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Long-term traffic-related air pollutant exposure and amyotrophic lateral sclerosis diagnosis in Denmark: A Bayesian hierarchical analysis

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Abstract:	Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Limited evidence suggests that ALS symptoms onset is associated with air pollution exposure and specifically to traffic-related pollutants. Methods: In this population-based case-control study, we used data on 3,939 ALS cases from the Danish National Patient Register diagnosed between 1989 – 2013 and matched on age, sex, year of birth and vital status to 19,298 population-based controls free of ALS at index date. We used predictions of nitrogen oxides (NO_x), carbon monoxide (CO), elemental carbon (EC), and fine particles ($PM_{2.5}$) from validated spatio-temporal models to assign 1-, 5-, and 10-year average exposures pre-ALS diagnosis at present and historical residential addresses of study participants. We used a Bayesian hierarchical conditional logistic model and adjusted for potential confounders to estimate the overall and joint association for the three traffic-related

	pollutants (NO x , CO, and EC), as well as pollutant-specific associations. Results: For a standard deviation (SD) increase in 5-year average concentrations, EC was individually associated with an increase in odds (11.5%; 95% credible interval [CrI]: -1.0%, 25.6%), with decreases individually for NO x (-4.6%;95%CrI -18.1%,8.9%) and CO (-3.2%; 95%CrI -14.4%, 10.0%) and a null effect of non-EC PM 2 . 5 (0.7%;95%CrI -9.2%,12.4%). We found no association for joint or overall traffic pollution. There was a 77.8% posterior probability of a positive association between the joint effect of pollutants and ALS diagnosis, 96.3% for EC, 27.8% for NO x and 26.7% for CO. Conclusions: Our results indicate a potential positive association between ALS diagnosis and pollutants, particularly for EC. Further work is needed to understand the role of air pollution on ALS pathogenesis and timing of onset.
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Dr Timothy L. Lash,
Editor-in-Chief, *Epidemiology*

Dear Dr Lash:

On behalf of my co-authors, I would like to submit our paper "*Long-term traffic-related air pollutant exposure and amyotrophic lateral sclerosis diagnosis in Denmark: A Bayesian hierarchical analysis*" for consideration in *Epidemiology as* an Original Research Article.

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease, currently without a cure. Approximately half of patients die within three years of symptom onset. Annually, there are nearly 30,000 cases of ALS in Europe and over 200,000 worldwide. Known inherited genetic variants only account for 5–10% of ALS cases. Environmental factors, therefore, are likely important in ALS pathogenesis. Ambient air pollution, especially urban air pollution, is a ubiquitous exposure that has been associated with several other neurodegenerative disorders, and is consistently linked to systemic inflammation, oxidative stress, and neuroinflammation, all of which, in turn, have been reported as key pathways to ALS pathogenesis. Despite the compelling plausibility, few studies to date have evaluated the association between air pollution and ALS.

With this study, *the largest case-control study of ALS and air pollution to date,* we used data on 3,939 ALS cases from the Danish National Patient Register diagnosed between 1989 – 2013 and matched on, sex, year of birth and vital status to 19,298 population-based controls free of ALS at index date. We used predictions of nitrogen oxides (NO_x), carbon monoxide (CO), elemental carbon (EC), and fine particles ($PM_{2.5}$) from validated spatio-temporal models to assign 1-, 5-, and 10-year average exposures pre-ALS diagnosis at present and historical residential addresses of study participants. Although the last year of data in our analyses is from eight years ago (2013), our findings remain timely due to the uniquely large number of ALS cases we have collected, that air pollution remains so pervasive, and that ALS prevalence is projected to increase nearly 70% by 2040.

We found that an increase in the joint exposure to traffic-related pollutants was associated with an increase in odds of ALS diagnosis, significant for elemental carbon for a 1-year average standard deviation increase, though not significant at the 95% credible interval level for other pollutants. Our results indicate that sources of air pollution with elemental carbon, such as diesel engines and woodburning stoves, might contribute to development of ALS.

This manuscript has not been previously published and is not under review in any other journal. All authors have contributed to the paper, have approved its submission, and take responsibility for its contents. The authors have no actual or potential competing financial interests. There is no closely related paper included with this submission.

The following people are qualified to assess its contents and their implications, and are independent of this work:

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We look forward to your response and would be happy to answer any questions that you may have on this paper.

Sincerely,

Robbie M. Parks, PhD

Type of Manuscript: Original Research Article

Manuscript Title: Long-term traffic-related air pollutant exposure and amyotrophic lateral sclerosis diagnosis in Denmark: A Bayesian hierarchical analysis

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Suggestions for running head: Traffic-related air pollutants and ALS

The authors declare they have no actual or potential competing financial interests.

