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Long-term air pollution exposure and Parkinson's disease mortality in a large pooled European cohort: An ELAPSE study

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ABSTRACT

Background: The link between exposure to ambient air pollution and mortality from cardiorespiratory diseases is well established, while evidence on neurodegenerative disorders including Parkinson's Disease (PD) remains limited.

Objective: We examined the association between long-term exposure to ambient air pollution and PD mortality in seven European cohorts.

Methods: Within the project 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE), we pooled data from seven cohorts among six European countries. Annual mean residential concentrations of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3), as well as 8 $PM_{2.5}$ components (copper, iron, potassium, nickel, sulphur, silicon, vanadium, zinc), for 2010 were estimated using Europe-wide hybrid land use regression models. PD mortality was defined as underlying cause of death being either PD, secondary Parkinsonism, or dementia in PD. We applied Cox proportional hazard models to investigate the associations between air pollution and PD mortality, adjusting for potential confounders.

Results: Of 271,720 cohort participants, 381 died from PD during 19.7 years of follow-up. In single-pollutant analyses, we observed positive associations between PD mortality and $PM_{2.5}$ (hazard ratio per 5 $\mu g/m^3$: 1.25; 95% confidence interval: 1.01–1.55), NO_2 (1.13; 0.95–1.34 per 10 $\mu g/m^3$), and BC (1.12; 0.94–1.34 per $0.5 \times 10^{-5} m^{-1}$), and a negative association with O_3 (0.74; 0.58–0.94 per 10 $\mu g/m^3$). Associations of $PM_{2.5}$, NO_2, and BC with PD mortality were linear without apparent lower thresholds. In two-pollutant models, associations with $PM_{2.5}$ remained robust when adjusted for NO_2 (1.24; 0.95–1.62) or BC (1.28; 0.96–1.71), whereas associations with NO_2 or BC attenuated to null. O_3 associations remained negative, but no longer statistically significant in models with $PM_{2.5}$. We detected suggestive positive associations with the potassium component of $PM_{2.5}$.

Conclusion: Long-term exposure to $PM_{2.5}$, at levels well below current EU air pollution limit values, may contribute to PD mortality.

1. Introduction

The association between exposure to air pollution and cardiovascular and respiratory diseases is well documented (WHO, 2021). Recently, attention has been drawn to the potential negative impact of air pollution on disorders that affect the brain and central nervous system, including neurodegenerative diseases such as dementia, Alzheimer's Disease, and Parkinson's Disease (PD) (Kim et al., 2020; Raggi and Leonardi, 2020). PD is the second most prevalent neurodegenerative disorder, affecting an estimated six million individuals globally, preceded in prevalence only by Alzheimer's Disease (Dorsey et al., 2018). Known risk factors for PD include age, being male, smoking, high consumption of dairy, exposure to pesticides, and genetic predisposition (Ascherio and Schwarzschild, 2016).

It has been suggested that both gaseous pollutants and fine particles can directly or indirectly damage the brain by crossing the blood–brain barrier, causing oxidative stress, neuroinflammation and abnormal aggregation of proteins, damaging the olfactory bulb and frontal cortex, leading to the development of PD (Ascherio and Schwarzschild, 2016). Despite PD being a progressive disease that leads to death in older age, epidemiological evidence on long-term exposure to air pollution and PD consists mainly of studies on the incidence of (rather than mortality from) PD. These studies on incidence present mixed findings, with some studies reporting associations with particulate matter of diameter < 10 μm (PM_{10}), particulate matter of diameter < 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2) or ozone (O_3) (Chen et al., 2017; Kirrane et al., 2015; Rhew et al., 2021;16(7):e0253253.; Ritz et al., 2016; Shi et al., 2020; Shin et al., 2018; Yu et al., 2021; Yuchi et al., 2020), while other studies find no associations (Cerza et al., 2018; Lee et al., 2016; Liu et al., 2016; Palacios et al., 2017; Palacios et al., 2014; Toro et al., 2019) (see supplemental Table S1). Only two studies examined long-term exposure to air pollution with respect to PD mortality: one only examining O_3, detecting significant positive associations (Zhao et al., 2021), and; another examining $PM_{2.5}$ and finding suggestive positive associations, which were weaker than those detected with incidence (compared to mortality) of PD in the same study (Rhew et al., 2021). Two studies went further to examine the association of specific components of $PM_{2.5}$ and PD. Nunez and colleagues examined black carbon (BC), organic matter (OM), nitrate, sulfate, sea salt, and soil $PM_{2.5}$ components, detecting associations of nitrate and OM with PD hospitalization (Nunez et al., 2021). Palacios and colleagues suggested an association of mercury with PD incidence (Palacios et al., 2014). Therefore, further study is warranted to elucidate the long-term effects of specific air pollution components, and strengthen the evidence base for potential effects at low pollutant concentrations, on mortality from neurodegenerative diseases including PD among large cohorts, such as through the 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) project. ELAPSE has recently been able to show that long-term exposure to low levels of air pollution was associated with premature mortality (Stafoggia et al., 2022; Strak et al., 2021), as well as incidence of cardiovascular diseases (Wolf et al., 2021), adult-onset asthma (Liu et al., 2021), chronic obstructive pulmonary disease (COPD) (Liu et al., 2021), lung cancer (Hvidtfeldt et al., 2021) and liver cancer (So et al., 2021), as well as mortality from dementia, psychiatric disorders, and suicide (Andersen et al., 2022). Here, we aimed to examine the association of long-term exposure to $PM_{2.5}$, NO_2, BC, and O_3, as well as eight $PM_{2.5}$ components, with mortality from PD among seven cohorts of the ELAPSE project.

