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

Authors:

Mome Mukherjee (mome.mukherjee@ed.ac.uk)
Andrew Stoddart (andrew.stoddart@ed.ac.uk)
Ramyani Gupta (rgupta@sgul.ac.uk)
Bright Nwaru (bright.nwaru@ed.ac.uk)
Angela Farr (A.Farr@swansea.ac.uk)
Martin Heaven (M.L.Heaven@swansea.ac.uk)
Deborah Fitzsimmons (D.Fitzsimmons@swansea.ac.uk)
Amrita Bandyopadhyay (A.Bandyopadhyay@swansea.ac.uk)
Chantelle Aftab (Chantelle.Anandan@ed.ac.uk)
Colin Simpson (c.simpson@ed.ac.uk)
Ronan Lyons (R.A.Lyons@swansea.ac.uk)
Colin Fischbacher (colin.fischbacher@nhs.net)
Christopher Dibben (Chris.Dibben@ed.ac.uk)
Michael Shields (m.shields@qub.ac.uk)
Ceri Phillips (C.I.Phillips@swansea.ac.uk)
David Strachan (sgjd950@sgul.ac.uk)
Gwyneth Davies (Gwyneth.Davies@swansea.ac.uk)
Brian McKinstry (Brian.McKinstry@ed.ac.uk)
Aziz Sheikh (Aziz.Sheikh@ed.ac.uk)

Version: 2 Date: 13 Jul 2016
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-16-00338R1)

Thank you for your email dated 5th July and for giving us the opportunity to respond to the reviewer’s comments. We have carefully noted the suggestions received and have made the required revisions to our manuscript. For your convenience, we have reproduced the reviewer’s 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 the second review of the manuscript entitled "The epidemiology, healthcare and societal burden and costs of asthma in the UK and its 2 member nations: analyses of standalone and linked national databases".

The authors have successfully addressed the previous comments. I have one request for an essential revision. All my other comments aside from typos corrections are discretionary.

Major comment:

1. Under the section "Economic modelling" the authors discuss the use of bootstrapping for quantifying uncertainty around cost estimates, and the use of beta distribution for modeling uncertainty around prevalence. It is not obvious what the content of the excel file is. Bootstrapping to quantify uncertainty is mostly used in the presence of individual-level data, whereas the use of the beta distribution for prevalence indicates dealing with aggregated data. More description of the methodology used for cost estimation, in particular modeling uncertainty around the estimates, is warranted.

R: Thank you for bringing the lack of clarity to our attention. While bootstrapping is often applied to individual level data as might be obtained from a clinical trial, it can also be used in
more aggregate level data modelling such as Markov models and the techniques applied here are more akin to the latter. We have now replaced the short description of the confidence interval calculation in the Appendix 6 with a dedicated subsection which provides a much more detailed description of the process used, including formulae applied in the percentile method, which should clarify the process to readers. That subsection reads:

“Confidence Interval Estimation

95% CIs around cost totals were estimated by bootstrap using the percentile method with a 5% alpha [1]. This process involves applying probability distributions to each parameter in the model based on method of moment estimators [2]. Following recommendations in standard modelling guidance [2], the uncertainty around prevalence estimates were simulated using beta distributions and uncertainty around cost estimates were simulated using gamma distributions or normal distributions where sample sizes were large and central limit theorem was expected to hold. Model parameters were then varied simultaneously by random draws from these parameters and ran through the model to capture the joint distribution over all model parameters generating a sample cost. The resulting cost estimate from each sample (called a replicate) were then saved and a new replicate generated. Random samples in each replicate are drawn “with replacement” which is to say it is possible for the same random draw to occur for a given parameter or parameters in different replicates. The results for all replaces are then ranked and the 100*(\alpha/2) and 100*(1-(\alpha/2)) values were taken as the lower and upper confidence interval respectively [1]. 10,000 replicates were used in this process.”

A cross reference to the appendix has also been added to the respective section in the main text to help guide interested readers to the relevant appendix.

Minor comments:

2. Abstract: background: "there are a lack of reliable data -> "the is a lack of reliable data"

R: We are referring to data as plural (as used in UK English) and have hence used ‘are’.

3. Not sure the last sentence of the abstract is supported by the results.

R: The Conclusion section of the manuscript summarises the main findings and also begins to tease out the implications of this work, which will help to increase interest in the piece from a broad international readership. We note that this is a discretionary revision and we would therefore like to retain this sentence, if possible. If however you feel strongly in this respect, this last sentence can be omitted.
4. Methods, line 94: current table 1 and 2 are very similar to each other and can potentially be combined. The previous suggestion to reporting the sources of data in a tabular format was based on the feeling that the reader might frequently need to resolve the meaning and content of different datasets referred to by their abbreviated names. Such a table would have databases as rows not outcome metrics.

R: We have now combined the two tables and have kept the outcome metrics approach for added benefit to readers so that they can find the dataset(s) depending on the outcome of interest.

5. Methods, under section 'prevalence' (line 165+): only annual prevalence is defined but the next sentence talks about lifetime and annual prevalence. These are defined in more details later on so rewording this section can help with the consistency and coherence of the paper.

R: We have now added definition of lifetime prevalence in the start of the section (see lines 167-169) to help with consistency and have kept the detailed definitions later for the coherence of the paper.

6. Methods, under 'prevalence': "while the questions for asthma were similar in England …" this sentence needs correction.

R: We have now changed this to “While the questions for asthma in the national health surveys were similar in England and Scotland…” (see lines 182-183).

7. Methods, line 443: "costs based on a sample 443 within a country, were extrapolated to population levels" there is an extra comma here.

R: We have removed the extra comma (line 390).

8. Results, under "financial costs of asthma": why the reported total costs and costs of medications the same (1.1b)? The reader might be confused unless additional description is added.

R: Thank you for raising this. It is unfortunate that these two figures happen to round to the same value when stated in billions. We have now added a short sentence to the section to clarify the situation to the reader, which reads “It is important to note that the parity between the £1.1bn total cost estimate from our model and the £1.1bn total cost of medications with an indication for asthma from PCA data is entirely co- incidental and occurs due to PCA providing an overestimate
of medication costs in this context, rather than being a component of the costs used in the model” (see lines 449-453).

9. Results, line 597 "burden of patients with asthma" is a vague phrase and needs revision.

R: We have now modified that part of the sentence to read “It is therefore important that these estimates are not confused with burden of asthma, but that these estimates are for burden of asthma in patients who utilised health and societal care when asthma was their main problem” (see line 535-537).

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.

Yours sincerely,

Ms Mome Mukherjee, on behalf of the co-authors