Author’s response to reviews

Title: Use of potentially inappropriate medication and polypharmacy in older adults: a repeated cross-sectional study

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Author’s response to reviews:

Karlskrona 30st August 2019
To the editors
BMC Geriatrics

Dear editors,

Thank you for considering our manuscript entitled: Use of potentially inappropriate medication and polypharmacy in older adults: a repeated cross-sectional study after revision for evaluation of publication in BMC Geriatrics.

We appreciate the reviewers’ feedback and the thoughtful suggestions of ways to strengthen the paper further. We have attempted to address the comments in full and enclose a point-by-point list of our responses in the uploaded file below. Please note that the changes in the revised manuscript are marked by Track Changes.

This manuscript has neither been published nor is currently under consideration for publication by any other journal. None of the authors have any conflicts of interest regarding the publication of this manuscript. All authors have read the final revised version of the manuscript and agree on its publication.

Yours sincerely,
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Editor Comments:

BMC Geriatrics operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Marci Dearing, PharmD (Reviewer 1): USE OF POTENTIALLY INAPPROPRIATE MEDICATION AND POLYPHARMACY IN ELDERLY: A REPEATED CROSS-SECTIONAL STUDY

Polypharmacy and PIMs and the risk of using these in older adults is a significant healthcare problem. With this cross-sectional study I am left wondering what it adds to the existing literature (refs 18-20) or how it is different from what has already been done/shown. Also, what are the implications of your results? Please see my specific comments below.

Answer: Thank you for identifying that we have been unclear in our aim of the study and what this study adds to the existing knowledge. To our knowledge, this is the first study where the prevalence of PIM has been analysed in different strata according to the number of chronic conditions and polypharmacy when individual based data has been used. We have now clarified this in the introduction and in the discussion.

Major comments:

An English language revision of the whole article would be beneficial. One example: Page 3, line 15-17: 'Except for drug-drug interactions that can increase the risk of the prescribing cascade, drug-diagnose interaction or contraindication can lead to an increased risk.' I am not following this sentence?

Answer: Thank you for identifying that we needed to clarify this sentence, which has been rewritten. We have also done a new English language revision on the manuscript.

Page 4, line 1: 'side effects and ADRs' - this is confusing as these terms can be used interchangeably. The terms side effects, ADRs, and ADEs are used frequently throughout the introduction. I would suggest either using a single term throughout and/or provide a definition for how you are using these terms.

Answer: Thank you for identifying that we need to use one term. We do agree. We have now updated the manuscript and only used ADE.

Page 4, line 6-18: 'The aim of this descriptive study was to analyse the prevalence of PIM in an elderly population and in different strata of the variables age, gender, number of chronic conditions and polypharmacy and how that prevalence changed over time.' To describe the impact of the national
campaign to improve care? It appears that the stated aims aren't a true reflection of the study and it seems you are looking at the change that occurred based on the national campaign - but this isn't stated explicitly in the aim or the discussion.

Answer: Thank you for identifying this. We have now clarified the setting and aim of the study.

Page 4, line 17-18: 'different strata of the variables age, gender, number of chronic conditions and polypharmacy and how that prevalence changed over time.' There was not really any reasons given as to why you looked at these variables or how things changed over time.

Answer: Thank you for identifying that the reasons for the choice of variables needed to be stated. We have now stated the reason for the choices of variables.

Page 5, line 6-7: why are these specific time periods chosen?
Answer: The national camping was between 2010 and 2014. The specific time points for collecting data in this study were chosen due to possibility of access to data. 1st January 2011 was the first month Blekinge county had data on dispensed medications. Therefore, the 31st of March was chosen so we would have a three-month period to estimate the medication list. 31st December 2013 was chosen because there was a change in the way data was encrypted in 2014. So, to ensure we had correct data we chose 31st December 2013.

Page 5, line 19-20: 'Therefore a three month period was used to construct a medicine list on both regularly used and as-needed medicines.' This time period seems short and may miss those who are just slightly non-compliant or may hoard medications. This is mentioned in the limitations section but it says from 'index date of hospitalisation and three months back' (page 17, lines 14-15). This is the first time hospitalization is mentioned in relation to your methods and requires clarification. Also, what are the implications of missing medication information?

Answer: Thank you for identifying a mistyping on page 17 lines 14-15. We have now corrected that sentence to: By constructing a medicine list on collected prescribed drugs from the inclusion date for the cohorts and three months back, it allowed us to determine, as closely as possible, to what medications the patient was using.

This is a validated method to identify medication use from pharmacy registry data [1]. The time period is based on the fact that in Sweden patients can only collect medications for a three-month period at a time within the high cost threshold. After 2/3 of that period has passed they can collect their medication again within the high cost threshold for medicines. This system makes it harder to hoard drugs. A wider time period could result in an overestimation of the drug use while this time period can underestimate the use of medication. However, as stated before and now clarified in the method and in the limitation section, this is a validated method for identifying medication use from pharmacy records/registers.


