Author’s response to reviews

Title: Prevalence and clinical associations of wheezes and crackles in the general population. The Tromsø Study

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Author’s response to reviews:

We appreciate all the comments made by the reviewers. We think that their observations have been useful to improve our manuscript. In the following lines is summarized how we have addressed all the comments.

Reviewer 1

1. Abstract/ Background/ P.2, Line 4; It is more appropriate to state "apparently healthy adults".

Response: We agree with the reviewer. The sentence has been modified as suggested.

2. Abstract/ Conclusions/P.2, Line20; It is more appropriate to state "over a quarter" rather than "nearly 1/3" - 28% is closer to 25% than 33%.

Response: We agree with the reviewer. The Sentence has been modified as suggested.

3. Background/ P.3, Lines 6-8. Interstitial (fibrotic) lung disease and bronchiectasis should be added to the list of conditions described.

Response: We agree with the reviewer. The Sentence has been modified as suggested.
4. Background/ P.3, Lines 8-10. This sentence does not convey a clear message and needs to be rephrased.

Response: We agree with the reviewer. The sentence has been rewritten to give a clearer message.

5. Background/ P.3, Line 11. This sentence could be made clearer by deleting "of ALS".

Response: We agree with the reviewer. The sentence has been modified as suggested.

6. Background/ P.3, Line 13. It is more appropriate to state "apparently healthy adults".

Response: We agree with the reviewer. The sentence has been modified as suggested.

7. Methods/ P.4, Line 2. Some outline of the purpose/ nature of the Tromso Study is required to set the present paper in context. A brief outline of methodology for that study would be appropriate and help inform the reader. That should be referenced. Please add.

Response: We agree with the reviewer. We have written two sentences to quickly describe the study. We have provided a reference where the study details (including questionnaires and variables included) can be consulted online. In addition, we have provided a reference where the cohort profile is described in detail.

8. Methods/ P.4, Line 6. It should say "were" not "where".

Response: We agree with the reviewer. The sentence has been modified as suggested.

9. Methods/ P.4, Line 13. Were interstitial lung disease and bronchiectasis asked about in the questionnaire? If so that should be mentioned here. As a linked point the questionnaire used could be made available (English version) in the online supplementary section.

Response: Bronchiectasis and interstitial lung disease were not included in the questionnaire. We agree with the reviewer that this is a limitation and we have included this point in the discussion section. We have included in the text a reference to the webviewer “Nesstar” where all the variables and questions included in the Tromsø study are available for consult. (http://tromsoundersokelsen.uit.no/tromso/)

10. Methods/ P.4, Line 23. Please state whether lung function was pre or post-bronchodilator as that is essential for correct interpretation of results.

Response: The spirometry protocol in the Tromsø Study did not include a post-bronchodilator measure. Therefore all the spirometry data could be considered as “pre-bronchodilator”. This has been made clear in the paragraph concerning spirometry. Page 5 Line 7:

“We did not perform post-bronchodilator measurements.”
11. Methods/ P.6, Line 1. It is mentioned that 2 observers independently listened to all the recordings but then lists 4 names which is confusing. Is it that JCA listened to all recordings and one of either RE, AD, CJ were the 2nd observer? This sentence could be made clearer to aid understanding.

Response: The reviewer has understood correctly the situation with the observers 1 and 2. We agree with the reviewer that it could be better explained. We have added the following sentence in page 6, line 10:

“J.C.A. was observer 1 and either R.E., A.D. or C.J. were observer 2.”

12. Methods/ P.6, Lines 14-15. Were these junior and senior observers the same as JCA, RE, AD and CJ or different? Please clarify.

Response: We agree with the reviewer. We have modified the sentence in Page 6 Line 22 to:

“At the third step, all recordings classified as containing ALS were re-classified by two pairs of observers consisting of one junior (J.C.A. and C.J.) and senior (H.P. and H.M.) lung sound researcher each.”

13. Statistics/ P.7, Line 22. Is there a justification for taking p-value of <0.05 for selecting parameters for entry into the multivariate logistic regression when many researchers would use a less conservative p-value (eg <0.1 or even <0.2) to identify them?

