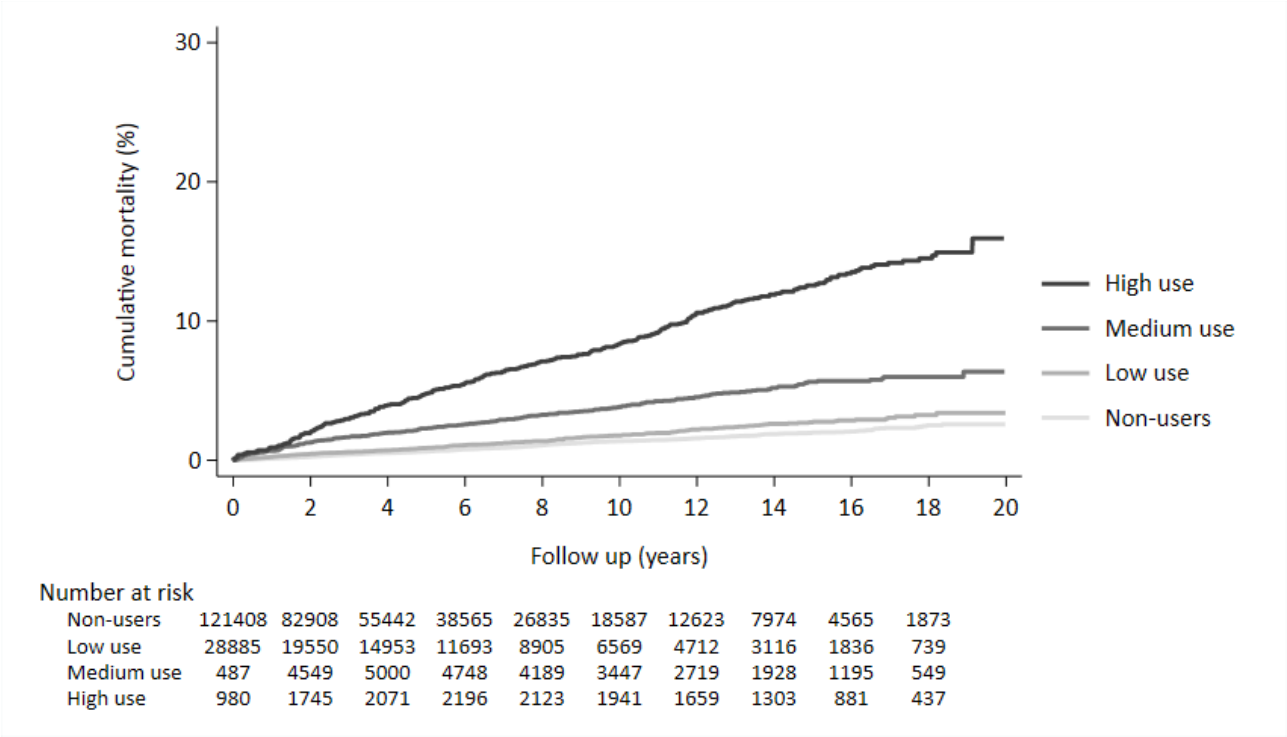

Figure 3: Kaplan-Meier estimates of the cumulative all-cause mortality among young adults with asthma stratified by cumulative oral corticosteroid (OCS) exposure (no use, low use ≤500 mg, medium use >500-2000 mg, high use >2000 mg) adjusted for age and sex

Supplementary material

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

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Table S1: Overview of the International Statistical Classification of Diseases and Related Health Problems' 10th Revision (ICD-10) codes available from The Danish National Patient Registry and Anatomical Therapeutic Chemical Classification (ATC) codes available from The Danish National Prescription Registry used to define the study variables

Variable	ICD-10 codes	ATC codes
Exposure		
Oral corticosteroid		H02AB
Asthma medication		
Inhaled corticosteroids (ICS)		R03BA
Inhaled selective β2-agonists		R03AC
Fixed inhalation combinations of β2-agonists and glucocorticoids		R03AK
Leukotriene receptor antagonists		R03DC
Xanthines		R03DA
*Exclusion criteria comorbidities**		
Chronic obstructive pulmonary disease (COPD)	J41-44.9, not including J44.8	
Cystic fibrosis	E84	
Sarcoidosis	D86	
Primary adrenocortical insufficiency	E271	
Pneumonitis due to external agents	J67-70	
Inflammatory bowel disease	K50-51	
Inflammatory polyarthropathies	M05-14	
Systemic connective tissue disorders	M30-36	
Inflammatory spondylopathies	M45-46	
Malignancy	C00-99	
Asthma-related conditions and co-medication		
Oral antihistamines		R06
Nasal corticosteroids		R01AD
Obesity	E66	
Anti-obesity products		A08A
Sleep apnoea	G473	
Antipsychotics		N05A
*Long-term comorbidities**		
Osteoporosis	M80-M82	
Fractures	T02, T08, T10, T12, T142, M484, M485, M80, M843, M844, S02 (excl. S025), S12 (excl. S128, S129), S22, S32, S42, S52, S62, S72, S82, S92	
Osteonecrosis	M87	
Diabetes mellitus type 2	E11	A10B
Adrenal insufficiency	E273, E274A, E274C	
Ischemic heart disease	I20-I25	

Heart failure	I11.0; I13.0; I13.2; I42.0; I42.6; I42.7; I 42.9; I50.0; I50.1; I50.9	
Depression/anxiety	F32-F33; F40-F41	N06AB
Peptic ulcer disease	K25-28	
Cataract	H25, H26, H28	
Mortality		
All cause	Any ICD-10 code	
Respiratory	J	
Asthma-specific	J45-J46	
Cardiovascular disease	I	
Infectious disease	A, B	
Endocrine disease	E	
Gastrointestinal disease	N	
Neurological disease	G	
Mental and behavioural disease	F	
Others	Any other than the above-mentioned	
Healthcare use		
All cause Emergency department visits	Any ICD-10 code	
Asthma-related emergency department visits	J45-J46 as primary (A) diagnoses, or as secondary (B) diagnosis if primary diagnosis is R04-R09.	
All cause Hospitalisation	Any ICD-10 code	
Asthma-related hospitalisation	J45-J46 as primary (A) diagnoses, or as secondary (B) diagnosis if primary diagnosis is R04-R09.	

