Annals of Internal Medicine ORIGINAL RESEARCH

Association Between Oral Corticosteroid Bursts and Severe Adverse Events

A Nationwide Population-Based Cohort Study

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Background: Long-term use of oral corticosteroids has known adverse effects, but the risk from brief oral steroid bursts (≤14 days) is largely unknown.

Objective: To examine the associations between steroid bursts and severe adverse events, specifically gastrointestinal (GI) bleeding, sepsis, and heart failure.

Design: Self-controlled case series.

Setting: Entire National Health Insurance Research Database of medical claims records in Taiwan.

Participants: Adults aged 20 to 64 years with continuous enrollment in the National Health Insurance program from 1 January 2013 to 31 December 2015.

Measurements: Incidence rates of severe adverse events in steroid burst users and non–steroid users, as well as incidence rate ratios (IRRs) for severe adverse events within 5 to 30 and 31 to 90 days after initiation of steroid therapy.

Results: Of 15 859 129 adult participants, 2 623 327 who received a single steroid burst were included. The most common indications were skin disorders and respiratory tract infections. The incidence rates per 1000 person-years in steroid bursts were 27.1 (95% CI, 26.7 to 27.5) for GI bleeding, 1.5 (CI, 1.4 to 1.6) for sepsis, and 1.3 (CI, 1.2 to 1.4) for heart failure. Rates of GI bleeding (IRR, 1.80 [CI, 1.75 to 1.84]), sepsis (IRR, 1.99 [CI, 1.70 to 2.32]), and heart failure (IRR, 2.37 [CI, 2.13 to 2.63]) significantly increased within 5 to 30 days after steroid therapy initiation and attenuated during the subsequent 31 to 90 days.

Limitation: Persons younger than 20 years or older than 64 years were not included.

Conclusion: Oral corticosteroid bursts are frequently prescribed in the general adult population in Taiwan. The highest rates of GI bleeding, sepsis, and heart failure occurred within the first month after initiation of steroid therapy.

Primary Funding Source: National Health Research Institutes, Ministry of Science and Technology of Taiwan, Chang Gung Medical Foundation, and Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Ann Intern Med. 2020;173:325-330. doi:10.7326/M20-0432 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 7 July 2020.

Previous studies have demonstrated that long-term treatment with oral corticosteroids is associated with various adverse effects, such as infections, gastrointestinal (GI) bleeding or ulcers, cardiovascular diseases, Cushing syndrome, diabetes and metabolic syndrome, cataracts, glaucoma, and osteoporosis (1–6). Nevertheless, few studies have examined adverse effects associated with steroid bursts, defined as short courses of oral corticosteroids for 14 or fewer days (7–15). Steroid bursts are reportedly associated with GI bleeding and perforation in hospitalized patients (8), as well as increased risks for fracture, venous thromboembolism, and sepsis in adults with diabetes mellitus (9). These adverse effects related to corticosteroid use are caused by impairment of innate and acquired immunity, alterations of calcium metabolism, cardiovascular homeostasis, fluid retention, and various endocrine effects (16, 17). In consideration of its well-known adverse effects, most clinical practice guidelines caution against long-term steroid use unless medically necessary (18).

Clinical guidelines recommend steroid bursts for treatment of inflammatory diseases, such as asthma, inflammatory bowel disease, and rheumatoid arthritis (19, 20). A recent clinical practice guideline for the management of sore throat suggests that corticosteroids increase the likelihood of pain relief after 48 hours of treatment (18). This recommendation may encourage physicians to prescribe steroid bursts to patients with acute sore throats who have acute respiratory tract infections. Furthermore, in a population-based study, Waljee and colleagues (7) documented that the most common use of steroid bursts is for upper respiratory tract infections, suggesting that more patients receive steroids in the real world than recommended. A growing concern about the use of steroid bursts has emerged (21).

Evidence regarding the potential risks of treatment with steroid bursts in real life is scarce. To address questions regarding the risk for adverse events related to steroid bursts, we did a nationwide population-based study in Taiwan to quantify the effect of steroid bursts on risk for GI bleeding, sepsis, and heart failure. The objective of this study was to examine the associations between steroid bursts and these 3 severe adverse events.

METHODS

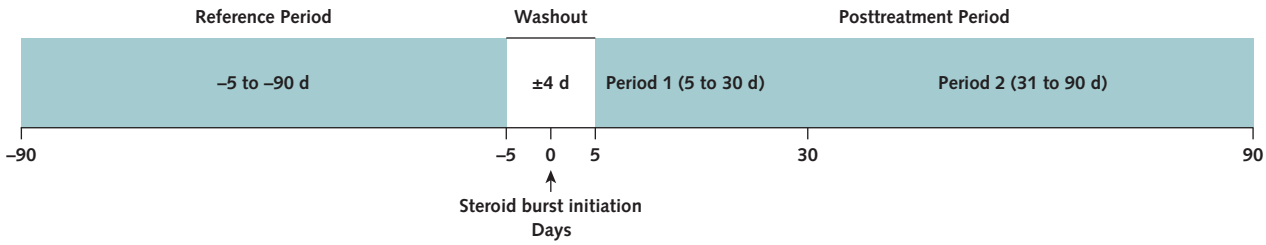
Data Source

The data used in this study were derived from deidentified records of inpatient and outpatient medical

See also:

Editorial comment 390

Figure 1. Time frame of self-controlled case series design.



