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Air pollution exposure and mortality from neurodegenerative diseases in the Netherlands: A population-based cohort study

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ABSTRACT

Background: Long-term exposure to ambient air pollution has been linked with all-cause mortality and cardiovascular and respiratory diseases. Suggestive associations between ambient air pollutants and neurodegeneration have also been reported, but due to the small effect and relatively rare outcomes evidence is yet inconclusive. Our aim was to investigate the associations between long-term air pollution exposure and mortality from neurodegenerative diseases.

Methods: A Dutch national cohort of 10.8 million adults aged ≥30 years was followed from 2013 until 2019. Annual average concentrations of air pollutants (ultra-fine particles (UFP), nitrogen dioxide (NO_2), fine particles ($PM_{2.5}$ and PM_{10}) and elemental carbon (EC)) were estimated at the home address at baseline, using land-use regression models. The outcome variables were mortality due to amyotrophic lateral sclerosis (ALS), Parkinson's disease, non-vascular dementia, Alzheimer's disease, and multiple sclerosis (MS). Hazard ratios (HR) were estimated using Cox models, adjusting for individual and area-level socio-economic status covariates.

Results: We had a follow-up of 71 million person-years. The adjusted HRs for non-vascular dementia were significantly increased for NO_2 (1.03; 95% confidence interval (CI) 1.02–1.05) and $PM_{2.5}$ (1.02; 95%CI 1.01–1.03) per interquartile range (IQR; 6.52 and 1.47 μg/m^3, respectively). The association with $PM_{2.5}$ was also positive for ALS (1.02; 95%CI 0.97–1.07). These associations remained positive in sensitivity analyses and two-pollutant models. UFP was not associated with any outcome. No association with air pollution was found for Parkinson's disease and MS. Inverse associations were found for Alzheimer's disease.

Conclusion: Our findings, using a cohort of more than 10 million people, provide further support for associations between long-term exposure to air pollutants ($PM_{2.5}$ and particularly NO_2) and mortality of non-vascular dementia. No associations were found for Parkinson and MS and an inverse association was observed for Alzheimer's disease.

1. Introduction

Research on the long-term effects of exposure to ambient air pollution has been largely focused on outcomes of all-cause mortality and cardiovascular and respiratory diseases (Hoek et al., 2013; Chen and Hoek, 2020; Cohen et al., 2017). Specifically, traffic-related air pollutants, such as nitrogen dioxide (NO_2), and particulate matter (PM) have been associated with cardiorespiratory mortality (Hoek et al., 2013). The World Health Organization therefore recommended new air quality levels in 2021 to decrease the global health burden resulting from exposure to air pollution (WHO, 2021).

The global number of people living with neurodegenerative diseases has increased substantially between 1990 and 2016 (GBD Dementia Collaborators, 2019a; Collaborators GBDPsD, 2018; GBD Motor Neuron Disease Collaborators, 2018; GBD Multiple Sclerosis Collaborators, 2019b) and associations with ambient air pollution have been suggested, although findings are not consistent. For dementia, for example, associations with exposures to NO_2, nitrogen oxides (NO_x), and PM have been suggested in the literature (Wilker et al., 2023; Livingston et al., 2020). A systematic review and meta-analysis on ambient air pollutants and Parkinson's disease indicated possible adverse associations between long-term exposure to $PM_{2.5}$, NO_2, ozon (O_3) and carbon monoxide (CO)

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and the risk of Parkinson, as well as short-term exposure to $PM_{2.5}$ increasing the aggravation of Parkinson (Kasdagli et al., 2019). Heterogeneity across the studies, however, was high. In a large Korean cohort study, a significant association was observed between NO_2 exposure and Parkinson's disease, but not for the other air pollutants, (Jo et al., 2021) whereas a US study reported significant associations with exposure to $PM_{2.5}$ (Shi et al., 2020). A Dutch case-control study, on the other hand, observed no associations between ambient air pollution and risk of Parkinson (Toro et al., 2019). Interestingly, exposure to $PM_{2.5}$ and NO_x was found to be associated with olfactory decline in older adults in Sweden, which may be an early sign of Parkinson's disease or dementia (Ekstrom et al., 2022).

There seem to be more consistent findings for amyotrophic lateral sclerosis (ALS), with several case-control studies reporting on associations with long-term exposure to traffic-related air pollution (including NO_2, $PM_{2.5}$, and elemental carbon (EC)), (Povedano et al., 2018; Seelen et al., 2017; Yu et al., 2021; Parks et al., 2022; Nunez et al., 2023) although evidence is yet limited. Few cohort studies have been published on (adult onset) multiple sclerosis (MS) and ambient air pollution, in which no associations were observed (Bai et al., 2018; Chen et al., 2017; Palacios et al., 2017).

