Author’s response to reviews

Title: The association between asthma control, health care costs, and quality of life in France and Spain

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

Again, 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 new comments of both reviewers. We hope that the editorial board will find this new version acceptable.

Kind regards,
Bruno Detournay

Reviewer: Mohsen Sadatsafavi

Minor Essential Revisions

1- Page 5, first paragraph: It is not really clear how the sample size is calculated. For a proportion, and in the absence of a well-defined null hypothesis (e.g., prevalence being different than 40%), sample size calculation can be based on a desired width of confidence interval. There is no null hypothesis in this section, and the authors do not mentioned how tight they wanted the CI around the prevalence to be. As a result, it is still unclear how the sample size of 380 for each wave is obtained.

To explain how the sample size of 380 was calculated, we changed a sentence p5: “Based on the percentage of patients with controlled asthma estimated to represent 40% to 50% of the overall population in previous studies, and knowing that the size of the sample needed to estimate percentage with a ± 5% value according to the confidence interval selected (alpha risk 5%, normal distribution), around 380 patients had to be enrolled quarterly”.

2- Data collection section: it is not clear how some important information had been collected for this study. For instance, it is mentioned that "all prescription drugs taken during the 3 months prior to doctor visit were recorded”. Is this a self-report? Or objective verification using, say, chart review? or something else? Similar concerns with regard to the other resource use items such as hospitalization, ER visits, and so on. For indirect costs, how the information on sick leaves and productivity loss was collected? There are validated instruments such as the Work Productivity and Activity Impairment Questionnaire (WPAI), but there is no mention of such instruments anywhere.

To detail data collection, the following sentence was added in the paragraph data collection p5:

For all medical resources consumption (including sick leaves) during the 3 months prior to GP visit, data were provided by GPs through the questionnaires used in the study. In France some data (i.e. prescription drugs related to asthma were also collected through the computerized medical files of the GPs).
3- Page 7, first paragraph: Not clear how the productivity loss using the human capital approach is estimated. Did the authors multiply the GDP/employed population/working days by the number of sick days? If so, the authors have collected the number of sick days for both countries (this should be mentioned somewhere).

Productivity loss was calculated like as mentioned by the reviewer. We provided more details on data collection (See answer to question 2).

4- Page 5: first paragraph under Data Collection: (FEV1)) has an extra closing parenthesis.

The parenthesis was removed.

5- Page 7, line 3 devised should change to divided.

It is now modified.

6- Table 1: Gender F: the letter F should be removed?

The “F” was removed.

7- Page 10: "but represented a major driver in partially controlled and controlled patients" should be "partially controlled and uncontrolled patients".

It is now modified.

8- Page 16: "must be assess" should read "must be assessed"

It is now modified.

Discretionary Revisions

9- Title: the word Impact implies causality. In this cross sectional study, causality between asthma control and outcomes cannot be established. A better title would be "The association between asthma control, health care costs, and quality of life in France and Spain".

It is now modified.

10- Abstract: (age greater or equal to 18) parentheses are not required.

Parentheses were removed.

11- Page 3 (first line of Introduction): asthma is a severe chronic disease. I would drop the word severe as asthma can be quite mild.

The word “severe” was removed.

12- Page 5: "The study was proposed to 750 GPs of this panel, randomly selected and 230 agreed to participate." will be read much better as "The study was proposed to 750 randomly selected GPs of this panel, and 230 agreed to participate."

It is now modified.
13- Data analysis section: I think more standard terminology for qualitative and quantitative variables are categorical and continuous, respectively.

It is now modified.

14- Results: It will be helpful if the authors also report the mean and SD of age, in addition to percentage of the population within each age range.

A line in the table 1 was added with mean and SD of age.

15- Page 9: 34.6% of French patients had exacerbations, and the rate was 2.3. For Spanish patients, the percentage of those experiencing exacerbation (43.6%) was higher, but the rate was lower (1.8). This is not necessarily wrong but needs verification.

We checked these data and they are correct. For France, 2.3 is the mean number of exacerbations among patients who experienced exacerbations. In Spain, 1.8 is the mean number of exacerbations among patients who experienced exacerbations. To avoid misunderstanding, we detailed in the text the unit as “episodes/patient with exacerbations/quarter”.

Reviewer: Pinar Karaca-Mandic

Original comment: Is it possible to control for asthma severity, and/or length of time since asthma diagnosis?

Authors added the “length of time since asthma diagnosis” in the descriptive statistics (Table 1). As Table 1 shows, there is large variation across individuals in this variable. I think it is important to control for it in the multivariate models as well (Table 4 and Table 6), which I don’t think the authors did.

Asthma severity was not measured in this survey.

With regard to the reviewer suggestion about the asthma history, we think that this parameter (which was added to the paper to answer to a previous reviewer comment) is too uncertain to be taken into account in the multivariate models. Length of time since asthma diagnosis is a very imprecise variable with important potential memory bias.

