

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to [508 standards](#) due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehp508@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

Supplemental Material

Long-Term Air Pollution Exposure and Amyotrophic Lateral Sclerosis in Netherlands: A Population-based Case-control Study

Meinie Seelen, Rosario A. Toro Campos, Jan H. Veldink, Anne E. Visser, Gerard Hoek, Bert Brunekreef, Anneke J. van der Kooi, Marianne de Visser, Joost Raaphorst, Leonard H. van den Berg, and Roel C.H. Vermeulen

Table of Contents

Table S1. Demographic characteristics of the original patient cohort compared to the final cohort, and of the eliminated patients by post hoc matching procedure

Table S2. Demographic characteristics of the original cohort compared to the final cohort, and of the eliminated controls by post hoc matching procedure

Table S3. Comparing the main analyses of the imputed dataset with the non-imputed dataset

Table S4. Pearson correlations between exposure to air pollutant concentrations at participant addresses

Table S5. Association between ALS risk and exposure to air pollutants for different time periods: last 5 years and last 1 year before symptom onset.

Table S6. Subgroup analyses taking out the exposure data of the last year and the last 5 years before symptom onset, to exclude a possible effect of incipient ALS

Table S7. Subgroup analyses taking out the participants who moved in the last year and last 5 years before symptom onset

Table S8. Subgroup analysis of non-smokers and current smokers for the association between ALS and exposure to air pollution

Table S9. Subgroup analyses for site of onset for the association between ALS and exposure to air pollution

Figure S1. Diagram of the matching procedure

Figure S2. Continuous analyses using splines of each pollutant separately

Table S1. Demographic characteristics of the original patient cohort compared to the final cohort, and of the eliminated patients by post hoc matching procedure

Characteristics	ALS patients			p Value
	original	eliminated	final	
Male, %	59.7	54.5	61.1	0.53
Age, y, median	63.5	63.8	63.5	0.91
Education, %				
Elementary school	8.7	11.5	8.1	
Secondary school/High school	65.6	65.0	65.8	0.87
College/University	25.7	23.5	26.2	
Area SES, median	20.0	19.8	20.0	0.46
Urbanization degree, addresses/km ² , % ^a				
Very high (≥2500)	13.2	13.1	13.2	
High (1500 - <2500)	27.2	30.2	26.6	
Moderately (1000 - <1500)	24.3	18.1	25.6	0.77
Low (500 - <1000)	26.0	22.6	26.7	
Very low (<500)	9.3	16.1	7.9	

Abbreviations: ALS = amyotrophic lateral sclerosis; SES = socioeconomic status. ^a Urbanization degree is based on district level.

P values were calculated for the comparison of the original and the final cohort of patients.

Table S2. Demographic characteristics of the original cohort compared to the final cohort, and of the eliminated controls by post hoc matching procedure

Characteristics	Controls			p Value
	original	eliminated	final	
Male, %	62.0	62.9	61.3	0.66
Age, y, median	63.5	63.6	63.5	0.83
Education, %				
Elementary school	6.3	5.9	7.1	
Secondary school/High school	65.1	66.4	63.9	0.85
College/University	28.6	27.6	28.9	
Area SES, median	20.0	20.0	20.6	0.50
Urbanization degree, addresses/km ² , % ^a				
Very high (≥2500)	8.2	8.7	9.1	
High (1500 - <2500)	26.4	25.3	25.7	
Moderately (1000 - <1500)	23.2	22.7	24.8	0.93
Low (500 - <1000)	30.2	31.6	28.4	
Very low (<500)	12.1	11.7	12.1	

Abbreviations: ALS = amyotrophic lateral sclerosis; SES = socioeconomic status. ^a Urbanization degree is based on district level.

P values were calculated for the comparison of the original and the final cohort of controls.

