Original Research Article

ENVIRONMENTAL EPIDEMIOLOGY

OPEN

Traffic-related air pollution, road traffic noise, and Parkinson's disease

Evaluations in two Dutch cohort studies

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Background: Environmental factors such as air pollution have been associated with Parkinson's disease (PD), but findings have been inconsistent. We investigated the association between exposure to several air pollutants, road traffic noise, and PD risk in two Dutch cohorts.

Methods: Data from 50,087 participants from two Dutch population-based cohort studies, European Prospective Investigation into Cancer and Nutrition in the Netherlands and Arbeid, Milieu en Gezondheid Onderzoek were analyzed. In these cohorts, 235 PD cases were ascertained based on a previously validated algorithm combining self-reported information (diagnosis, medication, and symptoms) and registry data. We assigned the following traffic-related exposures to residential addresses at baseline: NO_2, NO_x, particulate matter $(PM)_{2.5absorbance}$ (as a marker for black carbon exposure), PM with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), PM_{coarse} (size fraction 2.5–10 μm), ultrafine particles <0.1 μm (UFP), and road traffic noise (L_{den}). Logistic regression models were applied to investigate the associations with PD, adjusted for possible confounders.

Results: Both single- and two-pollutant models indicated associations between exposure to NO_x, road traffic noise, and increasing odds of developing PD. Odds ratios of fully adjusted two-pollutant models in the highest compared with the lowest exposure quartile were 1.62 (95% CI = 1.02, 2.62) for NO_x and 1.47 (95% CI = 0.97, 2.25) for road traffic noise, with clear trends across exposure categories.

Conclusions: Our findings suggest that NO_x and road traffic noise are associated with an increased risk of PD. While the association with NO_x has been shown before, further investigation into the possible role of environmental noise on PD is warranted.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder.[1] The incidence of PD rises with age. Men are approximately 1.5 times more likely to develop PD than women.[2] The underlying cause(s) of PD remain largely unknown but are believed to involve both genetic and nongenetic factors.[1]

Traffic-related air pollution (TRAP) mainly consists of nitrogen dioxide (NO_2), nitrogen oxides (NO_x), and different forms of particulate matter (PM), including ultrafine particles (UFP).[3] They are near-ubiquitous in the environment, and they may play a role in the development of neurodegenerative diseases. Different neurodegenerative diseases share common mechanisms, which result in the loss of neurons.[4,5] Exposure to TRAP may trigger such mechanisms and result in neuropathology.[4] Several observational studies suggested an increased risk of PD associated with air pollutants, in particular $PM_{2.5}$, NO_2,[6] ozone, and carbon dioxide, while others have found no clear evidence.[7–9] Research into UFP is especially of interest as small particles can translocate from the lungs to other organs, including the brain.[10]

The association between road traffic noise and the risk of developing PD has been rarely evaluated.[11] Noise has the ability to influence human health by inducing exhaustion, anger, stress-related symptoms, and sleep disturbance.[12,13] Stress can induce the release of high levels of dopamine and noradrenaline into the hypothalamus, which impairs the regulation of the prefrontal cortex, an area responsible for cognitive abilities.[14] People with PD show a rapid decline in a number of cognitive

What this study adds

The cause of Parkinson's disease (PD) for most patients is unknown. Air pollutants have been previously studied as risk factors, but they often included only single-exposure analyses. Previous research on the association between traffic-related noise and PD is limited. We investigated single-exposure and multiple-exposure associations between several traffic-related air pollutants, traffic-related noise, and PD. Our results add to the existing evidence regarding air-pollutant exposures, in particular exposure to NO_x and the risk of PD, while additionally suggesting that road traffic noise may have an independent effect on PD development. These new insights may contribute to expanding future options for PD prevention.

