Author’s response to reviews

Title: The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases

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Author’s response to reviews:

Dear Dr Lin Lee,

Re: The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases (BMED-D-16-00338)

Thank you for your email dated 15th April and for giving us the opportunity to respond to the reviewers’ comments. Thank you also for the accompanying thoughtful feedback from your expert peer-reviewers. We have carefully studied the constructive suggestions received and have, in the light of these, made a number of revisions to our manuscript. For your convenience, we have reproduced the reviewers’ feedback in full below, and then provided a point-by-point response to the issues raised (prefixed R). As requested, our revisions are clearly marked using track changes in the revised submission. Please note that the page and line numbers below refer to the tracked change version of the manuscript.

COMMENTS FOR THE AUTHOR(S)

Reviewer: 1

This is a nationwide study of the epidemiological and economic burden of asthma in the UK (Britain, Scotland, Wales, and Northern Ireland). The study capitalizes on multiple (27) different databases and uses a variety of data linkage and mapping to fill the identified data gaps.

This is quite a comprehensive study of the burden of asthma. It showcases the power of using a variety of public health, government, and administrative databases to estimate the burden of a chronic disease. The efforts in undertaking this study is likely to leave a legacy in terms of the data linkage and data collection generated. The fact that the study protocol has previously been peer-reviewed published (and it seems the authors have largely adhered to their proposed methods) is also a positive aspect.

R: Thank you for your positive comments.

Nevertheless, I have found the described methodology not to be quite clear and comprehensive enough. Specific details are lacking in several places, as detailed in major comment #1. This is not a threat against the validity of the methods rather a request to provide additional information to facilitate peer-review and improve the quality of the paper.
Major comments:

i) There is missing information in the methods section of the manuscript. The separately published protocol and the additional files do not cover the gaps. It is understandable that the complex methodology of the paper makes it impossible to present everything in the main text, but some important elements must appear there and not relegated to a published protocol. These include more detailed description of all included databases and their information content, and how they were used to estimate the reported metrics. It would be great if the authors could provide the relevant Read codes and list of asthma medications used in relevant data sets. It will help the review process and can also help future investigators to replicate the results using the same methodology in different jurisdictions.

R: We have now provided the additional requested information on description of all datasets in the text (see pages 7 - 16, lines 169 - 390), the data sources by outcome measures and numerators and denominators used are presented in Tables 2 - 5. Regarding how the information was used from the data sources is added in the text in pages 7 - 16, lines 176 – 390 and in page 17, lines 393-396 under “Analyses”. We have also now provided the relevant Read codes used in primary care, Appendix 1, list of asthma medications used coded using British National Formulary (BNF) codes and list of Read codes used in paediatric intensive care in Appendices 1-3, respectively.

ii) The authors have used two different definitions for incidence and seven for prevalence. These definitions must have affected, in substantial ways, the calculation of costs. Lack of detailed description has made it difficult to reconcile all the permutation of incidence/prevalence and the reported cost values. The reader would expect different estimates of costs per different definitions of prevalence. The relation between cost calculations and estimates of incidence/prevalence is a major gap in the methodology that should become clear in a revised version.

R: Our calculations on resource use were taken directly from healthcare utilisation data rather than by estimating per patient costs and then multiplying by a given incidence or prevalence estimate as may have been assumed here. The only use of prevalence in the model occurred where results that had to be extrapolated to another country due to a data gap. Here, in order to account for differences in prevalence rates between countries, additional rescaling was undertaken based on each country’s relative Quality and Outcomes Framework (QOF) prevalence (after population scale adjustment). QOF relates to “annual clinician-diagnosed and treated asthma rates” which, being based on treatment, was the most appropriate measure of healthcare utilisation. It was also the only available measure of prevalence measured in a uniform manner across all UK nations to facilitate this process.
It is not unreasonable that a reader could have also assumed that prevalence was multiplied by a cost per patient and thank you for highlighting the lack of clarity in our description of the methods employed. We have now included a summary of the process in the revised Methods section under “Economic modelling” (page 18, lines 438-455) and also added much more detail regarding this process in Appendix 6. Furthermore, we have now also highlighted some additional limitations associated with this approach in the revised Discussion (Page 23-24, lines 562-572).

