**Supplemental Materials**

**Long-term exposure to ultrafine particles, particulate matter constituents and amyotrophic lateral sclerosis**

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**Methods**

**Study population**

The PAN study is a population-based case-control study in the Netherlands which started on January 1, 2006 with an estimated capture rate of 81% of all ALS cases in the country (Huisman et al. 2011). The current analysis was based on ALS patients and controls enrolled in the PAN study up to December 31, 2018. All patients with a diagnosis of possible, laboratory supported probable, probable, or definite ALS according to the revised El Escorial criteria(Brooks et al. 2000) were included. Those who had a first-, second-, or third-degree family member with a motor neuron disease (N=211) were excluded.

Population-based controls were selected from the registers of the patients’ general practitioners (GP) and frequency matched by sex and age (±5 years). The health-care system in the Netherlands ensures that every inhabitant is registered with a GP, therefore giving a good representation of the source population. Biological relatives or spouses of the cases were not eligible for being controls. The PAN study was approved by the institutional review board of the University Medical Centre Utrecht. All participants gave written informed consent for inclusion in the study.

**Data collection**

Demographic information, including sex, date of birth, education level, body mass index (BMI), smoking, and alcohol consumption was collected via questionnaires filled in by the participants themselves. The residential history for each participant was derived via linkage of the PAN study to the Municipality database. Clinical data such as the date of symptom onset, the site of onset and the date of diagnosis were collected from the patients’ medical records. Area-level socio-economic status (SES) was calculated based on the percentage of residents with high income at the municipality of residency derived from Statistics Netherlands (CBS), defined as above the 80th percentile. The urban/rural region was defined based on the number of total inhabitants of the municipality (rural: <100,000/ urban: ≥100,000).

**Exposure assessment**

Air pollutant concentrations were estimated at the geocoded residential addresses of each participant based on land-use regression (LUR) models developed within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project. In brief, three 2-week measurements of nitrogen oxides (NO2 and NOx) were performed in the warm, cold and intermediate seasons between February 2009 and February 2010 at 80 sites across the Netherlands and Belgium(Beelen et al. 2013) . Further, at 40 of those sites gravimetric PM mass (PM10, PM2.5), PM elemental constituents and PM OP measurements were carried out(de Hoogh et al. 2013; Eeftens et al. 2012; Yang et al. 2015). All PM filter samples were analyzed for elemental composition using Energy Dispersive X-ray fluorescence (XRF). For elemental constituents, eight elements at both PM10 and PM2.5 fraction sizes were selected *a priori* in ESCAPE to reflect different anthropogenic sources(Viana et al. 2008): road traffic non-tailpipe emissions including brake lines (Cu, Fe, Zn) and tire wear (Zn); industrial emissions (Fe, Zn); crustal materials (Si, K); fossil fuel combustion (Ni, V, S); and biomass burning (K). For OP, two acellular methods were used including electron spin resonance (OP ESR) and dithiothreitol (OP DTT). The ESR method is based on the ability of PM to generate hydroxyl radicals in the presence of hydrogen peroxide and 5,5-dimethyl-1pyrroline-N-oxide and the DTT method measures the presence of reactive oxygen species due to transfer of electrons from DTT to oxygen. For UFP, a short-term monitoring campaign was conducted between January 2014 and February 2015 at 242 sites in three Dutch cities and their surroundings (Amsterdam, Utrecht and Maastricht) (van Nunen et al. 2017). Measurement of UFP were collected for 30-min periods per site and each site was visited three times (summer, winter and spring/autumn) to account for seasonal variations.

A variety of potential land use predictors such as traffic intensity and population density were derived from Geographic Information Systems (GIS) to explain spatial variation of specific pollutant component concentrations. LUR model performances were evaluated with leave-one-out cross-validation (CV) R2 and presented in Table S1 (Model R2: 0.31-0.92 across different pollutants). Next, these LUR models were applied to each residential address of the participants and a single mean concentration of each pollutant for each participant was calculated. For PM mass, PM2.5 absorbance, NO2 and NOx, with available routine assessment data, we extrapolated the estimated concentrations in 2009 to each year back to 1992, which was the earliest year of available routine air pollution monitor information (Beelen et al. 2014) . The concentrations of air pollutants from 2009 to 2018 were assumed constant. Subsequently, we averaged these pollutant concentrations from 1992 to the date of disease onset for cases or recruitment for controls. For UFP, PM elemental constituents and OP insufficient historical data were available for back-extrapolation, thus we assumed that the concentrations for these pollutants remained constant (as estimated in 2009 for PM elemental constituents and OP, and in 2014 for UFP) and calculated the average annual concentration from 1992 to the date of onset for cases or recruitment for controls taking residential history into consideration.

**Statistical analysis**

Categorical variables were presented as frequency (percentage) and continuous variables were presented as mean (standard deviation) or median (interquartile range (IQR)). P values for differences of characteristics between cases and controls were calculated using chi-square tests and t-tests for continuous variables. We used unconditional logistic regression models to estimate the association between exposure to air pollutants and ALS. Each pollutant was added separately as a continuous variable in regression models. Potential confounding factors were selected *a priori* including sex, age, education level (elementary school; middle/high school; college/university), BMI (underweight; normal weight; overweight; obese), smoking status (never; former; current smoker), alcohol consumption at recruitment (yes/no) and area SES to align with our previous work (Seelen et al. 2017). Missing data were imputed via multivariate imputation by chained equations (MICE) using 20 iterations (Buuren and Groothuis-Oudshoorn 2010). ORs were pooled over the 20 imputed datasets based on Rubin’s rule(Sterne et al. 2009; Van Buuren 2007). To allow for comparison between different air pollutants, ORs were presented as per IQR increment.

