Adv Ther (2025) 42:375–394
https://doi.org/10.1007/s12325-024-03024-3

ORIGINAL RESEARCH

Oral Corticosteroid-Related Healthcare Resource Utilization and Associated Costs in Patients with COPD

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Received: June 28, 2024 / Accepted: October 4, 2024 / Published online: November 19, 2024

ABSTRACT

Introduction: Oral corticosteroids (OCS) are used to manage chronic obstructive pulmonary disease (COPD) exacerbations but are associated with adverse outcomes that may increase healthcare resource utilization and costs. We compared attendance/costs associated with OCS-related adverse outcomes in patients who ever used OCS versus those who never used OCS and examined associations between cumulative OCS exposure and attendance/costs.

Methods: This direct matched observational cohort study used the UK Clinical Practice Research Datalink GOLD database (data range 1987–2019). Patients with a COPD diagnosis on/after April 1, 2003, and Hospital Episode Statistics linkage were included. Emergency room, specialist or primary care outpatient, and inpatient attendance were analyzed. Costs, estimated using Health and Social Care 2019 and National Health Service Reference Costs 2019–2020 reports, were adjusted for sex, age, exacerbation number, and inhaler type used in the 12 months before index date.

Results: The OCS cohort had higher annualized disease-specific (excluding respiratory) total attendance/costs versus the non-OCS cohort (adjusted incidence rate ratio [aIRR] with 95% confidence intervals [CIs]) ranging from 37%

Prior Publication: This manuscript is based on work presented at the 2022 annual meeting of the British Thoracic Society Winter Meeting (London, UK; November 23–25, 2022).

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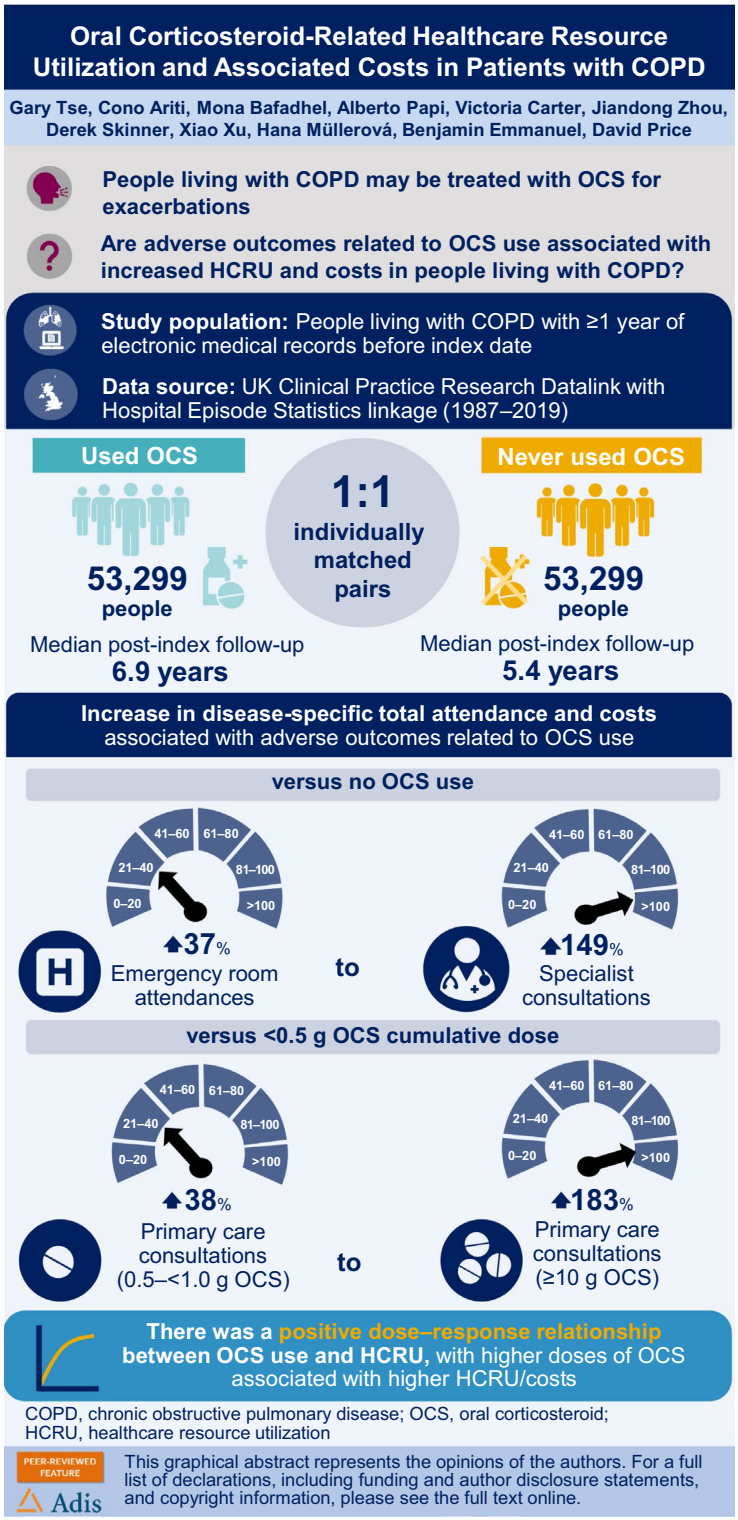
(1.37 [1.31, 1.43]) for emergency room attendances to 149% (2.49 [2.36, 2.63]) for specialist consultations. Disease-specific (excluding respiratory) attendance/costs increased in a positive dose–response relationship for most attendance categories versus the < 0.5 g reference dose. For the 0.5 to < 1.0 g cumulative dose category, the greatest increases in disease-specific (excluding respiratory) attendance/costs occurred for primary care consultations (aIRR [95% CI] 1.38 [1.32, 1.44]). For the ≥ 10 g cumulative dose category, the greatest increases were observed for primary care consultations (aIRR [95% CI] 2.83 [2.66, 3.00]), non-elective long stays (≥ 2 days; 2.54 [2.15, 2.99]), and non-elective short stays (≤ 1 day; 2.51 [2.12, 2.98]). Similar findings were observed for all-cause attendance/costs.

***Conclusion*:** Among patients with COPD, OCS-related adverse outcomes were associated with higher attendance and costs, with a positive dose–response relationship.

A graphical abstract is available with this article.

Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Many people living with chronic obstructive pulmonary disease (COPD) have "flare-ups", or exacerbations, at which time their symptoms suddenly worsen. To treat exacerbations, doctors may prescribe steroid tablets (oral corticosteroids or OCS for short). However, repeated OCS use may have negative health effects, leading to increased hospital visits or stays and higher healthcare systems costs. Using anonymized patient records from England, we compared attendance and associated costs to the healthcare system related to the negative health effects of OCS use for planned (elective) and non-planned (non-elective) hospital stays, emergency room visits, and primary care and specialist appointments in patients who have ever used OCS versus patients who have never used OCS. We also explored how the amount of OCS used by patients related to their attendance and costs. Patients were grouped into 53,299 pairs so every patient who ever used OCS was matched to one who never used OCS (e.g., those with the same age and sex), and their treatment and attendance was followed over approximately 6 years. We found that patients who received OCS had higher attendance and costs than those who did not, ranging from 37% higher for emergency room visits to 149% higher for specialist appointments. In patients who used OCS, costs were generally greater when more OCS was used, with the greatest increases observed for primary care appointments. These results show that the negative health effects of OCS lead to increased burden and healthcare costs in people living with COPD, with higher use incurring greater costs.

Keywords: Chronic obstructive pulmonary disease; Cohort study; Corticosteroids; Cost; Healthcare resource utilization; Observational; Primary care

Key Summary Points

Why carry out this study?

Oral corticosteroids (OCS) are used to manage exacerbations in patients with chronic obstructive pulmonary disease (COPD), but OCS use is related to adverse outcomes that may increase healthcare resource utilization and costs.

This analysis compared non-respiratory attendance and associated costs related to OCS use among patients with COPD who ever used versus never used OCS.

What was learned from the study?