The figure indicates 3 observation periods (reference period before initiation of steroid therapy and 2 posttreatment periods after initiation of steroid therapy).

claims from the entire National Health Insurance Research Database in Taiwan (**Appendix**, available at Annals.org). The Institutional Review Board of the National Health Research Institutes of Taiwan approved the study protocol, and informed consent was waived because all data were encrypted.

Study Design and Populations

We used the self-controlled case series study design to estimate risks for 3 severe adverse events (GI bleeding, sepsis, and heart failure) after initiation of a steroid burst. One major advantage of this design is that each participant serves as his or her own control because of unmeasured, time-invariant factors that are automatically adjusted for in the subsequent analyses (22). In this study, we compared risks during the period before steroid treatment (reference period: 5 to 90 days before initiation of a steroid burst) versus those during 2 posttreatment periods (5 to 30 and 31 to 90 days after initiation) among participants with a prescription for a single steroid burst (**Figure 1**). We used a conservative approach and modified the self-controlled case series design to include a washout period so that adverse events within a 4-day window before and after steroid initiation were excluded because they might be caused by other factors.

The study period was 1 January 2013 to 31 December 2015. We identified participants with continuous enrollment in the National Health Insurance program during and for at least 1 year before the study period. We determined their steroid use, baseline demographic characteristics, and comorbid conditions in the previous year. Inclusion criteria were age 20 to 64 years in 2013, no prescription for systemic or topical corticosteroids before 2013, and no diagnosis of the 3 severe adverse events investigated in this study before 2013. These adverse events were identified on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification, codes (**Appendix Table 1**, available at Annals.org) (7, 13, 23). We considered participants to have had an adverse event caused by a steroid burst if they had at least 1 prescription for a steroid burst and 1 of the investigated severe adverse events during the study period.

Exposures and Outcomes

The exposure was use of steroid bursts based on prescriptions. A steroid burst was defined as use of oral corticosteroids for 14 or fewer days. The duration of drug supply (total number of prescription days) of oral corticosteroids was summed using all consecutive days with a steroid prescription from the first prescription through all prescriptions in the follow-up period. To standardize doses, all corticosteroid doses were converted into a daily dose according to prednisone equivalents (**Appendix Table 2**, available at Annals.org).

We evaluated 3 severe adverse events—GI bleeding, sepsis, and heart failure—as outcomes. In addition, we identified episodes of syncope as a negative control outcome. All outcomes were identified on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification, codes provided in **Appendix Table 1**.

Statistical Analysis

We calculated incidence rates per 1000 person-years of the 3 severe adverse events for participants prescribed steroid bursts and those who were not prescribed steroids (**Appendix**). We estimated incidence rate ratios (IRRs) and compared incidence rates of the severe adverse events during the steroid pretreatment period versus during each steroid posttreatment period. Analyses were done using conditional fixed-effects Poisson regression. Time-varying factors were adjusted for acute conditions and concomitant medication use for each severe adverse event and the negative control event (**Appendix**). Sensitivity analyses were done to investigate the 3 assumptions of self-controlled case series (events do not affect subsequent exposure, events should not influence observation periods, and consecutive events are independent) and to evaluate potential unmeasured confounding. Subgroup analyses were done to evaluate the effect of comorbidity by classifying participants into 2 groups (Charlson Comorbidity Index score [24] equal to 0 and score greater than 0) and to assess the differential effect of steroid burst prescription by medical specialty (dermatology, otolaryngology, family practice, internal medicine, and pediatrics).

The **Appendix** shows details of the E-value measurement for assessing potential unmeasured confounding (25) and the statistical models and corresponding statistical codes. All analyses were done using R software, version 3.6.3 (R Project for Statistical Computing), and SAS, version 9.2 for Windows (SAS Institute).

Role of the Funding Source

This work was supported by grants from the National Health Research Institutes, Ministry of Science and Technology of Taiwan, Chang Gung Medical Foundation, and Eunice Kennedy Shriver National Institute of Child Health and Human Development. The funders had no role in study design, data collection or analysis, preparation of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

Baseline Characteristics of the Study Participants

The population consisted of 15 859 129 persons aged 20 to 64 years, of whom 25% (4 015 384) received at least 1 steroid burst during the 3-year study period. Following selection criteria, we included 2 623 327 participants with a prescription for a single steroid burst. Table 1 shows the baseline characteristics of the participants who received steroid bursts; 85% had a Charlson Comorbidity Index score equal to 0.

