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Health care resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma

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ABSTRACT

Background: Although systemic corticosteroid (SCS) treatment, irrespective of duration or dosage, is associated with adverse outcomes for patients with asthma, the longitudinal effects of this treatment on adverse outcomes, health care resource utilization (HCRU), and health care costs are unknown.

Methods: We identified patients initiating intermittent or long-term SCS who were diagnosed with active asthma from UK general practice with linked secondary care data. Control (non-SCS) patients were matched by sex and index date with those initiating SCS. Minimum baseline period was 1 year prior to index date; minimum follow-up duration was 2 years post index date. Cumulative incidence of SCS-associated adverse outcomes and associated HCRU and costs were compared between SCS and non-SCS patient groups and among average SCS daily exposure categories. Associations between exposure and annualized HCRU and costs were assessed, adjusted for confounders.

Results: Analyses included 9,413 matched pairs. Median (interquartile range) follow up was: SCS group: 7.1 (4.1–11.8) years; control group: 6.4 (3.8–10.0) years. Greater SCS dosages were correlated with greater cumulative incidence. For example, patients with type 2 diabetes receiving an average daily dosage of ≥7.5 mg had a 15-year cumulative incidence (37.5%) that was 1.5–5 times greater than those receiving lower dosages. HCRU and costs increased annually for SCS patients but not for non-SCS patients. Increases in all-cause adverse outcome (excluding asthma) associated HCRU and costs were dose-dependent.

Conclusions: Over the long term, adverse outcomes associated with SCS initiation were relatively frequent and costly, with a positive dosage–response relationship with SCS exposure.

Key words: adverse outcomes, asthma, health care costs, health care resource utilization, systemic corticosteroids

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1 INTRODUCTION

Frequent short- or long-term corticosteroid use is associated with substantial adverse effects including osteoporosis, peptic ulcers, cataracts, adrenal suppression, weight gain, hyperglycemia, hypertension, mood problems, and diabetes.[1-4] For example, Iribarren and colleagues[2] reported the risks of coronary heart disease and all-cause mortality increased 2.5- and 2.6-fold, respectively, for patients with asthma compared with matched controls. This was driven by asthma-associated oral corticosteroid (OCS) use. In addition, the increased risk of adverse effects is dependent on corticosteroid dosage.[2, 5-8] Dalal and colleagues[8] found that long-term corticosteroid users (≥6 months) with low- (<5 mg/day), medium- (≥5–10 mg/day), and high-dosage (>10 mg/day) exposure had, respectively, a 2.5-, 2.95-, and 3.32-fold greater adjusted relative risk of developing any steroid-related complication compared with steroid nonusers.

However, all previous studies had a relatively short baseline period that prevented true identification of systemic corticosteroid (SCS) initiators and, consequently, the study of longitudinal effects of SCS use from its initiation on adverse outcomes.[1-8] Furthermore, the longest follow-up period in previous studies was only up to 4 years, prohibiting the study of long-term impact of corticosteroid use on adverse outcomes. There are limited data available on the longitudinal impact of SCS exposure on health care systems, although the effect of SCS use on short-term health care resource utilization (HCRU) and associated costs has begun to be reported in the literature.[8, 9] In an analysis of adverse drug events (ADEs) in hospitals, Weiss and colleagues[9] found corticosteroid use to be among the top three causes of ADEs associated with hospital admission in the United States. Using a commercial database in the United States, Dalal and colleagues[8] found adjusted annual, incremental, steroid-related complication costs of $2,670, $4,639, and $9,162 (2014 US $) over a 1.5-year

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median follow-up period for long-term low-, medium-, and high-dosage steroid users, respectively, compared with nonusers.

In the current study, we compared the long-term incremental risks of adverse outcomes and their associated HCRU and costs for patients with asthma who did and did not initiate SCS (parenteral corticosteroid or OCS) and who had complete primary and secondary HCRU data. Furthermore, we explored how health care costs changed over time.

2 METHODS

Additional details regarding the methods for cost estimations, measures and definitions, and statistical analyses are contained in the online supporting information for this manuscript (Appendix A−D, Tables S1−S6).

2.1 Data source

We conducted a matched, historical cohort study using data from using the Clinical Practice Research Datalink (CPRD) database. The CPRD contains longitudinal data from 5 million active medical records from more than 600 subscribing practices throughout the UK. The CPRD data set contains patient records from June 1994 through January 2015, with 39% of patient data linked to Hospital Episode Statistics (HES), a data warehouse containing complete and reliable information on inpatient hospital admissions, with linkage available from April 1997 through February 2016.[10] CPRD also includes information from general practice (GP) visits. Public health researchers have used CPRD, formerly known as the General Practice Research Database, since 1987.[11] This study involved anonymized patient data that did not require ethics board approval.

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2.2 Study design and patients

The study used a minimum 1-year baseline period and a minimum 2-year outcome (follow-up) period. The index date was the date of the first recorded prescription for a parenteral corticosteroid or OCS in the SCS arm, whereas for the non-SCS arm, it was the nearest GP visit to the matched-case index date. We matched non-SCS patients to SCS patients 1:1 by sex, availability of HES linkage, and index date. SCS dosages were standardized into prednisolone equivalents (Table S3). To account for all HCRU outcomes, we included only the subset of unbroken matched pairs of active asthma patients with HES linkage in the final study population.[10] We followed patients in both arms from the index date to the end of follow up (i.e., death, leaving the primary care practice, end of available records, or last date of extraction).

Patients in the SCS arm were ≥18 years old at first SCS prescription and had ≥1 SCS prescription within 18 months after first SCS prescription. Patients could not have a diagnosis of adrenal insufficiency/Addison's disease at any time, diagnosis of cancer 5 years before or 3 months after index date, or tamoxifen prescriptions for breast cancer at any time.