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The project received funding from EXPOSOME-NL (NWO; project number 024.004.017), EXPANSE (EU-H2020 Grant number 874627) and by the Netherlands Organisation for Health Research and Development (ZonMw) within the Electromagnetic Fields and Health Research programme (grant numbers 85200001 and 85500003). The EPIC-NL study was funded by the Dutch Ministry of Health, Welfare and Sports (VWS); the Dutch ZonMw (Dutch Prevention funds); the World Cancer Research Fund (WCRF); Dutch Cancer Society (KWF); Julius Center; University Medical Center Utrecht and the National Institute for Public Health and the Environment (RIVM). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The data are from the European Prospective Investigation into Cancer and Nutrition in the Netherlands (EPIC-NL) and the Occupational and Environmental Health Cohort Study (in Dutch: Arbeid, Milieu en Gezondheid Onderzoek, AMIGO) and they contain personal and sensitive information, including patient identifying information. Researchers may reach a privacy agreement to access the data by contacting the corresponding author Dr. Anke Huss (a.huss@uu.nl).

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domains.[15] A study performed in the city of Madrid indicated a positive association between short-term road traffic noise exposure and PD exacerbation.[15]

The aim of this study is to investigate the association between TRAP, road traffic noise, and the risk of PD using two population-based cohort studies in the Netherlands.

Methods

Study population

This study was conducted within two population-based cohorts: the European Prospective Investigation into Cancer and Nutrition in the Netherlands (EPIC-NL)[17] and the Occupational and Environmental Health Cohort Study (in Dutch: Arbeid, Milieu en Gezondheid Onderzoek, AMIGO).[18] EPIC-NL participants were recruited between 1993 and 1997 into two cohorts: adults aged 21–64 years from the general population of three Dutch cities for the Monitoring Project on Risk Factors for Chronic Diseases (EPIC-MORGEN) and women aged 49–70 years who participated in a breast cancer screening program conducted in the city of Utrecht and neighboring towns (EPIC-Prospect).[17] The 40,011 participants of EPIC-NL received a baseline questionnaire between 1993 and 1997. The follow-up questionnaires were conducted between 1998 and 2002 in both MORGEN and Prospect (follow-up 1, n = 28,022), in 2002 and 2003 in EPIC-Prospect only (follow-up 2, n = 12,004), and in 2010 and 2011 in both MORGEN and Prospect (follow-up 3, n = 13, 960).[19] Participants in AMIGO were recruited via a Dutch national general practitioners (GP) network (the Netherlands Institute for Health Services Research [NIVEL] Primary Care Database) in 2011 and 2012. The 14,829 participants, aged 31 to 63 years, received a baseline questionnaire in 2011/2012.[17,18] The first follow-up questionnaire was conducted in 2015 (n = 7,905).[20] For this study, geocoding and assigning exposures based on the home address was successful for 35,274 EPIC-NL participants (88.2%), while for AMIGO, this number was 14,814 (99.8%), resulting in a total population of 50,087 participants.

Case ascertainment

Cases of PD were ascertained based on a combination of self-reported information from questionnaires, registry data, and a 9-item screening questionnaire for PD.[19] We previously developed and validated a PD probabilistic likelihood score with four categories (no PD, unlikely PD, possible PD, and likely PD) which was compared against cases that were confirmed by clinical records.[19] Only participants in the likely PD category were classified as cases for our analysis; the other three categories were classified as controls as the validation indicated they were unlikely to have PD. A detailed description of the algorithm and its validation is provided in Reedijk et al.[19]

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Environmental Epidemiology (2023) 7:e272

Received 30 June, 2023; Accepted 6 September, 2023

Published online 19 October 2023

DOI: 10.1097/EE9.0000000000000272

Environmental exposure assessment

Exposures were assigned to the baseline addresses of study participants, which were geocoded using data obtained from the Netherlands Cadastre, Land Registry and Mapping Agency (Kadaster, Netherlands). Long-term residential ambient air-pollutant concentrations of NO_2, NO_x, a marker for black carbon ($PM_{2.5absorbance}$), PM with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), and ranging from 2.5 μm to 10μm (PM_{coarse}), were assessed using land use regression (LUR) models developed within the European Study of Cohorts for Air Pollution Effects study with measurements taken in 2009[21,22] and successfully applied in epidemiological investigations.[23] Exposure to ultrafine particles (PM with an aerodynamic diameter <0.1 μm, UFP) was estimated with LUR models developed based on measurements taken in 2013 by Kerckhoffs et al.[24] The UFP LUR model has been applied in previous epidemiological investigations.[25] Exposure to road traffic noise was assessed using the Standard Model Instrumentation for Noise Assessments (STAMINA) developed by the Dutch National Institute for Public Health and the Environment.[26] Road traffic noise levels are expressed as L_{den} (day-evening-night noise level), applying penalties for noise measured in the evening and at night. A lower cutoff value of 24 dB L_{den} was applied in the noise models because of uncertainty in the modeling of noise at low levels and a lack of information on roads with low volumes of traffic.[26] The STAMINA model has also been applied in previous epidemiological investigations.[20] All exposure levels were assigned to participant baseline addresses without taking changes over time in noise or air-pollutant levels into account or changes of addresses of study participants.

