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, 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 (currently under review) in the Introduction of the revised manuscript as a foundation for this study in the revised manuscript (PP. 3-4, Lines 66-69):

Another study of ALS and $PM_{2.5}$ in Denmark examining critical windows of exposure found that more recent exposure to $PM_{2.5}$ (i.e., the previous 1 to 5 years) may be the most important driver of the potential association, though the constituents of $PM_{2.5}$ were not analyzed, neither together nor separately.[40]

We have now also adapted the Discussion to clarify how our results are consistent with the other paper in the revised manuscript (P. 15, Lines 327-330):

A study examining critical windows of exposure of $PM_{2.5}$ and ALS diagnosis in Denmark found that concentrations 1 to 5 years before exposure may be driving the association with ALS onset,[40] *consistent with our findings that the most recent 1-year average EC concentration exhibited 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).

The Editor is correct. We appreciate the suggestion. To clarify, we have changed the terms used in the definition of the average effect from 'overall' to 'average' throughout the revised manuscript, e.g., (PP. 8-9, Lines 180-185):

We employed a Bayesian hierarchical formulation because it enables estimates of (a) independent pollutant-outcome associations, (b) a joint association of the three pollutants (i.e., total percentage change in odds of ALS diagnosis with increase in each of EC, NO_x, CO), and (c) an average traffic association (i.e., average percentage change in odds of ALS diagnosis from each of EC, NO_x, CO), while accounting for the variance-covariance structure between the highly-correlated exposures and their coefficients.[67]

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. 1, Lines 11-14):

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

We have also maintained this order throughout the rest of the revised manuscript, e.g., (P. 4, Lines 73-77):

Using three air pollutants commonly used in health studies as traffic-related emissions tracers— elemental carbon (EC), nitrogen oxides (NO_x), and carbon monoxide (CO)— 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):

