Reviewer’s report

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

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Reviewer: Mohsen Sadatsafavi

Reviewer’s report:

This is the review of the manuscript entitled "Impact of asthma control on health care costs and quality of life in France and Spain".

The authors have attempted to measure the level of control in a sample of individuals with asthma according to the Global Initiative for Asthma (GINA) guidelines and to describe costs and quality of life according to the level of asthma control. The manuscript is based on the data obtained from France and Spain.

The manuscript investigates an important topic in asthma. The scientific body as well as policy makers need such knowledge in order to prioritize research efforts and policy decisions. Recognition of seasonality on the burden of asthma is also an advantage of the study. Reporting and data deposition are in accordance with current standards. Discussion and conclusions are generally balanced and supported by the data. Limitations of the work are well described in the Discussion, and the review of the literature is acceptable.

The analytic method, nevertheless, suffers from important shortcomings. In several places what the authors have done is not clear as the presentation is vague. Further details are provided below.

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/HRQL across control levels). This might be the reason why the adjusted estimates of difference 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.

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.

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.

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 need to mention this in the Discussion section that potential within-unit correlation in the data is not taken into account.

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

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.

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

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.

9) Page 6, paragraph 2: Normally unit costs used to calculated 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 costs provides clues as to the differences in costs across jurisdictions (Spain and France in this study).

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.

11) Table 1: P-values for all comparisons should be reported. Please replace the
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.

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?

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).

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.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests