Author's response to reviews

Title: Impact of asthma control on health care costs and quality of life in France and Spain

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Author's response to reviews: see over
Dear Editor,

We are grateful for your interest in our article. Please find enclosed a revised version of the manuscript: "Impact of asthma control on health care costs and quality of life in France and Spain" (Ref. No.: 2231928847525780). We took into consideration all comments of both reviewers. We hope that the editorial board will find this new version acceptable.

Kind regards,
Bruno Detournay

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Reviewer: Pinar Karaca-Mandic

Major comments

1) I would recommend that the authors strengthen the motivation and the contribution of their paper. The authors provide references to several similar studies in Europe, so it is not clear how this study differs from others.

   We revised the introduction adding some references to be more explicit on the contribution of our paper.
   We described the limits of published studies:
   - prevalence studies did not take into account the seasonality of symptoms and evaluated the asthma level of control using old GINA criteria,
   - few European studies have provided data on costs and quality of life related to asthma control using new criteria.

2) Is it possible to control for asthma severity, and/or length of time since asthma diagnosis?

   The study did not assess asthma severity.
   We added a line in table 1 with the length of time since asthma diagnosis showing that both in France and Spain, asthma control is related to the duration of the disease.

3) Patient selection into the study sample requires receiving at least one anti-asthmatic medicine. It would be important to distinguish between those on quick relief meds versus control therapy.

   In the Table 2 we added 2 lines to distinguish patients who had only a reliever treatment to patients who had only a controller treatment or a reliever + a controller treatment.

4) More information is needed on the sampling of the GPs. Please be specific, for each country, about the sampling frame, number of GPs eligible to participate, number of selected GPs and the number of GPs who participated. Please describe the response rate, and potential response biases.

   In France:
   The database used for recruiting general practitioners was a representative panel of 1,200 general practitioners. The panel's representativeness was established by three criteria: age, sex and region of practice. This representativeness for common criteria makes it possible to carry out national extrapolations. The study was presented to 750 general practitioners selected at random from among all 1,200 GPs.

   In Spain:
The study was put forward to 105 general practitioners of 18 autonomous communities belonging to 3 regions (North, South and Mediterranean), 87 of whom agreed to participate. A territorial representativeness was able to be obtained when the sample was constituted. Practitioners had to include patients in the usual context of their practice. To avoid a selection bias, the first two consecutive patients (the first five in Spain) corresponding to the inclusion/exclusion criteria visiting their doctor were included in each wave.

The text Page 5 was modified to provide such precisions.

5) Is there a way to assess whether the GPs who participated were similar to those who declined? In what ways were the participant GPs different than those who did not participate?
No data on GPs who declined to participate to the study were collected. However, the representativeness of the two samples was assessed using available criteria (i.e. age, sex and geographic distribution). This is now clearly exposed in the paper Page 5.

6) Similar to the above comment, it is important to show in the paper how the GPs included in the study were similar to the general population of GPs in each country. Currently page notes that GPs included in the study were similar to the general set of GPs in each county, but the results are not shown.
Please see above. Data are now included in the text.

7) Data on asthma control (FEV1) is collected from a single visit. More information is needed on whether information from a single visit is a good proxy for overall asthma control from a clinical perspective. The Discussion section (page 17) seems to suggest that GINA criteria recommends assessing asthma control over a 4-week period.
The period of time to be considered to assess asthma control is not explicitly defined. We chose to assess GINA criteria (asthma exacerbations, daytime symptoms, limitations of activities, nocturnal symptoms/awakening and need for reliever/ rescue treatment) on a 3-month period and the investigator had to ask his patient to complete all these clinical elements over that periods of time. Level of control of a patient was obtained combining all criteria together. However FEV1 was measured only during the inclusion visit (3 successive measures) and considered to be the FEV1 level over the two periods of time considered. This was a limitation of the study.
This point was added in the discussion.

8) Data analysis: Please explain why the data is weighted by the number of patients enrolled in each wave. In survey data weighting is typically important to produce nationally representative samples, or to adjust for non-response. It is not clear what the goal is here. Also, please provide tables that show whether/results are much different if the data are not weighted.
Data were weighted only for France to compensate the disproportion of inclusions observed among the different quarterly waves. Individual case weights were defined according to the ratio between the number of inclusions in wave 1 and the number of inclusions in the subsequent waves.
It is difficult to provide all tables without weighted results here as they are numerous. However, please find below a table which presents the weighting process.

