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

*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

*Elizabeth A Gibson, PhD*

Department of Environmental Health Sciences, Mailman School of Public Health, 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

Department of Environmental Science, Aarhus University, Roskilde, Denmark

*Matthias Ketzel, PhD*

Department of Environmental Science, Aarhus University, Roskilde, Denmark

Global Centre for Clean Air Research (GCARE), University of Surrey, Guildford, United Kingdom

*Jibran Khan, PhD*

Department of Environmental Science, Aarhus University, Roskilde, Denmark

*Jørgen Brandt, PhD*

Department of Environmental Science, Aarhus University, Roskilde, Denmark

iClimate – interdisciplinary Center for Climate Change, Aarhus University, Denmark

*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

*Jeff Goldsmith, PhD*

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

*Diane B. Re, PhD*

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

*Marc G. Weisskopf, PhD, ScD*

Departments of Environmental Health and Epidemiology, T. H. Chan School of Public Health, Harvard University, Boston, Massachusetts, 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 ambient air pollutants, individually and combined, associated with diagnosis of amyotrophic lateral sclerosis (ALS)?

**Findings:** In this large population-based case-control study of ALS diagnosis in Denmark, including 3,939 cases, we observed that a 5-year concentration of traffic-related pollutants was associated with a non-significant increase in odds of ALS diagnosis, but with a high posterior probability of a positive association for elemental carbon.

**Meaning:** Our results indicate a potential positive association between ALS diagnosis and traffic-related pollutants. 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 pollutants.

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

**Design, Setting, and Participants:** We used prospectively collected data from the Danish National Registers system from 3,939 ALS cases 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 from validated spatio-temporal models to assign 5-year average exposures prior to ALS diagnosis at present and historical residential addresses of study participants, specifically nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), and fine particles (PM2*.*5). In this population-based case-control study, we used a Bayesian hierarchical conditional logistic model and adjusted for potential confounders to estimate the overall traffic association, the joint association with the 3 traffic-related pollutants (NOx, CO, and EC), as well as pollutant-specific associations.

**Main Outcome Measure:** Adjusted odds ratio for ALS diagnosis associated with 5-year average overall traffic and specific traffic-related pollutant exposure.

**Results:** We found that for a standard deviation (SD) increase in 5-year average concentrations, the traffic-related pollutants (NOx, CO, EC) were jointly associated with an increase in odds of ALS diagnosis (1.9%; 95% credible interval [CrI]: -5.3%, 9.0%), with EC (SD=0.42 µg/m3) individually associated with an increase in odds (11.5%; 95%CrI: -1.6%, 26.2%), with small decreases individually for NOx and CO. Overall, there was a 69.3% posterior probability of a positive association between the joint effect of included traffic-related pollutants and ALS diagnosis, 95.5% for EC, 23.5% for NOx and 30.6% for CO.

**Conclusion:** Our results indicate a potential positive association between ALS diagnosis and traffic-related pollutants, particularly for EC. 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 currently without a cure,3 with approximately half of sufferers dying within three years of symptom onset.2 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 Despite great advances in our understanding of genetics, 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 challenging to conduct large-scale prospective studies. The lack of and the need for more and better epidemiologic studies of the etiology of ALS has been recognized and highlighted.5,8

Although air pollution is most commonly studied in association with respiratory- and cardiovascular-related outcomes,9–14 epidemiological and toxicological studies support several plausible biological mechanisms in association with the nervous system and neurodegeneration.15–34 Ambient air pollution, and especially urban air pollution, is a ubiquitous exposure that has been associated with several other neurodegenerative disorders,16–21 and 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 datehave evaluated the association between traffic-related air pollutants and ALS,35–38 and none has attempted to understand the combined and individual associations of traffic-related pollutants in a single model. Traffic-related pollutants have been consistently associated with adverse health, primarily in single pollutant analyses.13,17,39–41 However, they are highly correlated with one another.39 It is therefore a mixture modelling challenge to infer the association of traffic-related pollutants and health outcomes, and analyses should depend on the research question of interest.42 Using three air pollutants commonly used in health studies as traffic-related emissions tracers—nitrogen oxides (NOx), carbon monoxide (CO), and elemental carbon (EC)—we aimed to assess whether exposure to each individual traffic-related pollutant is independently associated with ALS diagnosis, and estimate their joint and the average overall traffic emissions associations.