* ICD-10 codes include both primary (A), secondary (B) and additional (+) diagnoses unless otherwise specified.

Table S2: Dosage equivalencies of oral corticosteroids

Drug	**ATC code**	**Equivalent dosage (mg)**[1]
Betamethasone	H02AB01	0.6
Dexamethasone	H02AB02	0.75
Methylprednisolone	H02AB04	4
Prednisolone	H02AB06	5
Prednisone	H02AB07	5
Hydrocortisone	H02AB09	20

ATC: Anatomical Therapeutic Chemical Classification

[1] Medscape. Corticosteroid Dose Equivalents. https://emedicine.medscape.com/article/2172042-overview Accessed June 30, 2020

Subgroup analysis 1

Primary outcome stratified by gender

Table S3.1 Incidence rates and hazard ratios of OCS-related morbidities (only males)

MALES	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-value	Hazard ratio (95% CI)	P-value
Any OCS-related comorbidity	3917	142245	27.5 (26.7;28.4)	2051	52375	39.2 (37.5;40.9)	11.6 (9.7;13.5)	<0.001	1.43 (1.35;1.51)	<0.001
Osteoporosis	87	261238	0.3 (0.3;0.4)	157	105924	1.5 (1.3;1.7)	1.1 (0.9;1.4)	<0.001	4.01 (3.07;5.24)	<0.001
Fractures	2348	177236	13.2 (12.7;13.8)	1116	71443	15.6 (14.7;16.6)	2.4 (1.3;3.4)	<0.001	1.20 (1.12;1.29)	<0.001
Osteonecrosis	12	261620	0.0 (0.0;0.1)	21	106478	0.2 (0.1;0.3)	0.2 (0.1;0.2)	<0.001	4.38 (2.17;8.86)	<0.001
Diabetes mellitus type 2	842	253726	3.3 (3.1;3.6)	616	101977	6.0 (5.6;6.5)	2.7 (2.2;3.2)	<0.001	1.66 (1.49;1.84)	<0.001
Adrenal insufficiency	(n<10)	261927	–	(n<10)	106658	–	–	–	–	–
Ischaemic heart disease	610	255232	2.4 (2.2;2.6)	428	102931	4.2 (3.8;4.6)	1.8 (1.3;2.2)	<0.001	1.58 (1.39;1.79)	<0.001
Heart failure	101	260973	0.4 (0.3;0.5)	205	105442	1.9 (1.7;2.2)	1.6 (1.3;1.8)	<0.001	4.73 (3.71;6.03)	<0.001
Depression/anxiety	2099	213568	9.8 (9.4;10.3)	1187	83625	14.2 (13.4;15.0)	4.4 (3.5;5.3)	<0.001	1.52 (1.42;1.63)	<0.001
Peptic ulcer disease	133	259338	0.5 (0.4;0.6)	119	105058	1.1 (0.9;1.4)	0.6 (0.4;0.8)	<0.001	2.12 (1.65;2.72)	<0.001
Cataract	241	259839	0.9 (0.8;1.1)	201	105362	1.9 (1.7;2.2)	1.0 (0.7;1.3)	<0.001	1.69 (1.40;2.04)	<0.001

Table S3.2 Incidence rates and hazard ratios of OCS-related morbidities (only females)

FEMALES	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-value	Hazard ratio (95% CI)	P-value
Any OCS-related comorbidity	6396	197439	32.4 (31.6;33.2)	3375	76978	43.8 (42.4;45.3)	11.4 (9.8;13.1)	<0.001	1.37 (1.32;1.43)	<0.001
Osteoporosis	334	352697	0.9 (0.9;1.1)	368	150417	2.4 (2.2;2.7)	1.5 (1.2;1.8)	<0.001	2.14 (1.84;2.48)	<0.001
Fractures	3197	275719	11.6 (11.2;12.0)	1751	117869	14.9 (14.2;15.6)	3.3 (2.5;4.1)	<0.001	1.25 (1.18;1.32)	<0.001
Osteonecrosis	20	354793	0.1 (0.0;0.1)	15	152306	0.1 (0.1;0.2)	0.0 (-0.0;0.1)	0.147	1.66 (0.87;3.18)	0.127
Diabetes mellitus type 2	1373	339674	4.0 (3.8;4.3)	873	144839	6.0 (5.6;6.4)	2.0 (1.5;2.4)	<0.001	1.42 (1.30;1.54)	<0.001
Adrenal insufficiency	(n<10)	354944	–	27	152350	0.2 (0.1;0.3)	–	–	–	–
Ischaemic heart disease	538	348334	1.5 (1.4;1.7)	441	148582	3.0 (2.7;3.3)	1.4 (1.1;1.7)	<0.001	1.76 (1.55;2.00)	<0.001
Heart failure	63	354292	0.2 (0.1;0.2)	161	151594	1.1 (0.9;1.2)	0.9 (0.7;1.1)	<0.001	5.57 (4.14;7.50)	<0.001
Depression/anxiety	4271	255880	16.7 (16.2;17.2)	2177	105511	20.6 (19.8;21.5)	3.9 (2.9;4.9)	<0.001	1.34 (1.27;1.41)	<0.001
Peptic ulcer disease	206	351744	0.6 (0.5;0.7)	154	150723	1.0 (0.9;1.2)	0.4 (0.3;0.6)	<0.001	1.70 (1.37;2.11)	<0.001
Cataract	332	352157	0.9 (0.8;1.0)	308	150517	2.0 (1.8;2.3)	1.1 (0.9;1.4)	<0.001	1.79 (1.53;2.09)	<0.001

Subgroup analysis 2

Primary outcome stratified by calendar year of index date (all follow-up limited to maximum five years)

Table S4.1 Incidence rates and hazard ratios of OCS-related morbidities (only individuals included during 1999-2004)

