**Multi-air pollutant exposure and amyotrophic lateral sclerosis (ALS) diagnosis in Denmark using Bayesian Hierarchical Regression Modelling**

*Robbie M Parks, PhD*

Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA

The Earth Institute, Columbia University, New York, New York, USA

*Arin Balilian, MD, MPH*

Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, USA

*Yanelli Nunez, PhD*

Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA

*Johnni Hansen, PhD*

Danish Cancer Society Research Center, Copenhagen, Denmark

*Ole Raaschou-Nielsen, PhD*

Danish Cancer Society Research Center, Copenhagen, Denmark

*Matthias Ketzel, PhD*

Department of Environmental Science, Aarhus University, Roskilde, Denmark

*Jibran Khan, PhD*

Department of Environmental Science, Aarhus University, Roskilde, Denmark

*Marc G. Weisskopf, ScB, PhD, ScD*

Department of Environmental Health, T. H. Chan School of Public Health, Harvard University, Boston, Massachusetts, USA

*Roel Vermeulen, PhD*

Institute for Risk Assessment Sciences, Universiteit Utrecht, Utrecht, the Netherlands

*Susan Peters, PhD*

Institute for Risk Assessment Sciences, Universiteit Utrecht, Utrecht, the Netherlands

*Diane B. Re, PhD*

Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA

*Marianthi-Anna Kioumourtzoglou, ScD*

Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA

**Corresponding Author:**

Robbie M Parks

Department of Environmental Health Sciences

Columbia University Mailman School of Public Health

722 West 168th Street, #1104

New York, New York, 10032

Email: [robbie.parks@columbia.edu](mailto:robbie.parks@columbia.edu)

**Word Count:**

Abstract: XX words

Main Text: XX words

**Key Points**

**Question:** How are traffic-related pollutant concentrations 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 increased risk of ALS diagnosis, with a 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 traffic- and non-traffic-related pollutants is associated with ALS diagnosis.

**Design:** In this case-control study, we used Bayesian Hierarchical Regression Modelling (BHRM) 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), fine particles (PM2*.*5), and ozone (O3) 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%). Overall, there was a 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**

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**Methods**

*Study population and Outcome Assessment*

We used data from the Danish National Registers system (NPR) 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.1 The NPR 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 NPR since 1995. In a previous validation study, we found that NPR data for ALS ascertainment are highly reliable, with a positive predictive value of 0.93 (95% CI, 0.88-0.96).2

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 found 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.3 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 NPR. We randomly matched five controls per case by age, sex and date of birth. Controls also had to be alive at the time of first mention of ALS in the NPR of the matched case. Descriptive statistics of included cases and controls can be found in Table XX.

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 the house of each house of the residential history of the participants. A previous study has demonstrated the accuracy of the geocoding of these addresses to be very high.4

*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.5,6 The predictions in pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.4,7–9

* Length of averages
* Missing data algorithms

*Covariate data*

* Details of individual covariates

*Statistical analysis*

* Case control
* Logistic regression
* Bayesian
* Bayesian Hierarchical Regression Modelling
* Model details

We conducted statistical analyses using the R Statistical Software, version XX (Foundation for Statistical Computing, Vienna, Austria), and XX (STAN) in R-STAN, version XX. All code for analysis and visualization presented in this manuscript will be publicly available via GitHub.

**Results**

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**Discussion**

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**Figure 1.** XX

**Figure 2.** XX

**Figure 3.** XX

**Figure 4**.XX

**Figure 5**. 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, and P42 ES010349

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