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Description of the process by which someone else could obtain the data and computing code required to replicate the results reported in your submission (or explanation why data or code are not available): Danish patient records are available via the Danish National Patient Register (https://econ.au.dk/the-national-centre-for-register-based-research/danish-registers/the-national-patient-register/browse). Danish population records are available via the Danish Civil Registration System (https://econ.au.dk/the-national-centre-for-register-based-research/danish-registers/the-danish-civil-registration-system-cpr/browse). Exposure data are available via the DEHM-UBM-AirGIS website (https://envs.au.dk/en/research-areas/air-pollution-emissions-and-effects/the-monitoring-program/air-pollution-models/airgis/about-airgis/). All code for analysis, results from analysis, and visualization presented in this manuscript will be publicly available via GitHub at https://github.com/rmp15/multipollutants_and_als_code_review.

Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Limited evidence suggests that ALS symptoms onset is associated with air pollution exposure and specifically to traffic-related pollutants.

Methods: In this population-based case-control study, we used data on 3,939 ALS cases from the Danish National Patient Register diagnosed between 1989 – 2013 and matched on age, sex, year of birth and vital status to 19,298 population-based controls free of ALS at index date. We used predictions of nitrogen oxides (NO_x), carbon monoxide (CO), elemental carbon (EC), and fine particles ($PM_{2.5}$) from validated spatio-temporal models to assign 1-, 5-, and 10-year average exposures pre-ALS diagnosis at present and historical residential addresses of study participants. We used a Bayesian hierarchical conditional logistic model and adjusted for potential confounders to estimate the overall and joint association for the three traffic-related pollutants (NO_x, CO, and EC), as well as pollutant-specific associations.

Results: For a standard deviation (SD) increase in 5-year average concentrations, EC was individually associated with an increase in odds (11.5%; 95% credible interval [CrI]: -1.0%, 25.6%), with decreases individually for NO_x (-4.6%;95%CrI -18.1%,8.9%) and CO (-3.2%; 95%CrI -14.4%, 10.0%) and a null effect of non-EC $PM_{2.5}$ (0.7%;95%CrI -9.2%,12.4%). We found no association for joint or overall traffic pollution. There was a 77.8% posterior probability of a positive association between the joint effect of pollutants and ALS diagnosis, 96.3% for EC, 27.8% for NO_x and 26.7% for CO.

Conclusions: Our results indicate a potential positive association between ALS diagnosis and pollutants, particularly for EC. Further work is needed to understand the role of air pollution on ALS pathogenesis and timing of onset.

Abbreviations:

ALS	Amyotrophic lateral sclerosis
BMI	Body mass index
CO	Carbon monoxide
CrI	Credible interval
EC	Elemental carbon
ICD	International Classification of Diseases
Non-EC $PM_{2.5}$	Non-elemental carbon fine particles
NO_x	Nitrogen oxides
O_3	Ozone
$PM_{2.5}$	Fine particles
SD	Standard deviation
SES	Socioeconomic status

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease,[1] currently without a cure.[2] Approximately half of patients die within three years of symptom onset.[3] Annually, there are nearly 30,000 cases of ALS in Europe and over 200,000 worldwide.[4] Known inherited genetic variants only account for 5–10% of ALS cases.[5,6] Environmental factors, therefore, are likely important in ALS pathogenesis.[7] However, because the disease is relatively rare, it is challenging to conduct large-scale prospective studies. There is a recognized need for more evidence of the environmental contributors of ALS.[5,8]

Although air pollution is commonly studied in association with respiratory- and cardiovascular-related outcomes,[9–14] epidemiologic and toxicological studies support several plausible biological mechanisms in association with the nervous system and neurodegeneration.[15–34] Ambient air pollution, especially urban air pollution, is a ubiquitous exposure that has been associated with several other neurodegenerative disorders,[16–21,35,36] and is consistently linked to systemic inflammation,[22–24] oxidative stress,[25–28] and neuroinflammation,[15,29] all of which, in turn, have been reported as key pathways to ALS pathogenesis.[30–34]

Despite the compelling plausibility, few studies to date have evaluated the association between air pollution and ALS.[35,37–39] A recent study found that traffic-related air pollutants may be driving observed associations.[38] No study has hitherto attempted to understand the combined and individual associations of the pollutants in a single model. Air pollutants have been consistently associated with adverse health, primarily in single pollutant analyses.[13,17,40–42] However, they are highly correlated with one another.[40] It is therefore a mixture modelling challenge to infer the

association of multiple air pollutants and health outcomes.[43] Using three air pollutants commonly used in health studies as traffic-related emissions tracers—nitrogen oxides (NO_x), carbon monoxide (CO), and elemental carbon (EC)— as well as fine particles ($PM_{2.5}$) and ozone (O_3), 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) overall traffic-related emissions associations.