<table>
<thead>
<tr>
<th>Weighting coefficients</th>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CRF completed</td>
<td>400</td>
<td>356</td>
<td>208</td>
<td>202</td>
<td>1,166</td>
</tr>
<tr>
<td>Number of inclusions</td>
<td>391</td>
<td>353</td>
<td>208</td>
<td>202</td>
<td>1,154</td>
</tr>
<tr>
<td>Average number of patients if each wave have same weight</td>
<td>288.5</td>
<td>288.5</td>
<td>288.5</td>
<td>288.5</td>
<td>1,154</td>
</tr>
<tr>
<td>Weighting coefficient</td>
<td>0.738</td>
<td>0.817</td>
<td>1.387</td>
<td>1.428</td>
<td>-</td>
</tr>
<tr>
<td>Theoretical number of inclusions after weighting</td>
<td>288.5</td>
<td>288.5</td>
<td>288.5</td>
<td>288.5</td>
<td>1,154</td>
</tr>
</tbody>
</table>

We added this sentence in the text page 6: “In France, data were weighted to compensate the disproportion of inclusions observed among the different quarterly waves. Individual case weights were defined according to the ratio between the number of inclusions in wave 1 and the number of
Inclusions in the subsequent waves. In Spain, as the number of inclusions was similar in each wave, it was not necessary to weight the data.

9) Please provide more information on the GINA criteria for the reader and describe the methodology for determining “controlled”, “partially controlled” and “uncontrolled”. Is it based on the FEV1 measurement on a single visit, or does it also incorporate responses to the questionnaire to capture information from the previous three months?
To provide more information for the reader, the first sentence of the data collection paragraph (page 5) was modified. Furthermore, the discussion paragraph was also modified to precise that the FEV1 was measured only on a single visit.

10) The multivariate regression analyses currently control for sex, age, episodes of asthma exacerbation, prescription of a controller treatment and follow-up by a lung specialist. It is important that the authors also control for other co-morbid conditions. Table 1 shows co-morbid conditions (such as depression) vary significantly by the asthma control level.
We added results of multivariate regression analysis for comorbidities.

11) Is it possible to control for asthma controller medication adherence?
It was not possible to control for asthma controller medication adherence. Only prescriptions of drugs were collected.

12) It is strange that the costs of anti-asthmatic drugs are much higher for the “uncontrolled” groups relative to partially controlled and controlled groups (Table 3). Presumably patients who are adherent to their asthma controller drugs should have better control. Such patients should also have higher cost of controller drugs. It would be helpful to divide the cost of drugs by long term control drugs versus short term quick relief drugs.
We acknowledge the comment of the reviewer. However, the study showed that patients with uncontrolled asthma have higher costs of reliever treatment BUT also higher costs of controllers, presumably to the fact that practitioners have already tried to solve the issue.
We provide detailed costs of drugs in the table 3 (Reliever treatment only, Controller treatment, Fixed association).

13) The Discussion section states that “the higher costs for patients with uncontrolled asthma were mainly due to costs of controller treatments and not to complications of asthma” (page 17). I do not believe that the authors have provided a statistical test or analysis to claim this. Is this based on Table 3 (which does provide components of the average costs, but does not test for differences)? Even then, Table 3 does not provide information on the components of “additional costs for patients with uncontrolled asthma” (relative to patients with controlled asthma).
Detail costs per level of control are presented in table 3. These data show that the cost of controller treatments is the main drivers of cost whatever the level of control.
Page 17, the sentence was modified.

Minor comments:

1) Overall, the paper would benefit from rewriting, tightening, and perhaps by having assistance of a professional editor
The paper was reviewed by an English native speaker.

2) Typo on abstract, line 3. Should be “adult patients”
This was modified.

3) Abstract: not clear what is meant by “resources consumption”. Please specify. I believe the authors mean “health care resources utilization”.
This was modified.

4) Abstract: not clear what is meant by “for all costs items”.
The corresponding sentence was modified.
“For all types of costs, the percentage of patients using health care resources varied significantly according to the level of asthma control”.


5) Page 5, line 3: clarify the sentence “In Spain, the GPs……” Was the sampling frame a GP society, or all GPs in the country? This paragraph was modified accordingly.

