Author’s response to reviews

Title: Health-related quality of life varies in different respiratory disorders: a multi-case control population based study

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Author’s response to reviews:

We thank you the reviewers for their precious comments. The answers to their requests are listed below.

Steven Ronsmans (Reviewer 1):

Abstract:
• In the Results section of the abstract p-values are given. I think it might be more useful to provide the effect estimates and confidence intervals (such as provided in the article).

We included the RRR and 95% confidence intervals, as suggested.

Introduction:

• Line 103: "Patients from CB HAVE impaired…". Same tense as the other statements

We have changed the whole sentence according to Reviewer 2 suggestions on Introduction.

Line 114: I think this statement is not correct: 10-40% of patients with rhinitis also have asthma (but over 80% of asthmatics have rhinitis) [Allergy. 2008 Apr;63 Suppl 86:8-160]. So it is common but not "usually".

The sentence has been rephrased in ‘Subjects suffering from AR commonly have current asthma (CA) and the effect of AR alone cannot be disentangled. Therefore, it can be of interest to analyse the role of AR in subjects without asthma.’

Methods

Line 128: How was this new random sampling done?

Line 133: What was the response to the invitations? What percentage did come to the clinical evaluation for each category (asthma, COPD/CB, AR, others, controls)

New details of sampling in the new random sample have been added in the Methods. In the Methods, there was also a misprint: ‘a sample of probable cases of AR(48%)’ changed in (44%).
In the Appendix 1, we have included a flow chart to describe the phases of the study. We have specified the response to the screening questionnaire and we have reported the selection of subjects according to their classification at the screening stage.

Line 136: You state that allergologic tests were done. What were these tests exactly? What specific IgEs were tested? What skin prick tests were done? Can you provide these? The reference you provide (n° 29) does not provide more information on allergologic tests.

Line 166: Same remark: What skin prick tests were done? Were they adapted to the history of the patient? If not, you might have some misclassification: eg in patients having allergic rhinitis to specific plants not tested with the skin prick tests (they would be classified as 'non-allergic')

The list of allergens has been added in Appendix 1. As our study is population-based, we used a fixed panel of allergens with its own limitations.

Line 179: What do you mean by 'ictus'

We have translated ‘ictus’ (Latin term) in ‘stroke’.

Results:

• Line 219: Percentage of females?

We have reported the percentages of females: ‘Cases of NAR and PA were prevalently females (61.1% and 57.9% respectively)’

Line 221: 52.2 YEARS

We have added ‘years’.
Line 222-224: "Never smokers were mainly controls, AR, …". I think the phrasing should be changed a bit: "Controls, AR and PA were mainly never smokers…"

We have rephrased the sentence as suggested: ‘Controls, AR and past asthmatics were mainly never smokers (52.8%, 58.9% and 53.2% respectively),…’

Line 232: The word 'other' should not be in this phrase

‘Other’ has been deleted.

Line 242-248 and Table 3: As the multinomial logistic regression is not a common technique I think it would be useful to provide some 'narrative' clarification in the discussion on how to interpret these RRR. What does a RRR of 0.615 mean for example? In the same paragraph and table 3: I think it is not necessary to report 3 digits as it can mislead the readers to think these effect estimates are very precise while they are base on relatively small groups (28-224 cases). I think 2 digits would be more appropriate.

The interpretation of RRR is similar to that of OR and RR.

‘As shown in the multinomial model (table 3), negative associations between a clinically important increment of 4 scale-points of PCS and respiratory diseases (that is, higher PCS scores for subjects without respiratory diseases) were significant for AR (RRR=0.80, p= 0.003, that is subjects with AR were ‘protected’ from having a higher HRQL), CB (RRR=0.74, p=0.003),…’

In the Results, we have provided some narrative sentences to facilitate the interpretation of RRR, as suggested, and we have changed the legend of table 3.

Table 3: RRRs for a 4 scale-points increment of PCS and MCS according to different phenotypes.

Line 310-311: You say that AR negatively affects HRQL especially at older ages and BMI. I could not find results in your study underpinning this statement. Could you provide these in the results section?
Thank you for your comment. We realised that no results have been reported for BMI and older ages, and we decided to focus our attention on the differences in HRQL in cases and controls. So we decided to drop this sentence from the discussion.

Line 312: You state that "even at the level of severity that is common in the general population, COPD and asthma have a significant impact". Is the level of severity in your study population different from previous studied (hospital) populations? Was there a higher percentage of 'mild' cases (based on for example lung function testing)? To underpin these conclusions it can be interesting to provide an overview of the spirometries of the asthma and COPD cases.