2. Materials and methods

2.1. Study population

Within the ELAPSE project, we analysed pooled data from seven cohorts (and their sub-cohorts) among six European countries (see supplemental Figure S1), including information on potential confounders:

(a) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort in Sweden, which combined four sub-cohorts: Stockholm Diabetes Prevention Program (SDPP) (Eriksson et al., 2008); Stockholm Cohort of 60-year-olds (SIXTY) (Wändell et al., 2007); Stockholm Screening Across the Lifespan Twin study (SALT) (Magnusson et al., 2013); Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (Lagergren et al., 2004);
(b) Danish Nurse Cohort (DNC) in Denmark (Hundrup et al., 2012), including two cohort recruitment rounds in 1993 and 1999;

(c) Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) in France (Clavel-Chapelon, 2015);
(d) European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort in the Netherlands, which included two sub-cohorts: Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (Morgen) and Prospect (Beulens et al., 2010);
(e) Heinz Nixdorf Recall study (HNR) in Germany (Schmermund et al., 2002);
(f) Cooperative Health Research in the Region of Augsburg (KORA) in Germany (Holle et al., 2005), combining two sub-cohorts from baseline rounds in 1994–1995 (S3) and 1999–2001 (S4); and;
(g) Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) in Austria (Ulmer et al., 2007).

The cohorts were recruited in the 1990s or early 2000s, from one or several large cities and their surrounding towns, except for the two nationwide cohorts E3N and DNC. Detailed information of each cohort has been described previously (Chen et al., 2021). All cohorts were approved by the medical ethics committees in their respective countries.

2.2. Air pollution exposure assessment

The method for assessment of air pollution exposure via modelling has previously been described in detail (Hvidtfeldt et al., 2021; Liu et al., 2021; de Hoogh et al., 2018). Briefly, annual mean concentrations of $PM_{2.5}$, NO_2, BC, and O_3 (limited to the maximum running 8-hour average in the boreal warm season, April-September) were estimated for 2010 at participants' baseline residential addresses utilising standardized Europe-wide hybrid land use regression (LUR) models (de Hoogh et al., 2018). These models were developed based on air pollution concentration data from routine and research study monitors, satellites, estimates from chemical transport models, and land use and road variables as predictors.

$PM_{2.5}$, NO_2, BC, and O_3 LUR models used a 100 m × 100 m (grid) spatial scale that performed satisfactorily in fivefold hold-out validation, explaining 66%, 58%, 51and 60%, respectively, of measured spatial variation. BC was measured by the reflectance of $PM_{2.5}$ filters from 2009 and 2010, expressed in absorbance units.

In addition, we extrapolated pollutant concentrations for each year from baseline to the end of follow-up (Hvidtfeldt et al., 2021; Liu et al., 2021), and incorporated dynamic residential address history during follow-up. The extrapolation method was applied by utilising estimated monthly average concentrations, at a spatial resolution of 26 km × 26 km, from the Danish Eulerian Hemispheric Model (DEHM) since 1990 (Brandt et al., 2012). The extrapolation was performed after checking the agreement between ground measurements versus DEHM predictions for the four pollutants, as detailed previously to show little impact by temporal misalignment (Chen et al., 2021). The DEHM provided predicted modelling exposure data for a complete database to perform harmonious extrapolation for the four pollutants; ground measurements for $PM_{2.5}$ components were not available back in time. Pollutant concentrations were extrapolated for cohorts with available residential history information, using both a difference method and a ratio method with 2010 as the reference year (Stafoggia et al., 2022; Strak et al., 2021).

We estimated exposure to eight components of $PM_{2.5}$ for 2010 at the participants' baseline residential addresses using Europe-wide LUR models based on the standardized ESCAPE project monitoring data, with model details published previously (Chen et al., 2020). The eight components were selected to represent major pollution sources: copper (Cu), iron (Fe), and zinc (Zn) for non-tailpipe traffic emissions; sulfur (S) for long-range transport of secondary inorganic aerosols; nickel (Ni) and vanadium (V) for mixed oil burning/industry; silicon (Si) for earth crustal material; and, potassium (K) for biomass burning. We included large-scale satellite-model and chemical transport-model estimates of components to represent background concentrations, in addition to land-use, road, population, and industrial point source data to model local spatial variability. We applied two algorithms, supervised linear regression (SLR) (de Hoogh et al., 2018), and random forest (RF) (Chen et al., 2019), to develop models for the eight components. The models explained a moderate-to-large fraction of the measured concentration variation at the European scale (ranging from 41% to 90% across components).

2.3. Mortality outcome definition

We defined PD mortality from mortality registries, based solely on the underlying cause of death (as contributing causes of death were not available) using the International Classification of Diseases (ICD)-9: 332 (PD); and, ICD-10: G20 (PD), G21 (secondary Parkinsonism), G22 (Parkinsonism in diseases classified elsewhere), and F02.3 (dementia in PD).

2.4. Statistical analysis

We performed Cox proportional hazards models with age as the underlying timescale (Thiébaut and Bénichou, 2004) to examine associations between long-term exposure to air pollution and PD, following the general analytical framework of ELAPSE (Samoli et al., 2021). Censoring occurred at the time of event of interest, death from other causes, emigration, loss to follow-up, or the end of follow-up (ranging from 2011 to 2015 depending on sub-cohort), whichever came first. The start of follow-up was the year of enrolment in individual cohorts which ranged from 1985 to 2001 (supplemental Table S2). Air pollution exposure was included in models as a linear term. We examined associations using three models including *a priori* defined individual and area-level covariates, all assessed at the cohort baseline. Model 1 included age (time axis), sex (strata), sub-cohort (strata), and calendar year of baseline (year of enrolment). Model 2 was additionally adjusted for smoking status (never, former, current), smoking duration (years) for current smokers, smoking intensity (linear and squared term: cigarettes/day) for current smokers, body mass index (BMI, categories: <18.5, 18.5–24.9, 25.0–29.9, and $\geq$ 30 kg/m^2), marital status (married/cohabiting, divorced/separated, single, widowed), and employment status (employed/self-employed, other). Model 3 (main model) was further adjusted for area-level mean annual (2001) income as a proxy for socio-economic status (SES). Only participants with complete exposure and covariate information for Model 3 were included in the analyses to ensure comparability among model results.

