**Comments from the editors**

We thank the Editors and Reviewers for their thoughtful and constructive suggestions. We have revised the manuscript in response to their comments, as detailed below.

All page/line/reference numbers refer to the clean revised manuscript.

**Comments from reviewers and editors' concerns**

**1.Thank you for your response to our follow-up e-mail regarding the Nunez et al. paper. We consider this to be a closely-related work, given the overlap in study design and data utilized, and that the two articles share the same overarching goal of understanding the impact of air pollution on ALS. We do recognize the distinction in the message of each paper and methods employed. We offer authors clear guidance on close-related works (see**[**https://edmgr.ovid.com/epid/accounts/ifauth.htm**](https://urldefense.proofpoint.com/v2/url?u=https-3A__edmgr.ovid.com_epid_accounts_ifauth.htm&d=DwQGaQ&c=009klHSCxuh5AI1vNQzSO0KGjl4nbi2Q0M1QLJX9BeE&r=ykV5JPPvmAdELecPI4gQKo5zva50B4qUC5BnFiMweT4&m=snn68A-M73J4tvlDEMOeUkn6O0w-SI07ZrY18tDqy_kIyYZc0n4shNdEd8Kv-CM1&s=F70-P7i17lcL2SPDOJA66E7KQg5I8X-3oeqkV3BUmbk&e=)**, under Essential Conditions). To abide by this guidance, and also provide clearer perspectives on this research to readers, please include reference to the Nunez et al. article (including as a placeholder in the reference list) and add text to set the two papers apart. In fact, the Nunez et al. article, with its focus on PM2.5 and lag structure, seems to set the stage for your current paper, including the selection of exposure averaging times and potentially interpretation of findings, given that PM2.5 EC appears to be the driver of the observed effects in your paper.**

We understand and appreciate the Editors’ concerns. We now reference the Nunez et al. article in the Introduction of the revised manuscript as a foundation for this study in the revised manuscript (P. XX, Lines XX-XX):

*Another study of ALS and PM2.5 in Denmark examining critical windows of exposure found that more recent exposure to PM2.5 (i.e., the previous 1-5 years) may be most important driver of the potential association, though the constituents of PM2.5 were not analyzed, neither together nor separately. x*

We have now also adapted the Discussion to clarify how our results are consistent with the other paper in the revised manuscript (P. XX, Lines XX-XX):

*A study examining critical windows of exposure of PM2.5 and ALS diagnosis in Denmark found that concentrations 1-5 years before exposure may be driving ALS onset, X consistent with our findings that the most recent 1-year average EC concentration showed the largest association.*

**2. The revised manuscript is much clearer in your goal of estimating individual, joint, and average (or overall) associations for the three traffic pollutants. However, the specific definitions need additional clarification, and the ordering and terminology used should be consistent throughout:**

**a) for definitions, those provided on page 8, lines 172-176, are helpful, but do not fully clarify the difference between joint and overall average effects. The joint effect is expressed as the percent change in odds of ALS diagnosis with a simultaneous increase in each of the three traffic pollutants. For the overall effect, is this the average percent change in the odds of ALS diagnosis with an increase in each of the three traffic pollutants independently? Please clarify the wording in this section. Furthermore, if I am understanding the definition of the 'overall' effect correctly, this may be best termed as the 'average' effect throughout the manuscript, since this more closely aligns with the definition applied (Figure 2 already uses 'Traffic\_average'). Similar clarification should also be made on line 216 (i.e., refer to average association across the three traffic pollutants).**

We have changed the terms used in the definition of the average effect from ‘overall’ to ‘average’ throughout the revised manuscript, e.g., (P. XX, Lines XX-XX):

*We used a Bayesian hierarchical conditional logistic model, adjusting for potential confounders, to estimate average and joint associations for the traffic-related pollutants (NOx, CO, EC), and pollutant-specific associations.*

**b) for ordering, please discuss the types of associations in the same order consistently throughout (e.g., including in abstract methods section lines 12-13, and suggest reordering Figure 2 to this order as well). I.e., referring to individual effects, joint effects, average effects in this order as is presented in the methods.**

We have done this in the Methods section of the Abstract in the revised manuscript (P. XX, Lines XX-XX):

*We used a Bayesian hierarchical conditional logistic model, adjusting for potential confounders, to estimate individual pollutant associations, well as average and joint associations for the traffic-related pollutants (NOx, CO, EC).*

We have also maintained this order throughout the rest of the revised manuscript, e.g., (P. XX, Lines XX-XX):

*Using three air pollutants commonly used in health studies as traffic-related emissions tracers—nitrogen oxides (NOx), carbon monoxide (CO), and elemental carbon (EC)— we aimed to assess whether exposure to (a) each individual air pollutant is independently associated with ALS diagnosis, and estimate their (b) joint and (c) average traffic-related emissions associations.*