Table S3. Comparing the main analyses of the imputed dataset with the non-imputed dataset

Air pollutant	Imputed dataset		Non-imputed dataset	
	OR (95% CI) ^a	<i>p</i> Value ^b	OR (95% CI) ^a	<i>p</i> Value ^b
<i>PM</i>₁₀				
Q1	Reference	0.006	Reference	0.02
Q2	0.77 (0.59-1.00)		0.66 (0.46-0.94)	
Q3	0.83 (0.62-1.10)		0.79 (0.55-1.15)	
Q4	1.29 (0.97-1.72)		1.14 (0.78-1.66)	
<i>PM</i>_{coarse}				
Q1	Reference	0.01	Reference	0.03
Q2	0.82 (0.64-1.05)		0.96 (0.69-1.33)	
Q3	0.95 (0.74-1.24)		1.04 (0.75-1.47)	
Q4	1.24 (0.95-1.61)		1.31 (0.93-1.84)	
<i>PM</i>_{2.5}				
Q1	Reference	0.10	Reference	0.23
Q2	0.98 (0.75-1.28)		0.96 (0.67-1.37)	
Q3	0.85 (0.62-1.16)		0.77 (0.52-1.15)	
Q4	1.35 (0.97-1.88)		1.26 (0.83-1.91)	
<i>PM</i>_{2.5} absorbance				
Q1	Reference	<0.001	Reference	0.002
Q2	1.14 (0.88-1.47)		1.17 (0.85-1.61)	
Q3	1.12 (0.86-1.47)		1.20 (0.85-1.68)	
Q4	1.67 (1.27-2.18)		1.63 (1.16-2.30)	
<i>NO</i>₂				
Q1	Reference	<0.001	Reference	<0.001
Q2	1.38 (1.09-1.76)		1.47 (1.08-2.00)	
Q3	1.25 (0.97-1.63)		1.50 (1.08-2.09)	
Q4	1.74 (1.32-2.30)		1.99 (1.40-2.84)	
<i>NO</i>_x				
Q1	Reference	0.004	Reference	0.01
Q2	0.98 (0.78-1.24)		0.99 (0.73-1.34)	
Q3	1.12 (0.87-1.43)		1.28 (0.94-1.76)	
Q4	1.38 (1.07-1.77)		1.41 (1.02-1.94)	

^a Model 1 was used for the comparison; this multivariate model is adjusted for sex, age, educational level, current smoking, current alcohol consumption, body mass index and socioeconomic status. ^b *P* value was calculated for linear trend.

Table S4. Pearson correlations between exposure to air pollutant concentrations at participant addresses

Air pollutant	PM₁₀	PM_{coarse}	PM_{2.5}	PM_{2.5} absorbance	NO₂	NO_x
PM ₁₀	1					
PM _{coarse}	0.828	1				
PM _{2.5}	0.645	0.497	1			
PM _{2.5} absorbance	0.779	0.661	0.667	1		
NO ₂	0.686	0.694	0.390	0.818	1	
NO _x	0.723	0.716	0.460	0.813	0.835	1

All correlations are significant at the 0.01 level.

Table S5. Association between ALS risk and exposure to air pollutants for different time periods: last 5 years and last 1 year before symptom onset

