ORIGINAL RESEARCH

A Long-Term Study of Adverse Outcomes Associated With Oral Corticosteroid Use in COPD

Gary Tse [ID][1,2], Benjamin Emmanuel [ID][3], Cono Ariti [ID][1], Mona Bafadhel [ID][4], Alberto Papi [ID][5], Victoria Carter [ID][1], Jiandong Zhou [ID][1], Derek Skinner [ID][1], Xiao Xu[3], Hana Müllerová [ID][6], David Price [ID][1,7]

[1]Observational and Pragmatic Research Institute, Singapore, Singapore; [2]School of Nursing and Health Studies, Hong Kong Metropolitan University, Hong Kong, People's Republic of China; [3]AstraZeneca, Gaithersburg, MD, USA; [4]Department of Immunobiology, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; [5]Respiratory Medicine, Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [6]AstraZeneca, Cambridge, UK; [7]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

Correspondence: David Price, Observational and Pragmatic Research Institute, 22 Sin Ming Lane, #06-76, Midview City, 573969, Singapore, Tel +65 3105 1489, Email dprice@opri.sg

Background: Oral corticosteroids (OCS) are often prescribed for chronic obstructive pulmonary disease (COPD) exacerbations.
Methods: This observational, individually matched historical cohort study used electronic medical records (1987–2019) from the UK Clinical Practice Research Datalink linked to English Hospital Episode Statistics (HES) to evaluate adverse outcomes in patients with COPD who used OCS (OCS cohort) and those not exposed to OCS (non-OCS cohort). Risk of 17 adverse outcomes was estimated using proportional hazard regression.
Results: Of 323,722 patients, 106,775 (33.0%) had COPD-related OCS prescriptions. Of the 106,775 patients in the overall cohort, 58,955 had HES linkage and were eligible for inclusion in the OCS cohort. The individual matching process identified 53,299 pairs of patients to form the OCS and non-OCS cohorts. Median follow-up post-index was 6.9 years (OCS cohort) and 5.4 years (non-OCS cohort). Adjusted risk of multiple adverse outcomes was higher for the OCS cohort versus the non-OCS cohort, including osteoporosis with/without fractures (adjusted hazard ratio [aHR] 1.80; 95% confidence interval [CI] 1.70–1.92), type 2 diabetes mellitus (aHR 1.44; 95% CI 1.37–1.51), cardiovascular/cerebro-vascular disease (aHR 1.26; 95% CI 1.21–1.30), and all-cause mortality (aHR 1.04; 95% CI 1.02–1.07). In the OCS cohort, risk of most adverse outcomes increased with increasing categorized cumulative OCS dose. For example, risk of cardiovascular/cerebrovascular disease was 34% higher in the 1.0–<2.5 g group versus the <0.5 g group (HR 1.34; 95% CI 1.26–1.42).
Conclusion: Any OCS use was associated with higher risk of adverse outcomes in patients with COPD, with risk generally increasing with greater cumulative OCS dose.

Plain Language Summary: Many patients with chronic obstructive pulmonary disease (COPD) have occasions when their symptoms suddenly worsen, called flare-ups or exacerbations. To treat flare-ups, doctors might prescribe a course of steroid tablets (oral corticosteroids or OCS for short). Doctors might also prescribe "rescue packs" containing OCS and antibiotics, to keep at home and start taking when needed.

While OCS may speed up recovery from flare-ups, repeated use may have negative health effects. We studied effects of OCS use in patients with COPD, using anonymized electronic patient medical records in England. These databases are made available following a high-quality research proposal to research and ethics committees.

Of 323,722 patients with COPD, around one-third received OCS for flare-ups. We studied 17 outcomes including important medical diagnoses and death. We grouped patients into 53,299 pairs so that every patient who used OCS matched a similar patient (eg, the same age and sex) who never used OCS. The patients were followed for an average of 6.9 years (used OCS) and 5.4 years (never used OCS).

Most diagnoses, including diabetes, osteoporosis, cardiovascular/cerebrovascular disease, and death, were more likely in patients who used OCS than those who never used OCS. Patients using larger amounts of OCS over time were generally more likely to experience diagnoses or die.

These results show risks of using OCS, even occasionally, in patients with COPD. Flare-up prevention is important, for example with appropriate daily "maintenance" medication, vaccinations for infections, and quitting smoking, thereby reducing health effects from OCS use for flare-ups.

Graphical Abstract
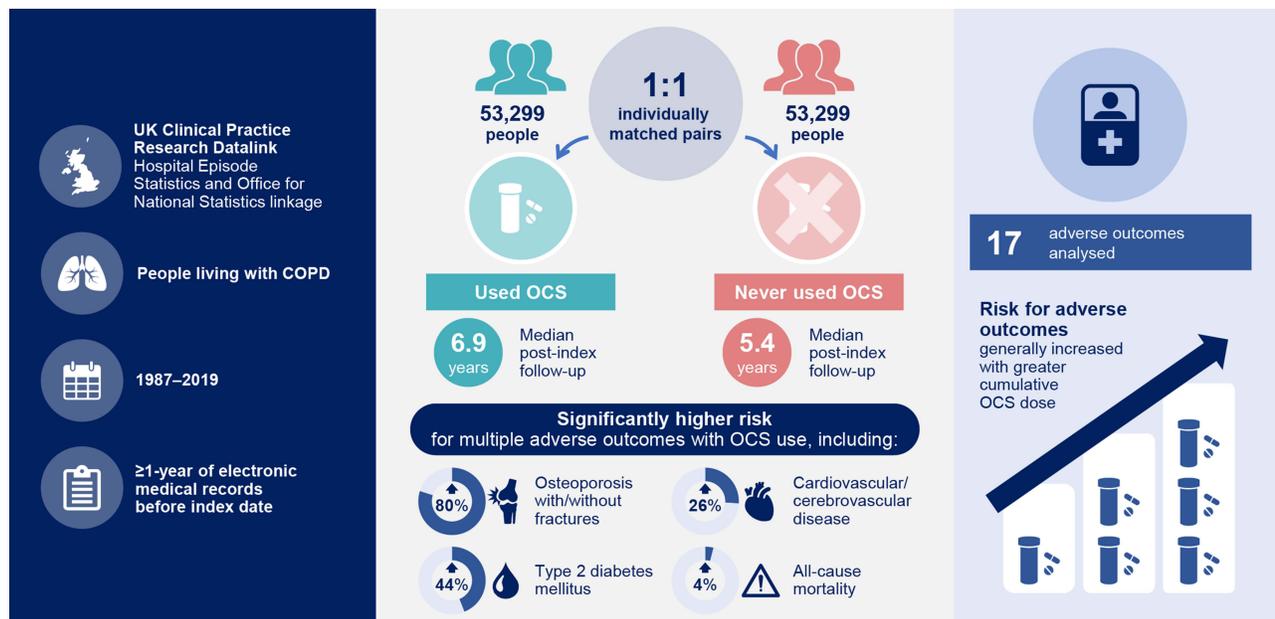
Introduction

Systemic (oral or parenteral) corticosteroids are increasingly used by patients with chronic obstructive pulmonary disease (COPD). Findings presented at the 2021 British Thoracic Society Winter Meeting[1] demonstrated that COPD was the second-leading contributor to total systemic corticosteroid dose among 27 conditions of interest in the UK, and systemic corticosteroid prescriptions in patients with COPD increased from 5.8% in 1990 to 34.8% in 2017. In 2020, a UK study reported that 44% of patients with COPD were prescribed oral corticosteroids (OCS).[2] A patient's COPD management plan may include a prescription of "rescue packs" of OCS and/or antibiotics to keep at home to self-administer if they begin to have an exacerbation.[3,4] In patients experiencing exacerbations, OCS may reduce hospital admissions,[5] shorten recovery time,[6] and improve lung function,[5–7] but there is not sufficient evidence to suggest an effect on mortality.[5] Benefits of OCS have been reported to vary by blood eosinophil count, with higher blood eosinophil count predicting greater treatment response.[8]

However, OCS have been associated with short- and long-term adverse outcomes when prescribed for various conditions, including upper respiratory tract infections, spinal conditions, allergies, and asthma.[9–12] In patients with asthma, OCS exposure has been associated with increased risk of cataracts, gastrointestinal ulcers/bleeds, hypertension, obesity, osteoporosis and fractures, and type 2 diabetes,[10] and a dose–response relationship with OCS exposure has been described for many of these adverse outcomes.[12,13] Given the increasing and common intermittent use of OCS in patients with COPD, it is important to understand potential long-term risks and dose-dependent relationships for different potentially OCS-related adverse outcomes.

In contrast to asthma and other chronic conditions, the potential short- and long-term risks associated with OCS use are not as well understood in patients with COPD.[14] Adverse outcomes associated with short-term OCS use for COPD exacerbations have been described in several studies[7,15,16] including weight gain and insomnia.[7] Long-term OCS use is also an independent predictor of all-cause mortality in patients with COPD.[17,18] A 4-year retrospective US claims analysis of patients newly diagnosed with COPD found that, compared with patients without OCS exposure, patients exposed to >1 g of OCS (prednisolone equivalent) in the 4 years after their COPD diagnosis experienced greater rates of cardiovascular disease, heart failure, hypertension, obesity, dyspepsia, infections, and depression/anxiety.[14] However, the

fragmented nature of health-care data in the United States and the relatively short-term duration of follow-up (average 37 months) complicated examination of long-term outcomes.[14]

An analysis of intermittent OCS use over a long-term follow-up period using robust, comprehensive real-world data is necessary to provide an extensive assessment of potential health risks of OCS in patients with COPD.[14] Therefore, this study evaluated associations between COPD-related OCS exposure and adverse outcomes, including all-cause mortality, in a large English population using one of the largest databases of longitudinal medical records from primary care in the world.[19] This is the first large-scale, long-term analysis of this kind in patients with COPD.

Methods
Study Design and Data Sources

This observational, individually matched historical cohort study of patients with a COPD diagnosis compared those who were exposed to OCS (the OCS cohort) with those who were never known to be exposed to any OCS (the non-OCS cohort) (Figure 1). Index date for patients in the OCS cohort was the date of their first recorded COPD-related OCS prescription.

To ensure characteristics between the cohorts were balanced, and to minimize bias due to confounding, patients in the non-OCS cohort were individually matched (1:1) to patients in the OCS cohort based on index date, age at index date, sex, and smoking status closest to index date. Index date and sex matching criteria were used per similar studies of systemic (oral or parenteral) corticosteroid use in patients with asthma;[12,21] as a COPD study, age and smoking status
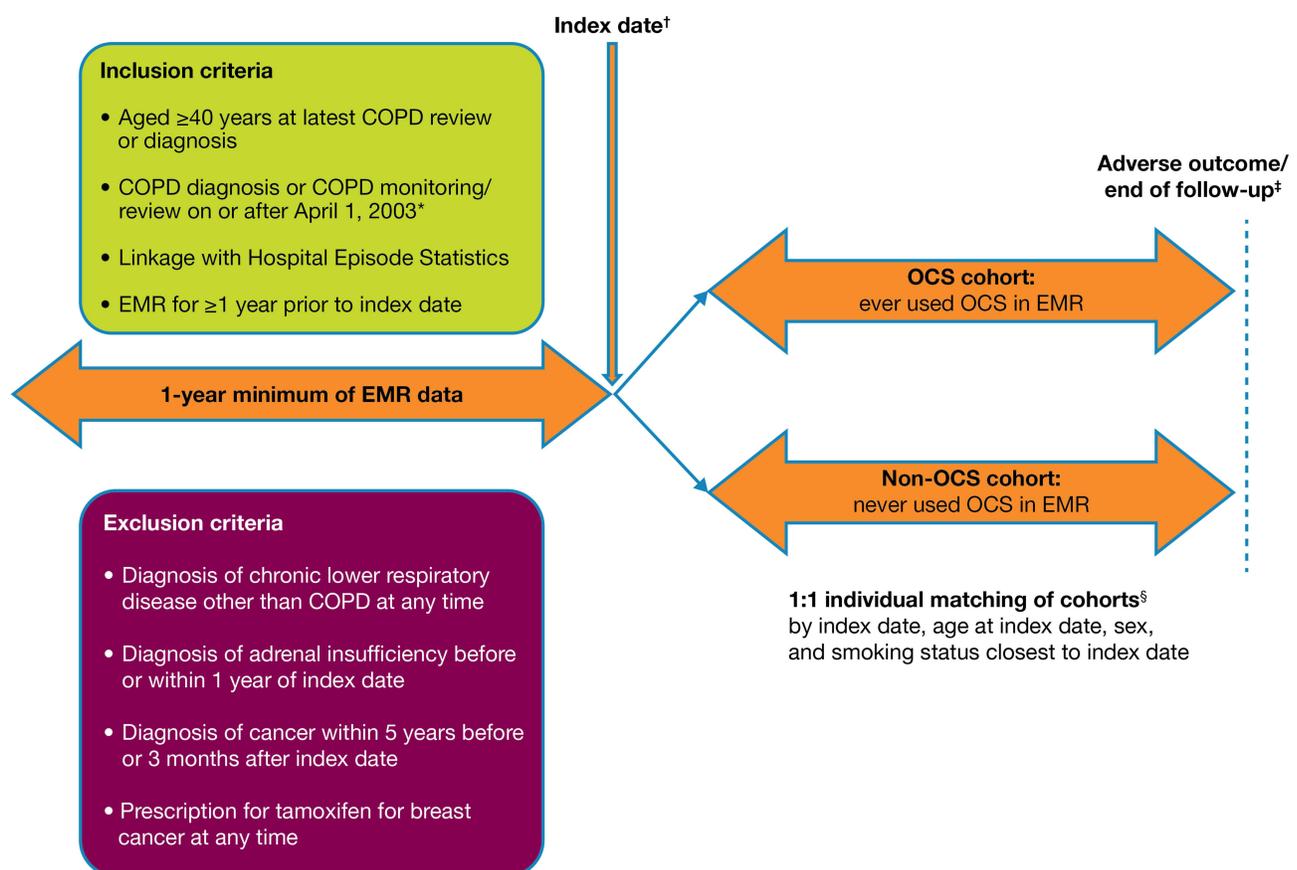
Figure 1 Study design. Data included in this analysis spanned from 1987 to 2019. *Date that primary care practitioners entered into a government contract providing additional payments for high-quality COPD care to aid with the diagnostic Quality and Outcomes Framework.[20] †OCS cohort: date of first COPD-related OCS prescription; non-OCS cohort, nearest primary care visit to the matched OCS patient index date. ‡Each patient was followed from index date until the first occurrence of an adverse outcome of interest or the end of the patient's available records (reasons for the last record included death, leaving the primary care practice, or last data extracted). §Index date and sex matching criteria were used per similar studies of systemic (oral or parenteral) corticosteroid use in patients with asthma;[12,21] as a COPD study, age and smoking status criteria were included to fully ensure similar covariate distribution.
Abbreviations: COPD, chronic obstructive pulmonary disease; EMR, electronic medical record; OCS, oral corticosteroid(s).

criteria were included. Due to the nature of UK primary care data and incentives related to the UK Quality and Outcomes Framework (QOF),[20] missingness is extremely rare for these variables. Index dates and patients in the non-OCS cohort were selected from a pool of available primary care consultation dates at random to be closest to the index date for the OCS cohort. Patients could only contribute once as a control in the non-OCS cohort.