Methods

Study Population and Outcome Assessment

We used data from the Danish National Patient Register during 1989-2013, through which details on demographic characteristics and certain health outcomes of all Danish residents can be linked based on a unique personal identifier.[44] The Register was established in 1977 and is comprehensive, including nationwide clinical and administrative records for all inpatient data, with outpatient data available since 1995.[45]

We identified ALS cases based on their International Classification of Diseases (ICD) discharge diagnoses, i.e., ICD-8 code 348.0 (ALS) until 1993 and ICD-10 code G12.2 (motor neuron disease) thereafter, using the date of the first relevant code as the diagnosis date. We only included patients who were at least 20 years old when diagnosed. In our validation study, Register data for ALS ascertainment were highly reliable.[46]

We obtained controls through the Danish Civil Registration System, established in 1968 and updated daily, which includes administrative records (e.g., date and place of birth, sex, vital

status, and history of civil status and addresses since 1971) on all persons living in Denmark; records are kept even when a person dies or emigrates.[47] We randomly matched five controls per case by age, sex, year of birth, and vital status. Controls were alive and free of diagnosed ALS at the ALS diagnosis date of the matched case (index date).

We obtained all addresses of cases and controls from January 1st 1979 onwards from the Danish Civil Registration System,[47] including the dates of moving to and from each address, prior to the index date. We then obtained the geographical coordinates at the door of each house of the residential history of the participants, with previous evidence of the high accuracy of this method of geocoding of addresses in Denmark.[17]

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

Exposure data

We obtained predictions on monthly concentrations of nitrogen oxides (NO_x), carbon monoxide (CO), elemental carbon (EC), and fine particles ($PM_{2.5}$) (as well as ozone (O_3) for a sensitivity analysis, usually negatively correlated with other pollutants due to its chemistry[48]), at residential addresses of study participants from the validated spatio-temporal air pollution modelling system (DEHM-UBM-AirGIS) with full space and time coverage over our study period, described in detail elsewhere.[49–52] These predicted pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.[17,53–55] The models have good predictive accuracy, with average monthly correlations between measured and modelled results of 0.85 for

NO_x, 0.91 for CO, 0.92 for O_3, 0.79 for EC, and 0.83 for annual concentrations of $PM_{2.5}$.[49,52] Because traffic is a major source of $PM_{2.5}$ and EC one of the main $PM_{2.5}$ components in urban environments,[56] we removed the EC concentration from the total $PM_{2.5}$ mass concentration (non-EC $PM_{2.5}$), to avoid overadjustment when including both in the models simultaneously.

Based on the residential history of each case or control, we calculated 1-, 5-, and 10-year average exposure to each pollutant ending at one year before the index date, as diagnosis has been shown previously to occur at a median of 12 months after symptoms onset.[57] A small number of Danish residents lack a complete address history (1.7%; lack of house number). To ensure we were including participants with adequately complete exposure records, we set the following minimum criteria for number of complete exposure record months to include cases and controls: (i) 1-year averages: 9 of 12 months, at least one measurement in each season; (ii) 5-year averages (main exposure): 30 of 60 months; and (iii) 10-year averages: 60 of 120 months.

Covariate data

We included a set of covariates to account for potential confounding bias. We used a five-category individual-level socioeconomic status (SES) definition developed by the Danish Institute of Social Sciences, based on job titles from income tax forms, which we have shown as having an association with ALS diagnosis in Denmark,[58]. Group 1 (highest status) includes corporate managers and academics; group 2: proprietors, managers of small businesses and teachers; group 3: technicians and nurses; group 4: skilled workers; and group 5: unskilled workers. We included a group for participants who were unemployed or unclassified (group 9). For each married participant, we used the higher of the couple's individual SES categories,

where available. We also used information on civil status (never married, married, divorced, widowed), last reported place of residence from postcode (Greater Copenhagen, big cities of Denmark, rest of Denmark, Greenland) and place of birth (Greater Copenhagen, big cities of Denmark, rest of Denmark, Greenland, foreign, unknown) to adjust for other potential family-specific, location-specific, and early-life confounders. As part of a sensitivity analysis, we also included parish-level SES, measured by percentage of residents with greater than high-school education, in the model. In Denmark, parishes are administrative units with an average population of ~2,500 residents.