Effects of particulate matter on the central nervous system, which include oxidative stress and neuro-inflammation, are possible explanations for the mechanism underlying the observed associations (Block et al., 2009; Costa et al., 2020). Furthermore, exposure to air pollution has been associated with increased expression of alpha-synuclein and beta-amyloid, as well as damage to the blood-brain barrier (Block et al., 2009; Costa et al., 2020).

Overall, suggestive associations between ambient air pollutants and neurodegeneration have been reported in the literature, but due to the small effect and relatively rare outcomes further large studies are needed to evaluate these associations. We therefore aimed to investigate the associations between long-term air pollution exposure and mortality from neurodegenerative diseases in a Dutch general population cohort of over 10 million people.

2. Methods

2.1. Study population, covariate and outcome variables

We created an administrative cohort consisting of 10.8 million adults in the Netherlands, aged 30 years and older on January 1st, 2013. Several databases from Statistics Netherlands (CBS), including the mortality, population, and tax registries, were used to create and follow the cohort. Methods have been described in more detail in previous air pollution analyses in this cohort (Bouma et al., 2023). Area-level indicators of socio-economic status (SES) (including mean income; percentage non-Western immigrants; unemployment rate; social assistance; and percentage of low education) were assessed for 2012 at both the neighbourhood level (n=11,900, representing on average approximately 600 addresses) and the regional level (Nomenclature of Territorial Units for Statistics (NUTS) level 3, n = 40). When the indicator was not available at the neighbourhood level, for example due to privacy concerns related to small numbers, the indicator at the district level (n=2,600, representing about 2900 addresses) was assigned to the specific neighbourhood.

Mortality based on the International Classification of Diseases 10th Revision (ICD-10) codes was followed-up from 1 January 2013 until 31 December 2019. We considered deaths from the following neurodegenerative diseases: ALS (G12.2), Parkinson's disease (G20), non-vascular dementia (G30; F03), Alzheimer's disease (G30), and multiple sclerosis (G35). The code F00 used in some studies, is not used on Dutch death certificates. These diseases had to be listed on the death certificate as the primary cause of death. Since 2013, causes of death are automatically coded. To prevent potential bias due to the COVID-19 pandemic, we ended follow-up in 2019.

2.2. Exposure assessment

The methods for assessing the exposure to air pollutants in this cohort have been described previously by Bouma et al. (2023) In brief, a nationwide land-use regression (LUR) model was used to predict the annual average outdoor UFP concentration at each residential address (Kerckhoffs et al., 2021). The model was based on a mobile monitoring of more than 14,000 road segments across the Netherlands in 2016–2017, and three times 14-days average regional background measurements coinciding with the mobile monitoring campaign. Because of the lack of routine monitoring data of UFP across the country, external validation for the UFP model was not possible. The UFP model explained 60% of the variation of measured average UFP concentrations at 42 sites in the cities of Amsterdam and Utrecht combined (Kerckhoffs et al., 2021). Similarly, the annual average exposures to $PM_{2.5}$, PM_{10}, NO_2, and EC in 2016 were estimated based on validated national dispersion models (Velders Gjmm et al., 2020; Wesseling et al., 2016). These models are based on nationwide and European regulatory emission databases and first developed models for 1 by 1 km grid average concentrations were supplemented with fine resolution (25 by 25m) models including traffic line sources (separate for urban and highway traffic) and large industrial point sources. The models explained variation of average concentrations measured in the national air quality monitoring network well, but the exact statistics are difficult to interpret because in earlier years dispersion models were calibrated to the measurements. Air pollution exposures were assigned to the residential address using the standard geo-coded database of buildings in the Netherlands. We did not have information on work address or time activity patterns in this administrative cohort.

2.3. Data analysis

We evaluated associations between air pollution exposure and mortality from neurodegenerative diseases with Cox proportional hazards models. Our analytical procedures followed previous analyses in this and other cohorts (Bouma et al., 2023; Stafoggia et al., 2022; Strak et al., 2021). Age was used as the time scale to limit possible confounding by age and the models were stratified by sex because of previous observations of non-proportional hazards. Following our previous studies, we *a priori* developed three confounder models. Model 1 only included age (time axis) and sex (strata). In model 2, we additionally adjusted for covariates at the individual level (marital status, region of origin (including Dutch, Western, Non-Western) and standardized household income), that were available in registries, including the population and tax registries. In model 3, we additionally adjusted for area-level (neighbourhood and region) SES variables. These area-level variables included mean income per income recipient, unemployment rate, social assistance, percentage non-Western immigrants, and percentage of low education level on the neighbourhood and regional level (Table S1). Model 3 was considered our main model. Following previous analyses, we preferred to address area-level confounding by including indicators of SES at neighbourhood and regional scale in the main model as these are more directly linked to health than urbanicity.