Two-pollutant models were performed for each air pollutant by additionally adjusting for the other air pollutants one-by-one. Variation Inflation Factors (VIFs) >3 was used to detect any multicollinearity problems. Subgroup analysis was conducted stratifying by sex, smoking status to explore potential effect modification. The significance of interaction effects was assessed on the multiplicative scale. Multinomial logistic regressions were fit for site of onset (bulbar or spinal onset) and *C9orf72* repeat expansion (determined by methods described elsewhere(DeJesus-Hernandez et al. 2011; Renton et al. 2011) to see whether there was any difference in effect between these groups. We also performed several sensitivity analyses. First, we additionally adjusted for the region of urban/rural in the main model to further control for possible differences in lifestyle and other environmental factors. Second, we restricted the analyses to participants with complete confounder data (*i.e.* complete case set) to exclude the effect of imputation. Third, we performed a post-hoc matching based on sex, age (±5 years), and year of enrollment (±1 year) and applied conditional logistic regression to these individual-matched data. We further excluded cases diagnosed as possible ALS (and corresponding controls) in the post-hoc matched dataset to assess the possible influence from the certainty of the diagnosis. Fourth, we restricted the analyses to participants who had not moved during one year or five years prior to the enrollment date (date of diagnosis for cases and date of recruitment for controls) to exclude the possibility of reverse causation (e.g. patients moving closer to medical centers where traffic-related pollution levels are generally higher). Fifth, we conducted a mixed-effect logistic regression assigning the municipality as the random intercept to correct for potential local residual confounding. All analyses were performed within R (version 3.6.1) and two-sided P-value less than 0.05 was considered statistically significant.

**Table S1** LUR model performances for PM, NO2, NOx, PM elemental constituents, oxidative potentials and UFPs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Components | LUR model | R2 | R2 LOOCV | Number of sites | Mean Conc [range] | Source |
| PM10 | 23.71 + 2.16E-8\*TRAFMAJORLOAD\_500 + 6.68E-6\*POP\_5000 + 0.02\*MAJORROADLENGTH\_50 | 0.68 | 0.60 | 40 | 27.1[21.9-37.0] | Eeftens et al, 2012 |
| PMcoarse | 7.59 + 5.02×10−9×TRAFLOAD\_1000 + 1.38×10−7\*PORT\_5000 + 5.38×10−5×TRAFNEAR | 0.51 | 0.38 | 40 | 9.3[6.4-15.0] | Eeftens et al, 2012 |
| PM2.5 | 9.46 + 0.42×REGIONALESTIMATE + 0.01×MAJORROADLENGTH\_50 + 2.28×10−9×TRAFMAJORLOAD\_1000 | 0.67 | 0.61 | 40 | 17.7[12.7-21.5] | Eeftens et al, 2012 |
| PM2.5 absorbance | 0.07 + 2.95×10−9×TRAFLOAD\_500 + 2.93×10−3×MAJORROADLENGTH\_50 + 0.85×REGIONALESTIMATE + 7.90×10−9×HLDRES\_5000 + 1.72×10−6×HEAVYTRAFLOAD\_50 | 0.92 | 0.89 | 40 | 1.7[0.9-3.0] | Eeftens et al, 2012 |
| NO2 | −7.80 + 1.18\*REGIONALESTIMATE + 2.30E-5\*POP\_5000 + 2.46E-6\*TRAFLOAD\_50 + 1.06E-4\*ROADLENGTH\_1000 + 9.84E-5\*HEAVYTRAFLOAD\_25 + 12.19\*DISTINVNEARC1 + 4.47E-7\*HEAVYTRAFLOAD\_25\_500 | 0.86 | 0.81 | 80 | 30.9[12.8-61.5] | Beelen et al, 2013 |
| NOx | 3.25þ0.74\*REGIONALESTIMATEþ4.22E-6\*TRAFLOAD\_50þ6.36E-4\*POP\_1000þ2.39E-6\*HEAVYTRAFLOAD\_500þ71.65\*DISTINVMAJOR1þ0.21\*MAJORROADLENGTH\_25 | 0.87 | 0.82 | 80 | 51.8[17.5-130.8] | Beelen et al, 2013 |
| UFP | 6487+4275\*TRAFNEAR+1522\*MAJORROADLENGTH\_X+2050\*(sum of low and high density residential land in a buffer of 500m)+3078\*(number of restaurants in buffer of 100) | 0.50 | 0.35 | 240 | 8747 (8190-30223) | Van Nunen et al, 2017 |
| PM10 Copper | 6.6 +8.0E-07\*PORT\_5000 +3.9E-04\*TRAFNEAR  +2.1E-06\*TRAFMAJORLOAD\_50 +1.6E-  07\*HEAVYTRAFMAJORLOAD\_1000 +8.8E-  02\*ROADLENGTH25 | 0.80 | 0.71 | 40 | 19[3.4-59] | De Hoogh et al, 2013 |
| PM2.5 Copper | 6.5 +4.8E-08\*HDLDRES\_5000 +5.0E-  07\*TRAFMAJORLOAD\_50 +1.0E-  02\*MAJORROADLENGTH50 -6.7E-06\*XPLUSY | 0.83 | 0.81 | 40 | 5.0[1.5-12] | De Hoogh et al, 2013 |
| PM10 Iron | 181.0 +6.0E-04\*POP\_5000 +7.3E-03\*TRAFNEAR  +2.2E-06\*TRAFMAJORLOAD\_500  +2.2E+00\*ROADLENGTH25 | 0.78 | 0.70 | 40 | 547[153-1673] | De Hoogh et al, 2013 |
| PM2.5 Iron | 149.0 +1.4E-06\*HDLDRES\_5000 +1.9E-  03\*TRAFNEAR +8.7E-06\*TRAFMAJORLOAD\_50 -  1.5E-04\*XPLUSY | 0.78 | 0.73 | 40 | 120[33-278] | De Hoogh et al, 2013 |
| PM10 Potassium | 173.0 +1.2E-04\*HDLDRES\_300 +4.0E-  07\*TRAFMAJORLOAD\_500 | 0.51 | 0.45 | 40 | 223[159-349] | De Hoogh et al, 2013 |
| PM2.5 Potassium | 155.0 +3.5E-07\*TRAFMAJORLOAD\_300 +1.4E-  04\*XMINUSY | 0.31 | 0.25 | 40 | 119[76-167] | De Hoogh et al, 2013 |
| PM10 Nickel | 4.1 +9.9E-08\*PORT\_5000 +1.6E-  09\*TRAFMAJORLOAD\_1000 -1.3E-05\*XCOORD | 0.78 | 0.73 | 40 | 2.8[0.96-5.7] | De Hoogh et al, 2013 |
| PM2.5 Nickel | 3.7 +8.6E-08\*PORT\_5000 -1.2E-05\*XCOORD | 0.76 | 0.72 | 40 | 2.3[0.61-4.5] | De Hoogh et al, 2013 |
| PM10 Sulphur | 1280.0 +1.3E-05\*PORT\_5000 +2.8E-03\*TRAFNEAR  -6.1E-04\*YCOORD | 0.48 | 0.39 | 40 | 1070[812-1341] | De Hoogh et al, 2013 |
| PM2.5 Sulphur | 1240.0 +1.1E-02\*POP\_500 -8.5E-04\*YCOORD | 0.32 | 0.27 | 40 | 915[448-1107] | De Hoogh et al, 2013 |
| PM10 Silicon | 282.0 +6.6E-04\*POP\_5000 +3.9E-  06\*TRAFMAJORLOAD\_300 | 0.40 | 0.26 | 40 | 475[151-1531] | De Hoogh et al, 2013 |
| PM2.5 Silicon | 146.0 +2.6E-03\*TRAFNEAR -1.1E-04\*XPLUSY | 0.46 | 0.39 | 40 | 101[38-285] | De Hoogh et al, 2013 |
| PM10 Vanadium | 6.7 +2.3E-07\*PORT\_5000 -2.0E-05\*XCOORD | 0.72 | 0.67 | 40 | 4.5[1.3-10] | De Hoogh et al, 2013 |
| PM2.5 Vanadium | 5.6 +2.0E-07\*PORT\_5000 -1.8E-05\*XCOORD | 0.68 | 0.63 | 40 | 3.7[1.3-9.0] | De Hoogh et al, 2013 |
| PM10 Zinc | 112.0 +7.1E-07\*TRAFLOAD\_300 +2.7E-  04\*XMINUSY | 0.65 | 0.57 | 40 | 43[19-139] | De Hoogh et al, 2013 |
| PM2.5 Zinc | 85.6 +2.0E-07\*TRAFMAJORLOAD\_300 +2.0E-  04\*XMINUSY | 0.66 | 0.58 | 40 | 28[13-87] | De Hoogh et al, 2013 |
| OPESR | 326.53554+0.56805\*REG\_EST\_opser+2.0309E-4\*TRAFLOAD\_50+8.1288E-4\*POPEEA\_5000 | 0.67 | 0.60 | 40 | 891[627-1897] | Yang et al, 2015 |
| OPDTT | 0.08096+0.76684\*REG\_EST\_opdtt+2.364E-5\*ROADLENGTH500+6.977E-05\*INTMAJORINVDIST-2.65222E-07\*NATURAL\_1000 | 0.60 | 0.47 | 40 | 0.808[0-1.478] | Yang et al, 2015 |