We have re-ordered Figure 2 accordingly in the revised manuscript (as below):

[[[NEW FIGURE 2]]]

**c) for terminology, the use of 'individual pollutant' effects should be used consistently throughout (e.g., in place of pollutant-specific, which currently appears in the abstract and several other places)**

We have changed ‘pollutant-specific’ to ‘individual pollutant’ throughout the revised manuscript, e.g., (P. XX, Lines XX-XX):

*In our model, , , and represent the independent individual pollutant associations with ALS diagnosis.*

**3. Use of the phrase 'potential associations' in the abstract (lines 16 and 24) and discussion (line 297) is unclear and does not appear to fully describe the actual results of the analysis. It seems that you are using this word to describe associations that had a high probability of being truly positive. I suggest rewording these sections for clarity.**

We have changed ‘potential associations’ to discussing the high probability of an association through the revised manuscript, e.g., (P. XX, Lines XX-XX):

*In the largest case-control study of ALS and traffic-related air pollution to date, we found that a joint increase in average concentrations of traffic-related pollutants had a high probability of being associated with an increase in odds of ALS diagnosis, with the clearest results for EC.*

**4. The abstract results section needs cleaning up. The wording in general is imprecise, in particular the last sentence referring to probabilities.**

We have cleaned up the Results section of the Abstract, maintaining the order from Points 2 and 3 above in the revised manuscript (P. XX, Lines XX-XX):

***Results:*** *For a standard deviation (SD) increase in 5-year average concentrations, EC (SD=0.42µg/m3) had a high probability of being individually associated with an increase in odds (11.5%; 95% credible interval[CrI]:-1.0%,25.6%), with negative associations for NOx (SD=20µg/m3) (-4.6%;95%CrI-18.1%,8.9%), CO (SD=106µg/m3) (-3.2%;95%CrI-14.4%,10.0%) and a null association for non-EC PM2.5 (SD=2.37µg/m3) (0.7%;95%CrI-9.2%,12.4%). There was a 96.3% posterior probability of a positive association between EC concentrations and ALS diagnosis, with 27.8% for NOx and 26.7% for CO. We found no association between ALS and joint or average traffic pollution concentrations.*

**5. Reviewer 1 had asked you to provide some additional information on the air pollution modeling system. While the system has been previously developed and validated, and also used in other epidemiological applications, it would be helpful to include a brief summary of how the models are developed. While it's interesting to know that air quality levels can be estimated efficiently by the system, it is more informative for readers to understand the underlying structure of the models. E.g., were these chemical transport models taking emissions and weather data into account? Were these outputs fused and/or calibrated with monitoring data?**

We have added further details of DEHM-UBM-AirGIS in this section of the revised manuscript (P. XX, Lines XX-XX):

*In brief, DEHM-UBM-AirGIS is a human exposure modelling system for traffic pollution, developed for application in Danish air pollution epidemiological studies. The modelling system integrates air pollution dispersion models, digital maps, national and local administrative databases, concentrations of air pollutants at regional, urban background and street level, meteorological data, and a Geographic Information System (GIS). The modelling system is therefore able to generate street configuration and traffic data based on digital maps and national databases, which enables estimation of air quality levels at a large number of addresses in an automatic and effective way.*

**6. Lines 124-127 - from your response to reviewer comments, it appears that the subtraction of EC from PM2.5 was appropriate here given how PM2.5 was estimated by the air pollution modeling system (i.e., constructed from individual components). This is important to point out, as the simple subtraction of EC from PM2.5 when using monitoring data, for example, can cause errors given different measurement approaches for each.**

We have added to the justification of how we recovered non-EC PM2.5 in the revised manuscript (P. XX, Lines XX-XX):

*Because traffic is a major source of PM2.5 and EC one of the main PM2.5 components in urban environments,59 we removed the EC concentration from the total PM2.5 mass concentration (non-EC PM2.5) by subtraction to avoid overadjustment when including both in the models simultaneously; this was valid since DEHM-UBM-AirGIS constructed PM2.5 concentrations by adding from specific species of pollutants, one of which was EC.52–55*

**7. Line 303-304 - suggested change from 'would have been' to 'were'**

We have done this in the revised manuscript (P. XX, Lines XX-XX):

*Overall conclusions for the association between EC and ALS diagnosis were similar from the single- or multi-pollutant models.*

**8. Lines 305-309 - since the EC effects were consistent across the single and multi-pollutant modeling, it seems that the conclusion of EC being a driver of the traffic-ALS association is supported. However, the point about the model having had 'limited success in identifying each individual pollutant's association with ALS' is unclear. Even though NO2 and CO may have had positive associations in their single-pollutant models, there could be reasons why EC effects predominated in the multi-pollutant context (either more relevant for ALS or less measurement error than the other pollutants). Please clarify.**

