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

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**Word Count:**

Abstract: XX words

Main Text: XX words

**Key Points**

**Question:** How are traffic-related pollutants, individually and together, associated with diagnosis of amyotrophic lateral sclerosis (ALS)?

**Findings:** In this largest study case-control study of ALS diagnosis to date that included 4,011 diagnoses of ALS in Denmark, we observed that a standard deviation increase of 5-year concentration of traffic-related pollutants was associated with a non-significant increase in odds of ALS diagnosis, but with an XX% posterior probability of a positive association.

**Meaning:** Our results indicate a potential positive association between ALS diagnosis and traffic-related pollution. Further work is needed to understand the role of air pollution on ALS pathogenesis and timing of onset.

**Abstract**

**Importance:** Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease. There is some limited evidence to suggest ALS onset is associated with exposure to air pollution, and specifically to traffic-related pollution.

**Objective:** To determine whether exposure to components of traffic-related pollution is associated with ALS diagnosis.

**Design:** In this case-control study, we used Bayesian hierarchical modelling in a conditional logistic model. We used prospectively collected data from the Danish National Registers system from 4,011 ALS cases diagnosed between 1989 – 2013 and matched on age, sex, and vital status to 20,055 controls. We used predictions from a validated spatio-temporal model to assign 5-year average exposures prior to diagnosis to combined traffic-related pollutants, as well as nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), and fine particles (PM2*.*5) at residential addresses of study participants.

**Setting:** We used prospectively collected ALS diagnosis case data from the Danish National Patient Register and control data from the Danish Civil Registration System.

**Participants:** All adults in Denmark between 1989 – 2013.

**Main Outcome Measure:** ALS diagnosis in Denmark during 1989 – 2013.

**Results:** We found that for a standard deviation (SD) increase in 5-year average concentrations, the joint effect of included traffic-related pollutants (NOx, CO, EC) was associated with an increase in odds of ALS diagnosis (XX%; 95% credible interval [CrI]:XX, XX%), with an increase in odds for elemental carbon (SD=XX µg/m3) (XX%; 95%CrI: -XX%, XX%), with small or negligible increases from NOx and CO. Overall, there was an XX% posterior probability of a positive association between the joint effect of included traffic-related pollutants and ALS diagnosis.

**Conclusion:** Our results indicate a potential positive association between ALS diagnosis and traffic-related pollution. Further work is needed to understand the role of air pollution on ALS pathogenesis and timing of onset.

**Introduction**

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease,1 with approximately half of the patients dying within three years of symptom onset.2 There is currently no cure for ALS.3 Annually, there are nearly 30,000 cases of ALS in Europe and over 200,000 worldwide, with the number projected to increase nearly 70% by 2040.4 Though great advances in our understanding of genetics have been made, known inherited mutated genes only account for 5–10% of ALS cases.5,6 Environmental factors therefore likely play an important role in ALS pathogenesis.7 However, because the disease is relatively rare, it is difficult to conduct large-scale prospective studies. The lack of and the need for more and better epidemiologic studies has been recognized and highlighted.5,8

Air pollution is most commonly studied in association with both acute and chronic respiratory- and cardiovascular-related outcomes.9–12 Toxicological studies also support several plausible biological mechanisms in association of the nervous system and neurodegeneration.13 Ambient air pollution, and especially urban air pollution, is a ubiquitous exposure that has been associated with several other neurodegenerative disorders,14–19 and consistently linked to systemic inflammation,20–22 oxidative stress,23–26 and neuroinflammation,13,27 all of which, in turn, have been reported as key pathways to ALS pathogenesis.28–3030– 35

Despite the compelling plausibility, few studies to datehave evaluated the association between ambient air pollution and ALS.31 etc. Traffic-related pollutants, particularly associated with adverse health,14,17,38–44 are highly correlated with one another. It is therefore also a mixture modelling challenge to infer the group effect of traffic-related pollutants, both combined and average, as well as the contribution of the individual components. Our aim for this study was to assess whether exposure to each individual traffic-related pollutant is associated with ALS diagnosis, as well as evaluating their total and average effect.