In patients with COPD, OCS-related adverse outcomes were associated with higher disease-specific (excluding respiratory) attendance/costs compared with non-OCS users, even at relatively low OCS doses.

There was a positive dose–response relationship, with higher doses of OCS associated with higher non-respiratory attendance/costs.

These findings emphasize that preventing exacerbations of COPD, and thereby minimizing OCS use, is not only of considerable clinical benefit to patients but may also contribute to reducing the currently substantial economic burden of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide. In 2019, 212.3 million cases of COPD were reported globally, and COPD accounted for approximately 74.4 million disability-adjusted life-years and 3.3 million deaths [1]. Moreover, COPD accounts for a significant economic and resource burden in healthcare systems. In the UK in 2013–2014, COPD accounted for £1.9 billion in spending (excluding intangible costs), representing approximately 29% of the total costs for respiratory disease [2].

COPD is characterized by a range of respiratory symptoms (e.g., dyspnea, cough, and sputum production) due to persistent, and in many cases progressive, airflow obstruction [3]. Patients with COPD experience exacerbations of the disease (defined as a worsening of respiratory symptoms), which are considered to be mild when treated solely with short-acting bronchodilators (SABDs), moderate when treated with SABDs plus oral corticosteroids (OCS) and/or antibiotics, or severe when resulting in hospitalization or an emergency room (ER) visit [3]. Notably, in a systematic literature review of 73 primary publications, increased direct costs, rates of hospitalizations, and primary care visits were associated with increased severity and frequency of exacerbations of COPD [4].

OCS use is associated with adverse outcomes, such as decreased serum osteocalcin, hyperglycemia, weight gain, insomnia, anxiety, and depression [5, 6], which may drive increased healthcare resource utilization (HCRU) and associated costs [7]. When considering the impact of systemic corticosteroid (SCS) use on clinical burden, many studies typically only examine short-term effects (10 days to 6 months) [8–14]. A recent, individually matched historical observational cohort study evaluated adverse outcomes with median follow-up times of 6.9 years for OCS users and 5.4 years for non-OCS users in a large population of patients from England with COPD, using the UK Clinical Practice Research Datalink (CPRD) GOLD database [15], which is linked to hospitalizations (Hospital Episode Statistics; HES) [16]. In that study, patients in the OCS cohort had increased risk for multiple adverse outcomes, including osteoporosis (with/without fractures), type 2 diabetes mellitus, cardiovascular/cerebrovascular disease, and all-cause mortality versus the non-OCS cohort, with risk increasing with OCS dose [15]. Using the same dataset, we now report associations between attendance and costs with adverse outcomes related to OCS use, including cumulative OCS dose, in patients with COPD.

METHODS

Study Design

This study used anonymized deidentified data and, as such, patient consent and relevant ethics approvals were not required. However, scientific and ethics review were sought through appropriate channels. Per best practice research standards for observational research and in compliance with the National Health Service (NHS) Health Research Authority Research Ethics Committee (REC reference 21/EM/0265 [17]) for deidentified data held by the CPRD, which includes approval for the governance processes that must be followed for individual studies using CPRD data, the protocol of this study was approved by the CPRD Independent Scientific Advisory Committee (reference number 20_159R) and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS35975). No patient-identifying information was accessible during the study.

This observational, individually matched, historical cohort study compared attendance and associated costs related to OCS-related adverse outcomes in patients with COPD who were exposed to OCS (OCS cohort) versus those who were never known to be exposed to OCS (non-OCS cohort), using anonymized patient records from the CPRD GOLD database (Fig. 1) [15]. For the OCS cohort, index date was the date of the first recorded prescription for COPD-related OCS. To ensure characteristics between the cohorts were balanced, and to minimize bias due to confounding, OCS and non-OCS cohorts were matched 1:1 by index date, age at index date, sex, and smoking status closest to index date. In the non-OCS cohort, patients and index dates were randomly selected from the pool of available primary care consultation dates so as to be closest to index date for the OCS cohort. Patients could only contribute to the non-OCS cohort once. Patients were followed up from index date to the end of their individual records, defined as either the date of the last data extraction from the primary care practice, the date of

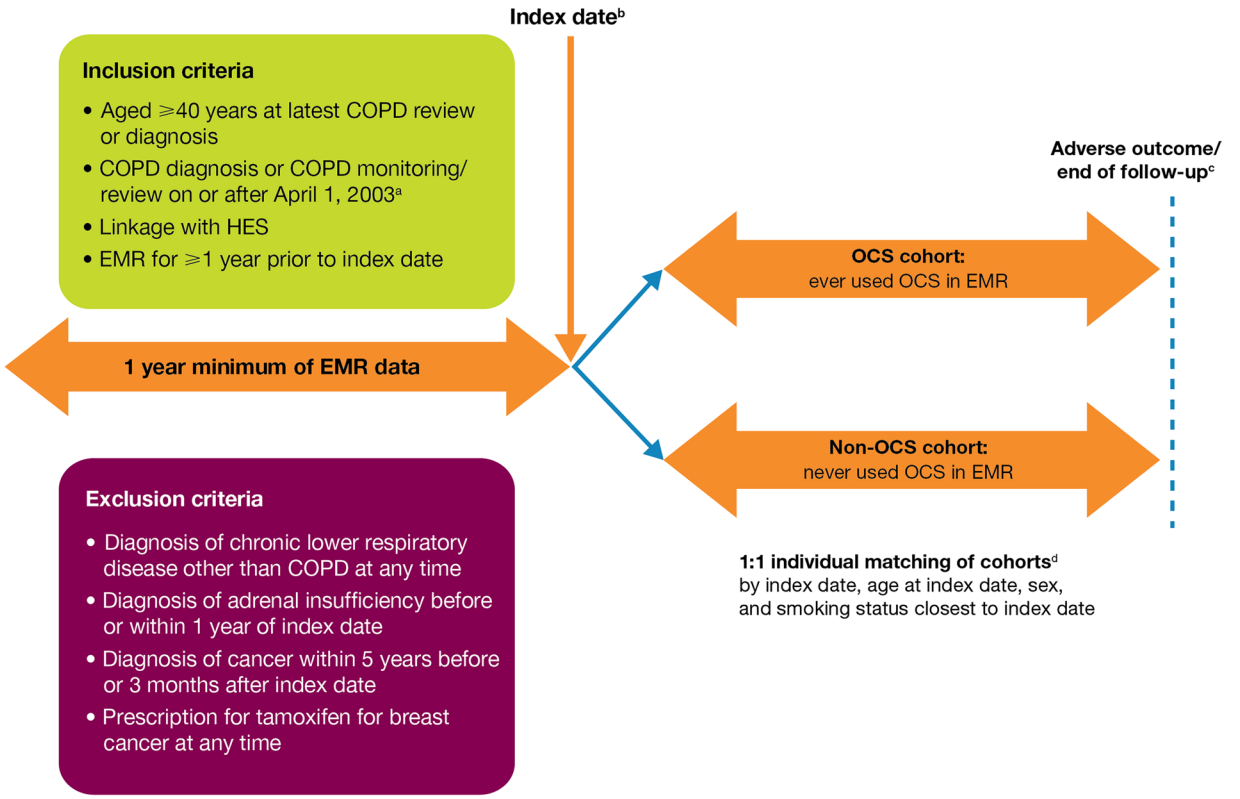


Fig. 1 Study design. Data included in this analysis spanned from 1987 to 2019. [a]Date that primary care practitioners entered into a government contract providing additional payments for high-quality COPD care to aid with the diagnostic QOF [21]. [b]OCS cohort: date of first COPD-related OCS prescription; non-OCS cohort: nearest primary care visit to the matched OCS patient index date. [c]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). [d]Index date and sex-matching criteria were used per similar studies of SCS (oral or parenteral) use in patients with asthma [7, 34]; as a COPD study, age and smoking-status criteria were included to fully ensure similar covariate distribution. *COPD* chronic obstructive pulmonary disease, *EMR* electronic medical record, *HES* Hospital Episode Statistics, *OCS* oral corticosteroids, *QOF* Quality and Outcomes Framework, *SCS* systemic corticosteroids. International Journal of COPD 2023:18 2565-2580—Originally published by (adapted) and used with permission from Dove Medical Press Ltd

leaving the primary care practice, or the date of death.