1999-2004	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-value	Hazard ratio (95% CI)	P-value
Any OCS-related comorbidity	2956	83895	35.2 (34.0;36.5)	1153	24871	46.4 (43.8;49.1)	11.1 (8.2;14.1)	<0.001	1.32 (1.23;1.41)	<0.001
Osteoporosis	42	124456	0.3 (0.2;0.5)	38	37294	1.0 (0.7;1.4)	0.7 (0.3;1.0)	<0.001	2.94 (1.90;4.56)	<0.001
Fractures	1370	100296	13.7 (13.0;14.4)	462	30736	15.0 (13.7;16.5)	1.4 (-0.2;2.9)	0.081	1.11 (1.00;1.23)	0.055
Osteonecrosis	(n<10)	124584	–	(n<10)	37352	–	–	–	–	–
Diabetes mellitus type 2	329	122680	2.7 (2.4;3.0)	157	36785	4.3 (3.7;5.0)	1.6 (0.9;2.3)	<0.001	1.56 (1.29;1.88)	<0.001
Adrenal insufficiency	(n<10)	124603	–	(n<10)	37363	–	–	–	–	–
Ischaemic heart disease	196	122968	1.6 (1.4;1.8)	97	36911	2.6 (2.2;3.2)	1.0 (0.5;1.6)	<0.001	1.61 (1.26;2.06)	<0.001
Heart failure	16	124291	0.1 (0.1;0.2)	39	37219	1.0 (0.8;1.4)	0.9 (0.6;1.3)	<0.001	8.08 (4.49;14.55)	<0.001
Depression/anxiety	1935	103665	18.7 (17.9;19.5)	800	31070	25.7 (24.0;27.6)	7.1 (5.1;9.1)	<0.001	1.38 (1.27;1.50)	<0.001
Peptic ulcer disease	86	123315	0.7 (0.6;0.9)	43	37042	1.2 (0.9;1.6)	0.5 (0.1;0.8)	0.010	1.66 (1.15;2.39)	0.007
Cataract	54	124137	0.4 (0.3;0.6)	33	37230	0.9 (0.6;1.2)	0.5 (0.1;0.8)	0.003	1.94 (1.26;2.99)	0.003

Table S4.1 Incidence rates and hazard ratios of OCS-related morbidities (only individuals included during 2005-2009)

2005-2009	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-value	Hazard ratio (95% CI)	P-value
Any OCS-related comorbidity	2168	66830	32.4 (31.1;33.8)	992	19258	51.5 (48.4;54.8)	19.1 (15.6;22.6)	<0.001	1.59 (1.47;1.71)	<0.001
Osteoporosis	87	121944	0.7 (0.6;0.9)	59	36084	1.6 (1.3;2.1)	0.9 (0.5;1.4)	<0.001	2.26 (1.62;3.15)	<0.001
Fractures	1058	89207	11.9 (11.2;12.6)	448	27237	16.4 (15.0;18.0)	4.6 (2.9;6.3)	<0.001	1.38 (1.24;1.54)	<0.001
Osteonecrosis	(n<10)	122383	–	(n<10)	36246	–	–	–	–	–
Diabetes mellitus type 2	460	117628	3.9 (3.6;4.3)	203	35047	5.8 (5.0;6.6)	1.9 (1.0;2.8)	<0.001	1.47 (1.24;1.73)	<0.001
Adrenal insufficiency	(n<10)	122498	–	(n<10)	36276	–	–	–	–	–
Ischaemic heart disease	209	119761	1.7 (1.5;2.0)	132	35547	3.7 (3.1;4.4)	2.0 (1.3;2.6)	<0.001	2.12 (1.70;2.64)	<0.001
Heart failure	25	122092	0.2 (0.1;0.3)	50	36090	1.4 (1.1;1.8)	1.2 (0.8;1.6)	<0.001	6.73 (4.14;10.92)	<0.001
Depression/anxiety	1537	91024	16.9 (16.1;17.8)	699	27134	25.8 (23.9;27.7)	8.9 (6.8;11.0)	<0.001	1.53 (1.40;1.67)	<0.001
Peptic ulcer disease	59	120845	0.5 (0.4;0.6)	38	35883	1.1 (0.8;1.5)	0.6 (0.2;0.9)	<0.001	2.13 (1.42;3.20)	<0.001
Cataract	107	121534	0.9 (0.7;1.1)	54	36020	1.5 (1.1;2.0)	0.6 (0.2;1.1)	0.003	1.64 (1.18;2.27)	0.003

Table S4.1 Incidence rates and hazard ratios of OCS-related morbidities (only individuals included during 2010-2014)

2010-2014	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-value	Hazard ratio (95% CI)	P-value
Any OCS-related comorbidity	1564	59342	26.4 (25.1;27.7)	640	17784	36.0 (33.3;38.9)	9.6 (6.6;12.7)	<0.001	1.37 (1.25;1.50)	<0.001
Osteoporosis	108	126326	0.9 (0.7;1.0)	76	37783	2.0 (1.6;2.5)	1.2 (0.7;1.6)	<0.001	2.31 (1.72;3.09)	<0.001
Fractures	1023	84726	12.1 (11.4;12.8)	400	26496	15.1 (13.7;16.7)	3.0 (1.4;4.7)	<0.001	1.24 (1.11;1.39)	<0.001
Osteonecrosis	(n<10)	127228	–	(n<10)	38058	–	–	–	–	–
Diabetes mellitus type 2	434	120089	3.6 (3.3;4.0)	198	36361	5.4 (4.7;6.3)	1.8 (1.0;2.7)	<0.001	1.50 (1.27;1.78)	<0.001
Adrenal insufficiency	(n<10)	127354	–	(n<10)	38080	–	–	–	–	–
Ischaemic heart disease	229	123190	1.9 (1.6;2.1)	106	37160	2.9 (2.4;3.5)	1.0 (0.4;1.6)	<0.001	1.53 (1.22;1.93)	<0.001
Heart failure	37	126850	0.3 (0.2;0.4)	61	37842	1.6 (1.3;2.1)	1.3 (0.9;1.7)	<0.001	5.58 (3.69;8.44)	<0.001
Depression/anxiety	955	88399	10.8 (10.1;11.5)	400	27319	14.6 (13.3;16.1)	3.8 (2.2;5.4)	<0.001	1.38 (1.23;1.56)	<0.001
Peptic ulcer disease	48	125658	0.4 (0.3;0.5)	40	37690	1.1 (0.8;1.4)	0.7 (0.3;1.0)	<0.001	2.74 (1.79;4.20)	<0.001
Cataract	128	125919	1.0 (0.9;1.2)	63	37747	1.7 (1.3;2.1)	0.7 (0.2;1.1)	0.002	1.59 (1.18;2.15)	0.003