We have added some information on lung function (FEV1% predicted, see new row in table 2) to support our hypothesis that even in the general population, COPD and asthma have a significant impairment in lung function: FEV1% predicted is different in the different groups of cases and controls, in particular subjects with COPD and to a lower extent subjects with asthma and BC show lower FEV1% predicted levels with respect to controls, on the contrary AR and NAR show FEV1%predicted similar to controls.

Line 315-316: I think that I understand what you mean by 'minor', 'major', 'marginal' diseases but I think it should be good to clarify this point and say who exactly is saying that these diseases are 'minor'. CB and AR are not marginal in terms of prevalence. It is mainly the perception of physicians (not the perception of patients) that diseases that cannot be 'objectified' (e.g. by lung function or imaging) are 'minor' diseases. I think this is a very interesting point. It would be interesting if you want to make this point that you refer to some literature on the perception of physicians of AR and asthma, or of 'not-objectified diseases' in general. I'm not very familiar with this literature but in the 'pain'-literature (pain = subjective) there are similar studies.

According to your suggestions, we have changed the final sentences in:

‘On the whole, these findings emphasise that, even at the mild level of severity that is common in the general population, COPD and asthma have a significant impact on HRQL. Moreover, our data indicate that also CB and AR, with lower impact on DALYs in comparison to COPD or CA [4], are not trivial conditions. It derives that clinicians should also carefully consider CB and AR in relation to HRQL of these patients.’
Sebastien Chanoine (Reviewer 2)

Major comments:

1. SF-36 questionnaire taps 8 health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It should be interesting to develop the results for each domain in a study focusing on HRQL.

   It would be very interesting to consider also all SF-36 domains (bodily pain, role limitation due to physical health problems…), but, as we pointed our attention on 5 respiratory diseases plus controls contemporarily, we decided to focus only on the synthetic indexes PCS and MCS in HRQL (Ware J, Kosinski M. Interpreting SF-36 summary health measures: A response. Quality of Life Research (2001) 10: 405-413). All the domains contribute in different proportions to the scoring of both PCS and MCS measures: these measures capture more than 80% of the variance of the 8 domains. Also, the consideration of 8 domains could be quite confusing in presenting the results.

2. How did the authors select the studied comorbidities? Why did they not include others disorders such as hormonal disturbances or cancers? Why did they study cardiovascular diseases alone (which did not include hypertension)?

   Originally, hypertension was included in ‘other hearth problems’: we specified it separately now. The hormonal disturbances have not been included in the GEIRD questionnaire and so we could not consider them. Cancer was considered, but it was reported in the Methods section with the Latin term ‘neoplasia’. Now we have changed it.

3. One of the criteria of COPD definition was age> 35 years old. Why did the authors use this threshold and not 40 as usually?

   As our study is population-based, we chose the threshold of 35 years of age to increase the likelihood of finding subjects with COPD, even if we were conscious that it would have been
difficult to really find them at younger ages. On the other hand, it would have been particularly interesting to find subjects with the disease and so young.

4. The authors identified a co-occurrence of asthma and COPD in some individuals (n=21, including CA and PA). Is it potential misdiagnosis?

Our study is population-based and the definitions have been previously defined, so that a percentage of missclassification is expected as a limitation intrinsic of this type of study.

5. Moreover, asthma and COPD define ACO, which is a specific phenotype characterized by a higher severity than asthma or COPD alone, and so a potential poorer health perception. This group of individuals should be studied separately.

It could be very interesting to study separately the subjects with both asthma and COPD, but, in our population-based study, we could detect only a little number of them, 16 (appendix 2; fig.S1), and so they could not be analised alone.

6.a. SF-36 questionnaire covers the previous 1 to 4 weeks and may vary over time. The authors did not discuss that point. Do they think that their results remain stable over time?

SF-36 can reflect very well the health status at the moment of the interview and it is habitually used also to see the difference in HRQL before and after a treatment, that is to identify changes in health status. HRQL is in itself a variable phenomenon. SF-36 is normally used in many studies measuring HRQL and so we decided to use it.

6.b. The study relies on a small population from a single centre. We can question the generalizability of the results.

We have added a sentence in the Discussion to explicitly show this limit of our study.
6.c. Gender differences in health perceptions have been showed. Women may have a worse health perception than men. What is the impact of this gender differences on the results of the study? This should be discussed.

To keep in account gender differences in quality of life perception, we adjusted the multinomial logistic regression model also for gender, as specified in the Methods (Potential determinants of HRQL and covariates) and in the notes of fig.3.

Minor comments:

1. The introduction section should be rewritten to avoid a list of diseases that have common characteristics.

The introduction has been modified according to this suggestion.