Data sources were anonymized, longitudinal primary care practice electronic medical records from the UK Clinical Practice Research Datalink (CPRD) GOLD database linked to hospital-admitted patient care (Hospital Episode Statistics [HES]) and mortality statistics from the UK Office for National Statistics (ONS). Data included in this analysis spanned from 1987 to 2019. The CPRD includes routinely collected data from a large number of patients from UK primary care practices, providing a longitudinal, representative UK population health dataset,[19] with 18 million patients registered as of 2023.[22] In addition to containing information on diagnoses, symptoms, tests, and prescriptions, the CPRD also contains key lifestyle data such as smoking status.[19] A patient's COPD is principally managed through primary care and by one practice, and the majority of prescribing outside of hospital-treated events is in primary care. A subset of CPRD patients (those from England) has linkage to HES, which records complete and detailed information on inpatient hospital admissions.[23] CPRD records are also linked to the UK ONS Mortality registry, which records all mortality data registered by age, sex, and selected underlying cause of death.[24]

The study population consisted of patients who had a diagnostic code for COPD or had a record of COPD monitoring on or after 1 April 2003, and who were registered at primary care practices in the UK that provide data to the CPRD. If patients had a first diagnostic code before 1 April 2003 but the diagnosis of COPD was reaffirmed after this date, they were also included. This date was chosen because at that date, primary care practitioners entered into a contract with the UK government that provided additional payments for high-quality care for patients with COPD, including use of post-bronchodilator spirometry to aid with diagnoses (the Quality and Outcomes Framework).[20] Eligible patients were aged ≥40 years at latest COPD review or diagnosis, had HES linkage (applicable to patients included in the matched OCS and non-OCS cohorts), and electronic medical record data for ≥1 year before index date. Patients were excluded if the records contained a diagnosis of chronic lower respiratory disease other than COPD at any time, adrenal insufficiency before or within 1 year of index date, or cancer within 5 years before or 3 months after index date. Patients were also excluded if they had been prescribed tamoxifen for breast cancer at any time.

The sample size and power calculation are described in the Supplementary Material.

The study protocol was approved by the CPRD Independent Scientific Advisory Committee (reference number 20_159R), and the study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EUPAS35975). No patient-identifying information was accessible during the study.

Study Variables and Outcomes

For the OCS cohort, a first-recorded COPD-related OCS prescription was defined as an oral prednisolone prescription in patients with a contemporary diagnostic code for COPD, a broad acute respiratory code (including chest infection, cough, wheezing, or breathlessness), or a prescription for antibiotics on the same day as the oral prednisolone prescription. After a patient's first COPD-related OCS prescription, all-cause OCS use was captured. OCS prescriptions outside of primary care were not captured in the database.

Cumulative OCS dose (grams) was estimated as the total OCS dose prescribed to a patient from index date to the occurrence of the adverse outcome of interest. The number of acute courses of OCS was calculated based on a single course being 30 mg daily for 5 to 10 days (0.15–0.30 g).

Pre-specified corticosteroid-related adverse outcomes were identified using varying approaches based on the persistence of the diagnoses or conditions, as summarized in Table 1. Separate, subsequent, risk cohorts were used for each adverse outcome assessment, where diagnoses or conditions were only included for patients with no prior history of the specific adverse outcome before index date. For example, a patient with a diagnosis of diabetes prior to index date was excluded from the risk cohort for analyzing risk of onset of diabetes. Each patient was followed from index date until the first occurrence of an adverse outcome of interest or the end of the patient's available records (reasons for the last record included death, leaving the primary care practice, or last data extracted).

Table 1 Adverse Outcomes Evaluated After Index Date and Exclusion Criteria Used for Each Specific Outcome (Risk) Cohort

Outcome	Definition Applied After Index Date (Follow-Up Period)*	Exclusion Criteria Applied Any Time Prior to Index Date*
Osteoporosis with/ without fractures	Hip fracture and/or wrist fracture and/or spinal fracture and/or treatment for osteoporosis	–
Pneumonia	Diagnosis of pneumonia	Diagnosis of pneumonia
Cardiovascular/ cerebrovascular disease	Diagnosis of cardiovascular disease (myocardial infarction, heart failure, stroke)	Diagnosis of cardiovascular/cerebrovascular disease (myocardial infarction, heart failure, stroke, peripheral artery disease, cardiomyopathy, arrhythmia)
Cataract	Diagnosis of cataract and/or surgery to remove the cloudy lens	Diagnosis of cataract and/or surgery to remove the cloudy lens
Sleep disorders	Diagnosis of sleep disorders and/or diagnosis of sleep disorders with hypnotic medication prescription	Diagnosis of sleep disorders or diagnosis of sleep disorders and hypnotic medication prescription
Sleep apnea	Diagnosis of sleep apnea and/or referral to a specialist with usage of continuous positive airway pressure device	Diagnosis of sleep apnea and/or referral to specialist and Read code or ICD-10 code for continuous positive airway pressure
Chronic kidney disease	Diagnosis of chronic kidney disease (eGFR <60 mL/min/1.73 m² and/or dialysis and/ or renal transplant)	Diagnosis of renal impairment and/or treatment for chronic kidney disease and/or dialysis and/or renal transplant
Anxiety/depression	Diagnosis of anxiety/depression and/or diagnosis of anxiety/depression with antidepressant medication prescription	Diagnosis of anxiety/depression or diagnosis of anxiety/depression and prescription of antidepressants and/or prescription of antipsychotic drugs
Peptic ulcer	Diagnosis of peptic ulcer disease (with endoscopy code for gastric ulcer and duodenal ulcer)	Diagnosis of peptic ulcer disease
Type 2 diabetes mellitus	Diagnosis of type 2 diabetes mellitus and/or antidiabetic medication prescriptions and/or ≥2 HbA_{1c} readings >6.5%	• Diagnosis of type 2 diabetes mellitus and/or antidiabetic medication[†] and/or ≥2 HbA_{1c} readings >6.5% • Diagnosis of type 1 diabetes mellitus • Diagnosis of gestational diabetes
Glaucoma	Diagnosis of glaucoma and/or treatment for glaucoma	Diagnosis of glaucoma and/or treatment for glaucoma
Weight gain[‡]	Change in BMI value in the outcome period compared to the pre-index BMI value	–
Hypertension	Diagnosis of hypertension	Diagnosis of hypertension and/or antihypertensive medication use
Dyslipidemia	Total cholesterol reading >6.5 mmol/L or LDL reading >4 mmol/L or triglyceride reading ≥2.3 mmol/L	Diagnosis of dyslipidemia and/or total cholesterol reading >6.5 mmol/L and/or LDL reading >4 mmol/L and/or triglyceride reading ≥2.3 mmol/L
Psychosis	Diagnosis of psychosis	Diagnosis of psychosis

(*Continued*)

Table 1 (Continued).