Statistical analysis

We analyzed the association between ALS diagnosis (binary) and exposure to traffic-related pollutants by applying a Bayesian formulation of the conditional logistic model, with Bayesian hierarchy on the traffic-related pollutants (EC, NO_x, CO).[59,60] The conditional approach automatically accounts for matching factors (age, sex, year of birth, vital status) between cases and controls within each matched stratum, i.e., groupings of case and matched controls.[59] Bayesian inference allows for full distributional estimation of parameters of interest.[60] 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., percentage change in odds of ALS diagnosis with increase in each of EC, NO_x, CO), and (c) an overall 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.[60] We included a linear term for each included

pollutant and adjusted for individual- and parish-level SES, civil status, last reported place of residence, and place of birth.

Specifically, via a logit function, we modelled the log-odds of ALS diagnosis, as follows:

$$logit[\Pr(\mathrm{Y}_{ci} = 1)] = \alpha_c +$$

$$\beta_{\mathrm{NO}_x}\mathrm{NO}_{x\,ci} + \beta_{CO}\mathrm{CO}_{ci} + \beta_{EC}\mathrm{EC}_{ci} +$$

$$\beta_{\mathrm{PM}_{2.5}}(\text{non-EC PM}_{2.5\,ci}) +$$

$$\beta_{\mathrm{SES}}\mathrm{SES}_{ci} + \beta_{\text{Civil Status}}\text{Civil Status}_{ci} + \beta_{\text{Residence}}\text{Residence}_{ci} + \beta_{\text{Birth}}\text{Birth}_{ci},$$

where Y_{ci} denotes whether subject i in matched stratum c was diagnosed with ALS, i.e., c represents a case and its matched controls; α_c the matched stratum-specific intercepts (not estimated in conditional logistic models); $\beta_{\mathrm{NO}_x}, \beta_{CO}, \beta_{EC}, \beta_{\mathrm{PM}_{2.5}}$ the pollutant-specific coefficients (log-odds) per standard deviation increase in concentration of NO_x, CO, EC, non-EC $\mathrm{PM}_{2.5}$ respectively, scaled by their respective standard deviations and centered at their means; and the rest as coefficients for subject-specific covariates. If other sources of air pollution are associated with ALS, then including non-EC $\mathrm{PM}_{2.5}$ adjusts for other air pollutants from other sources.[61] Therefore, $\beta_{\mathrm{PM}_{2.5}}$ is interpreted as the association with air pollutants not specifically included in our analysis. In urban European environments, traffic-related pollutants typically represent on-average 14% of $\mathrm{PM}_{2.5}$ concentrations.[62] In a sensitivity analysis, we included β_{O_3} to account for O_3 exposures in the model, and added $ns(\mathrm{SES}_{\mathrm{parish}_{ci}})$, as a natural spline with three degrees of freedom.

In our model, β_{NO_x}, β_{CO}, and β_{EC} represent the independent pollutant-specific associations with ALS diagnosis. In the same model, we estimated the joint association between these three pollutants and ALS diagnosis as:

$$Traffic_{Joint} = \sum_{p=NO_x,CO,EC} \beta_p p.$$

This sum quantifies the association (log-odds) with ALS of a one-SD increase in the three pollutants simultaneously.

Finally, we assumed that the traffic-related pollutant-specific associations arise from a distribution of the overall traffic association with ALS diagnosis. We placed a hierarchy on the traffic-specific pollutant terms in the model:

$$\beta_{Traffic} = \left[\beta_{\mathrm{NO}_x}, \beta_{CO}, \beta_{EC}\right],$$

$$\beta_{Traffic} \sim MVN(\mu, \Sigma),$$

$$\mu \sim N(\lambda, \sigma_\lambda),$$

$$\Sigma = \tau\Omega\tau,$$

where λ denotes the overall average one-SD association of traffic-related pollution with variance σ_λ. Σ, the estimated variance-covariance matrix among pollutant-specific estimates, was expressed as a decomposition into a positive-definite correlation matrix Ω and scale matrix τ.[63]

We used weakly-informative priors so that data drove parameter estimation. Hyper-priors for coefficients on non-EC $PM_{2.5}$ and covariates were N(0,10); for σ_λ and τ we used Half-Cauchy(0,10), as recommended by Gelman, Polson and Scott;[64,65] and Ω was defined by LKJCorr(1).[66] The exception to this was the prior for λ, the average association of traffic-related

pollutants, for which estimates became unrealistically high (approaching infinity and not converging with further iterations) with a non-informative prior. We therefore used a prior of N(0,0.1), which did not affect estimates of other parameters. We conducted sensitivity analyses to understand the influence of priors and the robustness of the results.

