

Supplementary Online Materials

Section 1

ICD-9 codes for infection

Block	Code	Diagnosis
1. Infections and parasitic diseases	001-139	
6. Diseases of the nervous system and sense organs	320-324	Meningitis, encephalitis, myelitis and encephalomyelitis
7. Diseases of the circulatory system	421	Acute and subacute endocarditis
8. Diseases of the respiratory system	460-466 480-488	Acute respiratory infections Pneumonia and influenza
10. Disorders of the genitourinary tract	590 595	Infections of kidney Cystitis
12. Diseases of the skin and subcutaneous tissues	680-4, 686	Infections of the skin and subcutaneous tissues
13. Diseases of the musculoskeletal system and connective tissue	711.0 711.9 730	Pyogenic arthritis Unspecified infective arthritis Osteomyelitis, periostitis and other infections involving bone

Section 2

Methods

Dealing with complex prescription patterns

More than one GC prescription could be dispensed on the same day. In these circumstances, the doses of the two prescriptions were summed for the period when the prescriptions overlapped. Where a second prescription was issued prior to the end of the first prescription, we assumed the second prescription overwrote the first and disregarded any prescribed GC from the first prescription after the dispensation date of the second.

Additional conventional models

Four additional conventional models were fitted. Models 12 and 13 accounted for the GC exposure over the entire past 3 years, by using a series of 7 separate variables, each corresponding to a specific (mutually exclusive) time interval (last 3 months, 3-6 months ago, 6-12 months ago, ..., 30-36 months ago). The difference between the two models is in the way the period-specific exposure is represented. Model 13 represented the exposure in each time interval by the average dose over this specific interval (similar to models 6 and 7 that used a single value of the average dose in, respectively, either last 30 or last 90 days). In contrast, model 12 ignored the doses and duration of use and included a series of 7 binary indicators of 'any use' within a given time window (similar to models 2 and 3). Because of concerns about the plausibility of the effect of GC exposures that occurred more than 1 year ago, we also fitted models 14 and 15 that were similar to, respectively, models 12 and 13, but restricted the exposure time window to 1 year before the index data. Accordingly,

each of models 14 and 15 used only 3 variables, corresponding to: last 3 months, 3-6 months ago, and 6-12 months ago.

Selection of the final weighted cumulative dose (WCD) model

All weight functions were *a priori* constrained to decay smoothly to zero at the end of the exposure time window, implying that drug doses taken before the corresponding time had no impact on the current risk.

For each exposure time window, we fitted three alternative spline-based constrained WCD models of gradually increasing flexibility and complexity with, respectively, 1, 2 or 3 interior knots, corresponding to 3, 4 or 5 degrees of freedom (df). The final flexible WCD model was selected from the 18 possible models (three levels of flexibility for each of the six exposure time windows) based on the Akaike Information Criterion (AIC) to penalize for the increased df of more complex models.

When calculating the AIC of the final flexible WCD model, we incorporated an additional penalty, equivalent to 2 additional df to account for *a posteriori* choice of the best-fitting final model among WCD models with alternative (i) exposure time windows and (ii) complexity of the estimated spline function. For example, if the 2-knot model was selected, then its df were calculated by adding 2 to the 4 df of the corresponding constrained cubic spline, i.e. were set at 6. This conservative approach implied that a bigger improvement in the fit to data (reduction in the model's deviance) was required for a flexible WCD model to yield better, i.e. lower, AIC than any of the conventional 1-df models.

Based on the final WCD model, we tested the significance of the adjusted association between the cumulative weighted GC dose and risk of serious infection using the likelihood ratio test with the appropriate degrees of freedom.

