**Author’s response to reviews**

**Title:** Age-specific incidence of allergic and non-allergic asthma

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**Author’s response to reviews:**

Dear Anna Melidoni/Editor of BMC Pulmonary Medicine

We thank you for the constructive comments on our manuscript. We have now revised the manuscript according to the suggestions and feel that it improved markedly by the good suggestions from the reviewer. We hope that the manuscript is suitable for publication in the revised form, and we are willing to do further changes if needed.

Yours sincerely,
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Point-by-point response to the Reviewer report:

Reviewer reports:

Stefania La Grutta (Reviewer 1): Manuscript PULM-D-19-00077

It is an interesting manuscript aiming at assessing the incidence of allergic and non-allergic asthma in relation to age from a cross-sectional sample of Finnish individuals aged 20-69 years. The Authors should address some issues as suggested below. Please note that this Reviewer will mention the page numbers (upper left) and the line numbers added by the authors (1 to 488) when referring to the text.

Title

Actually, the Authors do not assess the "Age at asthma diagnosis in subjects with and without allergy", but rather the "Age at diagnosis in asthmatic subjects with and without allergy". Indeed, all the individuals reported in Table 2 had an asthma diagnosis. Conversely, what is assessed over all individuals (not only asthmatics) is the incidence of allergic and non-allergic asthma in relation to age. The Authors may choose what they want to give a greater emphasis in the title: "Age at diagnosis in asthmatic subjects with and without allergy" (present title modified) or "Age-specific incidence of allergic and non-allergic asthma" (alternative title). Indeed, they are two ways of conveying a similar message.

- Thank you for the review, this is an important and good point about the title. The title was changed to "Age-specific incidence of allergic and non-allergic asthma".

Abstract

Page 2, line 39: as for the title, please reword the aim: "The purpose of the study was to assess the proportion and incidence of allergic and non-allergic asthma in adulthood in relation to the age at asthma diagnosis".

- The aim was changed to match the new title "The purpose of the study was to assess age-specific incidence of allergic and non-allergic asthma".

Page 3, line 55: "most new" → "most of the new".
Background

Page 4, line 62: "Backround" → "Background".

- The manuscript's text was corrected as suggested.

Pages 4-5, lines 82-85: please reword the aim as for the abstract; "in a population-based postal questionnaire study conducted in Finland" can be retained. In addition, this Reviewer would avoid the term "concomitant", since the time at the diagnosis of rhinitis is not known.

- The aim of the study was rephrased as follows "Our aim was to study the association between asthma onset age and allergy by assessing age at diagnosis and age-specific incidence of asthma in adult asthmatics with and without allergic rhinitis in a population-based postal questionnaire study conducted in Finland." The word "concomitant" was removed.

Methods

Page 5, line 96: what do the authors mean by "normal" age and gender distribution?

- With "normal" age and gender distribution we mean the same age and gender distribution as in the population of the geographical area. The word "normal" was removed and the sentence rephrased as follows "The study sample was obtained from the Finnish Population Register and it was matched to the age and gender distribution of the population in the geographical area of our study."

Page 5, lines 98-103: please describe Figure 1 more strictly (for example 7942 is not reported in Figure 1), and say "actual" (rather than "corrected") only for the final sample size used for the analyses (3967).

- The "7942 subjects" was added to Figure 1 to make it more precise and the steps of Figure 1 were more strictly described in the manuscript's text.

Page 5, line 103: please report the approval number.

- The approval number was added, as suggested.

Page 6, line 112: "which is a modified from version of the Swedish version translation of".
- The manuscript's text was corrected to read "which is modified from the Swedish translation of the British Medical Research Council (BMRC) questionnaire."

Page 6, line 113: "consists of" → "includes".

- The sentence was corrected as suggested.

Page 6, line 124: what do the Authors mean by "primarily"?

- The Reviewer is correct to question this, the word "primarily" should not be used in this sentence since allergic rhinitis was the only indicator of allergy used. The word "primarily" was removed.