We present all results as percentage change in odds of ALS diagnosis per standard deviation (SD) increase in pollutant concentration (calculated via e.g., $e^{\beta_{\mathrm{NO}_x}} - 1$, etc. obtained in the modelling process). We ran each model with four chains with a sample size of 1,000 each, after a warm-up of 1,000 samples, for 4,000 total samples. We assessed whether the models converged by checking that the Gelman-Rubin potential scale reduction statistic[67] was below 1.1 for all estimated model parameters. The reported 95% credible intervals (CrI) are the 2.5th to 97.5th percentiles of each parameter's posterior marginal distribution. To calculate the probability that an association estimate was greater than null, we used the 4,000 samples of the posterior and took the proportion of samples which were above a null association.

We conducted statistical analyses using the R Statistical Software, version 4.1.1[68] and R-STAN, version 2.21.2.[60] All code for analysis, results from analysis, and visualization presented in this manuscript will be publicly available via GitHub at https://github.com/rmp15/multipollutants_and_als_code_review.

We assessed the sensitivity of our results to hyper-prior assignment; running more iterations and warm-up per chain; inclusion of O_3; single traffic-related pollutant models adjusting for non-EC $PM_{2.5}$; as well as adjusting by parish-level SES. From the parish-level SES sensitivity analysis

we excluded those who lived in areas without parish-level SES data, namely: (i) 819 participants for 1-year average exposure; (ii) 826 participants for 5-year average exposure; and (iii) 838 participants for 10-year average exposure.

Results

After filtering the original 4,011 cases and 20,055 controls based on completeness of exposure records, we used information on 3,934 (98.1% of total) cases and 19,298 (96.2% of total) controls for 5-year average exposure. We also used 3,937 cases,19,333 controls for 1-year average exposure and 3,939 cases, 19,250 controls for 10-year average exposure. Descriptive statistics of included cases and controls for 5-year average exposure can be found in Table 1. For the main results, we present 5-year average exposure associations.

The 5-year average traffic-related pollutant concentrations were 27 $\mu g/m^3$ for NO_x (SD=20 $\mu g/m^3$), 238 $\mu g/m^3$ for CO (SD=106 $\mu g/m^3$) and 0.85 $\mu g/m^3$ for EC (SD=0.42 $\mu g/m^3$) (Table 2). Figure 1 shows Spearman correlations between pollutants for 5-year average exposures. Traffic-related pollutants (NO_x, CO, EC) were highly correlated in cases, controls and overall, ranging from correlations of 0.91 to 0.96. Otherwise, non-EC $PM_{2.5}$ was most highly correlated with CO. O_3 was negatively correlated with other pollutants.

For 5-year average pollutant concentrations, we observed the largest overall association for the individual standard deviation increase in EC (11.5%; 95% CrI: -1.0%, 25.6%; 96.3% posterior probability of positive association per 0.42 $\mu g/m^3$) (Figure 2). Standard deviation increases were associated with a decrease in odds of ALS diagnosis in NO_x (-4.6%; 95% CrI: -18.1%, 8.9% per

20 μg/m^3) and CO (-3.2%; 95% CrI: -14.4%, 10.0% per 106 μg/m^3). The joint association was 2.3% (95% CrI: -3.3%, 7.7%), with an 77.8% posterior probability of a positive association. Finally, the average overall traffic association was null (-0.1%; 95% CrI: -17.4%, 20.8%). Non-EC $PM_{2.5}$ was not associated with ALS diagnosis (0.7%; 95% CrI: -9.2%, 12.4%). 1-year EC average exposure was associated with a significant increase in odds of ALS diagnosis (15.4%; 95% CrI: 1.6%, 25.6%) (Figure 2). 10-year average exposure results were attenuated versions of the 1- and 5-year results. Single-pollutant models for each traffic-related pollutant adjusting for non-EC $PM_{2.5}$ (eFigure 1) resulted in positive associations for each of EC, NO_x, CO, with positive associations for non-EC $PM_{2.5}$ in all but the model with EC. Results from variations of the main model in the sensitivity analyses were robust to prior choices and inclusion of parish-level SES (eFigure 1).