**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.43 The Danish National Patient Register was established in 1977 and is a comprehensive register, including nationwide clinical and administrative records for all inpatient data. Outpatient data have been included since 1995 (Ref: Schmidt et al, 2016, Clin Epidemiol.)

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, Danish National Patient Registers data for ALS ascertainment were found to be highly reliable.44

We obtained controls through the Danish Civil Registration System, established in 1968, 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, and updated on a daily basis.45 We randomly matched five controls per case by sex, year of birth, and vital status. Further, 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,45 including the dates of moving to and leaving from each address, prior to the index 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.17

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

*Exposure data*

We obtained predictions on monthly concentrations of nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), ozone (O3), and fine particles (PM2*.*5) at residential addresses of study participants from validated spatio-temporal modelling system (DEHM-UBM-AirGIS) with full space and time coverage over our study period, described in detail elsewhere.46,47 We used the O3 concentrations for sensitivity analyses. These predicted pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.17,48–50 The models have good predictive accuracy, with average monthly correlations between measured and modelled results of 0.84 for NOx,46 0.8 for CO,46 XX for O3,46 XX for EC,47 and 0.91 for annual concentrations of PM2.5.51. 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 onset.52 A small number of people in the Danish Civil Registration System lack a complete address history (typically 1.7% from a lack of house number). 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 (main exposure): 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 confounding bias. We used a five-category individual-level socioeconomic status (SES) definitions developed by the Danish Institute of Social Sciences, based on job titles from income tax forms, which we have been previously shown as having an association with ALS diagnosis in Denmark,53. Group 1 (highest status) 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 additionally included a group for participants with unknown or unspecific job title (group 9). If a participant were married and information were 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 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 small administrative units with an average population of ~2,500 residents (ranging from <200 to >10.000 residents).

*Statistical analysis*

We analyzed the association between ALS diagnosis (binary; 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.54,55 The conditional approach automatically accounts for matching factors (age, sex, year of birth, and vital status) between cases and controls within each matched stratum, i.e., groupings of case and matched controls.54 Bayesian inference allows for full distributional estimation of the parameters of interest.55 We employed a Bayesian hierarchical formulation because it allows us to estimate (a) independent pollutant associations, (b) a joint association of the three pollutants, and (c) an overall average traffic association, while accounting for the variance-covariance structure between the highly correlated exposures and their coefficients.55 We included a linear term for each included pollutant and adjusted for individual- and parish-level SES, civil status, place of residence, and place of birth.

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

where denotes whether subject in matched stratum was diagnosed with ALS, i.e., represents a case and its matched controls; 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. If other sources of air pollution are associated with ALS, then including PM2.5 (an overall air pollution mixture which includes traffic-related pollutants) adjusts for other air pollutants from other sources.56 Therefore, would be interpreted as the association with non-traffic air pollutants. In a sensitivity analyses, we included to account for exposures in the model, and added , a natural spline with three degrees of freedom.

In the above model, the coefficients , , and represent the independent pollutant-specific associations with ALS diagnosis. Additionally, we estimated the joint association between these three pollutants and ALS diagnosis as:

Specifically, this sum quantifies the association (log-odds) with ALS of a one-SD increase in all three traffic-related pollutants simultaneously.

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

,  
,

where denotes the average overall association of traffic-related pollution with variance . , the estimated variance-covariance matrix among pollutant-specific estimates, was expressed as a decomposition into a positive-definite correlation matrix and scale matrix .57

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 and we used Half-Cauchy(0,10), as recommended by Gelman, Polson and Scott;58,59 and was defined by LKJCorr(1).60The exception to this was for the prior on , 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, and so we 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, as detailed below.