For explorative purposes, we performed a subset analysis with Model 3 by excluding participants of exposure levels above certain pre-defined values ($PM_{2.5}$: 25, 20, 15 μg/m^3; NO_2: 40, 30, 20 μg/m^3; BC: 3, 2.5, 2, 1.5 × 10^{-5}m^{-1}; O_3: 120, 100 μg/m^3), based partially on existing EU and US limit values and previous (2005) WHO guidelines. To assess the shape of concentration–response functions (associations from Model 3), we modelled pollutants as natural cubic splines with two degrees of freedom and tested for deviation of linearity by comparing with linear models using a likelihood ratio test. Further, for explorative purposes, we assessed a potential effect modification on these associations by age (<65 or $\geq$ 65 years old), sex (female or male), overweight status (BMI $\geq$ 25 kg/m^2 or not), smoking status (current, former, or never smoker), and employment status, by including an interaction term into Model 3 tested by the Wald test. In addition, we performed two-pollutant models based on Model 3 to investigate the contribution of individual pollutants.

We performed several sensitivity analyses to check the robustness of our associations. We compared the results of year 2010 exposure in Model 3 with results of back-extrapolated baseline year exposures and time-varying annual exposures. Time-varying (exposure) analyses were

performed for cohorts with available information on residential address history (CEANS, EPIC-NL, and VHM&PP), with 1-year strata of calendar time to account for time trends in air pollution and mortality. Finally, we compared effect estimates in Model 3 using different datasets excluding one cohort at a time.

The results are presented as hazard ratios (HR) and 95% confidence intervals (CI) for pollutant unit increases of 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, 0.5 × 10^{-5}m^{-1} for BC, 10 μg/m^3 for O_3, and IQR for $PM_{2.5}$ composition. All statistical analyses were performed in software R (version 3.4.0).

3. Results

3.1. Population description

Our pooled cohort included 324,728 participants. We excluded 53,008 of those participants with covariate data missing for Model 3. Of 271,720 remaining participants in the final analyses, 381 died from PD (380 from PD and 1 from secondary Parkinsonism) during a mean follow-up time of 19.7 years (Table 1) and a mean age at end of follow-up of 66.9 years (supplemental Table S2). The large VHM&PP cohort contributed with the majority (284, or ~ 75%) of the deaths. Baseline characteristics of participants varied widely across sub-cohorts (Table 1), supporting the use of strata for sub-cohorts to adjust for differences in baseline hazard. Mean age of participants at baseline was 47.1 years, ranging from 42.1 in VHM&PP to 72.9 years in CEANS-SNACK. The majority of participants (69%) were female, as three cohorts/sub-cohorts were female-only by design (DNC, E3N, and EPIC-NL-Prospect). The proportion of current smokers ranged from 13% in E3N to 37% in DNC-1993. Almost half of our participants (41%) were overweight, with the lowest proportion (21%) in E3N and the highest (74%) in HNR (Table 1).

Table 1
Baseline demographic characteristics of participants by the pooled cohort and sub-cohorts.

Cohort/ sub-cohort	N	Deaths, N	Follow-up time, years	Age, years	Female (%)	Current smokers (%)	Smoking duration, years*	Smoking intensity, n/day*	Over weight (%)ϕ	Married/ cohabiting (%)	Employed (%)	Mean income, euro†
Pooled Cohort	271,720	381	19.7	47.1 ± 14.0	69	22	21.9 ± 12.5	14.7 ± 8.9	41	72	68	20.1 ± 6.2
CEANS	20,702	12	13	56.3 ± 11.4	58	22	33.6 ± 11.0	13.1 ± 7.7	51	72	69	25.3 ± 5.6
SDPP	7,727	0	15.9	47.1 ± 4.9	61	26	27.9 ± 8.6	13.5 ± 7.4	52	84	91	24.3 ± 4.2
SIXTY	3,969	3	15.5	60.0 ± 0.0	52	21	36.3 ± 9.9	13.4 ± 7.6	65	74	68	24.7 ± 6.9
SALT	6,176	1	10.4	57.8 ± 10.6	55	21	37.9 ± 9.3	12.7 ± 8.0	40	68	64	25.3 ± 6.6
SNACK	2,830	8	7.4	72.9 ± 10.4	62	14	43.3 ± 13.6	11.7 ± 8.2	53	46	23	28.7 ± 2.2
DNC	25,171	27	17.3	53.5 ± 8.3	100	35	30.4 ± 9.5	13.7 ± 8.0	29	70	78	19.1 ± 2.5
1993	17,043	27	18.7	56.2 ± 8.4	100	37	31.6 ± 9.9	13.9 ± 8.2	28	68	70	19.2 ± 2.6
1999	8,128	0	14.4	47.9 ± 4.2	100	29	27.1 ± 7.1	13.3 ± 7.3	30	76	95	19.0 ± 2.4
E3N	39,006	29	16.7	53.0 ± 6.8	100	13	28.6 ± 7.6	11.4 ± 9.2	21	83	68	11.2 ± 3.0
EPIC-NL	32,872	17	16.7	49.5 ± 11.9	75	29	28.9 ± 11.2	15.0 ± 8.7	52	70	61	12.6 ± 1.6
Morgen	18,302	5	16.8	42.9 ± 11.2	55	35	24.8 ± 10.6	15.7 ± 8.6	50	65	69	12.2 ± 1.6
Prospect	14,570	12	16.4	57.7 ± 6.1	100	23	36.8 ± 7.6	13.7 ± 8.7	55	77	51	13.1 ± 1.4
HNR	4,733	8	12	59.7 ± 7.8	50	24	34.5 ± 9.4	18.6 ± 12.0	74	75	40	25.2 ± 8.2
KORA	4,853	4	14.3	49.4 ± 13.9	51	21	24.7 ± 11.8	16.1 ± 9.5	68	80	57	37.3 ± 6.0
S3	2,572	2	15.6	49.4 ± 13.9	51	20	25.2 ± 12.1	16.5 ± 9.5	67	80	55	36.7 ± 4.4
S4	2,281	2	12.9	49.3 ± 13.8	51	23	24.3 ± 11.6	15.7 ± 9.5	69	79	59	38.0 ± 7.3
VHM&PP	144,383	284	23.1	42.1 ± 15.0	56	20	13.4 ± 8.3	15.6 ± 8.9	43	69	70	22.9 ± 1.7

