Reviewer's report

Title: Proton Pump Inhibitors and the risk of pneumonia: a comparison of cohort and self-controlled case series designs

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Reviewer: Michele Jonsson Funk

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Major Compulsory Revisions

1. Time varying confounding in the SCCS
I am concerned about the presence of time-varying characteristics other than age and calendar time that are not controlled in the SCCS analysis. It seems possible (if not probable) that diagnoses, concurrent medications, aged-care status, and recent hospitalization would also be time-varying and could differ within individuals leading to residual confounding. If any of the time-varying covariates from the cohort study are risk factors for hospitalized pneumonia, then these should also be controlled for in the SCCS.

It would be helpful to examine and report the average follow-up time in the population. If the follow-up time is relatively short then this may be less of a concern.

It seems that age should be included in the SCCS not as ‘age at cohort entry’ (a fixed quantity for each patient) but as a time-varying characteristic (see Table 2 footnote and Methods, last paragraph, 3rd sentence from the end).

2. Pre-exposure period time
This aspect of the analysis is confusing. My understanding is that the pre-exposure time period(s) should ‘go back’ far enough that there is no association between prior hospitalization for pneumonia and subsequent drug initiation. It does not appear that going back 60 days is sufficient to remove this association.

The reason for identifying these pre-exposure periods and removing them from the baseline time should be made more explicit for the reader.

3. Short term (transient) vs. long term use of PPIs
One of the requirements for the use of the SCCS is that the exposure is transient. In order to support the case for using this study design, it would be helpful for the authors to present data on the patterns of use. In this case, the use of PPIs is presumably a mix of short term (transient) and long term use. I am somewhat concerned that much of the transient use may be driven by prior hospitalization, and that removing pre-exposure person-time (see #2 above) to prevent instances of reverse causality (not confounding by indication, as the
authors state) will result in primarily long term use in the remaining sample.

4. Mortality resulting from hospitalized pneumonia

Another assumption of the SCCS study design is that the occurrence of the outcome (hospitalization due to pneumonia, in this case) does not censor the observation period. In instances where the pneumonia was fatal, it clearly would do so – which the authors note. They report that 12% of cases died as a result, which appears to be too large of a fraction to dismiss.

The authors should examine the extent to which their results are sensitive to these instances – for instance, by excluding those cases in which the outcome was fatal. If so, they should implement the adjusted method of Farrington et al (JASA 2011), although this approach assumes that the exposure does not appreciably affect death except through the specific outcome under study (death due to pneumonia). The authors would likely need to consider the risk of death due to GI bleed, and the extent to which the use of PPIs would affect this outcome.


5. Comparison between SCCS and cohort study

I would also ask the authors to clarify the questions that are being answered by the two study designs. Specifically, what effect is being estimated (e.g., the average treatment effect, intent to treat, as treated effect of treatment in the treated)? Is the target population the same? Do these two study designs answer the same question? If not, then contrasting / comparing the effect estimates should be done with special care.

In order to allow the reader to assess the extent to which the cohort and SCCS approaches have potential for confounding, I would suggest adding a table (usually ‘Table 1’) in which the distributions of important covariates are reported in the cohort population and in the SCCS population, stratified by exposure status. (In the cohort, the groups are made up of individuals whereas in the SCCS sample the observations would be at the level of person-time.) To the same end, I would like to suggest that the authors report the crude (unadjusted) effect estimates in both study designs.

In other studies where results from a SCCS and cohort study are compared, the authors have argued that there is concern about confounding by some unmeasured, time invariant factor X and that the SCCS would address this important (potential) source of bias. The rationale for comparing the results of the SCCS and the cohort study in this case should be more explicit. There are several examples in the literature of SCCS vs cohort study, so this alone does not appear to be an adequate justification.

6. Re-classifying exposed person time during grace period
In the 3rd paragraph of the methods section, the authors describe the method by which they estimate the duration of exposure using a grace period. My concern is that only those cases who survive to the end of the grace period will have 2/3rds of that period reclassified as ‘unexposed’ time if there are no prescriptions by the end of it. The change from ‘exposed’ to ‘unexposed’ to happen at the end of the grace period in order to avoid the introduction of immortal person time. I suggest that the authors consider shortening the grace period if they are concerned that the majority of this person time is unexposed.

7. Completeness of PPI data
Are all dispensed PPIs included in the database used for this analysis? Specifically, I am curious about those dispensed in hospital or possibly over-the-counter. (These would not be included in many of the data sources typically used for pharmacoepidemiology research, and thus, it would be helpful to clarify whether or not these are included in this study.)

8. General Comments
The overall sense of the manuscript is that it is too brief and that more detail is needed to make it clear what has been done and why. I appreciate that word limits often lead to this dilemma. I would encourage the authors to provide additional details in an appendix if necessary to stay within the word limits. Particularly given that this journal has a methods focus, sufficient detail is needed to make it clear how this (somewhat novel) study design is implemented and the rationale for specific aspects of the design (such as the pre-exposure periods). A figure would be most helpful to convey the design of the SCCS.

Discretionary Revisions
9. Please consider including the absolute rates in Table 2 between the columns for ‘person-years’ and the adjusted rate ratio.

Minor Essential Revisions (not for publication)
10. I believe that the punctuation should appear immediately before the superscripted reference numbers.
11. In table 1, there is a missing space between “1.55” and “(1.26, 1.91)”.
12. In the first paragraph of the discussion, next to last line: ‘a odd ratio’ should be ‘an odds ratio’.
13. Also in the first paragraph of the discussion, the last sentence is an incomplete sentence.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**

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