Author’s response to reviews

Title: Potentially inappropriate prescribing among older people in the United Kingdom

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Author’s response to reviews:

We thank the reviewers for their helpful comments and have outlined a point-by-point response below

Reviewer 1

Major Compulsory Revisions
1. Concerning the cross-regional comparison of PIP (objectives and methods).
   It’s not currently clear to me why this is an objective of the study and then written into the methods section. Rather, it seems like this is just something that should go in the discussion section. The purpose of a discussion section is to compare the findings of a given study to prior studies – this is not typically presented as a study objective. I am guessing that some of the data presented in Table 2 concerning the NI and ROI sites is novel to this paper, and has not previously been reported, which is then the justification for the way this paper is structured. But I have to make that inference based on looking at the overlapping authors of the current study and the prior referenced studies in the bibliography (#16 and 17). If it’s the case that this truly is new data being presented in Table 2 for these other sites, then this should be more plainly stated in the methods. Conversely, if this is just comparing the findings from the UK to previously reported data from other studies, then this paper should be restructured so that these comparisons are made (more appropriately) in the discussion section only.

Response: We have modified the manuscript according to the reviewer’s request.
so that the cross-region comparison is addressed only in the discussion and is not described as an objective of the study. Instead we have emphasized the novelty of having been able to apply a larger proportion of the STOPP criteria to the CPRD data compared to previous studies which lacked clinical data.

2. Results, Main Outcomes, final paragraph. This type of analysis is generally presented in a table, first with unadjusted associations in one column and then the adjusted associations in a second column. First, it’s far more efficient. Second, the text is missing vital information. For example, an OR was only reported for the 70-74 age group, but not the others. Also, the lack of any unadjusted/bivariate findings makes the adjusted results difficult to interpret.

Response: This has been completed; please see table 3

3. Related to the prior comment, it would make much more sense to create multiple categories for number of drugs rather than a simple dichotomy for “polypharmacy”. Where to put the cut-point with a simple dichotomy is subject to debate and is not consistently agreed upon in the literature. Based on the chosen analysis strategy, there is no reason not to include at least 4 groups as was used for age. It would be more informative and less subject to criticism.

Response: Polypharmacy is not normally distributed and therefore when attempting to categorise the polypharmacy variable, many of the categories were unbalanced leading to inflated ORs for e.g. 8, 9 and >10 drugs- see table below. Therefore, we decided to use the ever/never polypharmacy variable as it provided more balanced categories.

<table>
<thead>
<tr>
<th>Number of study subjects in each category Adjusted* OR for PIP</th>
<th>Polypharmacy (categorical variable 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( number of repeat medications)</td>
<td></td>
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<tr>
<td>0-3</td>
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<td>4</td>
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<td>8</td>
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<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Polypharmacy (categorical variable 2)</td>
<td>(number of repeat medications)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>0-3 (ref)</td>
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<tr>
<td>4-6</td>
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<tr>
<td>7-9</td>
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</tbody>
</table>
4. Discussion, p16, para 3. In discussing the potential explanations for differences between the UK and NI/ROI findings, I was surprised that there was no mention of potential differences in how patients were selected to constitute the denominators. How do we know that the criteria used to select patients into the denominator across all studies were similar? I don’t recall seeing a discussion of the selection criteria used to generate the NI/ROI data. Such selection criteria can have a major impact on measured rates of drug use. The differences across populations in this study could be due to differences in how the denominator populations were selected and not the nominator prescribing rates, per se.

Response: All patients in these populations aged 70 years or older who obtained
prescriptions from their primary care providers were included in the studies. Those who did not receive prescriptions would not have been included but then they would not have been at risk for PIP.

Minor Essential Revisions
1. Please be consistent in the use of significant figures – this was very distracting. Sometimes there were no decimal points used (e.g. 28%) and then two decimals (e.g. 28.14%) used – even in the same sentence. Two decimal places is overkill. There is no need for that level of precision.
Response: All figures have been rounded to one decimal place

2. Introduction. I did not see any justification for why looking at correlates of PIP is interesting. Moreover, any theoretical basis/model for why certain variables were selected to examine. As the authors stated, most of the relationships with these variables have been previously reported (and in my mind, ad nauseam), and the authors have not made an argument for why it was important they do this analysis. How does this fill a vital gap in the literature?
Response: In this study we examined age, sex, and polypharmacy as correlates of PIP as we had done so in the previous studies and so for comparison purposes, it seemed relevant. The other studies lacked clinical data and so, with the additional clinical data in CPRD, we were able to assess the relationship between comorbidities and PIP as there is increasing interest in how best to manage a number of chronic diseases with a number (and perhaps an increasing number) of medicines in a patient, while minimizing iatrogenic disease.

3. Discussion, p14 (cross-regional comparisons). Were any of the cross-regional comparisons adjusted for age, sex and other factors presented in the correlates analysis? If no, then why not? What was the point of looking at correlates if they were going to be used as adjustment variables? If the authors have hands-on access to these other populations they should do similar analyses and make adjustments if they think this is meaningful.
Response: We do not have access to the raw data from the other previous studies referred to in the cross regional comparison and so no adjustments of the cross regional comparisons could be made. However, as we have amended the manuscript so that the cross regional comparison element is now used for discursive purposes only, we feel this is not necessary.

4. Consider combining Tables 1 and 2 for brevity – or shortening them both to present only pertinent differences or combined across the major category
groupings (e.g. cardiovascular system). Having 2 massive tables is cumbersome and the way they are organized seems to distract the reader from the major important findings.

Response: Table 1 is now table 2 and the old table 2 has been deleted as the focus is no longer on the cross regional comparison. Two further tables (1&3) have been added as suggested by the reviewers. We feel table 2 (previously table 1) cannot be shortened as it is important to get an overall perspective of the types of prescribing that are driving PIP in the UK.

Discretionary Revisions
1. Introduction, final paragraph. Consider writing more clear objective statements. For example, what do the authors mean by “to ‘investigate’ PIP in older people”? This statement doesn’t really say anything and these sentences are really important to the overall framing of the paper. For example, I suspect the authors really meant to say something like “to estimate the prevalence of PIP in older people” or something along those lines.

Response: This has been amended.

2. Consider adding a typical “Table 1” which provides the demographic/clinical characteristics of the study sample/population. And if this study truly has novel data from the NI/ROI samples, this data should really be presented for all 3 patient groups.

Response: This has been completed for the UK study. Please see table 1.

Reviewer 2
Comment 1
Polypharmacy was defined as the use of 4 or more repeated medications. This definition is not supported by any references. In the scientific literature, polypharmacy is usually defined as the use of 5 or more medications. The authors should support their choice to use a cut-point of 4 by providing some references or describing the reasons for adopting such a cut-point.

Response: A recent Cochrane review undertaken by some of the authors on this current study (1) described polypharmacy as “the ingestion of four or more medications” and so this is why this cut-point was chosen. A reference has been added to support this.

Comment 2
It should be useful and interesting to know the demographic and clinical
characteristics of the study sample and which characteristics other than polypharmacy are related to inappropriate drug use. I think you could add a table about the general information of sample (percentage: sex, age, diseases).

Response: This has been completed. Please see table 1

Minor Essential Revisions
Comment 1
The authors should underline in the title which are the three neighboring regions.
Response: Based on the other reviewer’s suggestions we have modified the manuscript and the title so that the cross region comparison aspect is not included

References