**Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study**

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**Supplementary methods**

***Ethical approvals for the study***

The Optimum Patient Care Research Database (OPCRD) has been reviewed and ethically approved by the NHS Health Research Authority to hold and process anonymized data as part of service delivery (Research Ethics Committee reference: 15/EM/0150).E1 The Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database, is a governmental, not-for-profit research service, jointly funded by the UK NHS National Institute for Health Research and the Medicines and Healthcare products Regulatory Agency.E2

The study was designed, implemented, and reported in accordance with the criteria of the European Network Centres for Pharmacoepidemiology and PharmacovigilanceE3 (ENCePP; registration number EUPAS15175). The study followed the ENCePP code of conductE4 and adhered to standards recommended for observational research.E5 The protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC reference number 17\_002) and the Anonymised Data Ethics Protocols and Transparency committee (ADEPT), the independent scientific advisory committee for the OPCRDE1; patient consent was not required because of the retrospective nature of this study, as approved by the committee (Approval Reference ADEPT0117). All access and use of anonymized data via the CPRD are carefully controlled under UK and European law and the rules and regulations operating in the NHS. The authors had no access to patient identifying information as part of this study.

***Patient matching process***

Descriptive statistics of all baseline characteristics were computed in the matched sample. Continuous variables were summarized using the number and percentage of non-missing observations. For normally distributed variables, mean and standard deviation (SD) were calculated, while median and interquartile range (IQR) were reported for non-normally distributed variables. Binary and categorical variables were summarized using the number and percentage of non-missing observations and the count and percentage by category.

The quality of the matching was evaluated using the standardized mean difference (SMD)in combination with the bias potential.E6,E7 Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on the variable. Bias potential was measured using the relative change in coefficient (RCC) of the exposure when a covariate was added into the model. An SMD >10% was considered to indicate relevant covariate imbalance, and a relative change in coefficient >2% was considered to indicate relevant bias potential.

***Statistical analysis***

Descriptive statistics of the at-risk cohorts during the follow-up period were provided, including the numbers of patients, the numbers of patient-years of follow-up, and the number of events (ie, reaching the outcome for which the cohort was at risk). The incidence rate of the outcome conditions in the SCS and non-SCS cohorts was reported as cases per 100 patient-years (pt-yr) of follow-up and compared between the cohorts using the incidence rate difference and the incidence rate ratio (RR), with their 95% confidence intervals (CIs).

In the protocol, we had included the risk of dialysis initiation as one of the original 18 adverse outcomes under study. However, we elected to exclude the dialysis risk cohort in this report, because no confounder adjustment could be made, probably because of the low number of events (n=25, 9 in the non-SCS arm and 16 in the SCS arm).

***Exposure measures***

The SCS exposure was quantified using prednisolone-equivalent doses, calculated as summarized below.

|  |  |
| --- | --- |
| **Drug** | **Prednisolone equivalence (mg) / mg** |
| Betamethasone | 6.67 |
| Betamethasone, injected | 8.338 |
| Cortisone acetate | 0.2 |
| Dexamethasone | 6.67 |
| Hydrocortisone | 0.25 |
| Methylprednisolone | 1.25 |
| Methylprednisolone, injected | 1.525 |
| Prednisolone, injected | 1.22 |
| Prednisone | 1.0 |

The following exposure measures were used to assess their association with the development of the outcome.

* SCS use vs. non-SCS use, a binary indicator of having initiated SCS (1) or not (0).
* In the SCS cohort only, the following measures were used as time-dependent exposures:
	+ Cumulative exposure, as grams of SCS used up to that moment in time:
		- Used as continuous variable
		- Use categorized as <0.5, 0.5 to <1.0, 1.0 to <2.5, 2.5 to <5, 5 to <10 and ≥10  g
	+ Mean daily exposure, as mg/day of SCS: Cumulative exposure used up to that moment in time, divided by the number of days since the index date:
		- Used as continuous variable
		- Use categorized as <0.5, 0.5 to <2.5, 2.5 to <5, 5 to <7.5, 7.5 to <15, ≥15 mg/day, and ≥7.5 mg/day.

***Confounder adjustment***

For each outcome model, three sets of variables were defined based on domain knowledge for each outcome cohort (Table E2):

1. The variables that should always be adjusted in the models, selected based on clinical knowledge, and all forced in the model (marked “1” in the table),
2. The variables that were available for bias potential assessment during model building (marked “2” in the table), and
3. The variables that were not used in the models (marked “3” in the table).

The variables available for bias potential assessment were evaluated as follows. Starting with a model containing the exposure measure and the variables that were forced into the model, all available variables (covariates) were assessed on their bias potential (the relative change in coefficient they cause by being added to the model). The variable with the highest bias potential of at least 2% was added first to the model, unless this led to a variance inflation of more than 2%. Then, this process was repeated, adding each variable one by one in descending order of their individual bias potential, using the same selection criteria. In case addition of a variable resulted in the model not being able to converge, the variable was skipped.

As a sensitivity analysis, we also included the Charlson comorbidity index in the models for adjustment, and the results did not change.

Dataset creation was performed using SAS version 9.4 (SAS Institute, Cary, NC), which handles large data volumes efficiently. Statistical analyses were conducted using Stata SE version 14.2, Stata MP/6 version 15.0 (StataCorp, College Station, TX). The latter is a parallel-processing version of Stata, which we used to speed up complex computing. Results were considered statistically significant if *P*≤0.05.

# Supplementary results

***Patients***

Among 307,213 matched pairs of patients, over half of patients in the SCS arms were prescribed SCS for a respiratory condition, including 117,409 (38%) prescribed SCS for asthma, 58,577 (19%) prescribed SCS for COPD, and 1536 (0.5%) prescribed SCS for asthma and COPD. Of the 23 other indications for SCS, ulcerative colitis was the next most common condition (27,847 patients, 9%).

**References**

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E3. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Available at: http://www.encepp.eu/index.shtml. Accessed March 28, 2018.

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E7. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol*. 1989;129:125–137.

