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Long-Term Exposure to Ultrafine Particles and Particulate Matter Constituents and the Risk of Amyotrophic Lateral Sclerosis

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Introduction

The etiology of amyotrophic lateral sclerosis (ALS) remains unknown but is considered to be an interplay of environmental exposures and genetic predisposition (van Es et al. 2017). Few epidemiological studies have examined the association between ambient air pollution and ALS. We previously reported an increased risk of developing ALS for long-term exposure to traffic-related air pollution in a Dutch case–control study (917 cases and 2,662 controls) (Seelen et al. 2017). Increased knowledge about the possible associations between particulate matter (PM) and its constituents and ALS will provide additional insight into the potential pathophysiology of ALS. We aimed to extend on our previous analyses by including 2,081 more cases and controls and by extending the exposure assessment to a broader range of air pollutants [ultrafine particles ($PM \leq 0.1$ μm in aerodynamic diameter or UFPs), PM elemental components, and oxidative potentials (OPs)].

Methods

Present analyses were based on ALS patients and controls enrolled in the Prospective ALS in the Netherlands (PAN) study (Huisman et al. 2011) from 1 January 2006 to 31 December 2018. All patients with a diagnosis of possible, probable, or definite ALS according to the revised El Escorial criteria (Brooks et al. 2000) were included. Population-based controls selected from the registers of the patients' general practitioners were frequency matched by sex and age (±5 y). Information including sex, date of birth, education level, body mass index, smoking, alcohol consumption, residential history, and area-level socioeconomic status (SES) was collected. Annual concentrations of air pollution constituents 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) and Exposomics projects (Beelen et al. 2013; de Hoogh et al. 2013; Eeftens et al. 2012; van Nunen et al. 2017) (see supporting information at https://github.com/kevininef/Airpollution-ALS). We averaged the air pollutant concentrations from 1992 to the date of onset for cases or recruitment for controls as the main exposure.

Unconditional logistic regression models were used to estimate the association between exposure to air pollution and ALS in single-pollutant models. Two-pollutant models were performed for each air pollutant by additionally adjusting for the other pollutants one by one. All analyses were performed within R software (version 3.6.1; R Development Core Team). Supporting information is available at https://github.com/kevininef/Airpollution-ALS. The PAN study was approved by the institutional review board of the University Medical Center Utrecht.

Results and Discussion

A total of 1,636 patients with ALS and 4,024 controls were included (see supporting information at https://github.com/kevininef/Airpollution-ALS), covering all of the Netherlands. We observed increased odds ratios (ORs) for ALS in association with most air pollutants, with the strongest associations for ($PM \leq 2.5$ μm absorbance) {OR = 1.19 [95% confidence interval (CI): 1.10, 1.28], nitrogen dioxide [NO_2] [OR = 1.25 (95% CI: 1.15, 1.34)], and nitrogen oxides [NO_x] [OR = 1.14 (95% CI: 1.07, 1.22)]} (Table 1). For UFPs, an elevated OR of 1.11 (95% CI: 1.05, 1.16) was observed. For particle elements, road traffic non-tailpipe emissions of copper (Cu), iron (Fe), nickel (Ni), sulfur (S), silicon (Si), and vanadium (V) were associated with significantly higher ORs for ALS in both $PM_{2.5}$ and PM_{10} fractions. Marginal effects for all air pollutants are presented in the supporting information at https://github.com/kevininef/Airpollution-ALS.

In two-pollutant models adjusted for PM mass, the associations of most air pollutant elements with ALS remained positive, whereas the association of PM mass became null (Figure 1). In two-pollutant models corrected for NO_2, the associations of most air pollutants were reduced toward the null, except for Si in the PM_{10} Si fraction ($PM_{10}Si$), whereas the estimated positive association for NO_2 remained, indicating independent associations between NO_2, $PM_{10}Si$, and the risk of ALS. Sensitivity analyses showed the associations of NO_2 and $PM_{10}Si$ with ALS were robust (see supporting information at https://github.com/kevininef/Airpollution-ALS).

