Author’s response to reviews

Title: Long-term follow-up in European respiratory health studies - patterns and implications

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Author’s response to reviews: see over
Dear editors at BMC Pulmonary Medicine, and dear referees.

We thank you so much for taking the time to assess our paper «Longterm follow-up in European respiratory health studies – patterns and implications». We deeply appreciate the referee comments, and believe that through addressing them we have now further improved the quality of our paper.

We list our point-by-point response to the referees’ comments below. All changes in the manuscript are written in red to make them easier to see for editors and referees. Also, in the revised version of the manuscript, we have conformed to the journal’s formatting style using the template found at [http://www.biomedcentral.com/authors/medicine_journals](http://www.biomedcentral.com/authors/medicine_journals).

We hope that you approve of our revision, and that the paper may proceed to publication. If anything is unclear or otherwise unsatisfactory, please let me know.

Best wishes on behalf of all authors,
Ane Johannessen.

RESPONSE TO REFEREES

Referee 1

Minor essential revisions:

C1. Consequences of bias of baseline "under-estimation" and "over-estimation" in longitudinal studies could be better discussed and exemplified in terms of effects on incidence, remission and risks (the latter seems not to be a major problem in the studies the paper is based upon) in the discussion section.

R1. We agree, and we have added the following paragraph in the revised Discussion focusing on such effects of baseline bias: «Bias in baseline prevalence estimates may also have consequences for follow-up estimations on incidence, remission and in some instances also risks. The lower baseline prevalence of respiratory symptoms among long-term participants as compared to total baseline participants that we found in the present study may indicate a healthy survivor effect in the study. Such an effect is most commonly observed in association with occupation, in that persons who remain employed tend to be healthier than those who leave employment. However, it is also plausible that persons who continue to participate in a study is healthier than persons who quit their study participation, especially in a study with such a long follow-up period as the RHINE and the Italian ECRHS have. Incidence and remission estimates in the follow-up stages of these studies may both be under-estimated compared to true population estimates if the follow-up population is generally healthier than the total population. However, in the present study we did not find very large variations in baseline prevalence estimates, and the effects on incidence and remission estimates later on in the study are consequently likely to be small. Future incidence investigations based on the three studies covered here should nevertheless take into
account the observed baseline differences between total baseline participants and long-term participants in the interpretation of results.

C2. There are published longitudinal studies, for instance on COPD also from the neighbouring countries of the first author, that have clearly recognized and discussed differences in baseline prevalence among all who participated in an initial study and the prevalence in the initial study among those who participated at a follow-up study. At least some of them could be referred to.

R2. There are indeed very good studies from neighbouring countries addressing the issue of non-response in both cross-sectional and longitudinal settings. In the initial version of our paper, we included reference to among others a paper by Rönmark et al (2009) on effects of non-response in a Swedish large-scale questionnaire survey, a paper by Kotaniemi et al (2001) on effects of non-responder bias on respiratory prevalence estimates, a paper by Eriksson et al (2012) on influence of non-response in a cohort study of diabetes, a paper by Rönmark et al (1999) on non-responders to a postal questionnaire on respiratory symptoms and diseases, and a paper by Vestbo et al (1992) on how baseline characteristics are not sufficient indicators of non-response bias in follow-up studies. However, we did not manage to find papers with specific focus on differences in baseline prevalence among total baseline populations and follow-up participants at baseline. If the referee has one or more specific papers in mind addressing this particular issue, we would be very happy if he could provide us with information on what paper(s) this is, so we could integrate them in the revised Discussion section of our manuscript.

C3. The text to the results section is absolutely too long. All, or most, of the significant results must not be mentioned in the text as they all can be found in the tables.

R3. We agree, and we have shortened the results section with approximately 200 words. We have especially deleted parts describing details of the analyses stratified by study centers in the online supplement, focusing instead on more general summaries.

C4. The discussion section has in parts a tendency to too much repeat the results. Please, consider that.

R4. We agree, and we have now removed parts of the Discussion that repeat results concerning predictors for participation and shortened the rather long paragraph concerning contradicting results in two Italian papers. We have also deleted the paragraph in the Discussion concerning center-specific analyses, since it in many ways just repeated what was already said about the main analyses. Due to the comments from the referees, we have also added certain new paragraphs on other topics, giving an (in our opinion) overall improved and more varied Discussion section.

Discretionary revisions:

C5. The authors refer to methods by Nielsen et al (ref 8, 16-19) in the methods section. Please, give a short summary.
R5. In fact, the whole section «Statistical methods» is a description of the methods by Nilsen et al, from his paper «Self-selection and bias in a large prospective pregnancy cohort in Norway». However, as the referee correctly points out, this is not clear to the reader. We have thus revised this paragraph, emphasizing that the paragraph is indeed a description of Nilsen’s methodology. To make this clear for the readers, we start the description with the following sentences in the revised «Statistical methods» section: «When examining if prevalence and association estimates differed between all baseline and long-term participants, we followed methods used by among others Nilsen et al, using baseline data as the reference [8, 16-19]. The methodology used by Nilsen et al is described in detail in the remainder of this section, applying it to the focus of interest in the present study.»

C6. I am not 100% happy with the terms "under-estimation" and "over-estimation". Of course they can be used, however, are there better terms you can find for this important item?