Table 2 shows that the top 10 indications for steroid bursts were skin disorders (contact dermatitis and eczema, urticaria, and pruritus and related conditions) and upper and lower respiratory tract infections (acute upper respiratory tract infections, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis). These conditions were responsible for 59% of steroid bursts. Dermatology, otolaryngology, family practice, internal medicine, and pediatrics were the 5 medical specialties most often associated with these prescriptions, accounting for 88% of steroid burst prescriptions (Table 2).

Incidence Rates of Severe Adverse Events

Table 3 presents the incidence rates of GI bleeding, sepsis, and heart failure in participants who were prescribed steroid bursts compared with those who were not prescribed steroids. The incidence rates per 1000 person-years among participants prescribed steroid bursts were 27.1 (95% CI, 26.7 to 27.5) for GI bleeding, 1.5 (CI, 1.4 to 1.6) for sepsis, and 1.3 (CI, 1.2 to 1.4) for heart failure, which were higher than those for non–steroid users (16.8 [CI, 16.7 to 16.8], 1.4 [CI, 1.4 to 1.4], and 0.4 [CI, 0.4 to 0.4], respectively). We observed rate differences of 10.3 (CI, 9.9 to 10.7) for GI bleeding, 0.1 (CI, 0.01 to 0.2) for sepsis, and 1.0 (CI, 0.9 to 1.1) for heart failure per 1000 person-years between the 2 groups (Table 3).

Self-controlled Case Series

We observed that IRRs for GI bleeding, sepsis, and heart failure across 2 periods after steroid treatment were significantly higher than those in the reference period (Figure 2). For all 3 severe adverse events, the IRRs decreased over time. Figure 2 shows that IRRs within 5 to 30 days after initiation of steroid bursts were 1.80 (CI, 1.75 to 1.84) for GI bleeding, 1.99 (CI, 1.70 to 2.32) for sepsis, and 2.37 (CI, 2.13 to 2.63) for heart failure. Significant increases were seen within 31 to 90 days after initiation of steroid bursts, although the increases were smaller than in the period of 5 to 30 days. The results in Appendix Table 3 (available at Annals.org) indicate no relation between steroid bursts and risk for syncope, a negative control outcome not affected by steroid use.

Table 1. Characteristics of Steroid Burst Users

Characteristic	Steroid Burst Users (*n* = 2 623 327)
Mean age (SD), *y*	38.0 (12.6)
Female sex, *n (%)*	1 450 514 (55.3)
Charlson Comorbidity Index score, *n (%)**	
0	2 217 540 (84.5)
1	183 857 (7.0)
2	116 023 (4.4)
3	62 014 (2.4)
4	28 888 (1.1)
≥5	15 005 (0.6)
Steroid use	
Median dosage (IQR), *mg/d*	10 (2–15)
Median duration (IQR), *d*	3 (3–3)
Incidence rate per 1000 person-years (95% CI)	
GI bleeding	27.1 (26.7–27.5)
Sepsis	1.5 (1.4–1.6)
Heart failure	1.3 (1.2–1.4)

GI = gastrointestinal; IQR = interquartile range.
* Diseases used for computing Charlson Comorbidity Index score are from 1 y before the index date.

Sensitivity Analyses

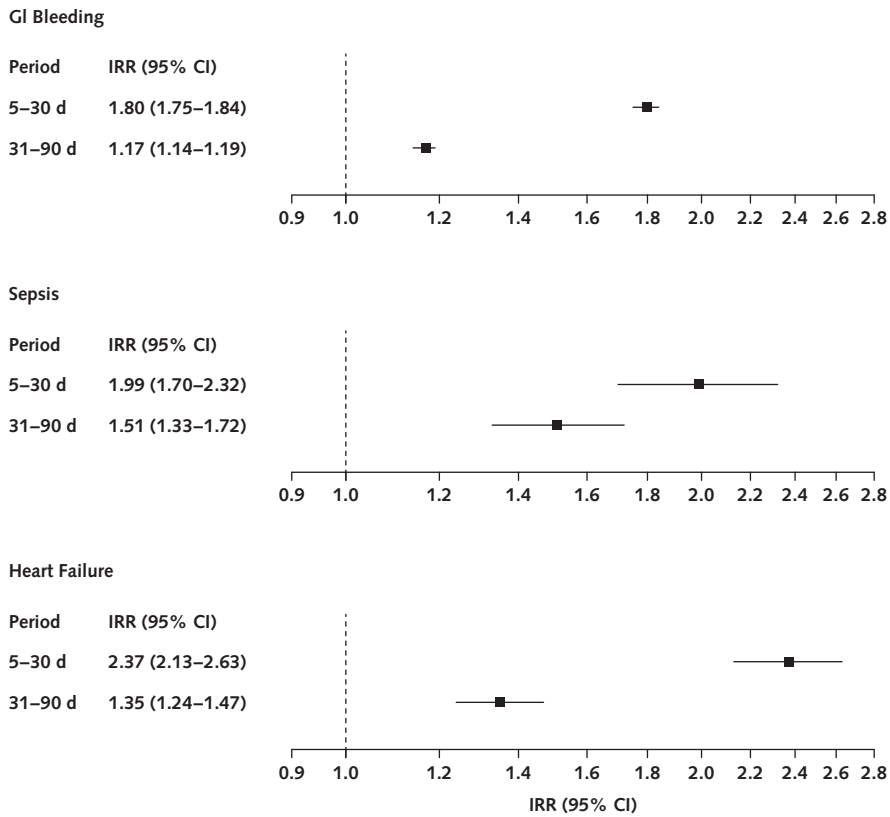
We did sensitivity analyses to address the 3 assumptions of the self-controlled case series analysis (26). For the first assumption, the results in the Appendix Figure (available at Annals.org) show that most se-