With an extended sample [nearly twice the size of the previous analyses by Seelen et al. (2017)], we here confirm the positive associations for NO_2 (see supporting information at https://github.com/kevininef/Airpollution-ALS). Moreover, restricting the analysis to the participants who were recruited after the previous publication showed consistent associations for air pollution and ALS, speaking

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Table 1. Association between long-term exposure to air pollution and ALS in single-pollutant models.

Exposure (IQR)[a]	Average exposure level[a]		OR (95% CI)[b]	p Value[c]
	Case ($N = 1,636$)	Control ($N = 4,024$)		
PM_{10} (2.0)	32.8 ± 2.2	32.6 ± 2.2	1.10 (1.04, 1.16)	0.001
$PM_{2.5}$ (1.5)	21.9 ± 1.5	21.8 ± 1.5	1.05 (0.92, 1.10)	0.153
PM_{coarse} (0.9)	11.0 ± 1.0	10.9 ± 1.0	1.06 (1.00, 1.12)	<0.001
$PM_{2.5}$ absorbance (0.3)	1.49 ± 0.24	1.46 ± 0.24	1.19 (1.10, 1.28)	<0.001
NO_2 (7.4)	27.1 ± 6.0	26.3 ± 5.6	1.25 (1.15, 1.34)	<0.001
NO_x (10.7)	46.2 ± 9.5	45.2 ± 9.6	1.14 (1.07, 1.22)	<0.001
UFPs (1,240)	9,450 ± 1,520	9,280 ± 1,370	1.11 (1.05, 1.16)	<0.001
$PM_{2.5}$ Cu (1.1)	3.28 ± 0.95	3.17 ± 0.88	1.18 (1.10, 1.27)	<0.001
PM_{10} Cu (3.6)	12.7 ± 3.65	12.5 ± 3.4	1.08 (1.02, 1.15)	0.019
$PM_{2.5}$ Fe (27.1)	82.1 ± 23.7	78.9 ± 21.8	1.22 (1.13, 1.31)	<0.001
PM_{10} Fe (125.0)	383 ± 119	368 ± 10	1.16 (1.09, 1.24)	<0.001
$PM_{2.5}$ K (13.3)	114 ± 9.26	114 ± 9.44	0.98 (0.90, 1.07)	0.764
PM_{10} K (17.3)	204 ± 15.8	203 ± 15.0	1.09 (1.02, 1.17)	0.008
$PM_{2.5}$ Ni (1.0)	1.96 ± 0.70	1.91 ± 0.67	1.15 (1.05, 1.25)	0.004
PM_{10} Ni (1.1)	2.34 ± 0.81	2.28 ± 0.76	1.17 (1.07, 1.28)	0.001
$PM_{2.5}$ S (63.8)	888 ± 52.3	885 ± 51.2	1.10 (1.02, 1.18)	0.021
PM_{10} S (47.3)	1,010 ± 44.2	1,010 ± 42.4	1.08 (1.01, 1.15)	0.034
PM_{10}Si (12.2)	82.4 ± 11.8	81.5 ± 11.1	1.12 (1.05, 1.19)	0.003
PM_{10}Si (80.7)	368 ± 87.4	356 ± 72.3	1.18 (1.11, 1.25)	<0.001
$PM_{2.5}$ V (1.5)	3.04 ± 1.12	2.96 ± 1.07	1.15 (1.05, 1.25)	0.004
PM_{10} V (1.6)	3.86 ± 1.26	3.77 ± 1.19	1.14 (1.05, 1.23)	0.004
$PM_{2.5}$ Zn (18.8)	25.8 ± 12.9	26.1 ± 13.1	0.96 (0.88, 1.04)	0.315
PM_{10} Zn (25.8)	35.3 ± 17.9	35.4 ± 18.2	0.99 (0.91, 1.08)	0.857
OP ESR (171.9)	901 ± 133	889 ± 128	1.14 (1.06, 1.23)	0.032
OP DTT (0.2)	0.81 ± 0.16	0.81 ± 0.16	1.01 (0.93, 1.09)	0.343

Note: ALS, amyotrophic lateral sclerosis; CI, confidence interval; Cu, copper; Fe, iron; IQR, interquartile range; K, potassium; Ni, nickel; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; $PM_{2.5}$ absorbance, $PM \leq 2.5$ μm absorbance; PM_{coarse}, particulate matter with aerodynamic diameter between 2.5 μm and 10 μm; OP DTT, oxidative potential metric with dithiothreitol; OP ESR, oxidative potential metric with electron spin resonance; OR, odds ratio; S, sulfur; SES, socioeconomic status; Si, silicon; UFPs, ultrafine particles; V, vanadium; Zn, zinc.