We have clarified in the Discussion to suggest that the association of EC concentrations with ALS diagnosis was consistent, along with inconsistent associations for NOx and CO, suggest that EC concentrations may have been most relevant in the revised manuscript (P. XX, Lines XX-XX):

*The inconsistent associations for NOx and CO in the multi- and single-pollutant models and the consistency of the EC association suggest that EC concentrations may have been more relevant than NOx and CO for ALS diagnosis.*

**9. Line 309 - suggested change from 'analysis' to 'study'**

We have done this in the revised manuscript (P. XX, Lines XX-XX):

*Nevertheless, the consistency of the sign of the central estimate of EC in all models suggests that EC may be a driver of the ALS and traffic-related pollutant association, though further study is required.*

**10. Line 353 on residual confounding - in the revision, you deleted a section on BMI and smoking, as per Reviewer 1 and gave responses to Reviewer 2 on this point. It is still not clear to me how factors such as BMI or smoking are not potential confounders in this analysis. A confounder is a factor that is a risk factor for the outcome, and a factor that is associated with the exposure. BMI and smoking would not be expected to 'cause' the exposure in this case, however, these factors could be geographically correlated in a way not captured by SES. It is not clear to me that SES necessarily blocks all potential confounding by these other factors and it would be helpful to include some additional discussion on this.**

We have explained below in the revised manuscript (P. XX, Lines XX-XX):

*To induce confounding bias, any unaccounted-for variable would have to be causally related to the dependent variable, in this case ALS diagnosis, and be correlated with the independent variable, in this case air pollution concentrations. This is the case with BMI and smoking; BMI76,77 and smoking prevalenceX have previously been associated with ALS diagnosis, and are correlated with air pollution. We have attempted to block this potential confounding path by including SES, itself correlated with BMIX and smoking prevalence. However, BMI and smoking could be geographically correlated with ALS in a way not fully captured by SES, which may not necessarily block all potential confounding.*

**11. Line 367 - was the use of BKMR not appropriate for your research question because it currently does not accommodate application in case-control studies? In this case, I suggest using 'since BKMR is currently not available for case-control study applications'.**

We have updated the language here in the revised manuscript (P. XX, Lines XX-XX):

*Other mixture model methods, such as Bayesian Kernel Machine Regression (BKMR)88 might be useful in further exploring the robustness of joint associations in a different framework, though BKMR was not appropriate for our particular research question, since BKMR is currently not available for case-control study applications.*

**\* \* \* \* \***

**Preparing a revision**

**1. For estimates of causal effects, we strongly discourage the use of categorized P-values and language referring to statistical significance, including whether a confidence interval covers the null. We prefer instead interval estimation, which conveys the precision of the estimate with respect to sampling variability. We are more open to testing with respect to modeling decisions, such as for tests of interaction and for tests for trend.**

We have avoided p-values throughout.

**2. We do not permit acronyms unless they are generally recognized by epidemiologists (e.g. HIV is okay, but LVA is not). When in doubt, we recommend that you spell out.**

We have been careful to introduce acronyms where used.

**3. Please do not include uninformative precision (excessive decimal places). For example, percents should be rounded to nn%, n.n%, or 0.0n% and risk ratios should be rounded to nn, n.n, or 0.nn unless clarity of the presentation and the sample size justify more significant digits.**

We have done this.

**4. Please be sure to include explicit information about approval of human subjects research by an independent review board. If no such review was required, include an explicit statement about why the requirement for review was waived.**

We have done this in the manuscript (P. XX, Lines XX-XX):

*This study was approved by the Institutional Review Board Committee at the Columbia University and the Danish Data Protection Agency.*

**5. Do not include public health policy recommendations in Brief Reports or Original Articles that present new research findings.**

We have not included any public health policy recommendations.

**6. Data appearing in the abstract must also be cited in the main text, not just in tables or figures.**

We have done this.

**7. Resubmissions must adhere to word limits. The word limits for main text (generally the introduction, methods, results, and discussion) are 1500 words for Brief Reports (plus 150 words for its abstract), 4000 words for Original Articles (plus 250 words for its abstract), 5000 words for reviews (plus 250 words for its abstract), 2000 words for Commentaries (no abstract), 600 words for Research Letters (no abstract), and 400 words for Letters to the Editor (no abstract).**

We have done this, with an Abstract of XX words and an Original Article of XX words in the revised manuscript.

**8. We advise that total word counts for Original Articles should not exceed 7500 words and for Brief Reports should not exceed 3500 words. The total word count includes main text (introduction, methods, results, and discussion), bibliography, figure legends, tables, and figures (250 words per figure, including each figure in a panel). The title page, abstract, acknowledgments, and funding information do not count in the total word count.**

We have adhered to this, with a total word count of XX words in the revised manuscript.