Outcome	Definition Applied After Index Date (Follow-Up Period)*	Exclusion Criteria Applied Any Time Prior to Index Date*
Hospitalized infections§	Hospitalization with diagnosis of infection(s) from the following list: • Gastrointestinal system: gastroenteritis, Campylobacter enteritis, salmonella (non-typhoid), shigellosis, typhoid fever, *Clostridium difficile* infection, biliary tract infection, peritonitis • Cardiovascular system: endocarditis • Respiratory system: *Hemophilus influenzae* epiglottitis, bronchitis, tuberculosis, pertussis • Central nervous system: meningitis • Urinary tract: pyelonephritis, prostatitis, lower urinary tract infection • Genital system: bacterial vaginosis, urethritis, gonorrhea, pelvic inflammatory disease, syphilis • Blood: septicemia • Musculoskeletal: osteomyelitis, septic arthritis • Eye: conjunctivitis • Ear, nose, and oropharynx: pericoronitis, gingivitis, periapical or periodontal abscess, periodontitis, throat infections, sinusitis, otitis externa, otitis media • Skin: impetigo, erysipelas, cellulitis, human bites, mastitis, acne	Hospitalization with diagnosis of infection(s) from the following list: • Gastrointestinal system: gastroenteritis, Campylobacter enteritis, salmonella (non-typhoid), shigellosis, typhoid fever, *Clostridium difficile* infection, biliary tract infection, peritonitis • Cardiovascular system: endocarditis • Respiratory system: *Hemophilus influenzae* epiglottitis, bronchitis, tuberculosis, pertussis • Central nervous system: meningitis • Urinary tract: pyelonephritis, prostatitis, lower urinary tract infection • Genital system: bacterial vaginosis, urethritis, gonorrhea, pelvic inflammatory disease, syphilis • Blood: septicemia • Musculoskeletal: osteomyelitis, septic arthritis • Eye: conjunctivitis • Ear, nose, and oropharynx: pericoronitis, gingivitis, periapical or periodontal abscess, periodontitis, throat infections, sinusitis, otitis externa, otitis media • Skin: impetigo, erysipelas, cellulitis, human bites, mastitis, acne

Notes: *Diagnoses were defined as diagnostic Read codes or ICD-10 codes. †Except patients with metformin prescriptions and clinician-diagnosed polycystic ovary syndrome. ‡Since weight gain is a fluctuating condition, analyses of this outcome were adjusted to account for prior history of the condition, with the distribution of BMI values explored in the outcome period and compared with pre-index values. §The study protocol also included antibiotic-treated infections. However, in practice, it was difficult to ascertain whether the antibiotics prescribed in primary care were exclusively respiratory-related (or not). Thus, the final analysis included only hospitalized infections (which could be cross-referenced to ICD-10 codes). All-cause mortality data were per the UK Office for National Statistics mortality registry.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA$_{1c}$, hemoglobin A$_{1c}$; ICD-10, International Classification of Diseases 10th Revision; LDL, low-density lipoprotein.

Statistical Analysis

Descriptive statistics for pre-index characteristics are reported for the matched cohorts. The quality of matching was evaluated using the standardized mean difference,[25] with values >0.2 considered to indicate relevant covariate imbalance. There was no imputation for missing data.

The incidence rate for each adverse outcome in the OCS and non-OCS cohorts (patients with events per 100 patient-years [PY] of follow-up) was calculated and then compared using the incidence rate difference and the incidence rate ratio (IRR) with 95% confidence intervals (CIs).

Risk of adverse outcomes was compared for the OCS and non-OCS cohorts using univariable and multivariable Cox proportional hazard regressions. The multivariable analyses of all adverse outcomes were adjusted for the following confounders estimated at or prior to index date: sex, age, type of inhaler use in the 12 months before index date (an inhaled corticosteroid [ICS]; an ICS and a long-acting β_2-agonist [LABA]; an ICS, a LABA, and a long-acting muscarinic antagonist [LAMA]; and a short-acting β_2-agonist [SABA] with or without a short-acting muscarinic antagonist [SAMA]), and number of exacerbations in the 12 months before index date. Data are presented using unadjusted HRs or adjusted hazard ratios (aHRs) and 95% CIs.

Within the OCS cohort, further analyses were conducted to examine risk of adverse outcome occurrence with increasing cumulative OCS dose. Risk of type 2 diabetes mellitus worsening, osteoporosis worsening, and pneumonia recurrence (as defined in Supplementary Table 1) were also analyzed by increasing cumulative OCS dose. Univariable Cox proportional hazard regression was used to compare risk of adverse outcomes across pre-specified cumulative dose categories (<0.5 g [reference dose] vs 0.5–<1.0 g, 1.0–<2.5 g, 2.5–<5.0 g, 5.0–<10.0 g, and ≥10.0 g). This analysis treated cumulative dose as a time-varying measure to account for the fact that patients with longer follow-up time accumulate more OCS exposure; this analysis allows for different hazard ratios to be generated over time in patients with comparable follow-up periods. Data are presented using HRs and 95% CIs.

Statistical analyses were conducted using Stata SE version 16 (StataCorp, College Station, TX), Python version 3.9.0 (Python Software Foundation), or RStudio Version 1.4.1717 (R Core Team, 2021).

Results

Patients

Of 323,722 patients with a diagnosis of COPD in the UK CPRD GOLD database (Supplementary Figure 1), 106,775 (33.0%) had ≥1 COPD-related OCS prescription and were included in the overall cohort. The median (interquartile range [IQR]) number of acute OCS courses was eight (3–24); 36.7% of patients (39,159/106,775) had ≤4 courses, 17.9% (19,107/106,775) had 5–9 courses, and 45.4% (48,509/106,755) had ≥10 courses. Longer-term OCS use (≥30-day continuous exposure) was reported in 8.1% (8637/106,755) of patients receiving OCS ever.

Of 106,775 patients in the overall cohort, 58,955 had HES linkage and were eligible for inclusion in the OCS cohort. The individual matching process identified 53,299 pairs of patients forming the OCS cohort and the non-OCS cohort (Supplementary Figure 1 and Table 2). Median (IQR) duration of data availability before index date was 15.0 (6.5–28.7) years (OCS cohort) and 12.2 (4.5–25.4) years (non-OCS cohort) and median (IQR) follow-up duration after index date was 6.9 (3.0–12.1) years (OCS cohort) and 5.4 (1.8–10.6) years (non-OCS cohort). Table 2 reports demographic and clinical characteristics. In the OCS cohort, the mean (SD) cumulative OCS dose was 3.4 (7.1) g and the median (IQR) cumulative OCS dose was 1.1 (0.4–3.3) g.