Air pollutant	Total population		Last 5 years before onset		Last year before onset	
	OR (95% CI) ^a	p Value ^b	OR (95% CI) ^a	p Value ^b	OR (95% CI) ^a	p Value ^b
<i>PM₁₀</i>						
Q1	Reference	0.006	Reference	0.02	Reference	0.006
Q2	0.77 (0.59-1.00)		0.82 (0.45-1.50)		2.58 (0.75-8.84)	
Q3	0.83 (0.62-1.10)		1.71 (0.77-3.82)		5.60 (0.47-66.3)	
Q4	1.29 (0.97-1.72)		3.04 (1.28-7.22)		4.94 (1.16-21.1)	
<i>PM_{coarse}</i>						
Q1	Reference	0.01	Reference	0.04	Reference	0.03
Q2	0.82 (0.64-1.05)		0.74 (0.49-1.17)		2.01 (1.04-3.88)	
Q3	0.95 (0.74-1.24)		1.24 (0.81-1.90)		0.78 (0.31-1.95)	
Q4	1.24 (0.95-1.61)		1.56 (1.05-2.33)		2.17 (1.09-4.31)	
<i>PM_{2.5}</i>						
Q1	Reference	0.10	Reference	0.03	Reference	0.20
Q2	0.98 (0.75-1.28)		1.29 (0.62-.271)		3.25 (0.95-11.1)	
Q3	0.85 (0.62-1.16)		4.61 (1.32-16.1)		0.78 (0.08-8.10)	
Q4	1.35 (0.97-1.88)		1.90 (0.57-6.29)		NA	
<i>PM_{2.5} absorbance</i>						
Q1	Reference	<0.001	Reference	0.01	Reference	0.001
Q2	1.14 (0.88-1.47)		1.27 (0.96-1.68)		1.40 (1.06-1.84)	
Q3	1.12 (0.86-1.47)		1.43 (0.95-2.15)		1.20 (0.83-1.75)	
Q4	1.67 (1.27-2.18)		1.38 (0.98-1.95)		1.73 (1.22-2.45)	
<i>NO₂</i>						
Q1	Reference	<0.001	Reference	<0.001	Reference	<0.001
Q2	1.38 (1.09-1.76)		1.02 (0.82-1.26)		1.15 (0.93-1.42)	
Q3	1.25 (0.97-1.63)		1.28 (0.99-1.65)		1.37 (1.05-1.80)	
Q4	1.74 (1.32-2.30)		1.75 (1.34-2.29)		1.71 (1.30-2.26)	
<i>NO_x</i>						
Q1	Reference	0.004	Reference	<0.001	Reference	<0.001
Q2	0.98 (0.78-1.24)		1.00 (0.77-1.29)		1.44 (1.10-1.90)	
Q3	1.12 (0.87-1.43)		1.72 (1.31-2.26)		1.93 (1.41-2.64)	
Q4	1.38 (1.07-1.77)		1.45 (1.12-1.89)		1.53 (1.14-2.05)	

^a Main model 1 was used for the comparison; this confounder model was adjusted for sex, age, educational level, current smoking, current alcohol consumption, body mass index and socioeconomic status. ^b P value was calculated for linear trend based on median values.

Table S6. Subgroup analyses taking out the exposure data of the last year and the last 5 years before symptom onset, to exclude a possible effect of incipient ALS