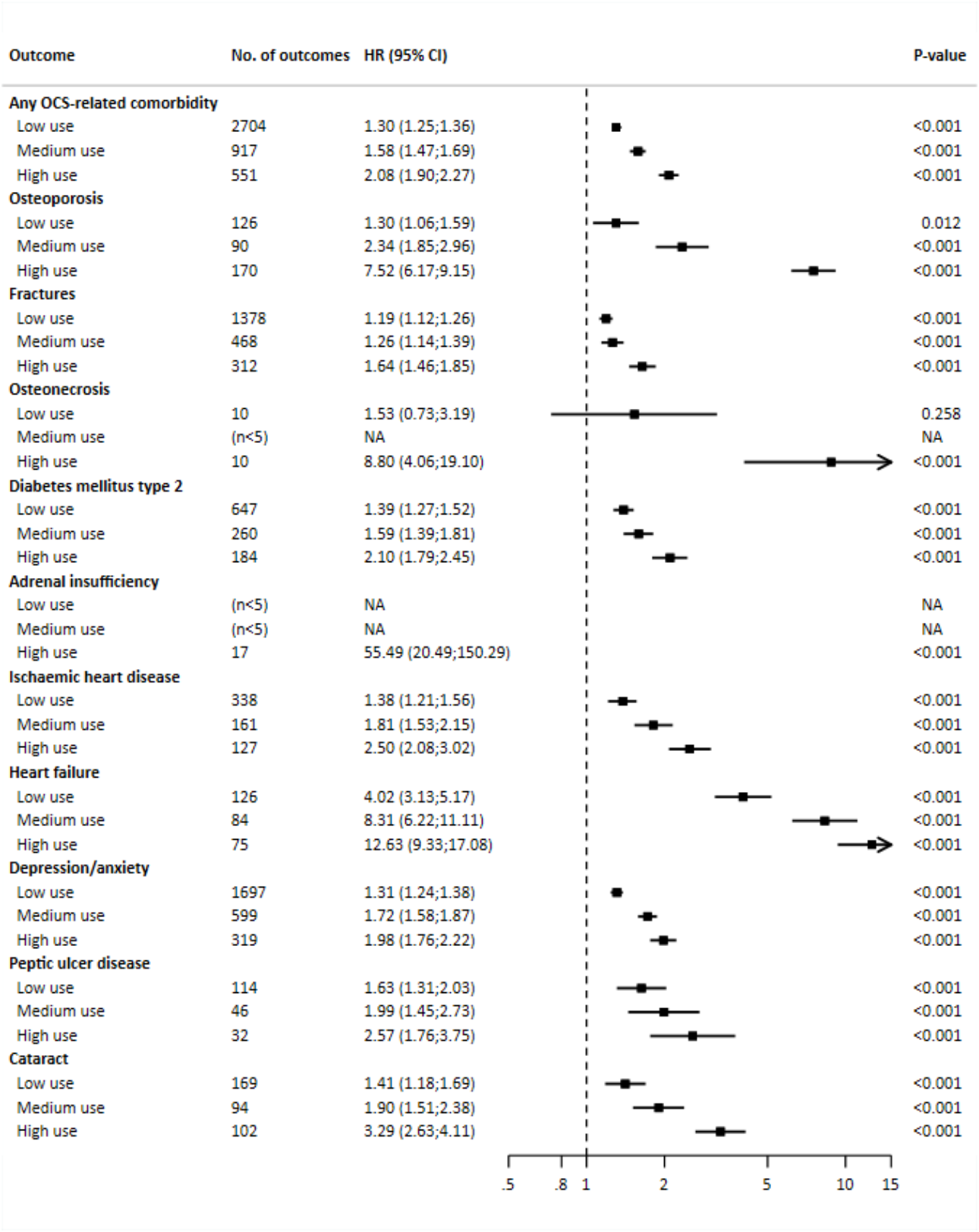
Sensitivity analysis 1

All users of non-oral systemic corticosteroids are excluded and censored upon incident use during follow-up to limit potential confounding from injectable steroids.

Table S5 Incidence rates and hazard ratios of OCS-related morbidities (exclusion: non-oral systemic steroids)