Statistical analyses

Descriptive statistics were applied to describe the study population characteristics at baseline of both EPIC-NL and AMIGO. Pearson's chi-square test (χ^2) for categorical variables (with continuity correction) and one-way analysis of variance (ANOVA) for continuous variables were used to test differences between the PD and control groups. Spearman correlations were used to describe relations between the different exposure variables at the baseline home addresses of the participants. We used logistic regression models to investigate associations between TRAP, road traffic noise, and PD because the AMIGO cohort had mainly prevalent cases and the year of diagnosis was not known for all PD cases in EPIC-NL. Minimally adjusted models included age (in years), age-squared, and sex as these are the two main established risk factors for PD. Fully adjusted models further included putative risk factors for PD: highest attained level of education (low; medium; or high), marital status (having a partner; divorced; widowed; or single), smoking status (never; former; or current), body mass index category (BMI; categories underweight BMI <18.5, normal BMI 18.5–<25, overweight BMI 25–<30 and obese: BMI 30 or more), and cohort.

Exposures were categorized into quartiles. *P* values for trend across quartiles were calculated using midpoint exposure levels for each quartile. For all exposure variables, fully adjusted models showed a smaller Akaike Information Criterion than minimally adjusted models, although risk estimates were not materially changed (Tables ST2A and ST2B; http://links.lww.com/EE/A241). For all exposures, we first ran single-exposure analyses to investigate individual associations between exposures and PD. Subsequently, two-exposure (i.e., bi-pollutant) models were performed to investigate whether a possible association with PD was confounded by another exposure by adjusting them one by one for the other exposure variables. We additionally repeated all analyses stratified by cohort and performed a sensitivity analysis where we calculated effect estimates only for those PD cases that had been validated by GPs (n = 80), excluding those participants for whom PD status could

not be verified due to nonparticipation of the GP in the validation exercise.[19] All analyses were performed using R (version 3.6.1; R Development Core Team, Vienna, Austria).

Results

Characteristics of the total EPIC-NL and AMIGO population at baseline are shown in Table 1. Among EPIC-NL participants included in this study, 168 persons were diagnosed with PD after a maximum of 20 years of follow-up, and 67 PD cases were identified within AMIGO participants after approximately 5 years of follow-up. Exposure distributions by cohort are provided in Tables ST1A and ST1B; http://links.lww.com/EE/A241. For both cohorts combined, very strong correlations between exposures (≥0.8) were observed for PM_{10} with NO_2, NO_x, $PM_{2.5abs}$, and PM_{coarse}; for NO_x with NO_2 and $PM_{2.5abs}$; and for UFP with PM_{10}. Similar patterns were observed separately for the EPIC-NL and AMIGO cohorts; Spearman correlations are provided in Table 2, and per cohort in Figures SF1A and SF1B; http://links.lww.com/EE/A241.

In single-pollutant models, positive trends in the PD odds per quartile of exposures were observed for all air pollutants (except $PM_{2.5}$) and road traffic noise with elevated odds ratios (ORs) for the highest (Q4) versus lowest quartile (Q1) of exposure: NO_2 OR = 1.48 (95% CI = 0.99, 2.25); NO_x OR = 2.08 (95% CI = 1.37, 3.22); $PM_{2.5}$ OR = 1.05 (95% CI = 0.72, 1.52); PM_{coarse} OR = 1.63 (95% CI = 1.13, 2.37); PM_{10} OR = 1.56 (95% CI = 1.04, 2.38); $PM_{2.5abs}$ OR = 1.70 (95% CI = 1.10, 2.65); UFP OR = 1.29 (95% CI = 0.87, 1.94); and road traffic noise OR = 1.64 (95% CI = 1.13, 2.43) (Table 3). Results stratified by cohort are given in Tables ST2A and ST2B; http://links.lww.com/EE/A241.