To evaluate the impact of SCS on the onset of an individual adverse outcome of interest, we removed patients having the individual adverse outcome of interest before the index date. Then we removed patients who were left without a paired counterpart. As such, the analysis samples for the different SCS-related risk cohorts were dissimilar. Adverse outcomes evaluated are listed in Table S4. Given that asthma-related costs are highly driven by disease severity and not necessarily by SCS-associated adverse outcomes, we reported HCRU and costs associated with all-cause (Table S5) adverse outcomes excluding asthma and those associated with asthma (defined as reported with an asthma or lower respiratory disease code)

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separately. Inclusion of asthma-related costs in all-cause adverse outcomes–associated costs would make the data very difficult to interpret.

2.3 Statistical analyses

HCRU and associated costs were assessed annually and annual averages for the entire follow-up period were calculated. We estimated HCRU-associated all-cause and cause-specific costs (2016 £) by multiplying HCRU outcomes by the estimated unit costs associated with each HCRU outcome from the Personal Social Services Research Unit,[12] National Health Service reference costs,[13] and the Dictionary of Medicines and Devices browser.[14] Prescription cost was obtained by multiplying cost by amount prescribed. Annualized HCRU and health care costs were reported.

We used generalized estimating equations with cluster robust standard errors, log link, and gamma distribution to estimate the effect of SCS initiation on annualized HCRU or costs found by bootstrapping using 1,000 random samples taken, with replacement, and adjusted for potential confounders. Besides reporting on adjusted mean, we also compared SCS and non-SCS patients using incidence rate ratio (IRR) for resources and cost ratios for cost with a 95% CI. Age and sex were used as forced covariates, and the remaining covariates were selected based on their incremental bias potential.

3 RESULTS

Of 24,117 matched pairs of asthma patients, 16,623 pairs came from the CPRD database. Of these, the patients with an HES linkage were selected, and the ones who lost their matched pair were removed, resulting in 9,413 total matched pairs that were included in all analyses of this study. A comparison of baseline characteristics showed that the subset of patients with

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available HES linkage was not meaningfully different from the subset of patients without HES linkage (data not shown).

Of patients included in this study, fewer than 10% had <2 years and half had ≥8 years of medical record history available before the index date. Patients had an average of 8.6 years of follow up (median [interquartile range {IQR}]: 7.1 [4.1–11.8]) in the SCS arm and an average of 7.7 years (median [IQR]: 6.4 [3.8–10.0]) in the non-SCS arm. In the SCS arm, 11.9% of patients had ≥4 refills of SCS per year; median daily dosage of the SCS prescribed was 10 mg, and median total dosage prescribed in one prescription was 200 mg.

Female patients comprised two-thirds (65.3%) of patients (Table 1). SCS-initiating patients were older than patients in the non-SCS arm (49 vs. 43 years) and had worse lung function (percent predicted normal 72.8% vs. 82.9%) (Table 1). In addition, a greater percentage of SCS-initiating patients had severe asthma (defined as Global Initiative for Asthma Step 4/5 OR uncontrolled asthma) based on HES linkage (40.3% vs. 21.7%) and prior year hospitalization for asthma (1.1% vs. 0.4%) than control patients. The baseline comorbidities were similar between the arms (standardized mean differences <10%).

3.1 Cumulative incidence of adverse outcomes

To assess the occurrence of adverse outcomes associated with SCS exposure, we examined cumulative incidence among patients who had no history of that specific outcome at baseline. Regardless of SCS dosage, 15-year cumulative incidence was higher in the SCS arm than the non-SCS arm (e.g., renal impairment: 27.9% vs. 12.5%; type 2 diabetes: 9.5% vs. 5.6%, respectively; Figure S1). Other adverse outcomes followed a similar trend. The 15-year cumulative incidences in the SCS vs. non-SCS arm, respectively, were as follows:

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pneumonia, 11.3% vs. 3.5%; cataracts, 11.0% vs. 4.4%; cerebrovascular accident, 10.0% vs. 5.1%; cardio-cerebrovascular disease, 9.9% vs. 3.6%; osteoporosis, 8.0% vs. 2.0%; myocardial infarction, 7.3% vs. 2.8%; heart failure, 3.6% vs. 1.1% and glaucoma, 3.4% vs. 1.7%.

Greater SCS dosages were also correlated with greater cumulative incidence. For example, for type 2 diabetes, SCS patients with an average daily dosage of ≥7.5 mg had a 15-year cumulative incidence of 37.5%, which was 1.5 to 5 times greater than that of patients receiving <0.5 mg/day (cumulative incidence, 7.0%), 0.5–<2.5 mg/day (11.3%), 2.5–<5.0 mg/day (16.3%), and 5.0–<7.5 mg/day (25.0%) (Figure S2). For patients with an average exposure of 2.5–5 mg/day, which corresponds to three steroid bursts per year, in a 5-, 10-, and 15-year period, 5%, 10%, and 16% of these patients would develop type 2 diabetes, respectively (Table S7). Similar trends were observed for all other adverse outcomes (data not shown).

3.2 Health care resource utilization

SCS-initiated patients with asthma had substantially greater frequency of all-cause adverse outcomes–associated (excluding asthma-related) HCRU, and asthma-related HCRU than patients without SCS initiation (Table 2). The adjusted IRR (95% CI) shown in Figure 1A for SCS initiation vs non-SCS were 1.22 (1.19–1.25) for GP visits, 1.12 (1.06–1.18) for specialist visits, 1.14 (1.06–1.23) for hospitalization, 1.26 (1.16–1.36) for accident and emergency (A&E) attendances, and 1.35 (1.27–1.43) for primary care prescriptions. All HCRU types showed a positive dosage–response relationship with the mean number of adverse outcomes associated-resources used, except the A&E attendances (Figure 1B, reference lowest dosage [<0.5 mg/day]). At an average dosage of 2.5 mg/day, patients initiating SCS started yielding a

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doubling of HCRU outcomes compared with patients not initiating SCS. Exposure to SCS at an average dosage of ≥7.5 mg/day resulted in 2.3–3.0 times greater HCRU from adverse outcomes compared with no exposure (Table 2).