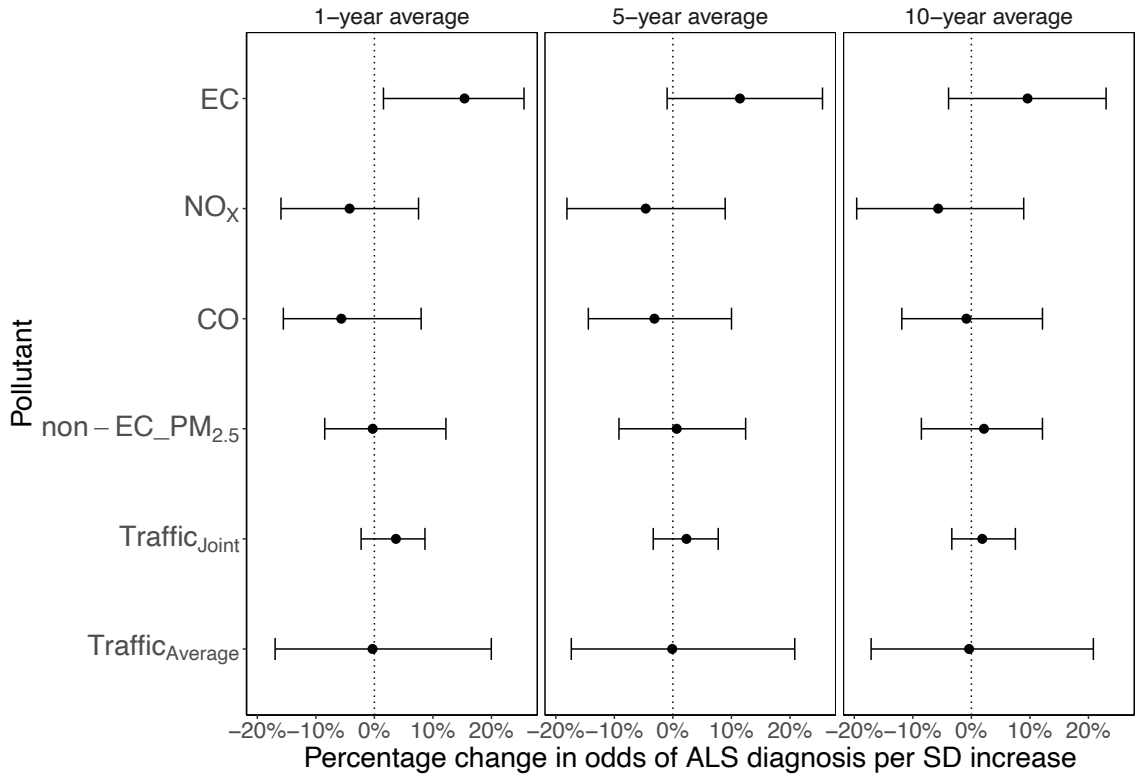

Figure 2. Percentage change in odds of ALS diagnosis per 1-, 5- and 10-year average standard deviation (SD) increase for each pollutant. Results are from the Bayesian hierarchical model including each of EC, NO_x CO, and non-EC $PM_{2.5}$ together, and were additionally adjusted by age, sex, year of birth, vital status, socioeconomic status, civil status, last reported place of residence, and place of birth.

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. 10, Lines 211-212):

In our model, β_{EC}, β_{NO_x}, and β_{CO} 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. 14, Lines 307-311):

In the largest case-control study of ALS and traffic-related air pollution to date, we found that EC had the largest-in-magnitude independent association with ALS diagnosis, while associations with NO_x and CO were negative with credible intervals overlapping the null, and

smaller in magnitude. A joint increase in concentrations of traffic-related pollutants had a high probability of being associated with an increase in odds of ALS diagnosis.

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

We have clarified the Results section of the Abstract, maintaining the order from Points 2 and 3 above in the revised manuscript (P. 1, Lines 16-23):

Results: *For a standard deviation (SD) increase in 5-year average concentrations, EC (SD=0.42μg/m^3) had a high probability of being individually associated with an increase in odds (11.5%; 95% credible interval[CrI]:-1.0%,25.6%; 96.3% posterior probability of a positive association), with negative associations for NO_x (SD=20μg/m^3) (-4.6%;95%CrI-18.1%,8.9%; 27.8% posterior probability of a positive association), CO (SD=106μg/m^3) (-3.2%;95%CrI-14.4%,10.0%; 26.7% posterior probability of a positive association) and a null association for non-EC $PM_{2.5}$ (SD=2.37μg/m^3) (0.7%;95%CrI-9.2%,12.4%). 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, focusing more on the details of the model, in this section of the revised manuscript (P. 6, Lines 121-128):

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 $PM_{2.5}$ in the revised manuscript (P. 6, Lines 132-136):

Because traffic is a major source of $PM_{2.5}$ and EC one of the main $PM_{2.5}$ components in urban environments,[60] we removed the EC concentration from the total $PM_{2.5}$ mass concentration (non-EC $PM_{2.5}$) by subtraction to avoid overadjustment when including both in the models simultaneously; this was valid since the DEHM-UBM-AirGIS modelling system constructed $PM_{2.5}$ concentrations by adding from specific species of pollutants, one of which was EC.[53–56]

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

We have done this in the revised manuscript (P. 14, Lines 314-315):

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 NO_x and CO, suggest that EC concentrations may have been most relevant in the revised manuscript (P. 14, Lines 315-317):

The inconsistent associations for NO_x 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 NO_x and CO for ALS diagnosis.

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

We have done this in the revised manuscript (PP. 14-15, Lines 317-319):

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.

The Editor is correct that although BMI and smoking cannot cause the predicted pollutant concentrations, given the current exposure assessment method, they can be correlated with

them through neighborhood-level SES. It is possible that there may be some residual confounding by SES, in which case further adjusting our models for BMI and smoking status may have helped address this potential concern. However, information on individual-level BMI and smoking status is not available in the Danish Civil Registration System. Given the Reviewers' and Editor's comments, we have adjusted the Limitations paragraph accordingly

We have explained below in the revised manuscript (P. 17, Lines 366-372):

Information on individual-level variables, such as body mass index (BMI) and smoking status is not currently available through the Danish Civil Registration System. These variables, however, are not expected to cause the predicted pollutant concentrations, given exposure assessment. If this information were available, it could be used to further adjust for SES.[86] To the extent that the variables we included in our models to adjust for household- and neighborhood-level SES are adequate, we would expect any residual SES-related confounding to be minimal.

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 per the Editor's suggestion in the revised manuscript (P. 17, Lines 382-385):

Other mixture model methods, such as Bayesian Kernel Machine Regression (BKMR)[89] 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.

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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. 5, Lines 112-113):

This study was approved by the Institutional Review Board Committee at 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 250 words and an Original Article of 4,120 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 6,643 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 .

We have reviewed these details.

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 now mention the Nunez et al. paper into our revised manuscript.

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 .

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.

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