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**Table S1** Exclusion criteria used for specific outcome (risk) cohorts

|  |  |
| --- | --- |
| **Outcome** | **Exclusion criteria applied with regard to data recorded before the index datea** |
| Type 2 diabetes mellitus | * Diagnosis of type 2 diabetes mellitus,b and/or antidiabetic medication and/or two or more HbA1c readings ≥6.5%, or
* Diagnosis of type 1 diabetes mellitus, or
* Diagnosis of gestational diabetes
 |
| Cardio-/cerebrovascular disease | * Cardiovascular disease (myocardial infarction, heart failure, and stroke) diagnosis
 |
| Myocardial infarction  | * Myocardial infarction diagnosis
 |
| Heart failure | * Heart failure diagnosis
 |
| Cerebrovascular accident | * Cerebrovascular accident diagnosis
 |
| Dyslipidemia | * Dyslipidemia diagnosis, or total cholesterol reading >6.5 mmol/L, or low-density lipoprotein reading >4 mmol/L, or triglyceride reading ≥2.3 mmol/L, or lipid-regulating medication use
 |
| Hypertension | * Hypertension diagnosis and/or antihypertensive medications
 |
| Weight gain (BMI increase ≥1 kg/m2) | * No BMI value available in 5 years before the index date
 |
| Osteoporosis diagnosisOsteoporosis diagnosis and osteoporotic fractures | * Osteoporosis diagnosis or osteoporotic fracture (hip, wrist, vertebral) and treatment for osteoporosis
 |
| Glaucoma | * Glaucoma diagnosis and/or treatment for glaucoma
 |
| Cataract | * Cataract diagnosis or surgery for cataract code
 |
| Renal impairment | * Chronic kidney disease stage 3a+ diagnosis, or estimated glomerular filtration rate (eGFR) <60 mL/min/1.72m2, or dialysis or renal transplant
 |
| Peptic ulcer | * Peptic ulcer diagnosis
 |
| Depression/anxiety | * Depression/anxiety diagnosis, or depression/anxiety diagnosis and prescription of antidepressants and/or prescription of anxiolytic drugs
 |
| Sleep apnoea | * Sleep apnea diagnosis and/or referral to specialist and use of a continuous positive airway pressure device
 |
| Pneumonia | * Pneumonia diagnosis
 |

**Notes**: aExclusion criteria were applied to all available data recorded ever before the index date unless otherwise noted.

bAll diagnoses were defined using recorded diagnostic Read codes.E8

**Abbreviations**: BMI, body mass index.

| **Table S2** Confounder candidates considered and/or adjusted for in the outcome models |
| --- |
|  | **Type 2 diabetes mellitus** | **Cardio-/cerebrovascular dz** | **Myocardial infarction** | **Heart failure** | **Cerebrovascular accident** | **Dyslipidemia** | **Hypertension** | **Weight gain (BMI increase ≥1 kg/m2)** | **Osteoporosis diagnosis** | **Osteoporosis diagnosis & fx** | **Glaucoma** | **Cataracts** | **Renal impairment** | **Peptic ulcer** | **Depression/anxiety** | **Sleep apnea** | **Pneumonia** |
| Sex (only in SCS cohort exposure models) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Age (years), categorized | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| BMI (kg/m²), closest in 5 years prior, categorized | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Smoking status, closest ever | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Antibiotic-treated infections, number, year prior | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 |
| Airflow limitation (FEV1 predicted <80% after bronchodilator withheld), year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Asthma medication use, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| SABA average daily dose (µg, salbutamol equivalent), year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| SABA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| SAMA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| FDC SABA/SAMA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| LABA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| LAMA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| FDC LABA/LAMA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| FDC ICS/LABA average daily dose (µg, fluticasone equivalent), year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| High dose ICS (≥500 µg/day fluticasone equivalent), year prior (only in the SCS arm exposure models) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| ICS (stand-alone), number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| FDC ICS/LABA, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Methylxanthines, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Leukotriene inhibitors, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Biologics, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| PDE4-inhibitor, number of prescriptions, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| ICU stay, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Mechanical ventilation, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Hypertension diagnosis, ever prior | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| Depression diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 |
| Peptic ulcer diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |
| Dyslipidemia diagnosis or elevated lipids (total cholesterol >6.5, LDL-C >4, triglycerides ≥2.3 mmol/L), ever prior | 1 | 1 | 1 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| Type 2 diabetes mellitus diagnosis or 2x HbA1c≥6.5%, ever prior | 3 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 1 |
| Cardio-/cerebrovascular disease (myocardial infarction, heart failure, stroke) diagnosis, ever prior | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Myocardial infarction diagnosis, ever prior | 2 | 2 | 3 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Heart failure diagnosis, ever prior | 2 | 2 | 1 | 3 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Cerebrovascular accident (stroke) diagnosis, ever prior | 2 | 2 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Glaucoma diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 2 |
| Sleep apnea diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 |
| Cataract diagnosis or surgery, ever prior | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Osteoporosis diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 2 | 2 | 2 |
| Osteoporosis diagnosis and probable osteoporotic fracture, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Renal impairment, eGFR-based stage, last prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 2 | 2 | 2 |
| Chronic respiratory diseases diagnosis, ever prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Pneumonia diagnosis, year prior | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 |

**Notes**: 1 denotes variables always used in the model, investigator selected based on clinical knowledge, eg, known confounder or strong predictor of outcomes.

2 denotes variables available for bias assessment.

3 denotes variables that were not considered.

**Abbreviations**: BMI, body mass index; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β-agonist; LDL-C, low density lipoprotein cholesterol; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist.

**Table S3** Confounders applied in the adjusted models in addition to sex,a age (categorized), smoking status, BMI (categorized), which were applied in all models