3.3 Health care resource utilization–associated costs

All-cause (excluding asthma) costs associated with adverse outcomes remained constant over the follow-up period in the non-SCS arm, but these costs increased over time in the SCS arm (Figure S3). Incremental all-cause adverse outcomes–associated yearly costs for SCS patients were 7% greater in the first year and 50%, 70%, and 110% greater by Years 5, 10, and 15, respectively. Similar patterns were observed for asthma-related costs, although they were not as striking (Figure S3). When SCS use was categorized by mean average daily exposure (e.g., >0–<0.5 mg), similar all-cause adverse outcomes–associated and asthma-related costs patterns to the overall SCS patients were observed (data not shown).

Compared with no SCS exposure, SCS use was associated with greater all-cause adverse outcomes–associated health care costs (adjusted cost ratio [95% CI]: 1.16 [1.10–1.23], $p<0.001$) and asthma-related health care costs (2.21 [2.13–2.29], $p<0.001$) (Figure 2A). Adverse outcome–related cost differences were largest for pneumonia, and overall costs were about 2.3-times greater for the SCS arm than the non-SCS arm. Respectively, associated average annual costs for adverse outcomes and asthma were £1,483 and £403 for SCS patients compared with £1,165 and £166 for non-SCS patients, representing 42% greater overall costs. Among the adverse outcome–associated costs, key cost drivers were cardio-cerebrovascular diseases, dialysis, and pneumonia.

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There was a positive dosage–response association between the SCS exposure and adverse outcome–associated annual costs. The cost ratio (95% CI) was 1.25 (1.18–1.31) for 0.5–<2.5 mg/day, 1.78 (1.58–2.00) for 2.5–<5.0 mg/day, 2.27 (1.53–3.36) for 5.0–<7.5 mg/day, 2.41 (2.02–2.88) for 7.5–<15.0 mg/day, and 3.86 (2.53–5.89) for ≥15.0 mg/day for the SCS arm compared with the non-SCS arm. Hospitalization and prescriptions were the largest contributors to HCRU differences; cost ratio (95% CI) was 4.92 (2.70–8.97) for hospitalization and 8.12 (3.93–16.75) for prescriptions in SCS arm exposed to an average daily dosage of ≥15 mg (all *p*-values <0.001) (Figure 2B). We observed doubling of non-SCS arm annual risk outcome–associated costs in the SCS arm starting at 2.5 mg/day (Table 3, Figure 3). Patients who were exposed to ≥7.5 mg/day SCS had a £3,226 annual cost of adverse outcomes and an £1,188 annual cost of asthma, which combined was 3.3-times greater than for non-SCS patients.

We found that when compared with patients who were exposed predominantly to acute SCS dosages (those in the lowest quartile of the refill rate), patients most likely on maintenance dosages of SCS (those in the highest quartile of the refill rate) incurred greater costs. Thus, maintenance SCS use seems to be associated with greater costs compared with acute SCS use (data not shown).

4 DISCUSSION

In this report, we present the longitudinal effects of SCS treatment, irrespective of duration or dosage, on adverse outcomes, HCRU, and health care costs. This study was distinct from previous studies in terms of the availability of data prior to index date (50% with ≥8 years of data), allowing for a more accurate assessment of baseline SCS use and therefore identification of SCS initiators, and the long duration of its follow-up period. We found a

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dose-dependent increase in adverse outcomes, HCRU, and health care costs associated with SCS usage. To the best of our knowledge, this is the first study to report the long-term ramifications of SCS usage, both acute and long-term, on these parameters and to present these results as a function of SCS dosage.

Patients with severe, uncontrolled asthma are more likely to use OCS frequently than patients with moderate disease.[16, 17] Approximately 30–40% of patients with severe asthma regularly use OCS to control their disease (intermittently or long-term).[16-20] Prior studies have indicated an increased risk of adverse outcomes associated with SCS use, but none have used longitudinal data to quantify cumulative incidence.

We found that SCS initiation compared with non-SCS initiation is associated with substantially greater cumulative incidence of adverse outcomes, resulting in greater health care burden, and there is a positive dosage–response relationship between cumulative incidence of adverse outcomes and amount of SCS exposure. Increased risks of adverse outcomes over time means that SCS use can accrue a considerable, long-term health care burden.

Using British Thoracic Society treatment guidelines of 30 mg/day for 14 days per exacerbation, we estimated that patients with severe asthma (assumed to have had ≥3 exacerbations in a year without long-term SCS use) are exposed to 1.26 g of corticosteroids per year (or 3.45 mg/day).[21] Even with three steroid bursts per year, over the long term, these patients would have elevated risks of developing type 2 diabetes, osteoporosis, cataracts, or having at least one cardio-cerebrovascular disease episode. This circumstance represents a tremendous long-term public health issue and health care burden associated with

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SCS use. Clinicians should therefore consider treating their patients with steroid-sparing agents to reduce the risks associated with SCS use.