Response: We were concerned that small differences would be statistically significant due to the large number of participants in our sample.

14. Results/ P.8, Line 8-9. The studied population in this paper is a small proportion of the Tromso 7 study population. There are a couple of clarifications needed here. Firstly that the Tromso 7 population is representative of the general Norwegian population. Secondly that the subgroup presented in this paper is representative of the main Tromso 7 population. It should be possible presumably for the authors to present some data on demographics of those in the main Tromso 7 group compared to those in this subgroup? That could be placed in the supplementary material but referred to in the text.

Response: The reviewer points at a legitimate concern. We have therefore made a table comparing all the participants of Tromsø 7 and the final sample included in our study. In this table we have included the main variables used in our analyses. From this table we conclude that our sample is representative of all the participants of the 7th Survey of the Tromsø Study. This supplement is referred in the text in page 8 line 16 an reads as following:

“A comparison of the main characteristics between all the participants of Tromsø 7 and the final study sample is presented in supplement 1.”

15. Results/P.8, Line 11 & P.19. Differences in a series of descriptive parameters are presented stratified by sex in Table 1. Looking at the values presumably none of the
differences are statistically significant. If so it would be useful to mention that in the associated text on page 8.

Response: We agree with the reviewer that the addition of P-values to the comparisons in table 1 would be useful. We have added the p-values of Chi square tests in the table 1. We have added the following sentence:

“We observed that women had lower proportion of myocardial infarction, heart failure and past smokers, but they presented a higher proportion of self-reported asthma, dyspnea (mMRC) and oxygen saturation ≤95%.”

16. Results/P.9, Line 1. There seems to be a discrepancy between the number included in the analysis reported here (n =262) and that reported in Line 5 (n =1131). I presume there is a logical explanation but it is not clear from the paper. Please clarify.

Response: We are describing two different proportions.

In the paragraph starting on P9 Line 1 we describe the prevalence of noise in the audio recordings as a measure of the quality of the material (262 of 4033). This sentence is under the subheading classification agreement.

In the paragraph that starts on P9 line 13 we are describing the prevalence of positive cases of ALS in our sample (1131 of 4033). This paragraph starts under the subheading “Prevalence of wheezes and crackles”.

These two numbers originate from two different analysis of the same sample. We believe the subheading marks a clear difference between the two paragraphs.

We have made a precision also from an observation from reviewer 2 and now the sentence in page 9 line 9 reads as following:

“The presented prevalence of ALS are based on six recordings in 3771 (93.5 %) participants. However, in 262 (6.5%) of the participants included in the analysis there was noise in one or more recordings. Five recording sites were considered in 223 (5.5%) participants and four or less recording sites in 39 (1 %) participants.”

17. Results/ P.9, Line 6-7 & P.20. A few comments here. The text on page 9 doesn't clearly summarise the findings in Table 2. Specifically it should summarise what comparisons were significantly different as there appear to be several highlighted in the table. Also, with regards to the table it states that the p-values relate to "as compared to absence of characteristic". This needs to be made clearer. Was "Normal" used as a standard reference for comparison of each auscultatory status? Or is the comparison different? Looking at the p-values presented it doesn't seem that "Normal" was used as a standard reference for comparison eg Age≥ 65 years "both crackles & wheeze" = 4.4% and "Normal" = 66.4% but no significant p-values seem to be annotated. Again I presume
there is a logical explanation but both in the text on page 9 and table 2 footnote there needs to be a clearer description of the comparison being presented.

Response: When it concerns the text summarizing the results of table 2, we did not want to repeat the information already provided in the table. It was our concern to write the shortest possible article and chose not to repeat the information in the table. That is why we have referred to the table in the text and the statistically significant comparison are highlighted.

We see the point of the reviewer about lack of clarification about the p values and the percentages in the table. For this reason we have written in the footnote of the table the following remarks:

“Percentages (%) represent the distribution of each variable between the different groups.

***p value <.001, **p value <.01, *p value <.05 as compared to normal.”

It is also possible to present the percentages of the prevalence of the trait in each different group, but we believe the table is more informative as it is now.