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Confounding variable applied** | **SCS vs. non-SCS** | **Cumulative exposure, continuous** | **Cumulative exposure, categorical** | **Mean daily exposure, continuous** | **Mean daily exposure, categorical** |
| **Type 2 diabetes mellitus** | Antibiotic-treated infections (year prior) | X | X | X | X | X |
| Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| **Cardio-/cerebrovascular disease** | Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| Airflow limitation in year prior | X |  |  |  |  |
| **Myocardial infarction** | Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| Heart failure | X | X | X | X | X |
| Stroke | X | X | X | X | X |
| Antibiotic-treated infections (year prior) | X |  |  |  |  |
| Airflow limitation in year prior | X |  |  |  |  |
| FDC SABA/SAMA (year prior) | X |  |  |  |  |
| **Heart failure** | Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| Myocardial infarction | X | X | X | X | X |
| Cerebrovascular accident | X | X | X | X | X |
| Airflow limitation in year prior |  | X |  |  |  |
| SAMA (year prior) |  | X |  |  |  |
| LABA (year prior) |  | X |  |  |  |
| **Cerebrovascular accident** | Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| Myocardial infarction | X | X | X | X | X |
| Heart failure | X | X | X | X | X |
| Airflow limitation in year prior | X |  |  |  |  |
| Depression / anxiety | X |  |  |  |  |
| **Dyslipidaemia** | Antibiotic-treated infections (year prior) | X |  |  |  |  |
| Airflow limitation in year prior | X |  |  |  |  |
| **Hypertension** | **No additional variable** |  |  |  |  |  |
| **Weight gain****(BMI increase ≥1 kg/m2)** | Type 2 diabetes mellitus | X | X | X | X | X |
| Airflow limitation in year prior | X |  | X |  |  |
| FDC SABA/SAMA (year prior) |  |  | X |  |  |
| LABA (year prior) |  |  | X |  |  |
| LAMA (year prior) |  |  | X |  |  |
| **Osteoporosis diagnosis** | Airflow limitation in year prior | X |  |  |  |  |
| SAMA (year prior) | X |  |  |  |  |
| Renal impairment | X |  |  |  |  |
| **Osteoporosis diagnosis and fracture** | **No additional variables** |  |  |  |  |  |
| **Glaucoma** | Antibiotic-treated infections (year prior) | X |  |  |  |  |
| SABA daily dose (year prior) | X |  |  |  |  |
| Theophylline (year prior) | X |  |  |  |  |
| Type 2 diabetes mellitus | X |  |  |  |  |
| **Cataract** | Type 2 diabetes mellitus | X | X | X | X | X |
| SABA daily dose (year prior) | X |  |  |  |  |
| **Renal impairment** | Hypertension | X | X | X | X | X |
| Dyslipidemia | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| **Peptic ulcer** | Antibiotics treated infections (year prior) | X |  |  |  |  |
| Airflow limitation in year prior | X |  |  |  |  |
| SABA (year prior) | X |  |  |  |  |
| Hypertension | X |  |  |  |  |
| Osteoporosis | X |  |  |  |  |
| Osteoporosis or osteoporotic fracture | X |  |  |  |  |
| Renal impairment | X |  |  |  |  |
| Chronic respiratory diseases combined | X |  |  |  |  |
| **Depression/anxiety** | Antibiotic-treated infections (year prior) | X |  |  |  |  |
| Airflow limitation in year prior | X |  |  |  |  |
| **Sleep apnoea** | Antibiotic-treated infections (year prior) | X |  |  |  |  |
| **Pneumonia** | Antibiotic-treated infections (year prior) | X | X | X | X | X |
| Type 2 diabetes mellitus | X | X | X | X | X |
| Airflow limitation in year prior | X |  |  |  |  |
| SAMA (year prior) | X |  |  |  |  |

**Notes**: aSex was not applied as a confounder in the SCS vs. non-SCS model.

**Abbreviations**: BMI, body mass index; FDC, fixed-dose combination; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

**Table S4** Onset of outcomes in relation to continuous and categorized cumulative systemic corticosteroid (SCS) exposure: SCS cohort