	Non-user			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-values	Hazard ratio (95% CI)	P-values
Any OCS-related comorbidity	8105	276376	29.3 (28.7;30.0)	4181	100267	41.7 (40.5;43.0)	12.4 (11.0;13.8)	<0.001	1.43 (1.38;1.48)	<0.001
Osteoporosis	353	502659	0.7 (0.6;0.8)	387	194391	2.0 (1.8;2.2)	1.3 (1.1;1.5)	<0.001	2.41 (2.08;2.79)	<0.001
Fractures	4339	365833	11.9 (11.5;12.2)	2160	144460	15.0 (14.3;15.6)	3.1 (2.4;3.8)	<0.001	1.25 (1.19;1.32)	<0.001
Osteonecrosis	25	505115	0.0 (0.0;0.1)	23	196233	0.1 (0.1;0.2)	0.1 (0.0;0.1)	3.620	2.30 (1.29;4.08)	0.004
Diabetes mellitus type 2	1742	483253	3.6 (3.4;3.8)	1096	187490	5.8 (5.5;6.2)	2.2 (1.9;2.6)	<0.001	1.52 (1.41;1.64)	<0.001
Adrenal insufficiency	6	505467	0.0 (0.0;0.0)	23	196397	0.1 (0.1;0.2)	0.1 (0.1;0.2)	<0.001	8.58 (3.50;21.06)	<0.001
Ischaemic heart disease	917	492697	1.9 (1.7;2.0)	626	191087	3.3 (3.0;3.5)	1.4 (1.1;1.7)	<0.001	1.62 (1.46;1.79)	<0.001
Heart failure	119	503311	0.2 (0.2;0.3)	285	194793	1.5 (1.3;1.6)	1.2 (1.1;1.4)	<0.001	5.88 (4.74;7.29)	<0.001
Depression/anxiety	4996	380238	13.1 (12.8;13.5)	2619	145641	18.0 (17.3;18.7)	4.8 (4.1;5.6)	<0.001	1.44 (1.38;1.52)	<0.001
Peptic ulcer disease	267	498727	0.5 (0.5;0.6)	192	194158	1.0 (0.9;1.1)	0.5 (0.3;0.6)	<0.001	1.81 (1.50;2.18)	<0.001
Cataract	434	500856	0.9 (0.8;1.0)	365	194151	1.9 (1.7;2.1)	1.0 (0.8;1.2)	<0.001	1.81 (1.57;2.08)	<0.001

Figure S1 Risk of OCS-related comorbidities by exposure group (exclusion: non-oral systemic steroids)



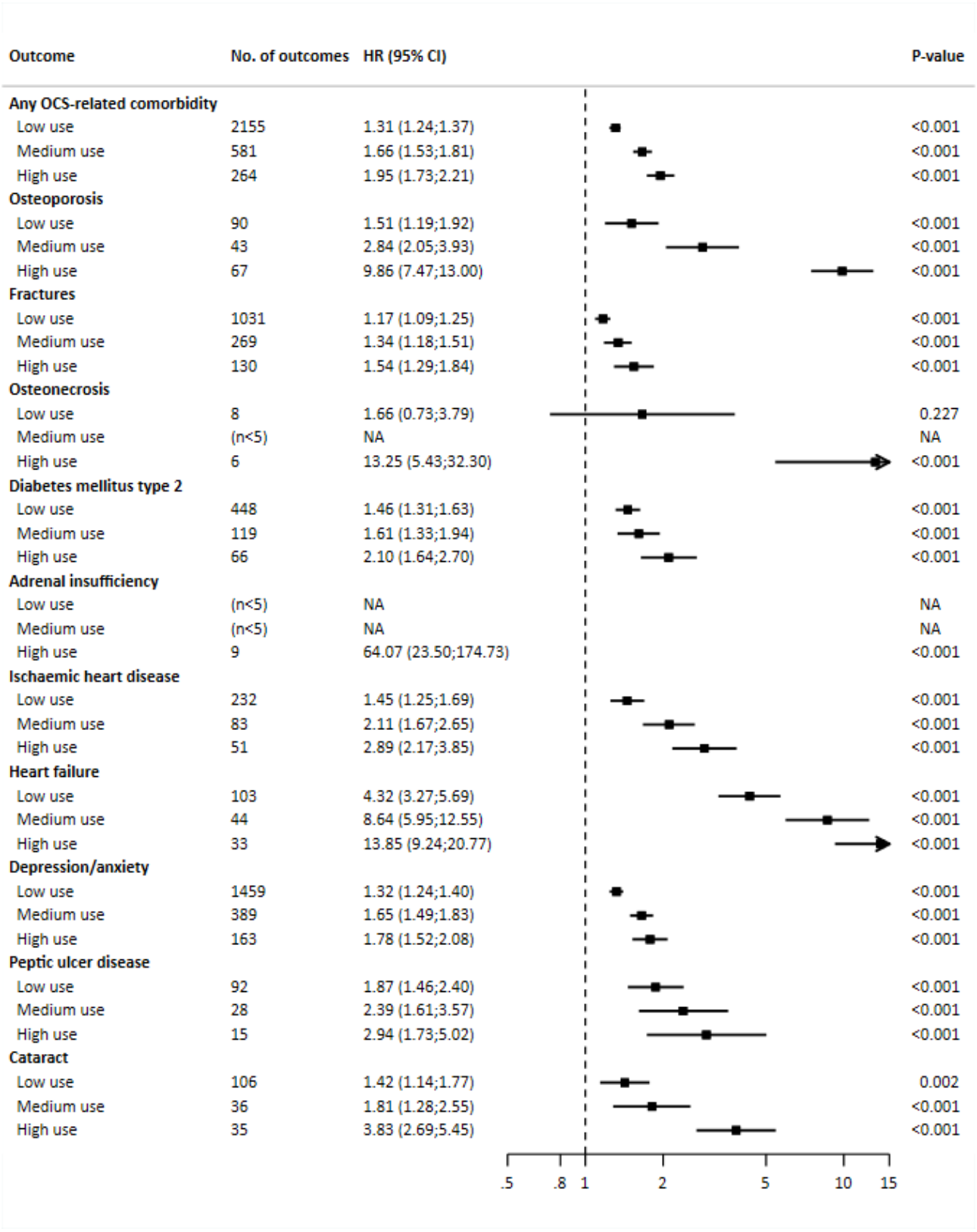
Sensitivity analysis 2

All individuals followed to a maximum of five years to limit bias due to long observational time

Table S6 Incidence rates and hazard ratios of OCS-related morbidities (limited to five years of follow-up)