Table 2. Top 10 Diagnoses and Top 5 Physician Specialties Associated With Steroid Bursts

Characteristic	Steroid Bursts, *n (%)*
ICD-9-CM code (diagnosis)	
692.xx (contact dermatitis and other eczema)	410 518 (15.6)
465.xx (acute upper respiratory tract infections of multiple or unspecified sites)	248 035 (9.5)
708.xx (urticaria)	221 851 (8.5)
466.xx (acute bronchitis and bronchiolitis)	130 982 (5.0)
461.xx (acute sinusitis)	123 595 (4.7)
463.xx (acute tonsillitis)	99 291 (3.8)
698.xx (pruritus and related conditions)	95 768 (3.7)
460.xx (acute nasopharyngitis [common cold])	71 067 (2.7)
464.xx (acute laryngitis and tracheitis)	55 873 (2.1)
462.xx (acute pharyngitis)	54 272 (2.1)
Physician specialty	
Dermatology	808 162 (30.8)
Otolaryngology	537 546 (20.5)
Family practice	482 196 (18.4)
Internal medicine	294 477 (11.2)
Pediatrics	164 884 (6.3)

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Figure 2. IRRs for GI bleeding, sepsis, and heart failure in 2 posttreatment periods (5–30 d and 31–90 d) associated with steroid bursts.



GI = gastrointestinal; IRR = incidence rate ratio.

vere adverse events occurred shortly after steroid burst initiation and suggest unlikely contraindication. We next investigated the second assumption by excluding patients who died as a result of each severe adverse event (Appendix Table 4, available at Annals.org). The results were similar to those in Figure 2. Instead of accounting for consecutive events (the third assumption), we included only the first event in the models and found that the results in Appendix Table 4 were similar to those in Figure 2, except for the period of 31 to 90 days after steroid burst initiation in GI bleeding.

Appendix Table 5 (available at Annals.org) shows the E-values for the point estimate and lower limit of the CI for GI bleeding, sepsis, and heart failure, separately. This analysis indicated no substantial unmeasured confounding (E-values for the point estimates [lower limits of the CI] were 3.00 [2.90], 3.39 [2.79], and 4.17 [3.68], respectively, for 5 to 30 days after steroid initiation and 1.62 [1.54], 2.39 [1.99], and 2.04 [1.79], respectively, for 31 to 90 days after steroid initiation).

Subgroup Analyses to Check for Effect Modification

Results were similar between participants with Charlson Comorbidity Index scores equal to 0 and those with scores greater than 0, but IRRs were smaller in the group with scores greater than 0 (Appendix Table 6, available at Annals.org). Likewise, similar results

Table 3. Incidence Rates of GI Bleeding, Sepsis, and Heart Failure in Participants With and Without Steroid Bursts

Adverse Event	Steroid Bursts			Non-Steroid Users			Rate Difference per 1000 Person-Years (95% CI)
	Cases, *n*	Person-Years, *n*	Incidence Rate per 1000 Person-Years (95% CI)	Cases, *n*	Person-Years, *n*	Incidence Rate per 1000 Person-Years (95% CI)	
GI bleeding	17 004	628 100	27.1 (26.7–27.5)	458 914	27 360 062	16.8 (16.7–16.8)	10.3 (9.9–10.7)
Sepsis	969	637 622	1.5 (1.4–1.6)	39 512	28 023 082	1.4 (1.4–1.4)	0.1 (0.01–0.2)
Heart failure	846	637 751	1.3 (1.2–1.4)	10 195	28 053 806	0.4 (0.4–0.4)	1.0 (0.9–1.1)

GI = gastrointestinal.

across medical specialties are shown in **Appendix Table 7** (available at Annals.org).

DISCUSSION

This study shows several key findings. First, steroid bursts are commonly prescribed in the general adult population in Taiwan, because 25% of adults received steroid bursts during the 3-year study period. Second, the most common indications for steroid bursts are skin disorders and respiratory tract infections. Third, the highest risk for GI bleeding, sepsis, and heart failure occurs within the first month after receipt of the steroid burst, and this risk is attenuated during the subsequent 31 to 90 days. Our findings are important for physicians and guideline developers because short-term use of oral corticosteroids is common and the real-world safety of this approach remains unclear.