We present all results as percentage change in odds of ALS diagnosis per standard deviation (SD) increase in pollutant concentration (calculated via e.g., , etc. obtained in the modelling process). We conducted statistical analyses using the R Statistical Software, version 4.1.1 (Foundation for Statistical Computing, Vienna, Austria),61 and R-STAN, version 2.21.2.55 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. We assessed whether the models converged by checking that the Gelman-Rubin potential scale reduction statistic62 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. All code for analysis, results from analysis, and visualization presented in this manuscript will be publicly available via GitHub.

We assessed the sensitivity of our results to hyper-prior assignment; running more iterations and warm-up per chain; inclusion of O3; single traffic-related pollutant models adjusting for PM2.5; as well as adjusting by parish-level SES.

**Results**

After filtering the original 4,011 cases and 20,055 controls based on completeness of exposure and covariate 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 (98.2% of total) cases and 19,333 (96.4% of total) controls for 1-year average exposure and 3,939 (98% of total) cases and 19,250 (96% of total) controls for 10-year average exposure. Descriptive statistics of included cases and controls can be found in Table 1.

A summary of means and standard deviations of 5-year average concentrations for each pollutant included in the analysis is presented in Table 2. The 5-year average traffic-related pollutant concentrations were 27 µg/m3 for NOx (SD=20 µg/m3), 238 µg/m3 for CO (SD=106 µg/m3) and 0.85 µg/m3 for EC (SD=0.42 µg/m3). Figure 1 shows Spearman correlations between pollutants for 5-year average exposures. In general, traffic-related pollutants (NOx, CO, EC) were highly correlated in cases and controls and overall, ranging from correlations of 0.91 to 0.96. Otherwise, PM2.5 was correlated with CO most highly, as well as NOx and EC to a lesser degree. O3 was negatively-correlated with all other included pollutants.

We analyzed the association between change in odds of ALS diagnosis per standard deviation increase in individual 5-year average pollutant concentrations, as well as the association with joint exposure to these three pollutants and the average traffic contribution (Figure 2). We observed the largest overall association for the individual standard deviation increase in EC (11.5%; 95% CrI: -1.6%, 26.2%; 95.5% posterior probability of positive association per 0.42 µg/m3). Standard deviation increases were associated with a decrease in odds of ALS diagnosis in both NOx (-4.9%; 95% CrI: -18.3%, 8.7% per 20 µg/m3) and CO (-3.3%; 95% CrI: -15.5%, 9.4% per 106 µg/m3). The joint association (i.e., the percentage change in odds of ALS diagnosis with a standard deviation increase in each of EC, NOx, CO) was 1.9% (95% CrI: -5.3%, 9.0%), with an 69.3% posterior probability of a positive association. Finally, the average overall traffic association was null (0.4%; 95% CrI: -16.9%, 19.8%). PM2.5 (which in this context represented the association of non-traffic-related PM2.5) was associated with an increase in odds of ALS diagnosis (1.3%; 95% CrI: -10.4%, 14.5%). For 1-year average exposure, EC was associated with a significant increase in odds of ALS diagnosis (12.7%; 95% CrI: 0.1%, 26.1%) (Figure 2). Single-pollutant models for each traffic-related pollutant adjusting for PM2.5 (eFigure 1) resulted in positive associations for each of EC, NOx, CO, with positive associations for PM2.5 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). From this sensitivity analysis we excluded: (i) 819 participants for the 1-year average exposure; (ii) 826 participants for the 5-year average exposure; and (iii) 838 participants for the 10-year average exposure who lived in areas without parish-level SES data.

**Discussion**

In the largest case-control study of ALS and traffic-related air pollution to date, we used 3,939 ALS cases in Denmark, pollutant predictions from well-validated spatio-temporal models, and a Bayesian hierarchical structure to examine how increases in traffic-related pollutant concentrations, individually and combined, are associated with ALS diagnosis. We found that an increase of 5-year concentration 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.

