**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

*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 pollutants, individually and combined, associated with diagnosis of amyotrophic lateral sclerosis (ALS)?

**Findings:** In this largest case-control study of ALS diagnosis to date, that included 3,939 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 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, which are highly-correlated.

**Objective:** To determine whether exposure to traffic-related pollutants 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 3,939 ALS cases diagnosed between 1989 – 2013 and matched on age, sex, date of birth and vital status to 19,298 controls. We used predictions from a validated spatio-temporal model to assign 5-year average exposures prior to ALS diagnosis at residential addresses of study participants, specifically nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC; of which black carbon is a constituent), and fine particles (PM2*.*5).

**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 over 20 years old 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 total association of included traffic-related pollutants (NOx, CO, EC) was associated with an increase in odds of ALS diagnosis (1.9%; 95% credible interval [CrI]: -5.3%, 9.0%), with elemental carbon individually associated with an increase in odds (SD=0.42 µg/m3) (11.5%; 95%CrI: -1.6%, 26.2%), with small decreases individually from NOx and CO. Overall, there was a 69.3% posterior probability of a positive association between the total 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, and particularly for elemental carbon. 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 of the etiology of ALS 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.9–14 Toxicological studies also support several plausible biological mechanisms in association of the nervous system and neurodegeneration.15 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 association of traffic-related pollutants in a single model. Traffic-related pollutants, particularly associated with adverse health,13,17,39–41 are highly correlated with one another.39 It is therefore also a mixture modelling challenge to infer the combined association of traffic-related pollutants,42 both total and average, as well as the association of the individual pollutants. 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 association.

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

We used expert co-author knowledge to identify 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.45 We identified controls as any person with no mention 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, date of birth and vital status. 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,45 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.17

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; of which black carbon is a constituent) and fine particles (PM2*.*5) and 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.46,47 We also obtained monthly ozone (O3) concentrations for sensitivity analyses from the same model. The predictions in pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.17,48–50 From previous work, average monthly correlations between measured and modelled results were 0.84 for NOx,46 0.8 for CO,46 XX for O3,46 and XX for EC,47 as well as 0.91 for annual concentrations of PM2.5.51. 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 average (median) of 12 months after onset.52 A small number of the Danish Civil Registration System lack a complete address history (typically 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) 5-year averages: at least 30 out of 60 months with complete exposure records; (ii) 1-year averages: 9 out of 12 months with complete exposure records, and at least one measurement in each season; 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, which have been previously shown as having an association with ALS diagnosis in Denmark,53 and income tax forms. Group 1, with the 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 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 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.54,55 The logistic regression model is appropriate for binary outcomes regressed against continuous or discrete variables.54 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.54 Bayesian inference allows for full distributional estimation of the parameters of interest.55 The Bayesian hierarchical formulation on the traffic-related pollutants is a mixture method which allows a combined association, as well as individual associations, while accounting for the associated variance-covariance structure between the highly-correlated exposures.55 We included a linear term for each included pollutant. We also adjusted by additional covariates 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 there was an ALS diagnosis for subject in group , where group 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. In a sensitivity analysis, we also included and respective concentration .

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

,  
,

where is the average association of traffic-related pollutants, and was expressed as a decomposition into a positive-definite correlation matrix and scale matrix .56

The total traffic-related association 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).57The exception to this was for the prior on , the average association of traffic-related pollutants, 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 (SD) increase in pollutant concentration (calculated via e.g., etc. and obtained in the modelling process). We conducted statistical analyses using the R Statistical Software, version 4.1.1 (Foundation for Statistical Computing, Vienna, Austria),58 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. 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 adjustment; inclusion of O3; as well as including parish-level SES as a covariate.

**Results**

After filtering the original 4,011 cases and 20,055 controls based on completeness of exposure and covariate records, we were left with 3,934 (98.1%) cases and 19,298 (96.2%) controls for 5-year average exposure. We were also left with 3,937 (98.2% of total) cases and 19,333 (96.4% of total) controls for 1-year average exposure and 3,939 (98%) cases and 19,250 (96%) controls for 10-year average exposure. Descriptive statistics of included cases and controls can be found in Table XX.

A summary of mean and standard deviation of 5-year average concentrations for each pollutant included in the analysis are found in Table XX. The highest concentration of pollutants included in the analysis for cases and controls was CO (Mean=238 µg/m3; SD=106 µg/m3), with EC the lowest (Mean=0.85 µg/m3; SD=0.42 µg/m3). O3, not included in the main analysis, had a mean of 51.9 µg/m3 and a standard deviation of 6.0 µg/m3. The Spearman correlation between pollutants for 5-year average exposure is found in Figure XX. 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 (0.77 to 0.78), as well as NOx (0.64 to 0.65) and EC (0.67 for each) to a lesser degree. O3 was negatively-correlated with all other included pollutants (-0.67 to -0.88).