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Npatients** | **Nevents** | **Unadjusted** | **Adjustedb** |
| **Outcome** | **Exposure** | **HR (95% CI)** | **P** | **HR (95% CI)** | **P** |
| **Type 2 diabetes mellitus** | **Cumulative SCS exposure (1g)a** | **21,808** | **1921** | **1.026 (1.020–1.032)** | **<0.0001** | **1.027 (1.021–1.033)** | **<0.0001** |
| >0 to <0.5 g | 20,595 | 454 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 16,981 | 457 | 1.19 (1.03–1.37) | 0.0154 | 1.16 (1.01–1.34) | 0.0395 |
| 1.0 to <2.5 g | 11,372 | 503 | 1.48 (1.28–1.72) | <0.0001 | 1.37 (1.18–1.58) | <0.0001 |
| 2.5 to <5 g | 5253 | 194 | 1.45 (1.20–1.76) | <0.0001 | 1.34 (1.11–1.63) | 0.0028 |
| 5 to <10 g | 2720 | 166 | 2.25 (1.83–2.75) | <0.0001 | 2.03 (1.65–2.50) | <0.0001 |
| ≥10 g | 1214 | 147 | 2.73 (2.20–3.38) | <0.0001 | 2.59 (2.07–3.24) | <0.0001 |
| **Cardio-/cerebrovascular disease** | **Cumulative SCS exposure (1g)a** | **22,112** | **1774** | **1.025 (1.018–1.031)** | **<0.0001** | **1.021 (1.015–1.026)** | **<0.0001** |
| >0 to <0.5 g | 20,910 | 374 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 17,196 | 387 | 1.28 (1.10–1.48) | 0.0015 | 1.14 (0.98–1.32) | 0.0867 |
| 1.0 to <2.5 g | 11,433 | 461 | 1.84 (1.57–2.14) | <0.0001 | 1.42 (1.22–1.66) | <0.0001 |
| 2.5 to <5 g | 5201 | 246 | 2.67 (2.23–3.21) | <0.0001 | 1.79 (1.49–2.14) | <0.0001 |
| 5 to <10 g | 2636 | 164 | 3.31 (2.69–4.07) | <0.0001 | 1.96 (1.59–2.41) | <0.0001 |
| ≥10 g | 1175 | 142 | 4.06 (3.25–5.06) | <0.0001 | 2.23 (1.79–2.77) | <0.0001 |
| **Myocardial infarction** | **Cumulative SCS exposure (1g)a** | **23,251** | **646** | **1.030 (1.023–1.037)** | **<0.0001** | **1.026 (1.018–1.033)** | **<0.0001** |
| >0 to <0.5 g | 21,968 | 142 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,206 | 127 | 1.02 (0.79–1.31) | 0.8960 | 0.92 (0.72–1.19) | 0.5340 |
| 1.0 to <2.5 g | 12,259 | 166 | 1.54 (1.20–1.97) | 0.0007 | 1.21 (0.94–1.55) | 0.1355 |
| 2.5 to <5 g | 5700 | 88 | 2.15 (1.59–2.91) | <0.0001 | 1.48 (1.09–2.00) | 0.0109 |
| 5 to <10 g | 2942 | 61 | 2.73 (1.95–3.82) | <0.0001 | 1.67 (1.19–2.33) | 0.0030 |
| ≥10 g | 1350 | 62 | 3.88 (2.76–5.45) | <0.0001 | 2.17 (1.55–3.05) | <0.0001 |
| **Heart failure** | **Cumulative SCS exposure (1g)a** | **23,570** | **858** | **1.030 (1.022–1.038)** | **<0.0001** | **1.029 (1.021–1.036)** | **<0.0001** |
| >0 to <0.5 g | 22,284 | 186 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,446 | 166 | 1.29 (1.02–1.62) | 0.0316 | 1.14 (0.90–1.43) | 0.2707 |
| 1.0 to <2.5 g | 12,397 | 222 | 2.24 (1.78–2.83) | <0.0001 | 1.63 (1.30–2.05) | <0.0001 |
| 2.5 to <5 g | 5731 | 126 | 3.69 (2.82–4.83) | <0.0001 | 2.27 (1.74–2.96) | <0.0001 |
| 5 to <10 g | 2931 | 77 | 4.35 (3.18–5.93) | <0.0001 | 2.33 (1.71–3.17) | <0.0001 |
| ≥10 g | 1340 | 81 | 6.66 (4.84–9.17) | <0.0001 | 3.36 (2.46–4.59) | <0.0001 |
| **Cerebrovascular accident** | **Cumulative SCS exposure (1g)a** | **23,228** | **823** | **1.019 (1.012–1.025)** | **<0.0001** | **1.012 (1.003–1.021)** | **0.0060** |
| >0 to <0.5 g | 21,949 | 148 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,220 | 193 | 1.35 (1.09–1.68) | 0.0069 | 1.21 (0.97–1.50) | 0.0895 |
| 1.0 to <2.5 g | 12,261 | 227 | 1.74 (1.39–2.17) | <0.0001 | 1.35 (1.08–1.68) | 0.0078 |
| 2.5 to <5 g | 5685 | 116 | 2.25 (1.74–2.92) | <0.0001 | 1.52 (1.18–1.96) | 0.0013 |
| 5 to <10 g | 2936 | 74 | 2.58 (1.92–3.48) | <0.0001 | 1.53 (1.13–2.07) | 0.0055 |
| ≥10 g | 1362 | 65 | 3.03 (2.21–4.17) | <0.0001 | 1.68 (1.22–2.31) | 0.0014 |
| **Dyslipidaemia** | **Cumulative SCS exposure (1g)a** | **16,903** | **3523** | **1.012 (1.006–1.018)** | **<0.0001** | **1.007 (1.000–1.014)** | **0.0429** |
| >0 to <0.5 g | 15,897 | 961 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 13,015 | 926 | 1.04 (0.95–1.15) | 0.3747 | 0.98 (0.89–1.08) | 0.7363 |