Study Database

In January 2019, the CPRD included medical records for over 35 million patients, including 10 million registered patients, from over 1150 UK-based primary care practices [18, 19]. The CPRD GOLD contains key data about patients' lifestyles, such as smoking status, in addition to information on diagnoses, tests, symptoms, and prescriptions [16]. In the UK, a patient's COPD is predominantly managed by a single primary care practice, with the majority of prescriptions outside of hospital-treated events being made in primary care. A subset of patients has linkage to the HES, a database containing details of inpatient hospital admissions in England [20]. As data included in the HES did not include patients in Northern Ireland, Scotland, or Wales, data from 1987 to 2019 were analyzed from anonymized, longitudinal electronic medical records from hospitals in England only.

Patient Population

The patient selection process has been previously reported in detail [15]. Patients were eligible for inclusion if they were aged ≥ 40 years at their most recent COPD review or diagnosis (as COPD is more common among this age cohort [3]), had a COPD diagnosis or monitoring/review on or after April 1, 2003, were registered at primary care practices in the UK that provide data to the CPRD, had HES linkage availability, and had electronic medical records for ≥ 1 year prior to index date. The date of April 1, 2003 was chosen because it represents the date high-quality COPD care, including post-bronchodilator spirometry use for diagnoses, was incentivized by the UK Quality and Outcomes Framework (QOF) [21]. Therefore, using this date as an inclusion criterion helped to focus the analyses on patients with more reliable COPD diagnoses. If patients had a diagnostic code before April 1, 2003, but the diagnosis of COPD was reaffirmed after this date, they were also included.

Patients were excluded if they had a diagnosis of chronic lower respiratory disease other than COPD at any time, had a diagnosis of adrenal insufficiency before or within 1 year of index date, had a diagnosis of cancer within 5 years before or 3 months after index date, or were prescribed tamoxifen for breast cancer at any time. As uncertainty during diagnosis of COPD may have led to some patients with COPD being assigned diagnostic codes for asthma prior to confirmation of a COPD-only diagnosis, patients with diagnostic codes for COPD and resolved codes for asthma were included in the study.

Study Variables and Outcomes

For the OCS cohort, an oral prednisolone prescription with a contemporary diagnostic code for COPD, an antibiotics prescription on the same day, or an acute respiratory code (including for chest infection, cough, wheezing, or breathlessness) was defined as the first recorded COPD-related OCS prescription. Following the first COPD-related prescription, all-cause OCS use was recorded and standardized using an oral prednisolone equivalent factor as follows: injectable prednisolone (1.22 equivalents), oral prednisone (1.0 equivalents), methylprednisolone (oral, 1.25 equivalents; injectable, 1.53 equivalents), betamethasone (oral, 6.67 equivalents; injectable, 8.34 equivalents), dexamethasone (6.67 equivalents), hydrocortisone (0.25 equivalents), and oral cortisone (0.20 equivalents). Cumulative OCS dose (grams) was estimated as the total dose prescribed to a patient during the follow-up period after first exposure (index date). OCS prescriptions made outside of primary care were not captured in the database.

Disease-specific (excluding respiratory) and all-cause costs, along with attendance, were measured as annualized attendance (healthcare facility visits, admissions, and hospitalizations) per 1000 patient-years. Disease-specific (excluding respiratory) attendances were examined to evaluate the effect of OCS use on attendance and costs related to non-respiratory adverse outcomes associated with OCS use, and were defined as inpatient cases and ER visits with International Classification of Disease, 10th revision codes for cardiovascular disease, cataract, chronic kidney disease, depression/anxiety, dyslipidemia, glaucoma, hospitalized antibiotic-related infections, hypertension, osteoporosis, peptic ulcer disease, psychosis, sleep apnea, sleep disorder, and type 2 diabetes mellitus; specialist consultations with clinic codes for non-respiratory OCS-related adverse outcomes except those used for COPD and respiratory causes; and primary care consultations of all read codes except those for respiratory events. Associated costs were estimated by multiplying each attendance outcome by the estimated average cost associated with the specific outcome. Unit costs were estimated using Health and Social Care 2019 and NHS Reference Costs 2019–2020 reports [22, 23].

Attendance and costs were stratified by attendance type, categorized as inpatient (elective day case, elective inpatient case, non-elective short stay, and non-elective long stay), ER attendance, specialist consultation, or primary care consultation. Elective admissions were defined as those

where admission decisions could be separated in time from the actual admission (i.e., where an admission date was known in advance, thus allowing for arrangements to be made before admission) and excluded patients transferred from another hospital provider. Length of stay was < 24 h for elective day cases, ≥ 1 day for elective inpatient cases, ≤ 1 day for non-elective short stays, and ≥ 2 days for non-elective long stays.

Statistical Analyses

The sample size and power calculation for this study have been described previously [15]. Descriptive statistics for pre-index characteristics for the matched cohorts have also been reported previously [15] and are briefly summarized. Standardized mean difference (SMD) was used to evaluate the results of matching [24], with values > 0.2 indicating relevant covariate imbalance. There was no imputation for missing data.

Differences in annualized attendance and costs were stratified by attendance type and compared between the OCS and non-OCS cohorts using adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (CIs). Within the OCS cohort, annualized attendance and associated costs were also compared across cumulative OCS dose categories (0.5 to < 1.0 g, 1.0 to < 2.5 g, 2.5 to < 5 g, 5 to < 10 g) versus the < 0.5 g reference dose. IRRs were calculated using generalized estimating equations with cluster-robust standard errors, log links, and gamma distributions, and were adjusted for sex, age, type of inhaler use in the 12 months before index use (inhaled corticosteroid [ICS], ICS + long-acting β_2-agonist [LABA], ICS + long-acting muscarinic antagonist [LAMA] + LABA, and short-acting β_2-agonist with/without short-acting muscarinic antagonist), and number of exacerbations in the 12 months before index. Patients were not matched for baseline COPD severity and baseline COPD severity was not used as a covariate because many patients experience exacerbations before their official COPD diagnosis [25] and may have been treated with OCS, and such use would have been a confounding variable. As costs were calculated as a direct function of attendance, IRRs for attendance are identical and are therefore not reported.

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) [26]. Similar methodologies to those described above have been presented elsewhere [15].

RESULTS

Baseline Patient Demographics and Clinical Characteristics

The full details of the patient population have been reported previously [15]. Briefly, of 323,722 patients with a diagnosis of COPD in the UK CPRD GOLD database, 106,775 (33.0%) had ≥ 1 COPD-related OCS prescription, met all inclusion/exclusion criteria, and were included in the overall cohort. Conversely, 86,384 patients had no evidence of OCS use and were eligible for the individual matching process to form the non-OCS cohort. In the overall cohort, the median (interquartile range [IQR]) number of acute OCS courses was 8 (3–24), with 36.7% of patients (39,159) having ≤ 4 courses, 17.9% (19,107) having 5–9 courses, and 45.4% (48,509) having ≥ 10 courses. In the OCS cohort, the mean (standard deviation [SD]) and median (IQR) cumulative OCS dose was 3.4 (7.1) g and 1.1 (0.4–3.3) g, respectively.