In this national longitudinal cohort of 15.9 million Taiwanese adults, the incidence of prescriptions for steroid bursts was approximately 8% per year. In a longitudinal analysis of 1.5 million U.S. adults (7), the approximate incidence of short-term use of oral corticosteroids (<30 days) was 7%, and short-term oral corticosteroids were most often prescribed for upper respiratory tract infections. Our findings are consistent with those findings (7) and show that steroid bursts can lead to increased risks for severe adverse events.

Our study used the entire national database of medical insurance claims in an Asian population; hence, potential for recall or selection bias is limited. The large sample size provides an opportunity to examine short-term adverse effects of steroid bursts. We did various sensitivity analyses to investigate whether the 3 main assumptions of self-controlled case series are met (26, 27); the results show that the self-controlled case series design we used does not generally violate these assumptions.

Nevertheless, several limitations deserve mention. First, data on disease severity and major lifestyle factors, such as alcohol use, smoking, and body mass index, are not available in the National Health Insurance Research Database. Because these factors are static, the effect can be eliminated using the self-controlled case series design. In addition, the observed risk ratios for the 3 severe adverse events within the first month after steroid initiation are 1.80, 1.99, and 2.37, whereas their E-values are 3.00, 3.39, and 4.17. Because the E-values are greater than known risk factors, unmeasured confounding cannot explain away the reported effects of steroid bursts on the 3 severe adverse events. Second, the reported IRRs tended to be smaller in participants with comorbid illnesses than in those without, indicating that physicians might avoid administering steroids to patients with comorbid conditions. Third, the adverse effects of steroid bursts might be underestimated because we did not include vulnerable populations, such as elderly (≥65 years) and younger (<20 years) persons. Fourth, the study relies on prescription data, so noncompliance is a potential confounder. However, it is likely independent of subsequent GI bleeding, sepsis, or heart failure and would attenuate the reported risk estimates toward the null.

Our study suggests that treatment with oral corticosteroid bursts is frequently prescribed in adults for common conditions, including skin disorders and respiratory tract infections. Prescriptions for steroid bursts are associated with a 1.8- to 2.4-fold increased risk for GI bleeding, sepsis, and heart failure within the first month after initiation of drug therapy. Physicians who consider prescribing steroid bursts should weigh the benefits against the risks for rare but potentially serious adverse events. Additional studies, such as prospective studies or clinical trials, are needed to determine optimal use of corticosteroids through an adverse event monitoring program for improving patient safety.

From Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan (T.Y.); Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan (Y.H., S.T., H.T.); National Cheng-Kung University, Tainan, Taiwan (S.C.); and Harvard Pilgrim Health Care Institute, Harvard Medical School, and Boston Children's Hospital, Boston, Massachusetts (A.C.W.).

Note: Drs. Yao and Tsai had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer: This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance of the Ministry of Health and Welfare, Taiwan. The interpretation and conclusions contained in this article do not represent those of the Bureau of National Health Insurance or the Ministry of Health and Welfare.

Acknowledgment: The authors thank staff members in the Data Science Center of the Ministry of Health and Welfare, Taiwan, for their data management and maintenance.

Grant Support: By grant PH-109-PP-08 from the National Health Research Institutes of Taiwan (Dr. Tsai), grants MOST 107-2314-B-400-031-MY3 (Dr. Tsai) and MOST 106-2314-B-182-051-MY3 (Dr. Yao) from the Ministry of Science and Technology of Taiwan, grant CMRPG3J0121 from the Chang Gung Medical Foundation (Dr. Yao), and grant 1R01HD085993-01 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (Dr. Wu).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-0432.

Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code:* See the **Appendix** (available at Annals.org).

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Critical revision of the article for important intellectual content: T.C. Yao, A.C. Wu, H.J. Tsai.
Final approval of the article: T.C. Yao, Y.W. Huang, S.M. Chang, S.Y. Tsai, A.C. Wu, H.J. Tsai.
Statistical expertise: S.M. Chang, S.Y. Tsai.
Obtaining of funding: T.C. Yao, A.C. Wu, H.J. Tsai.
Administrative, technical, or logistic support: S.Y. Tsai.
Collection and assembly of data: Y.W. Huang, H.J. Tsai.

Appendix: Additional Methods

Time-Varying Covariates

The time-varying factors–specifically, acute conditions (that is, contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis)–for the 3 severe adverse events were adjusted for in the models. Likewise, the adjusted concomitant medication use for each severe adverse event was provided as follows: nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and proton-pump inhibitors for GI bleeding; NSAIDs, aspirin, and systemic immunosuppressive agents for sepsis; and NSAIDs, hormone replacement therapy, bronchodilators, antidiabetic drugs, cardiac glycosides, antihypertensive drugs, nitrates, and antiplatelet drugs for heart failure.