1) Original comment: 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? Authors now state in page 5: “In France, investigators were a sample of GPs selected from a representative panel of 1,200 general practitioners. The panel’s representativeness was established by three criteria: age, sex, and region of practice. The study was proposed to 750 GPs of this panel, randomly selected, and 230 agreed to participate”. My original comment was not about the representativeness of the “panel”, but rather about the comparison of those who agreed to participate (230) relative to those who did not (520 of the 750 who did not). Given that authors designed the study sample, they must have at least the geographic region and gender information (and perhaps age as well) of the 520 who did not participate. It is important to at least illustrate that the participants were not very different than the non-participants to make generalizable and unbiased statements using results from this study.

My follow-up original comment thus remains not-answered as well: “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 7 notes that GPs included in the study were similar to the general set of GPs in each county, but the results are not shown."

We understand that it is important to insure the reviewer and the readers of our study that both GPs samples were representative in France and Spain. It is why we compared the sample of participating GPs to the overall GPs population in each country. We based such comparison on the available characteristics of the GPs in our study (age distribution, gender, geographical area of the practices). We did not compare the participant to the non-participant group as we did not collect any data on this last group of GPs. Due to the number of the tables included in the paper (6 tables + 1 figure) we thought it was not necessary to provide an additional table with the detailed figures about this validation.

2) Original comment: “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 unweighted” I am still not convinced why the data needs to be weighted to compensate the disproportionate number of observations in each quarterly wave. I did not see an argument or conceptual framework that claim the number of patients are spread equally across quarters of the year in real life. Especially for a disease like asthma, there is seasonality and weighting the data to impose equal number of observations in each wave digresses from that reality. At the minimum, authors should represent the unweighted versions of their main findings (all Tables preferably, but Tables 2, 3 and 4 at the minimum) to the editors to confirm the results don’t change much, or change in some expected direction, which they should discuss.

We agree with the reviewer that the symptomatology of asthma is seasonal. We estimated average symptomatology, control, medical resources consumption, etc. over the whole year 2010. As the number of patients enrolled in our survey varied quarterly, using unweighted data would result in overestimating the consequences of the waves with the highest number of patients. We still continue to think that we had to weight the data according to the number of patients enrolled in each wave. Furthermore, this approach was used only in the French part of the survey. In Spain, the number of patients enrolled in the survey was the same over the four 2010 quarter and results provided were therefore unweighted.

3) Original comment: 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.

The response letter states that the authors “added results of multivariate regression analysis for comorbidities”. I am not convinced, because they have collapsed multi-dimensional co-morbidities to a 1/0 variable of whether the patient has at least one co-morbidity (I think they mean other than asthma). Why not put separate indicators for all the co-morbidities they have?

Co-morbidities considered were only related to asthma.
We choose to consider the co-morbidities in the multivariate regression analysis as a binary variable (patients with at least one co-morbidity vs. patients without any co-morbidity) as the distribution of this parameter is mainly driven by the percentage of patients with allergic rhinitis as described in Table 1 page 9.

4) Original comment: 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).

Authors responded stating that detailed costs per level of control are presented in Table 3 and that these data show that the cost of controller treatments is the main driver of cost regardless of the control level.

This statement and the presentation on page 17 are somewhat misleading. First, it is correct that controller medications are large components of per-patient costs regardless of control level (51.8 euros for controlled, 69.9 for partially controlled, 95.1 for uncontrolled). Second it is correct that uncontrolled patients have higher costs (225.3 euros direct) relative to controlled (81.2 euros) and partially controlled (116.9 euros). However, these do not mean, as stated on page 17 that “In particular, the costs for patients with uncontrolled asthma were mainly due to costs of controller treatments and not to complications of asthma”.

First, due to a misclassification of some drugs, we corrected the data provided in table 3.

Secondly, we agree with the reviewer and we changed the wording of the whole paragraph in the discussion part (now p19). We deleted the sentence: “In particular, the costs for patients with uncontrolled asthma were mainly due to costs of controller treatments and not to complications of asthma”.

5) Please note that while hospitalization costs are very small (actually zero euros) for the controlled and partially controlled, they are 33.6 euros for the uncontrolled. Similarly, ER costs are $4 for the uncontrolled, while zero for controlled, and 1 euro for partially controlled. In other words, hospitalization and ER costs make up 17% of the direct cost per patient for the uncontrolled, and almost 0% for the other two groups. I am surprised authors do not point this out.

More importantly, this means that uncontrolled group suffers from much larger hospitalization and ER costs relative to the other groups. In fact, the share of controller meds in direct costs is much lower for the uncontrolled group (42%) relative to uncontrolled (64%) and partially controlled (60%). This interpretation needs to be corrected/clarified in the text.

We agree with the reviewer and we changed the wording of the whole paragraph see above.

“In our study, the average total cost per patient over a 3-month period was higher when asthma was poorly controlled. Hospitalizations for asthma and emergency room visits associated costs were
higher in patients with uncontrolled asthma and they represent a higher percentage of the total direct costs (16.7% and 18.6% of the total direct cost in France and Spain respectively versus 0% and 0.6% in patients with controlled asthma).