Although previous studies documented increased risks of corticosteroid-related onset of chronic complications, they examined different patient populations. Previous studies also did not explore the effect of dosage and duration of SCS exposure on chronic disease onset, associated disease prevalence, and HCRU and costs for patients with asthma.[22–26] Sullivan et al[22] observed an increase in the odds ratio of new adverse events combined with greater SCS use (1.04 vs. 1.29 for 1–3 vs. ≥4 prescriptions within the year), consistent with our findings for individual adverse events. In the Zazzali et al[23] study, increased health care utilization and adverse events associated with SCS use were reported, with adverse events further stratified by presence of chronic obstructive pulmonary disease. Hypertension and type 2 diabetes were the most common SCS-associated adverse events that were more prevalent in this group than the non-SCS group (62.9% vs. 56.9% and 34.0% vs. 28.4%, respectively). Effect of cumulative SCS dosage was not reported. Barry et al[24] estimated the increased costs of SCS-related morbidity, and O'Neill et al[26] estimated cost differences for patients using maintenance steroids versus those not on maintenance steroids. Neither study, however, collected information on initiation of treatment or cumulative dosage. Other prior studies that examined HCRU and costs did so over an average of 2 years, while previous studies on clinical outcomes related to SCS exposure only considered an average exposure period of 6 months and none investigated the impact of lifetime exposure. Unlike other studies,[22–26] our study was based on a large cohort of patients initiating SCS, and explored the long-term impact of SCS exposure. Our study had a greater amount of medical record history available (≥4 years for >75% of patients and ≥8 years for 50% of patients) than previous studies (≤2 years),[23, 24, 26] resulting in a more accurate determination of prior

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SCS exposure. To accurately assess the impact of SCS-associated adverse outcomes on patients, we excluded patients with adverse outcomes prior to index date (or first SCS dose). Patients in our analyses had an average of 8.6 years of follow up in the SCS arm and an average of 7.7 years in the non-SCS arm. The average age of our study patient population was 46 years, consistent with other asthma study patient populations.[6, 10, 18]

Our study is the first to demonstrate that the costs associated with SCS-associated adverse outcomes increased over the years according to SCS exposure, both overall and by SCS dosage. Incremental yearly costs for SCS patients were 7% greater in the first year and 1.5, 1.7, and 2.2 times greater by Years 5, 10, and 15, respectively. This is consistent with incremental cumulative incidence of the adverse outcomes in the SCS arm. Even though we also observed slight increases in the adverse outcome cumulative incidence in the non-SCS arm, their longitudinal annual costs remained flat, hinting potentially that the adverse outcomes observed in SCS arm could be more severe.

A UK study comparing nonasthma control (no exposure) with GINA step 2/3 patients (low exposure) and GINA step 5 patients (high exposure) estimated the annual cost (2013 values) of corticosteroid-induced morbidity was £224 for low-exposed group and £1,310 for high-exposed group.[25] It is unclear what the dosages were in a study by Berry et al 2017.[25] In our study, we observed a £44.70, £445.34, £1,262.82, £1,951.89, £1,878.60, and £3,283.70 incremental SCS adverse outcomes–associated average annual cost for SCS exposure of 0.5–<2.5 mg/day, 2.5–<5.0 mg/day, 5.0–<7.5 mg/day, 7.5–<15.0 mg/day, and ≥15.0 mg/day, respectively.

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4.1 Limitations

This study has several limitations. Although confounding by all measured patient characteristics was considered and addressed, as in all observational research, we cannot exclude confounding by characteristics we did not measure. As patients receiving SCS may be more likely to be screened for comorbidities, an overestimation of comorbidities in this group relative to the non-SCS group may have occurred.

When looking at the different resource types, we observed a low frequency of specialist consultations and A&E attendance. In the UK health care system, chronic diseases are typically managed under primary care, and there is a clear tendency toward keeping as much health care as possible at the primary care level. Therefore, our HCRU results underestimated the burden that may be carried under secondary or specialist care, where we could observe much greater HCRU-associated costs. This analysis excluded those who died due to the adverse outcomes prior to the 15-year mark and most likely underestimated incidence in the SCS arm more than the non-SCS arm.

For calculating costs for HCRU, we considered just the most prevalent SCS-related adverse outcomes rather than all possibilities. Weight gain was identified as one of the key adverse outcomes for SCS exposure. However, we could not link weight gain to any specific HCRU-related outcomes to account for the cost. Therefore, an inability to account for adverse health effects such as weight gain led to the underestimation of the SCS burden.

We have considered a large set of covariates as potential confounders in the models. However, it is possible that information on confounding factors was not available to use. The data we used were registered during regular care, and not for research purposes. As a result,

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disease history and onset could have been recorded incorrectly or not at all. These input-related variations could have led to over- or underestimation of the observed associations.

5 CONCLUSIONS

Our study is the first long-term follow-up study to examine SCS adverse outcome burden and document the longitudinal detrimental effect of SCS exposure among SCS initiators. We observed an increase in cumulative incidence of adverse outcomes and associated health care costs over time for SCS-exposed patients. A positive dosage–response relationship was observed between average daily SCS exposure and cumulative SCS adverse outcomes incidence, associated HCRU, and health care costs. Even low-grade exposure to SCS was related to long-term detrimental effects of adverse outcomes.

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CONFLICTS OF INTEREST

Jaco Voorham, David Price, Joanna Ling Zhi Jie, Marjan Kerkhof, and Mandy Ow are employees of the Observational Pragmatic Research Institute (OPRI), Singapore. Xiao Xu, Sarowar Golam, Jill Davis, and Trung N. Tran are employees of AstrZeneca.

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AUTHOR CONTRIBUTIONS

All authors participated in the conception and design of the study, the acquisition, analysis and interpretation of the data, the preparation, review and revision of the manuscript, and the approval to submit.