Air pollutant	Total population		Excluding last year		Excluding last 5 years	
	OR (95% CI) ^a	p Value ^b	OR (95% CI) ^a	p Value ^b	OR (95% CI) ^a	p Value ^b
<i>PM₁₀</i>						
Q1	Reference	0.006	Reference	0.02	Reference	0.95
Q2	0.77 (0.59-1.00)		0.95 (0.71-1.28)		1.20 (0.39-3.73)	
Q3	0.83 (0.62-1.10)		0.79 (0.58-1.09)		0.72 (0.31-1.66)	
Q4	1.29 (0.97-1.72)		1.22 (0.89-1.68)		0.84 (0.38-1.88)	
<i>PM_{coarse}</i>						
Q1	Reference	0.01	Reference	0.006	Reference	0.81
Q2	0.82 (0.64-1.05)		0.92 (0.69-1.22)		2.17 (0.63-7.51)	
Q3	0.95 (0.74-1.24)		0.98 (0.74-1.31)		1.70 (0.56-5.19)	
Q4	1.24 (0.95-1.61)		1.30 (0.97-1.75)		1.63 (0.54-4.94)	
<i>PM_{2.5}</i>						
Q1	Reference	0.10	Reference	0.34	Reference	0.93
Q2	0.98 (0.75-1.28)		0.94 (0.69-1.27)		0.94 (0.44-1.99)	
Q3	0.85 (0.62-1.16)		0.84 (0.60-1.18)		1.11 (0.54-2.27)	
Q4	1.35 (0.97-1.88)		1.13 (0.80-11.60)		1.03 (0.51-2.07)	
<i>PM_{2.5} absorbance</i>						
Q1	Reference	<0.001	Reference	<0.001	Reference	0.06
Q2	1.14 (0.88-1.47)		0.96 (0.74-1.24)		1.04 (0.73-1.50)	
Q3	1.12 (0.86-1.47)		1.09 (0.83-1.44)		1.00 (0.70-1.43)	
Q4	1.67 (1.27-2.18)		1.51 (1.15-1.99)		1.24 (0.87-1.78)	
<i>NO₂</i>						
Q1	Reference	<0.001	Reference	0.001	Reference	0.001
Q2	1.38 (1.09-1.76)		1.32 (1.04-1.69)		1.25 (0.95-1.63)	
Q3	1.25 (0.97-1.63)		1.24 (0.95-1.62)		1.10 (0.83-1.46)	
Q4	1.74 (1.32-2.30)		1.68 (1.28-2.22)		1.63 (1.23-2.16)	
<i>NO_x</i>						
Q1	Reference	0.004	Reference	0.002	Reference	0.003
Q2	0.98 (0.78-1.24)		0.87 (0.68-1.11)		0.97 (0.70-1.34)	
Q3	1.12 (0.87-1.43)		1.05 (0.81-1.35)		1.07 (0.78-1.47)	
Q4	1.38 (1.07-1.77)		1.34 (1.04-1.72)		1.35 (0.98-1.85)	

^a Main model 1 was used for the comparison; this confounder model was adjusted for sex, age, educational level, current smoking, current alcohol consumption, body mass index and socioeconomic status. ^b P value was calculated for linear trend based on median values.

Table S7. Subgroup analyses taking out the participants who moved in the last year and last 5 years before symptom onset

Air pollutant	Total population		Not moved in the last year ^a		Not moved in the last 5 years ^b	
	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d
PM₁₀						
Q1	Reference	0.006	Reference	0.004	Reference	0.04
Q2	0.77 (0.59-1.00)		0.73 (0.56-0.95)		0.69 (0.51-0.94)	
Q3	0.83 (0.62-1.10)		0.85 (0.63-1.14)		0.74 (0.52-1.04)	
Q4	1.29 (0.97-1.72)		1.32 (0.98-1.78)		1.20 (0.85-1.69)	
PM_{coarse}						
Q1	Reference	0.01	Reference	0.006	Reference	0.03
Q2	0.82 (0.64-1.05)		0.77 (0.60-1.00)		0.80 (0.60-1.06)	
Q3	0.95 (0.74-1.24)		0.98 (0.75-1.28)		0.95 (0.70-1.28)	
Q4	1.24 (0.95-1.61)		1.26 (0.96-1.65)		1.24 (0.91-1.68)	
PM_{2.5}						
Q1	Reference	0.10	Reference	0.03	Reference	0.03
Q2	0.98 (0.75-1.28)		1.01 (0.77-1.33)		0.98 (0.71-1.35)	
Q3	0.85 (0.62-1.16)		0.91 (0.66-1.26)		0.90 (0.62-1.31)	
Q4	1.35 (0.97-1.88)		1.52 (1.08-2.16)		1.58 (1.06-2.38)	
PM_{2.5} absorbance						
Q1	Reference	<0.001	Reference	<0.001	Reference	0.002
Q2	1.14 (0.88-1.47)		1.10 (0.84-1.44)		0.92 (0.68-1.25)	
Q3	1.12 (0.86-1.47)		1.10 (0.83-1.47)		1.06 (0.77-1.46)	
Q4	1.67 (1.27-2.18)		1.62 (1.23-2.15)		1.48 (1.08-2.04)	
NO₂						
Q1	Reference	<0.001	Reference	0.001	Reference	0.007
Q2	1.38 (1.09-1.76)		1.39 (1.08-1.79)		1.44 (1.09-1.91)	
Q3	1.25 (0.97-1.63)		1.23 (0.94-1.62)		1.39 (1.02-1.90)	
Q4	1.74 (1.32-2.30)		1.76 (1.32-2.34)		1.66 (1.19-2.30)	
NO_x						
Q1	Reference	0.004	Reference	0.01	Reference	0.06
Q2	0.98 (0.78-1.24)		0.96 (0.75-1.23)		0.93 (0.71-1.22)	
Q3	1.12 (0.87-1.43)		1.04 (0.81-1.34)		1.04 (0.78-1.39)	
Q4	1.38 (1.07-1.77)		1.32 (1.02-1.71)		1.26 (0.94-1.69)	