Risk of Adverse Outcomes with OCS Use

In the unadjusted analysis of the matched cohorts, incidence rates (Supplementary Table 2) and IRRs (Supplementary Figure 2) were higher for all adverse outcomes except psychosis in the OCS cohort versus the non-OCS cohort.

Adjusted risk was numerically higher for all adverse outcomes and significantly higher for all except psychosis and hospitalized infections in the OCS cohort versus the non-OCS cohort (Figure 2). Of particular clinical importance, adjusted risk in the OCS cohort versus the non-OCS cohort was 190% greater for pneumonia (aHR 2.90 [95% CI 2.77–3.03]), 80% greater for osteoporosis with/without fractures (aHR 1.80 [95% CI 1.70–1.92]), 44% greater for type 2 diabetes mellitus (aHR 1.44 [95% CI 1.37–1.51]), and 26% greater for cardiovascular/cerebrovascular disease (aHR 1.26 [95% CI 1.21–1.30]).

**Table 2** Demographic and Clinical Characteristics of the Matched Treatment Cohorts

	OCS Cohort (N=53,299)	Non-OCS Cohort (N=53,299)	SMD* (OCS vs Non-OCS)
Time from first record availability to index date (years), median (IQR)	15.0 (6.5–28.7)	12.2 (4.5–25.4)	N/A
Follow-up after index date (years), median (IQR)	6.9 (3.0–12.1)	5.4 (1.8–10.6)	N/A
Sex, n (%)			
Female	21,408 (40.2)	21,408 (40.2)	<0.01
Male	31,891 (59.8)	31,891 (59.8)	<0.01
Age at index date (years), mean (SD)	64.6 (12.5)	64.6 (12.5)	<0.01
Smoking status closest to index date, n (%)			
Smoker ever	50,232 (94.2)	50,232 (94.2)	<0.01
Smoker never	3067 (5.8)	3067 (5.8)	<0.01
Body mass index (kg/m^2) closest to index date,† mean (SD)	26.9 (6.7) [N=51,436]	26.4 (6.5) [N=50,093]	0.08
Antibiotic-treated exacerbations in the 12 months before index date			
Mean (SD)	0.5 (0.9)	0.2 (0.5)	0.45
0, n (%)	35,507 (66.6)	46,095 (86.5)	0.48
1, n (%)	11,630 (21.8)	5480 (10.3)	0.32
2, n (%)	4029 (7.6)	1260 (2.4)	0.24
3, n (%)	1354 (2.5)	306 (0.6)	0.16
4, n (%)	508 (1.0)	100 (0.2)	0.1
≥5, n (%)	271 (0.5)	58 (0.1)	0.07
COPD severity (airflow limitation) closest to index date,† n (%)	[N=31,150]	[N=23,107]	
Mild (FEV$_1$ ≥80%)	4988 (9.4)	5855 (11.0)	0.05
Moderate (FEV$_1$ <80% to ≥50%)	15,453 (29.0)	12,382 (23.2)	0.13
Severe (FEV$_1$ <50% to ≥30%)	8525 (16.0)	4100 (7.7)	0.26
Very severe (FEV$_1$ <30%)	2184 (4.1)	770 (1.4)	0.16
mMRC Dyspnea Scale score closest to index date,† n (%)	[N=48,749]	[N=42,435]	
0	5158 (9.7)	8159 (15.3)	0.17
1	28,699 (53.8)	23,011 (43.2)	0.21
≥2	14,892 (27.9)	11,265 (21.1)	0.16
FEV$_1$% predicted (recorded),† mean (SD)	[N=31,014] 59.3 (20.8)	[N=28,161] 66.8 (20.4)	0.36
COPD inhaler use in the 12 months before index date,‡ n (%)			
SABA with or without SAMA	8762 (16.4)	3762 (7.1)	0.29
LABA	413 (0.8)	270 (0.5)	0.03
LAMA	4674 (8.8)	3176 (6.0)	0.11
ICS	8686 (16.3)	2761 (5.2)	0.36
LABA/LAMA	474 (0.9)	262 (0.5)	0.05
LABA/ICS	4729 (8.9)	2505 (4.7)	0.17
LAMA/ICS	2232 (4.2)	834 (1.6)	0.16
Triple therapy (ICS/LABA/LAMA)	6435 (12.1)	2953 (5.5)	0.23

Notes: *Quality of matching evaluated using the SMD, with an SMD >0.2 suggesting an imbalance between cohorts. †There were missing data for some variables. The number of patients with missing data were: body mass index, OCS cohort n=1863 and non-OCS cohort n=3206; COPD severity (airflow limitation), OCS cohort n=22,149 and non-OCS cohort n=30,192; mMRC Dyspnea Scale score, OCS cohort n=4550 and non-OCS cohort n=10,864; and FEV$_1$% predicted (recorded), OCS cohort n=22,285 and non-OCS cohort n=25,138. For categorical variables, the percentages in the table do not sum to 100% due to missing data. ‡COPD inhaler use categories are not mutually exclusive; the amount of missing data is not evaluable.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IQR, interquartile range; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; N/A, not applicable; OCS, oral corticosteroid(s); SABA, short-acting β$_2$-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SMD, standardized mean difference.