Informed by the single-exposure models of the analysis of the pooled cohort, we focused on NO_2, NO_x, and road traffic noise in the two-pollutant models (Table 4). Effect estimates and trends for NO_2 in the two-pollutant models were more variable and often attenuated towards the null, presumably due to the correlations among exposures. For NO_x, effect estimates and trends remained more similar within the two-pollutant models, with the effect estimate of Q4 versus Q1 varying from the single-exposure model (OR = 2.08; 95% CI = 1.37, 3.22) to ORs between 1.62 (95% CI = 1.02, 2.62) (model including road traffic noise) and 2.88 (95% CI = 1.47, 5.63) (model including NO_2). For the effect of road traffic noise, almost no variance was found between the effect estimate of Q4 versus Q1 in the single-pollutant model and two-pollutant models. Results of the two-exposure models for all environmental exposures (adjusted one by one) for EPIC-NL and AMIGO are given in Tables ST3A and ST3B; http://links.lww.com/EE/A241, respectively. Sensitivity analyses in GP-validated cases had lower power due to fewer identified cases but displayed similar patterns in effect estimates (Tables ST4 and ST5; http://links.lww.com/EE/A241).

Discussion

In this study of TRAP, road traffic noise, and PD in two cohort studies in the Netherlands, we observed associations between increased exposures to air pollutants (in particular NO_x) and road traffic noise with PD. These observed associations, based on established LUR models, were consistent across cohorts and remained robust when limiting the analyses to clinically confirmed PD cases.

One of the unique aspects of this study is that we looked at a broad range of air pollutants including ultrafine particulates. It has been hypothesized that especially these very small particles (<100 nm) could be detrimental for brain health, as these particles may translocate to the brain and cause localized inflammation and oxidative stress in the brain.[27] As UFP only represents a small portion of the mass of PM, it is not well characterized by the regulated

Table 1.

Baseline characteristics of EPIC-NL and AMIGO cohort study by disease status

	EPIC-NL			AMIGO		
	Controls	PD cases	*P* value	Controls	PD cases	*P* value
Number of participants	35,106	168		14 747	67	
Age at baseline						
mean (SD)	50.5 (11.2)	59.1 (7.22)	<0.001	50.6 (9.37)	56.7 (7.88)	<0.001
Sex						
Male	8,194 (23.3%)	28 (16.7%)	0.05	6,515 (44.2%)	38 (56.7%)	0.05
Female	26,912 (76.7%)	140 (83.3%)		8,232 (55.8%)	29 (43.3%)	
Education						
Low	21,986 (63.1%)	118 (71.1%)	0.09	4,503 (30.6%)	29 (43.3%)	0.08
Medium	6,075 (17.4%)	21 (12.7%)		4,609 (31.2%)	17 (25.4%)	
High	6,808 (19.5%)	27 (16.3%)		5,626 (38.2%)	21 (31.3%)	
Missing	237	2		9	0	
Marital status						
Partner	25,209 (72.2%)	118 (70.7%)	0.01	12,184 (82.8%)	50 (74.6%)	0.05
Divorced	2,767 (7.9%)	11 (6.6%)		886 (6.0%)	9 (13.4%)	
Widowed	1,965 (5.6%)	19 (11.4%)		346 (2.3%)	3 (4.5%)	
Single	4,975 (14.2%)	19 (11.4%)		1,307 (8.9%)	5 (7.5%)	
Missing	190	1		24	0	
Smoking status						
Never smoker	13,260 (37.9%)	82 (49.4%)	<0.001	6,710 (45.6%)	24 (35.8%)	0.07
Past smoker	11,278 (32.3%)	60 (36.1%)		5,711 (38.8%)	26 (38.8%)	
Current smoker	10,420 (29.8%)	24 (14.5%)		2,304 (15.6%)	17 (25.4%)	
Missing	148	2		22	0	
Body mass index						
Underweight	283 (0.8%)	1 (0.6%)	0.196	92 (0.6)	0	0.001
Normal	15,249 (43.5%)	61 (36.3%)		6,628 (45.1%)	20 (29.9%)	
Overweight	14,334 (40.9%)	82 (48.8%)		5,691 (38.7%)	25 (37.3%)	
Obese	5,215 (14.9%)	24 (14.3%)		2,282 (15.5%)	22 (32.8%)	
Missing	25	0		54	0	

BMI categories (see text).