	Non-user			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-values	Hazard ratio (95% CI)	P-values
Any OCS-related comorbidity	6792	216464	31.4 (30.6;32.1)	3009	67795	44.4 (42.8;46.0)	13.0 (11.3;14.8)	<0.001	1.41 (1.35;1.47)	<0.001
Osteoporosis	246	391375	0.6 (0.6;0.7)	201	124414	1.6 (1.4;1.9)	1.0 (0.8;1.2)	<0.001	2.46 (2.04;2.96)	<0.001
Fractures	3546	283762	12.5 (12.1;12.9)	1431	93347	15.3 (14.6;16.1)	2.8 (1.9;3.7)	<0.001	1.22 (1.15;1.30)	<0.001
Osteonecrosis	20	393113	0.1 (0.0;0.1)	16	124990	0.1 (0.1;0.2)	0.1 (0.0;0.1)	8.086	2.50 (1.29;4.85)	0.006
Diabetes mellitus type 2	1255	377361	3.3 (3.1;3.5)	636	120878	5.3 (4.9;5.7)	1.9 (1.5;2.4)	<0.001	1.54 (1.40;1.70)	<0.001
Adrenal insufficiency	7	393389	0.0 (0.0;0.0)	14	125058	0.1 (0.1;0.2)	0.1 (0.0;0.2)	<0.001	6.53 (2.65;16.12)	<0.001
Ischaemic heart disease	654	383798	1.7 (1.6;1.8)	366	122633	3.0 (2.7;3.3)	1.3 (0.9;1.6)	<0.001	1.68 (1.48;1.92)	<0.001
Heart failure	97	391917	0.2 (0.2;0.3)	180	124418	1.4 (1.3;1.7)	1.2 (1.0;1.4)	<0.001	5.71 (4.45;7.32)	<0.001
Depression/anxiety	4475	295605	15.1 (14.7;15.6)	2016	95134	21.2 (20.3;22.1)	6.1 (5.0;7.1)	<0.001	1.40 (1.33;1.48)	<0.001
Peptic ulcer disease	201	388413	0.5 (0.5;0.6)	135	123847	1.1 (0.9;1.3)	0.6 (0.4;0.8)	<0.001	2.04 (1.64;2.55)	<0.001
Cataract	304	390068	0.8 (0.7;0.9)	177	124211	1.4 (1.2;1.7)	0.6 (0.4;0.9)	<0.001	1.70 (1.42;2.05)	<0.001

Figure S2 Risk of OCS-related comorbidities by exposure group (limited to five years of follow-up)



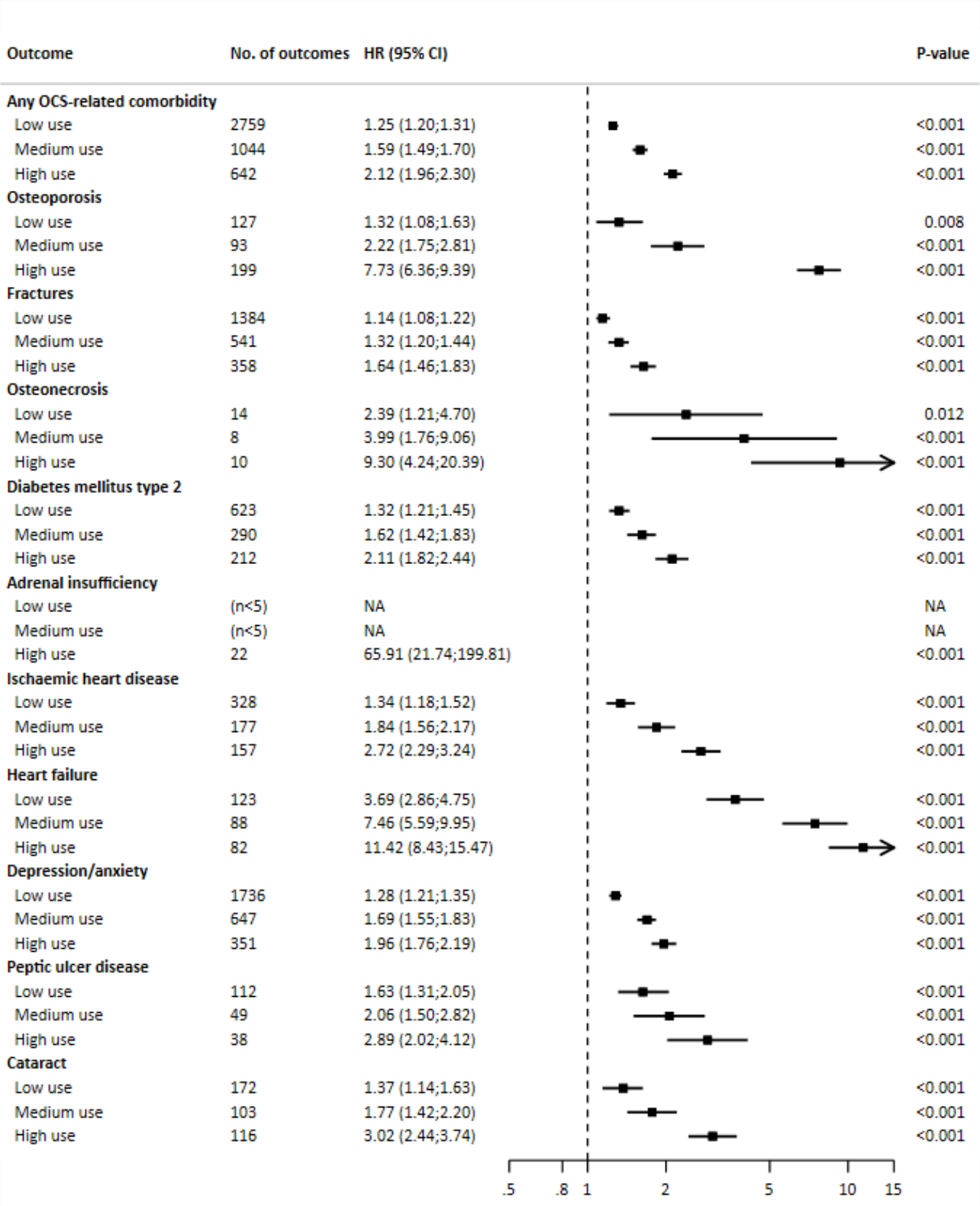
Sensitivity analysis 3

Individuals censored after two consecutive years of not collecting any asthma medication to limit effects from patients with apparent remitted asthma

Table S7 Incidence rates and hazard ratios of OCS-related morbidities (censoring of remitted asthma)