Results of participants' characteristics at baseline are presented as Mean ± SD, Number, or Percentage.
*: Smoking duration and smoking intensity are only for current smokers. We set these variables to zero for never and former smokers.
ϕ: BMI ≥ 25 kg/m^2 indicates overweight according to the World Health Organization (WHO) categories.
†: Area-level mean year income in euros × 1,000 in the year 2001. The spatial scale of an area varied from neighborhoods and city districts (CEANS, E3N, EPIC-NL, and HNR) to municipalities (DNC, KORA, and VHM&PP).
Definition of abbreviation: BMI, body mass index; SD, standard deviation.

3.2. Air pollution description

Fig. 1 represents the distribution of air pollution levels in 2010 by pooled cohort and sub-cohorts. Exposure distributions varied between cohorts with the lowest concentrations of $PM_{2.5}$ and BC in the Nordic cohorts (CEANS and DNC). Almost all participants were exposed to annual $PM_{2.5}$ levels below the EU limit value (25 μg/m^3) but above the US limit value (12 μg/m^3) and the new WHO guideline (5 μg/m^3). Similarly, almost all participants were exposed to annual NO_2 levels below the EU limit value (40 μg/m^3) but above the new WHO guideline (10 μg/m^3) (Fig. 1). We also observed varying exposure levels across cohorts and sub-cohorts for the baseline year exposure (supplemental Figure S2). Comparing with 2010 exposure levels, the concentrations of $PM_{2.5}$ were much higher at baseline, with smaller differences observed for the other pollutants. Pearson correlations between NO_2 and BC were moderate to high in sub-cohorts (0.67–0.93) except for in CEANS-SNACK (0.43; Table S3). $PM_{2.5}$ was moderately positively correlated with exposure to BC and NO_2 in most sub-cohorts, and (warm season) O_3 was moderately negatively correlated with other pollutants in most sub-cohorts (Table S3).

3.3. Main analyses

In our fully adjusted model (Model 3), significant positive associations were observed between $PM_{2.5}$ exposure and PD mortality (HR: 1.25; 95% CI: 1.01–1.55), while suggestive positive associations were evident for NO_2 (1.13; 0.95–1.34) and BC (1.12; 0.94–1.34) (Table 2). We observed a negative association for O_3 (0.74; 0.58–0.94). Adjustment for individual covariates minimally affected the air pollution effect estimates (Model 2 versus Model 1). Adjustment for area-level income mildly decreased the effect estimates (Model 3 versus Model 2).

In two-pollutant models, the association with $PM_{2.5}$ was reasonably robust when including NO_2 or BC although with attenuation towards the null for either pollutant, and the association with O_3 was mostly unchanged (Table 2). Two-pollutant results as contributions of NO_2 and BC individually are difficult to interpret because of the high correlations between NO_2 and BC in some sub-cohorts (Table S3).

We observed linear associations of $PM_{2.5}$, NO_2, and BC with PD mortality, with no evidence of a lower threshold below which air pollution was not associated with PD mortality (Fig. 2, Table S4). At the extremes of concentration distribution, the uncertainty of the shape of