Cumulative OCS Dose and Adverse Outcome Risk in the OCS Cohort

Positive dose–response associations were observed for risk of most adverse outcomes by categorized, cumulative OCS dose from as low as 0.5–<1.0 g and with more significant associations with doses ≥1.0 g (Figure 3). Risk of osteoporosis with/without fractures was 45% higher for the 0.5–<1.0 g dose category versus the <0.5 g reference group (HR 1.45
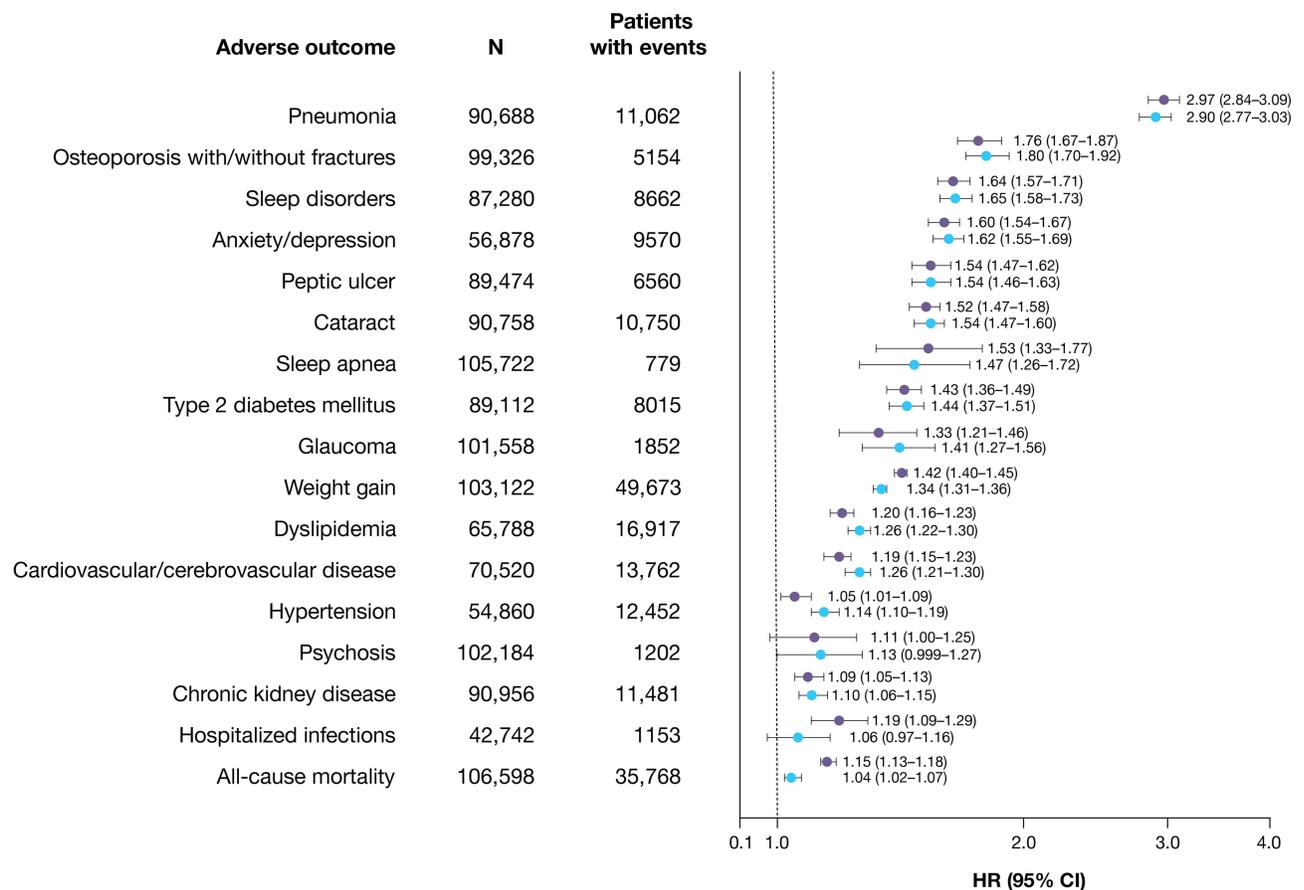
Figure 2 Relative risk of adverse outcomes in the OCS cohort versus the non-OCS cohort (univariable and multivariable Cox regression*). *The purple data points represent unadjusted univariable results; the blue data points represent the multivariable adjusted results. The multivariable analysis adjusted for sex, age, type of inhaler use in the 12 months before index date (ICS; ICS and LABA; ICS, LABA, and LAMA; and SABA with or without SAMA), and number of exacerbations in the 12 months before index date.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid(s); LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; N, number of patients in the risk cohort for each adverse outcome; OCS, oral corticosteroid(s); SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist.

[95% CI 1.30–1.62]) and increased to 89% higher for the 1.0–<2.5 g dose category versus the <0.5 g reference group (HR 1.89 [95% CI 1.70–2.11]). Similar dose–response associations were seen for sleep apnea, pneumonia, type 2 diabetes mellitus, weight gain, glaucoma, hospitalized infections, anxiety/depression, cataract, sleep disorders, cardiovascular/cerebrovascular disease, peptic ulcer, and chronic kidney disease.

Additionally, positive dose–response associations were observed for risk of pneumonia recurrence and type 2 diabetes mellitus worsening; a positive dose–response trend was observed for osteoporosis worsening, but the 95% CIs were wide and overlapping (Figure 4).

Risk of All-Cause Mortality

Unadjusted incidence rates for all-cause mortality were 3.32 and 2.88 per 100 PY in the matched OCS and non-OCS cohorts, respectively (Supplementary Table 2). Adjusted all-cause mortality risk was 4% higher in the OCS cohort versus the non-OCS cohort (aHR 1.04 [95% CI 1.02–1.07]; Figure 2). All-cause mortality risk increased as cumulative OCS dose increased (Figure 3). In the 0.5–<1.0 g dose category, all-cause mortality risk was 74% higher versus the <0.5 g reference group (HR 1.74 [95% CI 1.65–1.83]) and increased to 145% higher in the 1.0–<2.5 g dose category (HR 2.45 [95% CI 2.33–2.58]; Figure 3).

Discussion

This was the first long-term comprehensive analysis of adverse outcomes associated with OCS use in patients with COPD. Patients with COPD exposed to any OCS experienced a significantly higher risk for onset of multiple pre-
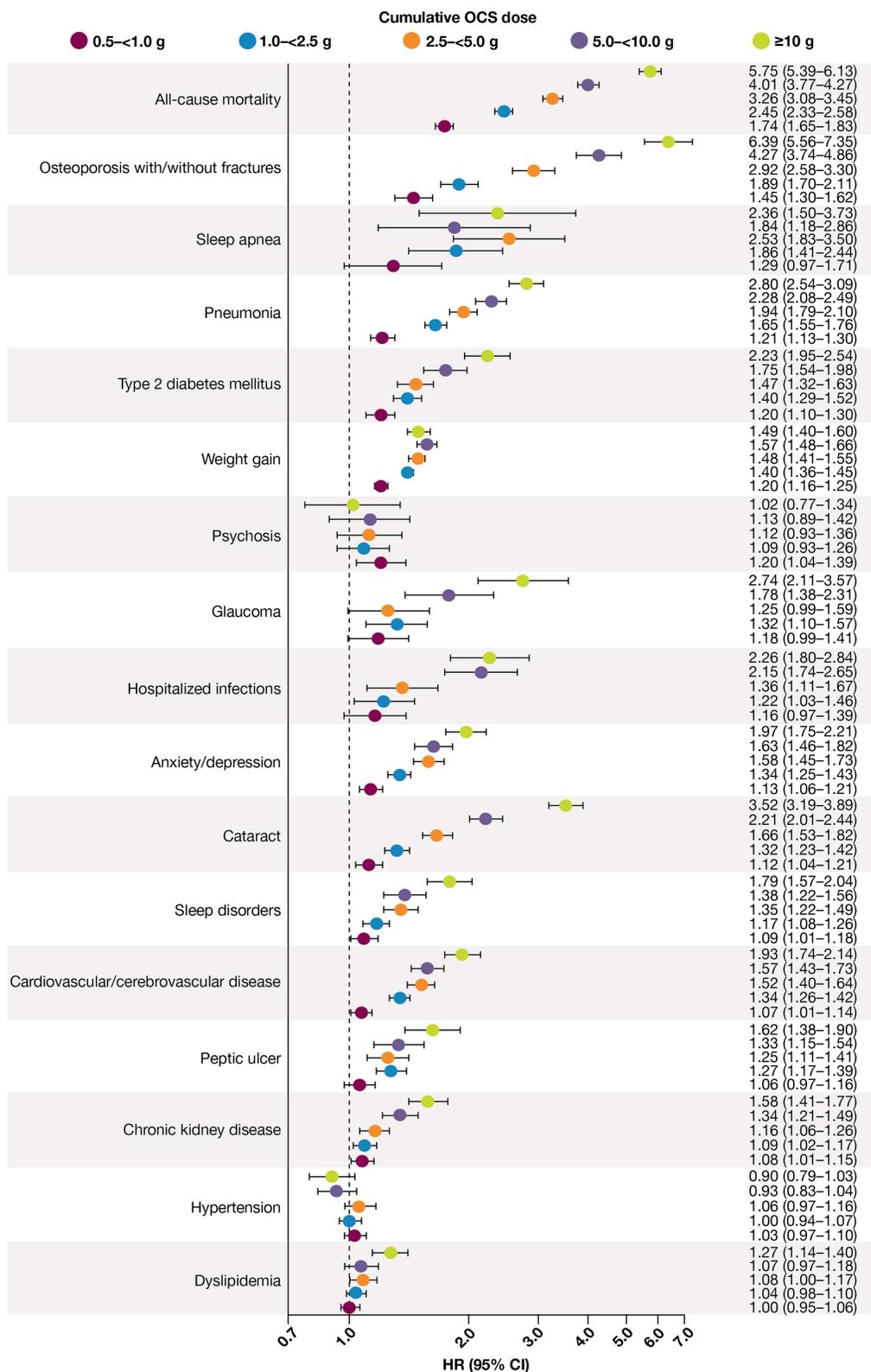
Figure 3 Relative risk of adverse outcomes in the OCS cohort by cumulative OCS dose* versus <0.5 g reference group (unadjusted univariable Cox regression; time-varying analysis). *Cumulative OCS dose was estimated as the total OCS dose prescribed to a patient from index date to the occurrence of the adverse outcome of interest.
Abbreviations: CI, confidence interval; HR, hazard ratio; OCS, oral corticosteroid(s).