	Non-user			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-values	Hazard ratio (95% CI)	P-values
Any OCS-related comorbidity	8010	263517	30.4 (29.7;31.1)	4455	105665	42.2 (40.9;43.4)	11.8 (10.4;13.2)	<0.001	1.40 (1.35;1.46)	<0.001
Osteoporosis	319	472493	0.7 (0.6;0.8)	420	202828	2.1 (1.9;2.3)	1.4 (1.2;1.6)	<0.001	2.49 (2.15;2.89)	<0.001
Fractures	4224	345301	12.2 (11.9;12.6)	2285	150772	15.2 (14.5;15.8)	2.9 (2.2;3.6)	<0.001	1.24 (1.18;1.30)	<0.001
Osteonecrosis	21	474578	0.0 (0.0;0.1)	32	204691	0.2 (0.1;0.2)	0.1 (0.1;0.2)	<0.001	3.50 (2.02;6.06)	<0.001
Diabetes mellitus type 2	1621	455183	3.6 (3.4;3.7)	1131	196072	5.8 (5.4;6.1)	2.2 (1.8;2.6)	<0.001	1.50 (1.39;1.62)	<0.001
Adrenal insufficiency	5	474887	0.0 (0.0;0.0)	28	204868	0.1 (0.1;0.2)	0.1 (0.1;0.2)	<0.001	10.34 (3.92;27.25)	<0.001
Ischaemic heart disease	846	463664	1.8 (1.7;2.0)	662	199561	3.3 (3.1;3.6)	1.5 (1.2;1.8)	<0.001	1.65 (1.49;1.82)	<0.001
Heart failure	119	473204	0.3 (0.2;0.3)	293	203384	1.4 (1.3;1.6)	1.2 (1.0;1.4)	<0.001	5.42 (4.36;6.73)	<0.001
Depression/anxiety	4926	362716	13.6 (13.2;14.0)	2739	153107	17.9 (17.2;18.6)	4.3 (3.5;5.1)	<0.001	1.42 (1.36;1.49)	<0.001
Peptic ulcer disease	245	469071	0.5 (0.5;0.6)	199	202581	1.0 (0.9;1.1)	0.5 (0.3;0.6)	<0.001	1.87 (1.55;2.27)	<0.001
Cataract	415	470775	0.9 (0.8;1.0)	391	202618	1.9 (1.7;2.1)	1.0 (0.8;1.3)	<0.001	1.74 (1.51;2.00)	<0.001

Figure S3 Risk of OCS-related comorbidities by exposure group (censoring of remitted asthma)



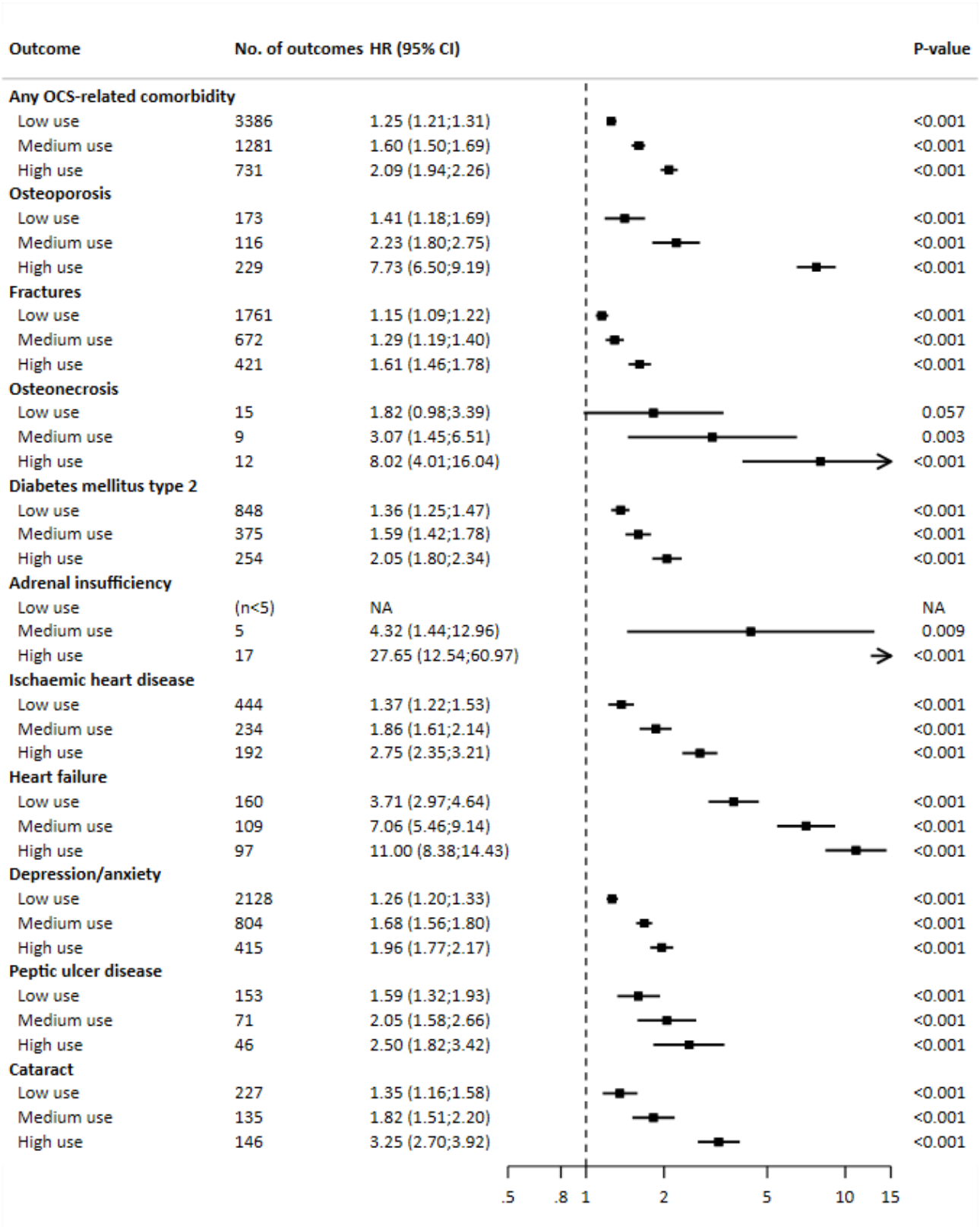
Sensitivity analysis 4 (post hoc)

All patients receiving biological treatment are excluded at baseline and censored upon incident use during follow-up. Biological treatment for asthma is only available through hospital care in Denmark, and identified by procedure codes (BOHJ19A1, BOHJ19I2, BOHJ19I3, BOHJ19I1).