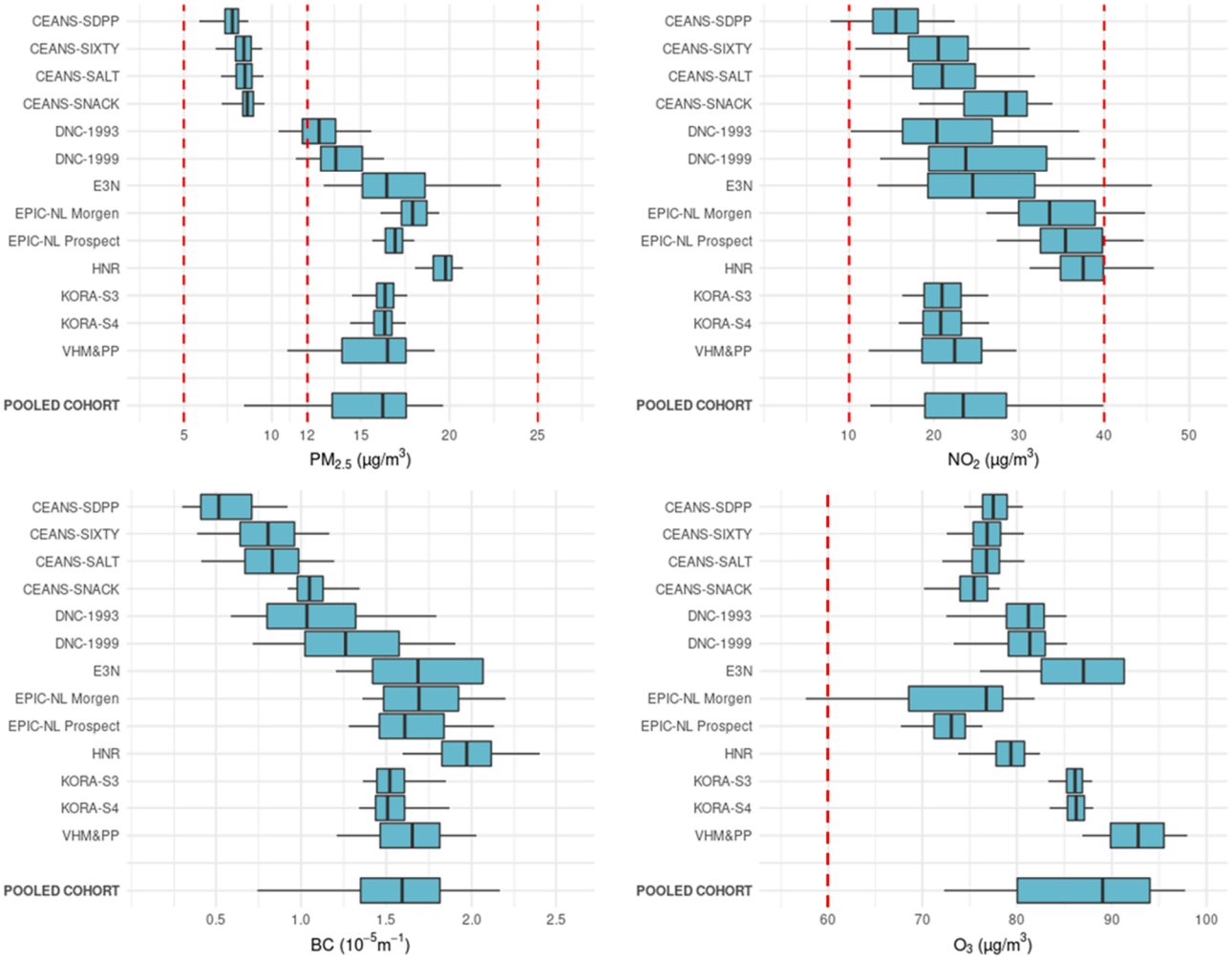

Fig. 1. Distribution of annual average concentrations of air pollution for the year 2010 by pooled cohort and sub-cohorts (N = 271,720). The bold lines in the middle of the box indicate the median values (the 50th percentile). The lower and upper hinges correspond to the 25th and 75th percentiles. The lower and upper whiskers extend to the 5th and 95th percentiles. Red dashed lines represent different limited values in EU, U.S., and WHO guidelines (2021 version). For $PM_{2.5}$, they indicate the annual average limited/guideline values of WHO (5 μg/m^3), U.S. (12 μg/m^3), and EU (25 μg/m^3). For NO_2, they indicate the annual average limited/guideline values of WHO (10 μg/m^3) and EU (40 μg/m^3). For O_3, it indicates the 8-hour mean, peak season guideline value of WHO (60 μg/m^3). O_3 was in the boreal warm season from April 1st through September 30th. Definition of abbreviation: $PM_{2.5}$, particulate matters with aerodynamic diameters of less than 2.5 μm; NO_2, nitrogen dioxide; BC, black carbon (measured by the reflectance of $PM_{2.5}$ filters from 2009 and 2010, expressed in absorbance units); O_3, ozone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Associations between long-term air pollution exposure and Parkinson's disease mortality (N = 271,720).

	Model 1	Model 2	Model 3	Model 3 + NO_2	Model 3 + $PM_{2.5}$	Model 3 + BC	Model 3 + O_3
Parkinson's disease (381deaths)							
NO_2	1.19 (1.01, 1.40)	1.18 (1.01, 1.39)	1.13 (0.95, 1.34)	/	1.01 (0.81, 1.26)	1.11 (0.74, 1.68)	0.93 (0.72, 1.20)
$PM_{2.5}$	1.30 (1.05, 1.60)	1.30 (1.05, 1.60)	1.25 (1.01, 1.55)	1.24 (0.95, 1.62)	/	1.28 (0.96, 1.71)	1.11 (0.85, 1.45)
BC	1.18 (1.00, 1.40)	1.17 (0.99, 1.39)	1.12 (0.94, 1.34)	1.02 (0.67, 1.55)	0.97 (0.76, 1.25)	/	0.91 (0.71, 1.18)
O_3	0.70 (0.56, 0.89)	0.70 (0.56, 0.89)	0.74 (0.58, 0.94)	0.68 (0.48, 0.98)	0.79 (0.59, 1.07)	0.67 (0.47, 0.96)	/

Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increases: 10 $\mu g/m^3$ for NO_2, 5 $\mu g/m^3$ for $PM_{2.5}$, 0.5 $\times$ $10^{-5}m^{-1}$ for BC and 10 $\mu g/m^3$ for O_3. BC was measured by the reflectance of $PM_{2.5}$ filters from 2009 and 2010, expressed in absorbance units.
Model 1: adjusted for age (time axis), sex (strata), sub-cohort (strata), and calendar year of baseline;
Model 2: additionally adjusted for smoking (status, duration, intensity, and intensity^2), BMI (category), marital status, and employment status;
Model 3: further adjusted for area-level mean year income.