A total of 106,775 patients were included in the overall cohort, and of these 58,955 were eligible for inclusion in OCS cohort, as they had HES linkage. Ultimately, 53,299 individually matched pairs of patients comprised each of the OCS and non-OCS cohorts. In the OCS cohort, data were available for a median (IQR) of 15.0 (6.5–28.7) years before index date and 6.9 (3.0–12.1) years after index date. In the non-OCS cohort, data were available for a median (IQR) of 12.2 (4.5–25.4) years before index date and 5.4 (1.8–10.6) years after index date. Demographic and clinical characteristics of both cohorts have been reported previously

[15]. In both the OCS and non-OCS cohorts, 40.2% of patients were female, mean (SD) age was 64.6 (12.5) years, and most patients (94.2%) were current or former smokers. Smoking status, body mass index, COPD severity (with the exception of severe airflow limitation, as measured by a forced expiratory volume in 1 s [FEV_1] ≥ 30% to < 50%), modified

Table 1 All-cause costs per 1000 patient-years for OCS versus non-OCS cohorts

Attendance type	Cohort	Total attendance per 1000 patient-years (95% CI)	Total cost per 1000 patient-years, £ (95% CI)	Unadjusted rate ratio, OCS vs non-OCS (95% CI)
Inpatient attendances				
Elective day case	OCS	272.6 (270.6, 274.6)	204,992.7 (203,493.0, 206,500.6)	1.19 (1.18, 1.20)
	Non-OCS	229.0 (227.2, 230.8)	172,212.7 (170,849.1, 173,584.4)	
Elective inpatient case	OCS	59.9 (58.9, 59.9)	224,717.7 (221,216.8, 224,695.0)	1.24 (1.23, 1.24)
	Non-OCS	48.5 (47.6, 49.3)	181,994.7 (178,870.0, 185,160.3)	
Non-elective short stay	OCS	102.2 (100.9, 101.8)	64,468.9 (63,699.4, 64,226.3)	1.45 (1.43, 1.47)
	Non-OCS	70.2 (69.2, 71.3)	44,325.1 (43,692.4, 44,964.7)	
Non-elective long stay	OCS	279.9 (277.9, 282.0)	854,615.0 (848,445.1, 860,818.5)	1.55 (1.54, 1.56)
	Non-OCS	180.3 (178.7, 181.9)	550,332.7 (545,422.5, 555,276.1)	
ER	OCS	211.7 (210.0, 213.5)	38,532.0 (38,212.2, 38,853.8)	1.44 (1.41, 1.46)
	Non-OCS	147.4 (146.0, 148.9)	26,833.5 (26,568.8, 27,100.1)	
Specialist consultation	OCS	998.4 (994.5, 1002.2)	134,777.5 (134,261.9, 135,294.7)	2.68 (2.65, 2.70)
	Non-OCS	373.1 (370.7, 375.4)	50,362.9 (50,050.3, 50,676.9)	
Primary care consultation	OCS	8727.2 (8715.9, 8738.6)	340,362.3 (339,921.6, 340,803.5)	1.52 (1.51, 1.53)
	Non-OCS	5750.6 (5741.5, 5759.8)	224,275.0 (223,920.0, 224,630.3)	

CI confidence interval, *ER* emergency room, *OCS* oral corticosteroids

Medical Research Council Dyspnoea Scale score (with the exception of a score of 1), and use of most COPD inhaler types (LAMA, LABA, LAMA + LABA, LAMA + ICS, LABA + ICS) in the 12 months before index date were balanced between cohorts, as assessed by an SMD of <0.2.

Rates of cardiovascular comorbidities during the pre-index period were roughly comparable

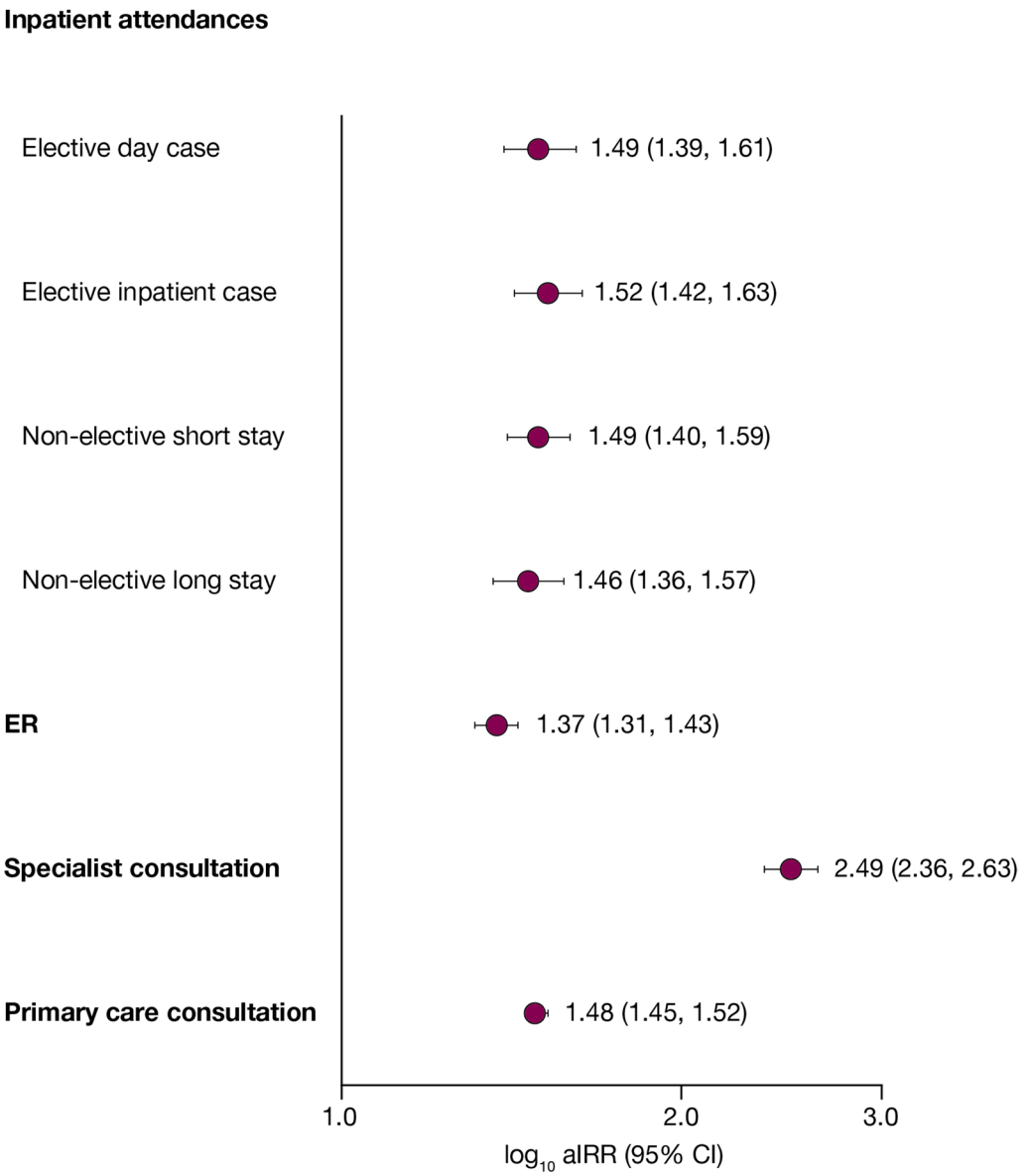


Fig. 2 aIRRs[a] (OCS versus non-OCS cohort) for annualized disease-specific (excluding respiratory) costs. [a]aIRRs were calculated using generalized estimating equations with cluster-robust standard errors, log links, and gamma distributions, and were adjusted for sex, age, number of exacerbations in the 12 months before index date, and the type of inhaler use in the 12 months before index date (ICS; ICS and LABA; ICS, LABA, and LAMA; short-acting β_2-agonist with or without short-acting muscarinic antagonist). *aIRR* adjusted incidence rate ratio, *CI* confidence interval, *ER* emergency room, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *OCS* oral corticosteroids

between cohorts, with 19.8% and 23.9% of patients having cardiovascular/cerebrovascular disease in the OCS and non-OCS cohorts, respectively. This was also the case for rates of cardiovascular risk factors during the pre-index period, with 16% and 11.9% having dyslipidemia, and 31.3% and 35.7% having hypertension in the OCS and non-OCS cohorts, respectively.

