Author’s response to reviews

Title: Asthma and treatment with inhaled corticosteroids: associations with hospitalisations with pneumonia

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Author’s response to reviews:

Dear Editor

Thank you for you and your reviewer’s comments on our manuscript: PULM-D-19-00186 "Asthma and treatment with inhaled corticosteroids: associations with hospitalisations with pneumonia"
Pierre Ernst (Reviewer 1):

Asthma (and severity by number of symptoms) defined by questionnaire 1999-2000 Outcome pneumonia hospitalization any position (would have preferred primary position) Principal finding is that pneumonia more common in asthma.
A: Yes we agree that the principal finding is that pneumonia is more common in asthma and this is also reported as the main finding in the first paragraph of the discussion.

Only 19 asthma patients with pneumonia (26 events) ICS only a risk if used in each of the 6 years; risk with fluticasone based on 5 exposed events.
A: Yes this is the main weakness and this is also reported as a main weakness in the second last paragraph in the discussion.

How comparable were fluticasone and budesonide users?
A: The two groups were quite similar in regard to age, sex, smoking history and number of symptoms. This information has now been added in the third paragraph of the result section.

Hugo Farne (Reviewer 2): This was an interesting paper that adds to the literature on pneumonia risk in patients on ICS, especially those with asthma for whom there is little evidence. Some minor comments:

1. Background p3 - after the paragraph on pneumonia, it would be useful to have a short paragraph on ICS use and the rationale for it. In asthma in particular there is very good evidence that ICS reduces exacerbations, and so they are included in every major guideline I know of, and I think this should be included to give a more balanced picture.
A: We agree and have added this in the second paragraph of the discussion.

2. Background p3 - whilst most studies in COPD find an increase risk of pneumonia with ICS use, this is usually a slight increase and is not universally the case e.g. Sin te al Lancet 2009 "Budesonide and the risk of pneumonia: a meta-analysis of individual patient data" found no increase when pooling data from 7 RCTs of budesonide +/- formoterol). I would be tempted to cite the Cochrane meta-analysis on this topic from 2014 (Kew & Seniukovich "Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease") which suggests a borderline increase with budesonide, and puts the magnitude of risk in context - 18 excess pneumonias per 1000 patients on fluticasone, 6 excess pneumonias per 1000 patients on budesonide. I would like to see a bit more nuance here.
A: Excellent suggestion. This has been added.
3. Background p3 - the last sentence doesn't make sense? "To examine risk factors for hospitalisations with pneumonia in a general population sample with special emphasis on asthma and the use of ICS in asthmatics."
A: Our mistake this sentence should have started with The aim of this investigation. This has now been corrected.

4. Methods p5 - the current wording states that "asthma severity" was assessed by the number of asthma-related symptoms, that do not seem to have been validated like e.g. the Asthma Control Test or Asthma Control Questionnaire? No other mention is made of "severity". Ongoing symptoms may reflect "control" rather than "severity" (you can have severe asthma but be well controlled e.g. if you require oral steroids or biologicals). Moreover asthma waxes and wanes, whereas the symptom scores are from a single timepoint 1999-2000 (the start of the pneumonia data collection period). I think it would be better to refer to these simply as symptoms (as you do in tables 3+4).
A: We agree and have changed the text in the methods section accordingly.

5. Methods p5 - a single ICS prescription for a year feels like a very low threshold for saying someone is treated with ICS - most of these inhalers have 1-2 months medication, if taken at the correct dose. How many only had 1 prescription in a year? Is it possible to change this to e.g. ≥5 prescriptions a year? Does that materially change the results?
A: In Sweden, a prescription is meant to last at least 3 months. In our opinion a patient that collects at least one prescription, every year 6 years in a row is on regular treatment with ICS.

6. Results p7 - the wording "borderline statistical association (p=0.07)" is a bit generous to my mind. I would prefer "non-significant trend". You can discuss that the numbers of pneumonias are relatively small and so you may have been underpowered.
A: We agree and have changed the text according to the reviewer’s suggestion.

7. Results p7 / Figure 3 - could you include how many patients are in each bracket e.g. how many treated with fluticasone for all 6 years assessed? I think it is useful for the reader to appreciate that ultimately these numbers are quite small (total 26 pneumonias in 19 patients) so they can interpret with caution.
A: This information has now been added in Figure 3.

8. Discussion - couple of typos, p8 there is an extra "and" ("obese had and an increased") and p9 "a strength" (instead of "as strength")
A: Thank you. The typos have been corrected.

9. Table 3 - there are a surprisingly large number of people prescribed ICS for a limited period of time (39% of those not hospitalised and 21% of those hospitalised) - would the authors care to comment on this? How many of them were just a single prescription in one year e.g. potentially as a trial for post-viral wheeze, or chronic cough? It probably merits a mention in the results section as it is quite striking.
A: We had 55 subjects with asthma that only used ICS during a single year. Irregular ICS treatment is, however, quite common in patient data from general populations see Janson et al. Pharmacological treatment of asthma in a cohort of adults during a 20-year period: results from
10. Limitations -

a) I think it needs to be re-stated and made clearer that the hospitalisation data is for 10 years 2000-10 but the prescription data is just for six years 2005-10 (also why is this? availability of data?), and the data on who had asthma was self-reported (so not a confirmed physician diagnosis) and along with the symptom data came from a single timepoint 1999-2000 (so would exclude new diagnoses 2001-10).

A: The different duration of the analyses is because the Swedish Prescribed Drug Register from started 1st of July 2005. This is also reported in the method section (page4, last paragraph). Furthermore, we have tried to describe difference in duration of the analyses in figure 1. The fact that asthma was self-reported is already stated in the limitation paragraph. From an epidemiological perspective, I think it is an advantage that we only included those that had asthma at baseline. We would therefore not include that in the limitation section.

b) I am no expert on statistics but if I understand correctly, the methods applied have controlled for potential confounders included in the model (e.g. smoking, BMI, age)? However I do not believe this will have controlled for severity of asthma (as discussed above the snapshot self-reported answers to unvalidated symptom questions does not equate to disease severity)? This is very difficult to do in these studies anyway as it is hard to define severity and even harder to separate it from treatment i.e. those with more severe disease are on higher doses of ICS. It is therefore difficult to attribute findings to ICS dose rather than disease severity. This confounder should be recognised.

A: Yes we agree and have added that in the limitation paragraph.

c) The authors might also want to comment on other confounders the were unable to control for, e.g. treatment with long-term oral corticosteroids (OCS) and/or number of courses of OCS, and limitations of the data, e.g. unable to confirm compliance with ICS, which is known to be poor (~30-70%).

A: Yes we agree and have added this.

Thank you once again for these valuable comments and for the chance of improving our manuscript

Yours sincerely on behalf of all the authors

Christer Janson