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

Editors' concerns

Dear authors, thank you for your responses and revision. There are just a few more minor comments to handle prior to moving this manuscript forward:

1. The abstract reads much better than before. A few additional suggested changes:
a. Abstract Results, line 17 – please add 'with an increase in odds of ALS'.

We have added this to the revised manuscript (P. 1, Lines 16-18):

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 of ALS […]

b. Abstract Conclusions, lines 25-27 – suggested revision to 'This study found a high probability of a positive association between ALS diagnosis and EC concentrations. Further work is needed…' I suggest removing reference to the results being inconclusive, as this seems inconsistent with conclusion of the high probability finding for EC.

We have added this to the revised manuscript (P. 2, Lines 25-27):

This study found a high probability of a positive association between ALS diagnosis and EC concentration. Further work is needed to understand the role of traffic-related air pollution on ALS pathogenesis.

2. Thank you for including reference to the Nunez et al. article. This reference should be helpful for readers to place the air pollution-ALS literature into context. If I'm not mistaken, the outcome database as well as the source of the pollution data (despite the different specific pollutants examined) are largely overlapping between your work and that of Nunez et al. For further transparency, I suggest:

a. Adding a mention at the very end of the introduction or beginning of the methods, that this study builds on (or pairs with) the work of Nunez et al.

We have added a recognition that this study builds on the work of Nunez et al. to the revised manuscript (P. 4, Lines 77-78):

This study pairs with and complements the work of Nunez et al.[40]

b. When citing references to epidemiology studies that use the predicted pollutant concentrations in Denmark (line 129), please include the Nunez et al. citation #40

We have added the citation of Nunez et al. here in the revised manuscript (P. 6, Lines 129-130):

These predicted pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.[17,40,57–59]

3. The definitions and terminology for the joint and average traffic pollution effects are much clearer than before. A couple of suggestions to further clarify:

a. On line 182, suggest '… i.e., total percentage change in the odds of ALS diagnosis with a simultaneous increase in each of EC, NOx, CO).'

We have added this to the revised manuscript (PP. 8-9, Lines 182-184):

[…] (b) a joint association of the three pollutants (i.e., total percentage change in odds of ALS diagnosis with a simultaneous increase in each of EC, NO_x, CO) […]

b. On line 183-184, suggest '… i.e., average percentage change in the odds of ALS diagnosis with increases in each of EC, NOx, CO),…'

We have added this to the revised manuscript (P. 9, Lines 184-185):

[…] and (c) an average traffic association (i.e., average percentage change in odds of ALS diagnosis with increases in each of EC, NO_x, CO), […]

4. Currently, eFigure 2 is referenced at the very end of the results section (lines 302-304). From a flow perspective, this sentence seems better placed in the second paragraph of the results, when discussing pollutant concentrations. As such, I suggest switching the order of eFigure 2 and eFigure 1.

We have moved the sentence and switched the order of the eFigures to match this in the revised manuscript (P. 13, Lines 283-285):

Maps of average concentration of included pollutants (EC, NO_x, CO, $PM_{2.5}$, O_3) across Denmark for a representative year (2000; middle of study period 1989-2013) is also available in eFigure 1.

5. Paragraph 3 of the results section needs a few clarifications.

a. Please reference 'odds of ALS diagnosis' as the outcome when introducing observed associations on lines 284-286.

We have added this to the revised manuscript (P. 13, Lines 287-288):

For 5-year average pollutant concentrations, we observed the largest overall increase in odds of ALS diagnosis for the individual SD increase in EC […]

b. Please also specify the units for the increases. E.g., they are specifically mentioned for EC, NOx, and CO on lines 284-289, however missing for non-EC PM2.5 on line 290 and 1-year EC on line 291.

We have added units for the increases to the revised manuscript (P. 13, Lines 292-296):

Non-EC $PM_{2.5}$ was not associated with ALS diagnosis (0.7%; 95% CrI: -9.2%, 12.4% per 2.37 $\mu g/m^3$; 54.1% posterior probability of positive association). 1-year EC average exposure was associated with an increase in odds of ALS diagnosis (15.4%; 95% CrI: 1.6%, 25.6% per 0.42 $\mu g/m^3$; 98.9% posterior probability of positive association).

c. It also occurs to me that while the SD increases for 5-year exposures are included in Table 2, the SD increases for 1-year and 10-year exposure measures are not specified anywhere. Please consider either adding summaries for these exposures to Table 2, or perhaps include the SD units for each pollutant and averaging time in the Figure 2 title notes.