Traffic-related pollutants are hazardous in many ways.9–21,39–41 Overall, while not significant at 95% CrI for 5-year averages, our results indicate that traffic-related pollutants may also be associated with ALS diagnosis. Our finding—that increases in traffic-related pollutants, and specifically 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.36 Another case-control study in the Netherlands also found a significant association with PM2.5.37 A population-based study in New York State found an association with ALS disease aggravation and PM2.5,38 while another based in Catalonia, Spain found ALS cases clustered around key road infrastructure.63 Although we did not find an association with PM2.5 in our study, our results are not directly comparable to those of the other studies, as our PM2.5 effect estimates capture the non-traffic PM2.5 components.

Our results indicate that EC exposure—a large part of which comes from diesel combustion in European urban centers, where prevalence of diesel cars is high64—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 exhausts, were at higher relative risk than those in other employments.53 Truck drivers, for whom diesel exposure is common, are also at increased risk of sporadic ALS.65 EC has been associated with inflammation,66 mitochondrial dysfunction67 and DNA damage,67,68 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 NOx in our analyses, in contrast with a previous study, though that study did not include EC.36 NOx 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 traffic-related emissions in urban environments. EC exposure was more strongly associated with 1-year than for 5- or 10-year average concentration, which may indicate that the previous year may be the most relevant exposure window, or also perhaps due to less error in more recent estimates. 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.

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) and explicitly for many common covariates (age, sex, year of birth, SES, civil status, place of birth), we cannot rule out residual confounding. However, to induce confounding bias, any unaccounted-for variable would have to covary with both ALS diagnosis and air pollution. Body Mass Index (BMI) for example, previously associated with ALS,69,70 would not be a confounder of the association between traffic-related air pollution and ALS;71 concentrations of pollutants for this study were derived from air pollution models independent from the geographical BMI distribution of the Danish population. 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 would therefore be expect any bias to be towards the null.72

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

**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, Weisskopf, Hansen, Goldsmith.

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

*Drafting of the manuscript:* Parks, Kioumourtzoglou.

*Critical revision of the manuscript for important intellectual content:* Gibson, Balilian, Nunez, Hansen, Raaashou-Nielsen, Ketzel, Khan, Brandt, Vermeulen, Peters, Goldsmith, Re, Weisskopf.

*Statistical analysis:* Parks, Kioumourtzoglou, Goldsmith.

*Obtained funding*: Kioumourtzoglou.

*Administrative, technical, or material support:* Parks, Balilian, Nunez.

*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 AG066793, R21 ES028472, P30 ES009089, and P30 ES000002.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**References**

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *New England Journal of Medicine*. 2001;344(22):1688-1700.

2. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *The Lancet*. 2007;369(9578):2031-2041.

3. Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotrophic Lateral Sclerosis*. 2009;10(5-6):310-323.

4. Arthur KC, Calvo A, Price TR, Geiger JT, Chio A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nature Communications*. 2016;7(1):1-6.

5. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nature Reviews Neurology*. 2013;9(11):617-628.

6. Hardiman O, Al-Chalabi A, Chio A, et al. Amyotrophic lateral sclerosis. *Nature reviews Disease primers*. 2017;3(1):1-19.

7. Oskarsson B, Horton DK, Mitsumoto H. Potential environmental factors in amyotrophic lateral sclerosis. *Neurologic Clinics*. 2015;33(4):877-888.

8. Longinetti E, Fang F. Epidemiology of amyotrophic lateral sclerosis: An update of recent literature. *Current Opinion In Neurology*. 2019;32(5):771.

9. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA*. 2006;295(10):1127-1134.