port (PORT\_X); natural land (NATURAL\_X);the sum of highand lowdensity residential land (HDLDRES\_X);the sum of (traffic intensity \*length of all road segments) within a buffer (vehicles day-1m) for all roads(TRAFLOAD\_X),for all major roadsegments (TRAFMAJORLOAD\_X), for heavy traffic(HEAVYTRAFLOAD\_X) and heavy traffic on major roads(HEAVYTRAFMAJORLOAD\_X); population data on an European level (N) (POPEEA\_X); total length (m) of all roads(ROADLENGTH\_X) and all major roadsegments (MAJORROADLENGTH\_X);traffic intensity on the nearest road (TRAFNEAR); X-coordinate (XCOORD); Y-coordinate (YCOORD); the product of inverse distance to the nearest major road and the traffic intensity on this major road (INTMAJORINVDIST); inverse distance (m-1) to the nearest major road in the local network (DISTINVMAJOR1); UFP, ultrafine particles

Reference：

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**Table S2** Demographic and clinical characteristics of participants

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | ALS (n=1,636)a | Control (n=4,024) | *P*-valueb |
| Male, n(%) | 994 (60.8) | 2703 (67.2) | <0.001 |
| Age, median (IQR) | 64.4 (10.6) | 63.8 (9.8) | 0.007 |
| Bulbar site of onset, n(%) | 557 (34.0) |  | - |
| C9*orf*72 repeat expansion, n(%) | 89 (5.4) | - | - |
| El Escorial classification, n(%) |  |  | - |
| Definite | 327 (20.0) | - |  |
| Probable | 669 (40.9) | - |  |
| Probable lab supported | 335 (20.5) | - |  |
| Possible | 306 (18.7) | - |  |
| Educationc, n(%) |  |  | <0.001 |
| Elementary school | 142 (8.7) | 243 (6.0) |  |
| Secondary school/high school | 1074 (65.6) | 2494 (62.0) |  |
| College/university | 420 (25.7) | 1287 (32.0) |  |
| Body mass indexc, kg/m2, n(%) |  |  | <0.001 |
| Underweight (<18.5) | 64 (3.9) | 29 (0.7) |  |
| Normal weight (18.5-<25.0) | 937 (57.3) | 1686 (41.9) |  |
| Overweight (25.0-<30.0) | 492 (30.1) | 1811 (45.0) |  |
| Obese (≥30.0) | 143 (8.7) | 498 (12.4) |  |
| Smoking status, n(%) |  |  | 0.068 |
| Current | 222 (13.6) | 429 (10.7) |  |
| Former | 753 (46.0) | 2123 (52.8) |  |
| Never | 661 (40.4) | 1472 (36.6) |  |
| Current alcohol consumption, n(%) | 1307 (79.9) | 3285 (87.0) | <0.001 |
| Area SESd, median (IQR) | 20.8 (5.43) | 21.3 (5.86) | 0.007 |
| Residing in urban regione, n(%) | 490 (30.0) | 930 (23.1) | <0.001 |
| Note: -, not applicable; ALS, amyotrophic lateral sclerosis; SES, socioeconomic status;  a983 cases and 2714 controls were included in the previous analyses (Seelen et al, 2017).  b *P*-values were calculated using chi-square test for categorical variables and the Mann-Whitney U test for continuous variables;  c Missing values of education level were imputed using Multiple Imputation via Chain Equations.  dDefined as percentage of high income per municipality  eUrban region is defined as municipalities with a population equal to or more than 100,000. | | | |