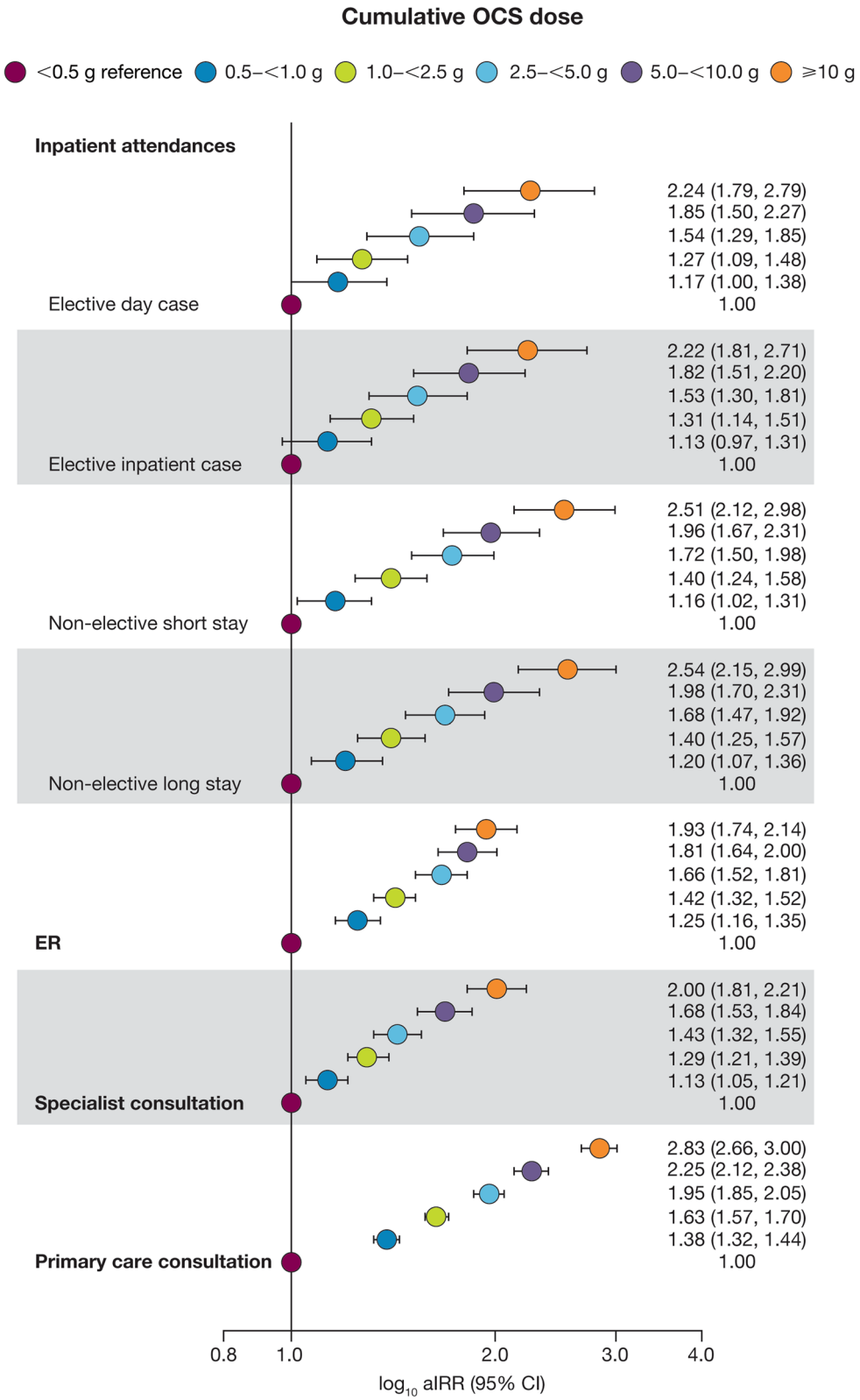
Attendance Rates and Costs

Unadjusted total attendance per 1000 patient-years and total costs were higher for the OCS cohort than for the non-OCS cohort across all attendance categories (Table 1). In the non-OCS and OCS cohorts, respectively, total costs per 1000 patient-years ranged from £26,833.5 and £38,532.0 for ER attendances to £550,332.7 and £854,615.0 for non-elective long stays. aIRRs indicated that disease-specific (excluding respiratory) costs associated with OCS-related adverse outcomes were significantly higher for the OCS cohort than for the non-OCS cohort (Fig. 2). Across attendance categories, disease-specific (excluding respiratory) cost increases ranged from 37% for ER attendances (aIRR [95% CI] 1.37 [1.31, 1.43]) to 149% for specialist consultations (aIRR [95% CI] 2.49 [2.36, 2.63]) in the OCS cohort versus the non-OCS cohort (Fig. 2). Within the OCS cohort, positive dose–response associations for disease-specific (excluding respiratory) costs from OCS-related adverse outcomes were observed across almost all attendance categories versus the <0.5 g reference dose (Fig. 3). At the 0.5 to <1.0 g dose, costs ranged from 13% to 38% higher versus the <0.5 g reference dose, with the greatest increase observed for primary care consultations (1.38 [1.32, 1.44]); at the ≥10 g dose, costs ranged from 93% to 183% higher, with the greatest cost increases observed for primary care consultations (2.83 [2.66, 3.00]), non-elective long stays (2.54 [2.15, 2.99]), and non-elective short stays (2.51 [2.12, 2.98]).

Similar results were observed for all-cause costs, which ranged from 21% to 59% higher in the OCS cohort versus the non-OCS cohort across most attendance categories, with a substantially higher increase of 150% for specialist consultations (aIRR [95% CI] 2.50 [2.39, 2.61]; Fig. 4). Positive dose–response associations were also observed for all-cause costs from OCS-related adverse outcomes, with aIRRs 15% to 40% higher in the 0.5 to <1.0 g dose category compared with the <0.5 g reference dose, except for elective day cases, which were only significantly higher in the ≥10 g dose category versus the non-OCS cohort (aIRR [95% CI] 1.43 [1.03, 1.99]; Fig. 5). In the ≥10 g dose category, all-cause costs ranged from 43% to 264% higher in the non-OCS cohort, with the greatest increases observed for primary care consultations (aIRR [95% CI] 3.02 [2.86, 3.19]) and non-elective long stays (aIRR [95% CI] 3.64 [3.35, 3.96]).

DISCUSSION

In this large historical cohort study, patients with COPD who received OCS had higher attendance and associated costs from OCS-related adverse outcomes versus patients who did not receive OCS. Costs increased as the level of OCS exposure increased, with doses as low as 0.5 to <1.0 g of OCS being associated with significant increases in disease-specific (excluding respiratory) costs versus the <0.5 g reference dose; similar findings were observed for all-cause costs. The greatest increase in costs for patients who have ever versus never used OCS was observed for specialist consultations, with 149% and 150% increases in disease-specific (excluding respiratory) and all-cause costs observed, respectively. Moreover, for patients with a cumulative OCS dose of 0.5 to <1.0 g, the largest observed increase in costs versus the <0.5 g reference dose was for primary care consultations, with a 38% increase in disease-specific (excluding respiratory) costs and a similar increase in all-cause costs. In patients with a cumulative OCS dose ≥10 g, the greatest cost increases versus the <0.5 g reference dose were observed in primary care consultations and non-elective long stays.