R6. We agree that these are not optimal terms. In the revised version of the manuscript we have re-placed «under-estimation» and «over-estimation» with «higher prevalence» / «stronger associations» and «lower prevalence» / «weaker associations». For example in the first paragraph of the revised Discussion: «When comparing long-term participants to all baseline participants, we found lower baseline prevalence of several respiratory symptoms among long-term participants compared to all baseline participants.» Revisions of this kind has been performed throughout the manuscript, marked in red font.

Referee 2

Minor essential revisions:

C1. The submitted paper lack page numbers.

R1. Indeed, we forgot the page numbers in the initial version of the manuscript. We have now added page numbers to the revised manuscript.

C2. Throughout the paper, the phrase “compared with” has been used. However, in some cases it is more correct to say “compared to”. Please make the appropriate changes in the manuscript.

R2. We agree that «compared to» is more appropriate than «compared with». In the revised version of the manuscript, we have replaced «compared with» with «compared to» in the 14 instances where this wording was used.

Discretionary Revisions:

C3. Introduction. The aim includes a description of the method (“to quantify bias in 10 prevalence estimates” and “we analyzed data from (...)”). This information is redundant in the aim which should focus on the objective of the study.
R3. We agree. The revised aim now reads: «The aim of the present paper was to examine long-term participation and consequences of loss to follow-up in Northern European and Italian study centers. We aimed to identify predictors for long-term participation, and to quantify bias in selected respiratory outcomes and exposure-outcome associations.»

C4. Method. Understanding of the study design could be facilitated by a flow chart.

R4. We agree, and have added a flow chart figure of the three studies in the revised version of the manuscript (Figure 1. Flow chart of the RHINE, I-ECRHS and ISAYA studies).

C5. Result and Discussion. The sections entitled «Baseline prevalence of respiratory symptoms» and «Associations of age and sex...» could be considerably shortened. Presenting only the most important results from each table in fewer sentences would facilitate the reading.

R5. We agree, and we have shortened the sections entitled «Baseline prevalence of respiratory symptoms» and «Associations of age and sex...» with approximately 200 words. We have especially deleted parts describing details of the analyses stratified by study centers in the online supplement, focusing instead on the most important results and on general summaries.

C6. The study showed that the prevalence of respiratory symptoms was underestimated among the long-term participants. One aspect that could explain part of the result is a selection bias caused by the healthy survivor effect. This should be included in the discussion.

R6. This is a good point, and we have included the following paragraph on healthy survivor effect and its effect on selection bias in the revised Discussion: «Bias in baseline prevalence estimates may also have consequences for follow-up estimations on incidence, remission and in some instances also risks. The lower baseline prevalence of respiratory symptoms among long-term participants as compared to total baseline participants that we found in the present study may indicate a healthy survivor effect in the study. Such an effect is most commonly observed in association with occupation, in that persons who remain employed tend to be healthier than those who leave employment. However, it is also plausible that persons who continue to participate in a study is healthier than persons who quit their study participation, especially in a study with such a long follow-up period as the RHINE and the Italian ECRHS have. Incidence and remission estimates in the follow-up stages of these studies may both be under-estimated compared to true population estimates if the follow-up population is generally healthier than the total population. However, in the present study we did not find very large variations in baseline prevalence estimates, and the effects on incidence and remission estimates later on in the study are consequently likely to be small. Future incidence investigations based on the three studies covered here should nevertheless take into account the observed baseline differences between total baseline participants and long-term participants in the interpretation of results.»

C7. In several places in the Discussion (as well as in the abstract), the authors state that the exposure-outcome associations were mainly unaffected by loss to follow-up. However, a more appropriate term would be “unchanged”. The prevalence of respiratory symptoms was
higher (and the prevalence of smokers was probably also higher) among those lost to follow-up and if they would have been participated in the follow-up surveys, the exposure-outcome associations would probably have yielded different results. This aspect should be included in the discussion.

R7. We agree that the term «unchanged» is better suited than «unaffected» in this context, and have changed the Results and Discussion section accordingly.

As the referee has noted, the baseline prevalence of respiratory symptoms was lower among long-term participants. If those lost to follow-up had participated in the follow-up surveys exposure-outcome associations may have yielded different results. Although the focus for this paper has been baseline associations and not follow-up associations, we appreciate this point of view from the referee and have included the following sentences in the revised Discussion section: «It should be noted, however, that the focus of the present paper was associations at baseline. Exposure-outcome associations based on one of the follow-up studies with both the follow-up population and those lost to follow-up included might have resulted in different estimates. Since those lost to follow-up per definition will never be included in a follow-up study, this will of course be a purely theoretical speculation.»

C8. In the Discussion, under the headline Characteristics and bias..., fifth paragraph, last sentence, the authors state that the results from the present study should be taken into account in future prevalence reports from RHINE, I-ECRHS and ISAYA. Please give an example of how it should be taken into account (in analyses?) and in what way the prevalence should be interpreted differently.

R8. We have added the following in the revised Discussion following the mentioned sentence: «For instance, knowing that the baseline prevalence of wheeze in RHINE was 8% lower among long-term participants than among the total baseline participants should have consequences for the interpretation of wheeze prevalence in a later follow-up study. If wheeze prevalence at a follow-up study is for instance 25%, we should take into account that the “true” wheeze prevalence is likely to be approximately 8% higher, i.e. 27%. Also, knowing that the baseline prevalence of rhinitis in ISAYA was 14% higher among long-term participants than among the total baseline participants would infer a similar interpretation of rhinitis prevalence in a later follow-up study: a rhinitis prevalence of for instance 20% in a follow-up study would indicate a “true” rhinitis prevalence to be 14% higher, i.e. 22.8%.»