As sensitivity analyses, we additionally adjusted for urbanicity (five categories), limited the analyses to subjects who had lived at their baseline address for five years or more, limited the analyses to subjects who were 60 years or older at baseline, and applied the indirect adjustment method for smoking (Bouma et al., 2023; Stafoggia et al., 2022). Exposure was entered as a static variable, specifically for the year 2016. Given the short follow-up period and previous documentation of stable spatial contrasts of outdoor air pollution, we did not specify time-varying exposure analyses. Two-pollutant models were applied to assess potential mutual confounding.

We conducted all statistical analyses in R (https://www.R-project.org/), version 3.6.2.

3. Results

The mean age of the cohort at baseline was 54.3 years and most subjects were of Dutch origin (Table 1). Area-level characteristics are presented in Table S1. During 7,008,209 person-years of follow-up of 10,735,734 subjects, 3300 ALS deaths were recorded, 11,410 cases of Parkinson mortality, 88,822 cases of non-vascular dementia mortality (of whom 25,236 cases of Alzheimer's disease mortality) and 1756 cases of MS mortality (Table 2).

Interquartile ranges (IQRs) for the exposure estimates were 2723 particles/cm^3 UFP; 6.52 μg/m^3 NO_2; 2.06 μg/m^3 PM_{10}; 1.47 μg/m^3 $PM_{2.5}$; and 0.24 μg/m^3 EC (Table S2). PM_{10} and $PM_{2.5}$ were highly correlated (Pearson's R = 0.92), as was EC with both NO_2 (R = 0.93) and $PM_{2.5}$ (R = 0.90) (Table S3).

The individual- and area-level adjusted HRs for non-vascular dementia were significantly increased for NO_2 (1.03; 95% confidence interval (CI) 1.02–1.05), PM_{10} (1.02 (1.00–1.03)), $PM_{2.5}$ (1.02; 95%CI 1.01–1.03) and EC 1.02 (1.01–1.03)) (Table 3). These associations remained positive for NO_2 and $PM_{2.5}$ in the sensitivity analyses (Table S4), including further adjustment for urbanicity. For ALS, the associations were non-significantly positive with UFP (1.01 (0.96–1.06)), NO_2 (1.01 (0.94–1.09)), $PM_{2.5}$ (1.02; 95%CI 0.97–1.07), and EC (1.01 (0.94–1.07) (Table 3). In two-pollutant models for non-vascular dementia, associations were most consistent for NO_2, whereas the associations for the other pollutants were mostly attenuated towards unity (Table 4). There was no indication for an increased risk of Parkinson's disease, Alzheimer's disease or MS with any of the air pollutants (Table 3), with most HRs being non-significantly below unity. For Alzheimer's disease, HRs for NO_2, $PM_{2.5}$, and EC were significantly below unity, which effects remained for $PM_{2.5}$ and EC in the two-pollutant models (Table 4). Also for MS, HRs were signicanly lower than 1 for some pollutants.

Unadjusted and individual-level adjusted models are shown in Table S4. In general, differences in HRs between the models were modest. For non-vascular dementia, HRs increased after adjustment for individual level covariates and decreased after adjustment for area-level confounders. For Alzheimer disease, HRs were generally significantly increased in the crude and individual models, but below unity in the main model further adjusting for area-level variables. Indirect adjustment for smoking resulted in associations that were very similar to the main model associations. Two-pollutant models for all diseases are presented in Table S5.

Table 1
Characteristics of the study population at baseline.

		Mean (sd) or N (%)
Age		54.3 (15.0)
Sex	Male	5,227,876 (48.7%)
	Female	5,507,858 (51.3%)
Marital status	Married	6,554,479 (61.1%)
	Widowed	852,964 (7.9%)
	Divorced	1,174,803 (10.9%)
	Single	2,153,488 (20.1%)
Region of origin	Dutch	8,732,131 (81.3%)
	Western	1,055,828 (9.8%)
	Other non-Western	319,633 (3.0%)
	Suriname	200,271 (1.9%)
	Turkey	197,419 (1.8%)
	Morocco	163,338 (1.5%)
	Antilles Netherlands	67,114 (0.6%)
Standardized household income	<1%	141,753 (1.3%)
	1–5%	192,802 (1.8%)
	5–10%	347,895 (3.2%)
	10–25%	1,306,536 (12.2%)
	25–50%	2,610,783 (24.3%)
	50–75%	2,920,752 (27.2%)
	75–90%	1,894,331 (17.6%)
	90–95%	657,075 (6.1%)
	95–99%	532,320 (5.0%)
	>99%	131,487 (1.2%)

Table 2
Description of mortality outcomes (persons at risk n = 10,735,734; person-years at risk n = 71,008,209).