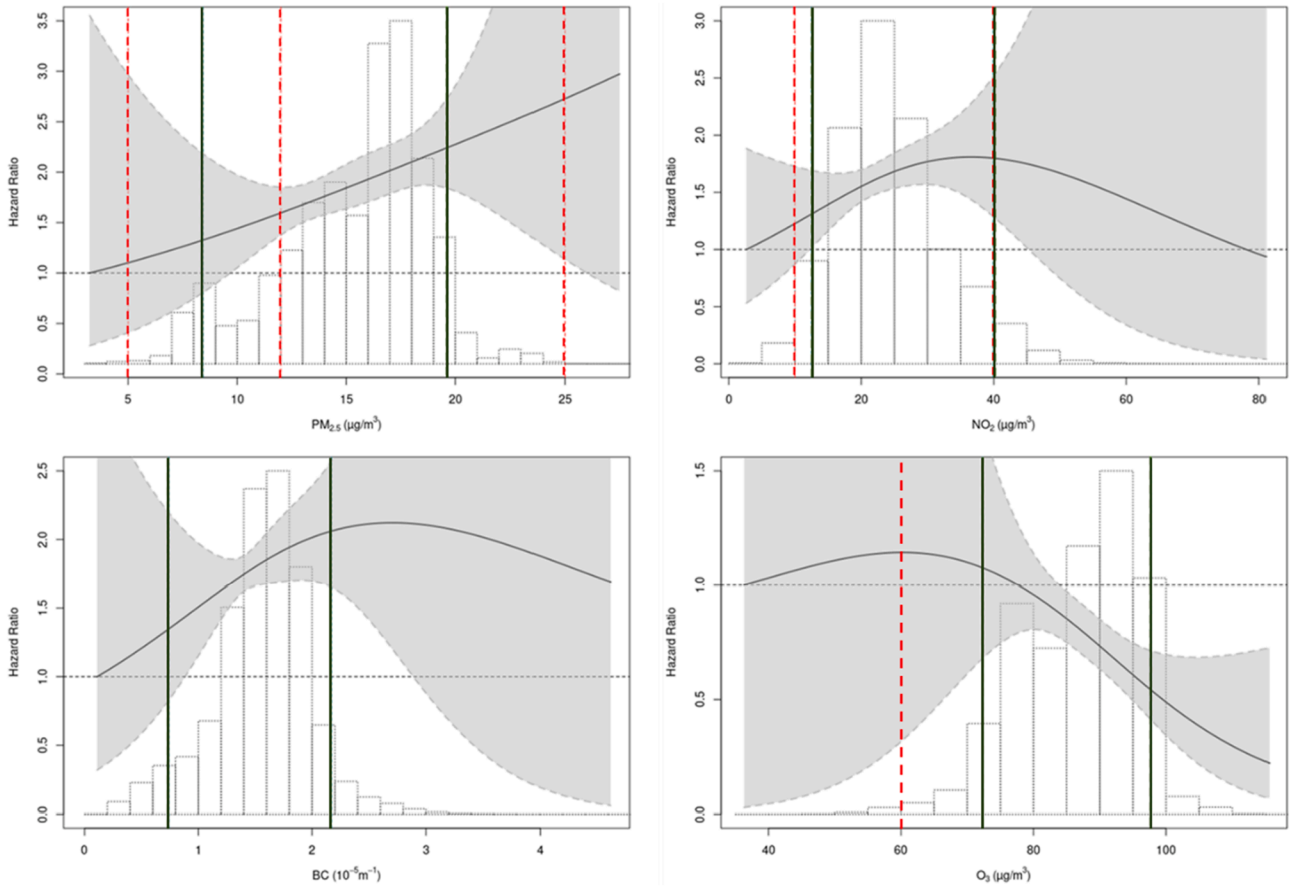

Fig. 2. Concentration-response curves for the associations between long-term exposure to air pollution and Parkinson's disease mortality. Natural cubic splines with two degrees of freedom were fit for air pollutants based on Model 3, where the hazard ratios equal to one were for minimum pollutant exposures. Solid black (horizontal) lined-curves indicate hazard ratio values and dashed black lines (with grey shading) indicate their 95% confidence intervals. Solid black (vertical) lines indicate the 5th and 95th percentiles of air pollutants' concentrations. Dashed red (vertical) lines represent existing EU, US, and WHO guideline limit values. The histograms show the distributions of exposures in 2010. X-axes are truncated at 60 $\mu g/m^3$ for NO_2 and 3 $\times$ $10^{-5}m^{-1}$ for BC. Definition of abbreviation: $PM_{2.5}$, particulate matter with aerodynamic diameter of less than 2.5 μm; NO_2, nitrogen dioxide; BC, black carbon (measured by the reflectance of $PM_{2.5}$ filters from 2009 and 2010, expressed in absorbance units); O_3, ozone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the relationship was large (Fig. 2). The likelihood ratio test (results not shown) indicated no significant deviations from a linear relationship. The majority of participants (74% to 100%) in the two Nordic cohorts (CEANS, DNC) were exposed to $PM_{2.5}$ levels mostly below 15 $\mu g/m^3$ (Fig. 1). This disparity in exposure level across sub-cohorts was less prevalent for NO_2 and O_3 but not for BC (Fig. 1).

We observed that the association between PD mortality with $PM_{2.5}$ was statistically stronger in participants who were normal or under weight, as compared to overweight participants (*p*-value for interaction = 0.05). We also note stronger association in males, although no significant effect modification was observed (Table S5).

3.4. Sensitivity analyses

A number of sensitivity analyses showed robustness in associations for all pollutants. Associations with $PM_{2.5}$, NO_2 and BC were (borderline) significant when using either of the back-extrapolated (ratio or difference method) baseline year exposures (Table S6). The HRs and confidence intervals for all three pollutants were substantially smaller because of the higher exposure levels and variability of baseline

exposure compared to 2010 exposure (Figure S2). For time-varying exposures, available in a subset of three cohorts (N = 132,952) with available data (CEANS, EPIC-NL, and VHM&PP), HRs were generally very similar compared to those with the 2010 exposure (Table S7). Further, the associations with PD mortality were largely robust to excluding one sub-cohort at a time, except for NO_2 association when excluding DNC. Associations for $PM_{2.5}$, NO_2 and BC became very imprecise and non-significant when excluding the large VHM&PP which contributed the majority of PD deaths (Table S8).

$PM_{2.5}$ component data were available in a subset of 271,003 participants. Exposure to the eight $PM_{2.5}$ components estimated by the two different models, SLR and RF, and their correlation with $PM_{2.5}$ mass and NO_2 can be seen in Supplementary Material (Tables S9-S12). In single SLR models, Cu, Fe, K, and S were positively associated with PD mortality, and associations were attenuated in two-pollutant models with $PM_{2.5}$ and NO_2 (Fig. 3). Single-pollutant RF models showed significant associations between K and PD mortality, and no associations for other components (Fig. 3).