^a Participants who did not move in the last year, no. of cases=861, no. of controls=2376. ^b Participants who did not move in the last five years, no. of cases=719, no. of controls=1759. ^c Main model 1 was used for the comparison; this confounder model was adjusted for sex, age, educational level, current smoking, current alcohol consumption, body mass index and socioeconomic status. ^d P value was calculated for linear trend based on median values.

Table S8. Subgroup analysis of non-smokers and current smokers for the association between ALS and exposure to air pollution

Air pollutant	Total population		Current non-smokers ^a		Current smokers ^b	
	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d
<i>PM₁₀</i>						
Q1	Reference	0.006	Reference	0.04	Reference	0.88
Q2	0.77 (0.59-1.00)		0.80 (0.65-0.98)		0.95 (0.58-1.54)	
Q3	0.83 (0.62-1.10)		0.86 (0.70-1.06)		0.82 (0.51-1.34)	
Q4	1.29 (0.97-1.72)		1.18 (0.98-1.42)		0.97 (0.61-1.53)	
<i>PM_{coarse}</i>						
Q1	Reference	0.01	Reference	0.02	Reference	0.93
Q2	0.82 (0.64-1.05)		0.83 (0.67-1.02)		1.02 (0.63-1.67)	
Q3	0.95 (0.74-1.24)		0.95 (0.78-1.16)		0.98 (0.61-1.58)	
Q4	1.24 (0.95-1.61)		1.17 (0.96-1.41)		0.93 (0.59-1.48)	
<i>PM_{2.5}</i>						
Q1	Reference	0.10	Reference	0.44	Reference	0.70
Q2	0.98 (0.75-1.28)		0.99 (0.81-1.22)		0.99 (0.62-1.56)	
Q3	0.85 (0.62-1.16)		0.90 (0.72-1.11)		0.68 (0.40-1.13)	
Q4	1.35 (0.97-1.88)		1.11 (0.91-1.35)		1.17 (0.76-1.80)	
<i>PM_{2.5}absorbance</i>						
Q1	Reference	<0.001	Reference	0.003	Reference	0.33
Q2	1.14 (0.88-1.47)		0.99 (0.80-1.22)		1.58 (0.97-2.57)	
Q3	1.12 (0.86-1.47)		1.03 (0.83-1.28)		1.05 (0.62-1.78)	
Q4	1.67 (1.27-2.18)		1.30 (1.07-1.59)		1.39 (0.89-2.18)	
<i>NO₂</i>						
Q1	Reference	<0.001	Reference	0.005	Reference	0.57
Q2	1.38 (1.09-1.76)		1.21 (0.98-1.50)		1.41 (0.87-2.29)	
Q3	1.25 (0.97-1.63)		1.16 (0.93-1.43)		1.04 (0.61-1.78)	
Q4	1.74 (1.32-2.30)		1.38 (1.12-1.70)		1.26 (0.79-2.00)	
<i>NO_x</i>						
Q1	Reference	0.004	Reference	0.01	Reference	0.69
Q2	0.98 (0.78-1.24)		0.99 (0.80-1.22)		1.01 (0.63-1.63)	
Q3	1.12 (0.87-1.43)		1.13 (0.92-1.40)		0.82 (0.50-1.36)	
Q4	1.38 (1.07-1.77)		1.24 (1.02-1.52)		1.09 (0.70-1.69)	

^a Non-smokers: no. of cases = 763, no. of controls = 2316. ^b Current smokers: no. of cases = 154, no. of controls = 346. ^c Model 1 was used for the comparison; this multivariate model was adjusted for sex, age, educational level, current alcohol consumption, body mass index and socioeconomic status. ^d P value was calculated for linear trend based on median values.