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TABLES

Table 1. Demographics and baseline clinical characteristics of HCRU analysis cohort (overall SCS population)

Variable	SCS (n=9,413)	Non-SCS (n=9,413)	SMD (%)
Sex (male), n (%)	3,268 (34.7)	3,268 (34.7)	0.0
Age categories (years), n (%)			
18–40	3,284 (34.9)	4,890 (51.9)	28.6
41–60	3,468 (36.8)	2,593 (27.5)	
61–80	2,378 (25.3)	1,618 (17.2)	
>80	283 (3.0)	312 (3.3)	
BMI (kg/m²), closest in 5 years prior, categorized, n (%)			
N (% nonmissing)	6,511 (69.2)	6,757 (71.8)	19.2
<18.5	140 (2.2)	183 (2.7)	
18.5–<25	2,180 (33.5)	2,816 (41.7)	
25–<30	2,127 (32.7)	2,092 (31.0)	
≥30	2,064 (31.7)	1,666 (24.7)	
Uncontrolled asthma,[a,b] n (%)	2,863 (30.4)	1,253 (13.3)	42.3
Severe asthma year prior,[b,c] n (%)	3,794 (40.3)	2,043 (21.7)	41.1
Hospitalization with asthma year prior,[b,d] n (%)	106 (1.1)	35 (0.4)	8.8
A&E with asthma year prior,[b,e] n (%)	71 (0.8)	32 (0.3)	5.6
High-dosage ICS year prior,[f] n (%)	582 (6.2)	365 (3.9)	10.6
SCS refills per year,[g] n (%)			
<1	2,342 (28.4)	NA	NA
1–<2	2,777 (33.7)	NA	NA
2–<3	1,443 (17.5)	NA	NA
3–<4	694 (8.4)	NA	NA
4–<7	636 (7.7)	NA	NA
≥7	348 (4.2)	NA	NA
Hypertension diagnosis,[h] n (%)	1,628 (17.3)	1,325 (14.1)	8.9
Depression diagnosis,[h] n (%)	2,842 (30.2)	2,436 (25.9)	9.6
Peptic ulcer diagnosis,[h] n (%)	200 (2.1)	155 (1.6)	3.5

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Variable	SCS (n=9,413)	Non-SCS (n=9,413)	SMD (%)
Dyslipidemia diagnosis or elevated lipids,[h,i] n (%)	1,234 (13.1)	1,065 (11.3)	5.5
Type 2 diabetes mellitus diagnosis or 2x HbA1c≥6.5%,[h] n (%)	370 (3.9)	458 (4.9)	4.6
Cardio-cerebrovascular disease (MI, HF, CVA) diagnosis, ever prior, n (%)	382 (4.1)	364 (3.9)	1.0
MI diagnosis	165 (1.8)	144 (1.5)	1.8
HF diagnosis	95 (1.0)	119 (1.3)	2.4
CVA diagnosis	162 (1.7)	167 (1.8)	0.4
Glaucoma diagnosis, ever prior, n (%)	114 (1.2)	106 (1.1)	0.8
Sleep apnea diagnosis, ever prior, n (%)	23 (0.2)	19 (0.2)	0.9
Cataract diagnosis or surgery, ever prior, n (%)	327 (3.5)	303 (3.2)	1.4
Osteoporosis diagnosis, ever prior, n (%)	145 (1.5)	121 (1.3)	2.2
Renal impairment, eGFR-based stage, closest prior, n (%)			
Stage 3a to Stage 5, eGFR <60	933 (9.9)	807 (8.6)	
Pneumonia diagnosis, year prior, n (%)	50 (0.5)	25 (0.3)	4.2
Charlson comorbidity index, new weights, n (%)[15]			
0–4	3,881 (41.2)	3,852 (40.9)	
5–8	4,304 (45.7)	4,400 (46.7)	
9–12	329 (3.5)	315 (3.3)	
13–16	386 (4.1)	308 (3.3)	
≥17	513 (5.4)	538 (5.7)	

[a]Uncontrolled asthma defined as either poor symptom control (either Asthma Control Questionnaire score >1.5, Asthma Control Test score <20, or "not well control" based on National Asthma Education and Prevention Program or GINA guidelines), frequent severe exacerbations requiring ≥2 bursts of SCS for >3 days in the previous year, serious exacerbation requiring at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year, or , airflow limitation (prebronchodilator FEV1 <80% predicted in presence of FEV_1/FVC less than lower limit of normal); [b]Based on HES data; [c]Severe asthma defined as GINA Step 4/5 or uncontrolled asthma; [d]Hospitalization with

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asthma/lower respiratory code on same day; [e]A&E with asthma/lower respiratory code on same day; [f]High-dosage ICS defined as >500 µg/day fluticasone equivalent; [g]Based on follow-up period, N=8,240; [h]Any prior diagnosis ever; [i]Defined as TC>6.5, LDL>4, or TG≥2.3.

A&E, accident and emergency; BMI, body mass index; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; HbA1c, glycosylated hemoglobin; HCRU, health care resource utilization; HES, Health Episode Statistics database; HF, heart failure; ICS, inhaled corticosteroids; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; SCS, systemic corticosteroids; SD, standard deviation; SMD, standardized mean differences; TC, total cholesterol; TG, triglycerides.

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Table 2. Mean (SD) annualized HCRU for all-cause adverse outcomes and asthma