**Table S3** Association between long term exposure to air pollution and ALS in single pollutant models presented by marginal effects

|  |  |  |  |
| --- | --- | --- | --- |
| Air pollutants | Average concentrations (IQR) | Marginal effects (95%CI)a | *P* valueb |
| PM10, µg/m3 | 32.2 (2.0) | 1.77% (0.74%, 2.80%) | 0.002 |
| PMcoarse, µg/m3 | 10.7 (0.9) | 0.85% (-0.29%, 1.99%) | 0.171 |
| PM2.5, µg/m3 | 21.7 (1.5) | 2.29% (1.22%, 3.35%) | <0.001 |
| PM2.5 absorbance, 10-5/m | 1.4 (0.3) | 3.30% (1.87%, 4.72%) | <0.001 |
| NO2, µg/m3 | 26.1 (7.4) | 4.25% (2.79%, 5.70%) | <0.001 |
| NOx, µg/m3 | 44.1 (10.7) | 2.54% (1.29%, 3.80%) | 0.003 |
| UFP, particle/m3 | 8820 (1240) | 1.77% (0.90%, 2.63%) | 0.003 |
| PM2.5 Cu, ng/m3 | 3.2 (1.1) | 3.22% (1.82%, 4.61%) | <0.0001 |
| PM10 Cu, ng/m3 | 11.9 (3.6) | 1.49% (0.31%, 2.68%) | 0.018 |
| PM2.5 Fe, ng/m3 | 79.3 (27.1) | 3.77% (2.40%, 5.15%) | 0.003 |
| PM10 Fe, ng/m3 | 354.1 (125.0) | 2.95% (1.68%, 4.21%) | 0.003 |
| PM2.5 K, ng/m3 | 113.1 (13.3) | -0.34% (-2.00%, 1.31%) | 0.744 |
| PM10 K, ng/m3 | 205.2 (17.3) | 1.66% (0.36%, 2.96%) | 0.018 |
| PM2.5 Ni, ng/m3 | 1.9 (1.0) | 2.84% (1.06%, 4.61%) | 0.003 |
| PM10 Ni, ng/m3 | 2.2 (1.1) | 3.08% (1.39%, 4.76%) | 0.001 |
| PM2.5 S, ng/m3 | 888.8 (63.8) | 1.80% (0.38%, 3.21%) | 0.018 |
| PM10 S, ng/m3 | 1008.3 (47.3) | 1.48% (0.23%, 2.73%) | 0.025 |
| PM2.5 Si, ng/m3 | 82.1 (12.2) | 2.12% (0.88%, 3.36%) | 0.002 |
| PM10 Si, ng/m3 | 336.7 (80.7) | 3.18% (2.04%, 4.32%) | <0.001 |
| PM2.5 V, ng/m3 | 2.9 (1.5) | 2.65% (1.02%, 4.28%) | 0.003 |
| PM10 V, ng/m3 | 3.7 (1.6) | 2.53% (0.97%, 4.08%) | 0.003 |
| PM2.5 Zn, ng/m3 | 24.2 (18.8) | -0.88% (-2.58%, 0.81%) | 0.349 |
| PM10 Zn, ng/m3 | 32.9 (25.8) | -0.24% (-1.91%, 1.42%) | 0.806 |
| OPESR, A.U. /m3 | 882.8 (171.9) | 2.58% (1.08%, 4.08%) | 0.002 |
| OP (DTT), nmol DTT/min/m3 | 0.82 (0.2) | 0.17% (-1.33%, 1.68%) | 0.820 |

IQR: Interquartile range.

a Average marginal effects per interquartile range (IQR) increment were presented. Results were adjusted for sex, age (age at diagnosis for cases and at recruitment for controls), education level, body mass index, smoking status, alcohol consumption, and area SES.

b *P* values corrected for multiple testing using Benjamini&Hochberg method were presented.