6) Page 5, under Data collection: Not clear what is meant by “all prescriptions dated prior to the observation period were accounted if the prescription period was included wholly or partially within the observation period (last 3 months).” Do you mean that all prescription drugs taken during the 3 months prior to doctor visit were recorded and included as controls? As the cost was measured over the last 3 months before inclusion, it was important to take into account all drugs prescribed during this period including drugs prescribed prior to the beginning of the study period and for the study period. The sentence was modified in the text.

7) On page 6: be specific about the list of “qualitative variables” versus “quantitative variables”. We specified the corresponding variables in the text p 6.

8) On page 6, the term “indirect cost” is used for the first time. Describe what you mean by that (i.e. costs associated with sick leave) when it is first introduced The corresponding sentence was modified. “The cost analysis was carried out according to a societal perspective and took into account both direct and indirect costs (costs associated with sick leave”).

9) Tables should be self-contained so that a reader can understand them without referring to the text. They should have better labels and notes. Similarly, the units should be clear. In Table 2, I assume authors are reporting costs in Euros? I also assume authors are reporting averages per group (controlled, partially controlled, uncontrolled). These need to be stated. Also, it is not clear to which test the p-value corresponds. Is it the p-value for a test of the difference between controlled and uncontrolled? Between partially controlled and uncontrolled? Something else? We agree with the reviewer comment and modified the tables accordingly. The tests were performed to compare controlled, partially controlled and uncontrolled patients. The sign € was added at the beginning of each line in the table 3 to help the understanding without referring to the text. The table 2 refers to health care utilization and data correspond to percentage of patients who consumed health cares.

10) The text does not refer to Table 3. That is the key table describing the unadjusted costs and should be discussed in the text. A reference to the Table 3 was added twice in the text p 10.

11) The unadjusted EQ-5D-3L scores are reported in Table 5, while the multivariate analyses of EQ-5D-3L scores are presented in Table 4. For a better flow of the paper, unadjusted estimates should be presented before the multivariate estimates. Tables 4 and 5 were ordered as suggested.

12) On a related note, authors show unadjusted estimates of VAS scores (Table 5), but do not report multivariate analysis results for VAS scores. They should be reported. Results of VAS scores were added. To avoid presenting to many data in the same table and to improve the understanding of the tables, results of multivariate analysis are now presented in 2 tables (table 5 and table 6).

Reviewer: Mohsen Sadatsafavi

Major Compulsory Revisions:

1) Page 6, paragraph 2: It is mentioned that the multivariate analysis of costs and quality of life in relation to control level is adjusted for potentially confounding factors such as episodes of exacerbations, prescription of controller treatment, and follow-up by a lung specialist. But such factors are most likely on the causal pathway between the level of control and cost/quality of life. For example, uncontrolled asthma is associated with higher rate of exacerbations, and exacerbations are major
determinants of costs and quality of life. It is inappropriate to adjust a model for such intermediate variables as the resulting effect sizes (cost associated with each level for control) will be biased towards null (equivalence of costs/QoL across control levels). This might be the reason why the adjusted estimates of differences in costs per levels of control are so much lower than the unadjusted values. The coefficient associated with the level of control in this framework is difficult to interpret and can be misleading.

The relation between level of control and cost and QoL (absolute value) is presented in tables 3 and 5 (univariate model). These data show that cost and QoL are varying according to the level of control. We agree that potential interaction between the covariables considered in the multivariate model lead to some difficulties in the interpretation of the coefficients. A sentence was added p 10 in the text to avoid misinterpretation of this statistical analysis.

2) In several places in the text, EQ-5D utility values have been reported only up to one digit after decimal point. This makes such values useless for any practical purpose. Rounding error of 0.1 level dwarves the change in HRQL from many ground-breaking interventions. Much more precision is required in reporting EQ-5D values.

We added precision on EQ-5D utility values where it was necessary (both in table 5 and in the text).

3) Page 5, under Data Analysis heading: it appears that the individuals in this study have received a 'weight' in this analysis, but it is far from clear what is the rationale and purpose of such weighting. "data….. were weighted accordingly to the number of patients enrolled during each wave" is too vague to be informative.

This question was already answered before (see question 8 of the first reviewer).

Minor Essential Revisions:

4) Appropriate analysis of the clustered data: Data from 2671 patients is obtained from 155 investigators in France and 83 investigators in Spain. The investigators (primary care providers who agreed to be part of this study) are most likely determinant of health care use by patients. This, in addition to the inevitable differences in the practice of interviewing individuals will result in estimates from individuals recruited by the same investigator to be correlated. A proper analysis of such data requires taking this aspect of the design into consideration. The author at least needs to mention this in the Discussion section that potential within-unit correlation in the data is not taken into account.