			Mean average daily exposure (mg)					
HCRU	**No SCS**	**Overall SCS**	**>0–<0.5**	**0.5–<2.5**	**2.5–<5.0**	**5.0–<7.5**	**7.5–<15.0**	**≥15.0**
	n=9,413	n=9,413	n=5,152	n=3,497	n=436	n=174	n=134	n=20
All-cause adverse outcomes–associated HCRU (excluding asthma-related)								
General practitioner visits	9.18 (7.76)	12.42 (8.73)	10.55 (7.90)	13.79 (8.87)	17.54 (10.65)	19.81 (12.66)	20.09 (12.15)	28.45 (17.17)
Specialist visits	1.17 (1.94)	1.47 (2.91)	1.29 (2.15)	1.55 (2.37)	1.93 (2.92)	2.54 (4.35)	2.72 (3.59)	3.10 (5.90)
Hospitalizations	0.32 (1.94)	0.40 (0.97)	0.33 (0.72)	0.44 (0.59)	0.68 (1.04)	0.78 (2.11)	0.84 (1.04)	1.48 (2.01)
Accident and emergency visits	0.15 (0.97)	0.20 (0.97)	0.18 (0.72)	0.23 (0.59)	0.23 (0.63)	0.21 (0.40)	0.26 (0.69)	0.90 (1.79)
Prescriptions	10.08 (23.28)	14.04 (24.26)	11.37 (23.69)	15.32 (23.65)	23.09 (24.85)	30.82 (37.46)	28.38 (22.23)	39.42 (31.75)
Asthma-related HCRU								
General practitioner visits	1.34 (1.94)	2.65 (1.94)	2.01 (1.44)	3.21 (1.77)	4.23 (2.92)	4.44 (3.30)	4.37 (3.24)	6.26 (3.53)
Specialist visits	0.07 (0.97)	0.23 (0.97)	0.12 (0.72)	0.26 (1.18)	0.70 (1.67)	0.91 (4.35)	1.13 (1.74)	3.10 (6.89)
Hospitalizations	0.00	0.02	0.01	0.03	0.06	0.04	0.21	0.33

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	(0.00)	(0.00)	(0.00)	(0.00)	(0.21)	(0.13)	(1.39)	(0.45)
Accident and emergency visits	0.00 (0.00)	0.01 (0.00)	0.01 (0.00)	0.01 (0.00)	0.02 (0.21)	0.00 (0.00)	0.04 (0.35)	0.05 (0.22)
Prescriptions	5.35 (5.82)	10.61 (9.70)	7.85 (7.18)	12.59 (9.46)	19.01 (13.36)	21.31 (15.43)	21.23 (15.05)	25.62 (17.62)

HCRU, health care resource utilization; SCS, systemic corticosteroids; SD, standard deviation.

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Table 3. Mean (SD) annualized costs per patient for all-cause adverse outcomes and asthma (2016 £)

			Mean average daily exposure (mg/day)					
HCRU	**No SCS**	**Overall SCS**	**>0–<0.5**	**0.5–<2.5**	**2.5–<5.0**	**5.0–<7.5**	**7.5–<15.0**	**≥15.0**
	n=9,413	n=9,413	n=5,152	n=3,497	n=436	n=174	n=134	n=20
All-cause adverse outcomes–associated costs (excluding asthma-related costs)								
All resources	1,164.83 (5,756.23)	1,483.03 (2,294.54)	1,209.53 (1,844.68)	1,610.17 (2,110.54)	2,427.65 (2,743.92)	3,116.72 (7,560.37)	3,043.43 (2,893.84)	4,448.53 (4,573.52)
General practitioner visits	330.58 (285.24)	447.26 (327.93)	379.89 (289.26)	496.42 (326.43)	631.56 (383.99)	713.26 (453.90)	723.35 (436.64)	1,024.11 (618.45)
Specialist visits	137.22 (263.90)	171.34 (290.09)	151.37 (259.83)	180.99 (296.27)	225.80 (331.58)	297.36 (514.45)	317.61 (413.26)	362.79 (689.25)
Hospitalizations	592.59 (5,503.01)	726.57 (1,851.15)	558.52 (1,359.46)	792.17 (1,649.88)	1,343.17 (2,152.16)	1,812.85 (7,376.75)	1,779.20 (2,472.25)	2,598.14 (3,515.41)
Accident and emergency visits	21.05 (89.26)	28.15 (70.83)	25.14 (66.04)	31.34 (74.51)	31.19 (75.80)	28.36 (54.61)	36.49 (87.17)	124.50 (248.74)
Prescriptions	83.60 (396.81)	110.19 (496.75)	95.07 (524.69)	109.11 (361.91)	197.96 (740.22)	268.56 (1,008.97)	191.03 (314.86)	362.46 (628.34)
Asthma-related HCRU costs								
All resources	166.39 (209.56)	402.93 (478.31)	272.98 (269.88)	493.08 (487.28)	785.76 (731.03)	784.56 (915.05)	1,077.87 (1,296.15)	1,925.37 (1,347.81)
General	48.16	95.24	72.21	115.70	152.45	159.73	157.30	225.20

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			Mean average daily exposure (mg/day)					
HCRU	**No SCS**	**Overall SCS**	**>0–<0.5**	**0.5–<2.5**	**2.5–<5.0**	**5.0–<7.5**	**7.5–<15.0**	**≥15.0**
practitioner visits	(52.39)	(72.77)	(53.12)	(72.15)	(103.57)	(119.64)	(117.03)	(127.72)
Specialist visits	10.27 (91.20)	36.64 (160.08)	18.80 (65.32)	40.67 (138.38)	109.19 (252.66)	142.19 (676.96)	177.32 (279.09)	486.79 (1,083.06)
Hospitalizations	2.99 (45.60)	46.86 (291.06)	14.47 (95.46)	68.66 (356.00)	126.68 (456.66)	98.34 (439.26)	296.76 (1,011.61)	717.26 (925.33)
Accident and emergency visits	0.22 (2.91)	1.36 (10.67)	0.82 (7.18)	1.85 (12.42)	2.77 (14.20)	0.55 (5.41)	4.91 (39.36)	7.49 (30.77)
Prescriptions	106.08 (145.53)	226.72 (224.12)	170.41 (190.93)	270.51 (214.07)	397.81 (290.03)	386.63 (279.12)	444.47 (406.66)	492.93 (405.04)

BMI, body mass index; SCS, systemic corticosteroids; SD, standard deviation.