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| --- | --- | --- | --- | --- | --- |
| **Table S4** Comparing the association of exposure to conventional pollutants with or without back-extrapolation in single pollutant model | | | | | |
| Air pollutant | With back-extrapolation | |  | Without back-extrapolation | |
|  | OR (95%CI) | P value |  | OR (95%CI) | P value |
| **PM10** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 0.97 (0.79, 1.18) | 0.733 |  | 1.12 (0.93, 1.34) | 0.235 |
| Q3 | 1.05 (0.85, 1.30) | 0.649 |  | 1.12 (0.91, 1.38) | 0.286 |
| Q4 | 1.12 (0.94, 1.34) | 0.221 |  | 1.07 (0.86, 1.33) | 0.566 |
| Per IQR | 1.10 (1.04, 1.16) | 0.007 |  | 1.06 (1.04, 1.09) | 0.005 |
| **PM2.5** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 0.99 (0.84, 1.17) | 0.931 |  | 1.03 (0.87, 1.22) | 0.713 |
| Q3 | 1.08 (0.91, 1.28) | 0.403 |  | 1.10 (0.93, 1.30) | 0.281 |
| Q4 | 1.14 (0.96, 1.35) | 0.129 |  | 1.15 (0.97, 1.36) | 0.105 |
| Per IQR | 1.05 (0.92, 1.10) | 0.482 |  | 1.05 (0.93, 1.19) | 0.454 |
| **PMcoarse** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 1.00 (0.84, 1.19) | 0.998 |  | 0.98 (0.83, 1.16) | 0.821 |
| Q3 | 1.14 (0.95, 1.37) | 0.171 |  | 1.01 (0.84, 1.21) | 0.938 |
| Q4 | 1.10 (0.91, 1.34) | 0.335 |  | 1.01 (0.83, 1.22) | 0.931 |
| Per IQR | 1.06 (1.00, 1.12) | 0.066 |  | 1.02 (0.92, 1.13) | 0.704 |
| **PM2.5 absorbance** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 1.18 (0.99, 1.39) | 0.056 |  | 0.99 (0.83, 1.17) | 0.905 |
| Q3 | 1.23 (1.04, 1.45) | 0.016 |  | 1.12 (0.95, 1.32)) | 0.186 |
| Q4 | 1.51 (1.28, 1.78) | <0.001 |  | 1.37 (1.16, 1.61) | <0.001 |
| Per IQR | 1.19 (1.10, 1.28) | <0.001 |  | 1.14 (1.04, 1.26) | 0.007 |
| **NO2** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 1.09 (0.92, 1.29) | 0.305 |  | 1.12 (0.95, 1.32) | 0.184 |
| Q3 | 1.25 (1.06, 1.48) | 0.008 |  | 1.24 (1.05, 1.46) | 0.013 |
| Q4 | 1.47 (1.25, 1.73) | <0.001 |  | 1.47 (1.24, 1.73) | <0.001 |
| Per IQR | 1.25 (1.15, 1.34) | <0.001 |  | 1.26 (1.16, 1.36) | <0.001 |
| **NOx** |  |  |  |  |  |
| Q1 | Reference | - |  | Reference | - |
| Q2 | 1.07 (0.91, 1.27) | 0.410 |  | 1.06 (0.90, 1.25) | 0.504 |
| Q3 | 1.26 (1.07, 1.48) | 0.007 |  | 1.14 (0.96, 1.35) | 0.125 |
| Q4 | 1.46 (1.24, 1.72) | <0.001 |  | 1.44 (1.22, 1.69) | <0.001 |
| Per IQR | 1.14 (1.07, 1.22) | <0.001 |  | 1.13 (1.06, 1.21) | <0.001 |
| Note: All results were adjusted for age, sex, body mass index, smoking status, alcohol consumption, education, area SES. Odds ratios (ORs) are presented for the interquartile range increments: 1.5 µg/m3 for PM2.5, 0.9 µg/m3 for PMcoarse, 2 µg/m3 for PM10, 0.3×10-5m-1 for PM2.5 absorbance, 7.4 µg/m3 for NO2 and 10.7 µg/m3 for NOx. | | | | | |

**Table S5** Comparison of the effect of air pollution between the sample recruitment before and after 1 January 2013

|  |  |  |  |
| --- | --- | --- | --- |
| Air pollutants | Total sample (Case 1636/Control 4024) | Before 2013(Case 1008/Control 2714) | After 2013 (Case 628/Control 1310) |
| PM2.5 | 1.05 (0.92, 1.10) | 1.07 (0.91, 1.25) | 0.94 (0.76,1.17) |
| PM10 | 1.10 (1.04, 1.16) | 1.12 (1.07, 1.18) | 1.06 (0.92,1.20) |
| PMcoarse | 1.06 (1.00, 1.12) | 1.06 (1.03, 1.08) | 1.03 (1.00, 1.06) |
| PM2.5 absorbance | 1.19 (1.10, 1.28) | 1.17 (1.04, 1.32) | 1.14 (0.97, 1.34) |
| NO2 | 1.25 (1.15, 1.34) | 1.29 (1.17, 1.43) | 1.22 (1.07, 1.39) |
| NOx | 1.14 (1.07, 1.22) | 1.24 (1.15, 1.34) | 0.96 (0.86, 1.06) |
| UFP | 1.11 (1.05, 1.16) | 1.13 (1.06, 1.2) | 1.09 (1.01, 1.18) |
| PM2.5 Cu | 1.18 (1.10, 1.27) | 1.22 (1.12, 1.33) | 1.16 (1.03, 1.30) |
| PM10 Cu | 1.08 (1.02, 1.15) | 1.09 (1.01, 1.17) | 1.07 (0.96, 1.18) |
| PM2.5 Fe | 1.22 (1.13, 1.31) | 1.24 (1.14, 1.36) | 1.20 (1.07, 1.35) |
| PM10 Fe | 1.16 (1.09, 1.24) | 1.20 (1.11, 1.30) | 1.16 (1.04, 1.29) |
| PM2.5 K | 0.98 (0.90, 1.07) | 0.96 (0.87, 1.07) | 1.04 (0.91, 1.19) |
| PM10 K | 1.09 (1.02, 1.17) | 1.14 (1.05, 1.23) | 1.08 (0.97, 1.21) |
| PM2.5 Ni | 1.15 (1.05, 1.25) | 1.20 (1.07, 1.34) | 1.09 (0.94, 1.27) |
| PM10 Ni | 1.17 (1.07, 1.28) | 1.22 (1.10, 1.36) | 1.10 (0.95, 1.26) |
| PM2.5 S | 1.10 (1.02, 1.18) | 1.11 (1.01, 1.22) | 1.10 (0.98, 1.23) |
| PM10 S | 1.08 (1.01, 1.15) | 1.08 (1.00, 1.17) | 1.08 (0.98, 1.20) |
| PM2.5 Si | 1.12 (1.05, 1.19) | 1.11 (1.03, 1.21) | 1.11 (1.00, 1.23) |
| PM10 Si | 1.18 (1.11, 1.25) | 1.17 (1.06, 1.30) | 1.17 (1.02, 1.33) |
| PM2.5 V | 1.15 (1.05, 1.25) | 1.18 (1.07, 1.31) | 1.09 (0.95, 1.25) |
| PM10 V | 1.14 (1.05, 1.23) | 1.17 (1.06, 1.29) | 1.08 (0.95, 1.50) |
| PM2.5 Zn | 0.96 (0.88, 1.04) | 0.93 (0.84, 1.04) | 1.02 (0.89, 1.18) |
| PM10 Zn | 0.99 (0.91, 1.08) | 0.97 (0.87, 1.08) | 1.05 (0.91, 1.21) |
| OP ESR | 1.14 (1.06, 1.23) | 1.15 (1.05, 1.27) | 1.11 (0.98, 1.24) |
| OP DDT | 1.01 (0.93, 1.09) | 1.05 (0.95, 1.15) | 0.98 (0.86, 1.12) |