Table S8 Incidence rates and hazard ratios of OCS-related morbidities (exclusion of biological treatment)

	Non-user			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-values	Hazard ratio (95% CI)	P-values
Any OCS-related comorbidity	10032	332037	30.2 (29.6;30.8)	5408	128825	42.0 (40.9;43.1)	11.8 (10.5;13.0)	<0.001	1.40 (1.35;1.45)	<0.001
Osteoporosis	419	611818	0.7 (0.6;0.8)	519	255387	2.0 (1.9;2.2)	1.3 (1.2;1.5)	<0.001	2.49 (2.19;2.84)	<0.001
Fractures	5399	442994	12.2 (11.9;12.5)	2856	188599	15.1 (14.6;15.7)	3.0 (2.3;3.6)	<0.001	1.23 (1.18;1.29)	<0.001
Osteonecrosis	30	614779	0.0 (0.0;0.1)	36	257778	0.1 (0.1;0.2)	0.1 (0.0;0.1)	<0.001	2.80 (1.72;4.54)	<0.001
Diabetes mellitus type 2	2206	588065	3.8 (3.6;3.9)	1483	245843	6.0 (5.7;6.3)	2.3 (1.9;2.6)	<0.001	1.50 (1.40;1.60)	<0.001
Adrenal insufficiency	11	615256	0.0 (0.0;0.0)	25	258012	0.1 (0.1;0.1)	0.1 (0.0;0.1)	<0.001	4.75 (2.37;9.54)	<0.001
Ischaemic heart disease	1147	598850	1.9 (1.8;2.0)	870	250522	3.5 (3.2;3.7)	1.6 (1.3;1.8)	<0.001	1.66 (1.52;1.81)	<0.001
Heart failure	155	612867	0.3 (0.2;0.3)	366	256034	1.4 (1.3;1.6)	1.2 (1.0;1.3)	<0.001	5.31 (4.38;6.43)	<0.001
Depression/anxiety	6204	459256	13.5 (13.2;13.8)	3352	188369	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	346	606810	0.6 (0.5;0.6)	270	254801	1.1 (0.9;1.2)	0.5 (0.3;0.6)	<0.001	1.80 (1.53;2.12)	<0.001
Cataract	572	609500	0.9 (0.9;1.0)	508	254880	2.0 (1.8;2.2)	1.1 (0.9;1.2)	<0.001	1.75 (1.55;1.98)	<0.001

Figure S4 Risk of OCS-related comorbidities by exposure group (exclusion of biological treatment)



Sensitivity analysis 5 (post hoc)

All patients with asthma-related admissions or emergency department visits are excluded as baseline and censored during follow-up upon incident event.

Table S9 Incidence rates and hazard ratios of OCS-related morbidities (exclusion of asthma-related admissions or emergency department visits)

No asthma-related acute visits	**Non-user**			**OCS-user**						
	Cases, n	Person years	IR/1000 person years (95% CI)	Cases, n	Person years	IR/1000 person years (95% CI)	IRD	P-values	Hazard ratio (95% CI)	P-values
Any OCS-related comorbidity	8566	287847	29.8 (29.1;30.4)	4170	103039	40.5 (39.3;41.7)	10.7 (9.3;12.1)	<0.001	1.36 (1.31;1.42)	<0.001
Osteoporosis	433	523557	0.8 (0.8;0.9)	387	198031	2.0 (1.8;2.2)	1.1 (0.9;1.3)	<0.001	2.01 (1.75;2.31)	<0.001
Fractures	4748	384604	12.3 (12.0;12.7)	2194	148544	14.8 (14.2;15.4)	2.4 (1.7;3.1)	<0.001	1.18 (1.12;1.24)	<0.001
Osteonecrosis	24	526186	0.0 (0.0;0.1)	27	199741	0.1 (0.1;0.2)	0.1 (0.0;0.1)	<0.001	2.85 (1.64;4.95)	<0.001
Diabetes mellitus type 2	1922	501778	3.8 (3.7;4.0)	1160	190580	6.1 (5.7;6.4)	2.3 (1.9;2.6)	<0.001	1.50 (1.39;1.61)	<0.001
Adrenal insufficiency	7	526574	0.0 (0.0;0.0)	18	199930	0.1 (0.1;0.1)	0.1 (0.0;0.1)	<0.001	5.87 (2.47;13.95)	<0.001
Ischaemic heart disease	1007	512041	2.0 (1.8;2.1)	655	194324	3.4 (3.1;3.6)	1.4 (1.1;1.7)	<0.001	1.58 (1.43;1.74)	<0.001
Heart failure	136	524547	0.3 (0.2;0.3)	283	198485	1.4 (1.3;1.6)	1.2 (1.0;1.3)	<0.001	5.24 (4.25;6.45)	<0.001
Depression/anxiety	5039	393396	12.8 (12.5;13.2)	2435	148268	16.4 (15.8;17.1)	3.6 (2.9;4.4)	<0.001	1.36 (1.30;1.43)	<0.001
Peptic ulcer disease	293	519619	0.6 (0.5;0.6)	206	197461	1.0 (0.9;1.2)	0.5 (0.3;0.6)	<0.001	1.82 (1.52;2.18)	<0.001
Cataract	532	521456	1.0 (0.9;1.1)	393	197580	2.0 (1.8;2.2)	1.0 (0.8;1.2)	<0.001	1.63 (1.43;1.86)	<0.001

Figure S5 Risk of OCS-related comorbidities by exposure group (exclusion of asthma-related admissions or emergency department visits)