Minor comments:

iii) Abstract, second paragraph: ‘costs were estimated for’ should be corrected.
R: Thank you for pointing that out. We have now removed the word “for”.

iv) Abstract: no date range provided so the reader cannot understand to which time periods these numbers apply.
R: We have now added the years, so as to read “We obtained and analysed asthma-relevant data from 27 datasets: these comprised national health surveys for 2010–11, and routine administrative, health and social care datasets for 2011–12; 2011–12 costs were estimated in pounds sterling using economic modelling.” in lines 43-44.

v) Cost currency (year) should be provided in the abstract
R: Thank you again – this has now been added.

vi) Background, line 53: ‘report’ should be 'reported'
R: This has now been corrected.

vii) Study outcomes, lines 39-43: this paragraph is out of place. Why suddenly talking about absenteeism where you just described the data?
R: This has now been moved under “Outcome measures and datasets used”.

viii) Study outcomes, paragraph starting at line 46: the narrative starts from prevalence, then switches to incidence, and back to prevalence. Suggest rewriting the paragraph. In general, given the many study outcomes, this section could have subheadings.

R: This section has been revised and we now also use subheadings, as suggested (see page 7-12, lines 176-295).

ix) It will help if a table is put in the main text that describes all the 27 databases and the essential information therein (what they contain, what date range, how many records/individuals, and why they were used). This information is an integral part of the methods and should not be relegated to the Appendix.

R: We have now included in the main text Table 1 on “Study outcomes by sources of data used in each UK nation” and Table 2 on “Outcomes measured using data sources in Table 1, data type, demographic information and time-trends availability”.

x) Early on please explain what the four countries are. For readers not familiar with the UK context it might not be clear.

R: We have now added the names of the countries in a new sentence “We also, for the first time, had a focus on all the four nations of UK (i.e. England, Scotland Wales and Northern Ireland) and UK-wide estimates.” on page 5, lines 123-124.

xi) The paper should more deeply discuss the situation with COPD. Asthma-COPD overlap syndrome (ACOS) is a recognized disease phenotype and the paper should at least discuss the implications of censoring patients who had coexisting COPD. Ideally a sensitivity analysis should be done that includes these patients otherwise the authors should acknowledge that the reported results are underestimates of the true burden of asthma.

R: Our aim was to estimate the epidemiology, burden and costs of asthma, irrespective of these patients having COPD or any other comorbidities; thus patients with both asthma and COPD were not censored. To this effect, we have now added a paragraph on page 7, lines 164-167. Additional explanatory text has also been added in the Discussion on pages 24-25, lines 593-599 to specify that these estimates were not for the burden of patients with asthma and comorbidities, but that these estimates were for burden of asthma in patients whose health and societal care utilisation was mainly for asthma. Please note that we have ongoing follow-on work focusing on the burden of asthma co-morbidities, which we hope to report within the next 24 months.
xii) Seven different definitions for prevalence were used, but the results section in the text does not provide the results of such prevalence estimates. Table 2 does but textual description is also required for clarity.

R: This is now included in the text on pages 19-20, lines 473-481.

xiii) Discussion: It might be worth mentioning that the calculated costs and health resource use are 'attributable' to asthma and they do not incorporate the burden of coexisting and comorbid conditions. It is known that asthma is associated with a potentially wide spectrum of comorbid conditions and the true burden of asthma also includes the excess burden of such conditions (Gershon et. al. Thorax. 2010 Jul;6)

R: Thank you; this point is now added to the revised Methods and Discussion (please see page 7, lines 164-167 and pages 24-25, lines 593-599 respectively).

Reviewer: 2

This paper is well researched and well written, addresses an important question and provides recent epidemiological data on the burden and costs of asthma in the United Kingdom (UK). This will be useful for commissioners and researchers interested in provision of asthma care in the UK.

R: Thank you for your kind comments.

I have some comments which would help clarify some issues:

i) Estimates of asthma prevalence: The authors have utilized 7 different methods for defining asthma prevalence. I would like to suggest some additional considerations for inclusion in the discussion:

a. Page 6 i) this probably underestimates the true prevalence - for eg QOF only includes patients over 8 years old with asthma (should but doesn't always include evidence of airflow limitation)

R: We have included the main asthma register (Indicator name Asthma 01; see Table below) which includes people of all ages who were prescribed asthma-related drugs by GPs for their symptoms of asthma in the last 12 months [1].