All results were adjusted for age, sex, body mass index, smoking status, alcohol consumption, education and area SES.

**Table S6** Recalculated exposure values between case and control groups

|  |  |  |  |
| --- | --- | --- | --- |
| Exposure (mean ± SD)a | Case (N=1636) | Control (N=4024) | P-value |
| PM10, µg/m3 | 32.8±2.2 | 32.6±2.2 | <0.001 |
| PMcoarse, µg/m3 | 11.0±1.0 | 10.8±1.0 | <0.001 |
| PM2.5, µg/m3 | 21.9±1.5 | 21.9±1.5 | 0.340 |
| PM2.5 absorbance, 10-5/m | 1.49±0.24 | 1.46±0.24 | <0.001 |
| NO2, µg/m3 | 27.1±6.0 | 26.2±5.6 | <0.001 |
| NOx, µg/m3 | 46.2±9.6 | 45.0±9.7 | <0.001 |
| UFP, particle/m3 | 9440±1510 | 9240±1380 | <0.001 |
| PM2.5 Cu, ng/m3 | 3.27±0.95 | 3.16±0.88 | <0.001 |
| PM10 Cu, ng/m3 | 12.7±3.63 | 12.4±3.46 | 0.003 |
| PM2.5 Fe, ng/m3 | 82.0±23.6 | 78.7±21.9 | <0.001 |
| PM10 Fe, ng/m3 | 384±119 | 365±106 | <0.001 |
| PM2.5 K, ng/m3 | 114±9.29 | 114±9.52 | 0.826 |
| PM10 K, ng/m3 | 205±15.9 | 203±15.3 | 0.002 |
| PM2.5 Ni, ng/m3 | 1.96±0.69 | 1.91±0.67 | 0.016 |
| PM10 Ni, ng/m3 | 2.34±0.80 | 2.27±0.76 | 0.003 |
| PM2.5 S, ng/m3 | 888±52.2 | 884±51.5 | 0.019 |
| PM10 S, ng/m3 | 1010±44.2 | 1010±42.5 | 0.044 |
| PM2.5 Si, ng/m3 | 82.3±11.7 | 81.5±11.4 | 0.010 |
| PM10 Si, ng/m3 | 368±87.0 | 354±72.0 | <0.001 |
| PM2.5 V, ng/m3 | 3.03±1.12 | 2.95±1.07 | 0.011 |
| PM10 V, ng/m3 | 3.85±1.26 | 3.76±1.19 | 0.011 |
| PM2.5 Zn, ng/m3 | 25.8±12.9 | 26.1±13.1 | 0.373 |
| PM10 Zn, ng/m3 | 35.4±17.9 | 35.4±18.4 | 0.968 |
| OPESR, A.U. /m3 | 900±132 | 888±129 | 0.002 |
| OP (DTT), nmol DTT/min/m3 | 0.82±0.16 | 0.81±0.16 | 0.319 |

Exposure concentrations for PM10, PMcoarse, PM2.5, PM2.5 absorbance, NO2 and NOx were back-extrapolated to 1992 based on the available routine assessment. All exposures were average annual concentrations at the residential address from 1992 to the time of onset for cases and 1-year prior to recruitment for controls.

**Table S7** Imputation of education level via multiple imputation of chained equation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable | Original dataset | |  | Imputation dataseta | | |
|  | ALS (N=1636) | Control (N=4024) |  | ALS (N=1636) | Control (N=4024) |
| Education level, n(%) |  |  |  |  |  |
| Elementary school | 119 (7.3) | 208 (5.2) |  | 142 (8.7) | 243 (6.0) |
| Secondary school/high school | 877 (53.6) | 2115 (52.6) |  | 1074 (65.6) | 2494 (62.0) |
| College/university | 353 (21.6) | 1111 (27.6) |  | 420 (25.7) | 1287 (32.0) |
| Missing | 287 (17.5) | 590 (14.7) |  | - | - |
| Body mass index, n(%) |  |  |  |  |  |
| Underweight | 58 (3.5) | 27 (0.7) |  | 64 (3.9) | 29 (0.7) |
| Normal weight | 838 (51.2) | 1577 (39.2) |  | 937 (57.3) | 1686 (41.9) |
| Overweight | 462 (28.2) | 1724 (42.8) |  | 492 (30.1) | 1811 (45.0) |
| Obese | 132 (8.1) | 481 (12.0) |  | 143 (8.7) | 498 (12.4) |
| Missing | 146 (8.9) | 215 (5.3) |  |  |  |

a: Multiple Imputation via chained equation was used for imputation.