10. Bennett JE, Tamura-Wicks H, Parks RM, et al. Particulate matter air pollution and national and county life expectancy loss in the USA: A spatiotemporal analysis. *PLOS Medicine*. 2019;16(7):e1002856. doi:10.1371/journal.pmed.1002856

11. Schwartz J. Particulate air pollution and chronic respiratory disease. *Environmental Research*. 1993;62(1):7-13.

12. Schwartz J. The distributed lag between air pollution and daily deaths. *Epidemiology*. 2000;11(3):320-326.

13. Brook RD, Rajagopalan S, Pope III CA, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121(21):2331-2378.

14. Dockery DW, Pope CA, Xu X, et al. An Association between Air Pollution and Mortality in Six U.S. Cities. *New England Journal of Medicine*. 1993;329(24):1753-1759. doi:10.1056/NEJM199312093292401

15. Block ML, Elder A, Auten RL, et al. The outdoor air pollution and brain health workshop. *Neurotoxicology*. 2012;33(5):972-984.

16. Zanobetti A, Dominici F, Wang Y, Schwartz JD. A national case-crossover analysis of the short-term effect of PM 2.5 on hospitalizations and mortality in subjects with diabetes and neurological disorders. *Environmental Health*. 2014;13(1):1-11.

17. Ritz B, Lee P-C, Hansen J, et al. Traffic-related air pollution and Parkinson’s disease in Denmark: a case–control study. *Environmental Health Perspectives*. 2016;124(3):351-356.

18. Kioumourtzoglou M-A, Schwartz JD, Weisskopf MG, et al. Long-term PM2. 5 exposure and neurological hospital admissions in the northeastern United States. *Environmental health perspectives*. 2016;124(1):23-29.

19. Levesque S, Surace MJ, McDonald J, Block ML. Air pollution & the brain: Subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. *Journal of Neuroinflammation*. 2011;8(1):1-10.

20. Heusinkveld HJ, Wahle T, Campbell A, et al. Neurodegenerative and neurological disorders by small inhaled particles. *Neurotoxicology*. 2016;56:94-106.

21. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro III A, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environmental Health Perspectives*. 2011;119(5):682-687.

22. Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environmental Health Perspectives*. 2006;114(7):992-998.

23. Ruckerl R, Ibald-Mulli A, Koenig W, et al. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *American Journal of Respiratory and Critical Care Medicine*. 2006;173(4):432-441.

24. Hoffmann B, Moebus S, Dragano N, et al. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environmental Health Perspectives*. 2009;117(8):1302-1308.

25. Kelly FJ. Oxidative stress: Its role in air pollution and adverse health effects. *Occupational and Environmental Medicine*. 2003;60(8):612-616.

26. Chuang K-J, Chan C-C, Su T-C, Lee C-T, Tang C-S. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *American journal of respiratory and critical care medicine*. 2007;176(4):370-376.

27. Li N, Sioutas C, Cho A, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environmental Health Perspectives*. 2003;111(4):455-460.

28. Sørensen M, Daneshvar B, Hansen M, et al. Personal PM2. 5 exposure and markers of oxidative stress in blood. *Environmental health perspectives*. 2003;111(2):161-166.

29. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends in neurosciences*. 2009;32(9):506-516.

30. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nature Reviews Immunology*. 2007;7(2):161-167.

31. Bergeron C. Oxidative stress: its role in the pathogenesis of amyotrophic lateral sclerosis. *Journal of the neurological sciences*. 1995;129:81-84.

32. Mhatre M, Floyd RA, Hensley K. Oxidative stress and neuroinflammation in Alzheimer’s disease and amyotrophic lateral sclerosis: common links and potential therapeutic targets. *Journal of Alzheimer’s disease*. 2004;6(2):147-157.

33. D’Amico E, Factor-Litvak P, Santella RM, Mitsumoto H. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. *Free radical biology and medicine*. 2013;65:509-527.

34. Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. *Nature Reviews Neurology*. 2010;6(4):193-201.

35. Malek AM, Barchowsky A, Bowser R, et al. Exposure to hazardous air pollutants and the risk of amyotrophic lateral sclerosis. *Environmental Pollution*. 2015;197:181-186.