AMIGO indicates Arbeid, Milieu en Gezondheid Onderzoek; EPIC-NL, European Prospective Investigation into Cancer and Nutrition in the Netherlands; PD, Parkinson's disease; SD, standard deviation.

Table 2.

Spearman correlations of TRAP and road traffic noise across both cohorts combined

	NO_2 (µg/m³)	NO_x (µg/m³)	$PM_{2.5abs}$ ($10^{-5}m^{-1}$)	PM_{coarse} (µg/m³)	$PM_{2.5}$ (µg/m³)	PM_{10} (µg/m³)	UFP (particl./cm³)
NO_2 (µg/m³)	1						
NO_x (µg/m³)	0.90	1					
$PM_{2.5abs}$ ($10^{-5}m^{-1}$)	0.78	0.84	1				
PM_{coarse} (µg/m³)	0.79	0.80	0.72	1			
$PM_{2.5}$ (µg/m³)	0.27	0.39	0.66	0.36	1		
PM_{10} (µg/m³)	0.82	0.85	0.89	0.82	0.42	1	
UFP (particl./cm³)	0.75	0.75	0.79	0.74	0.40	0.85	1
Road traffic noise L_{den} (dB)	0.46	0.52	0.46	0.50	0.25	0.50	0.51

dB indicates decibel; NO_2, nitrogen dioxide; NO_x nitrogen oxides; $PM_{2.5abs}$, marker for black carbon, PM_{coarse}, particulate matter 2.5 –10µm; $PM_{2.5}$, particulate matter ≤2.5 µm; PM_{10}, particulate matter ≤10 µm; road traffic noise L_{den}, day-evening-night level; TRAP, traffic-related air pollutants; UFP, ultrafine particles <0.1µm.

Table 3.

Parkinson's disease risk (OR) associated with air pollutants and road traffic noise in single-exposure logistic regression models

	Exposure quartile (range), midpoint	OR (95% CI)	*P* value for trend
NO_2 (µg/m³)	Q1 (10.3, 19.6), 14.90	Ref.	0.04
	Q2 (19.6, 23.2), 21.35	1.03 (0.67, 1.59)	
	Q3 (23.2, 28.4), 25.80	1.34 (0.90, 2.02)	
	Q4 (28.4, 68.4), 48.40	1.48 (0.99, 2.25)	
NO_x (µg/m³)	Q1 (17.3, 28.1), 22.75	Ref.	<0.001
	Q2 (28.1, 33.4), 30.75	1.27 (0.82, 1.99)	
	Q3 (33.4, 41.2), 37.30	1.53 (1.00, 2.37)	
	Q4 (41.2, 109), 75.10	2.08 (1.37, 3.22)	
$PM_{2.5}$ (µg/m³)	Q1 (15.0, 16.4), 15.7	Ref.	0.49
	Q2 (16.4, 16.7), 16.55	0.82 (0.55, 1.21)	
	Q3 (16.7, 17.1), 16.9	0.89 (0.62, 1.30)	
	Q4 (17.1, 21.0), 19.05	1.05 (0.73, 1.52)	
PM_{coarse} (µg/m³)	Q1 (7.60, 7.83), 7.72	Ref.	0.01
	Q2 (7.83, 8.15), 7.99	1.17 (0.80, 1.72)	
	Q3 (8.15, 8.67), 8.41	0.85 (0.56, 1.28)	
	Q4 (8.67, 14.2), 11.43	1.63 (1.13, 2.36)	
PM_{10} (µg/m³)	Q1 (23.7, 24.1), 23.9	Ref.	0.10
	Q2 (24.1, 24.6), 24.35	1.27 (0.84, 1.92)	
	Q3 (24.6, 25.7), 25.15	1.46 (0.98, 2.18)	
	Q4 (25.7, 34.7), 30.20	1.56 (1.04, 2.37)	
$PM_{2.5abs}$ ($10^{-5}m^{-1}$)	Q1 (0.85, 1.16), 1.00	Ref.	0.08
	Q2 (1.16, 1.28), 1.22	1.40 (0.92, 2.16)	
	Q3 (1.28, 1.42), 1.35	1.76 (1.16, 2.70)	
	Q4 (1.42, 2.9), 2.16	1.70 (1.10, 2.65)	
UFP (particles/cm³)	Q1 (7.19, 8.80), 8.0	Ref.	0.17
	Q2 (8.80, 9.92), 9.36	1.01 (0.68, 1.50)	
	Q3 (9.92, 11.9), 10.91	1.13 (0.75, 1.70)	
	Q4 (11.9, 42.1), 27.0	1.29 (0.87, 1.93)	
Road traffic noise L_{den} (dB)	Q1 (22.3, 51.8), 37.05	Ref.	0.005
	Q2 (51.8, 54.8), 53.30	0.86 (0.55, 1.34)	
	Q3 (54.8, 58.07), 56.45	1.47 (0.99, 2.18)	
	Q4 (58.07, 75.3), 66.70	1.64 (1.13, 2.43)	