Table S9. Subgroup analyses for site of onset for the association between ALS and exposure to air pollution

Air pollutant	Total population		Bulbar site of onset ^a		Spinal site of onset ^b	
	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d	OR (95% CI) ^c	p Value ^d
<i>PM₁₀</i>						
Q1	Reference	0.006	Reference	0.10	Reference	0.65
Q2	0.77 (0.59-1.00)		0.77 (0.48-1.23)		0.72 (0.52-1.00)	
Q3	0.83 (0.62-1.10)		0.81 (0.47-1.41)		0.76 (0.52-1.10)	
Q4	1.29 (0.97-1.72)		1.41 (0.76-2.61)		1.00 (0.66-1.51)	
<i>PM_{coarse}</i>						
Q1	Reference	0.01	Reference	0.14	Reference	0.56
Q2	0.82 (0.64-1.05)		0.86 (0.56-1.33)		0.72 (0.52-0.98)	
Q3	0.95 (0.74-1.24)		1.13 (0.70-1.84)		0.73 (0.52-1.02)	
Q4	1.24 (0.95-1.61)		1.36 (0.79-2.34)		0.94 (0.65-1.36)	
<i>PM_{2.5}</i>						
Q1	Reference	0.10	Reference	0.60	Reference	0.26
Q2	0.98 (0.75-1.28)		1.05 (0.66-1.67)		0.87 (0.62-1.22)	
Q3	0.85 (0.62-1.16)		0.87 (0.50-1.49)		0.78 (0.53-1.15)	
Q4	1.35 (0.97-1.88)		1.19 (0.67-2.13)		1.28 (0.84-1.93)	
<i>PM_{2.5} absorbance</i>						
Q1	Reference	<0.001	Reference	0.004	Reference	0.09
Q2	1.14 (0.88-1.47)		1.17 (0.73-1.87)		1.08 (0.79-1.48)	
Q3	1.12 (0.86-1.47)		1.22 (0.72-2.07)		1.02 (0.72-1.47)	
Q4	1.67 (1.27-2.18)		2.07 (1.17-3.68)		1.36 (0.92-2.02)	
<i>NO₂</i>						
Q1	Reference	<0.001	Reference	<0.001	Reference	0.90
Q2	1.38 (1.09-1.76)		1.19 (0.76-1.87)		1.33 (0.98-1.18)	
Q3	1.25 (0.97-1.63)		1.77 (1.08-2.93)		0.91 (0.63-1.33)	
Q4	1.74 (1.32-2.30)		2.85 (1.53-5.33)		1.15 (0.74-1.79)	
<i>NO_x</i>						
Q1	Reference	0.004	Reference	0.03	Reference	0.76
Q2	0.98 (0.78-1.24)		0.98 (0.63-1.52)		0.90 (0.67-1.21)	
Q3	1.12 (0.87-1.43)		1.51 (0.94-2.42)		0.81 (0.58-1.13)	
Q4	1.38 (1.07-1.77)		1.61 (0.97-2.68)		1.01 (0.70-1.45)	

^a Bulbar site of onset: no. of cases=324, no. of controls = 940. ^b Spinal site of onset: no. of cases=596, no. of controls = 1731. ^c Model 1 was used for the comparison; this multivariate model was adjusted for sex, age, educational level, current smoking, current alcohol consumption, body mass index and socioeconomic status. ^d P value was calculated for linear trend based on median values.