Section 3

To emphasize the statistical significance of the differences in AIC, shown in Table 2 of the manuscript, we may use an approximate analogy to standard likelihood ratio tests (LRT), which are employed to assess the significance of the improvement in model predictions (as measured by a decrease in model's deviance) due to adding extra parameters, i.e. extra df. As explained in section 2 above, our final WCD model used 3 df, i.e. 2 df more than the conventional models 1-10, each of which used a single (1 df) parameter to estimate the exposure effect. Thus, assuming the models were nested (which is only approximately correct), the differences in the deviance of conventional versus WCD model could be approximately tested with a 2-df chi-square LRT. When the differences in AIC (shown in Table 2) were converted into differences in deviance, the WCD model was found to reduce the deviance by at least 31 points, compared to any of the conventional models. Thus, the corresponding LRT test statistics will yield values of 31 or higher, which correspond to $p < 0.0001$ for a 2-df chi-square test (notice that the critical value for $\alpha = 0.0001$ for a 2-df chi-square test is 18.4). Thus, even accounting for the fact that some of the conventional models are not exactly nested within the WCD model, we can safely consider these differences as 'statistically very significant'.

Results

Extension to Table 2

Model	Among cases (% or mean)	Among controls (% or	OR (95% CI) **	OR for 5mg increase (95% CI)	AIC***	AIC – AIC of the WCD model
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	*	mean) *				
<i>Flexible model incorporating weighting by recency of treatment</i>						
(11) Final WCD (3-year with 3 degrees of freedom)	****	****	****	****	6059.8	0 (minimum AIC)
<i>GC exposure over the last 3 years, divided into seven mutually exclusive time periods</i>						
(12) Any use in last:						
- 0-3 months	58.6%	34.7%	1.72 (1.42, 2.10)	---	6082.2	22.4
- 3-6 months	53.1%	31.6%	1.37 (1.08, 1.74)			
- 6-12 months	51.7%	32.7%	0.96 (0.76, 1.22)			
- 12-18 months	44.4%	28.5%	1.07 (0.84, 1.35)			
- 18-24 months	38.6%	25.3%	1.04 (0.81, 1.34)			
- 24-30 months	32.7%	21.9%	0.87 (0.67, 1.12)			
-30-36 months	29.1%	18.8%	1.16 (0.92, 1.47)			
(13) Average dose in last:						
- 0-3 months	7.1mg PEQ	5.4mg PEQ	1.06 (1.04, 1.08)	1.32 (1.21, 1.44)	6065.5	5.7
- 3-6 months	6.6mg PEQ	5.5mg PEQ	1.02 (1.00, 1.04)	1.10 (0.99, 1.22)		

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- 6-12 months	5.8mg PEQ	4.8mg PEQ	1.02 (0.99, 1.05)	1.11 (0.96, 1.27)		
- 12-18 months	5.8mg PEQ	4.8mg PEQ	1.00 (0.97, 1.04)	1.02 (0.88, 1.19)		
- 18-24 months	5.5mg PEQ	4.6mg PEQ	1.02 (0.99, 1.06)	1.11 (0.94, 1.32)		
- 24-30 months	5.5mg PEQ	4.6mg PEQ	1.03 (0.99, 1.07)	1.14 (0.94, 1.37)		
-30-36 months	5.2mg PEQ	4.6mg PEQ	0.99 (0.96, 1.02)	0.95 (0.81, 1.12)		
<i>GC exposure over the last 1 year, divided into three mutually exclusive time periods</i>						
(14) Any use in last:						
- 0-3 months	58.6%	34.7%	1.74 (1.43, 2.11)	---	6076.7	16.9
- 3-6 months	53.1%	31.6%	1.39 (1.09, 1.76)			
- 6-12 months	51.7%	32.7%	1.01 (0.83, 1.24)			
(15) Average dose in last:						
- 0-3 months	7.1mg PEQ	5.4mg PEQ	1.06 (1.04, 1.08)	1.33 (1.23, 1.45)	6068.4	8.6
- 3-6 months	6.6mg PEQ	5.5mg PEQ	1.02 (1.00, 1.04)	1.11 (1.00, 1.23)		
- 6-12 months	5.8mg PEQ	4.8mg PEQ	1.04 (1.02, 1.06)	1.22 (1.08, 1.36)		

**** Because the (non-parametric) WCD model estimates exposure effect using flexible spline

functions, the estimated effect cannot be summarized by a single parameter. See Figure 1 for the estimated weight function