Statistical Analysis

Incidence Rate of Severe Adverse Events

We first defined participants with at least 1 prescription for a steroid burst (≤14 days) during the study period as steroid burst users. Non–steroid users were defined as those without any prescription record for corticosteroids in 2012 and during the entire study period. We calculated overall incidence rates per 1000 person-years of the 3 severe adverse events we investigated (GI bleeding, sepsis, and heart failure) for steroid burst users and non–steroid users.

E-Values

We computed E-values using the methodology proposed by VanderWeele and Ding (25). Specifically, the E-values quantify what the risk ratio would need to be for unmeasured confounders to explain away the observed associations of the 3 severe adverse events in the present study.

Statistical Models and R Code

Following the construction of Whitaker and colleagues (28), we denote Y_{ij} as the number of events occurring for individual i in risk period j. In particular, we assume that the random variable Y_{ij} follows a nonhomogeneous Poisson process with incidence rate λ_{ij} m_{ij}, where m_{ij} records the days spent by individual i in risk period j and λ_{ij} is the incidence rate per day. Following the work of Farrington (29) and Whitaker and colleagues (28), we assume that:

$$\log(\lambda_{ik}) = \phi_i + \beta_{ij}$$

Here, ϕ_i consists of time-invariant covariates, such as sex, education level, and short-term economic status, for the ith individual, which will be canceled out later when the conditional likelihood is applied. Thus, we no longer discuss this component. Next, β_{ij} represents the effect of the jth risk period, which is of major interest along with the sum of specific time-varying effects, such as concomitant medication use (for example, bronchodilator use) or acute conditions like eczema. Finally, the log-conditional likelihood has the form:

$$l(\alpha, \beta) \quad = \quad \Sigma_{ij}\, y_{ij} \log\left[\frac{m_{ix}\exp\{\beta_{ij}\}}{\Sigma_r\, m_{ir}\exp\{\beta_{ir}\}}\right]$$

In this study, only 1 event occurred for each individual. Thus, this model reduces to a conditional logistic regression model that can be fitted using the clogit command in R (30). R codes used for the 3 investigated severe adverse events (GI bleeding, sepsis, and heart failure) and episodes of syncope, a negative control outcome, are as follows:

```
mod.gi <- clogit(sum_gi ~ as.factor(stata_period) + nsaid + aspirin + ppi + eczema + uri + urticaria + bronchitis + sinusitis + tonsillitis + pruritus + nasopharyngitis + laryngitis + pharyngitis + strata(id_stata) + offset(loginterval), method="breslow", data = gi)

mod.sepsis <- clogit(sum_sepsis ~ as.factor(stata_period) + nsaid + aspirin + sisa + eczema + uri + urticaria + bronchitis + sinusitis + tonsillitis + pruritus + nasopharyngitis + laryngitis + pharyngitis + strata(id_stata) + offset(loginterval), method="breslow", data = sepsis)

mod.heart <- clogit(sum_gi ~ as.factor(stata_period) + nsaid + hrt + broncho + antidiabetic + cardiac + ht + nitrates + antiplatelet + eczema + uri + urticaria + bronchitis + sinusitis + tonsillitis + pruritus + nasopharyngitis + laryngitis + pharyngitis + strata(id_stata) + offset(loginterval), method="breslow", data = heart)

mod.syncope <- clogit(sum_ syncope ~ as.factor(stata_period) + nsaid + aspirin + eczema + uri + urticaria + bronchitis + sinusitis + tonsillitis + pruritus + nasopharyngitis + laryngitis + pharyngitis + strata(id_stata) + offset(loginterval), method="breslow", data = syncope)
```

Appendix Table 1. ICD-9-CM Codes of 3 Severe Adverse Events and the Negative Control Outcome

Diagnosis	ICD-9-CM Code
Adverse events	
GI bleeding	531.xx, 532.xx, 533.xx, 534.xx, 578.xx, 556.xx, 530.2x, 569.3x, 456.0x, 530.4x, 569.85, 569.86, 537.84, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 530.82, 537.83, 562.02, 562.12, 562.13, 569.82, 569.83, 456.20
Sepsis	038.xx, 790.7x, 785.52, 995.91, 995.92
Heart failure	428.xx
Negative control outcome	
Syncope	780.2

GI = gastrointestinal; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Appendix Table 2. Equivalent Doses of Corticosteroids Investigated in This Study