We have now added 1-year and 5-year exposure measures to Table 2 in the revised manuscript, copied below for convenience:

Table 2. Summary of 1,- 5-, and 10-year average pollutant concentrations (all in μg/m^3).

	Pollutant	Overall, N = 23,270[a]	Case, N = 3,937[a]	Control, N = 19,333[a]
1-year average	EC	0.81 (0.42)	0.83 (0.44)	0.81 (0.42)
	NO_X	26 (19)	26 (20)	26 (19)
	CO	224 (97)	226 (101)	224 (96)
	non-EC $PM_{2.5}$	11.17 (2.32)	11.20 (2.34)	11.17 (2.31)
	O_3	52.6 (6.1)	52.4 (6.2)	52.6 (6.1)
	Pollutant	Overall, N = 23,232[a]	Case, N = 3,934[a]	Control, N = 19,298[a]
5-year average	EC	0.85 (0.42)	0.86 (0.45)	0.85 (0.42)
	NO_X	27 (20)	28 (21)	27 (20)
	CO	238 (106)	239 (112)	237 (105)
	non-EC $PM_{2.5}$	11.76 (2.37)	11.78 (2.41)	11.76 (2.37)
	O_3	51.9 (6.0)	51.9 (6.1)	52.0 (6.0)
	Pollutant	Overall, N = 23,179[a]	Case, N = 3,929[a]	Control, N = 19,250[a]
10-year average	EC	0.89 (0.43)	0.89 (0.46)	0.88 (0.43)
	NO_X	29 (20)	29 (22)	29 (20)
	CO	253 (115)	255 (122)	253 (113)
	non-EC $PM_{2.5}$	12.53 (2.55)	12.55 (2.59)	12.52 (2.55)
	O_3	51.3 (6.0)	51.3 (6.1)	51.4 (6.0)

[a]Mean (SD)

6. Line 295, referring to the EC single-pollutant model in eFigure 1, should this be model F (not model D)?

We thank the Editor for pointing this out. We have corrected this in the revised manuscript (P. 14, Lines 299-301):

The 95% credible interval for EC in the single-pollutant model (eFigure 1; model F) overlapped with the credible intervals of the EC term in the multi-pollutant models (eFigure 1; models A to C, G to P).

7. Lines 315-319, the sentences here seem somewhat duplicative. Consider tightening the wording.

We have tightened up the language by merging the two referenced sentences in the revised manuscript (PP. 14-15, Lines 318-321):

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, though further study is required.

8. Regarding the discussion on BMI and smoking, the previous reviewer and I both questioned the likelihood of these as potential confounders independent of SES. It seems plausible that BMI and smoking could co-vary with pollution levels, independently of SES; this wouldn't depend on these factors being included in the air pollution modeling system. In any case, if I understand your argument correctly, may I suggest the following revision simply to clarify your discussion of this (starting on line 367): '….not currently available through the Danish Civil Registration System. These variables, while potential risk factors for ALS, are not likely confounders in this analysis as they are not expected to be associated with pollutant concentrations in a manner independent of neighborhood SES. If information on these variables were available, it could be used to further adjust for SES. … '

We have added this to the revised manuscript (P. 17, Lines 368-373):

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, while potential risk factors for ALS, are not likely confounders in this analysis as they are not expected to be associated with pollutant concentrations in a manner independent of neighborhood SES. If this information were available, it could be used to further adjust for SES.[86]

* * * * *

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 113-114):

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).

Based on Editors' suggestions, we now have an Abstract of 251 words and an Original Article of 4,154 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.

Our total word count of 6,784 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 footnotes in Tables 1 and 2 use 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 28 Sep 2022. If you are not able to meet this deadline, please notify the editorial office.

We have submitted before 28th 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.
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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.
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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.