Cumulative OCS dose
<0.5 g reference
0.5–<1.0 g
1.0–<2.5 g
2.5–<5.0 g
5.0–<10.0 g
≥10 g
Inpatient attendances
2.24 (1.79, 2.79)
1.85 (1.50, 2.27)
1.54 (1.29, 1.85)
1.27 (1.09, 1.48)
1.17 (1.00, 1.38)
1.00
Elective day case
2.22 (1.81, 2.71)
1.82 (1.51, 2.20)
1.53 (1.30, 1.81)
1.31 (1.14, 1.51)
1.13 (0.97, 1.31)
1.00
Elective inpatient case
2.51 (2.12, 2.98)
1.96 (1.67, 2.31)
1.72 (1.50, 1.98)
1.40 (1.24, 1.58)
1.16 (1.02, 1.31)
1.00
Non-elective short stay
2.54 (2.15, 2.99)
1.98 (1.70, 2.31)
1.68 (1.47, 1.92)
1.40 (1.25, 1.57)
1.20 (1.07, 1.36)
1.00
Non-elective long stay
1.93 (1.74, 2.14)
1.81 (1.64, 2.00)
1.66 (1.52, 1.81)
1.42 (1.32, 1.52)
1.25 (1.16, 1.35)
1.00
ER
2.00 (1.81, 2.21)
1.68 (1.53, 1.84)
1.43 (1.32, 1.55)
1.29 (1.21, 1.39)
1.13 (1.05, 1.21)
1.00
Specialist consultation
2.83 (2.66, 3.00)
2.25 (2.12, 2.38)
1.95 (1.85, 2.05)
1.63 (1.57, 1.70)
1.38 (1.32, 1.44)
1.00
Primary care consultation
0.8
1.0
2.0
3.0
4.0
log10 aIRR (95% CI)

◂**Fig. 3** aIRRs[a] in the OCS cohort for annualized disease-specific (excluding respiratory) costs by cumulative OCS dose category versus < 0.5 g reference dose. [a]aIRRs were calculated using generalized estimating equations with cluster-robust standard errors, log links, and gamma distributions, and were adjusted for sex, age, number of exacerbations in the 12 months before index date, and the type of inhaler use in the 12 months before index date (ICS; ICS and LABA; ICS, LABA, and LAMA; short-acting β_2-agonist with or without short-acting muscarinic antagonist). *aIRR* adjusted incidence rate ratio, *CI* confidence interval, *ER* emergency room, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *OCS* oral corticosteroids

Given the key role that primary care performs in the UK by providing the first point of contact to the NHS and management of long-term conditions, the substantial dose-dependent increase observed for disease-specific (excluding respiratory) and all-cause primary care costs is indicative of the burden placed on healthcare systems by adverse outcomes related to high OCS use. Notably, even at relatively low doses (0.5 to < 1.0 g), increases in disease-specific (excluding respiratory) costs were observed in almost all attendance categories (except elective inpatient cases) versus the < 0.5 g reference dose, with similar results observed for all-cause costs (except for elective day cases). For context, the recommended dose of OCS to treat exacerbations of COPD in the UK is 30 mg daily for 5 days (totaling 0.15 g) [27]. In this study, the median number of OCS courses was 8 (1.2 g for a 5-day course), with 63.3% and 45.4% of patients having ≥ 5 courses (≥ 0.75 g for a 5-day course) and ≥ 10 courses (≥ 1.5 g for a 5-day course), respectively. This suggests that OCS-related adverse outcomes lead to increased healthcare costs for many patients who use OCS to treat exacerbations of COPD.

A similar matched, historical cohort study using data from the CPRD reported dose-dependent increases in HCRU and associated costs with SCS use (oral or parenteral) in patients with asthma [7]. Furthermore, increases in disease-specific (excluding asthma) HCRU and costs were observed at relatively low doses versus the < 0.5 g reference dose in most HCRU categories, including ER attendances, hospitalizations, specialist consultations, and primary care consultations [7]. Thus, these findings in patients with COPD are consistent with those in patients with asthma.

Short-acting bronchodilators and OCS (with or without antibiotics) are used in the treatment of moderate exacerbations [3]. However, OCS use is associated with adverse outcomes in patients with COPD, including anxiety/depression, cataracts, glaucoma, osteoporosis, peptic ulcer, pneumonia, and sleep disorder [15]. Here, we demonstrate that those adverse outcomes related to OCS use are associated with increased attendance and costs. These findings are consistent with the associations between increased OCS use and increased healthcare costs reported in prior studies in patients with other chronic diseases, including asthma and systemic lupus erythematosus [7, 28–30]. Indeed, a systematic literature review in 2009 estimated that costs for the seven most costly OCS-related adverse outcomes in the UK (non-Hodgkin's lymphoma, myocardial infarction, cataract, stroke, peptic ulcer, diabetes, and fracture) amounted to £165,000 per 1000 patient-years [31], with fracture being the most costly. Moreover, the current findings are consistent with an analysis of US patient claims with a diagnosis of COPD that reported significant increases in all-cause HCRU in patients with chronic OCS use, including for pharmacy, outpatient, inpatient, and ER costs [32]. The current analysis in patients with COPD expands upon existing evidence by providing greater insight into the impact of OCS use through stratification of hospitalizations by duration and elective/non-elective status.

To the best of our knowledge, this is the first in-depth economic evaluation that examines the impact of OCS-related adverse outcomes on attendance and costs by cumulative OCS dose in patients with COPD compared with individually matched patients with COPD without OCS exposure. Moreover, the study has a number of strengths. Firstly, although previous studies