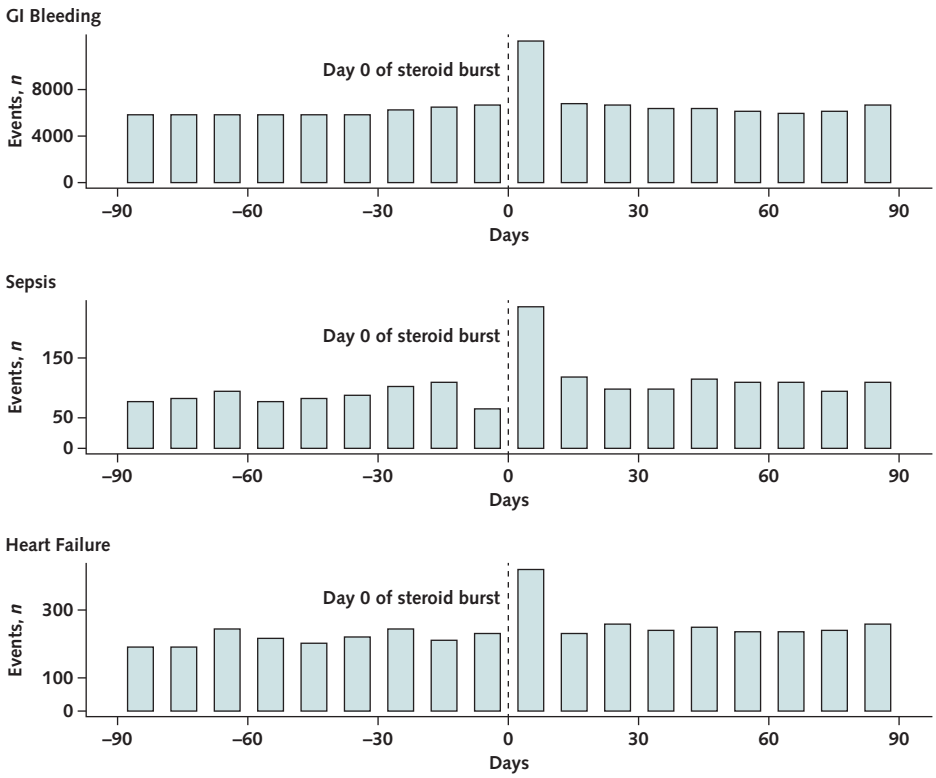
Corticosteroid	Equivalent Dose
Betamethasone	0.6 mg
Dexamethasone	0.75 mg
Methylprednisolone	4 mg
Triamcinolone	4 mg
Prednisone	5 mg
Prednisolone	5 mg
Hydrocortisone	20 mg
Cortisone	25 mg

Appendix Table 3. Incidence Rate Ratios for Syncope (Negative Control Outcome) Associated With Steroid Bursts

Adverse Event	Patients, *n*	Median Daily Dosage (IQR), *mg/d*	Median Duration of Steroid Use (IQR), *d*	Incidence Rate Ratio (95% CI)*	
				5–30 Days	31–90 Days
Syncope	840	10 (2–15)	3 (3–5)	1.00 (0.82–1.22)	0.91 (0.78–1.06)

IQR = interquartile range.
* Common covariates (acute conditions) adjusted for in the model: contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis.

Appendix Figure. Interval between steroid bursts and 3 severe adverse events in study participants.



Assumption: events do not affect subsequent exposure. GI = gastrointestinal.

Appendix Table 4. Sensitivity Analyses of Investigating 2 Self-controlled Case Series Assumptions

Adverse Event	Patients, *n*	Incidence Rate Ratio (95% CI)*	
		5–30 Days	31–90 Days
Assumption: events should not influence observation periods			
GI bleeding	62 761	1.80 (1.75–1.84)	1.17 (1.14–1.19)
Sepsis	1398	1.86 (1.58–2.18)	1.50 (1.31–1.70)
Heart failure	3447	2.36 (2.12–2.62)	1.35 (1.24–1.47)
Assumption: consecutive events are independent			
GI bleeding	22 682	1.90 (1.85–1.95)	0.82 (0.80–0.84)
Sepsis	1147	2.04 (1.74–2.39)	1.42 (1.25–1.62)
Heart failure	873	2.53 (2.27–2.81)	1.18 (1.09–1.29)

GI = gastrointestinal.
* Common covariates (acute conditions) adjusted for in 3 adverse events: contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis. GI bleeding was adjusted for nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and proton-pump inhibitors, and common covariates; sepsis was adjusted for NSAIDs, aspirin, systemic immunosuppressive agents, and common covariates; and heart failure was adjusted for NSAIDs, hormone replacement therapy, bronchodilators, antidiabetic drugs, cardiac glycosides, antihypertensive drugs, nitrates, antiplatelet drugs, and common covariates.

Appendix Table 5. Incidence Rate Ratios and E-Values for Severe Adverse Events Associated With Steroid Bursts

Adverse Event	Patients, *n*	Median Daily Dosage (IQR), *mg/d*	Median Duration of Steroid Use (IQR), *d*	5–30 Days*		31–90 Days*	
				Incidence Rate Ratio (95% CI)	E-Value for Point Estimate (E-Value for Lower Limit of CI)	Incidence Rate Ratio (95% CI)	E-Value for Point Estimate (E-Value for Lower Limit of CI)
GI bleeding	62 818	10 (2–15)	3 (3–3)	1.80 (1.75–1.84)	3.00 (2.90)	1.17 (1.14–1.19)	1.62 (1.54)
Sepsis	1429	10 (2–15)	3 (3–3)	1.99 (1.70–2.32)	3.39 (2.79)	1.51 (1.33–1.72)	2.39 (1.99)
Heart failure	3468	10 (2–15)	3 (3–3)	2.37 (2.13–2.62)	4.17 (3.68)	1.35 (1.24–1.47)	2.04 (1.79)