**Methods**

*Study population and Outcome Assessment*

We used data from the Danish National Registers system during 1989 – 2013, through which details on demographic characteristics and certain health outcomes of all Danish residents can be linked based on a 10-digit unique personal identifier.32 The Danish National Registers system was established in 1977 and is a comprehensive patient register, including nationwide clinical and administrative records for all somatic inpatient data. Outpatient data have also been included in the Danish National Registers system since 1995. In a previous validation study, we found that Danish National Registers system data for ALS ascertainment are highly reliable.33

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. For the diagnosis date, we used the date of the first relevant code. We only included patients who were at least 20 years old when diagnosed. We obtained controls through the Danish Civil Registration System, which was established in 1968 and includes administrative records (e.g., date and place of birth, vital status, and history of civil status and addresses) on all persons living in Denmark; records are kept even when a person dies or emigrates.34 We identified controls as any person with no mention – up to the diagnosis date for the matched case – of ICD-8 code 348.0 or ICD-10 G12.2 in the Danish National Registers system. We randomly matched five controls per case by age, sex and date of birth. Controls were alive in the Danish National Registers system at the time of first mention of ALS of the matched case.

We obtained all addresses of cases and controls from January 1st 1979 onwards from the Danish Civil Registration System, including the dates of moving to and leaving from each address, prior to the case diagnosis date. We then obtained the geographical co-ordinates 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.15

This study was approved by the Institutional Review Board at the Columbia University.

*Exposure data*

We obtained predictions on monthly concentrations of nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), fine particles (PM2*.*5), and ozone (O3) at residential addresses of study participants from a validated spatio-temporal model with full space and time coverage over our study period, described in detail elsewhere.35,36 The predictions in pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.15,37–39 Based on the residential history of each case or control, we then calculated 1-, 5-, and 10-year average exposure to each pollutant ending at one year before the date of the associated case’s ALS diagnosis, as diagnosis has been shown previously to occur at an median of 12 months after onset.40 A small number of the Danish Civil Registration System lack a complete address history, indicated when the address history for a subject is incomplete (typically lack of house number: ≈1.7% of addresses). To ensure we were including participants with adequately complete exposure records, we set the following criteria for including cases and controls across the length of exposure averages: (i) 1-year averages: 9 out of 12 months with complete exposure records, and at least one measurement in each season; (ii) 5-year averages: at least 30 out of 60 months with complete exposure records; and (iii) 10-year averages: at least 60 out of 120 months with complete exposure records.

*Covariate data*

We included a set of covariates to account for potential variation between the matched cases and controls. We used the five-category socioeconomic status (SES) definitions developed by the Danish Institute of Social Sciences, which are based on job titles and income tax forms. The group with the highest status (group 1) includes corporate managers and academics; group 2 includes proprietors, managers of small businesses and teachers; group 3 includes technicians and nurses; group 4 includes skilled workers; and group 5 includes unskilled workers. We also included an additional group for unemployed participants (group 9). If a participant were married and information was available, we used the higher of the couple’s individual SES ranks. We also used information on civil status (never married, married, divorced and widowed), place of residence (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 family-specific, location-specific and early-life potential confounders. As part of the sensitivity analysis, we also the included area-level parish-level SES covariate in the model.

*Statistical analysis*

We analyzed the association between ALS diagnosis (binary outcome; 1 for diagnosed cases and 0 for matched controls) and exposure to traffic-related pollutants by applying a Bayesian formulation of the conditional logistic model, with Bayesian hierarchy on the traffic-related pollutants. The logistic regression model is appropriate for binary outcomes regressed against continuous or discrete variables.41 The conditional approach automatically accounts for matching factors (age, sex and date of birth) between cases and controls within each strata, which here are the groupings of case and matched controls.41 Bayesian inference allows for full distributional estimation of the parameters of interest.42 The Bayesian hierarchical formulation on the traffic-related pollutants is a mixture method which allows a group effect, as well as the individual component effects, while accounting for the associated variance-covariance structure between the highly-correlated exposures.42 We included a linear term for each included pollutant. We also adjusted by covariates SES, civil status, place of residence and place of birth.