Disease group	ICD-10	**Deaths (n)**	**Median age at death**	**Male (n)**	**Female (n)**
Amyotrophic Lateral Sclerosis	G12.2	3300	70.6	1800	1500
Parkinson's Disease	G20	11,410	82.2	6689	4721
Non-vascular dementia	G30, F03	88,822	87.5	27,574	61,248
Alzheimer's Disease	G30	25,236	86.7	7993	17,243
Multiple sclerosis	G35	1756	64.7	660	1096

4. Discussion

In this population-based cohort study, we observed an increased risk of mortality from non-vascular dementia associated with long-term exposure to air pollutants, specifically NO_2 and $PM_{2.5}$. Associations with NO_2 remained positive in two-pollutant models and sensitivity analyses. No associations were found for Parkinson and MS and inverse associations were observed for Alzheimer's disease. For ALS mortality, a non-significant positive association was observed with $PM_{2.5}$.

4.1. Non-vascular-dementia and Alzheimer's disease

Our findings for non-vascular dementia are in line with previous studies, which also indicated $PM_{2.5}$ and NO_2 to be associated with dementia (Shi et al., 2020; Delgado-Saborit et al., 2021). Remarkably, we did not see the same associations when limited to Alzheimer's disease, which comprised about 30% of all non-vascular dementia deaths. Instead, we observed an inverse association between NO_2, $PM_{2.5}$ and EC and Alzheimer's disease. We do not have a clear explanation for the negative associations with Alzheimer's disease, but note these associations appeared in the fully adjusted model. Overadjustment could be an explanation, though we never observed this with other outcomes (Bouma et al., 2023; Stafoggia et al., 2022). Another speculation is undefined differences in coding of type of dementia across the country.

This observation may indicate that the observed positive associations for NO_2 and $PM_{2.5}$ were mainly with the other dementias, but case ascertainment on death certificates has its limitations. Specificity is typically high and reporting of dementia has improved over time, but a recent study in England and Wales showed that still less than half of dementia cases were reported on death certificates (Gao et al., 2018). Dementia as (underlying) cause of death is more often recorded when it is severe, or when death occurred in a long-term care facility. When an individual died in a hospital, dementia was less likely to be recorded (Gao et al., 2018). Furthermore, the vast majority of dementia deaths recorded are unspecified (±70%), (Gao et al., 2018) which is similar to what we observed in our study, while Alzheimer's disease is the most common type of dementia that may account for 60–70% of all cases (WHO, 2023). Hence, cautiousness is warranted in drawing conclusions regarding associations between exposure to ambient air pollutants and type of dementia based on death certificates.

4.2. Amyotrophic lateral sclerosis

We observed a positive, though non-significant, association between $PM_{2.5}$ and ALS in our cohort, which has also been reported in a Danish population-based case-control study (Nunez et al., 2023). In other ALS studies, however, associations with NO_2 (Seelen et al., 2017; Yu et al., 2021), $PM_{2.5}$ absorbance, (Seelen et al., 2017) and EC (Parks et al., 2022) were reported based on multi-pollutant models. We did not

Table 3
Hazard ratios and 95% CIs of long-term exposure to air pollution and neurodegenerative mortality outcomes per IQR increment[a].

	ALS	Parkinson's disease	Non-vascular dementia	Alzheimer's disease	Multiple sclerosis
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
UFP	1.01 (0.96–1.06)	0.99 (0.97–1.02)	0.99 (0.98–1.00)	1.00 (0.98–1.01)	1.00 (0.94–1.06)
NO_2	1.01 (0.94–1.09)	0.98 (0.94–1.02)	1.03 (1.02–1.05)	0.96 (0.94–0.99)	0.97 (0.87–1.07)
PM_{10}	0.99 (0.93–1.06)	0.99 (0.95–1.02)	1.02 (1.00–1.03)	0.98 (0.96–1.01)	0.89 (0.81–0.98)
$PM_{2.5}$	1.02 (0.97–1.07)	0.99 (0.96–1.02)	1.02 (1.01–1.03)	0.96 (0.94–0.98)	0.91 (0.84–0.97)
EC	1.01 (0.94–1.07)	0.98 (0.95–1.02)	1.02 (1.01–1.03)	0.95 (0.93–0.97)	0.97 (0.89–1.06)

Strata for sex, age as time axis and adjusted for individual-level covariates (marital status, region of origin, standardized household income), and area-level (neighbourhood and region) covariates (mean income, unemployment rate, social assistance, % non-Western immigrants, and % low education level).
[a] IQRs for UFP 2723 particles/cm^3; NO_2 6.52 μg/m^3; PM_{10} 2.06 μg/m^3; $PM_{2.5}$ 1.47 μg/m^3; EC 0.24 μg/$m.^3$.

