Author's response to reviews

Title: Clinical, Economic, and Humanistic Burden of Asthma in Canada: A Systematic Review

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Author's response to reviews: see over
Responses to Reviewers’ Comments

The following comments have been received for the submitted manuscript, “Clinical, Economic, and Humanistic Burden of Asthma in Canada: A Systematic Review” (BMC 1805238209847576). The authors appreciate the thoughtful comments from the reviewer(s), which will allow us to strengthen the manuscript, and below, we provide our responses to comments made by the reviewers that require a response.

Reviewer 1: Matthew Rank

This is a systematic review of the clinical, economic, and economic burden of asthma in Canada from 2000-2011. The authors conclude that the data from this study can assist those who make decisions about asthma treatment selection and guideline management.

1. Is the question posed by the authors well defined?

This is a descriptive systematic review, with the goal of describing the burden of asthma in Canada from 2000-2011. The stated goals are to have these data be available to those making decisions about asthma treatments in the future. There is not a specific research question or hypothesis stated. The link between their data summary and how this can be used for decisions on asthma treatment could be explained more clearly.

Authors’ response:

Our objective in conducting this systematic review was to provide a comprehensive summary of the clinical, economic and humanistic burden of asthma in Canada (our research hypothesis is that asthma poses significant clinical, economic and humanistic burden in Canada). The review, which provides the direct and indirect costs of asthma per patient, the key drivers of healthcare resource utilization, and the humanistic impact of asthma on patients’ quality of life (QoL), provides clinicians, payers and other health care stakeholders with a single source for the most recent information related to asthma and its burden in Canada. We believe this will be a critical review for readers. We have revised the last paragraph in the background section to clarify the overall scope, objectives and expected contribution of the review to the overall asthma literature.

2. Are the methods appropriate and well described?

The methods for systematic review are, in general, well described in this manuscript. They employ the usual standards for a systematic review including an appendix detailing their search strategy, duplicate review, and a quality assessment of the selected articles using previously reported and accepted instruments.

There are some methodological concerns. The major concern is about efforts to detect publication bias. It is unclear what methods were used to assess this. Many of the studies that examine burden of disease are funded by companies which make medicines or drugs to treat these conditions. If a study was conducted and the burden found to be low, it is possible that the study would never be published. It is unclear if the authors made an attempt to find such data. Furthermore, the funding of the studies was not clearly displayed for the reader, especially in the summary tables. The confidence in the estimates of burden, then, may be lower by readers who share this concern. Secondary methodologic concerns regard the heterogeneity of definitions and outcomes in the studies that were identified. The authors make no attempt to synthesize data into a common estimate using meta-analysis methods, presumably due to heterogeneity of study designs. The authors should state whether they attempted this, which could have been an initial goal of the study. Such a summary estimate may prove more useful for those who would use these data to determine guideline or coverage decisions for asthma medications. Another concern is the interpretation of the humanistic burden; without non-asthmatic normal control groups understanding the attributable humanistic burden of asthma is challenging. It is not clear how many of these studies included non-asthma patients and if the difference between a control and asthma patient was detected and what the mean difference was. A lesser concerns is how initial review was
conducted; it is unclear if title or abstract review occurred at the first level of exclusion. Another lesser concern is that the authors do not justify their selection of using the 2000-2011 time period.

Authors’ response:

We agree with the reviewer on the importance of assessing methodological quality of included articles in the systematic review and the importance of minimizing potential for publication bias. In order to overcome these limitations, in this review, we have critically appraised the methodological quality of studies that met our inclusion criteria using checklists provided in the NICE Guidelines Manual [14] and the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [15,16]. One of the items in the STROBE guideline is “funding”. The results of the methodological quality of the included articles are currently displayed in Appendix Table 2 and Table 3. To address the reviewer’s comment, we have moved the tables from appendix into the body of the manuscript for clarity. However, there are technical difficulties to eliminate the publication bias since the health outcome studies are not required to register in centralized database such as clinicaltrial.gov. Thus it is difficult to eliminate publication bias with our study and other similar studies.

We acknowledge that we did not conduct meta-analyses. This was not conducted primarily because of the heterogeneity of the data presented in the literature, including, but not limited to, the different study designs, inclusion criteria and even definition of asthma. As a result, it would also have been difficult to perform a comparison of non-asthma controls vs asthma patients as data were not readily available in the studies reviewed. This is a key finding in this review, which we have added to the discussion section.

The initial review included a review of title and a abstract at which point literature reports not meeting the inclusion criteria were excluded. The time frame of 2000-2011 was included as this was deemed most appropriate to report more recent developments and advances in the management of asthma. We have added sentences in the methods section to clarify these points.

3. Are the data sound?

The data presented resulted from a comprehensive search of the published literature. The authors assess and recognize the low quality of many of the studies included, as well as the heterogeneity of definitions used for inclusion/exclusion and outcomes.

Authors’ response:

Thank you for this comment. The heterogeneity of the studies and definitions used for inclusion/exclusion and outcomes speaks to the difficulty in conducting any meta-analysis of the data.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Yes, the authors use and report the standard methods for performing a systematic review.