[a]Units are $\mu g/m^3$ for PM_{10}, $PM_{2.5}$, PM_{coarse}, NO_2 and NO_x; $10^{-5}/m$ for $PM_{2.5}$ absorbance; particle numbers/cm^3 for UFPs; ng/m^3 for all PM elemental constituents; atomic units $/m^3$ for OP ESR; and mol DTT/min per meter cubed for OP DTT.

[b]Results were adjusted for sex, age (age in y at diagnosis for cases and at recruitment for controls), education level, body mass index, smoking status, alcohol consumption, and area SES using unconditional logistic regression models; ORs are presented as per IQR increment.

[c]p-Values corrected for multiple testing using Benjamini and Hochberg method (Benjamini and Hochberg 1995) are presented.

to the robustness of the associations (see supporting information at https://github.com/kevininef/Airpollution-ALS). We also broadened our previously published analyses to a wider range of air pollutants and found that the association between long-term air pollution exposure and ALS, as previously hypothesized (Seelen et al. 2017), is mainly driven by local traffic-related constituents. NO_2 primarily comes from tailpipe emissions and predictors in the Si LUR models were also traffic variables. The NO_2 concentrations were already below the current World Health Organization air quality guidelines ($40\ \mu g/m^3$), suggesting potential benefits of tightening the guidelines and regulatory limits of NO_2 (World Health Organisation Fact Sheet 2018).

A potential limitation might be that we used the disease onset date for cases in calculating the exposure period, subsequently resulting in a slightly different etiological time window for cases than controls. However, we reestimated the average concentrations for controls from 1992 to 1 y prior to the recruitment date (see supporting information at https://github.com/kevininef/Airpollution-ALS) and generated essentially the same exposure values.

Using the air pollution models developed in 2010 for PM elements and in 2014 for UFPs to predict historical exposure might also be a concern, but this is supported by previous studies that reported that the spatial contrasts in measured and modeled annual average levels were stable over time (Eeftens et al. 2011; Downward et al. 2018). Sensitivity analysis of the present study using concentrations without back- extrapolation rendered essentially similar results (see supporting information at https://github.com/kevininef/Airpollution-ALS). Possible residual confounding cannot be excluded given that data regarding medical comorbidities, for example, were not included in the present analysis.

Overall, we found that long-term exposures to NO_2 and PM_{10}Si were independently associated with ALS in a large population-based case–control study. These associations hint toward the potential health relevance of both tailpipe and non-tailpipe emissions of motorized traffic contributing to ALS risk.