Table 4
Two-pollutant models with the main effects of UFP, NO_2, PM_{10}, $PM_{2.5}$, and EC for neurodegenerative mortality. HR per IQR increment, main model.

	Main model	Adj. for UFP	Adj. for NO_2	Adj. for PM_{10}	Adj. for $PM_{2.5}$	Adj. for EC
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ALS						
UFP	1.01 (0.96–1.06)	–	1.01 (0.95–1.07)	1.01 (0.96–1.07)	1.00 (0.95–1.06)	1.01 (0.95–1.07)
NO_2	1.01 (0.94–1.09)	1.00 (0.91–1.11)	–	1.03 (0.92–1.16)	0.98 (0.88–1.10)	1.01 (0.85–1.20)[a]
PM_{10}	0.99 (0.93–1.06)	0.98 (0.91–1.06)	0.97 (0.88–1.07)	–	0.86 (0.73–1.01)[a]	0.96 (0.86–1.08)
$PM_{2.5}$	1.02 (0.97–1.07)	1.02 (0.96–1.08)	1.03 (0.95–1.11)	1.13 (1.00–1.28)[a]	–	1.05 (0.95–1.17)[a]
EC	1.01 (0.94–1.07)	1.00 (0.93–1.08)	1.00 (0.86–1.16)[a]	1.03 (0.93–1.157)	0.95 (0.84–1.09)[a]	–
Non-vascular dementia						
UFP	0.99 (0.98–1.00)	–	0.97 (0.96–0.98)	0.98 (0.97–0.99)	0.98 (0.97–0.99)	0.97 (0.96–0.98)
NO_2	1.03 (1.02–1.05)	1.07 (1.05–1.09)	–	1.04 (1.02–1.06)	1.03 (1.01–1.05)	1.05 (1.02–1.09)[a]
PM_{10}	1.02 (1.00–1.03)	1.03 (1.02–1.05)	0.99 (0.97–1.01)	–	0.98 (0.95–1.01)[a]	1.00 (0.97–1.02)
$PM_{2.5}$	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.00 (0.99–1.02)	1.03 (1.01–1.06)[a]	–	1.01 (0.99–1.03)[a]
EC	1.02 (1.01–1.03)	1.04 (1.03–1.06)	0.98 (0.95–1.01)[a]	1.02 (1.00–1.05)	1.01 (0.98–1.03)[a]	–
Alzheimer's disease						
UFP	1.00 (0.98–1.01)	–	1.02 (1.00–1.04)	1.01 (0.99–1.02)	1.02 (1.00–1.04)	1.03 (1.01–1.05)
NO_2	0.96 (0.94–0.99)	0.94 (0.91–0.96)	–	0.94 (0.91–0.98)	1.01 (0.97–1.05)	1.07 (1.01–1.15)[a]
PM_{10}	0.98 (0.96–1.01)	0.98 (0.95–1.01)	1.02 (0.96–1.06)	–	1.19 (1.13–1.26)[a]	1.08 (1.03–1.12)
$PM_{2.5}$	0.96 (0.94–0.98)	0.95 (0.93–0.97)	0.95 (0.93–0.98)	0.85 (0.81–0.89)[a]	–	0.97 (0.93–1.01)[a]
EC	0.95 (0.93–0.97)	0.93 (0.91–0.96)	0.90 (0.85–0.95)[a]	0.90 (0.86–0.93)	0.99 (0.94–1.03)[a]	–

[a] These two-pollutant models are difficult to interpret because of high correlations (R=>0.90) between components (see Table S3).

observe these in our population, as any suggestion of these associations attenuated to unity when adjusted for $PM_{2.5}$ (Table 3). The association with $PM_{2.5}$ is also supported by a US study on ALS aggravation, which further suggested that organic matter in $PM_{2.5}$ was the most relevant component (Nunez et al., 2022). The Danish study further indicated that $PM_{2.5}$ exposure within six years before diagnosis represented the critical time window for ALS (Nunez et al., 2023). Since ALS has a poor prognosis, with a median survival of about 30 months after the first symptoms, (Kiernan et al., 2011) we have captured this period in our models. Moreover, the registration of ALS mortality in the Netherlands appeared to be representative of the clinically diagnosed cases (de Jongh et al., 2021).