36. Yu Z, Peters S, van BL, et al. Long-Term Exposure to Ultrafine Particles and Particulate Matter Constituents and the Risk of Amyotrophic Lateral Sclerosis. *Environmental Health Perspectives*. 2021;129(9):097702. doi:10.1289/EHP9131

37. Seelen M, Toro CRA, Veldink JH, et al. Long-Term Air Pollution Exposure and Amyotrophic Lateral Sclerosis in Netherlands: A Population-based Case–control Study. *Environmental Health Perspectives*. 2017;125(9):097023. doi:10.1289/EHP1115

38. Nunez Y, Boehme AK, Weisskopf MG, et al. Fine Particle Exposure and Clinical Aggravation in Neurodegenerative Diseases in New York State. *Environmental health perspectives*. 2021;129(2):027003.

39. Strak M, Weinmayr G, Rodopoulou S, et al. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. *BMJ*. 2021;374:n1904. doi:10.1136/bmj.n1904

40. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. *Environmental Health Perspectives*. 2015;123(11):1107-1112.

41. Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia, Parkinson’s disease, and multiple sclerosis: a population-based cohort study. *The Lancet*. 2017;389(10070):718-726.

42. Gibson EA, Nunez Y, Abuawad A, et al. An overview of methods to address distinct research questions on environmental mixtures: an application to persistent organic pollutants and leukocyte telomere length. *Environmental Health*. 2019;18(1):1-16.

43. Frank L. When an entire country is a cohort. *Science*. 2000;287(5462):2398-2399.

44. Kioumourtzoglou M-A, Seals RM, Himmerslev L, Gredal O, Hansen J, Weisskopf MG. Comparison of diagnoses of amyotrophic lateral sclerosis by use of death certificates and hospital discharge data in the Danish population. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. 2015;16(3-4):224-229.

45. Pedersen CB. The Danish civil registration system. *Scandinavian journal of public health*. 2011;39(7\_suppl):22-25.

46. Ketzel M, Berkowicz R, Hvidberg M, Jensen SS, Raaschou-Nielsen O. Evaluation of AirGIS: a GIS-based air pollution and human exposure modelling system. *International Journal of Environment and Pollution*. 2011;47(1-4):226-238.

47. Ketzel M, Burman M, Nøjgaard JK, Christensen JH, Im U, Brandt J. High resolution modelling of elemental carbon for Denmark. In: *18th International Conference on Harmonisation within Atmospheric Dispersion Modelling for Regulatory Purposes, HARMO 2017*. ; 2017.

48. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, et al. Lung cancer incidence and long-term exposure to air pollution from traffic. *Environmental health perspectives*. 2011;119(6):860-865.

49. Raaschou-Nielsen O, Sørensen M, Ketzel M, et al. Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. *Diabetologia*. 2013;56(1):36-46.

50. Sørensen M, Hoffmann B, Hvidberg M, et al. Long-term exposure to traffic-related air pollution associated with blood pressure and self-reported hypertension in a Danish cohort. *Environmental health perspectives*. 2012;120(3):418-424.

51. Khan J, Kakosimos K, Raaschou-Nielsen O, et al. Development and performance evaluation of new AirGIS–a GIS based air pollution and human exposure modelling system. *Atmospheric environment*. 2019;198:102-121.

52. Galvin M, Gaffney R, Corr B, Mays I, Hardiman O. From first symptoms to diagnosis of amyotrophic lateral sclerosis: perspectives of an Irish informal caregiver cohort—a thematic analysis. *BMJ Open*. 2017;7(3). doi:10.1136/bmjopen-2016-014985

53. Dickerson AS, Hansen J, Kioumourtzoglou M-A, Specht AJ, Gredal O, Weisskopf MG. Study of occupation and amyotrophic lateral sclerosis in a Danish cohort. *Occup Environ Med*. 2018;75(9):630-638. doi:10.1136/oemed-2018-105110

54. Rothman KJ, Greenland S, Lash TL, others. *Modern Epidemiology*. Vol 3. Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia; 2008.

55. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian Data Analysis, Third Edition*. CRC Press; 2013.

56. Mostofsky E, Schwartz J, Coull BA, et al. Modeling the association between particle constituents of air pollution and health outcomes. *American journal of epidemiology*. 2012;176(4):317-326.