Discussion

In the largest case-control study of ALS and traffic-related air pollution to date, we found that an increase in average concentrations of traffic-related pollutants was associated with an increase in odds of ALS diagnosis, though not significant at the 95% credible interval level, apart from EC for 1-year average SD increase. We found that EC had the largest-in-magnitude independent association with ALS diagnosis, while the non-significant associations with NOx and CO were negative and smaller in magnitude.

Our results indicate that traffic-related pollutants, hazardous in many ways,[9–21,40–42] may also be associated with ALS diagnosis. Our finding—that increases in EC, are potentially positively associated with ALS diagnosis—is plausible. A recent case-control study in the Netherlands

reported that ultrafine particles, another traffic emissions-related surrogate, were associated with ALS diagnosis,[38] while another based in Catalonia, Spain found ALS cases clustered around key road infrastructure.[69] Although we did not find an association with non-EC $PM_{2.5}$ in our study, our results are not directly comparable to those of the other studies, as our $PM_{2.5}$ effect estimates capture the $PM_{2.5}$ components not accounted for by other pollutants in the analysis.

Our results indicate that EC exposure—a large part of which comes from diesel combustion and small combustion sources (such as wood stoves) in European urban centers, where prevalence of diesel cars is high[70]—has a high probability of a positive association with ALS diagnosis. In our previous study of ALS and occupational exposures in Denmark we found that those working in agriculture and construction, associated with exposure to diesel engine exhausts, were at higher relative risk than those in other employments.[58] Truck drivers, for whom diesel exposure is common, are also at increased risk of sporadic ALS.[71] EC exposure has been associated with inflammation,[72] mitochondrial dysfunction[73] and DNA damage,[73,74] all of which are plausible pathways of neurodegeneration. These factors have also previously been identified as particular pathways to pathogenesis of ALS.[30–34]

We did not find a high probability of a positive association with NO_x in our analyses, in contrast with a previous study, though that study did not include EC.[38] NO_x is also highly correlated with EC (0.95 to 0.96 in our study), which is expected given that they are both combustion products commonly associated with emissions in urban environments. EC exposure was more strongly associated with 1-year than for 5-/10-year average concentrations, which may indicate that the previous year may be the most relevant exposure window. We do not expect that these results are

attributed to reverse causation, as we have lagged these 1-year exposures by one year already prior to diagnosis, and there was likely little substantial residential movement in the year before ALS diagnosis.[75]

Our study used one the largest number of ALS patients ever included in an environmental health study. Another strength of our study is that we leveraged highly correlated traffic pollutants and Bayesian hierarchical modeling and were able to estimate independent and joint traffic-related pollutant associations, as well as an overall traffic estimate. Although we have adjusted implicitly (by matching; age, sex, year of birth, vital status) and explicitly for many common covariates (SES, civil status, residence, place of birth), we cannot rule out residual confounding (e.g., from smoking or body mass index (BMI)). However, to induce confounding bias, any unaccounted-for variable would have to influence both ALS diagnosis and air pollution. BMI, previously associated with ALS,[76,77] would not confound the association between traffic-related air pollution and ALS,[75] as pollutant concentrations are derived independently from BMI distribution. Any BMI-air pollution association in our study, thus, would be via SES, for which we adjusted at both the individual and parish level. Exposure measurement error is inevitable, as any modelled exposure will be inaccurate to some degree. However, any error is not likely correlated with ALS diagnosis, and therefore any bias would be towards null.[78]

Future research might use larger cohort data to understand the importance of each respective pollutant in a single model. The timing of exposure will also be an important study route. ALS is projected to increase in prevalence over the next few decades all over the world.[4] Understanding ALS pathogenesis and identifying modifiable risk factors is critical for preventive action.

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Table 1. Demographic characteristics of cases and controls for 5-year average exposure group.