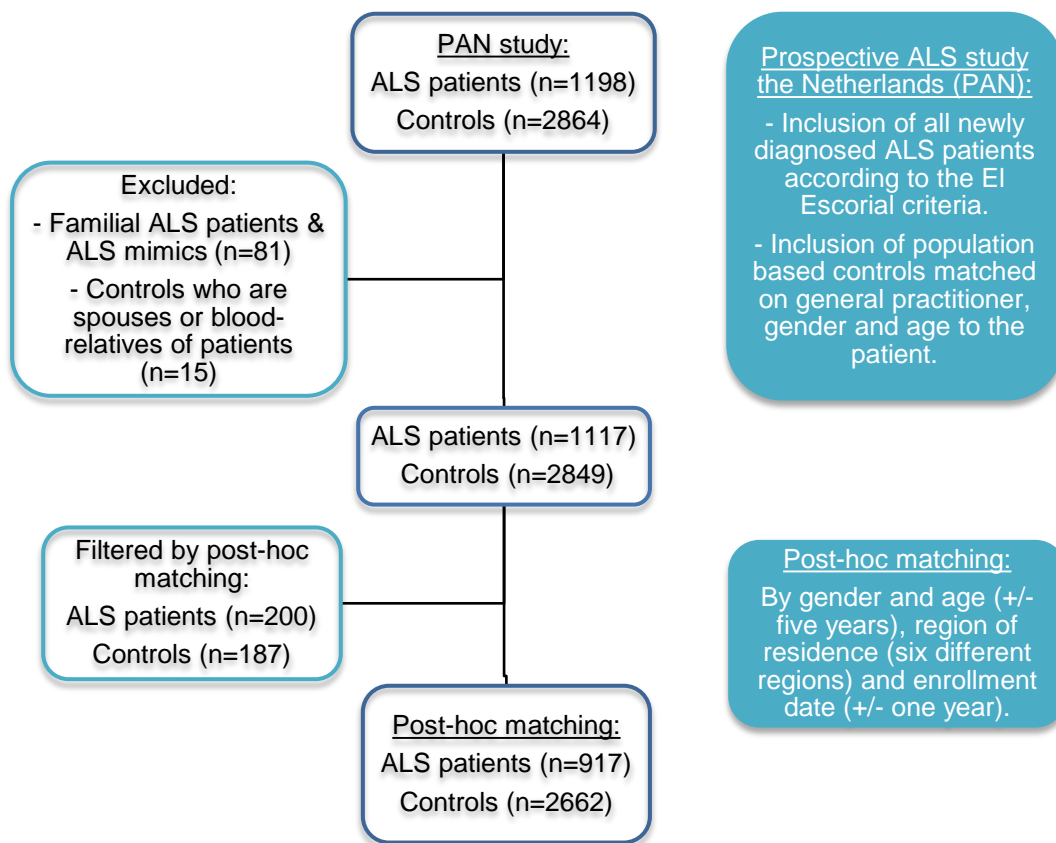


Figure S1. Diagram of the matching procedure

ALS patients and controls were included in the PAN study between 2006 and 2013 (original population matching). The population based controls were selected through the register of the general practitioner (GP) of the patient. However, the size of the area covered by one GP (who serves on average ~2000 patients) can be relatively small especially in urban settings, and the inclusion date of controls can be years apart from the date of symptom onset in cases in the original population matching (because of the time lag between date of diagnosis and date of symptom onset in ALS cases), which both can be related to exposure to air pollution. Therefore, we broke the original match (including 1117 cases and 2849 controls) and applied post-hoc matching to the cases by gender and age (+/- five years), region of residence (six different regions) and enrollment date (+/- one year). This resulted in a more uniform distribution of enrollment dates between cases (n=917) and controls (n=2662) and broader spatial matching between cases and controls.