18. Discussion/ P.10, Line 23. This should more appropriately read "not always related to clinically diagnosed disease".

Response: We agree with the reviewer. The sentence has been modified as suggested.

19. Discussion/ P.12, Line 18. The omission of interstitial lung disease and bronchiectasis form the conditions at present defined in the paper is a significant one. Either that data should be presented if available or this should be noted as a limitation in this section of the Discussion. Both conditions would be expected to show an incident rise with advancing age and be associated with crackles on auscultation. It may therefore be that a proportion of subjects presently defined as healthy in this study actually had such disease.

Response: We agree with the reviewer that the undescribed presence of interstitial lung disease and bronchiectasis constitutes a limitation in our study. This is a useful observation. However, the questionnaires of Tromsø 7 did not ask about these two conditions and as a consequence we have no data on this respect. We have acknowledged this limitation in the discussion and reads as following in page 13 line 11:

“The questionnaires employed at Tromsø 7 did not ask about the presence of interstitial lung disease and bronchiectasis. Both conditions have an increased prevalence with age and are associated with the presence of crackles. It is possible that participants with these conditions were categorized as apparently healthy and this constitutes a limitation of our study.”

20. Discussion/P.13, Line 11. The conclusions reported here are different to those reported in the abstract. From the manner in which the data are presented it isn't clear that the findings support the conclusion of not being concerned about wheeze or crackle in a single location. Also local obstruction eg inhaled foreign body or tumour could, for
instance, cause localised wheeze and be concerning. That abnormal physical signs are not uncommon in this group is a potential reminder to consider the presence of subclinical disease in otherwise apparently healthy individuals. This certainly merits emphasis in the conclusion whilst caution should be exercised in overstating that these signs are occurring in healthy individuals - they are potentially simply "apparently healthy" or "under-diagnosed". Please modify the conclusions here and align to those presented in the abstract.

Response: The reviewer raises an interesting and valid point. We have tried to address this by writing the following sentences in the discussion section page 14 Line 5:

“The presence of wheezes or crackles in one lung location did not strongly predicted the outcomes analyzed. Nonetheless, it is possible that these solitary findings are a manifestation of lung senescence and/or represent subclinical disease in apparently healthy subjects.”

Reviewer 2

1.-A flow-chart of the study population might be useful. Pg 8, line 8 - which 4033 of the 6035 persons with recordings were included for classification of the sounds?

Response: Due to time constrains to classify all the recordings we accumulated we decided to limit the amount of participants. In order to do this, we included all the participants with lung sound recordings in 2015 and all the participants who were randomized to an echocardiographic examination. This has been now explained and better described in a flow chart that can be uploaded as a online supplement.

2.-PG 9 line 2 - please also state those with recordings from all six sites.

Response: Agree. We have modified the sentence in page 9 line 9 to:

“The presented prevalence of ALS are based on six recordings in 3771 (93.5 %) participants. However, in 262 (6.5%) of the participants included in the analysis there was noise in one or more recordings. Five recording sites were considered in 223 (5.5%) participants and four or less recording sites in 39 (1 %) participants.”

3.-Were the variables dichotomized or not - pg 7 lines 6-9 seems contradictory to lines 15-17.

Response: The variables were dichotomized in the univariate analysis. In the multivariate analysis we decided to use the continuous variables without dichotomization. This, in order to avoid loss of data in the final multivariate analysis and to make the interpretation of the results more intelligible.
4.- Is the 0.05 significance level too strict for this purpose?

Response: We were concerned that small differences would be statistically significant due to the large number of participants in our sample. We wanted to be cautious in our analysis. Therefore, we chose a strict criterion.

5.- Would this be different if auscultation was used to support a clinical suspicion of disease? Please discuss this. Analyse in a different setting or suggest further analyses to the scientific community. I suggest a new paper in which you match with national prescription and death registry data, to investigate whether the presence of sounds are related to subsequent disease/mortality.

Response: We appreciate your ideas about new analyses and I must say we find them interesting. However, we feel that including these points in the discussion would make the article even longer and might distract the reader from the main points we are trying to highlight.