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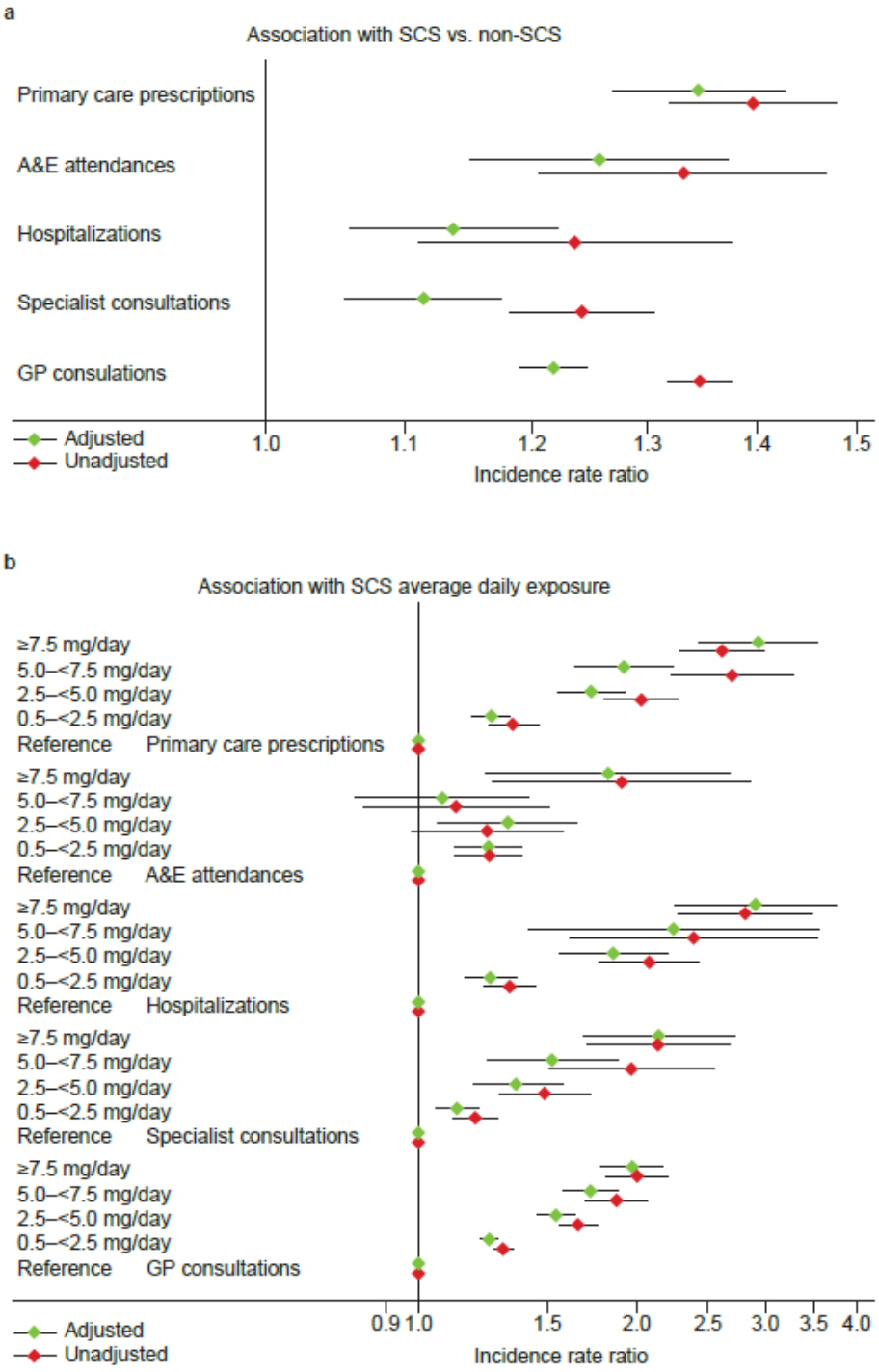
FIGURES

Figure 1. Incidence rate ratio of HCRU for all SCS-related adverse outcomes[a] by SCS status and average daily exposure[b]



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[a]Excluding asthma. Error bars represent 95% confidence interval. For adjustment, age and sex were used as forced covariates, with BMI, smoking status, antibiotic-treated infections, airflow limitation, asthma medication used (general and specified), intensive care unit stay, mechanical ventilation usage, and diagnosis of and/or treatment for diseases (Table S6) selected based on their incremental bias potential. [b]Reference categories for daily exposure were for the lowest dosage (<0.5 mg/day).

A&E, accident and emergency; BMI, body mass index; GP, general practice; SCS, systemic corticosteroids.

