Author's response to reviews

Title: Design of cohort studies in chronic diseases using routinely collected databases when a prescription is used as surrogate outcome

Authors:

Sara Lodi (sal@ctu.mrc.ac.uk)
James Carpenter (james.carpenter@lshtm.ac.uk)
Peter Egger (peter.j.egger@gsk.com)
Stephen Evans (stephen.evans@lshtm.ac.uk)

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Author's response to reviews: see over
Dear Editor,

On behalf of all the co-authors, I am pleased to resubmit the revised manuscript entitled “Design of cohort studies in chronic diseases using routinely collected databases when a prescription is used as surrogate outcome” for consideration by the BMC Medical Research Methodology following the peer review.

Thank you for the helpful comments. We note that while the first referee found the study well structured and easy to understand, with excellent use of language, the second referee found it difficult to follow. We have striven to clarify the manuscript, and carefully address all the issues raised by the Editor and the reviewers. Please find below our responses. In particular, we have modified the manuscript stressing its methodological purpose and avoiding overlap with a previous clinical paper [Lodi et al, ref 8] published in the British Journal of Clinical Pharmacology.

I look forward to hearing from you.

Yours faithfully

Sara Lodi

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Reviewer #1:
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GENERAL
The authors of the report aimed at comparing two different cohort study approaches in analyses that use a prescription as surrogate outcome. The principal idea of the research question is relevant for the actors in the pharmaepidemiology and the clinical scenario is feasible taking into account the clinical conducts at the time of the study. They use a typical database for pharmaepi, based a health care insurance claims. Both the exposure and the outcome are clearly defined. Special thanks to the informative figures. Methods used are appropriate, and the conclusions made are based on the study. The text is well structured and easy to understand. The language is excellent

Thank you

MINOR
1. I’m confused to find a kind of a replication of a previous study presented as part of the current one. How does this comply with the journal policy? More specifically: the first part of the results are published previously (reference number 8) but this is not acknowledged clearly enough in the methods (2.1. Cohort study for…), although the reference can be found three times in the results section. As the aim of the study is comparison between different approaches it is obvious that all the options have to be presented clearly for the readers. Would it be possible to describe ‘the cohort study for time to change in the inflammatory status’ in the Discussion? However, if the current
structure of the manuscript complies with the journal policy, could the results of the Cox model presented in the table 1 be also referenced by the number 8 as well as the chapter 2.1.

Authors’ reply.
As you and the Editor point out, the first part of the results have been published by the same group in the British Journal of Clinical Pharmacology [ref 8]. In that paper our focus was the scientific question, ie the anti-inflammatory effects of statins in RA patients, and we presented the results using our preferred method, but with no presentation of alternative methods or discussion of the pros and cons. Thus, this manuscript has a clear, distinct, methodological focus.

Nevertheless, we have revised the manuscript to further minimise overlap between the two papers, and to strengthen and clarify the methodological message.

First, as you suggest, we now cite ref 8 in the methods section and cite it only once in the results section (instead of three times).

Second, we modified the methods section, shortening the description of the first study design (page 5 beginning section 2.1), and directing the reader to ref 8 for a more detailed description of the method. “This study design … same group [8]”. We also shortened the text in the next paragraph.

Third, we modified the discussion section to reduce the emphasis on the clinical question regarding the anti-inflammatory effects of statins in RA. In particular, we deleted a paragraph in the conclusion section “The increasing evidence… anti-inflammatory effects of statins” together with the sentence “While all gave similar conclusions… RA flare-ups”.

Fourth, as you suggest, ref 8 has been cited in Table 1.

We have not followed up your suggestion of not referring to the time-to-event study until the discussion, as we think this would make the paper very difficult to read, especially since we conclude the time-to-event approach is superior to the matched cohort approach.

Given these changes, we think we fully comply with the BMC policy that “The article is original, has not been formally published in any other peer-reviewed journal, is not under consideration by any other journal and does not infringe any existing copyright or any other third party rights”.