4.3. Parkinson's disease

Although previous studies reported on suggestive associations between various air pollutants and the risk of Parkinson's disease (Kasdagli et al., 2019; Jo et al., 2021; Shi et al., 2020; Cole-Hunter et al., 2023; Lomme et al., 2023; Krzyzanowski et al., 2023), none of these associations was confirmed in our study. One explanation may be that we relied on mortality data, whereas mean duration from Parkinson diagnosis until death ranges between 7 and 14 years and before the diagnosis there is typically a prodromal phase of many years, (Macleod et al., 2014; Siderowf and Lang, 2012) so that we did not capture the most relevant exposure period. Furthermore, Parkinson will be underreported on death certificates, although the number of false positives will be low (Phillips et al., 1999). Finally, we were not able to adjust for individual lifestyle factors, such as smoking, which is inversely associated with risk of Parkinson's disease (Gallo et al., 2019). In an earlier Dutch case-control study where we were able to adjust for lifestyle factors, however, we also did not observe any association with air pollutants (Toro et al., 2019). The evidence for associations between ambient air pollution and the risk of Parkinson is therefore still insufficient.

4.4. Multiple sclerosis

For MS, our null-findings confirmed the previous reports from population-based cohorts from the US and Canada (Bai et al., 2018; Palacios et al., 2017). We identified MS cases via mortality records, however, which may have resulted in an underestimation of the number of cases. We may also not have captured the most relevant exposure period, since the median survival time for MS is 38 years from symptom onset (Hirst et al., 2008).

4.5. Potential biases

The inability of taking into account individual smoking could have affected our findings, as smoking has been associated with an increased risk of non-vascular dementia, Alzheimer's disease, ALS and MS (Zhong et al., 2015; Peters et al., 2020; Ascherio and Munger, 2016). Earlier analyses within the Netherlands showed similar $PM_{2.5}$ exposure levels across smoking strata, and mildly higher NO_2 concentrations for current smokers compared with never smokers (Klompmaker et al., 2021). Sensitivity analyses using indirect adjustment methods for smoking showed virtually the same results as the main model (Table S4), suggesting that missing smoking data for the full cohort (the most important missing lifestyle factor), likely has not biased our associations. The small change in effect estimates is consistent with observations in the Netherlands from other outcomes (Bouma et al., 2023) and explained by the weak relationship between air pollution exposure and smoking. We

further note that we adjusted in detail for SES at the individual, neighbourhood and regional level. We included multiple indicators of SES. This is important as relationships between air pollution and lifestyle factors, such as smoking, are likely mediated through SES. Despite all efforts, we cannot fully exclude residual confounding.

UFP was not associated with any of the outcomes, in contrast to our findings for natural cause, cardiovascular, respiratory and lung cancer mortality (Bouma et al., 2023). UFP was hypothesized to be associated with neurodegenerative outcomes, because of experimental evidence including its ability to enter the bloodstream and pass the blood brain barrier (Block et al., 2009). For UFP, there was only a suggested association with ALS, which was in line with findings from a case-control study in the Netherlands, (Yu et al., 2021) but this association attenuated when adjusting for $PM_{2.5}$. Given our previous work in the same cohort on other outcomes (*e.g.,* cardiovascular and respiratory mortality (Bouma et al., 2023; Klompmaker et al., 2021)) where we did observe clear associations with individual air pollutants (including UFP), the study design as well as the exposure assessment method have shown to perform as expected. Hence, if there was an association in this cohort, we would have been able to detect these.

We assessed exposure for a single year (2016), because this was the only year for which UFP data were available. We thus assessed exposure in the middle of the follow-up period. Previous studies have documented that spatial contrasts in air pollution are stable for multiple years (Strak et al., 2021). We did not use time-varying exposure models because we were unable to assess UFP exposure for multiple years and because we hypothesized that the biologically relevant exposure is not exposure in the specific year of the event, but a prolonged period before the event.

Because of high correlations between some pollutants (*e.g.,* EC and NO_2; Table S3), we were limited in our ability to separate assocoiations of all pollutants. Most two-pollutant models did not show substantial variance inflation, as indicated by similar width of the confidence intervals compared to single pollutant models, suggesting these models should be intepreted with caution. For a more detailed discussion, we refer to previous work (Strak et al., 2021). We interpreted both single and two-pollutant models and therefore conclude on associations between air pollutants and non-vascualr dementia.

We ended follow-up in 2019, because of concerns with potential bias related to the COVID-19 pandemic. Death certificates of people who died during the pandemic may be biased as neurodegeneration would not be listed as cause of death. Moreover, disproportional mortality of people with dementia during the COVID pandemic has been reported (Livingston et al., 2020).

In conclusion, our study provides further support for possible associations between long-term exposure to air pollution ($PM_{2.5}$ and especially NO_2) and mortality of non-vascular dementia. No associations were found for Parkinson and MS and an inverse association was observed for Alzheimer's disease.

Ethics approval

Approval for this study was provided by the authorized review board of Statistics Netherlands (7267).

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CRediT authorship contribution statement

Susan Peters: Writing – original draft, Conceptualization. **Femke Bouma:** Writing – review & editing, Formal analysis. **Gerard Hoek:** Writing – review & editing, Methodology, Conceptualization. **Nicole Janssen:** Writing – review & editing, Methodology, Conceptualization. **Roel Vermeulen:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119552.