We acknowledge that this was a potential limitation of the statistical analysis mainly in Spain. A sentence was added in the discussion part.

5) Page 3, near bottom of the page: HRQL is not defined before.

We defined HRQL page 3.

6) Page 4, bottom of the page: it appears the author have provided a justification for the sample size using power calculations. However, the outcome measure is not obvious. "380 patients had to be enrolled" is not enough, and additional information is needed; specifically the statistics of interest and desired type I and II error levels.

The proportion of well-controlled and uncontrolled asthma patients was estimated between 40% and 50% in several studies. The number of patients required for this study has been calculated by taking into account the accuracy of estimating the average cost of the smallest group (well controlled patients) for each period in each country. Considering that 40% of patients were well controlled, the plan was to include at least 380 patients per country and per wave to obtain sufficient accuracy for the averages calculated for each study stage.

Page 5, the corresponding sentence was modified as follows:

"Based on the percentage of patients with controlled asthma estimated to represent 40% of the overall population in previous studies, and knowing that the size of the sample needed to estimate percentage value according to the confidence interval selected (alpha risk 5%, normal distribution), around 380 patients had to be enrolled quarterly”.

7) Reference [20] needs to be expanded. If it is just a URL it should be provided in parenthesis not as a reference.

The reference was modified as follows:
8) Page 6, paragraph 2: the purpose of statistical tests are not explained. "For qualitative variables, Pearson's Chi2 test or Fisher's Exact Test were applied". These tests were applied to what purpose? To measure associations in contingency tables, for example? This needs explanation.
Tests were performed to compare the 3 groups (controlled, partially controlled and uncontrolled) of patients.
Page 6, we modified the sentence as follows: “According to GINA 2009 criteria, patients were classified in 3 subgroups (“controlled, “partially controlled” and “uncontrolled” patients); statistic tests were performed to compare these 3 subgroups”.

9) Page 6, paragraph 2: Normally unit costs used to calculate expenditures from medical resource use data are provided in a Table. This is indeed very informative for the audience to judge the appropriateness of the values. Also, such unit cost provides clues as to the differences in costs across jurisdictions (Spain and France in this study).
We agree with the reviewer that a table with unit costs will be very informative. However, there were so many antiasthmatic drugs in both countries that we thought this would have been confusing for the reader to present these data.

10) Page 6 Important information on the calculation of costs associated with productivity loss is relegated to footnotes. These are important part of the methodology of the work and should be given due attention and be moved to the main text.
These footnotes were moved in the main text (page 6).

11) Table 1: P-values for all comparisons should be reported. Please replace the asterisk and blank spaces with actual p-values.
P-values were added in table 1. To keep homogeneity of the document, exact p-values were added in all tables.

12) Table 1: Without proper reporting of p-values, it is difficult to discern what form of analysis has been used in comparing control level across groups. For example, there is an asterisk for Male and another for Female in Table 1 (for France). The test of association between gender and control level should generate one p-value! Similar concerns for many other variables in Table 1.
It is true that p-values in the table 1 are not easy to read. We followed suggestions of the reviewer and added all p-values in the table. To keep homogeneity of the document, exact p-values were added in all tables.

Discretionary Revisions:

13) Page 5: "to avoid a selection bias at this level": this sentence will benefit from further explanation; what is the concern for the potential selection bias and how by using the stated approach such selection bias is minimized?
It is usual in such studies, to avoid selection bias, to ask investigators to include consecutive patients visiting their office and corresponding to inclusion/criteria. This helps to prevent from selecting (voluntarily or involuntarily) some specific patients (only controlled patients for example).
We also deleted “at this level” in the sentence at it may be confusing.

14) Page 6, top of the page; it will help the audience to be reminded how the level of control is determined according to GINA (e.g., symptoms, spirometry, etc).
To answer the question of the first reviewer, we detailed GINA criteria on page 5. We think to add again details of GINA criteria on page 6 may be redundant.

15) Page 6, paragraph 2: It will be helpful to mention that cost is the dependent variable and control level is the independent (explanatory) variable.
A sentence was added page 7: The costs or HRQL levels were the dependent variable and control level was the independent (explanatory) variable.