We analyzed the association between change in odds of ALS diagnosis per standard deviation increase in individual 5-year average pollutant concentration, as well as total and average traffic contribution (Figure XX). We observed the largest overall association for the individual standard deviation increase in EC (SD=0.42 µg/m3) (11.5%; 95% CrI: -1.6%, 26.2%; 95.5% posterior probability of positive association). Standard deviation increases were associated with a slight percentage decrease in odds of ALS diagnosis in both NOx (SD=20 µg/m3) (-4.9%%; 95% CrI: -18.3%, 8.7%) and CO (SD=106 µg/m3) (-3.3%; 95% CrI: -15.5%, 9.4%). The total traffic 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. The average traffic association (i.e., the average association of EC, NOx, CO) was 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 averages, elemental carbon was associated with an increase in odds of ALS diagnosis which was significant at a 95% CrI (12.7 %; 95% CrI: 0.1%, 26.1%) (Figure XX). Individual models for each traffic-related pollutants with PM2.5 (i.e., one of EC, NOx, CO + PM2.5) (eFigure XX) 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 XX).

**Discussion**

In the largest case-control study of ALS and traffic-related air pollution of its kind to date, we used 3,939 ALS diagnoses in Denmark, pollutant predictions from a validated spatio-temporal, along with a Bayesian hierarchical structure to examine how increases in traffic-related pollutant concentrations, individually and combined, are associated with percentage change in odds of ALS diagnosis. We found that a standard deviation increase of 5-year concentration of traffic-related pollutants was associated with an increase in odds of ALS diagnosis, though not significant at a 95% credible interval level. We found that elemental carbon had the largest individual pollutant association with ALS diagnosis, with slight non-significant decreases in NOx and CO.

Traffic-related pollutants pose great danger to public health in many ways.9–21,39–41 Overall, while not significant at 95% CrI for 5-year averages, our results that indicate that traffic-related pollutants may also be associated with ALS diagnosis. That we found that total increases in traffic-related pollutants, and individually elemental carbon, were potentially positively associated with ALS diagnosis is plausible. A recent case-control study in the Netherlands used an unconditional logistic model to show that individual traffic-related ultrafine pollutants 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 and PM2.5,38 while another based in Catalonia, Spain found ALS cases clustered around key road infrastructure.59

Our results indicate that elemental carbon concentration, a large part of which comes from diesel combustion,60 has a high probability of a positive association with ALS diagnosis. A previous study of ALS diagnosis and occupation in Denmark found that those working in agriculture and construction, associated with exposure to diesel exhausts, were at higher relative risk than those in other employment.53 Truck drivers, for whom diesel exposure is common, are also at increased risk of sporadic ALS.61 Elemental carbon has been associated with inflammation,62 mitochondrial dysfunction63 and DNA damage,63,64 all of which are plausible pathways of neurodegeneration in the human body. Though our results did not find as strong an association with PM2.5 as previous studies did, our full model additionally contained constituents of PM2.5 in the model. 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 elemental carbon.36 NOx is also highly correlated with elemental carbon (0.95 to 0.96 in our findings).

Leveraging the largest number of ALS diagnoses ever collected, a great strength of our study is that we have created a study design which identifies individual as well as combined associations of highly-correlated traffic-related pollutants with ALS diagnosis using a Bayesian hierarchical conditional logistic model. Though it is the largest dataset ever collected for this purpose, we predict that more cases would further help power future studies. We have adjusted implicitly and explicitly by many common covariates (age, sex, date of birth, SES, civil status, place of birth), we cannot rule out residual confounding, though to induce residual confounding, an unaccounted-for variable would have to covary with both ALS diagnosis and air pollution. Exposure misclassification is also likely, as any modelled exposure will be inaccurate to some degree. However, any misclassification is likely not expected necessarily to be correlated with ALS diagnosis, and would therefore be expected to be biased towards the null.65

Future research should use larger cohort and collected data to understand the importance of each respective pollutant in a single model. The timing of exposure, as well as when exposure occurs during a lifetime, 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 is critical for both preventive action, as well as eventually to finding a full cure.

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

| Characteristic | Overall, N = 23,2321 | Case, N = 3,9341 | Control, N = 19,2981 |
| --- | --- | --- | --- |
| **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%) |
| 1Mean (SD); n (%) | | | |

**Table 2.** Summary of 5-year average pollutant concentrations.

| Pollutant | Overall, N = 23,2321  (µg/m3) | Case, N = 3,9341  (µg/m3) | Control, N = 19,2981  (µg/m3) |
| --- | --- | --- | --- |
| **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.

****

**eFigure 1**. Sensitivity of percentage change in odds of ALS diagnosis per 1-, 5- and 10-year average standard deviation increase for each pollutant.



**eFigure 2:** Other parameters estimated in models.

**eFigure 3**. Potential figure map of pollutants?

**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.

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

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

57. 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.

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

59. 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.

60. Fruin SA, Winer AM, Rodes CE. Black carbon concentrations in California vehicles and estimation of in-vehicle diesel exhaust particulate matter exposures. *Atmospheric Environment*. 2004;38(25):4123-4133.

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

62. 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

63. 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

64. 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

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