**9. Figure labels: Make font size as large as possible, so as to be legible when figures are reduced for publication (typically one column [8.5cm] in width).**

We have made the Figure labels large and legible.

**10. Footnotes to tables and figures should use superscript lowercase letters to link content to the footnote, not symbols or numerals.**

The footnote in Table 1 uses a superscript lowercase letter.

**11. Do not use parenthetical phrases like “(data not shown), (results not shown), or (available from the authors upon request).” In these circumstances, the data or results should be provided in Supplementary Digital Content.**

We have avoided any use of these phrases.

**12. Additional details regarding submission requirements can be found in the Instructions for Authors, which are posted at**[**http://edmgr.ovid.com/epid/accounts/ifauth.htm**](https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_epid_accounts_ifauth.htm&d=DwQGaQ&c=009klHSCxuh5AI1vNQzSO0KGjl4nbi2Q0M1QLJX9BeE&r=ykV5JPPvmAdELecPI4gQKo5zva50B4qUC5BnFiMweT4&m=snn68A-M73J4tvlDEMOeUkn6O0w-SI07ZrY18tDqy_kIyYZc0n4shNdEd8Kv-CM1&s=7HMhF8H1IwY4RmAdcja1FChJ90yBFSAB4rzyiZ3jfuE&e=)**.  
  
Preparing for resubmission**

**13. Prepare a response document for the Editor that responds point-by-point to the reviewers' comments (presenting each comment followed by your response). Give the page number where revised text can be found and, where practical, paste revised text directly into the reply document.**

We have done this.

**14. Submit versions of the manuscript with and without your changes displayed.**

We have submitted clean and tracked versions of the revised manuscript.

**15. Supplementary Digital Content should be submitted as a single PDF file, and you should use our convention - e.g. eFigure 1, eAppendix 2 - to label and refer to online content.**

We have done this.

**16. Authors should submit copies of any closely related manuscripts (published, in press, or under review).**

As discussed with the Editors, we are incorporating the Nunez et al. paper into our submission.

**17. Please revisit information about page charges and color printing charges available in the Instructions for Authors, which are posted at**[**http://edmgr.ovid.com/epid/accounts/ifauth.htm**](https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_epid_accounts_ifauth.htm&d=DwQGaQ&c=009klHSCxuh5AI1vNQzSO0KGjl4nbi2Q0M1QLJX9BeE&r=ykV5JPPvmAdELecPI4gQKo5zva50B4qUC5BnFiMweT4&m=snn68A-M73J4tvlDEMOeUkn6O0w-SI07ZrY18tDqy_kIyYZc0n4shNdEd8Kv-CM1&s=7HMhF8H1IwY4RmAdcja1FChJ90yBFSAB4rzyiZ3jfuE&e=)**.**

We acknowledge the charges on the link provided.

**18. We request that the complete revised manuscript (with all tables and figures) be completed by 14 Sep 2022. If you are not able to meet this deadline, please notify the editorial office.**

We have submitted before 14th September 2022.

**Resubmitting via Editorial Manager**

**19. Log-in to Editorial Manager as an author using the credentials above.**

**20. Click on the "Submissions Needing Revision" link.**

**21. To view the previous decision letter and reviewer comments, please click the blue**

**decision term listed under the View Decision menu.**

**22. If you would like to download the previous manuscript to make revisions, click on "Download Files" under the Action menu.**

**23. To begin the resubmission: Click "Submit Revision" under the Action menu.**

**24. Proof each screen to ensure the information is still correct (the Title, Authors, etc.), then click Next at the bottom of each page.**

**25. On the Attach Files screen, select each previous submission item that you would like to carry forward to the resubmission.**

**26. Upload the revised versions of the main text (with and without tracked changes), and order them with the highlighted version first.**

**27. Upload the point-by-point reply to review.**

**28. When you are finished uploading, please click Next.**

**29. Click "Build PDF for My Approval."**

**30. Click "Go to Submissions Waiting for Author’s Approval."**

**31. Wait for the PDF to build. When it has been built, you will see the link "View Submission" in the Action menu. Click "View Submission," and open the manuscript to proof your work.**

**32. If you find problems with the manuscript, click "Edit Submission" from the Action menu. Make the required changes, and begin again at the file uploads.**

**33. Once the submission is complete and acceptable, click "Approve Submission" from the Action menu.**

**34. If you have difficulty with these procedures, you may send questions to**[**timothy.lash@epidemiology-journal.com**](mailto:timothy.lash@epidemiology-journal.com)**.**

Thank you for the resubmission instructions. We have followed them.

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