P for trend based on an analysis on mid-points of quartile categories. Fully adjusted models.
CI, indicates confidence interval; dB, decibel; NO_2, nitrogen dioxide; NO_x nitrogen oxides; $PM_{2.5abs}$, marker for black carbon, PM_{coarse}, particulate matter 2.5–10µm; $PM_{2.5}$, particulate matter ≤2.5 µm; PM_{10}, particulate matter ≤10 µm; OR, odds ratio; PD, Parkinson's disease; road traffic noise L_{den}, day-evening-night level; UFP, ultrafine particles <0.1µm.

PM mass fractions ($PM_{2.5}$/PM_{10}). To the best of our knowledge, our study is the first to address the association between UFP and PD. We found no suggestion of an effect of UFP exposure on PD risk. In addition, only limited evidence was seen for the particulate mass fractions and PD. However, the observed effect with NO_x may suggest, especially considering the weaker association with NO_2, a potential role for primary traffic-related pollutants in PD pathology. Although we validated our UFP models previously, their historical relevance is less certain. Several studies have indicated that spatial variation of regulated air pollutants (i.e., NO_2, NO_x, and PM-fractions) and traffic noise exposure levels are stable over periods of about 10 years in Western countries,[28,29] but this is less clear for UFP where we found previously moderate correlations with historical measurements.[30] As PD pathology may have a long latency, the actual biologically relevant time window of exposure may be statistically more favorable to evaluate possible risks from the studied regulated pollutants than from UFP.

With the exception of UFP, we consistently observed the highest risk estimates of TRAP and noise on PD risk in EPIC-NL and AMIGO in the highest quartiles of exposure. However, individual estimates varied (ST2A and ST2B) and several characteristics between the cohorts may have contributed to this effect: at baseline, AMIGO cohort participants were slightly younger than EPIC-NL participants, had a much shorter time period of follow-up (5 vs. 20 years). It is therefore conceivable that PD cases in AMIGO with an average age of 57 years at baseline (Table 1) represented a fraction of younger and more severe PD cases as compared with EPIC-NL cases. Also, AMIGO participants were included in the cohort at a later point in time (2011 vs. 1993–1997), which may have affected diagnostic accuracy. Unfortunately, given the low number of PD cases in AMIGO with the resulting low statistical power, we were unable to disentangle possible underlying reasons for any differences in observed risk estimates at this point in time.

Air-pollutant exposures have been linked to α-synuclein aggregation in the midbrain, microglial activation and other signs of neuroinflammation, and the loss of dopaminergic neurons in the substantia nigra.[31–33] These findings have been interpreted as providing biological plausibility that exposure to ambient air pollution may affect PD occurrence.[34] Recent systematic reviews and meta-analyses of epidemiological studies generally reported associations between exposure to TRAP (especially NO_2, $PM_{2.5}$, ozone, carbon monoxide, or black carbon) and PD, although heterogeneity between study results was observed.[6–9,35,36] Differences across study results may be attributable to several factors, including the study population, the study design, the confounders that were taken into consideration, the statistical modeling used for the exposure assessment, or the way the outcome was assessed (incidence vs. mortality). It is also conceivable that in some studies other factors may contribute to the inability to identify underlying risks, such as low contrast in the exposure concentrations, generally quite low exposure levels,[9] or exposure to other pollutants that were not accounted for in the analysis, especially nontailpipe exposures.[6,9] Additionally, air pollutants can be highly correlated: in our study, NO_2 and NO_x concentrations had a Spearman correlation coefficient of 0.9, and similar patterns have been observed in other studies.[29,37] Such high correlations can hamper the ability to disentangle and clearly identify the underlying exposures associated with PD.