Page 7, lines 128-145: please move to "statistical analysis". The methodology used for estimating age-specific incidence from cross-sectional data looks correct, despite it has some drawbacks as pointed out by the Authors in the discussion (generational effect). However, this Reviewer had some difficulties to understand its description. It seems that longitudinal data were retrospectively reconstructed from the answers to the questionnaire, like if the 3967 subjects were actually a cohort of new-borns recruited starting from 69 years ago until 20 years ago. Strictly speaking, a "time-to-event" (actually an "age-to-event") was recorded for each individual, and the population at risk at each time (age) was updated according to standard, survival analysis methodology, i.e. both events (subjects reporting asthma diagnosed at younger age than the age for which the population at risk was calculated) and censorships (asthma-naive responders younger than the age for which population at risk was calculated) were subtracted from time to time. Please make an effort for improving clearness.

- Lines 128-145 were moved to "statistical analysis" and we have clarified the description of the methods according to the suggestions.

Statistical analysis

Page 7 line 149: "continuous variables".

- The manuscript's text was corrected as suggested.

Results

Page 8, line 159: "In addition" → "More in detail".

- The manuscript's text was corrected as suggested.
Page 8, line 163: "cohort"→ "sample".

- This is part of a sentence rephrased and the word "cohort" was deleted.

Pages 8-9, lines 182-198: difficult to follow. Please describe Tables and Figures sequentially and one by one (avoid switching repeatedly from Figure 2 to Figure 3). Moreover, try to be consistent with the abstract: where did you report that "Among subjects with asthma diagnosis at ages 0-19, 20-39, 40-49 and 50-69 years, 67%, 55%, 38% and 23%, respectively, were allergic"?

- The manuscript's text has been totally revised to make it easier to follow. The age groups and the proportions (%) of allergic asthmatics have been changed in the abstract to match the numbers presented in the results section of the manuscript.

Page 10, line 193: "Accordingly"→ "Therefore".

- The manuscript's text was corrected as suggested.

Page 11, line 194: "distinctly"→ "markedly".

- The manuscript's text was corrected as suggested.

Page 11, lines 206 to 212 (from "When calculating..." to "... 40 years"): please move to statistical analysis.

- The text in lines 206-212 was moved to "statistical analysis".

Page 11, line 208: "Since different age cohorts have also different overall incidence of atopy": did the Authors check that?

- We have now checked that in our sample the prevalence of allergic rhinitis was lower in the older age groups as compared to younger age groups (prevalence of allergic rhinitis was 23.4%, 27.2%, 23.5%, 15.6% and 10.5% in the age groups 20-29, 30-39, 40-49, 50-59 and 60-69 years, respectively, p = 0.036). This is now stated in the Results section.

Page 11, line 209: "relative proportion".

- The manuscript's text was corrected as suggested.

Page 11, line 211: "age cohorts"→ "age groups".
- The manuscript's text was corrected as suggested.

Page 11, line 212: "before the age of 40 years" actually, it seems that the Authors compare three age groups: <40, 40-60 (not simply "older than 40") and >60.

- We have now modified this analysis so that we compare three separate groups according to their current age: <40 years, 40-60 years and >60 yrs.

Table 1: Would it be worth creating a unique "allergy" variable with the following categories? 1=no; 2=pollen only; 3=non-pollen only; 4="both" (percentages will then sum up to 100). Same for Table 2.

- Thank you for a very good idea. Tables 1 and 2 were corrected and the presence and cause of allergic rhinitis have been described under a new term "allergic rhinitis".

Table 2: Would it be worth highlighting that non-allergic asthmatics were more frequently ex-smokers?

- Yes, it would be a very good notice. A sentence considering the matter was included in the Results section and it was also covered in the Discussion section (as suggested in the later comment of the Reviewer about page 14, line 266).

Why do the authors report three p-values for smoking?

- We reported p-values (as determined by chi-square test) separately for never, ex and current smokers. However, we have now modified the analyses by producing only one p-value for smoking status by chi-square test. Furthermore, some inconsistencies in the data were corrected regarding smoking status.