Specifically, via a logit function, we modelled ALS diagnosis, as follows:

where denotes whether there was an ALS diagnosis for subject in group ; the matched stratum-specific intercepts (not estimated in the conditional logistic model); ,,,the pollutant-specific coefficients (log-odds) per standard deviation increase in concentration of , , , respectively, scaled by their respective standard deviations and centered at their means; and the rest as coefficients for subject-specific covariates.

In addition, we placed a hierarchy on the traffic-specific pollutant terms in the model:

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,

where was estimated by decomposing into a positive-definite correlation matrix and scale matrix .43

The overall increase in log-odds in ALS diagnosis based on a standard deviation increase in all traffic-related pollutants was calculated by:

We used weakly-informative priors so that parameter estimation was driven by the data. Hyper-priors for coefficients on and covariates were N(0,10); for , they were Half-Cauchy(0,10); and was defined by LKJCorr(1).44The exception to this was for the prior on , for which estimates diverged with a non-informative prior, and so was given 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, as detailed below.

We present all results as percentage change in odds of ALS diagnosis per standard deviation increase in pollutant concentration. We conducted statistical analyses using the R Statistical Software, version 4.1.1 (Foundation for Statistical Computing, Vienna, Austria),45 and R-STAN, version 2.21.2.42 We ran each model with four chains with a sample size of 1,000 each, after a warm-up of 1,000 samples, which resulted in 4,000 total samples. The reported 95% credible intervals (CrI) are the 2.5th to 97.5th percentiles of each parameter’s posterior marginal distribution. All code for analysis and visualization presented in this manuscript will be publicly available via GitHub.

We assessed the sensitivity of our results to hyper-prior adjustment; inclusion of O3; as well as including parish-level SES as a covariate. Our results were robust to these sensitivity analyses (Figure SX).

**Results**

After filtering the original 4,011 cases and 20,055 controls based on completeness of exposure and covariate records, we were left with (i) XX cases and XX controls for 1-year average exposure; (ii) XX cases and XX controls for 5-year average exposure; and (iii) XX cases and XX controls for 5-year average exposure. Descriptive statistics of included cases and controls can be found in Table 1.

* Paragraph about exposure, referring to Table 2 and Figure 1
* Paragraph about correlations, justifying use of BHRM, referring to Figure 2.
* Paragraph about results, referring to Figure 3.

**Discussion**

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**Table 1.** Summary of patients characteristics by case/control/not included.

**Table 2.** Summary of pollutant concentrations.

**Figure 1**.Correlation plot.

**Figure 2**. Results.

**Figure XX**. (potential figure map of pollutants? Ask Matthias)

**eFigure XX**. For 1- and 10-year averages

**eTable XX**.

**Acknowledgements**

**Author contributions**: Dr Parks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Parks, Kioumourtzoglou.

*Acquisition, analysis, or interpretation of the data:* Parks, Kioumourtzoglou, Balilian, Nunez, Hansen, Ketzel, Weisskopf, XX.

*Drafting of the manuscript:* Parks, Kioumourtzoglou.

*Critical revision of the manuscript for important intellectual content:* XX

*Statistical analysis:* Parks, Kioumourtzoglou.

*Obtained funding*: Kioumourtzoglou.

*Administrative, technical, or material support:* XX

*Study Supervision*: Kioumourtzoglou.

**Conflict of interest disclosures:** None reported.

**Funding/Support:** Robbie M Parks was partially supported by the Earth Institute post-doctoral research fellowship at Columbia University. Funding was also provided by the National Institute of Environmental Health Sciences (NIEHS) grants R01 ES030616, R01 ES028805, R01 ES028033, R01 MD012769, R01 AG066793, R01 ES029950, R21 ES028472, P30 ES009089, P30 ES000002, and P42 ES010349.

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