Authors’ response:

No response required.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The authors speculate about the future need for new asthma treatments in the discussion rather than focus on the heterogeneity of the data and the need for more standardized methods to assess the burden of asthma. The authors make this point in the discussion section “…our study suggests a significant knowledge gap in understanding the comprehensive burden of asthma across Canada.” The discussion should, in my opinion, focus on the gaps that they identified in the data types and study designs (especially the flaws) and put forward study designs, inclusion/exclusion criteria, and outcome reporting methods that they would believe would lead to improved ability to assess asthma burden (and
would ultimately allow them to obtain data that could be synthesized into estimates that those who make treatment, guideline, and coverage decisions could rely on). The authors choose, instead, to make a conclusion that the burden is high (a statement that is made in the background section as a fact that is known already) and that new treatments for asthma are needed. The other area in the discussion section that is not addressed is the risk for publication bias. How those making decisions about asthma coverage and guidelines should use these data and how confident they should be in the results of this study are not clearly laid out in the discussion section.

**Authors’ response:**

*Thank you for this comment. We have added commentary on this critical gap in the discussion section of the revised manuscript. The reviewer’s comment about publication bias and the use of this review has further been clarified in the revised manuscript.*

6. Are the limitations of the work clearly stated?

The main concern about publication bias and heterogeneity of the included studies are stated above.

**Authors’ response:**

*Limitations highlighted by the reviewer have been added or clarified in the section on limitations.*

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

The authors reference #9, a 2009 review not restricted to Canada, that assesses the economic burden of asthma. The authors do not compare their data with the findings and conclusions from this review. How do these findings compare to other countries or other chronic diseases within Canada?

**Authors’ response:**

*Thank you for this comment. The intention of our review was to survey the literature related to the burden of asthma in Canada. It is correct that we have included the reference #9 (Bahadori et al, 2009), because it did include information related to Canada. However, we do not compare our data to Bahadori et al, 2009 [9], because that review was not restricted to Canada. Furthermore, its results were reported in a different format. We note in our discussion and in our limitations that we present the results of the reviewed studies, but no comparisons among them are made due to the high heterogeneity of methodologies.*

8. Do the title and abstract accurately convey what has been found?

Yes

9. Is the writing acceptable?

Yes, the writing is generally clear. The authors could display their results more concisely in tables (the current tables could have less words that could convey the same messages). The text in the results section could be considerably shortened if the tables were used more effectively. Displaying funding source in the tables would also be important.

**Authors’ response:**

*Thank you for this comment. We have attempted to further shorten the manuscript where possible; however, given the comprehensive nature of the review, we believe it is important to ensure that key data and information is not lost in the further editing of the manuscript. Percentage of studies reporting funding sources are now displayed in the tables included in the body of the manuscript.*

Discretionary revisions: Table revisions and minor methodological concerns.
Minor essential revisions: None

Major compulsory revisions: Addressing risk of publication bias, restructuring discussion section to focus on gaps and problems with currently available studies so that future studies can be more informative, attempting to report the humanistic burden as attributable to asthma, and establishing a clearer link between the data presented (and the confidence in the estimates) and how someone is deciding about coverage, guidelines, or public health can use this information.

Authors’ response:
Once again, we thank the reviewer for his extensive comments which have helped us strengthen this manuscript. We have responded to the reviewer’s comments and made appropriate revisions to the paper. We believe that this is an important body of work that adds to the knowledge about asthma in Canada and will be useful reference to health care stakeholders.
Reviewer #2: Francis Gilchrist

Reviewer's report:
The objective of this study was to provide a comprehensive evaluation of the published literature that reports on the clinical, economic, and humanistic burden of asthma in Canada. The authors have undertaken a detailed review of the relevant literature using good methodology and produced a very detailed report which will be of interest to clinicians in this field.

The main issue with this article is the length of the results section. I know it is difficult to summarise such a large volume of literature but I think that its current length will put people off reading it. Currently there is too much written information about each article. For each section the authors should summarise the main findings and then refer the reader to the relevant table if they require further information. There is also a lack of clarity in paragraphs 1&2 of the results section. In both paragraphs they are explaining how articles were excluded but they use completely different formats. They should stick to the same format and use numbers of articles and not percentages (used once in paragraph 1). In paragraph 1 there is also information missing on how the remaining 88 articles were excluded.

In summary this is a good quality review that does add the field. I think that the results section needs to be edited / re-written to maximise the number of people that will read the article and therefore take on board it important content.

Level of interest: An article of importance in its field

Authors’ response:
Thank you for this comment. We have attempted to further shorten the manuscript where possible, and have made consistent the way we have reported numbers of articles included or excluded in the review. As well, we have included commentary on the excluded articles. As you have correctly pointed out, there is significant information reported in this review, and we have attempted to further consolidate without losing critical data or information relevant to the review.

We trust that we have adequately responded to both reviewers’ comments. Please, let us know if any additional information is required to complete our submission.