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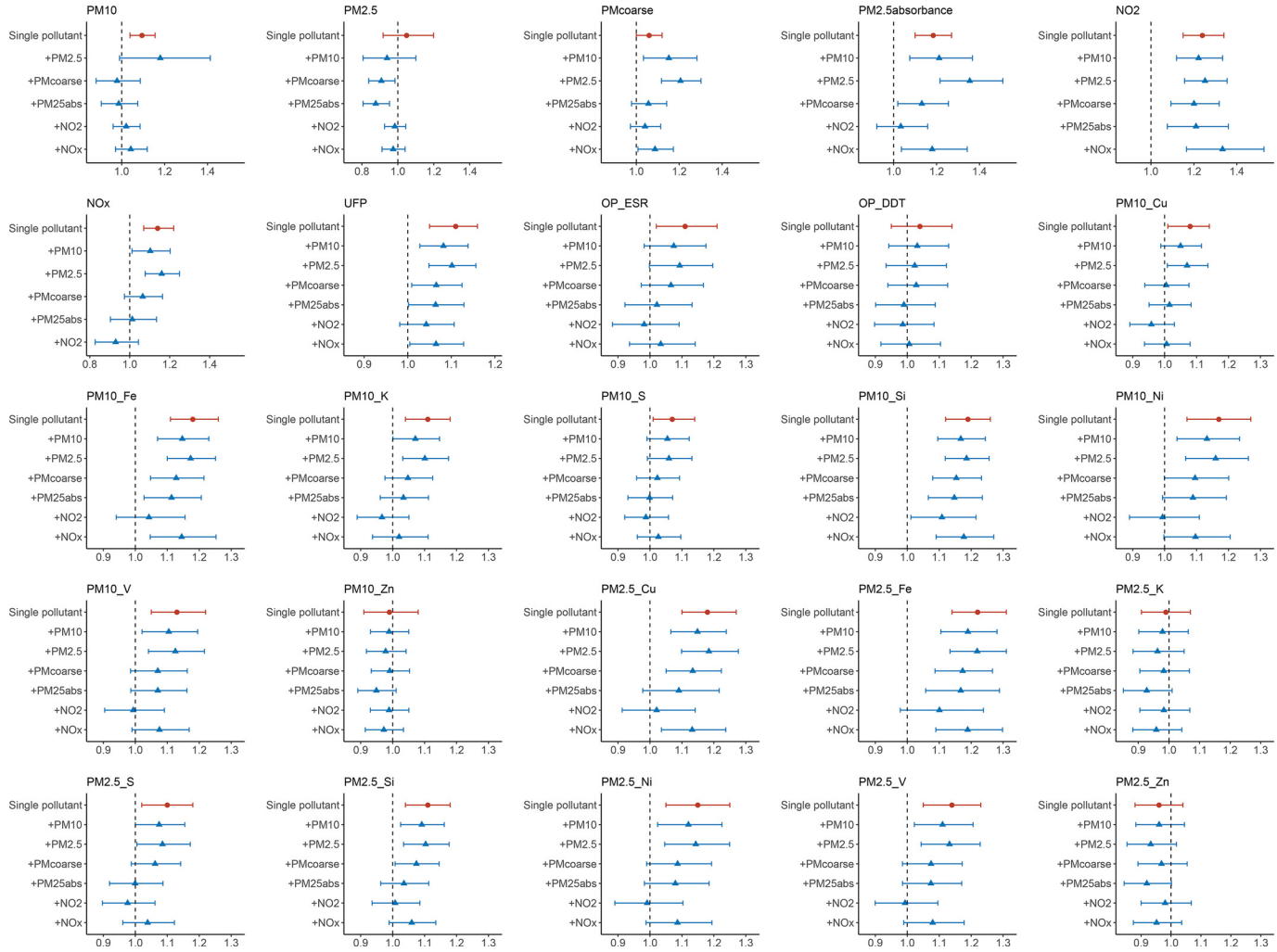

Figure 1. Two-pollutant model with the main effects of PM mass, absorbance, NO_2, NO_x, UFPs, PM OP, and PM elemental compositions. The *x*-axis represents the estimate of certain air pollution constituents, the *y*-axis represents the pollutants adjusted in the two-pollutant models. All results were adjusted for sex, age, education level, body mass index, smoking status, alcohol consumption, and area SES using unconditional logistic regression models. The PM_{10} model adjusted for $PM_{2.5}$ and PM_{coarse} is difficult to interpret because PM_{10} is the sum of these two. The models including both NO_2 and NO_x are also difficult to interpret because NO_2 is included in NO_x. Red dots stand for single-pollutant models; blue triangles stand for two-pollutant models. Numeric data of this figure are presented in supporting information at https://github.com/kevininef/Airpollution-ALS. Note: Cu, copper; Fe, iron; K, potassium; Ni, nickel; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OP DTT, oxidative potential metric with dithiothreitol; OP ESR, oxidative potential metric with electron spin resonance; PM, particulate matter; $PM_{2.5}$, particulate matter with aerodynamic diameter $\leq$2.5 μm; PM_{10}, particulate matter with aerodynamic diameter $\leq$10 μm; $PM_{2.5}$ absorbance, PM $\leq$ 2.5 μm absorbance; PM_{coarse}, particulate matter with aerodynamic diameter between 2.5 μm and 10 μm; PM OP, particulate matter oxidative potential; S, sulfur; SES, socioeconomic status; Si, silicon; UFPs, ultrafine particles; V, vanadium; Zn, zinc.

Supporting information can be found at the GitHub online repository at https://github.com/kevininef/Airpollution-ALS.

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