Characteristic	Overall, N = 23,232[a]	Case, N = 3,934[a]	Control, N = 19,298[a]
Average age (years)	66 (12)	66 (12)	66 (12)
Sex			
Female	10,973 (47%)	1,854 (47%)	9,119 (47%)
Male	12,259 (53%)	2,080 (53%)	10,179 (53%)
Socioeconomic status (SES)			
Group 1 (Highest)	2,337 (10%)	451 (11%)	1,886 (9.8%)
Group 2	2,839 (12%)	499 (13%)	2,340 (12%)
Group 3	4,360 (19%)	785 (20%)	3,575 (19%)
Group 4	6,598 (28%)	1,076 (27%)	5,522 (29%)
Group 5 (Lowest)	4,419 (19%)	717 (18%)	3,702 (19%)
Group 9 (Unemployed or unclassified)	2,679 (12%)	406 (10%)	2,273 (12%)
Place of birth			
Greater Copenhagen	4,858 (21%)	831 (21%)	4,027 (21%)
Big cities of Denmark	7,923 (34%)	1,357 (34%)	6,566 (34%)
Rest of Denmark	9,009 (39%)	1,548 (39%)	7,461 (39%)
Greenland	243 (1.0%)	53 (1.3%)	190 (1.0%)
Foreign	1,065 (4.6%)	122 (3.1%)	943 (4.9%)
Unknown	134 (0.6%)	23 (0.6%)	111 (0.6%)
Civil status			
Married	14,158 (61%)	2,411 (61%)	11,747 (61%)
Divorced	2,703 (12%)	433 (11%)	2,270 (12%)
Widowed	4,224 (18%)	726 (18%)	3,498 (18%)
Never married	2,147 (9.2%)	364 (9.3%)	1,783 (9.2%)
Last reported place of residence			
Greater Copenhagen	1,887 (8.1%)	335 (8.5%)	1,552 (8.0%)
Big cities of Denmark	9,385 (40%)	1,590 (40%)	7,795 (40%)
Rest of Denmark	11,954 (51%)	2,008 (51%)	9,946 (52%)
Greenland	6 (<0.1%)	1 (<0.1%)	5 (<0.1%)

[a]Mean (SD); n (%)

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

Pollutant	Overall, N = 23,232[a]	Case, N = 3,934[a]	Control, N = 19,298[a]
NO_x	27 (20)	28 (21)	27 (20)
CO	238 (106)	239 (112)	237 (105)
EC	0.85 (0.42)	0.86 (0.45)	0.85 (0.42)
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)

[a]Mean (SD)

Figure Captions

Figure 1. Spearman correlation of 5-year average pollutant concentrations.

Figure 2. Percentage change in odds of ALS diagnosis per 1-, 5- and 10-year average standard deviation 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.