**Table S8** Air pollution exposure levels for the participants in the PAN study

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Air pollutants | P25 | Mean | P50 | P75 | P95 | IQR |
| PM10, µg/m3 | 31.5 | 32.7 | 32.2 | 33.6 | 36.99 | 2.0 |
| PMcoarse, µg/m3 | 10.4 | 10.9 | 10.7 | 11.3 | 12.67 | 0.9 |
| PM2.5, µg/m3 | 21.0 | 21.9 | 21.7 | 22.5 | 25.03 | 1.5 |
| PM2.5 absorbance, 10-5/m | 1.3 | 1.5 | 1.4 | 1.6 | 1.9 | 0.3 |
| NO2, µg/m3 | 22.5 | 26.5 | 26.1 | 29.9 | 36.85 | 7.4 |
| NOx, µg/m3 | 39.3 | 45.5 | 44.1 | 50.0 | 63.43 | 10.7 |
| UFP, particle/m3 | 8428 | 9328 | 8820 | 9667 | 14189 | 1240 |
| PM2.5 Cu, ng/m3 | 2.6 | 3.2 | 3.2 | 3.7 | 4.7 | 1.1 |
| PM10 Cu, ng/m3 | 10.5 | 12.6 | 11.9 | 14.1 | 19.2 | 3.6 |
| PM2.5 Fe, ng/m3 | 65.8 | 79.8 | 79.3 | 92.9 | 118.1 | 27.1 |
| PM10 Fe, ng/m3 | 297.9 | 372.6 | 354.1 | 423.3 | 571.8 | 125.0 |
| PM2.5 K, ng/m3 | 107.5 | 114.4 | 113.1 | 120.8 | 132.0 | 13.3 |
| PM10 K, ng/m3 | 195.1 | 203.7 | 205.2 | 212.4 | 226.8 | 17.3 |
| PM2.5 Ni, ng/m3 | 1.4 | 1.9 | 1.9 | 2.4 | 3.1 | 1.0 |
| PM10 Ni, ng/m3 | 1.7 | 2.3 | 2.2 | 2.8 | 3.6 | 1.1 |
| PM2.5 S, ng/m3 | 857.0 | 885.7 | 888.8 | 920.9 | 962.9 | 63.8 |
| PM10 S, ng/m3 | 989.7 | 1012.4 | 1008.3 | 1037 | 1085.9 | 47.3 |
| PM2.5 Si, ng/m3 | 75.8 | 81.8 | 82.1 | 87.9 | 98.7 | 12.2 |
| PM10 Si, ng/m3 | 304.7 | 359.3 | 336.7 | 385.4 | 514.2 | 80.7 |
| PM2.5 V, ng/m3 | 2.2 | 3.0 | 2.9 | 3.7 | 4.9 | 1.5 |
| PM10 V, ng/m3 | 2.9 | 3.8 | 3.7 | 4.6 | 5.9 | 1.6 |
| PM2.5 Zn, ng/m3 | 16.1 | 26.0 | 24.2 | 35.0 | 50.1 | 18.8 |
| PM10 Zn, ng/m3 | 21.9 | 35.4 | 32.9 | 47.8 | 68.8 | 25.8 |
| OPESR, A.U. /m3 | 793.0 | 892.0 | 882.8 | 964.4 | 1120.4 | 171.9 |
| OP (DTT), nmol DTT/min/m3 | 0.73 | 0.81 | 0.82 | 0.90 | 1.04 | 0.2 |
| IQR: Interquartile range; Exposure concentrations for PM10, PMcoarse, PM2.5, PM2.5 absorbance, NO2 and NOx were back-extrapolated to 1992 based on the available routine assessment. All exposures were average annual concentrations at the residential address from 1992 to the time of onset for cases and recruited for controls | | | | |  |  |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S9** Subgroup analysis by sex, smoking status, site of onset, and *C9orf72* repeat expansion for the association between ALS and exposure to NO2 and PM10 silicon | | | | | | | | | |
| Subgroup | Case/Control |  | ORs (95%CI)a | | | | | | |
|  |  |  | NO2 | | |  | PM10 Silicon | | |
| Sex |  |  |  |  |  |  |  |  |  |
| Male | 994/2703 |  | 1.18 (1.07, 1.30) | | |  | 1.15 (1.07, 1.24) | | |
| Female | 642/1321 |  | 1.37 (1.20, 1.56) | | |  | 1.23 (1.11, 1.37) | | |
| *P* value |  |  | 0.049 | | |  | 0.447 | | |
| Smoking status |  |  |  |  |  |  |  |  |  |
| Current smoker | 222/429 |  | 1.28 (1.05, 1.57) | | |  | 1.23 (1.05, 1.45) | | |
| Former smoker | 753/2123 |  | 1.27 (1.14, 1.42) | | |  | 1.18 (1.08, 1.28) | | |
| Never smoker | 661/1472 |  | 1.20 (1.06, 1.36) | | |  | 1.16 (1.05, 1.28) | | |
| *P* value |  |  | 0.919 | | |  | 0.861 | | |
| Site of onsetb |  |  |  |  |  |  |  |  |  |
| Spinal | 1017/4024 |  | 1.22 (1.12, 1.33) | | |  | 1.18 (1.10, 1.26) | | |
| Bulbar | 557/4024 |  | 1.26 (1.13, 1.41) | | |  | 1.17 (1.07, 1.28) | | |
| *P* value |  |  | 0.793 | | |  | 0.814 | | |
| C9*orf*72 repeat expansionb,c |  |  |  |  |  |  |  |  |  |
| Yes | 89/4024 |  | 1.16 (0.89, 1.51) | | |  | 1.04 (0.85, 1.27) | | |
| No | 1408/4024 |  | 1.24 (1.13, 1.34) | | |  | 1.17 (1.10, 1.25) | | |
| *P* value |  |  | 0.440 | | |  | 0.212 | | |

Note: ALS, amyotrophic lateral sclerosis; UFP, ultrafine particles

aORs (95%CI) were presented as per interquartile range increment: 7.4 μg/m3 for NO2, 1240 particle/cm3 for UFP, 27.1 ng/m3 for PM2.5 Fe and 80.7 ng/m3 for PM10 Silicon. All results were adjusted for sex, age, education level, body mass index, smoking status, alcohol consumption, area SES (where appropriate).