Cumulative OCS dose
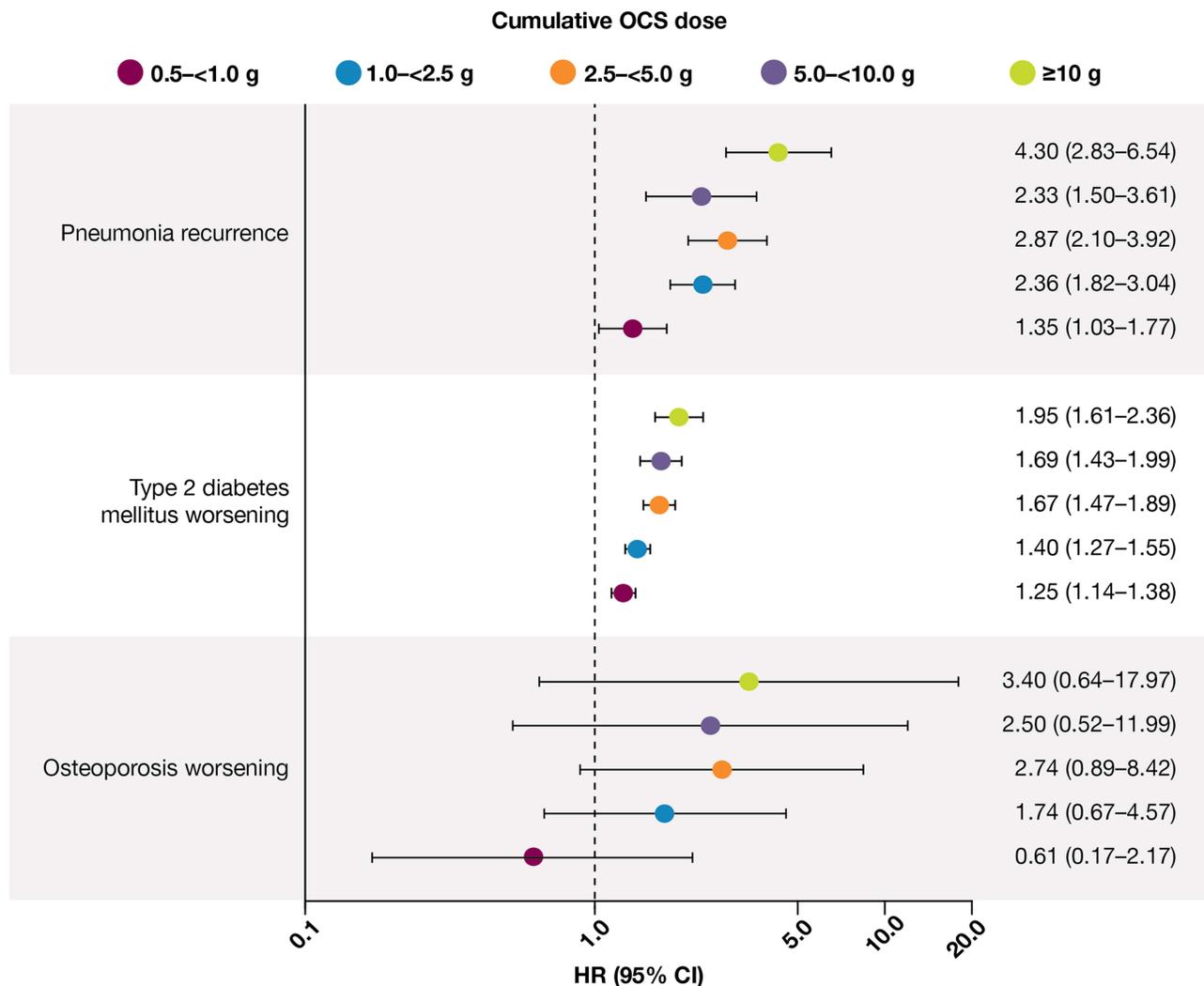
Figure 4 Relative risk of worsening or recurrence of adverse outcomes in the OCS cohort by cumulative OCS dose* versus <0.5 g reference group (unadjusted univariable Cox regression; time-varying analysis). *Cumulative OCS dose was estimated as the total OCS dose prescribed to a patient from index date to the occurrence of the adverse outcome of interest.
Abbreviations: CI, confidence interval; HR, hazard ratio; OCS, oral corticosteroid(s).

specified adverse outcomes versus patients without any OCS exposure. Risk of most adverse outcomes increased with increasing cumulative OCS dose. At cumulative OCS doses of ≥1.0 g, significant increases in risk were seen for 14 of the 17 assessed adverse outcomes and two of the three assessed worsening or recurrence of adverse outcomes. These included clinically important adverse outcomes such as pneumonia and recurrence of the condition, osteoporosis with/ without fractures, cardiovascular/cerebrovascular disease, type 2 diabetes mellitus and worsening of the condition, and all-cause mortality. Importantly, even relatively low OCS doses (0.5–<1.0 g) were associated with higher risk of many of the adverse outcomes versus the <0.5 g OCS reference group.

To place these findings in context, the recommended OCS dose for COPD exacerbations in the UK is 30 mg daily for 5 days (equivalent to 0.15 g),[26] although this dose may be taken for up to 14 days.[27] In this study, the median number of OCS courses in the overall cohort was eight (equivalent to 1.2 g), with more than 60% of patients having ≥5 OCS courses. As the cumulative dose analysis findings indicate as few as four OCS courses within current UK recommendations (equivalent to 0.6 g) increase adverse outcome risk, our findings suggest a large proportion of patients with COPD who use OCS for exacerbations are exposed to doses that could substantially increase their risk of adverse outcomes.