Table: Asthma indicators that are used for QOF
Indicator name in QOF guidance

Indicator name in QOF calculator

Domain

Indicator description

ASTHMA 1 ASTHMA01 CLINICAL The practice can produce a register of patients with asthma; excluding patients with asthma who have been prescribed no asthma-related drugs in the previous twelve months

ASTHMA 8 ASTHMA08 CLINICAL The percentage of patients aged eight and over diagnosed as having asthma from 1st April 2006 with measures of variability or reversibility

ASTHMA 9 ASTHMA09 CLINICAL The percentage of patients with asthma who have had an asthma review in the preceding 15 months that includes an assessment of asthma control using the 3 Royal College of Physician (RCP) questions

ASTHMA 10 ASTHMA10 CLINICAL The percentage of patients with asthma between the ages of 14 and 19 in whom there is a record of smoking status in the previous 15 months

Please note we had not used Asthma 8/9/10. By using Asthma 1, we have been able to capture people of all ages.

b. The authors have excluded those on asthma treatment who have not been coded with an asthma Read Code - Problem here is that i) it is not uncommon for asthma treatment to be prescribed for patients with uncoded asthma - this should be acknowledged on page 7 lines 4-8 and in the discussion.

R: We too were concerned about the possibility of your point (i) and therefore included everyone in the analysis of prescription cost who had been prescribed medications used for asthma in primary care, irrespective of whether they were diagnosed with asthma. To make this clear, we have now added the following additional text: “Some medications indicated for use in asthma can also be prescribed to treat other conditions, primarily chronic obstructive pulmonary disease (COPD). We therefore confined our analysis of medications to people with a clinician-recorded diagnosis of asthma, but without a diagnosis of COPD To address this issue, medications of patients who had COPD and asthma were included so long they received the list of asthma
medication we had (Appendix 2), but patients with COPD but no asthma were excluded.” on page 13, lines 307-312).

c. Linked to b) the authors seem to have excluded patients with combined asthma and COPD - the so called ACOS Syndrome described by GINA and GOLD.

R: As noted in our response to Reviewer #1 above, we have revised the text to make clear that we included patients whose main problem was asthma, with or without COPD (see page 7, lines 164-167 and pages 24-25, lines 593-599).

ii) Page 6 line 23/24: How did the authors determine the accuracy of A&E attendances for asthma? In my experience in London - it is extremely difficult because these episodes are not always accurately coded. Suggest include in discussion.

R: We interrogated relevant A&E datasets, but we recognise this may be a limitation as some people presenting to A&E with an asthma exacerbation may have been recorded as presenting with, for example, shortness of breath or wheeze in free text. This is now acknowledged in the revised Discussion (see page 23, lines 554-556).

iii) There is an area of asthma health care utilisation that hasn't been included - ie Urgent Care Clinic (UCC) attendances - many CCGs in England (and I assume in other parts of the UK) have designated Urgent care clinics, staffed by sessional/part time GPs and nurses, where people with asthma consult - problem here, and I assume this is why its been excluded, is that these attendances are not coded accurately. As a result health care utilization (and cost - at between £60-£80 per attendance) is underestimated. This and the A&E data should in my view be included in the discussion as potential additional costs which should be considered by commissioners.- this may help increase allocation of resources for asthma care.

R: Thank you for pointing this out. We now recognise this as an additional reason why we may have under-estimated costs when discussing the limitations of this work (see line 551).

iv) Otherwise, I think the paper is suitable for publication.

R: Thank you.
Editorial Requests

i) Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

R: We have included this (see lines 646-647).

ii) Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

R: Not applicable (see line 648).

iii) Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

R: We have included this now (see lines 649-654).

The opportunity to respond to the reviewers comments has helped us to strengthen the quality of our work, for which we are grateful. We believe we have responded to the comments raised and trust that our revisions are to your satisfaction. We look forward to your decision in due course.
Yours sincerely,

Ms Mome Mukherjee, on behalf of the co-authors

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Reference