| 1.0 to <2.5 g | 8639 | 881 | 1.09 (0.99–1.20) | 0.0949 | 0.97 (0.87–1.07) | 0.4925 |
| 2.5 to <5 g | 4014 | 357 | 1.08 (0.95–1.23) | 0.2504 | 0.92 (0.80–1.05) | 0.2089 |
| 5 to <10 g | 2099 | 217 | 1.14 (0.98–1.33) | 0.0956 | 0.94 (0.80–1.10) | 0.4139 |
| ≥10 g | 960 | 181 | 1.33 (1.13–1.58) | 0.0008 | 1.08 (0.91–1.29) | 0.3663 |
| **Hypertension** | **Cumulative SCS exposure (1g)a** | **12,248** | **1626** | **1.011 (1.003–1.018)** | **0.0088** | **0.999 (0.989–1.010)** | **0.9165** |
| >0 to <0.5 g | 11,565 | 387 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 9437 | 426 | 1.16 (1.01–1.34) | 0.0411 | 1.04 (0.90–1.20) | 0.6139 |
| 1.0 to <2.5 g | 6136 | 436 | 1.28 (1.10–1.49) | 0.0012 | 1.04 (0.90–1.22) | 0.5862 |
| 2.5 to <5 g | 2759 | 191 | 1.40 (1.16–1.69) | 0.0005 | 1.02 (0.84–1.23) | 0.8589 |
| 5 to <10 g | 1409 | 97 | 1.27 (1.01–1.61) | 0.0450 | 0.91 (0.71–1.16) | 0.4450 |
| ≥10 g | 642 | 89 | 1.54 (1.20–1.97) | 0.0008 | 1.00 (0.77–1.30) | 0.9855 |
| **Weight gain (BMI increase ≥1 kg/m2)** | **Cumulative SCS exposure (1g)a** | **12,894** | **7677** | **1.003 (0.993–1.014)** | **0.5481** | **1.000 (0.990–1.010)** | **0.0502** |
| >0 to <0.5 g | 12,339 | 3772 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 7543 | 2057 | 1.00 (0.95–1.06) | 0.9714 | 1.01 (0.96–1.07) | 0.6533 |
| 1.0 to <2.5 g | 3974 | 1311 | 1.10 (1.03–1.18) | 0.0078 | 1.12 (1.05–1.21) | 0.0012 |
| 2.5 to <5 g | 1332 | 325 | 1.04 (0.92–1.18) | 0.4829 | 1.10 (0.97–1.24) | 0.1453 |
| 5 to <10 g | 564 | 151 | 1.12 (0.95–1.33) | 0.1802 | 1.22 (1.03–1.45) | 0.0240 |
| ≥10 g | 198 | 61 | 0.97 (0.74–1.26) | 0.8032 | 1.03 (0.79–1.35) | 0.8147 |
| **Osteoporosis diagnosis** | **Cumulative SCS exposure (1g)a** | **23,422** | **964** | **1.040 (1.031–1.049)** | **<0.0001** | **1.041 (1.034–1.049)** | **<0.0001** |
| >0 to <0.5 g | 22,132 | 130 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,354 | 151 | 1.33 (1.04–1.69) | 0.0217 | 1.20 (0.94–1.53) | 0.1357 |
| 1.0 to <2.5 g | 12,344 | 224 | 2.30 (1.81–2.90) | <0.0001 | 1.87 (1.48–2.36) | <0.0001 |
| 2.5 to <5 g | 5706 | 184 | 5.12 (3.99–6.58) | <0.0001 | 3.65 (2.84–4.70) | <0.0001 |
| 5 to <10 g | 2865 | 128 | 6.92 (5.25–9.10) | <0.0001 | 4.65 (3.52–6.14) | <0.0001 |
| ≥10 g | 1294 | 147 | 12.37 (9.40–16.27) | <0.0001 | 8.23 (6.20–10.91) | <0.0001 |
| **Osteoporosis diagnosis and fracture** | **Cumulative SCS exposure (1g)a** | **21,251** | **159** | **1.030 (1.020–1.040)** | **<0.0001** | **1.033 (1.022–1.043)** | **<0.0001** |
| >0 to <0.5 g | 20,066 | 20 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 16,776 | 26 | 1.50 (0.83–2.74) | 0.1822 | 1.34 (0.74–2.44) | 0.3309 |
| 1.0 to <2.5 g | 11,400 | 48 | 3.28 (1.86–5.79) | <0.0001 | 2.60 (1.48–4.56) | 0.0009 |
| 2.5 to <5 g | 5376 | 20 | 3.59 (1.79–7.20) | <0.0001 | 2.39 (1.20–4.79) | 0.0137 |
| 5 to <10 g | 2793 | 24 | 7.96 (4.12–15.38) | <0.0001 | 4.96 (2.56–9.63) | <0.0001 |
| ≥10 g | 1290 | 21 | 9.66 (4.75–19.66) | <0.0001 | 5.79 (2.82–11.88) | <0.0001 |
| **Glaucoma** | **Cumulative SCS exposure (1g)a** | **23,424** | **433** | **1.022 (1.013–1.031)** | **<0.0001** | **1.017 (1.005–1.028)** | **0.0051** |
| >0 to <0.5 g | 22,126 | 89 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,388 | 112 | 1.37 (1.03–1.82) | 0.0294 | 1.23 (0.93–1.64) | 0.1465 |
| 1.0 to <2.5 g | 12,426 | 102 | 1.37 (1.02–1.86) | 0.0394 | 1.10 (0.81–1.48) | 0.5494 |
| 2.5 to <5 g | 5811 | 56 | 1.91 (1.33–2.75) | <0.0001 | 1.35 (0.94–1.93) | 0.1062 |
| 5 to <10 g | 3002 | 34 | 2.12 (1.38–3.25) | 0.0006 | 1.37 (0.89–2.10) | 0.1545 |
| ≥10 g | 1403 | 40 | 3.32 (2.16–5.10) | <0.0001 | 1.99 (1.30–3.05) | 0.0016 |
| **Cataract** | **Cumulative SCS exposure (1g)a** | **22,648** | **1736** | **1.029 (1.022–1.035)** | **<0.0001** | **1.028 (1.022–1.034)** | **<0.0001** |