We extended our TRAP analyses by including road traffic noise because of previous reports linking road traffic noise to PD[16] and other neurological diseases such as dementia (including PD dementia).[38] A study in Madrid indicated a positive association between short-term road traffic noise and PD exacerbation.[16] Contrasting to our results, a registry-based study on PD in Vancouver, Canada, did not observe associations with residential noise exposure but instead found associations with NO_2 and $PM_{2.5}$.[11] Although the

Table 4.

Parkinson's disease risk (OR) associated with air pollutants and road traffic noise in two-pollutant logistic regression models

OR (95% CI) and P-trend			Adjusted for							
NO_2 (µg/m³)	Single-exposure		NO_2 (µg/m³)		NO_x (µg/m³)		$PM_{2.5}$ (µg/m³)		PM_{coarse} (µg/m³)	
Q1 (10.3, 19.6)	Ref.	0.04	—	—	Ref.	0.80	Ref.	0.10.	Ref.	0.49
Q2 (19.6, 23.2)	1.03 (0.67, 1.59)		—		0.96 (0.62, 1.50)		1.00 (0.65, 1.54)		1.00 (0.65, 1.53)	
Q3 (23.2, 28.4)	1.34 (0.90, 2.02)		—		1.16 (0.75, 1.83)		1.30 (0.87, 1.97)		1.22 (0.80, 1.89)	
Q4 (28.4, 68.4)	1.48 (0.99, 2.25)		—		1.11 (0.63, 1.97)		1.39 (0.91, 2.14)		1.22 (0.74, 2.04)	
NO_2 (µg/m³)			PM_{10} (µg/m³)		$PM_{2.5abs}$ ($10^{-5}m^{-1}$)		UFP (particles/cm³)		Road traffic noise L_{den} (dB)	
Q1 (10.3, 19.6)			Ref.	0.17	Ref.	0.44	Ref.	0.14	Ref.	0.48
Q2 (19.6, 23.2)			0.97 (0.65, 1.54)		0.99 (0.64, 1.53)		1.03 (0.67, 1.60)		0.93 (0.60, 1.43)	
Q3 (23.2, 28.4)			1.23 (0.81, 1.89)		1.24 (0.81, 1.92)		1.35 (0.89, 2.07)		1.13 (0.75, 1.73)	
Q4 (28.4, 68.4)			1.18 (0.68, 2.04)		1.25 (0.74, 2.16)		1.50 (0.90, 2.52)		1.13 (0.73, 1.77)	
NO_x (µg/m³)			NO_2 (µg/m³)		NO_x (µg/m³)		$PM_{2.5}$ (µg/m³)		PM_{coarse} (µg/m³)	
Q1 (17.3, 28.1)	Ref.	<0.001	Ref.	0.006	—	—	Ref.	0.01	Ref.	0.009
Q2 (28.1, 33.4)	1.27 (0.82, 1.99)		1.40 (0.88, 2.23)		—		1.26 (0.81, 1.98)		1.27 (0.81, 1.99)	
Q3 (33.4, 41.2)	1.53 (1.00, 2.37)		1.86 (1.09, 3.20)		—		1.51 (0.98, 2.35)		1.51 (0.97, 2.40)	
Q4 (41.2, 109)	2.08 (1.37, 3.23)		2.88 (1.47, 5.63)		—		2.03 (1.30, 3.22)		2.05 (1.23, 3.45)	
NO_x (µg/m³)			PM_{10} (µg/m³)		$PM_{2.5abs}$ ($10^{-5}m^{-1}$)		UFP (particles/cm³)		Road traffic noise L_{den} (dB)	
Q1 (17.3, 28.1)			Ref.	0.009	Ref.	0.004	Ref.	<0.001	Ref.	0.04
Q2 (28.1, 33.4)			1.29 (0.83, 2.01)		1.31 (0.84, 2.08)		1.29 (0.83, 2.02)		1.17 (0.76, 1.85)	
Q3 (33.4, 41.2)			1.57 (1.00, 2.50)		1.63 (1.03, 2.64)		1.66 (1.07, 2.62)		1.34 (0.87, 2.10)	
Q4 (41.2, 109)			2.25 (1.27, 3.97)		2.39 (1.35, 4.28)		2.49 (1.50, 4.15)		1.62 (1.02, 2.62)	
Road traffic noise L_{den} (dB)			NO_2 (µg/m³)		NO_x (µg/m³)		$PM_{2.5}$ (µg/m³)		PM_{coarse} (µg/m³)	
Q1 (22.3, 51.8)	Ref.	0.005	Ref.	0.03	Ref.	0.05	Ref.	0.01	Ref.	0.04
Q2 (51.8, 54.8)	0.86 (0.55, 1.34)		0.83 (0.53, 1.30)		0.84 (0.54, 1.30)		0.86 (0.55, 1.34)		0.84 (0.54, 1.31)	
Q3 (54.8, 58.07)	1.47 (1.00, 2.18)		1.38 (0.93, 2.09)		1.39 (0.93, 2.09)		1.46 (0.99, 2.17)		1.39 (0.93, 2.10)	
Q4 (58.07, 75.3)	1.64 (1.13, 2.43)		1.51 (1.00, 2.29)		1.47 (0.97, 2.25)		1.60 (1.07, 2.38)		1.51 (1.01, 2.29)	
Road traffic noise L_{den} (dB)			PM_{10} (µg/m³)		$PM_{2.5abs}$ ($10^{-5}m^{-1}$)		UFP (particles/cm³)		Road traffic noise L_{den} (dB)	

