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

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**Key Points**

**Question:** How are ambient air pollutants associated with diagnosis of amyotrophic lateral sclerosis (ALS)?

**Findings:** In this population-based case-control study of ALS diagnosis in Denmark, including 3,939 cases, we observed that elemental carbon at a residence was associated with an increase in odds of ALS diagnosis.

**Meaning:** Our results indicate that sources of air pollution with elemental carbon, such as diesel engines and woodburning stoves, might contribute to development of ALS. The result needs confirmation in future studies before any conclusion can be reached.

**Abstract**

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

**Objective:** To determine whether exposure to air pollutants is associated with ALS diagnosis.

**Design, Setting, and Participants:** In this population-based case-control study, we used data on 3,939 ALS cases from the Danish National Patient Register diagnosed between 1989 – 2013 and matched on, sex, year of birth and vital status to 19,298 population-based controls free of ALS at index date. We used predictions from of nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), and non-EC fine particles (PM2*.*5) from validated spatio-temporal models to assign 1-, 5-, and 10-year average exposures pre-ALS diagnosis at present and historical residential addresses of study participants. We used a Bayesian hierarchical conditional logistic model and adjusted for potential confounders to estimate the overall and joint association for the three traffic-related pollutants (NOx, CO, and EC), as well as pollutant-specific associations.

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

**Results:** For a standard deviation (SD) increase in 5-year average concentrations, EC was individually associated with an increase in odds (11.5%; 95% credible interval [CrI]: -1.0%, 25.6%), with decreases individually for NOx (-4.6%;95%CrI -18.1%,8.9%) and CO (-3.2%; 95%CrI -14.4%, 10.0%) and a null effect of non-EC PM2*.*5 (0.7%;95%CrI -9.2%,12.4%). We found no association for joint or overall traffic pollution. There was a 77.8% posterior probability of a positive association between the joint effect of pollutants and ALS diagnosis, 96.3% for EC, 27.8% for NOx and 26.7% for CO.

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

**Introduction**

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disease,1 currently without a cure,2 with approximately half of sufferers dying within three years of symptom onset.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 Despite great advances in our understanding of genetics, known inherited genetic variants 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. There is a recognized need for more and better epidemiologic studies of the environmental contributors of ALS.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,16–21,35,36 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 air pollution and ALS.35,37–39 A recent study found that traffic-related air pollutants may be driving observed associations. To date, no study has attempted to understand the combined and individual associations of the pollutants in a single model. Air pollutants have been consistently associated with adverse health, primarily in single pollutant analyses.13,17,40–42 However, they are highly correlated with one another.40 It is therefore a mixture modelling challenge to infer the association of air pollutants and health outcomes.43 Using three air pollutants commonly used in health studies as traffic-related emissions tracers—nitrogen oxides (NOx), carbon monoxide (CO), and elemental carbon (EC)— as well as fine particles (PM2.5) and ozone (O3), we aimed to assess whether exposure to (a) each individual air pollutant is independently associated with ALS diagnosis, and estimate their (b) joint and (c) overall traffic-related emissions associations.

**Methods**

*Study Population and Outcome Assessment*

We used data from the Danish National Patient Register during 1989 – 2013, through which details on demographic characteristics and certain health outcomes of all Danish residents can be linked based on a 10-digit unique personal identifier.44 The Register was established in 1977 and is comprehensive, including nationwide clinical and administrative records for all inpatient data. Outpatient data have been included since 1995.45

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

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.47 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,47 including the dates of moving to and leaving from each address, prior to the index date. We then obtained the geographical coordinates at the door of each house of the residential history of the participants, with previous evidence of the high accuracy of this method of geocoding of addresses in Denmark.17

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

*Exposure data*

We obtained predictions on monthly concentrations of nitrogen oxides (NOx), carbon monoxide (CO), elemental carbon (EC), and fine particles (PM2*.*5) (as well as ozone (O3) for a sensitivity analysis, expected to be negatively correlated with other pollutants due to its chemistry48), at residential addresses of study participants from the validated spatio-temporal air pollution modelling system (DEHM-UBM-AirGIS) with full space and time coverage over our study period, described in detail elsewhere.49–52 These predicted pollutant concentrations have been extensively used in previous air pollution epidemiologic studies in Denmark.17,53–55 The models have good predictive accuracy, with average monthly correlations between measured and modelled results of 0.85 for NOx, 0.91 for CO, 0.92 for O3, 0.79 for EC, and 0.83 for annual concentrations of PM2.5.49,52 Because traffic is a major source of PM2.5 and EC one of the main PM2.5 components in urban environments, we subtracted the EC concentration from the total PM2.5 mass concentration (non-EC PM2.5), to avoid overadjustment when including both in the models simultaneously.