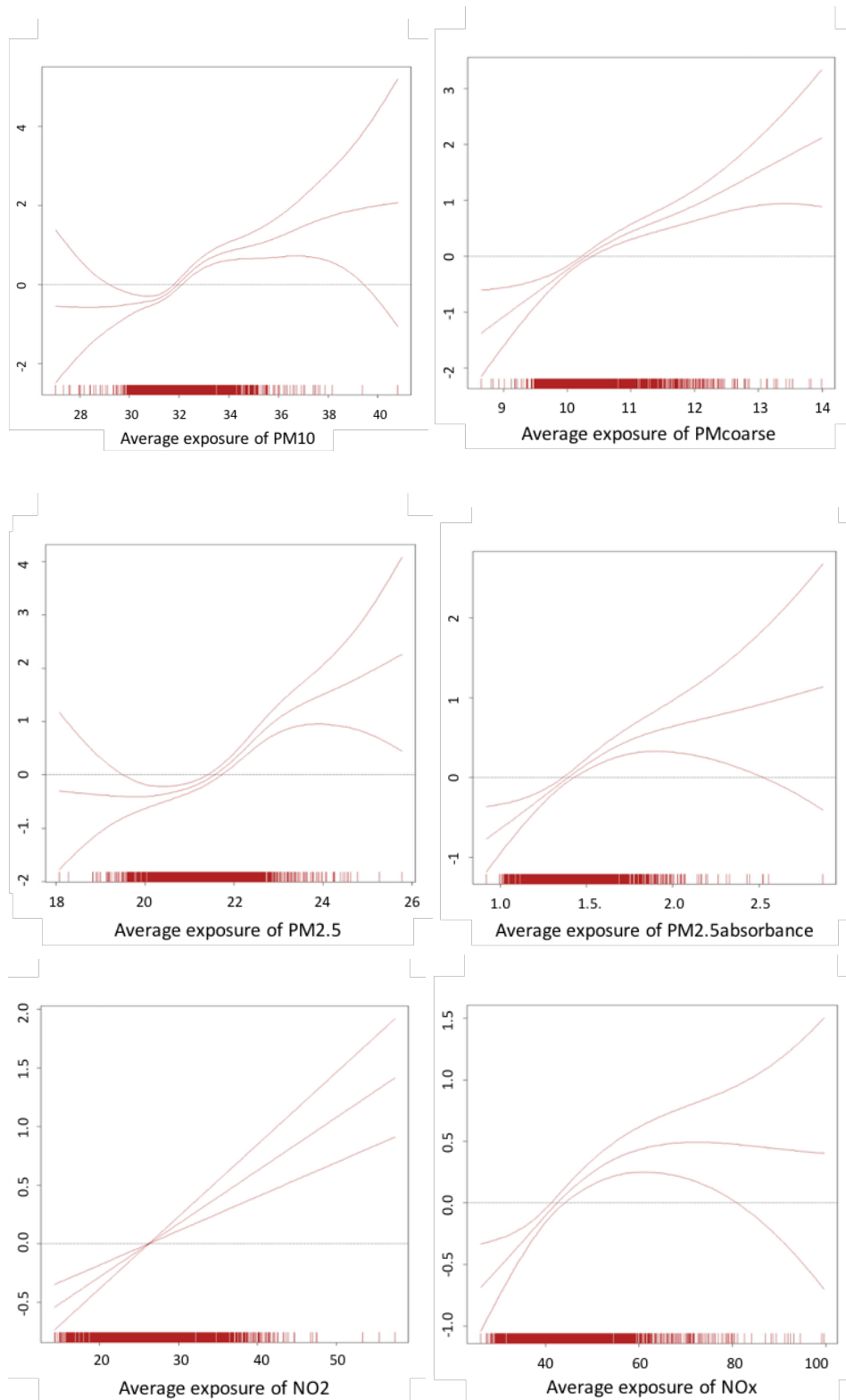


Figure S2. Continuous analyses using splines of each pollutant separately.