(Continued)

Table 4.
(Continued)

OR (95% CI) and P-trend				Adjusted for			
NO_2 (µg/m³)	Single-exposure	NO_2 (µg/m³)	NO_x (µg/m³)		$PM_{2.5}$ (µg/m³)		PM_{coarse} (µg/m³)
Q1 (22.3, 51.8)		Ref.	Ref.	0.03	Ref.	0.01	— — —
Q2 (51.8, 54.8)		0.85 (0.54, 1.32)	0.85 (0.55, 1.33)		0.86 (0.55, 1.34)		— — —
Q3 (54.8, 58.07)		1.41 (0.94, 2.11)	1.42 (0.96, 2.13)		1.46 (0.98, 2.20)		— — —
Q4 (58.07, 75.3)		1.51 (1.00, 2.29)	1.54 (1.02, 2.34)		1.64 (1.09, 2.49)		— — —
P-trend	0.04						

Odds ratio ([95% confidence interval) and *P* value for trend. The models for these analyses were adjusted for age, age-squared, sex, education, marital status, smoking status, BMI category and cohort.
P for trend based on an analysis on mid-points of quartile categories.
CI, indicates confidence interval; dB, decibel; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5abs}$, marker for black carbon, PM_{coarse}, particulate matter 2.5–10µm; $PM_{2.5}$, particulate matter ≤2.5 µm; PM_{10}, particulate matter ≤10 µm; OR, odds ratio; PD, Parkinson's disease; road traffic noise L_{den}, day-evening-night level; UFP, ultrafine particles <0.1µm.

epidemiological evidence for an association between road traffic noise and PD remains weak, there is biological support suggesting noise exposure can influence neurological diseases through induced stress reactions,[39] and through sleep disturbance, which could lead to systemic inflammation.[40,41]

In conclusion, our study adds to the existing evidence base that TRAP, in particular NO_x, is associated with an increased risk of PD. We extend the evidence base by suggesting that, next to TRAP, road traffic noise may have an independent effect on PD development. Given the small evidence base on the potential effect of noise on PD risk, further studies carefully accounting for multiple air pollutants are warranted.

Conflicts of interest

The authors declare that they have no conflicts of interest with regard to the content of this report.

Acknowledgements

The authors are grateful to Inka Pieterson for data management.

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