These findings on the long-term risks and dose-dependent relationships of OCS in COPD are important considering OCS are commonly and increasingly prescribed.[1,2] Of particular importance are OCS-containing rescue packs, which patients keep at home to self-administer if they begin to experience an exacerbation.[4] Physicians must identify whether rescue packs are suitable for a patient, including assessment of the patient's risk for OCS-related comorbidities, and patients should be educated on appropriate rescue pack usage and potential long-term risks of OCS.[4] Physicians should also consider OCS-sparing strategies, as the triggers and mechanisms of exacerbations are heterogeneous and there is evidence to suggest that not all exacerbations require, nor are responsive to, OCS.[28] Additional proposed actions to minimize long-term risks of OCS rescue use include clinical review of a patient after a course of OCS rescue medication and specialist referral after a threshold number of OCS rescue courses is reached. Exacerbation risk must be carefully managed in order to stabilize and control COPD, which will thereby reduce exposure to OCS. In addition to managing a patient's COPD with appropriate maintenance medication, other key factors to minimize risk of exacerbations include smoking cessation and vaccinations to prevent respiratory infections.[26,29,30]

COPD is associated with an increased risk of cardiovascular disease and cardiovascular-related mortality.[31,32] Use of appropriate and effective maintenance therapy for COPD should reduce the frequency of exacerbations,[6] thereby reducing the need to use OCS that could further increase overall cardiovascular disease risk.[33] The ETHOS and IMPACT studies both reported reduced exacerbation rates[34,35] and fewer deaths due to cardiovascular causes[35,36] in patients with COPD receiving fixed-dose triple ICS/LAMA/LABA therapy versus LAMA/LABA dual therapy. It is plausible that the reduced risk of cardiovascular death observed with ICS/LAMA/LABA therapy versus LAMA/LABA therapy in ETHOS and IMPACT could, at least in part, be related to a reduced need for OCS to treat exacerbations. Indeed, findings of the current study indicate that risk of cardiovascular/cerebrovascular disease in patients with COPD could be significantly reduced through OCS dose-sparing strategies. For example, in patients with a cumulative OCS dose of <0.5 g, risk of cardiovascular/cerebrovascular disease was 34% lower versus patients with a cumulative OCS dose of 1.0–<2.5 g and 93% lower versus patients with a cumulative OCS dose of ≥10 g.

The findings of this study are generally consistent with the increased risk for adverse outcomes reported in prior studies in patients with asthma.[12,13] In patients who initiated systemic corticosteroids, dose–response relationships for most adverse outcomes were observed to start at cumulative corticosteroid doses as low as 1.0–<2.5 g.[12] In patients with intermittent OCS use, dose–response relationships were observed to begin from cumulative doses of 0.5–<1.0 g for almost all adverse outcomes.[13]

Similarly, a Cochrane database review reported evidence for increased likelihood of hyperglycemia, weight gain, and insomnia with systemic (oral or parenteral) corticosteroid use for COPD exacerbations.[15] However, the studies included in the review only assessed short-term effects (10 days to 6 months) in patients who participated in randomized clinical trials.[7,16,37–39] Additionally, a retrospective US claims analysis found that patients treated with >1 g of prednisolone-equivalent OCS had a higher risk of adverse outcomes including cardiovascular disease, heart failure, hypertension, obesity, dyspepsia, infections, and depression/anxiety, compared with patients with no OCS use.[14] However, this analysis was limited to patients newly diagnosed with COPD and mean follow-up was 37 months.[14] In contrast, a strength of the current study is that it followed patients over a longer duration (median follow-up of 6.9 and 5.4 years in the OCS cohort and non-OCS cohort, respectively), enabling a more in-depth study of the association between OCS exposure and the risk of multiple adverse outcomes.

Further strengths include that the CPRD GOLD database is large and well established, with high-quality long-term electronic medical record data from a broad, representative patient population,[19] supporting a generalizable interpretation of the current findings. Additionally, data pertaining to OCS use and disease diagnoses are recorded prospectively and not influenced by recall bias. Finally, a major strength is that, based on availability of data before index date, it was possible to confirm that patients were OCS-naive when entering the observation period, as evidenced by median pre-index data availability of almost 16 years in the OCS cohort.

Study limitations include that the datasets represent information collected for clinical and routine use rather than for research. OCS exposure was estimated based on the number of prescriptions over time, and correct administration of all OCS doses as prescribed is not guaranteed, particularly in the case of OCS in "rescue packs" for a patient to use as-needed at home. Additionally, study patients might have been exposed to OCS earlier than 1987, from a period when prescription records were not available in electronic medical records. OCS prescriptions outside primary care were not captured in the database. However, COPD is

typically managed at primary care level in the UK. Whilst the analysis of adverse outcomes in the OCS cohort versus the non-OCS cohort was adjusted for key confounders (sex, age, type of inhaler use, and exacerbation history), data were not available to adjust for other possible confounders such as socioeconomic status, frailty, and primary care practice. Additionally, the disease and its severity are probably the strongest confounders of the relationship between OCS and adverse outcomes. Matching patients based on baseline COPD severity can be difficult since many patients use OCS before their official COPD diagnosis. Based on standardized mean differences, the OCS and non-OCS cohorts were generally well-matched in terms of disease severity (assessed by airflow limitation), with the exception of the proportion of patients with severe airflow limitation. However, as matched pairs were employed and the analysis of adverse outcomes in the OCS cohort versus the non-OCS cohort was adjusted for exacerbation history, the current findings would not be expected to change after accounting for disease severity. Whilst the standardized mean difference for baseline FEV_1 predicted was >0.2, indicating a degree of imbalance between cohorts, the imbalance was considered sufficiently minimal that, combined with evidence that FEV_1 alone has limited ability to predict exacerbations,[40] it was decided to not adjust the analyses for FEV_1. Finally, whilst there was some missing data for a number of baseline characteristics, there was minimal missing data for most key characteristics owing to the nature of UK medical record data.

Conclusions

In this large population of patients with COPD followed for a median post-index period of 6.9 years (OCS cohort) and 5.4 years (non-OCS cohort), exposure to even low OCS doses increased the risk of multiple corticosteroid-related adverse outcomes, including all-cause mortality, pneumonia, osteoporosis with/without fractures, cardiovascular/cerebrovascular disease, and type 2 diabetes mellitus. Moreover, risk of most adverse outcomes, including all-cause mortality, increased with increasing cumulative OCS dose. These findings highlight the importance of improving awareness of OCS-related adverse outcomes in patients with COPD, particularly as these patients are often older[41] and already at increased risk for comorbidities that overlap with the adverse outcomes in this study.[42–45] Furthermore, these findings underscore the need to evaluate individual patients and identify treatments to manage and reduce exacerbation risk, and, hence, reduce exposure to OCS.

Data Sharing Statement

Per the Clinical Practice Research Datalink Independent Scientific Advisory Committee guidance, the data will not be made available for sharing.

Ethical Approval

The study protocol was approved by the CPRD Independent Scientific Advisory Committee (reference number 20_159R), and the study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EUPAS35975). No patient-identifying information was accessible during the study.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported. DP and VC contributed to study conception or design, data acquisition, data analysis, and data interpretation. MB and AP contributed to data interpretation. GT, CA, and JZ contributed to data analysis and data interpretation. DS contributed to data acquisition, data analysis, and data interpretation. XX, HM, and BE contributed to study conception or design and data interpretation. All authors took

part in drafting, revising, or critically reviewing the article, gave final approval for the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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