| >0 to <0.5 g | 21,407 | 320 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 17,654 | 350 | 1.16 (0.99–1.35) | 0.0699 | 1.04 (0.89–1.22) | 0.6021 |
| 1.0 to <2.5 g | 11,802 | 440 | 1.62 (1.39–1.89) | <0.0001 | 1.25 (1.07–1.47) | 0.0046 |
| 2.5 to <5 g | 5418 | 260 | 2.52 (2.11–3.01) | <0.0001 | 1.73 (1.44–2.07) | <0.0001 |
| 5 to <10 g | 2742 | 175 | 3.13 (2.56–3.84) | <0.0001 | 1.96 (1.60–2.41) | <0.0001 |
| ≥10 g | 1234 | 191 | 4.84 (3.93–5.95) | <0.0001 | 2.92 (2.36–3.62) | <0.0001 |
| **Renal impairment** | **Cumulative SCS exposure (1g)a** | **20,137** | **3215** | **1.023 (1.017–1.030)** | **<0.0001** | **1.020 (1.015–1.026)** | **<0.0001** |
| >0 to <0.5 g | 18,999 | 837 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 15,411 | 747 | 1.16 (1.05–1.29) | 0.0043 | 1.05 (0.95–1.16) | 0.3583 |
| 1.0 to <2.5 g | 10,153 | 825 | 1.53 (1.38–1.71) | <0.0001 | 1.20 (1.08–1.34) | 0.0009 |
| 2.5 to <5 g | 4592 | 367 | 1.83 (1.60–2.10) | <0.0001 | 1.23 (1.07–1.42) | 0.0032 |
| 5 to <10 g | 2325 | 231 | 2.16 (1.84–2.53) | <0.0001 | 1.34 (1.14–1.57) | 0.0004 |
| ≥10 g | 1026 | 208 | 2.95 (2.49–3.50) | <0.0001 | 1.85 (1.55–2.21) | <0.0001 |
| **Peptic ulcer** | **Cumulative SCS exposure (1g)a** | **23,149** | **219** | **1.024 (1.014–1.034)** | **<0.0001** | **1.021 (1.009–1.033)** | **0.0006** |
| >0 to <0.5 g | 21,889 | 51 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,157 | 49 | 1.26 (0.84–1.91) | 0.2669 | 1.17 (0.77–1.77) | 0.4591 |
| 1.0 to <2.5 g | 12,253 | 55 | 1.75 (1.14–2.71) | 0.0113 | 1.48 (0.96–2.30) | 0.0771 |
| 2.5 to <5 g | 5703 | 31 | 2.78 (1.65–4.68) | <0.0001 | 2.12 (1.26–3.57) | 0.0049 |
| 5 to <10 g | 2927 | 17 | 2.92 (1.61–5.30) | <0.0001 | 2.10 (1.14–3.85) | 0.0166 |
| ≥10 g | 1368 | 16 | 3.90 (2.08–7.33) | <0.0001 | 2.68 (1.41–5.10) | 0.0027 |
| **Depression/anxiety** | **Cumulative SCS exposure (1g)a** | **7961** | **1554** | **1.007 (0.994–1.019)** | **0.2906** | **1.015 (1.004–1.027)** | **0.0066** |
| >0 to <0.5 g | 7422 | 570 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 6018 | 435 | 1.08 (0.94–1.23) | 0.2656 | 1.15 (1.01–1.31) | 0.0387 |
| 1.0 to <2.5 g | 3991 | 329 | 1.14 (0.98–1.33) | 0.0802 | 1.30 (1.12–1.51) | 0.0006 |
| 2.5 to <5 g | 1913 | 111 | 1.12 (0.90–1.38) | 0.3126 | 1.33 (1.07–1.65) | 0.0109 |
| 5 to <10 g | 1053 | 67 | 1.23 (0.95–1.61) | 0.1207 | 1.54 (1.17–2.02) | 0.0019 |
| ≥10 g | 516 | 42 | 1.17 (0.84–1.64) | 0.3475 | 1.56 (1.11–2.20) | 0.0101 |
| **Sleep apnoea** | **Cumulative SCS exposure (1g)a** | **23,980** | **205** | **1.021 (1.006–1.037)** | **0.0073** | **1.028 (1.012–1.044)** | **0.0005** |
| >0 to <0.5 g | 22,646 | 50 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,854 | 52 | 1.17 (0.78–1.75) | 0.4606 | 1.20 (0.80–1.81) | 0.3748 |
| 1.0 to <2.5 g | 12,769 | 46 | 1.13 (0.73–1.74) | 0.5878 | 1.17 (0.75–1.84) | 0.4802 |
| 2.5 to <5 g | 5991 | 23 | 1.39 (0.81–2.38) | 0.2258 | 1.55 (0.89–2.68) | 0.1214 |
| 5 to <10 g | 3112 | 20 | 2.15 (1.21–3.81) | 0.0092 | 2.59 (1.41–4.75) | 0.0021 |
| ≥10 g | 1450 | 14 | 1.92 (1.00–3.70) | 0.0513 | 2.47 (1.25–4.85) | 0.0089 |
| **Pneumonia** | **Cumulative SCS exposure (1g)a** | **24,065** | **1220** | **1.028 (1.021–1.034)** | **<0.0001** | **1.027 (1.021–1.033)** | **<0.0001** |
| >0 to <0.5 g | 22,731 | 246 | Reference |  | Reference |  |
| 0.5 to <1.0 g | 18,773 | 227 | 1.26 (1.04–1.52) | 0.0196 | 1.17 (0.97–1.42) | 0.1063 |
| 1.0 to <2.5 g | 12,613 | 301 | 2.00 (1.65–2.42) | <0.0001 | 1.70 (1.41–2.05) | <0.0001 |
| 2.5 to <5 g | 5811 | 183 | 3.26 (2.62–4.06) | <0.0001 | 2.52 (2.02–3.14) | <0.0001 |
| 5 to <10 g | 2951 | 141 | 4.65 (3.66–5.90) | <0.0001 | 3.36 (2.65–4.26) | <0.0001 |
| ≥10 g | 1342 | 122 | 5.71 (4.42–7.38) | <0.0001 | 3.98 (3.09–5.14) | <0.0001 |