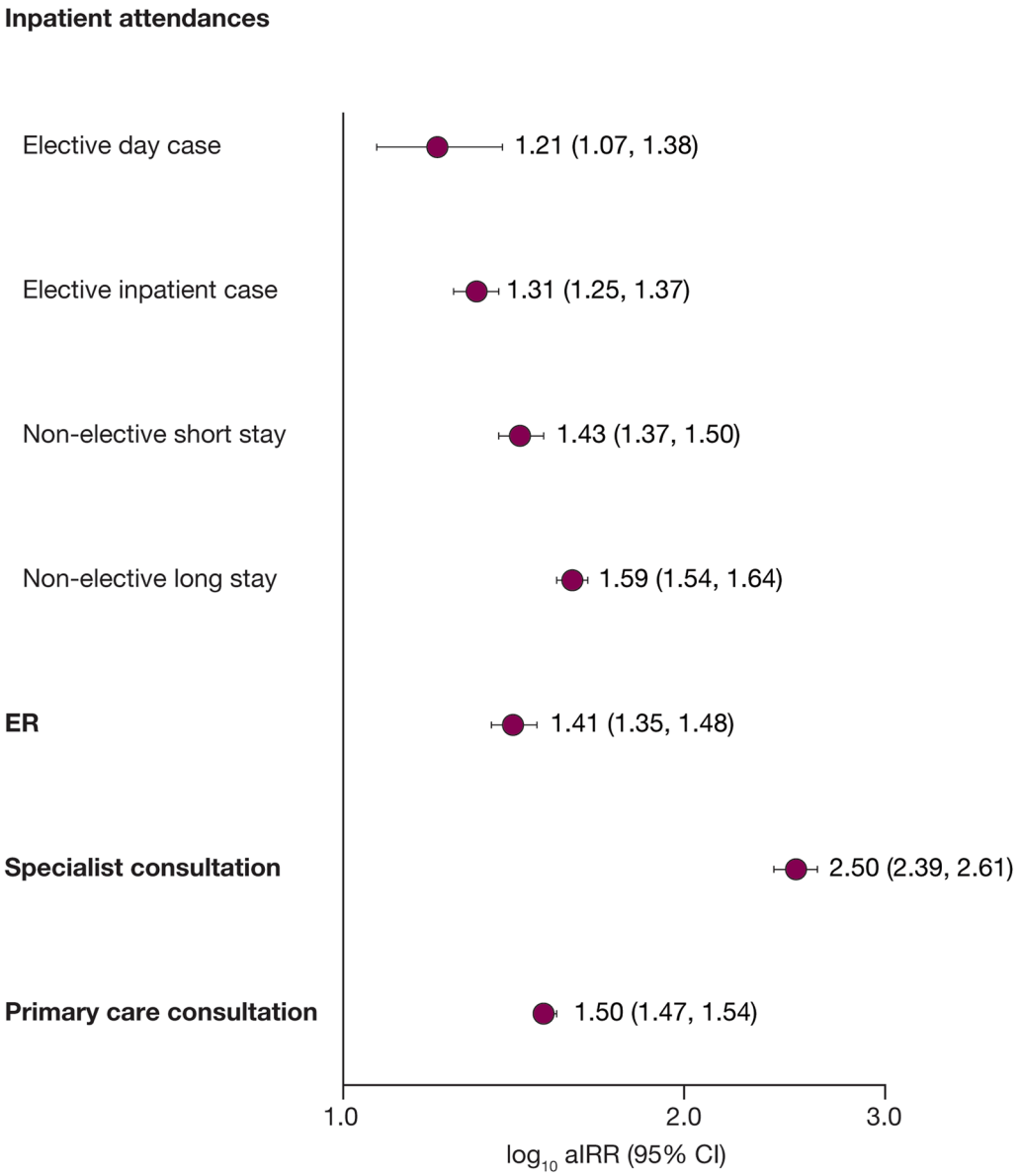
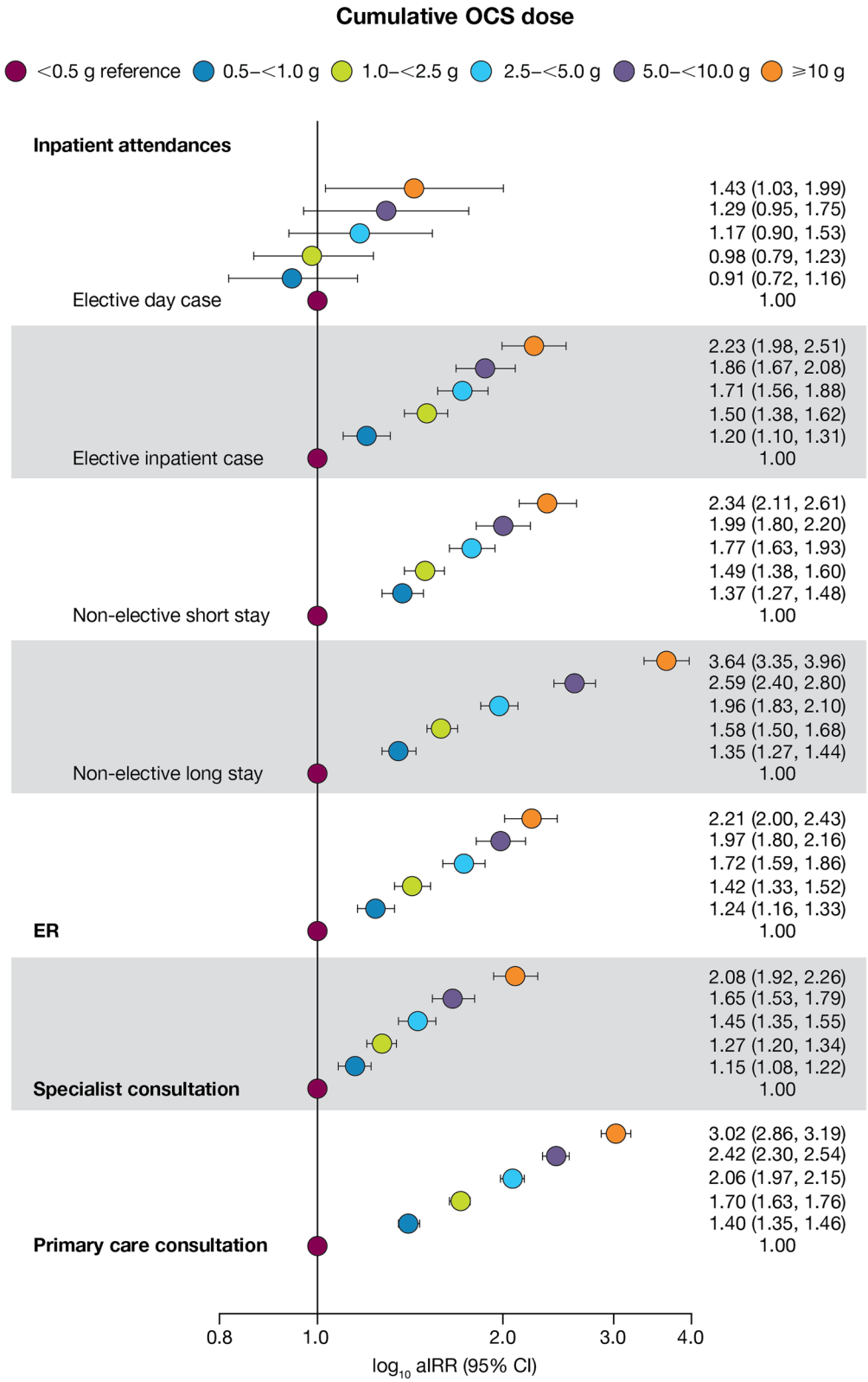


Fig. 4 aIRRs[a] (OCS versus non-OCS cohort) for annualized all-cause costs. [a]aIRRs were calculated using generalized estimating equations with cluster-robust standard errors, log links, and gamma distributions, and were adjusted for sex, age, number of exacerbations in the 12 months before index date, and the type of inhaler use in the 12 months before index date (ICS; ICS and LABA; ICS, LABA, and LAMA; short-acting β_2-agonist with or without short-acting muscarinic antagonist). *aIRR* adjusted incidence rate ratio, *CI* confidence interval, *ER* emergency room, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *OCS* oral corticosteroids

have reported associations between chronic SCS use with increased all-cause HCRU and costs in patients with COPD in the USA and China [32, 33], this is the first dedicated economic evaluation in patients with COPD in the UK to identify a dose–response relationship between OCS dose and attendance and costs. Secondly, the median follow-up of 6.9 years for the OCS

cohort in this study is much longer than the follow-up period of previous similar studies of SCS use (10 days to 6 months) [8–14], enabling a more in-depth study of the association between adverse outcomes related to OCS exposure and attendance and costs. Thirdly, this study used 53,299 pairs of individually matched patients from a broad, representative patient population from the large and well-established CPRD GOLD database [16]. As such, the current findings are generalizable to the overall patient population. Fourthly, in similarity with other studies evaluating SCS (oral or parenteral) use in patients with asthma [7, 34], patients were individually matched by index date and sex. Patients were also matched by age and smoking status because of the focus of this study on COPD. Missing data for these variables were extremely rare as a result of primary care data collection practices in the UK and UK QOF-related incentives [21]. Finally, data for disease diagnoses and OCS use were recorded prospectively and thus are not affected by recall bias. As a result of the median pre-index availability of 15 years, patients were reliably confirmed as never known to have been exposed to OCS when entering the observation period.

Limitations of this analysis include that the data were collected for routine and clinical use, not for research purposes. As such, although extensive quality control and validity checks are conducted at the practice level, the validity and completeness of individual patient records cannot be assessed. Notably, while the HES is generally a reliable source of hospitalization costings, outpatient appointments and ER consultations are less reliably coded compared with other attendance types. This can lead to difficulty in differentiating between respiratory-related and non-respiratory-related attendance. It should also be noted that data collection stopped in 2019. This was necessary as a result of the COVID-19 pandemic, which had changed the way people were accessing healthcare both during and after the pandemic. Also, the number of OCS prescriptions over time was used to estimate OCS exposure. However, it cannot be confirmed that all OCS doses were correctly administered, particularly since OCS prescribed in a "rescue pack" are kept at home by patients to use as needed [35], and OCS prescriptions made outside of primary care were not captured. The reported associations of OCS-related adverse outcomes with costs are confounded by COPD severity. While more severe disease results in increased OCS use and consequently increased HCRU and cost, it also directly contributes to cardiac adverse outcomes, HCRU, and cost. In addition, the frequent use of OCS by patients before they are formally diagnosed with COPD increases the difficulty of matching patients by baseline COPD severity; however, patients were well matched by disease severity (as assessed by FEV_1), with an SMD between the OCS and non-OCS cohorts of <0.2 for all severity categories except for severe COPD ($FEV_1 \geq 30\%$ to $<50\%$). It should also be noted that although the OCS and non-OCS cohorts were not matched for race/ethnicity or general physical condition as a result of incomplete reporting of these characteristics in the database, these variables are unlikely to substantially confound these analyses given the OCS and non-OCS cohorts were matched for key baseline and clinical characteristics and the analyses were adjusted for other clinically relevant covariates. Moreover, patients with specific diagnoses were excluded from these analyses, further negating the potential for confounding due to differences in physical condition between the OCS and non-OCS cohorts. Furthermore, it is not expected that the current findings would change after adjusting for disease severity owing to the use of matched pairs. In these analyses, patients were not matched for baseline COPD severity and baseline COPD severity was not used as a covariate because many patients experience exacerbations before their official COPD diagnosis [25] and may have been treated with OCS. Such use could have been a confounding variable. Finally, although this study reports positive associations between OCS-related adverse outcomes and attendance and costs, it does not attempt to evaluate the costs of each specific OCS-related adverse outcome. As such, additional studies may be warranted to further elucidate the economic burden of OCS use in patients with COPD in other health systems.