Based on the residential history of each case or control, we calculated 1-, 5-, and 10-year average exposure to each pollutant ending at one year before the index date, as diagnosis has been shown previously to occur at a median of 12 months after symptoms onset.56 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) definition 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,57. 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), last reported place of residence from postcode (Greater Copenhagen, big cities of Denmark, rest of Denmark, Greenland) and place of birth (Greater Copenhagen, big cities of Denmark, rest of Denmark, Greenland, foreign, unknown) to adjust for other potential family-specific, location-specific, and early-life confounders. As part of a sensitivity analysis, we also included parish-level SES, measured by percentage of residents with greater than high-school education, in the model. In Denmark, parishes are 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) and exposure to traffic-related pollutants by applying a Bayesian formulation of the conditional logistic model, with Bayesian hierarchy on the traffic-related pollutants (EC, NOx, CO).58,59 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.58 Bayesian inference allows for full distributional estimation of the parameters of interest.59 We employed a Bayesian hierarchical formulation because it allows us to estimate (a) independent pollutant-outcome associations, (b) a joint association of the three pollutants (i.e., the percentage change in odds of ALS diagnosis with increase in each of EC, NOx, CO), and (c) an overall average traffic association (i.e., the average percentage change in odds of ALS diagnosis from each of EC, NOx, CO), while accounting for the variance-covariance structure between the highly correlated exposures and their coefficients.59 We included a linear term for each included pollutant and adjusted for individual- and parish-level SES, civil status, last reported place of residence, and place of birth.

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

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 non-EC PM2.5 adjusts for other air pollutants from other sources.60 Therefore, would be interpreted as the association with air pollutants not specifically included in our analysis. In urban European environments, traffic-related pollutants typically represent on-average 14% of PM2.5 concentrations.61 In a sensitivity analysis, we included to account for exposures in the model, and added , as a natural spline with three degrees of freedom.

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

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

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

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where denotes the average overall one-SD 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 .62

We used weakly-informative priors so that parameter estimation was driven by the data. Hyper-priors for coefficients on non-EC and covariates were N(0,10); for and we used Half-Cauchy(0,10), as recommended by Gelman, Polson and Scott;63,64 and was defined by LKJCorr(1).65The 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.

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 ran each model with four chains with a sample size of 1,000 each, after a warm-up of 1,000 samples, for 4,000 total samples. We assessed whether the models converged by checking that the Gelman-Rubin potential scale reduction statistic66 was below 1.1 for all estimated model parameters. The reported 95% credible intervals (CrI) are the 2.5th to 97.5th percentiles of each parameter’s posterior marginal distribution. To calculate the probability that an association estimate was greater than null, we used the 4,000 samples of the posterior and took the proportion of samples which were above a null association.

We conducted statistical analyses using the R Statistical Software, version 4.1.1 (Foundation for Statistical Computing, Vienna, Austria),67 and R-STAN, version 2.21.2.59 All code for analysis, results from analysis, and visualization presented in this manuscript will be publicly available via GitHub at https://github.com/rmp15/multipollutants\_and\_als\_code\_review.

We assessed the sensitivity of our results to hyper-prior assignment; running more iterations and warm-up per chain; inclusion of O3; single traffic-related pollutant models adjusting for non-EC PM2.5; as well as adjusting by parish-level SES. From the parish-level SES sensitivity analysis we excluded those who lived in areas without parish-level SES data, namely: (i) 819 participants for the 1-year average exposure; (ii) 826 participants for the 5-year average exposure; and (iii) 838 participants for the 10-year average exposure.

**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 cases and 19,333 controls for 1-year average exposure and 3,939 cases and 19,250 controls for 10-year average exposure. Descriptive statistics of included cases and controls for the 5-year average exposure can be found in Table 1. For the main results, we present 5-year average exposure associations.

The 5-year average traffic-related pollutant concentrations were 27 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) (Table 2). 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, total PM2.5 was most highly correlated with CO, as well as NOx and EC to a lesser degree. O3 was negatively-correlated with all other included pollutants.

For 5-year average pollutant concentrations, we observed the largest overall association for the individual standard deviation increase in EC (11.5%; 95% CrI: -1.0%, 25.6%; 96.3% posterior probability of positive association per 0.42 µg/m3) (Figure 2). Standard deviation increases were associated with a decrease in odds of ALS diagnosis in both NOx (-4.6%; 95% CrI: -18.1%, 8.9% per 20 µg/m3) and CO (-3.2%; 95% CrI: -14.4%, 10.0% per 106 µg/m3). The joint association was 2.3% (95% CrI: -3.3%, 7.7%), with an 77.8% posterior probability of a positive association. Finally, the average overall traffic association was null (-0.1%; 95% CrI: -17.4%, 20.8%). Non-EC PM2.5 was not associated with ALS diagnosis (0.7%; 95% CrI: -9.2%, 12.4%). For 1-year average exposure, EC was associated with a significant increase in odds of ALS diagnosis (15.4%; 95% CrI: 1.6%, 25.6%) (Figure 2). 10-year average exposure results were attenuated versions of the 1- and 5-year results. Single-pollutant models for each traffic-related pollutant adjusting for non-EC PM2.5 (eFigure 1) resulted in positive associations for each of EC, NOx, CO, with positive associations for non-EC 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).