4. Discussion

In the pooled analysis of 271,720 adults from seven European cohorts, we found that long-term exposure to $PM_{2.5}$, NO_2, and BC were associated with PD mortality, with the strongest and most robust associations for $PM_{2.5}$. We observed that associations persisted at low-levels of pollutant concentration, well below current EU limit values. This study of a large European dataset on Europeans from seven countries contributes to the evidence base on air pollution and PD risk, albeit that this evidence base remains mixed. Air pollution is a complex mix of PM and gases, with some components able to access the brain through the circulatory or olfactory system. While further research into the relevant biological pathways is required, several hypotheses exist including that air pollution components enter the brain and disrupt proteostatis, causing injury to mitochondria and inducing inflammation.

Of 14 studies investigating the association of long-term exposure to $PM_{2.5}$ with PD development or mortality, the majority reported positive associations, in agreement with our findings (Table S1). Seven of these studies were included in a recent review and *meta*-analysis of $PM_{2.5}$ and PD incidence, reporting a relative risk (RR) estimate of 1.08 (95% CI: 0.98–1.19) per 10 μg/m^3 increase (Han et al., 2020), which is weaker than our HR estimate of 1.25 (95% CI: 1.01–1.55) per 5 μg/m^3. A similar comparison can be made for NO_2, for which Han and colleagues reported a RR of 1.03 (95% CI: 0.99–1.07) per 10 μg/m^3 compared to our HR of 1.13 (95% CI: 0.95–1.34) per 10 μg/m^3. We found generally stronger associations than those reported in the literature, which are in line with generally stronger associations reported in the ELAPSE project with overall mortality (Stafoggia et al., 2022; Strak et al., 2021) compared to those in the literature and recent *meta*-analyses (Chen and Hoek, 2020). We observed a clear linear $PM_{2.5}$ exposure–response function with PD mortality, with a linear function for NO_2 and BC exposure especially at lower levels, suggesting that there are no lower threshold levels below which air pollution is not harmful (Fig. 2), consistent with observations made for other health outcomes in ELAPSE and other studies (Stafoggia et al., 2022; Strak et al., 2021).

Our results on long-term exposure to NO_2 and PD mortality are in accordance with current evidence of a suggestive positive association, however, not to O_3, as reported by a 2019 *meta*-analysis by Kasdagli and colleagues (Kasdagli et al., 2019). They found a significant positive association with O_3, while we found a negative association with O_3 in single pollutant models. In two-pollutant models with $PM_{2.5}$, associations with O_3 remained negative but no longer statistically significant. Our negative association with O_3 may be due to its negative correlation with $PM_{2.5}$, BC and NO_2, the small exposure contrasts within each sub-cohort (Fig. 1), or generally low levels of O_3 exposure in our study. The inverse relationship between O_3 and PD mortality could also be explained by the moderate-to-strong negative correlation of O_3 with NO_2 in our pooled cohort, and strong negative correlations of O_3 with NO_2 and BC in some of our larger populated sub-cohorts (e.g., VHM&PP) (Table S3). Alternatively, this negative association between O_3 and PD mortality could be explained by bias related to the study design and lack of power due to low numbers of cases. In our study, we exploit exposure contrasts within relatively small study areas compared to other studies, making it thus less informative for O_3 which tends to vary on a large spatial scale (Brunekreef et al., 2021). Moreover, one previous study has shown that ambient ozone concentration is not a suitable surrogate for individual exposure assessment and may lead to large misclassification of exposure (Niu et al., 2018). A large US study has previously suggested the existence of a threshold at 56 ppb (~110 μg/m^3) for the effect of warm-season O_3 on all-cause mortality (Jerrett et al., 2009). Of five studies on O_3 and PD incidence, three (Shin et al., 2018; Cerza et al., 2018; Zhao et al., 2021) have detected positive associations, whereas two have found none (Chen et al., 2017; Lee et al., 2016). We present the

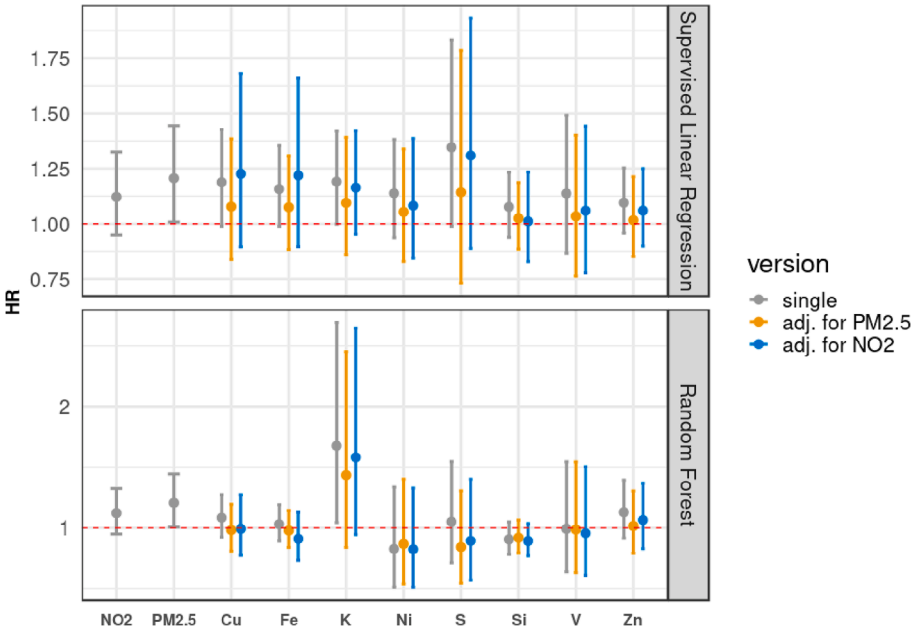

Fig. 3. Associations of $PM_{2.5}$ components with Parkinson's disease mortality in single-pollutant and two-pollutant models in SLR and RF analyses. (N = 271,003; Parkinson's mortality = 381). Results are presented as hazard ratio and 95% confidence interval [HR (95%CI)] for the following increments: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for NO_2, and IQR increments for each $PM_{2.5}$ component. The main model was adjusted for sub-cohort identification, age, sex, year of enrollment, smoking (status, duration, intensity, and intensity^2), BMI categories, marital status, employment status, and 2001 neighborhood-level mean income. In two-pollutant models, $PM_{2.5}$ and NO_2 exposures were estimated using LUR. Definition of abbreviation: BMI, body mass index; CI, confidence interval; Cu, copper; Fe, iron; HR, hazard ratio; K, potassium; Ni, nickel; $PM_{2.5}$, fine particulate matter; S, sulfur; Si, silicon; V, vanadium; Zn, zinc.