bMultinomial logistic regression

cData on *C9orf72* repeat expansion was missing for 129 case

**Table S10** Association between air pollution and risk of ALS stratified by urban/rural regions

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Rural (N=4,240) | | |  | Urban (N=1,420) | | |
|  | Controls (N=1,146) | Cases (N=3,094) | OR (95%CI) |  | Controls (N=930) | Cases (N=490) | OR (95%CI) |
| PM10 (2.0) | 32.3±2.1 | 32.4±2.0 | 1.06 (0.99,1.14) |  | 33.4±2.3 | 33.7±2.3 | 1.09 (0.99,1.20) |
| PM2.5 (1.5) | 21.8±1.5 | 21.8±1.56 | 1.04 (0.97,1.12) |  | 22.0±1.5 | 22.0±1.5 | 1.02 (0.91,1.14) |
| PMcoarse (0.9) | 10.7±0.9 | 10.8±0.8 | 1.08 (1.01,1.16) |  | 11.3±1.1 | 11.4±1.1 | 1.14 (1.03,1.25) |
| PM2.5 absorbance (0.3) | 1.42±0.2 | 1.44±0.2 | 1.13 (1.02,1.24) |  | 1.58±0.2 | 1.62±0.2 | 1.17 (1.02,1.34) |
| NO2 (7.4) | 25.1±5.1 | 25.4±5.1 | 1.14 (1.03,1.27) |  | 30.0±5.7 | 31.3±5.9 | 1.30 (1.12,1.51) |
| NOx (10.7) | 43.7±8.9 | 44.0±8.3 | 1.08 (0.99,1.18) |  | 50.1±10.3 | 51.3±10.0 | 1.13 (1.00,1.28) |
| UFP (1240) | 9070±1150 | 9120±1200 | 1.06 (0.99,1.14) |  | 9980±1750 | 10200±1890 | 1.10 (1.02,1.19) |
| PM2.5 Cu (1.1) | 3.0±0.8 | 3.1±0.9 | 1.09 (0.99,1.2) |  | 3.6±0.9 | 3.8±1.0 | 1.21 (1.06,1.39) |
| PM10 Cu (3.6) | 12.1±3.1 | 12.2±3.2 | 1.04 (0.95,1.12) |  | 13.7±4.0 | 14.1±4.3 | 1.09 (0.98,1.20) |
| PM2.5 Fe (27.1) | 74.9±20.0 | 75.9±21.2 | 1.13 (1.03,1.24) |  | 92.3±22.1 | 96.6±23.1 | 1.25 (1.09,1.43) |
| PM10 Fe (125.0) | 346±90.0 | 348±91.3 | 1.06 (0.96,1.17) |  | 441±120 | 464±137 | 1.18 (1.06,1.32) |
| PM2.5 K (13.3) | 114±9.3 | 114±9.2 | 1.02 (0.92,1.13) |  | 115±9.8 | 114±9.4 | 0.96 (0.82,1.14) |
| PM10 K (17.3) | 201±14.3 | 201±14.6 | 1.00 (0.92,1.09) |  | 210±15.1 | 212±15.6 | 1.17 (1.03,1.34) |
| PM2.5 Ni (1.0) | 1.9±0.6 | 1.9±0.7 | 1.05 (0.94,1.18) |  | 2.0±0.7 | 2.1±0.7 | 1.23 (1.04,1.47) |
| PM10 Ni (1.1) | 2.2±0.7 | 2.2±0.8 | 1.05 (0.94,1.17) |  | 2.5±0.8 | 2.6±0.8 | 1.27 (1.08,1.50) |
| PM2.5 S (63.8) | 882±51.6 | 883±52.6 | 1.06 (0.97,1.16) |  | 895±48.4 | 900±49.8 | 1.12 (0.97,1.30) |
| PM10 S (47.3) | 1010±40.6 | 1010±42.4 | 1.07 (0.99,1.16) |  | 1020±47.5 | 1010±42.4 | 1.08 (0.96,1.21) |
| PM2.5 Si (12.2) | 81.1±10.8 | 81.6+±11.8 | 1.06 (0.96,1.17) |  | 82.9±12.1 | 84.2±11.6 | 1.10 (0.98,1.24) |
| PM10 Si (80.7) | 338±56.4 | 339±56.3 | 1.09 (1.01,1.18) |  | 414±87.2 | 436±107 | 1.21 (1.10,1.33) |
| PM2.5 V (1.5) | 2.9±1.0 | 2.9±1.1 | 1.05 (0.94,1.17) |  | 3.1±1.2 | 3.3±1.2 | 1.20 (1.03,1.39) |
| PM10 V (1.6) | 3.7±1.1 | 3.7±1.2 | 1.05 (0.95,1.16) |  | 4.0±1.4 | 4.2±1.3 | 1.18 (1.03,1.37) |
| PM2.5 Zn (18.8) | 26.3±13.0 | 26.5±12.9 | 1.02 (0.92,1.13) |  | 25.5±13.3 | 24.1±12.5 | 0.90 (0.75,1.08) |
| PM10 Zn (25.8) | 35.1±18.0 | 35.4±17.8 | 1.02 (0.92,1.13) |  | 36.4±18.9 | 35.2±18.1 | 0.97 (0.82,1.15) |
| OP ESR (171.9) | 874±121 | 880±121 | 1.09 (0.99,1.21) |  | 937±138 | 95±147 | 1.13 (0.98,1.29) |
| OP DTT (0.2) | 0.81±0.2 | 0.81±0.2 | 1.00 (0.92,1.09) |  | 0.83±0.1 | 0.83±0.1 | 1.06 (0.89,1.27) |

All results were adjusted for sex, age, education level, body mass index, smoking status, alcohol consumption, area SES.



**Figure S1**. Sensitivity analyses on the associations between exposure to NO2, UFP, PM2.5 iron, PM10 silicon and ALS. Odds ratios (OR) were presented as per interquartile range increment. All results were adjusted for sex, age, education level, body mass index, smoking status, alcohol consumption, and area SES.



**Figure S2.** Pearson correlations between predicted air pollutant concentrations. P values for all correlation indexes were <0.001.

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