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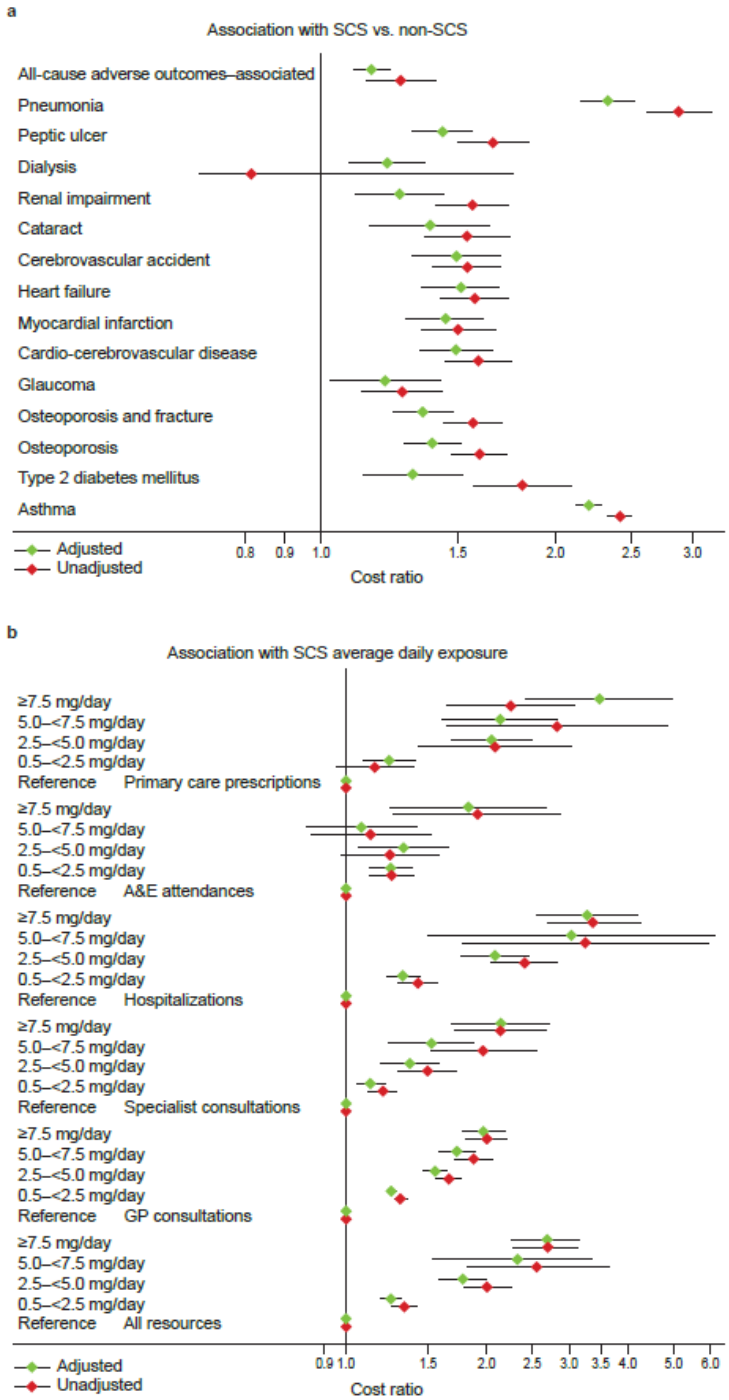
Figure 2. Association of all-cause adverse outcome[a]–related costs with SCS status and average daily exposure



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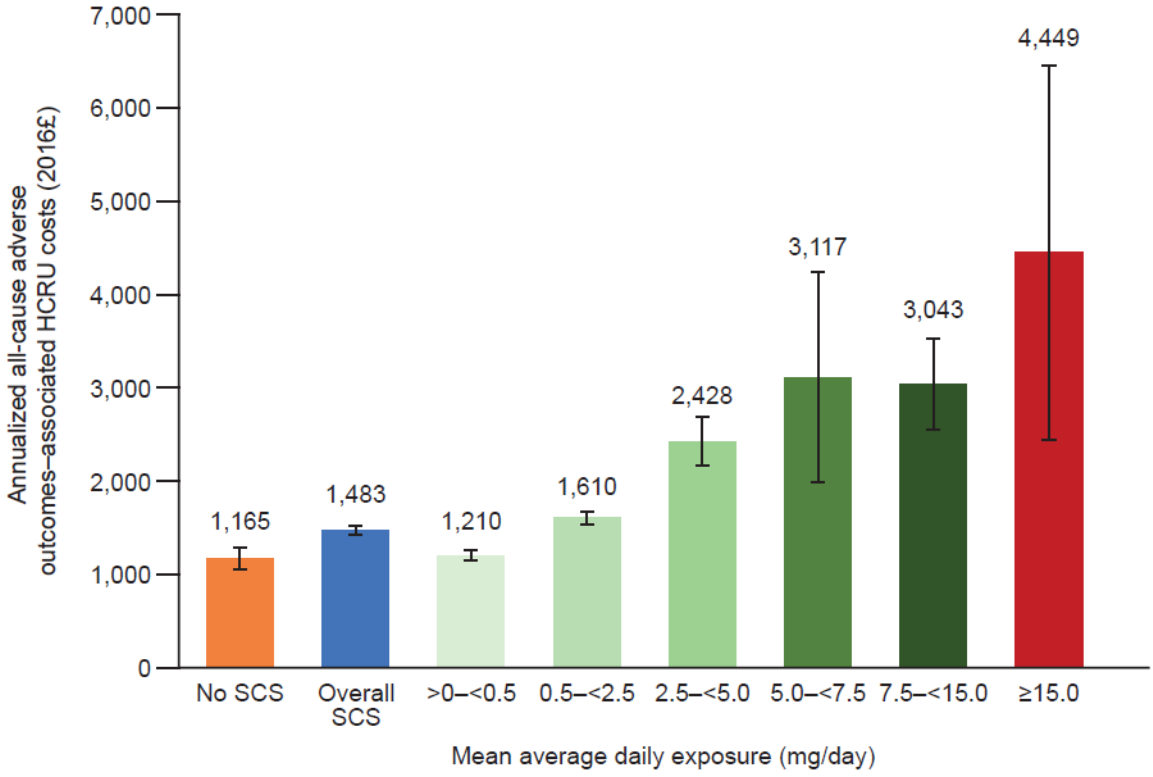
[a]Excluding asthma. Error bars represent 95% confidence interval. For adjustment, age and sex were used as forced covariates, with BMI, smoking status, antibiotic-treated infections, airflow limitation, asthma medication used (general and specified), intensive care unit stay, mechanical ventilation usage, and diagnosis of and/or treatment for diseases (Table S6) selected based on their incremental bias potential.

BMI, body mass index; SCS, systemic corticosteroids.

Figure 3. Mean annualized all-cause adverse outcomes–associated[a] cost



[a]Excluding asthma. Error bars represent 95% confidence interval.

BMI, body mass index; SCS, systemic corticosteroids.

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