**Notes**: See Online Repository Table E3 for list of confounders.

aFor cumulative SCS exposure, hazard ratios are presented per 1-g increase in cumulative SCS dose as a continuous variable.

bConfounders applied in the adjusted models are summarized in Table E3.

**Abbreviations**: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCS, systemic corticosteroid.

**Table S5** Onset of outcomes in relation to continuous and categorized mean daily systemic corticosteroid (SCS) exposure: SCS cohort

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Npatients** | **Nevents** | **Unadjusted** | **Adjustedb** |
| **Outcome** | **Exposure** | **HR (95% CI)** | **P** | **HR (95% CI)** | **P** |
| **Type 2 diabetes mellitus** | **Mean daily exposure (5 mg/day)a** | **21,808** | **1921** | **1.37 (1.25–1.49)** | **<0.0001** | **1.29 (1.18–1.42)** | **<0.0001** |
| >0 to <0.5 mg/day | 14,226 | 662 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 16,450 | 893 | 2.26 (2.04–2.49) | <0.0001 | 2.10 (1.90–2.32) | <0.0001 |
| 2.5 to <5 mg/day | 5951 | 167 | 3.25 (2.73–3.85) | <0.0001 | 3.17 (2.66–3.78) | <0.0001 |
| 5 to <7.5 mg/day | 4674 | 72 | 4.03(3.15–5.16) | <0.0001 | 4.13 (3.21–5.33) | <0.0001 |
| ≥7.5 mg/day | 4678 | 127 | 8.37 (6.90–10.16) | <0.0001 | 8.60 (7.00–10.58) | <0.0001 |
| **Cardio-/cerebrovascular disease** | **Mean daily exposure (5 mg/day)a** | **22,112** | **1774** | **1.37 (1.25–1.50)** | **<0.0001** | **1.29 (1.18–1.41)** | **<0.0001** |
| >0 to <0.5 mg/day | 14,512 | 510 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 16,701 | 869 | 2.90 (2.60–3.24) | <0.0001 | 2.36 (2.12–2.63) | <0.0001 |
| 2.5 to <5 mg/day | 5930 | 207 | 5.47 (4.64–6.44) | <0.0001 | 3.61 (3.06–4.26) | <0.0001 |
| 5 to <7.5 mg/day | 4667 | 96 | 7.29 (5.85–9.10) | <0.0001 | 4.29 (3.42–5.37) | <0.0001 |
| ≥7.5 mg/day | 4668 | 92 | 7.90 (6.28–9.94) | <0.0001 | 4.75 (3.77–5.99) | <0.0001 |
| **Myocardial infarction** | **Mean daily exposure (5 mg/day)a** | **23,251** | **646** | **1.38 (1.26–1.51)** | **<0.0001** | **1.31 (1.20–1.43)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,391 | 197 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,612 | 298 | 2.58 (2.16–3.08) | <0.0001 | 2.11 (1.77–2.53) | <0.0001 |
| 2.5 to <5 mg/day | 6334 | 78 | 5.24 (4.03–6.81) | <0.0001 | 3.51 (2.69–4.57) | <0.0001 |
| 5 to <7.5 mg/day | 4979 | 35 | 6.43 (4.50–9.17) | <0.0001 | 3.97 (2.78–5.69) | <0.0001 |
| ≥7.5 mg/day | 4963 | 38 | 8.06 (5.71–11.39) | <0.0001 | 4.89 (3.45–6.92) | <0.0001 |
| **Heart failure** | **Mean daily exposure (5 mg/day)a** | **23,570** | **858** | **1.40 (1.28–1.53)** | **<0.0001** | **1.33 (1.22–1.45)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,548 | 199 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,825 | 410 | 3.37 (2.85–3.99) | <0.0001 | 2.69 (2.27–3.19) | <0.0001 |
| 2.5 to <5 mg/day | 6386 | 115 | 7.30 (5.80–9.19) | <0.0001 | 4.70 (3.72–5.93) | <0.0001 |
| 5 to <7.5 mg/day | 5048 | 65 | 11.67 (8.83–15.43) | <0.0001 | 6.34 (4.78–8.41) | <0.0001 |
| ≥7.5 mg/day | 5032 | 69 | 13.78 (10.46–18.15) | <0.0001 | 7.61 (5.75–10.08) | <0.0001 |
| **Cerebrovascular accident** | **Mean daily exposure (5 mg/day)a** | **23,228** | **823** | **1.33 (1.22–1.46)** | **<0.0001** | **1.25 (1.15–1.35)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,328 | 265 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,603 | 427 | 2.81 (2.41–3.27) | <0.0001 | 2.26 (1.94–2.64) | <0.0001 |
| 2.5 to <5 mg/day | 6310 | 76 | 3.86 (2.99–4.99) | <0.0001 | 2.48 (1.91–3.21) | <0.0001 |
| 5 to <7.5 mg/day | 4988 | 33 | 4.76 (3.31–6.85) | <0.0001 | 2.79 (1.93–4.02) | <0.0001 |
| ≥7.5 mg/day | 4960 | 22 | 3.64 (2.35–5.63) | <0.0001 | 2.27 (1.47–3.50) | <0.0001 |
| **Dyslipidemia** | **Mean daily exposure (5 mg/day)a** | **16,903** | **3523** | **1.53 (1.47–1.61)** | **<0.0001** | **1.51 (1.44–1.58)** | **<0.0001** |
| >0 to <0.5 mg/day | 10,625 | 1320 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 12,770 | 1726 | 2.13 (1.99–2.29) | <0.0001 | 1.95 (1.82–2.10) | <0.0001 |
| 2.5 to <5 mg/day | 4686 | 256 | 2.36 (2.06–2.71) | <0.0001 | 2.13 (1.85–2.45) | <0.0001 |
| 5 to <7.5 mg/day | 3631 | 111 | 2.90 (2.38–3.54) | <0.0001 | 2.67 (2.18–3.27) | <0.0001 |
| ≥7.5 mg/day | 3623 | 110 | 3.40 (2.79–4.14) | <0.0001 | 3.17 (2.60–3.87) | <0.0001 |
| **Hypertension** | **Mean daily exposure (5 mg/day)a** | **12,248** | **1626** | **1.29 (1.17–1.41)** | **<0.0001** | **1.21 (1.10–1.32)** | **0.0001** |
| >0 to <0.5 mg/day | 8105 | 665 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 9212 | 756 | 2.05 (1.85–2.28) | <0.0001 | 1.77 (1.59–1.96) | <0.001 |
| 2.5 to <5 mg/day | 3242 | 109 | 2.28 (1.86–2.80) | <0.0001 | 1.78 (1.45–2.20) | <0.001 |
| 5 to <7.5 mg/day | 2510 | 39 | 2.45 (1.76–3.41) | <0.0001 | 1.83 (1.30–2.58) | 0.0006 |
| ≥7.5 mg/day | 2489 | 57 | 4.15 (3.13–5.50) | <0.0001 | 3.02 (2.26–4.06) | <0.001 |
| **Weight gain (BMI increase ≥1 kg/m2)** | **Mean daily exposure (5 mg/day)a** | **12,894** | **7677** | **1.32 (1.22–1.43)** | **<0.0001** | **1.33 (1.23–1.44)** | **<0.0001** |
| >0 to <0.5 mg/day | 5872 | 1889 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 9296 | 4150 | 2.71 (2.58–2.85) | <0.0001 | 2.82 (2.68–2.97) | <0.0001 |
| 2.5 to <5 mg/day | 3216 | 814 | 5.24 (4.78–5.74) | <0.0001 | 5.91 (5.38–6.48) | <0.0001 |
| 5 to <7.5 mg/day | 2736 | 349 | 6.86 (5.99–7.86) | <0.0001 | 8.03 (6.98–9.23) | <0.0001 |
| ≥7.5 mg/day | 2806 | 475 | 8.58 (7.39–9.97) | <0.0001 | 10.54 (9.08–12.24) | <0.0001 |