Moreover, how do you define ex smokers?

- Ex-smoker was defined by an answer "yes" to the question "Have you previously been a smoker, but have quit smoking over a year ago? ". The definitions of the terms "current smokers", "ex-smokers" and "never smokers" were added in the "definitions" section of the manuscript.

Did you also ask about "passive smoking"?
There was a question about "passive smoking" in the questionnaire but the answer was merely "yes" or "no". We did not ask about the length or quantity of passive smoking and for this reason, we did not include it in our analyses.

Figure 2 and Additional File 2: please replace "Age at asthma diagnosis" simply with "Age group" in the x axis label (do the Authors agree?).

- Yes, we agree and changed it as suggested.

Discussion

Page 12, line 224: "accepted"→ "recognized".

- The manuscript's text was corrected as suggested.

Page 12, lines 229-230: "total incidence of asthma": do the authors refer to the sum of the incidence rates of allergic and non-allergic asthma?

- A very good observation and yes, we did mean that. The manuscript's text was corrected to be clearer on the matter: "In our study, the combined incidences of allergic and non-allergic asthma were highest…"

Page 12, lines 232-235: which studies are the Authors referring to?

- Apologies for the missing references. They were included in the manuscript's text as follows:


Page 12, line 235: "onset ages"→ "onset age classes".

- The manuscript's text was corrected as suggested.

Page 13, line 242: "prevalence"→ "proportion".

- The manuscript's text was corrected as suggested.
Page 13, line 245: "Many"◊ "Several".

- The manuscript's text was corrected as suggested.

Page 13, line 245: "have also reported".

- The manuscript's text was corrected as suggested.

Page 13, lines 249-251: "A cluster of…been reported": unclear.

- The word "cluster" was changed to phenotype, which is more appropriate in this context.

Page 14, line 264: "prevalence"◊ "proportion".

- This is part of a sentence rephrased and partly deleted (as suggested in the next comment of the Reviewer about page 14, line 264).

Page 14, line 264: "The reason for the decline in the prevalence of atopy with increasing age at asthma diagnosis…": better to say "The reason for the decline in the incidence of allergic asthma with increasing age..."

- The sentence was corrected as suggested.

Page 14, line 266: "may be related to cumulative exposure to irritating factors": may the higher proportion of ex-smokers among non-allergic asthmatics (Table 2) confirm this hypothesis?

- Yes, this is a good point and a sentence referring to this was included in the Discussion section as follows "Indeed, the higher proportion of ex-smokers among the non-allergic asthmatics in our study would support this hypothesis."

Page 14, lines 267-269: "Another phenomenon that may affect the results of cross-sectional studies estimating incidence is cohort effect"◊ "Another reason may be the cohort effect that may affect incidence when estimated from cross-sectional data".

- The manuscript's text was corrected as suggested.

Page 14, line 271: "Moreover, according to population-based studies, …".
- The manuscript's text was corrected as suggested.

Page 14, lines 271-273: "According to population-based studies, the prevalence of allergic sensitization in general decreases with increasing age due to low incidence and higher remission": the Authors then reported evidence from several studies; did the Authors check the overall prevalence of allergy by age group in their own dataset?

- We have now shown that the prevalence of allergic rhinitis is lower in the oldest age cohorts of our sample (see the Results section) but among asthma cases diagnosed before the age of 40 years, the proportion of allergic asthma did not differ between these age cohorts. This is now mentioned in the Results and in the Discussion sections.

Pages 14-15, lines 284-287: "Consequently…main finding": unclear.

- The Reviewer is correct, these are unclear sentences and both of them were removed from the manuscript.

Page 15, line 285-286: "the slight increase of prevalence in the proportion".

- This is part of the sentences deleted.

Page 16, line 319: why only "specificity"? What about "sensitivity"?

- The word "specificity" was changed to "reliability" to be more accurate since we did not have possibility to do any statistical analyses to check this.