References

Ascherio, A., Munger, K.L., 2016. Epidemiology of multiple sclerosis: from risk factors to prevention-an update. Semin. Neurol. 36 (2), 103–114.
Bai, L., Burnett, R.T., Kwong, J.C., et al., 2018. Long-term exposure to air pollution and the incidence of multiple sclerosis: a population-based cohort study. Environ. Res. 166, 437–443.
Block, M.L., Calderon-Garciduenas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32 (9), 506–516.
Bouma, F., Janssen, N.A., Wesseling, J., et al., 2023. Long-term exposure to ultrafine particles and natural and cause-specific mortality. Environ. Int. 175, 107960.
Chen, J., Hoek, G., 2020. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. Environ. Int. 143, 105974.
Chen, H., Kwong, J.C., Copes, R., et al., 2017. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. Lancet 389 (10070), 718–726.
Cohen, A.J., Brauer, M., Burnett, R., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389 (10082), 1907–1918.
Cole-Hunter, T., Zhang, J., So, R., et al., 2023. Long-term air pollution exposure and Parkinson's disease mortality in a large pooled European cohort: an ELAPSE study. Environ. Int. 171, 107667.
Costa, L.G., Cole, T.B., Dao, K., Chang, Y.C., Coburn, J., Garrick, J.M., 2020. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. Pharmacol. Ther. 210, 107523.
de Jongh, A.D., van Eijk, R.P.A., Peters, S.M., et al., 2021. Incidence, prevalence, and geographical clustering of motor neuron disease in The Netherlands. Neurology 96 (8), e1227–e1236.
Delgado-Saborit, J.M., Guercio, V., Gowers, A.M., Shaddick, G., Fox, N.C., Love, S., 2021. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. Sci. Total Environ. 757, 143734.
Ekstrom, I.A., Rizzuto, D., Grande, G., Bellander, T., Laukka, E.J., 2022. Environmental air pollution and olfactory decline in aging. Environ. Health Perspect. 130 (2), 27005.
Gallo, V., Vineis, P., Cancellieri, M., et al., 2019. Exploring causality of the association between smoking and Parkinson's disease. Int. J. Epidemiol. 48 (3), 912–925.
Gao, L., Calloway, R., Zhao, E., et al., 2018. Accuracy of death certification of dementia in population-based samples of older people: analysis over time. Age Ageing 47 (4), 589–594.
Collaborators GbdpsD, 2018. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17 (11), 939–953.
GBD Motor Neuron Disease Collaborators, 2018. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17 (12), 1083–1097.