| **Osteoporosis diagnosis** | **Mean daily exposure (5 mg/day)a** | **23,422** | **964** | **1.43 (1.30–1.57)** | **<0.0001** | **1.39 (1.26–1.52)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,459 | 228 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,741 | 462 | 3.67 (3.13–4.30) | <0.0001 | 3.10 (2.64–3.63) | <0.0001 |
| 2.5 to <5 mg/day | 6371 | 133 | 8.50 (6.86–10.54) | <0.0001 | 6.25 (5.00–7.80) | <0.0001 |
| 5 to <7.5 mg/day | 5033 | 61 | 11.73 (8.82–15.60) | <0.0001 | 8.32 (6.22–11.13) | <0.0001 |
| ≥7.5 mg/day | 5027 | 80 | 19.15 (14.72–24.91) | <0.0001 | 14.72 (11.12–19.49) | <0.0001 |
| **Osteoporosis diagnosis and fracture** | **Mean daily exposure (5 mg/day)a** | **21,251** | **159** | **1.40 (1.27–1.54)** | **<0.0001** | **1.35 (1.22–1.50)** | **<0.0001** |
| >0 to <0.5 mg/day | 14,147 | 38 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 16,085 | 79 | 3.59 (2.43–5.29) | <0.0001 | 2.94 (1.99–4.35) | <0.0001 |
| 2.5 to <5 mg/day | 5826 | 25 | 8.76 (5.29–14.50) | <0.0001 | 6.02 (3.61–10.05) | <0.0001 |
| 5 to <7.5 mg/day | 4596 | 6 | 6.01 (2.54–14.25) | <0.0001 | 3.75 (1.56–9.00) | 0.0031 |
| ≥7.5 mg/day | 4587 | 11 | 13.62 (6.97–26.62) | <0.0001 | 9.79 (4.95–19.36) | <0.0001 |
| **Glaucoma** | **Mean daily exposure (5 mg/day)a** | **23,424** | **433** | **1.36 (1.24–1.49)** | **<0.0001** | **1.29 (1.18–1.41)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,497 | 156 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,775 | 200 | 2.18 (1.77–2.68) | <0.0001 | 1.82 (1.48–2.24) | <0.0001 |
| 2.5 to <5 mg/day | 6389 | 35 | 2.94 (2.04–4.24) | <0.0001 | 2.06 (1.42–2.97) | 0.0001 |
| 5 to <7.5 mg/day | 5036 | 25 | 5.99 (3.91–9.18) | <0.0001 | 3.80 (2.46–5.85) | <0.0001 |
| ≥7.5 mg/day | 5024 | 17 | 4.64 (2.81–7.67) | <0.001 | 3.03 (1.82–5.06) | <0.001 |
| **Cataract** | **Mean daily exposure (5 mg/day)a** | **22,648** | **1736** | **1.38 (1.26–1.51)** | **<0.0001** | **1.29 (1.18–1.42)** | **<0.0001** |
| >0 to <0.5 mg/day | 14,906 | 568 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,111 | 808 | 2.55 (2.29–2.83) | <0.0001 | 2.08 (1.86–2.31) | <0.0001 |
| 2.5 to <5 mg/day | 6126 | 196 | 4.94 (4.20–5.83) | <0.0001 | 3.37 (2.85–3.98) | <0.0001 |
| 5 to <7.5 mg/day | 4832 | 75 | 5.59 (4.38–7.13) | <0.0001 | 3.49 (2.71–4.50) | <0.0001 |
| ≥7.5 mg/day | 4826 | 89 | 7.70 (6.09–9.73) | <0.0001 | 5.32 (4.18–6.77) | <0.0001 |
| **Renal impairment** | **Mean daily exposure (5 mg/day)a** | **20,137** | **3215** | **1.65 (1.57–1.73)** | **<0.0001** | **1.56 (1.50–1.63)** | **<0.0001** |
| >0 to <0.5 mg/day | 12,799 | 994 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 15,161 | 1590 | 2.65 (2.45–2.86) | <0.0001 | 2.14 (1.98–2.32) | <0.0001 |
| 2.5 to <5 mg/day | 5411 | 329 | 4.24 (3.73–4.82) | <0.0001 | 2.98 (2.61–3.41) | <0.0001 |
| 5 to <7.5 mg/day | 4249 | 119 | 4.65 (3.84–5.62) | <0.0001 | 3.15 (2.59–3.83) | <0.0001 |
| ≥7.5 mg/day | 4299 | 183 | 7.57 (6.39–8.98) | <0.0001 | 5.35 (4.49–6.37) | <0.0001 |
| **Peptic ulcer** | **Mean daily exposure (5 mg/day)a** | **23,149** | **219** | **1.39 (1.27–1.53)** | **<0.0001** | **1.35 (1.22–1.49)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,379 | 59 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 17,546 | 124 | 3.44 (2.53–4.69) | <0.0001 | 3.05 (2.24–4.14) | <0.0001 |
| 2.5 to <5 mg/day | 6306 | 17 | 3.62 (2.11–6.19) | <0.0001 | 2.82 (1.64–4.88) | 0.0002 |
| 5 to <7.5 mg/day | 4962 | 7 | 4.26 (1.96–9.26) | <0.0001 | 3.12 (1.42–6.86) | 0.0046 |
| ≥7.5 mg/day | 4940 | 12 | 8.36 (4.55–15.36) | <0.0001 | 6.12 (3.30–11.34) | <0.0001 |
| **Depression/anxiety** | **Mean daily exposure (5 mg/day)a** | **7961** | **1554** | **1.59 (1.51–1.68)** | **<0.0001** | **1.70 (1.61–1.80)** | **<0.0001** |
| >0 to <0.5 mg/day | 4837 | 460 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 5882 | 787 | 2.58 (2.30–2.88) | <0.0001 | 2.86 (2.56–3.21) | <0.0001 |
| 2.5 to <5 mg/day | 2256 | 170 | 3.77 (3.16–4.51) | <0.0001 | 4.76 (3.97–5.71) | <0.0001 |
| 5 to <7.5 mg/day | 1701 | 52 | 2.95 (2.20–3.94) | <0.0001 | 4.05 (3.01–5.47) | <0.0001 |
| ≥7.5 mg/day | 1776 | 85 | 5.14 (4.04–6.53) | <0.0001 | 7.46 (5.82–9.56) | <0.0001 |
| **Sleep apnea** | **Mean daily exposure (5 mg/day)a** | **23,980** | **205** | **1.35 (1.23–1.48)** | **<0.0001** | **1.36 (1.23–1.50)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,883 | 70 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 18,189 | 104 | 2.46 (1.83–3.32) | <0.0001 | 2.54 (1.88–3.42) | <0.0001 |
| 2.5 to <5 mg/day | 6558 | 14 | 2.53 (1.42–4.51) | 0.0016 | 3.12 (1.73–5.61) | 0.0001 |
| 5 to <7.5 mg/day | 5180 | 9 | 4.65 (2.33–9.28) | <0.0001 | 6.34 (3.14–12.83) | <0.0001 |
| ≥7.5 mg/day | 5157 | 8 | 4.77 (2.33–9.73) | <0.0001 | 6.49 (3.14–13.40) | <0.0001 |
| **Pneumonia** | **Mean daily exposure (5 mg/day)a** | **24,065** | **1220** | **1.40 (1.28–1.53)** | **<0.0001** | **1.35 (1.24–1.47)** | **<0.0001** |
| >0 to <0.5 mg/day | 15,827 | 319 | Reference |  | Reference |  |
| 0.5 to <2.5 mg/day | 18,179 | 592 | 3.15 (2.75–3.61) | <0.0001 | 2.79 (2.44–3.20) | <0.0001 |
| 2.5 to <5 mg/day | 6521 | 147 | 5.98 (4.91–7.29) | <0.0001 | 4.72 (3.87–5.75) | <0.0001 |
| 5 to <7.5 mg/day | 5157 | 64 | 7.20 (5.52–9.40) | <0.0001 | 5.30 (4.04–6.95) | <0.0001 |
| ≥7.5 mg/day | 5170 | 98 | 11.95 (9.47–15.08) | <0.0001 | 9.13 (7.22–11.55) | <0.0001 |

**Notes**: See Online Repository Table E3 for list of confounders.

aFor mean daily SCS exposure, hazard ratios are presented per 5-mg/day increase in mean daily SCS exposure as a continuous variable.

bConfounders applied in the adjusted models are summarized in Table E3.

**Abbreviations**: BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCS, systemic corticosteroid.