Figure 1

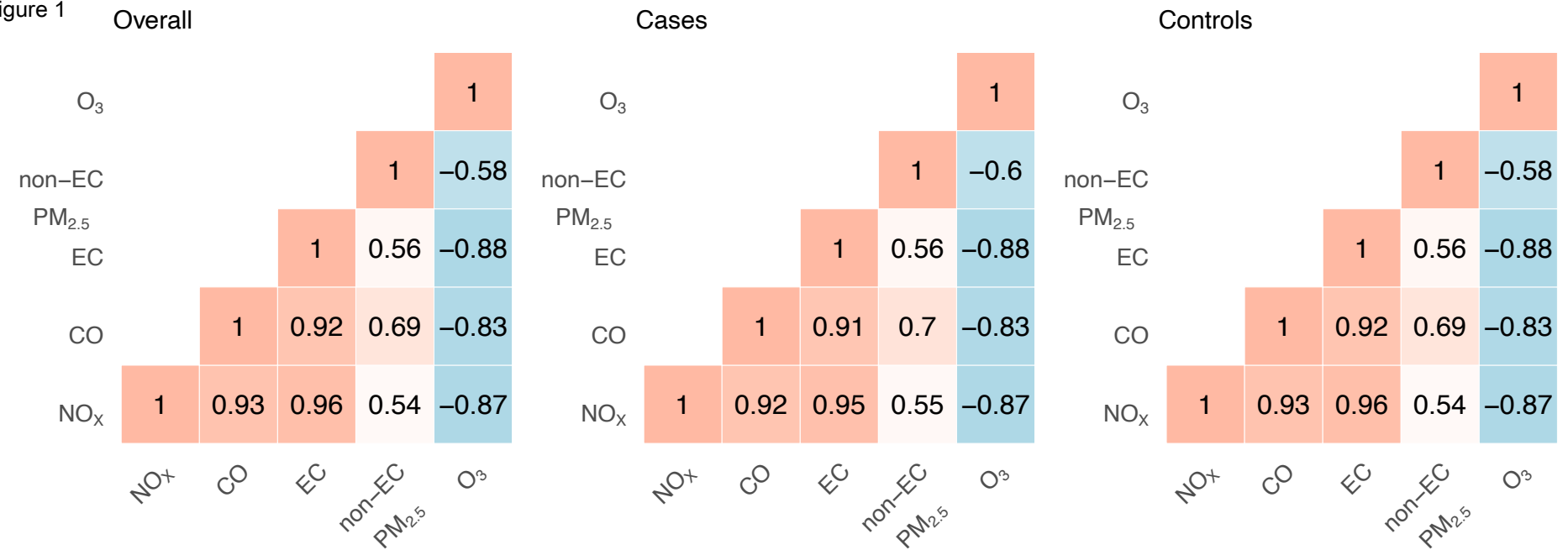
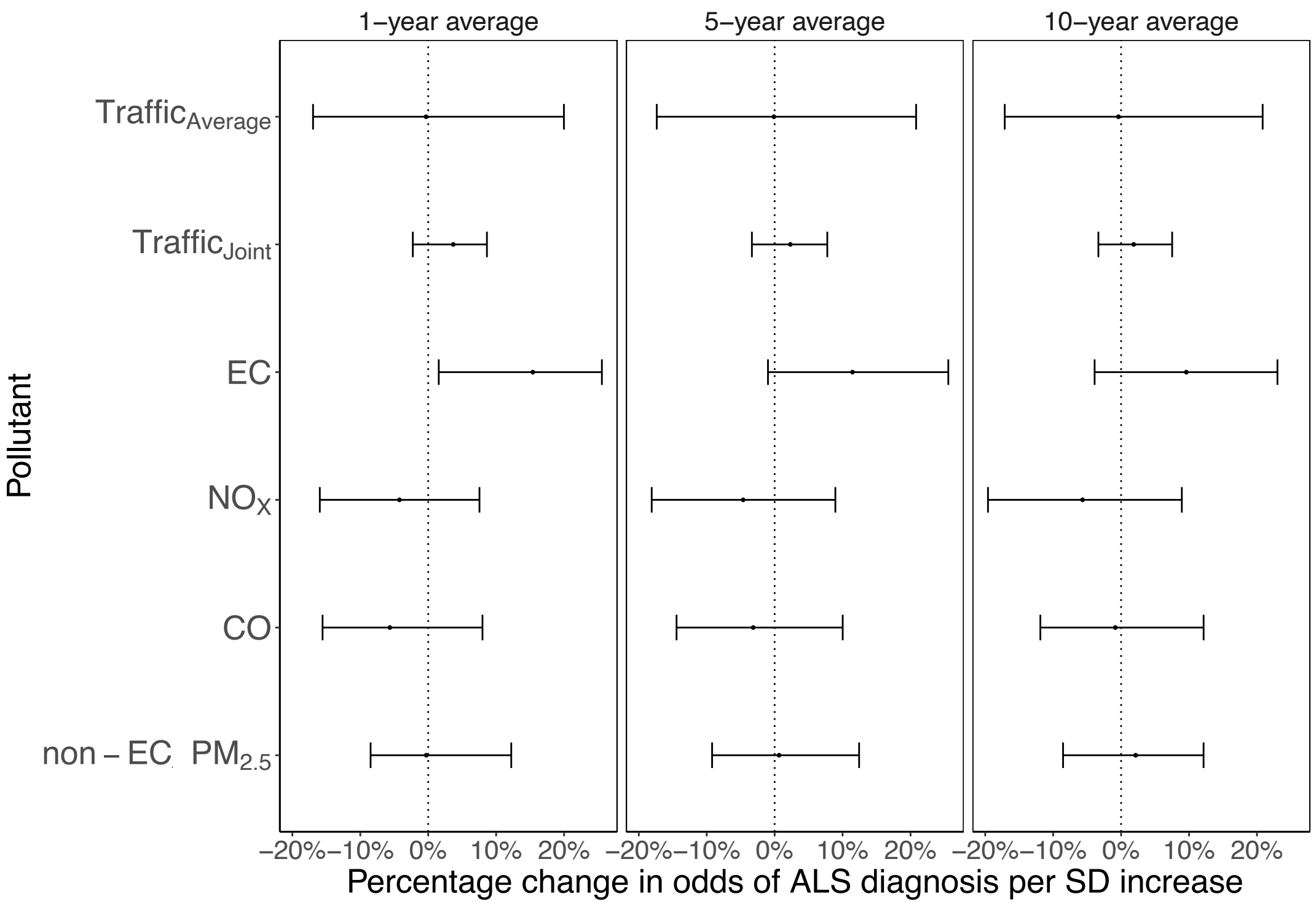

Overall
Cases
Controls
O3
non–EC PM2.5
EC
CO
NOX
1
0.93
0.96
0.54
−0.87
0.92
0.69
−0.83
0.56
−0.88
−0.58
0.91
0.7
−0.6
0.95
0.55

Figure 2


1–year average
5–year average
10–year average
Pollutant
Traffic Average
Traffic Joint
EC
NOX
CO
non – EC PM2.5
–20% –10% 0% 10% 20%
Percentage change in odds of ALS diagnosis per SD increase

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