Collaborators, G.B.D.D., 2019a. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18 (1), 88–106.
Collaborators, G.B.D.M.S., 2019b. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18 (3), 269–285.
Hirst, C., Swingler, R., Compston, D.A., Ben-Shlomo, Y., Robertson, N.P., 2008. Survival and cause of death in multiple sclerosis: a prospective population-based study. J. Neurol. Neurosurg. Psychiatry 79 (9), 1016–1021.
Hoek, G., Krishnan, R.M., Beelen, R., et al., 2013. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environ. Health 12 (1), 43.
Jo, S., Kim, Y.J., Park, K.W., et al., 2021. Association of NO2 and other air pollution exposures with the risk of Parkinson disease. JAMA Neurol. 78 (7), 800–808.
Kasdagli, M.I., Katsouyanni, K., Dimakopoulou, K., Samoli, E., 2019. Air pollution and Parkinson's disease: a systematic review and meta-analysis up to 2018. Int. J. Hyg Environ. Health 222 (3), 402–409.
Kerckhoffs, J., Hoek, G., Gehring, U., Vermeulen, R., 2021. Modelling nationwide spatial variation of ultrafine particles based on mobile monitoring. Environ. Int. 154, 106569.
Kiernan, M.C., Vucic, S., Cheah, B.C., et al., 2011. Amyotrophic lateral sclerosis. Lancet 377 (9769), 942–955.
Klompmaker, J.O., Janssen, N.A.H., Bloemsma, L.D., et al., 2021. Effects of exposure to surrounding green, air pollution and traffic noise with non-accidental and cause-specific mortality in the Dutch national cohort. Environ. Health 20 (1), 82.
Krzyzanowski, B., Searles Nielsen, S., Turner, J.R., Racette, B.A., 2023. Fine particulate matter and Parkinson disease risk among medicare beneficiaries. Neurology 101 (21), e2058–e2067.
Livingston, G., Huntley, J., Sommerlad, A., et al., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396 (10248), 413–446.
Lomme, J., Reedijk, M., Peters, S., et al., 2023. Traffic-related air pollution and road traffic noise and Parkinson's disease – evaluations in two Dutch cohort studies. Environmental Epidemiology 7, e272.
Macleod, A.D., Taylor, K.S., Counsell, C.E., 2014. Mortality in Parkinson's disease: a systematic review and meta-analysis. Mov. Disord. 29 (13), 1615–1622.
Nunez, Y., Boehme, A.K., Goldsmith, J., et al., 2022. PM(2.5) composition and disease aggravation in amyotrophic lateral sclerosis: an analysis of long-term exposure to components of fine particulate matter in New York State. Environ Epidemiol 6 (2), e204.
Nunez, Y., Balalian, A., Parks, R.M., et al., 2023. Exploring relevant time windows in the association between PM2.5 exposure and amyotrophic lateral sclerosis: a case-control study in Denmark. Am. J. Epidemiol. 192 (9), 1499–1508.
Palacios, N., Munger, K.L., Fitzgerald, K.C., et al., 2017. Exposure to particulate matter air pollution and risk of multiple sclerosis in two large cohorts of US nurses. Environ. Int. 109, 64–72.
Parks, R.M., Nunez, Y., Balalian, A.A., et al., 2022. Long-term traffic-related air pollutant exposure and amyotrophic lateral sclerosis diagnosis in Denmark: a bayesian hierarchical analysis. Epidemiology 33 (6), 757–766.
Peters, S., Visser, A.E., D'Ovidio, F., et al., 2020. Effect modification of the association between total cigarette smoking and ALS risk by intensity, duration and time-since-quitting: euro-MOTOR. J. Neurol. Neurosurg. Psychiatry 91 (1), 33–39.
Phillips, N.J., Reay, J., Martyn, C.N., 1999. Validity of mortality data for Parkinson's disease. J. Epidemiol. Community Health 53 (9), 587–588.
Povedano, M., Saez, M., Martinez-Matos, J.A., Barcelo, M.A., 2018. Spatial assessment of the association between long-term exposure to environmental factors and the occurrence of amyotrophic lateral sclerosis in catalonia, Spain: a population-based nested case-control study. Neuroepidemiology 51 (1–2), 33–49.
Seelen, M., Toro Campos, R.A., Veldink, J.H., et al., 2017. Long-term air pollution exposure and amyotrophic lateral sclerosis in Netherlands: a population-based case-control study. Environ. Health Perspect. 125 (9), 097023.
Shi, L., Wu, X., Danesh Yazdi, M., et al., 2020. Long-term effects of PM(2.5) on neurological disorders in the American Medicare population: a longitudinal cohort study. Lancet Planet. Health 4 (12), e557–e565.
Siderowf, A., Lang, A.E., 2012. Premotor Parkinson's disease: concepts and definitions. Mov. Disord. 27 (5), 608–616.
Stafoggia, M., Oftedal, B., Chen, J., et al., 2022. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet. Health 6 (1), e9–e18.
Strak, M., Weinmayr, G., Rodopoulou, S., et al., 2021. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. BMJ 374, n1904.
Toro, R., Downward, G.S., van der Mark, M., et al., 2019. Parkinson's disease and long-term exposure to outdoor air pollution: a matched case-control study in The Netherlands. Environ. Int. 129, 28–34.
Velders Gjmm, R.J.M., Geilenkirchen, G.P., de Leeuw, F.A.A.M., Ligterink, N.E., Ruyssenaars, P., de Vries, W.J., Wesseling, J., 2020. Effects of European emission reductions on air quality in The Netherlands and the associated health effects. Atmos. Environ. 221, 117109.
Wesseling, J., Nguyen, L., Hoogerbrugge, R., 2016. Gemeten en berekende concentraties stikstof(di)oxiden en fijnstof in de periode 2010 t/m 2015 (Update) : Een test van de standaardrekenmethoden 1 en 2.
WHO, 2023. Factsheet on Dementia who.int/news-room/fact-sheets/detail/dementia#:~:text=Alzheimer%20disease%20is%20the%20most,60%E2%80%9370%25%20of%20cases. (Accessed 3 May 2023).
WHO, 2021. WHO global air quality guidelines. In: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Oxide, Sulfur Dioxide and Carbon Monoxide. World Health Organisation, Geneva.
Wilker, E.H., Osman, M., Weisskopf, M.G., 2023. Ambient air pollution and clinical dementia: systematic review and meta-analysis. BMJ 381, e071620.
Yu, Z., Peters, S., van Boxmeer, L., et al., 2021. Long-term exposure to ultrafine particles and particulate matter constituents and the risk of amyotrophic lateral sclerosis. Environ. Health Perspect. 129 (9), 97702.
Zhong, G., Wang, Y., Zhang, Y., Guo, J.J., Zhao, Y., 2015. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. PLoS One 10 (3), e0118333.