**Discussion**

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

Traffic-related pollutants are hazardous in many ways.9–21,40–42 Overall our results indicate that traffic-related pollutants may also be associated with ALS diagnosis. Our finding—that increases in EC, are potentially positively associated with ALS diagnosis—is plausible. A recent case-control study in the Netherlands reported that ultrafine particles, another traffic emissions-related surrogate, were associated with ALS diagnosis,38 while another based in Catalonia, Spain found ALS cases clustered around key road infrastructure.68 Although we did not find an association with non-EC 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 PM2.5 components not accounted for by other pollutants in the analysis.

Our results indicate that EC exposure—a large part of which comes from diesel combustion and small combustion sources (such as wood stoves) in European urban centers, where prevalence of diesel cars is high69—has a high probability of a positive association with ALS diagnosis. In our previous study of ALS and occupational exposures in Denmark we found that those working in agriculture and construction, associated with exposure to diesel engine exhausts, were at higher relative risk than those in other employments.57 Truck drivers, for whom diesel exposure is common, are also at increased risk of sporadic ALS.70 EC exposure has been associated with inflammation,71 mitochondrial dysfunction72 and DNA damage,72,73 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.38 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 emissions in urban environments. EC exposure was more strongly associated with 1-year than for 5- or 10-year average concentrations, 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, and there was likely little substantial residential movement in the year before ALS diagnosis.74

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 (e.g., from smoking or body mass index, BMI). However, to induce confounding bias, any unaccounted-for variable would have to influence both ALS diagnosis and air pollution. BMI, previously associated with ALS,75,76 would not confound the association between traffic-related air pollution and ALS,74 as pollutant concentrations are derived independently from BMI distribution. Any BMI – air pollution association in our study, thus, would be via SES, for which we adjusted at both the individual and parish level. Exposure measurement error is inevitable, as any modelled exposure will be inaccurate to some degree. However, any error is not likely correlated with ALS diagnosis, and would therefore any bias would be towards the null.77

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

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**References**

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

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

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

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. 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.

36. Nunez Y, Boehme AK, Li M, et al. Parkinson’s disease aggravation in association with fine particle components in New York State. *Environmental Research*. 2021;201:111554.

37. 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.

38. 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

39. 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

40. 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

41. 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.

42. 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.

43. 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.

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

45. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical epidemiology*. 2015;7:449.

46. 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.

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

48. Sillman S. The relation between ozone, NOx and hydrocarbons in urban and polluted rural environments. *Atmospheric Environment*. 1999;33(12):1821-1845.

49. 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.

50. Brandt J, Christensen JH, Frohn LM, Palmgren F, Berkowicz R, Zlatev Z. Operational air pollution forecasts from European to local scale. *Atmospheric Environment*. 2001;35:S91-S98.

51. Brandt J, Christensen J, Frohn L, Berkowicz R. Air pollution forecasting from regional to urban street scale—-implementation and validation for two cities in Denmark. *Physics and Chemistry of the Earth, Parts A/B/C*. 2003;28(8):335-344.

52. Frohn LM, Ketzel M, Christensen JH, et al. Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979-2018–Part 1: Regional and urban scale modelling and evaluation. *Atmospheric Environment*. 2021;264:118631.

53. 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.

54. 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.

55. 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.

56. 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

57. 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

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

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

60. 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.

61. Thunis P, Degraeuwe B, Pisoni E, et al. PM2.5 source allocation in European cities: A SHERPA modelling study. *Atmospheric Environment*. 2018;187:93-106.

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

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

64. 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

65. 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.

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

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

68. 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.

69. von Schneidemesser E, Mar KA, Saar D. Black carbon in Europe: Targeting an air Pollutant and climate forcer. Published online 2017.

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

71. 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

72. 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

73. 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

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

75. 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.

76. 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.

77. 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 for 5-year average exposure group.

| 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%) |
| **Last reported place of residence** |  |  |  |
| Greater Copenhagen | 1,887 (8.1%) | 335 (8.5%) | 1,552 (8.0%) |
| Big cities of Denmark | 9,385 (40%) | 1,590 (40%) | 7,795 (40%) |
| Rest of Denmark | 11,954 (51%) | 2,008 (51%) | 9,946 (52%) |
| Greenland | 6 (<0.1%) | 1 (<0.1%) | 5 (<0.1%) |
| 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. Results are from the Bayesian hierarchical model including each of EC, NOx, CO, and non-EC PM2.5 together, and were additionally adjusted by SES, civil status, last reported place of residence, and place of birth.