2. In this study, the assumption of the start of anti-inflammatory effect of statin therapy after the first 90 days is based on one small study in which simvastatin 20 mg and
fluvasatin 40 mg were analyzed. However, while defining the statin exposure as 90 days or more, the authors do not consider the statin dosage. During the study years, the most frequently used statin dosages were lower than nowadays, e.g. the strength of the most popular simvastatin preparations was 10 mg. And, if an assumption of one tablet per day -regimen is applied, the 10 mg may not equal to 20 mg causing anti-inflammatory effects. Therefore, the negative results of the anti-inflammatory effect of statin therapy in patients with rheumatoid arthritis may be due to strong assumptions made in the current study. From the clinical point of view, the research questions may still remain unanswered. Please, consider comments about this issue in the discussion.

Authors’ reply.

We agree this is a relevant point, and we reported a number of sensitivity analyses around the exposure in the clinical paper [Lodi et al, ref 8]. Since our current focus is methodology, we modified the text by adding a sentence referring to ref 8 at the end of the first paragraph of the discussion.

3. The heading the report reminds more of a review article than an analytic study. Could it be more specific?

Authors’ reply. Thanks for this suggestion. We have changed the title of the manuscript from “Cohort studies in chronic diseases using routinely collected databases when a prescription is used as surrogate outcome” to “Design of cohort studies in chronic diseases using routinely collected databases when a prescription is used as surrogate outcome”.

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Reviewer #2:  
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The authors aimed to examine several methods of estimating drug effectiveness from routinely collected pharma data. This is an important issue that attracted growing attention with the increasing number of computerized medical database available for pharmacoepidemiological analyses. It is unclear, however, whether it is a methodological or observational paper. For methodological paper, the authors provide no satisfactory generalization for their point other than an empirical finding on very specific case. For observational paper, the study suffers major limitations.

Authors’ reply. This is a methodological paper, whose aim is to describe the pros and cons of two contrasting designs when using large, routinely collected databases for estimating the secondary effects of drug exposure on the prognosis of a chronic disease.
We regret that this was not as clear as it could have been, and have revised the manuscript to emphasise the focus, referring to our previous paper [Lodi et al, ref 8] where there is a full discussion of the disease specific issues. To this end, we have deleted the last paragraph of the Discussion section, page 11 “The increasing evidence ... anti-inflammatory effects of statins”. We have also deleted the sentence in the Conclusion section, pag 11 “While all gave similar conclusions... RA flare-ups”. We have added a sentence in page 10 “We illustrated how a drug prescription... chronic disease”. In response to your second point, in the discussion we have highlighted six general points, each of which are illustrated using our study. We have revised the text of the discussion to make this clear.

The paper is very difficult to follow. It has many unnecessary repetitions as well as missing information of important issues.

Authors’ reply. We regret this, and have revised the manuscript to improve readability and clarity.

For example, while figure 1 presents a trivial presentation of censoring in the unmatched cohort analysis, the authors provide no table on this important analysis. Other figures and tables are not much more helpful either. What is t in figure 2?, why exit from cohort occurs after event cessation in figure 2(1)? In tables A1 and A2, How come OS s is both a dependent variable and a covarite? And more importantly, it is unclear how the results prove the superiority of one analytic method over the other ?

Authors’ reply. We have redrawn both Figures 1 and 2. Exit from cohort means loss of follow-up from the LifeLink database. We have clarified this in the Figures 1 and 2. The results of the analyses referred to are in Table 1 and more detailed results are described in the text and in Tables 1 and 2 in Lodi et al [ref 8]. This is stated in the first paragraph of the Result section (page 7).

In Table A1 and A2 the covariate OS means “use of OS before the index date”. This has been clarified in the Methods section, page 7, penultimate paragraph and in the captions in Tables A1 and A2.

As mentioned above, we have modified the discussion to clarify our argument that awkward statistical and epidemiological issues which beset the analyst with the matched cohort study approach are avoided with the time-to-event approach. To underline this, we have added the following sentence on page 10 “These methodological considerations... by a surrogate prescription”.

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