novel result of a positive association between long-term exposure to BC and PD mortality, with a HR of 1.12 (0.94, 1.34) per 0.5 $\times$ $10^{-5}m^{-1}$, which is in contrast to the only other study on BC and incidence of PD reporting an inverse association (RR: 0.96; 95%CI: 0.94–0.99) (Yang et al., 2018). These varied findings could be partly explained by a lack of specificity regarding particle component exposure levels across studies, with components expected to vary in presence and level across study sites due to varying air pollution sources contributing to the same component (Nunez et al., 2021).

In our particle component analysis, we detected a suggestive association between the $PM_{2.5}$ component of K and mortality from PD (Fig. 3). This association, however, was attenuated when adjusting for either $PM_{2.5}$ mass or NO_2. The particle component results shed some light on the potential local contributing (combustion or otherwise) sources. K has been seen as a tracer of biomass burning, which in Europe may be in the form of residential wood fire places or municipal water boilers. K has also been seen in roadside samples of Poland as an element of salt sprinkles used by local authorities to de-ice road surfaces during winter, which may suspend as airborne particles outside of winter (Skorbiłowicz and Skorbiłowicz, 2019). An analysis from the US suggested that 80% of the variability of K can be explained by factors associated with soil dust, traffic and biomass burning, however more accurately indicating traffic when considered alongside Fe (for which we saw a less suggestive association) (Pachon et al., 2013). Our findings differ from those of Nunez and colleagues, who detected associations of traffic-related nitrate and OM with PD hospitalization (Nunez et al., 2021), as well as of Palacios and colleagues, who found the relevance of mercury for PD incidence (Palacios et al., 2014). OM is a complex mixture of compounds including the potentially neurotoxic polycyclic aromatic hydrocarbons, which are known to evoke an inflammatory response and contribute to degenerative disease-like syndromes in animal studies (Nunez et al., 2021). While our study was not able to analyse this specific PM component, it is moderately-to-highly correlated with $PM_{2.5}$ and may explain those associated findings. Based on the literature, more studies are needed to determine which PM component is most biologically relevant for neuropathology related to PD (Nunez et al., 2021).

We observed significant effect modification for the associaton of $PM_{2.5}$ with PD mortality by BMI, with the strongest associations in those who were not overweight (BMI $<$ 25 kg/m^2, as defined by WHO), which may be indicative of PD-related weight loss with progressive disease stages due to malnutrition (van der Marck et al., 2012). We hypothesise that those individuals with more progressed disease and that are closer to death would have a lower body weight, also as a function of age-related weight loss – suggested separately by a stronger association of $PM_{2.5}$ with PD mortality among individuals $\geq$ 65 years of age.

A strength of our study is the pooling of data from seven European cohorts within the ELAPSE framework, which allows for a larger sample size to investigate mortality from PD. Another strength is that we had harmonized exposure data based on the Europe-wide hybrid LUR models of a fine spatial scale. Furthermore, we had detailed and harmonised information available on potential confounders including sample characteristics at the individual and area level. While we did have information on an individual's history of smoking, we did not have information on history of traumatic brain injury, another major personal risk factor for PD, which is somewhat controlled for in our models by controlling for sex: males show increased likelihood to suffer this injury due to their greater exposure to events such as road traffic accidents or contact sports; as well as more likely to smoke, as another major personal risk factor (Rocca, 2018).

The main limitation of our study is related to the definition of PD based on mortality data. Numerous studies show that PD is not well ascertained in death certificates and it underestimates the true burden of PD (Shi and Counsell, 2021; Hobson and Meara, 2018). Furthermore, many PD patients die from competing illnesses, and it is a weakness that we could not identify those, as we did not have information on deaths from PD as a contributing cause. Although the sample size achieved by pooling seven European cohorts was large, we had limited statistical power due to a small number of deaths due to PD. Another limitation is that exposure data were based on the year 2010, and applied at the baseline of the cohorts recruited in the 1990s and early 2000s. A previous study reported stable spatial distribution of NO_2 over 10 years in the Netherlands prior to 2011 (Eeftens et al., 2011). Furthermore, predictions from our year 2010 model were highly correlated ($R^2 > 76\%$) with year 2000 and 2005 models for NO_2 and O_3, and the year 2013 model for $PM_{2.5}$ (de Hoogh et al., 2018), indicating a limited impact of temporal misalignment by exposures based on the year 2010. Furthermore, our sensitivity analyses showed robust associations when using either back-extrapolated baseline year exposure (Table S6) or time-varying annual exposure in three cohorts with available information on address history (Table S7). Another limitation is inherent exposure misclassification due to lack of information on time spent outdoors and commuting to work (as personal exposure from outdoor sources), other sources of air pollution indoors, as well as outdoor and indoor sources at work. Finally, we did not have environmental noise exposure information for the VHM&PP cohort, which contains the majority of our cases, to treat as a potential confounder for the effect of air pollution on PD mortality.

5. Conclusions

In conclusion, we found that long-term exposure to $PM_{2.5}$, NO_2 and BC were associated with the risk of dying from PD, with $PM_{2.5}$ found to be the most relevant pollutant for this risk. We also found that associations persisted at low levels of pollutant concentration, well below current EU air quality standards. This study based on a large European population adds strong novel evidence in support of an association between air pollution and PD.

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

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107667.

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