57. Martin R, Peters G, Wilkinson J. Symmetric decomposition of a positive definite matrix. *Numerische Mathematik*. 1965;7(5):362-383.

58. Polson NG, Scott JG. On the half-Cauchy prior for a global scale parameter. *Bayesian Analysis*. 2012;7(4):887-902.

59. Gelman A. Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). *Bayesian Anal*. 2006;1(3):515-534. doi:10.1214/06-BA117A

60. Lewandowski D, Kurowicka D, Joe H. Generating random correlation matrices based on vines and extended onion method. *Journal of multivariate analysis*. 2009;100(9):1989-2001.

61. R Core Team. R: A language and environment for statistical computing. Published online 2013.

62. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statistical science*. 1992;7(4):457-472.

63. Povedano M, Saez M, Martinez-Matos J-A, Barceló MA. Spatial assessment of the association between long-term exposure to environmental factors and the occurrence of amyotrophic lateral sclerosis in Catalonia, Spain: a population-based nested case-control study. *Neuroepidemiology*. 2018;51(1-2):33-49.

64. von Schneidemesser E, Mar KA, Saar D. Black Carbon in Europe: Targeting an Air Pollutant and Climate Forcer. Published online 2017.

65. Pamphlett R, Rikard-Bell A. Different occupations associated with amyotrophic lateral sclerosis: Is diesel exhaust the link? *PloS One*. 2013;8(11):e80993.

66. Zhang R, Dai Y, Zhang X, et al. Reduced pulmonary function and increased pro-inflammatory cytokines in nanoscale carbon black-exposed workers. *Part Fibre Toxicol*. 2014;11:73. doi:10.1186/s12989-014-0073-1

67. Gao X, Xu H, Shang J, et al. Ozonized carbon black induces mitochondrial dysfunction and DNA damage. *Environ Toxicol*. 2017;32(3):944-955. doi:10.1002/tox.22295

68. Kyjovska ZO, Jacobsen NR, Saber AT, et al. DNA damage following pulmonary exposure by instillation to low doses of carbon black (Printex 90) nanoparticles in mice. *Environ Mol Mutagen*. 2015;56(1):41-49. doi:10.1002/em.21888

69. Nakken O, Meyer HE, Stigum H, Holmøy T. High BMI is associated with low ALS risk: A population-based study. *Neurology*. 2019;93(5):e424-e432.

70. Jawaid A, Murthy SB, Wilson AM, et al. A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS. *Amyotrophic Lateral Sclerosis*. 2010;11(6):542-548.

71. Weisskopf MG, Webster TF. Trade-offs of personal vs. more proxy exposure measures in environmental epidemiology. *Epidemiology (Cambridge, Mass)*. 2017;28(5):635.

72. Carroll RJ, Ruppert D, Stefanski LA, Crainiceanu CM. *Measurement Error in Nonlinear Models: A Modern Perspective*. CRC press; 2006.

**Table 1.** Demographic characteristics of cases and controls.

| Characteristic | Overall, N = 23,232a | Case, N = 3,934a | Control, N = 19,298a |
| --- | --- | --- | --- |
| **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%) |
| **Family 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) | 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%) |
| Widower | 4,224 (18%) | 726 (18%) | 3,498 (18%) |
| Never married | 2,147 (9.2%) | 364 (9.3%) | 1,783 (9.2%) |
| **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%) |
| aMean (SD); n (%) | | | |

**Table 2.** Summary of 5-year average pollutant concentrations (all in μg/m3).

| Pollutant | Overall, N = 23,2321 | Case, N = 3,9341 | Control, N = 19,2981 |
| --- | --- | --- | --- |
| **NOX** | 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) |
| **PM2.5** | 12.61 (2.64) | 12.64 (2.68) | 12.60 (2.63) |
| **O3** | 51.9 (6.0) | 51.9 (6.1) | 52.0 (6.0) |
| 1Mean (SD) | | | |

**Figure 1**. Spearmancorrelation 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.