GI = gastrointestinal; IQR = interquartile range.
* Common covariates (acute conditions) adjusted for in 3 adverse events: contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis. GI bleeding was adjusted for nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and proton-pump inhibitors, and common covariates; sepsis was adjusted for NSAIDs, aspirin, systemic immunosuppressive agents, and common covariates; and heart failure was adjusted for NSAIDs, hormone replacement therapy, bronchodilators, antidiabetic drugs, cardiac glycosides, antihypertensive drugs, nitrates, antiplatelet drugs, and common covariates.

Appendix Table 6. Subgroup Analyses of Patients With CCIS Equal to 0 or Greater Than 0

Adverse Event	Patients, *n*	Incidence Rate Ratio (95% CI)*	
		5–30 Days	31–90 Days
Patients with CCIS = 0			
GI bleeding	19 173	5.30 (5.04–5.58)	3.74 (3.57–3.92)
Sepsis	611	2.79 (2.17–3.58)	2.20 (1.78–2.72)
Heart failure	1578	2.58 (2.19–2.99)	1.31 (1.15–1.49)
Patients with CCIS > 0			
GI bleeding	43 645	1.24 (1.20–1.27)	0.74 (0.73–0.76)
Sepsis	818	1.55 (1.25–1.90)	1.16 (0.98–1.37)
Heart failure	1890	2.16 (1.86–2.50)	1.36 (1.22–1.52)

CCIS = Charlson Comorbidity Index score; GI = gastrointestinal.
* Common covariates (acute conditions) adjusted for in 3 adverse events: contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis. GI bleeding was adjusted for nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and proton-pump inhibitors, and common covariates; sepsis was adjusted for NSAIDs, aspirin, systemic immunosuppressive agents, and common covariates; and heart failure was adjusted for NSAIDs, hormone replacement therapy, bronchodilators, antidiabetic drugs, cardiac glycosides, antihypertensive drugs, nitrates, antiplatelet drugs, and common covariates.

Appendix Table 7. Subgroup Analyses of Steroid Bursts Prescribed by Medical Specialties

Adverse Event	Patients, *n*	Incidence Rate Ratio (95% CI)*	
		5–30 Days	31–90 Days
Dermatology			
GI bleeding	15 624	1.76 (1.68–1.85)	1.20 (1.15–1.24)
Sepsis	356	1.45 (1.04–2.02)	1.38 (1.06–1.79)
Heart failure	682	1.91 (1.48–2.45)	1.41 (1.17–1.71)
Otolaryngology			
GI bleeding	11 904	1.80 (1.71–1.91)	1.17 (1.12–1.23)
Sepsis	212	3.02 (1.98–4.61)	2.32 (1.62–3.31)
Heart failure	477	2.36 (1.76–3.17)	1.57 (1.25–1.96)
Family practice			
GI bleeding	11 763	1.90 (1.80–2.01)	1.21 (1.16–1.27)
Sepsis	261	2.15 (1.52–3.03)	1.27 (0.93–1.74)
Heart failure	773	2.78 (2.21–3.49)	1.46 (1.22–1.75)
Internal medicine			
GI bleeding	8207	1.78 (1.67–1.90)	1.16 (1.10–1.23)
Sepsis	187	2.53 (1.62–3.97)	1.92 (1.30–2.83)
Heart failure	479	2.73 (2.06–3.61)	1.38 (1.09–1.74)
Pediatrics			
GI bleeding	2675	1.74 (1.54–1.96)	1.20 (1.09–1.33)
Sepsis	50	1.91 (0.82–4.42)	1.10 (0.49–2.47)
Heart failure	154	2.81 (1.71–4.63)	1.64 (1.09–2.46)
Others			
GI bleeding	12 645	1.76 (1.67–1.86)	1.09 (1.04–1.14)
Sepsis	363	1.64 (1.18–2.27)	1.37 (1.06–1.77)
Heart failure	903	2.08 (1.68–2.57)	1.08 (0.92–1.28)

GI = gastrointestinal.
* Common covariates (acute conditions) adjusted for in 3 adverse events: contact dermatitis and eczema, acute upper respiratory tract infections, urticaria, acute bronchitis and bronchiolitis, acute sinusitis, acute tonsillitis, pruritus, acute nasopharyngitis, acute laryngitis and tracheitis, and acute pharyngitis. GI bleeding was adjusted for nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and proton-pump inhibitors, and common covariates; sepsis was adjusted for NSAIDs, aspirin, systemic immunosuppressive agents, and common covariates; and heart failure was adjusted for NSAIDs, hormone replacement therapy, bronchodilators, antidiabetic drugs, cardiac glycosides, antihypertensive drugs, nitrates, antiplatelet drugs, and common covariates.

Web-Only References

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