Cumulative OCS dose
<0.5 g reference
0.5–<1.0 g
1.0–<2.5 g
2.5–<5.0 g
5.0–<10.0 g
⩾10 g
Inpatient attendances
1.43 (1.03, 1.99)
1.29 (0.95, 1.75)
1.17 (0.90, 1.53)
0.98 (0.79, 1.23)
0.91 (0.72, 1.16)
1.00
Elective day case
2.23 (1.98, 2.51)
1.86 (1.67, 2.08)
1.71 (1.56, 1.88)
1.50 (1.38, 1.62)
1.20 (1.10, 1.31)
1.00
Elective inpatient case
2.34 (2.11, 2.61)
1.99 (1.80, 2.20)
1.77 (1.63, 1.93)
1.49 (1.38, 1.60)
1.37 (1.27, 1.48)
1.00
Non-elective short stay
3.64 (3.35, 3.96)
2.59 (2.40, 2.80)
1.96 (1.83, 2.10)
1.58 (1.50, 1.68)
1.35 (1.27, 1.44)
1.00
Non-elective long stay
2.21 (2.00, 2.43)
1.97 (1.80, 2.16)
1.72 (1.59, 1.86)
1.42 (1.33, 1.52)
1.24 (1.16, 1.33)
1.00
ER
2.08 (1.92, 2.26)
1.65 (1.53, 1.79)
1.45 (1.35, 1.55)
1.27 (1.20, 1.34)
1.15 (1.08, 1.22)
1.00
Specialist consultation
3.02 (2.86, 3.19)
2.42 (2.30, 2.54)
2.06 (1.97, 2.15)
1.70 (1.63, 1.76)
1.40 (1.35, 1.46)
1.00
Primary care consultation
0.8
1.0
2.0
3.0
4.0
log10 aIRR (95% CI)

◂**Fig. 5** aIRRs[a] in the OCS cohort for annualized all-cause costs by cumulative OCS dose category versus < 0.5 g reference dose. [a]aIRRs were calculated using generalized estimating equations with cluster-robust standard errors, log links, and gamma distributions, and were adjusted for sex, age, number of exacerbations in the 12 months before index date, and the type of inhaler use in the 12 months before index date (ICS; ICS and LABA; ICS, LABA, and LAMA; short-acting β_2-agonist with or without short-acting muscarinic antagonist). *aIRR* adjusted incidence rate ratio, *CI* confidence interval, *ER* emergency room, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *OCS* oral corticosteroids

CONCLUSION

In this large cohort study of patients with COPD, OCS-related adverse outcomes were associated with increased disease-specific (excluding respiratory) costs, as measured by annualized categorical attendance, compared with individually matched patients with no exposure to OCS. Moreover, costs increased in a positive dose–response relationship for most attendance categories, even at relatively low OCS doses. These findings emphasize that preventing exacerbations of COPD, and thereby minimizing OCS use, is not only of considerable clinical benefit to patients but also contributes to reducing the currently substantial economic burden of COPD [4]. Moreover, increasing clinician and patient awareness of the potential consequences of OCS use is required to reduce inappropriate use, such as with patient-administered "rescue packs". Identifying, implementing, and optimizing appropriate treatments for patients with COPD is key to improving both patient outcomes and reducing costs and burden on healthcare systems.

Medical Writing/ Editorial and Other Assistance. The authors thank Hilda de Jong, PhD (the PHARMO Institute, Utrecht, the Netherlands) for her assistance in developing the study protocol and Dr Jeffrey Shi Kai Chan, MBChB, MPH, FESC (Observational and Pragmatic Research Institute, Singapore, Singapore) for his assistance in developing the study report. The authors also thank Dr Sharen Lee, MBChB (Cardiovascular Analytics Group, Hong Kong, China) for her technical assistance in generating the figures for the dose-dependent relationship between OCS dose and attendance/costs. Medical writing support, under the guidance of the authors, was provided by Daniel Spindlow, MSc, CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP 2022) guidelines [36].

Author Contributions. All authors made a significant contribution to the work reported. David Price and Victoria Carter contributed to study conception or design, data acquisition, data analysis, and data interpretation. Mona Bafadhel and Alberto Papi contributed to data interpretation. Gary Tse, Cono Ariti, and Jiandong Zhou contributed to data analysis and data interpretation. Derek Skinner contributed to data acquisition, data analysis, and data interpretation. Xiao Xu, Hana Müllerová, and Benjamin Emmanuel contributed to study conception or design and data interpretation. All authors took part in drafting, revising, or critically reviewing the article, gave final approval of 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.

Funding. This study, the Rapid Service Fee, the Open Access fee, and medical writing support was funded by AstraZeneca.

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

Declarations

Conflict of Interest. Gary Tse, Cono Ariti, and Jiandong Zhou are former employees of the Observational and Pragmatic Research Institute (OPRI), which was funded by AstraZeneca to conduct this study. Gary Tse is a

current employee of Hong Kong Metropolitan University (Hong Kong SAR, China). Cono Ariti is a current employee of Oxon Epidemiology (Madrid, Spain). Jiandong Zhou is a current employee of the Department of Family Medicine and Primary Care at the University of Hong Kong (Hong Kong SAR, China). Victoria Carter and Derek Skinner are employees of OPRI, which was funded by AstraZeneca to conduct this study. Mona Bafadhel has received research grants to her institution from AstraZeneca; honoraria to her institution from AstraZeneca, Chiesi, and GlaxoSmithKline; and is an advisory board member for Albus Health and ProAxsis. Alberto Papi has received scientific grants to his institution from Agenzia Italiana del Farmaco, AstraZeneca, Chiesi, GlaxoSmithKline, and Sanofi; has received consulting fees from AstraZeneca, Avillion, Chiesi, ELPEN Pharmaceuticals, GlaxoSmithKline, Novartis, and Sanofi; has received payment or honoraria for lectures, presentations, speaker bureaus, or educational events from AstraZeneca, Avillion, Chiesi, Edmond Pharma, ELPEN Pharmaceuticals, GlaxoSmithKline, IQVIA, Menarini, Mundipharma, Novartis, Sanofi, and Zambon; and is an advisory board member for AstraZeneca, Avillion, Chiesi, ELPEN Pharmaceuticals, GlaxoSmithKline, IQVIA, MSD, Novartis, and Sanofi. Xiao Xu, Hana Müllerová, and Benjamin Emmanuel are employees of AstraZeneca and hold stock and/or stock options in the company. David Price is an employee of OPRI, which was funded by AstraZeneca to conduct this study; has advisory board memberships with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Thermofisher; has consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mundipharma, Mylan, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure Inc, Strategic North Limited, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance, and WebMD Global LLC; has received grants and unrestricted funding for investigator-initiated studies (conducted through OPRI) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance, and UK NHS; has received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mundipharma, Mylan, Novartis, Regeneron Pharmaceuticals, and Sanofi Genzyme; has received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, and Thermofisher; has stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of OPRI (Singapore); has a 5% shareholding in Timestamp, which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation Programme and Health Technology Assessment; and has been an expert witness for GlaxoSmithKline. David Price is an Editorial Board member of *Advances in Therapy*. David Price was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This study used anonymized deidentified data and, as such, patient consent and relevant ethics approvals were not required. However, scientific and ethics review were sought through appropriate channels. Per best practice research standards for observational research and in compliance with the NHS Health Research Authority Research Ethics Committee (REC reference 21/EM/0265 [17]) for deidentified data held by the CPRD, which includes approval for the governance processes that must be followed for individual studies using CPRD data, the protocol of this study was approved by the CPRD Independent Scientific Advisory Committee (reference number 20_159R) and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS35975). No patient-identifying information was accessible during the study.

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