Page 6, lines 7-18: The description of how PIMs were classified is a little unclear. Mainly it is not clear how you identified PIMs and how this related to their medical condition.

Answer: Thank you for identifying that we needed to clarify how PIM was identified. We have now clarified how we have defined PIM in this study both in the introduction and in the method (e.g. medications that are potentially inappropriate regardless of the individual’s medical conditions, in older adults).
Page 7, lines 5-6: 'Polypharmacy is known to increase the risk of ADR and therefore we wanted to analyse polypharmacy in the different strata.' I'm not sure I understand the reason.
Answer: Thank you identifying that we needed to clarify the reasons. We have now tried to explain the reasons better.

Page 9, table 1: I would suggest that actual p values be given, not just 'ns' or '<0.05'. The same applies for the rest of the tables.
Answer: Thank you for the suggestion. We have now written all the p-values in the tables.

Page 9, line 3: regarding use of PIM, did the authors look at whether the change in PIM use was driven by changes in specific drug classes - this would be interesting, suggest adding.
Answer: Thank you for that suggestion, that would be an interesting study to do as a follow-up to this one. However, in this study we have focused on PIM as a whole group.

Page 15, line 5-6: 'The positive trend of the reduced prevalence of PIM users found in this study corresponds with results from other reports in Sweden during the same time period.' If this was previously done in the same country covering similar time periods, what does this study add?
Answer: Thank you for pointing out that we needed to clarify what this study added. We have now done that on page 15 row 6-8.

Page 15, lines 10-11: 'Therefore, quality indicators that aim to decrease the use of PIM can lead to an improvement of quality in drug treatment in elderly.' this comment needs much greater qualification/context - impact of this/national campaign, what the campaign involved, any other influences as to why this change might have occurred?
Answer: Thank you for pointing out that we needed to put this in context. We have now rewritten and tried to improve the statement and the context.

Page 15, lines 15-16: 'However, the use of medication did increase; just not polypharmacy in comparison with the rest of the population.' Could you hypothesis why there way as change in MM but not PP? Also given that PIMs decreased, how could these all be related/explained - does this truly reflect better use of medications in older adults in Sweden?
Answer: Thank you for the question. There has been a great focus on drug treatment in older adults, on the risk with PIM and also polypharmacy. A hypothesis is that prescribers are more hesitant to prescribe medications to older adults and recommend non pharmacological treatments instead. This decrease in PIM use does not totally reflect better use of medications in older adults in Sweden. What it does reflect is that it is possible in a relatively short time period to change a prescribing pattern. This is what we have tried to clarify in the discussion.

Page 15/16, lines 17-25, 1-5: this whole paragraph is background information and not linked with the findings of the study.
Answer: Thank you for identifying paragraphs that made our introduction better. We have now moved and rewritten these paragraphs to a better place in the introduction Page 3.

Page 16, lines 13-22: Again, how does this relate to the findings of your study - how do these small interventions compare to the national campaign?
Answer: Thank you this point. The discussion is now updated to better reflect the findings in the study. This paragraph has been removed to make room for a new paragraph about new findings from a new analysis as suggested by another reviewer.
Minor comments:

The term 'elderly' is generally not recommended anymore as it has been associated with stigma against older adults, I suggest using an alternative term (such as older adults).

Answer: Thank you for that suggestion, we have now changed elderly to older adults.

Elisa Zengarini (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

1) The authors may more consistently explain the clinical relevance and consequences of polypharmacy and PIM as well as of ADE/ADR whose they are risk factors
Answer: Thank you for this point. We have now updated the introduction to better explain this.

2) The meaning of the sentence "Except for drug-drug interactions that can increase the risk of the prescribing cascade, drug-diagnose interaction or contraindication can lead to an increased risk" is not enough clear.
Answer: Thank you identifying that we needed to clarify this sentence. We have now rewritten the sentence.

3) The authors may better explain the choice of consider two "different" cohort (2011 and 2013) with 78% individuals present in both cohort. Indeed, the logistic regression included only individuals present in both cohort. Maybe the descriptive analyses could be also realized in the cohort 2011 and 2013 composed of the same individuals.
Answer: Thank you for that suggestion. If we had used only the individuals present in both cohorts the results would have been affected by the fact the population had aged. Using two cohorts gives us use of PIM according to the different variables used in the study. It would have been harder to draw any conclusions if we had used the same individuals since the population ages and thus also increases the number of chronic conditions.

4) The reduction of PIM between 2011 and 2013 is an interesting and clinically relevant result. But which factors/variables significantly influence the odd of having less PIM in 2013?
Answer: Thank you that suggestion, we have now analysed this and the results are implemented in the manuscript on page 14 and 16 in the result section. And in the discussion on page

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